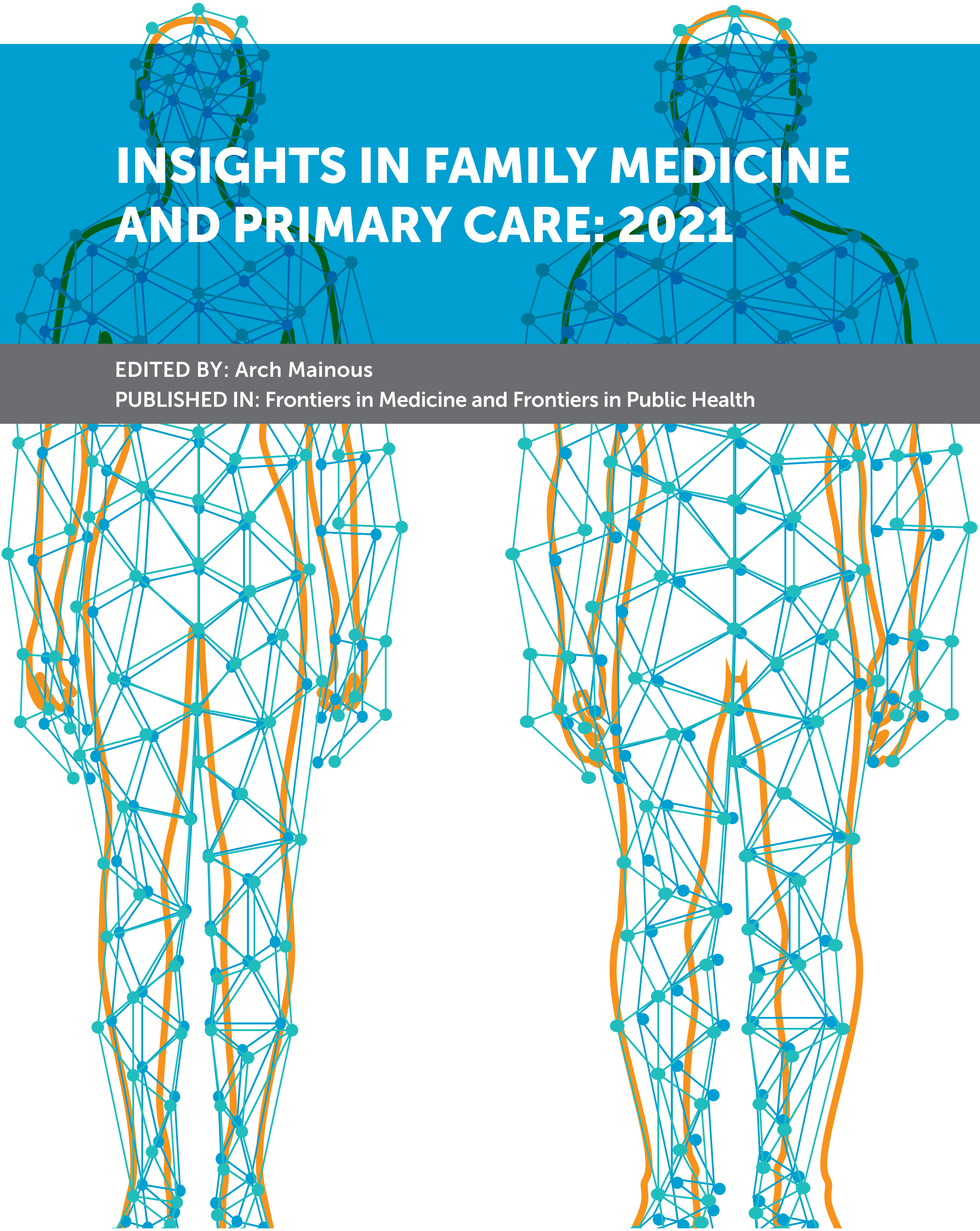

INSIGHTS IN FAMILY MEDICINE AND PRIMARY CARE: 2021

EDITED BY: Arch Mainous

PUBLISHED IN: Frontiers in Medicine and Frontiers in Public Health

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-83250-643-1
DOI 10.3389/978-2-83250-643-1

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INSIGHTS IN FAMILY MEDICINE AND PRIMARY CARE: 2021

Topic Editor:
Arch Mainous, University of Florida, United States

Citation: Mainous, A., ed. (2022). Insights in Family Medicine and Primary Care: 2021. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83250-643-1

Table of Contents

frontiers in Medicine

SYSTEMATIC REVIEW
published: 05 February 2021
doi: 10.3389/fmed.2021.620044

Obesity and Mortality Among Patients Diagnosed With COVID-19: A Systematic Review and Meta-Analysis

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Coronavirus disease 2019 (COVID-19) has already raised serious concern globally as the number of confirmed or suspected cases have increased rapidly. Epidemiological studies reported that obesity is associated with a higher rate of mortality in patients with COVID-19. Yet, to our knowledge, there is no comprehensive systematic review and meta-analysis to assess the effects of obesity and mortality among patients with COVID-19. We, therefore, aimed to evaluate the effect of obesity, associated comorbidities, and other factors on the risk of death due to COVID-19. We did a systematic search on PubMed, EMBASE, Google Scholar, Web of Science, and Scopus between January 1, 2020, and August 30, 2020. We followed Cochrane Guidelines to find relevant articles, and two reviewers extracted data from retrieved articles. Disagreement during those stages was resolved by discussion with the main investigator. The random-effects model was used to calculate effect sizes. We included 17 articles with a total of 543,399 patients. Obesity was significantly associated with an increased risk of mortality among patients with COVID-19 (RR_{adjust}: 1.42 (95%CI: 1.24–1.63, $p < 0.001$). The pooled risk ratio for class I, class II, and class III obesity were 1.27 (95%CI: 1.05–1.54, $p = 0.01$), 1.56 (95%CI: 1.11–2.19, $p < 0.01$), and 1.92 (95%CI: 1.50–2.47, $p < 0.001$), respectively). In subgroup analysis, the pooled risk ratio for the patients with stroke, CPOD, CKD, and diabetes were 1.80 (95%CI: 0.89–3.64, $p = 0.10$), 1.57 (95%CI: 1.57–1.91, $p < 0.001$), 1.34 (95%CI: 1.18–1.52, $p < 0.001$), and 1.19 (1.07–1.32, $p = 0.001$), respectively. However, patients with obesity who were more than 65 years had a higher risk of mortality (RR: 2.54; 95%CI: 1.62–3.67, $p < 0.001$). Our study showed that obesity was associated with an increased risk of death from COVID-19, particularly in patients aged more than 65 years. Physicians should aware of these risk factors when dealing with patients with COVID-19 and take early treatment intervention to reduce the mortality of COVID-19 patients.

Keywords: COVID-19, SARS-CoV-2, obesity, body mass index (BMI), mortality

Edited by:
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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Medicine

Received: *21 October 2020*
Accepted: *06 January 2021*
Published: *05 February 2021*

Citation:
Poly TN, Islam MM, Yang HC, Lin MC, Jian W-S, Hsu M-H and Jack Li Y-C (2021) Obesity and Mortality Among Patients Diagnosed With COVID-19: A Systematic Review and Meta-Analysis. Front. Med. 8:620044. doi: 10.3389/fmed.2021.620044

INTRODUCTION

Rationale

The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), has spread globally and created mounting concern (1). Healthcare organizations and providers are trying to find solutions to reduce the spread of disease and fatality rates. The rapid increase in the number of cases has created an unbearable burden on the healthcare system, especially in developing counties where healthcare systems are more fragile (2, 3). Early diagnosis of severe patients is essential to improve patient conditions and reduce mortality. Earlier classification of mild and severe COVID-19 patients could facilitate the proper utilization of limited resources (4). Multiple studies reported changes in several laboratory parameters [(e.g., the number of lymphocytes, C-reactive protein (CRP), interleukin-6 (IL-6), and erythrocyte sedimentation rates (ESR)] in the COVID-19 patients, but data are not sufficient to show their correlation according to severity and mortality (5, 6). Therefore, finding an appropriate risk factor is essential to classify mild and severe patients at an early stage.

Obesity is defined as abnormal fat accumulation and is a common, costly condition (7). According to the WHO report, obesity is classified into three groups based on body mass index (BMI). The prevalence of obesity has tripled since 1975 and is an established risk factor of other diseases such as diabetes, hypertension, heart disease, and cancers (8–10). Paradoxically, obesity has been shown to decrease mortality among patients diagnosed with pneumonia and ARDS (11–14). Recent epidemiological studies have shown obesity to be associated with both neutral and increased risk of mortality among patients diagnosed with COVID-19 (15, 16), but mechanisms underlying this are still unclear. Previous studies noted that the number of hospitalization and mechanical ventilation cases is higher in patients with obesity that can be associated with an increased rate of mortality (17, 18). Moreover, obesity is related to the downregulation of the inflammatory pathway, which leads to increase expression of inflammatory molecules, including interleukin-6 (IL-6). Age and elevated IL-6 were proclaimed as significant predictors of in-hospital mortality (19, 20).

Goal of Investigation

The objectives of the current comprehensive and rigorous meta-analysis were to investigate relevant epidemiological studies for evaluating the association between obesity and mortality of COVID-19 patients. The findings of this study could help healthcare providers to take preventive actions and use early treatment strategies for these high-risk groups.

Research Aims

- To determine whether obesity is associated with an increased rate of mortality among the patients diagnosed with COVID-19.
- To calculate the strength of association between class I, class II, and class III obesity and mortality of COVID-19 patients.
- To elucidate the association between associated factors (e.g., diabetes, CKD, COPD, smoking) and mortality of COVID-19 patients.

METHODS

Meta-Analysis Guidelines

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to select potential study inclusion. Moreover, the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were also considered for this study (21) (**Supplementary Table 1**).

Search Strategy

We did a compressive systematic search to collect all relevant articles that evaluated the effect of COVID-19 on patients in terms of obesity and mortality. Any article published in English was considered for inclusion; an article search strategy was developed to retrieve all articles between January 1 and August 30, 2020. Articles search were conducted in the most popular electronic databases such as Scopus, PubMed, EMBASE, and Web of Science. The following search terms were used to retrieve articles: "Obesity" OR "BMI," OR "Overweight" AND "mortality related to COVID-19" OR "death related to COVID-19" (**Supplementary Table 2**). We removed all duplicate articles, and a final search for relevant articles was performed on the reference list of retrieved articles.

Selection Criteria

We developed a priori inclusion criteria and included articles of COVID-19 patients' mortality due to obesity, associated risk factors such as demographic factors, and comorbidities. Articles were included if they (a) were peer-reviewed, (b) were published in English, (c) were cohort or comparison design, (d) included patients with more than 20, (e) and reported effect size as odds ratio (OR), risk ratio (RR) or hazard ratio (HR). We excluded studies if they were published as a review or case series.

Study Selection

Two authors (MdI and TP) screened titles and abstracts from the search results. Predefined selection criteria were used to select relevant full-text articles during the screening process. Afterward, all full-text articles were evaluated carefully for inclusion and data extraction. The same two authors (MdI and TP), however, independently evaluated each potential article for inclusion. Any disagreement during those screening process was resolved by the main investigator (Y-CL).

Data Extraction

All the selected studies were then finally reviewed to extract potential information regarding obesity and mortality of patients with COVID-19 and associated risk factors. One author collected information about author name, publication years, study design, number of patients with COVID-19, number of alive patients and number of dead patients, percentage of mortality, risk factors, inclusion and exclusion criteria, and effect sizes.

Quality Assessment

The Quality In Prognosis Studies (QUIPS) tool was utilized to examine the risk of bias (RoB), which is recommended by the Cochrane Prognosis Methods group (22). The QUIPS tool has six evaluation domains that are used to evaluate validity and bias in studies of prognostic factors: (a) study participation, (b) study attrition, (c) prognostic factor measurement, (d) outcome measurement, (e) study confounding, and (f) statistical analysis and reporting (23). RoB is classified into three groups: low, moderate, and high risk. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was considered to assess the confidence in the estimate of effect. GRADE was utilized to determine the quality of evidence based on several factors such as risk of bias, inconsistency, imprecision, indirectness, and publication bias.

Statistical Analysis

The primary outcome was the mortality of patients with COVID-19 due to obesity, and secondary outcomes were increased risk of mortality among class I, class II, and class III obesity. In subgroup analyses, we also evaluated the risk of mortality associated with comorbidities, age, gender, and other factors. Risk ratios with 95%CIs were calculated from the HRs or ORs. We used a random-effects model to calculate the heterogeneity between studies. However, studies heterogeneity was assessed using Cochran Q statistics and inconsistency statistics (I^2). We followed previous studies that considered heterogeneity as very low, low, medium, and high if I^2 value 0∼25%, 25–50%, 50∼75%, and >75% (24, 25). The Forest plot was drawn to present effect size, and the funnel plot was drawn to present publication bias.

RESULTS

Study Selection

A total of 3,513 unique articles were retrieved after searching for electronic databases. Of those, 3,492 articles were excluded after reviewing their titles and abstracts because they have not fulfilled pre-specified selection criteria. Overall, 21 articles went to full-text review and were scrutinized for final inclusion. However, four studies were further excluded because they have been published in the form of a review. Finally, 17 articles met the inclusion criteria for meta-analysis (15, 16, 26–40). **Figure 1** shows the overall study selection process.

Study Characteristics

Table 1 shows the clinical characteristics of the included studies. Of those, 16 studies had a retrospective cohort study design, and one study had a prospective design. Eleven studies used data from North American patients, four studies used data from European countries (France, Italy, and the UK), and one study used data from 47 countries. The range of male patients was 43.3–80.2%. All of the studies used demographics, clinical variables.

Quality of Evidence

The QUIPS tool was used to evaluate the risk bias among the included studies. Thirteen studies were of low risk bias, and four studies were of moderate risk bias (**Figure 2**). The overall quality of evidence is strong in the meta-analysis. **Supplementary Table 3** presents a summary of the GRADE evidence profile for our meta-analysis. For the increased rate of mortality among obese patients, the certainty was "low."

Primary Outcome

Obesity and Mortality of Patients With COVID-19

Of the 17 studies considered in our meta-analysis, 16 studies reported a significantly increased risk of mortality among patients with COVID-19, and one study reported a decreased risk of mortality. All the studies adjusted their effect size with potential variables to reduce potential bias. Collectively, our meta-analysis suggested a significantly increased risk of mortality with obesity, with a pooled RR of 1.42 (95%CI: 1.24–1.63, $p < 0.001$) (**Figure 3**). The I^2 statistics among the studies was 67.94%, indicating a moderate risk of heterogeneity.

Secondary Outcome

Types of Obesity and COVID-19 Mortality

We also pooled RR to evaluate the risk of mortality based on three types of obesity such as class I, class II, and class III obesity. Class III obesity was strongly associated with an increased risk of mortality, with a pooled $\text{RR}_{\text{adjust}}$ of 1.92 (95%CI: 1.50–2.47, $p < 0.001$). There was insignificant low heterogeneity among the studies ($I^2 = 31.99$, $Q = 5.88$, $\text{tau}^2 = 0.02$, $p = 0.20$) (**Figure 4A**). Class I and class II obesity also showed a strong association with an increased risk of mortality, with a pooled $\text{RR}_{\text{adjust}}$ of 1.27 (95%CI: 1.05–1.54, $p = 0.01$), and 1.56 (95%CI: 1.11–2.19, $p < 0.01$), respectively (**Figures 4B,C**). There was significant moderate heterogeneity among the studies for Class I ($I^2 = 60.00$, $Q = 5$, $\text{tau}^2 = 0.03$, $p = 0.02$) and higher heterogeneity among the studies were observed for class II ($I^2 = 80.34$, $Q = 25.43$, $\text{tau}^2 = 0.12$, $p < 0.001$).

Subgroup Analysis

Subgroup analyses are presented in **Table 2**. The 7 studies reported the risk of mortality among patients with obesity who were more than 65 years old. The pooled $\text{RR}_{\text{adjust}}$ was 2.54 (95%CI: 1.62–3.97, $p < 0.001$) and heterogeneity among the studies was ($I^2 = 89.33$, $Q = 56.24$, $\text{tau}^2 = 0.24$, $p < 0.001$). Furthermore, six studies evaluated the risk of COVID-19 mortality among male patients and showed a significantly higher risk ($\text{RR}_{\text{adjust}}$: 1.38, 95%CI: 1.25–1.51, $p < 0.001$). There was a lower risk of heterogeneity among the studies ($I^2 = 9.57$, $Q = 5.53$, $\text{tau}^2 = 0.001$, $p = 0.35$).

We also evaluated the risk of mortality among obese COVID-19 patients with various comorbidity such as diabetes, hypertension, CKD, COPD, and stroke. The pooled RR for COVID-19 mortality among patients with diabetes was 1.19 (95%CI: 1.07–1.32, $p = 0.001$). However, the pooled RR among the patients with stroke, CKD, COPD, and hypertension were 1.80 (95%CI: 0.89–3.64, $p = 0.10$), 1.57 (95%CI: 1.57–1.91, $p < 0.001$), 1.34 (95%CI: 1.18–1.52, $p < 0.001$), and 1.07 (95%CI: 0.92–1.25, $p = 0.35$), respectively.

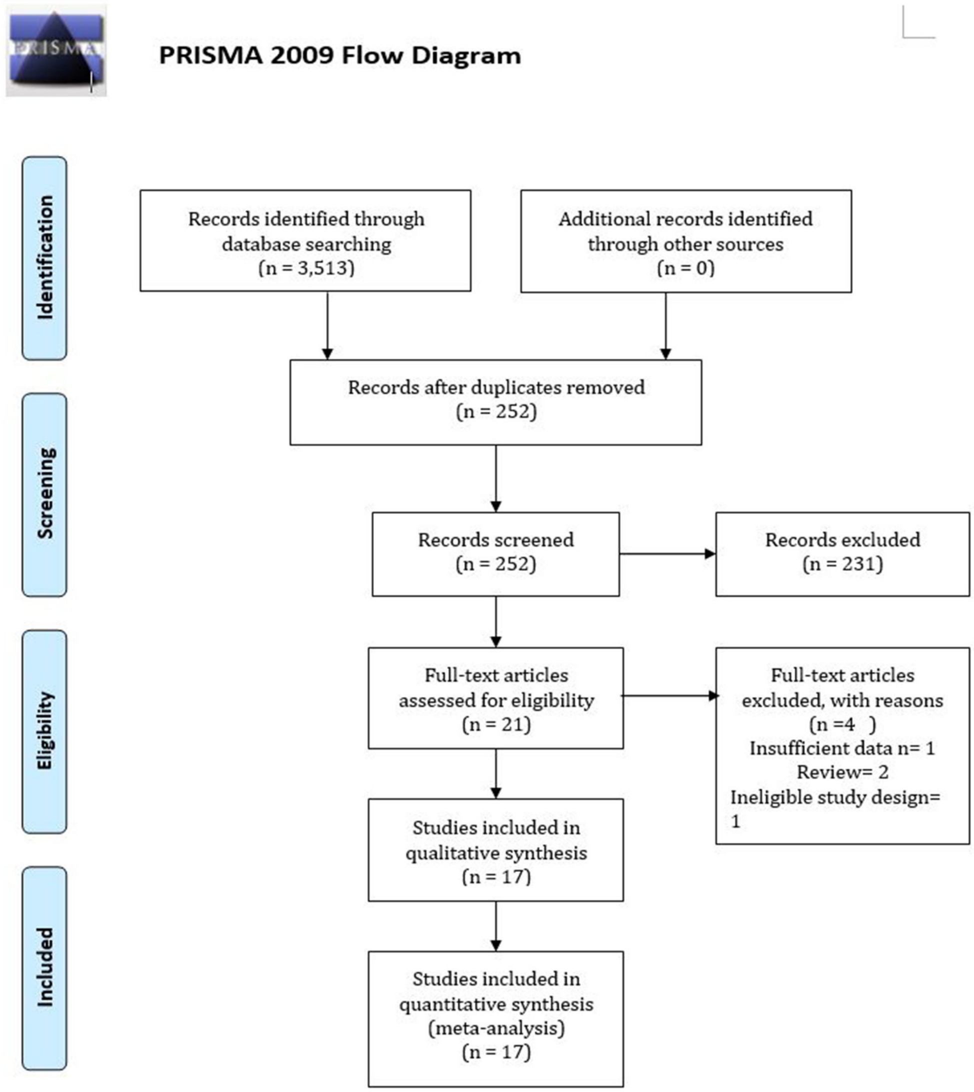


FIGURE 1 | Flow diagram of the study selection process.

Risk of Bias

Figure 5A depicts the funnel plot that indicates no publication bias among the studies. Egger's regression test was used to evaluate the funnel asymmetry, which showed no publication bias ($p < 0.05$). Moreover, **Figure 5B** shows the funnel plot with missing studies imputed by the trim and fill method. There was no missing study to be filled in the plot, and the overall log risk ratio became 1.42 95%CI (1.24–1.63).

DISCUSSION

Main Findings

This rigorous meta-analysis of 17 studies showed that obesity is associated with an increased risk of mortality among patients with COVID-19, especially patients aged more than 65 years. Furthermore, class III obesity patients observed a greater risk of mortality compared to class I and class II obesity. The risk of mortality was varied in COVID-19 patients with various comorbidities. Our findings may help to categorized patients at different risk groups and to make potential early prevention and treatment strategies possible.

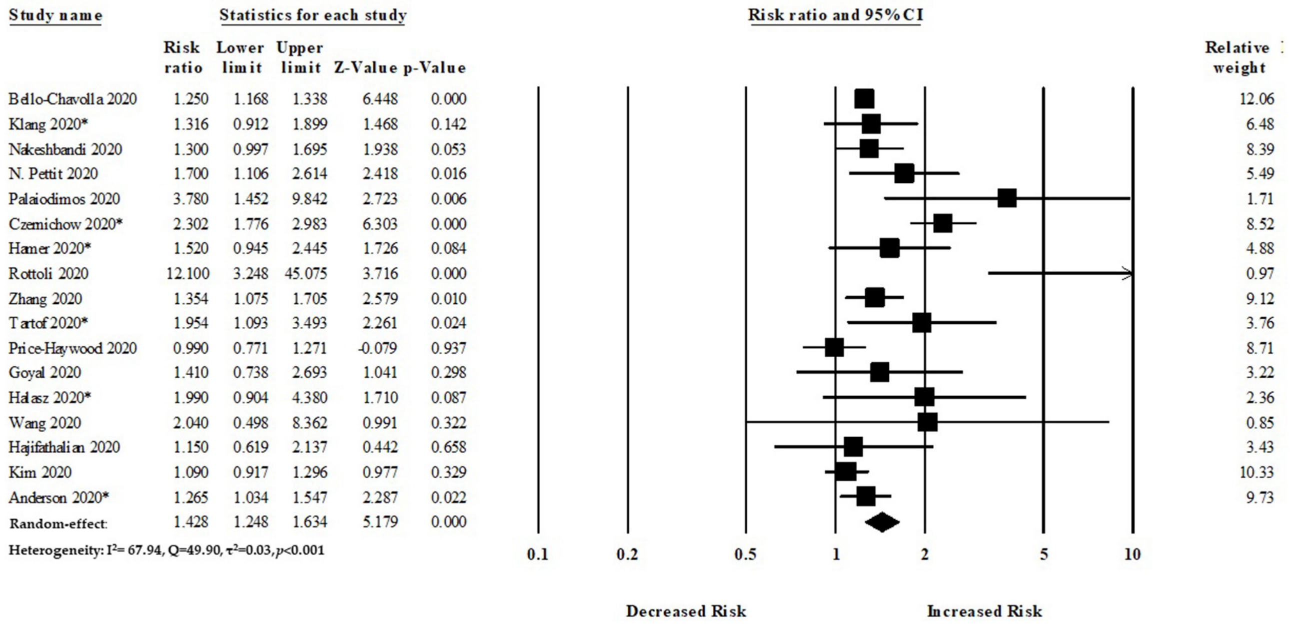
Comparison With Previous Studies

Our study findings are similar to those of two previous studies (41, 42). Hussain et al. (41) included 14 studies, but only 6 studies were used to assess the relationship between obesity and mortality in COVID-19. This study lacks statistical power in subgroup analyses and included no consideration of different types of obesity and risk of mortality of patients with COVID-19. Another study showed a positive relation, though lack of evidence because they included preprints (non-peer-reviewed articles), and there were no subgroup analyses (42).

Study	Study participants	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall risk bias
Bello-Chavolla 2020	🟩	🟨	🟩	🟩	🟨	🟩	🟩
Klang 2020	🟩	🟨	🟩	🟩	🟨	🟩	🟩
Nakeshbandi 2020	🟩	🟨	🟩	🟩	🟩	🟨	🟩
N. Pettit 2020	🟩	🟨	🟩	🟩	🟩	🟩	🟩
Palaiodimos 2020	🟩	🟨	🟩	🟩	🟩	🟩	🟩
Czernichow 2020	🟩	🟨	🟩	🟩	🟩	🟩	🟩
Hamer 2020	🟩	🟨	🟩	🟩	🟩	🟨	🟩
Rottoli 2020	🟨	🟨	🟨	🟩	🟨	🟥	🟨
Zhang 2020	🟩	🟨	🟨	🟩	🟥	🟥	🟨
Tartof 2020	🟩	🟨	🟩	🟩	🟩	🟩	🟩
Price-Haywood 2020	🟨	🟨	🟨	🟩	🟨	🟥	🟨
Goyal 2020	🟩	🟨	🟨	🟩	🟩	🟩	🟩
Halasz 2020	🟩	🟨	🟨	🟩	🟨	🟨	🟨
Wang 2020	🟨	🟨	🟩	🟩	🟩	🟩	🟩
Hajifathalian 2020	🟩	🟨	🟨	🟩	🟨	🟩	🟩
Kim 2020	🟩	🟨	🟩	🟩	🟩	🟩	🟩
Anderson 2020	🟩	🟨	🟩	🟩	🟩	🟩	🟩

🟩	Low risk
🟨	Moderate risk
🟥	High risk

FIGURE 2 | Risk of bias according to the QUIPS tool.



Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Bello-Chavolla 2020	1.250	1.168	1.338	6.448	0.000	12.06
Klang 2020*	1.316	0.912	1.899	1.468	0.142	6.48
Nakeshbandi 2020	1.300	0.997	1.695	1.938	0.053	8.39
N. Pettit 2020	1.700	1.106	2.614	2.418	0.016	5.49
Palaiodimos 2020	3.780	1.452	9.842	2.723	0.006	1.71
Czernichow 2020*	2.302	1.776	2.983	6.303	0.000	8.52
Hamer 2020*	1.520	0.945	2.445	1.726	0.084	4.88
Rottoli 2020	12.100	3.248	45.075	3.716	0.000	0.97
Zhang 2020	1.354	1.075	1.705	2.579	0.010	9.12
Tartof 2020*	1.954	1.093	3.493	2.261	0.024	3.76
Price-Haywood 2020	0.990	0.771	1.271	-0.079	0.937	8.71
Goyal 2020	1.410	0.738	2.693	1.041	0.298	3.22
Halasz 2020*	1.990	0.904	4.380	1.710	0.087	2.36
Wang 2020	2.040	0.498	8.362	0.991	0.322	0.85
Hajifathalian 2020	1.150	0.619	2.137	0.442	0.658	3.43
Kim 2020	1.090	0.917	1.296	0.977	0.329	10.33
Anderson 2020*	1.265	1.034	1.547	2.287	0.022	9.73
Random-effect:	1.428	1.248	1.634	5.179	0.000	

Heterogeneity: I^2= 67.94, Q=49.90, τ^2=0.03, p<0.001

FIGURE 3 | Association between obesity and risk of mortality among COVID-19 patients.

TABLE 1 | Characteristics of the included studies assessing the risk of mortality of COVID-19 patients with obesity.

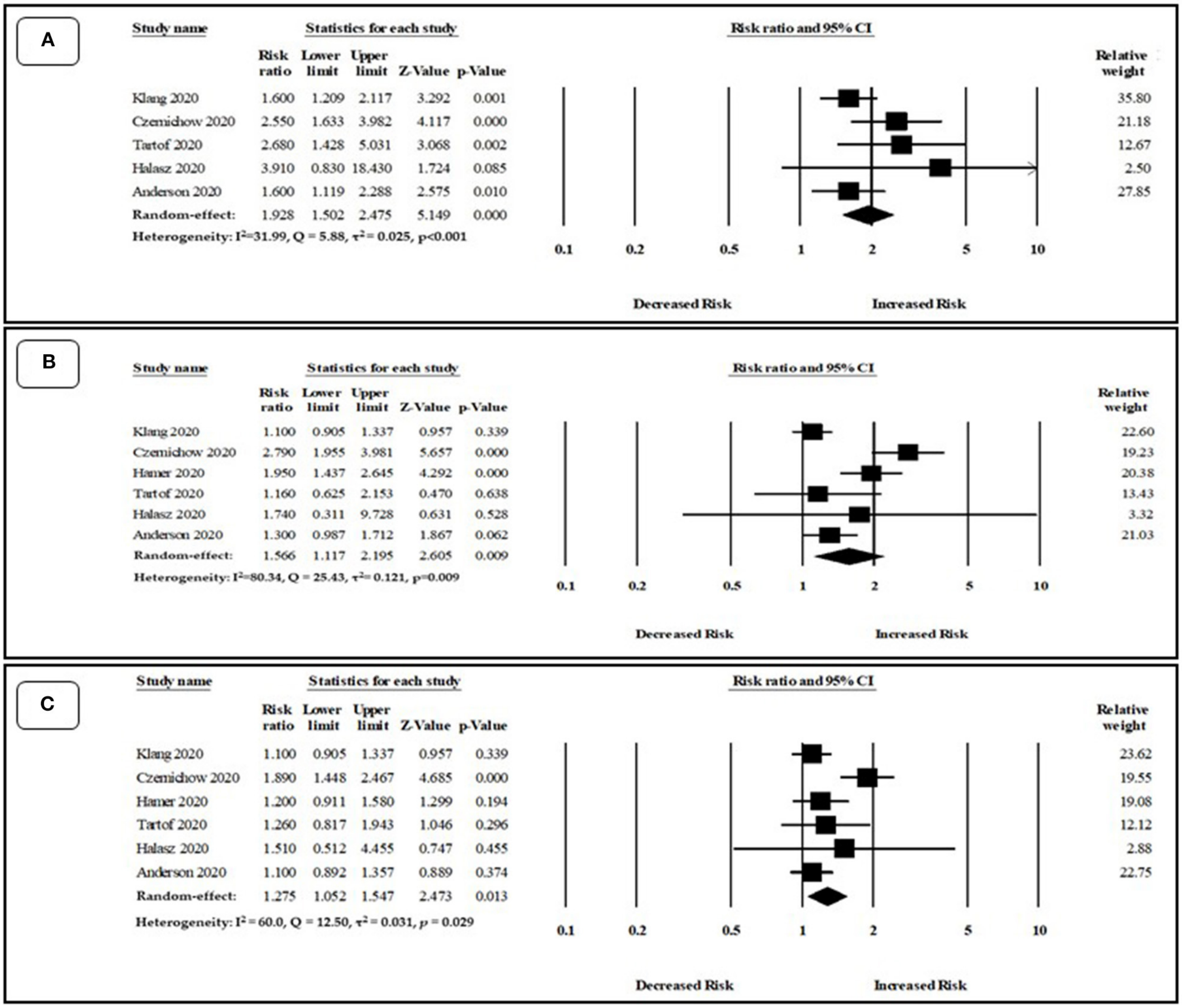
Author	Country	Design	Total sample	Male (%)	Age (mean/median)	Variable	Findings
Bello-Chavolla et al. (33)	Mexico	Retrospective	177,133	57.70	63.5	Demographics, clinical, smoking	1.25 (1.17–1.34)
Klang et al. (35)	USA	Retrospective	3,406	56	76	Demographics, clinical, smoking	1.31 (0.91–1.89)
Nakeshbandi et al. (36)	USA	Retrospective	504	52	68	Demographics, clinical, smoking	1.30 (0.99–1.93)
Pettit et al. (37)	USA	Retrospective	238	47.5	58.5	Demographic, clinical, smoking	1.70 (1.10–2.61)
Palaiodimos et al. (29)	USA	Retrospective	200	49	64	Demographics, clinical, smoking, symptoms	3.78 (1.45–9.84)
Czernichow et al. (34)	France	Prospective	5,795	65.41	59.6	Demographics, and clinical	2.30 (1.77–2.98)
Hamer et al. (15)	UK	Retrospective	334,329	45.5	56.4	Demographics, biomarker, smoking	1.52 (0.94–2.44)
Rottoli et al. (38)	Italy	Retrospective	482	N/A	N/A	Demographic, clinical	12.10 (3.24–45.07)
Zhang et al. (40)	China	Retrospective	3,201	N/A	N/A	laboratory	1.35 (1.07–1.70)
Tartof et al. (31)	USA	Retrospective	6,916	44.98	49.1	Demographics, smoking, clinical characteristics	1.95 (1.09–3.49)
Price-Haywood et al. (16)	USA	Retrospective	3,481	43.3	55.5	Demographics, clinical, locations	0.99 (0.77–1.27)
Goyal et al. (39)	USA	Retrospective	1,687	60	66.5	Demographics, clinical, laboratory, smoking, in-hospital events	1.41 (0.73–2.69)
Halasz et al. (27)	Italy	Retrospective	242	80.2	64	Demographics, clinical, laboratory	1.99 (0.90–4.38)
Wang et al. (30)	USA	Retrospective	58	52	67	Demographics, laboratory, clinical	2.04 (0.49–8.36)
Hajifathalian et al. (28)	USA	Retrospective	770	61	63.5	Demographics, clinical, laboratory data, clinical outcomes	1.15 (0.61–2.13)
Kim et al. (26)	Multiple countries	Retrospective	2,491	53.2	62	Ethnicity, time of hospitalization, smoking status, clinical characteristics	1.09 (0.91–1.29)
Anderson et al. (32)	USA	Retrospective	2,466	58	67	Demographics, clinical	1.26 (1.03–1.54)

Biological Plausibility

Several biological mechanisms have been reported to explain the association between obesity and increase the risk of mortality. First, it is reported that both ectopic fat and COVID-19 are responsible for upregulation of pro-inflammatory, angiotensin II (ATII), and prothrombotics. Patients with obesity observe a decreased level of inflammatory adipokines, adiponectin, which is liked to an increased rate of ATII (43, 44). Similarly, coronavirus reduces the activity of ACE2 inhibitor, which leads to increase ATII level (45, 46). Higher levels of ATII might contribute to the progression of lung injury among patients diagnosed with COVID-19 by triggering NADH/NADPH oxidase system (47) and promoting contraction and vasoconstriction (48). Furthermore, an increased expression of inflammatory molecules enhances the production of cytokines [e.g., tumor necrosis factor alpha (TNF-α) and IL-6] (49), which are associate with alveolar damage and an increased rate of mortality (50).

Public Health Implication

COVID-19 pandemic has created serious concern globally, and people are eagerly waiting for potential vaccines. There is no exact and effective treatment for this virus so far, and global morbidity and mortality thus increase day by day (51). COVID-19 shows a wide spectrum of symptoms; some patients recovered without complications. However, some patients affected by serious illness have needed to transfer to the ICU, require a prolonged hospital stay, and may even die (52). Elderly patients were more vulnerable in this disease because they have multiple diseases. A significant number of studies reported that elderly patients and patients with diabetes, stroke, CKD, and COPD are associated with bad outcomes (53, 54). Obesity, especially class 3 obesity, was associated with an increased rate of mortality among patients diagnosed with COVID-19. It is, however, not surprising because patients with obesity who had the H1N1 influenza virus also observed prolong hospitalization, mechanical ventilation, and death when it was calculated as an independent risk factor (55, 56).



A

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Klang 2020	1.600	1.209	2.117	3.292	0.001	35.80
Czemichow 2020	2.550	1.633	3.982	4.117	0.000	21.18
Tartof 2020	2.680	1.428	5.031	3.068	0.002	12.67
Halasz 2020	3.910	0.830	18.430	1.724	0.085	2.50
Anderson 2020	1.600	1.119	2.288	2.575	0.010	27.85
Random-effect:	1.928	1.502	2.475	5.149	0.000	

Heterogeneity: I^2=31.99, Q = 5.88, τ^2= 0.025, p<0.001

B

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Klang 2020	1.100	0.905	1.337	0.957	0.339	22.60
Czemichow 2020	2.790	1.955	3.981	5.657	0.000	19.23
Hamer 2020	1.950	1.437	2.645	4.292	0.000	20.38
Tartof 2020	1.160	0.625	2.153	0.470	0.638	13.43
Halasz 2020	1.740	0.311	9.728	0.631	0.528	3.32
Anderson 2020	1.300	0.987	1.712	1.867	0.062	21.03
Random-effect:	1.566	1.117	2.195	2.605	0.009	

Heterogeneity: I^2=80.34, Q = 25.43, τ^2= 0.121, p=0.009

C

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Klang 2020	1.100	0.905	1.337	0.957	0.339	23.62
Czemichow 2020	1.890	1.448	2.467	4.685	0.000	19.55
Hamer 2020	1.200	0.911	1.580	1.299	0.194	19.08
Tartof 2020	1.260	0.817	1.943	1.046	0.296	12.12
Halasz 2020	1.510	0.512	4.455	0.747	0.455	2.88
Anderson 2020	1.100	0.892	1.357	0.889	0.374	22.75
Random-effect:	1.275	1.052	1.547	2.473	0.013	

Heterogeneity: I^2 = 60.0, Q = 12.50, τ^2 = 0.031, p = 0.029

FIGURE 4 | Association between **(A)** Class III, **(B)** class II, **(C)** class I obesity and risk of mortality among COVID-19 patients.

TABLE 2 | Subgroup analyses.

		Pooled estimate		Test of heterogeneity		
	N	**RR with 95% CI**	**p-Value**	τ^2	I^2	**p-Value**
Demographic						
Male	6	1.38 (1.25–1.51)	**<0.001**	0.001	9.57	0.35
≥65 years	7	2.54(1.62–3.97)	**<0.001**	0.24	89.33	<0.001
Comorbidity						
Diabetes	11	1.19 (1.07–1.32)	**0.001**	0.012	54.15	0.016
Hypertension	9	1.07 (0.92–1.25)	0.351	0.029	60.58	0.009
CKD	7	1.57 (1.29–1.91)	**<0.001**	0.036	69.18	0.003
CPOD	5	1.34 (1.18–1.52)	**<0.001**	0.004	16.12	0.312
Stroke	2	1.80 (0.89–3.64)	0.100	0	0	0.37
Others						
Smoking	6	1.13 (0.91–1.40)	0.242	0.027	46.57	0.09

N, number of study; RR, risk ratio; CI, confidence Interval; CKD, chronic kidney disease; CPOD, chronic obstructive pulmonary disease. Bold value indicates subgroup and significant p-value.

Several population-based cohort studies reported that obesity is linked to increased comorbidity like diabetes, hypertension, and heart disease. However, the mortality rate among patients with obesity proportionally increased with BMI (57, 58). Moreover, obesity makes patients' conditions worse if patients develop infections by downregulating the inflammatory cascade. Hyperactivation of inflammatory pathways surge the level of cytokines, adiponectin, and leptin and distort both macro- and micro-vascular responses (59). Obesity is also associated with lung function impairment, which involves altering mechanics and airway resistance and decreasing gas exchange (60, 61). The findings of our study suggest that physicians should focus more on COVID-19 patients with obesity because this group of patients is at high risk of worse consequences. Moreover, our results highlight the need for vigilance, priority on testing, and an earlier start to treatment in obese patients with COVID-19. Previous studies also mentioned that obesity increased the rate of hospitalization, worsened patient conditions, and increased

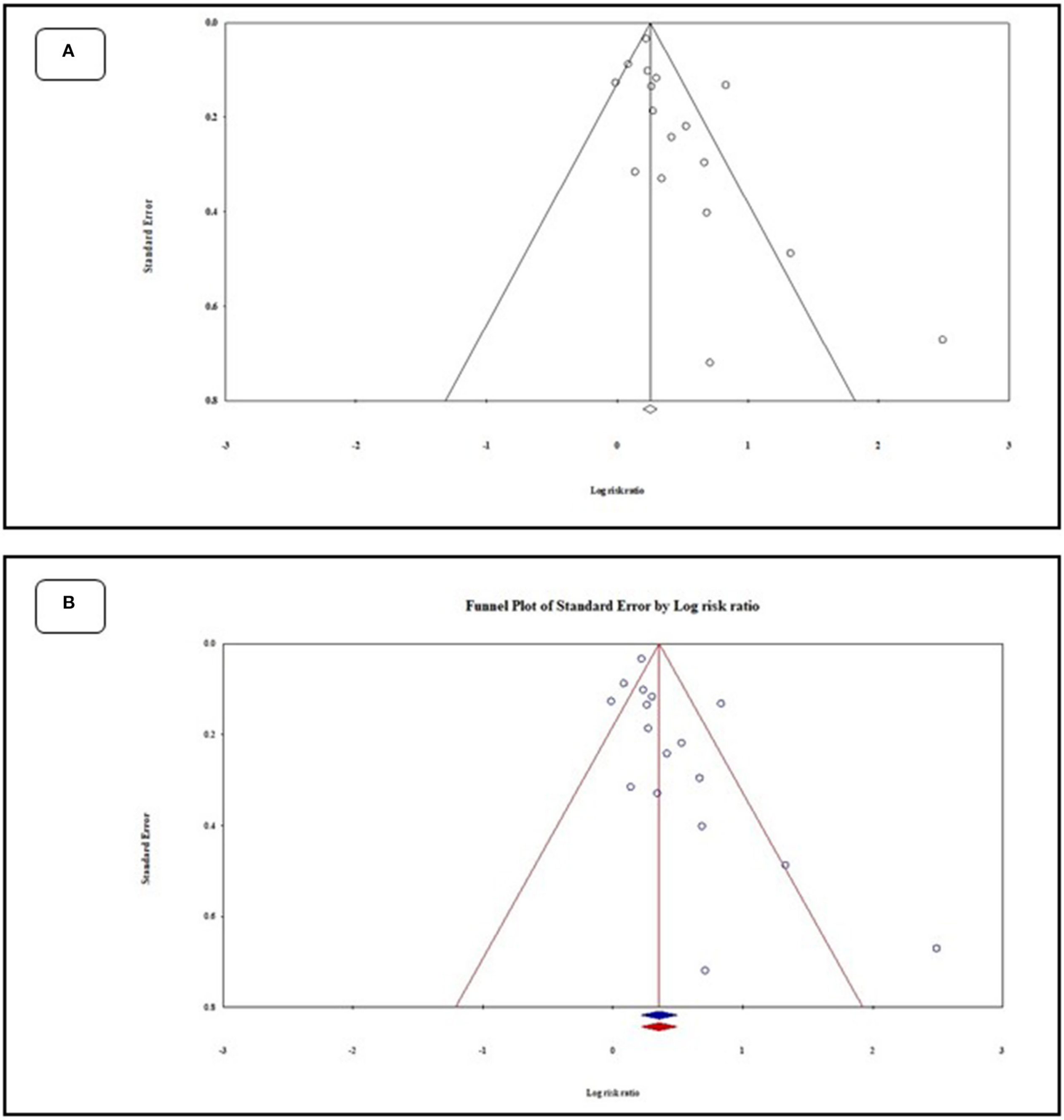


FIGURE 5 | Funnel plots of meta-analysis before **(A)** and after **(B)** applying the fill and trim method.

invasive mechanical ventilation in those diagnosed with COVID-19 (15, 62).

Strengths and Limitations

Our study has several strengths. First, this is the first comprehensive and rigorous meta-analysis that assessed the association between obesity and the risk of mortality among patients with COVID-19. This meta-analysis included 17 studies, and only peer-reviewed articles were included for calculating the magnitude of risk because preprint articles have lots of room for improvement. Second, the risk of bias is low, and heterogeneity among the study is moderate. However, several factors showed higher heterogeneity among the studies. Third, this meta-analysis also evaluated associated factors that can contribute to a high risk of mortality. Finally, only adjusted effect size was considered to calculate pooled RR, which indicates strong evidence with a low risk of bias. Our study has several limitations that need to be addressed. First, we could not compare risk among patients aged <65 due to data constraints. Second, pneumonia is a high-risk factor for mortality among COVID-19 patients because only one study reported about this issue. This study showed the association between COPD and the risk of mortality among patients with COVID-19. Third, our study did not show the difference in the rate of mortality among various races and locations; this could have added value to the present evidence.

CONCLUSION

We conducted a comprehensive systematic review and rigorous meta-analysis of studies reporting the risk of mortality among COVID-19 patients with obesity. Our study findings showed that obesity is associated with an increased risk of mortality among patients with COVID-19. Importantly, the risk of mortality was higher among class III obesity than class I and II obesity. Physicians should be aware of these risk factors and make a quick decision for intervention. Future studies are urgently needed to clarify the pathophysiological relationship between obesity and the risk of mortality among COVID-19 patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

TP and MI: conceptualization. TP and HY: methodology. MI: Software, resources, data curation and writing —original draft preparation. ML, W-SJ, and Y-CL: validation. TP: formal analysis and visualization. M-HH: investigation. Y-CL: writing —review and editing and supervision. All authors contributed to the article and approved the submitted version.

FUNDING

This research was funded in part by the Ministry of Education (MOE) under grants MOE 109-6604-001-400 and DP2-109-21121-01-A-01 and the Ministry of Science and Technology (MOST) under grant MOST 109-282 3-8-038-004.

ACKNOWLEDGMENTS

We would like to thanks our colleague who is a Native English Speaker for editing this manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.620044/full#supplementary-material

REFERENCES

1. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. (2020) 395:507–13. doi: 10.1016/S0140-6736(20)30211-7
2. Ornell F, Schuch JB, Sordi AO, Kessler FHP. "Pandemic fear" and COVID-19: mental health burden and strategies. *Braz J Psychiatry*. (2020) 42:232–5. doi: 10.1590/1516-4446-2020-0008
3. McKibbin, Warwick J., Fernando, Roshen, The global macroeconomic impacts of COVID-19: seven scenarios (March 2, 2020). CAMA Working Paper No. 19/2020. doi: 10.2139/ssrn.3547729 Available online at: https://ssrn.com/abstract$=$3547729
4. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Heart Lung Transplant*. (2020) 39:405. doi: 10.1016/j.healun.2020.03.012
5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. (2020) 323:1061–9. doi: 10.1001/jama.2020.1585
6. Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. *J Infect*. (2020) 80:388–93. doi: 10.1016/j.jinf.2020.02.016
7. Skinner AC, Skelton JA. Prevalence and trends in obesity and severe obesity among children in the United States, 1999–2012. *JAMA Pediatr*. (2014) 168:561–6. doi: 10.1001/jamapediatrics.2014.21
8. Stengel B, Tarver-Carr ME, Powe NR, Eberhardt MS, Brancati FL. Lifestyle factors, obesity and the risk of chronic kidney disease. *Epidemiology*. (2003) 14:479–87. doi: 10.1097/01.EDE.0000071413.55296.c4
9. Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyrén O. Obesity and risk for chronic renal failure. *J Am Soc Nephrol*. (2006) 17:1695–702. doi: 10.1681/ASN.2005060638
10. Hales CM, Carroll MD, Fryar CD, Ogden CL. *Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017–2018*. NCHS Data Brief, no 360. Hyattsville, MD: National Center for Health Statistics (2020).
11. Zhi G, Xin W, Ying W, Guohong X, Shuying L. "Obesity paradox" in acute respiratory distress syndrome: asystematic review and meta-analysis. *PLoS ONE*. (2016) 11:e0163677. doi: 10.1371/journal.pone.0163677
12. King P, Mortensen EM, Bollinger M, Restrepo MI, Copeland LA, Pugh MJV, et al. Impact of obesity on outcomes for patients hospitalised with pneumonia. *Eur Respir J*. (2013) 41:929–34. doi: 10.1183/09031936.00185211
13. Nie W, Zhang Y, Jee SH, Jung KJ, Li B, Xiu Q. Obesity survival paradox in pneumonia: a meta-analysis. *BMC Med*. (2014) 12:61. doi: 10.1186/1741-7015-12-61
14. Corrales-Medina VF, Valayam J, Serpa JA, Rueda AM, Musher DM. The obesity paradox in community-acquired bacterial pneumonia. *Int J Infect Dis*. (2011) 15:e54–7. doi: 10.1016/j.ijid.2010.09.011
15. Hamer M, Gale CR, Kivimäki M, Batty GD. Overweight, obesity, and risk of hospitalization for COVID-19: a community-based cohort study of adults in the United Kingdom. *Proc Natl Acad Sci*. (2020) 117:21011–3. doi: 10.1073/pnas.2011086117
16. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with COVID-19. *N Engl J Med*. (2020) 382:2534–43. doi: 10.1056/NEJMsa2011686
17. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ*. (2020) 369:m1966. doi: 10.1136/bmj.m1966
18. Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, et al. Obesity in patients younger than 60 years is a risk factor for

COVID-19 hospital admission. *Clinical Infectious Diseases*. (2020) 71:896–7. doi: 10.1093/cid/ciaa415

19. Maeda T, Obata R, Dahlia Rizk DO, Kuno TJ. The association of interleukin-6 value, interleukin inhibitors, and outcomes of patients with COVID-19 in New York City. *J Med Virol*. (2020) 96:463–71. doi: 10.1002/jmv.26365
20. Aziz M, Fatima R, Assaly RJ. Elevated interleukin-6 and severe COVID-19: a meta-analysis. *J Med Virol*. (2020) 92:2283–5. doi: 10.1002/jmv.25948
21. Moher D, Liberati A, Tetzlaff J, Altman DG, med PGJP. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. (2010) 8:336–41. doi: 10.1016/j.ijsu.2010.02.007
22. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med*. (2013) 158:280–6. doi: 10.7326/0003-4819-158-4-201302190-00009
23. Hemingway H, Riley RD, Altman DG. Ten steps towards improving prognosis research. *BMJ*. (2009) 339:b4184. doi: 10.1136/bmj.b4184
24. Islam MM, Iqbal U, Walther B, Atique S, Dubey NK, Nguyen P-A, et al. Benzodiazepine use and risk of dementia in the elderly population: a systematic review and meta-analysis. *Neuroepidemiology*. (2016) 47:181–91. doi: 10.1159/000454881
25. Poly T, Islam M, Yang H-C, Wu C. Proton pump inhibitors and risk of hip fracture: a meta-analysis of observational studies. *Osteoporosis International*. (2019) 30:103–14. doi: 10.1007/s00198-018-4788-y
26. Kim L, Garg S, O'Halloran A, Whitaker M, Pham H, Anderson EJ, et al. Interim analysis of risk factors for severe outcomes among a cohort of hospitalized adults identified through the Us coronavirus disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET). *medRxiv*. (2020) 28:1606–12.
27. Halasz G, Leoni ML, Villani GQ, Nolli M, Villani M. Obesity, overweight and survival in critically ill patients with SARS-CoV-2 pneumonia: is there an obesity paradox? Preliminary results from Italy. *Euro J Prev. Cardiol*. (2020). doi: 10.1177/2047487320939675
28. Hajifathalian K, Kumar S, Newberry C, Shah S, Fortune B, Krisko T, et al. Obesity is associated with worse outcomes in COVID-19: analysis of Early Data From New York City. *Obesity*. (2020) 28:1606–12. doi: 10.1002/oby.22923
29. Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. *Metabolism*. (2020) 108:154262. doi: 10.1016/j.metabol.2020.154262
30. Wang B, Van Oekelen O, Mouhieddine T, Del Valle DM, Richter J, Cho HJ, et al. A tertiary center experience of multiple myeloma patients with COVID-19: lessons learned and the path forward. *J Hematol Oncol*. (2020) 13:94. doi: 10.1186/s13045-020-00934-x
31. Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, et al. Obesity and mortality among patients diagnosed with COVID-19: results from an integrated health care organization. *Annals Intern Med*. (2020) 173:773–81. doi: 10.7326/M20-3742
32. Anderson MR, Geleris J, Anderson DR, Zucker J, Nobel YR, Freedberg D, et al. Body mass index and risk for intubation or death in SARS-CoV-2 Infection: a retrospective cohort study. *Ann Intern Med*. (2020) 173:782–90. doi: 10.7326/M20-3214
33. Bello-Chavolla OY, Bahena-Lopez JP, Antonio-Villa NE, Vargas-Vázquez A, González-Díaz A, Márquez-Salinas A, et al. Predicting mortality due to SARS-CoV-2: a mechanistic score relating obesity and diabetes to COVID-19 outcomes in Mexico. *J Clin Endocrinol Metab*. (2020) 105:dgaa346 doi: 10.1210/clinem/dgaa346
34. Czernichow S, Beeker N, Rives-Lange C, Guerot E, Diehl JL, Katsahian S, et al. Obesity doubles mortality in patients hospitalized for SARS-CoV-2 in Paris hospitals, France: a cohort study on 5795 patients. *Obesity (Silver Spring)*. (2020) 12:2282–89. doi: 10.1002/oby.23014
35. Klang E, Kassim G, Soffer S, Freeman R, Levin MA, Reich DL. Morbid obesity as an independent risk factor for COVID-19 mortality in hospitalized patients younger than 50. *Obesity*. (2020) 28:1595–9. doi: 10.1002/oby.22913
36. Nakeshbandi M, Maini R, Daniel P, Rosengarten S, Parmar P, Wilson C, et al. The impact of obesity on COVID-19 complications: a retrospective cohort study. *Int J Obesy*. (2020) 44:1832–7. doi: 10.1038/s41366-020-0648-x
37. Pettit NN, MacKenzie EL, Ridgway J, Pursell K, Ash D, Patel B, et al. Obesity is associated with increased risk for mortality among hospitalized patients with COVID-19. *Obesity*. (2020) 28:1806–10. doi: 10.1002/oby.22941
38. Rottoli M, Bernante P, Belvedere A, Balsamo F, Garelli S, Giannella M, et al. How important is obesity as a risk factor for respiratory failure, intensive care admission and death in hospitalised COVID-19 patients? Results from a single Italian Centre. *Eur J Endocrinol*. (2020) 183:389–97. doi: 10.1530/EJE-20-0541
39. Goyal P, Ringel JB, Rajan M, Choi JJ, Pinheiro LC, Li HA, et al. Obesity and COVID-19 in New York City: a retrospective cohort study. *Ann Intern Med*. (2020) 173:855–8. doi: 10.7326/M20-2730
40. Zhang F, Xiong Y, Wei Y, Hu Y, Wang F, Li G, et al. Obesity predisposes to the risk of higher mortality in young COVID-19 patients. *J Med Virol*. (2020) 92:2536–42. doi: 10.1002/jmv.26039
41. Hussain A, Mahawar K, Xia Z, Yang W, Shamsi E-H. Obesity and mortality of COVID-19. Meta-analysis. *Obes Res Clin Pract*. (2020) 14:295–300. doi: 10.1016/j.orcp.2020.07.002
42. Popkin BM, Du S, Green WD, Beck MA, Algaith T, Herbst CH, et al. Individuals with obesity and COVID-19: a global perspective on the epidemiology and biological relationships. *Obes Rev*. (2020) 21:e13128. doi: 10.1111/obr.13128
43. Fujita K, Maeda N, Sonoda M, Ohashi K, Hibuse T, Nishizawa H, et al. Adiponectin protects against angiotensin II-induced cardiac fibrosis through activation of PPAR-α. *Arterioscler Thromb Vasc Biol*. (2008) 28:863–70. doi: 10.1161/ATVBAHA.107.156687
44. Ran J, Hirano T, Fukui T, Saito K, Kageyama H, Okada K, et al. Angiotensin II infusion decreases plasma adiponectin level *via* its type 1 receptor in rats: an implication for hypertension-related insulin resistance. *Metabolism*. (2006) 55:478–88. doi: 10.1016/j.metabol.2005.10.009
45. Cheng H, Wang Y, Wang GQJ. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. *J Med Virol*. (2020) 92:726–30. doi: 10.1002/jmv.25785
46. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong J-C, Turner AJ, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. *Circ Res*. (2020) 126:1456–74. doi: 10.1161/CIRCRESAHA.120.317015
47. Zhang Y, Murugesan P, Huang K, Cai H. NADPH oxidases and oxidase crosstalk in cardiovascular diseases: novel therapeutic targets. *Nat Rev Cardiol*. (2020) 17:170–94. doi: 10.1038/s41569-019-0260-8
48. Dhaun N, Webb DJ. Endothelins in cardiovascular biology and therapeutics. *Nat Rev Cardiol*. (2019) 16:491–502. doi: 10.1038/s41569-019-0176-3
49. Um J-Y, Chung H-S, Song M-Y, Shin H-D, Kim H-M. Association of interleukin-1β gene polymorphism with body mass index in women. *Clin Chem*. (2004) 50:647–50. doi: 10.1373/clinchem.2003.025858
50. Zhang C, Wu Z, Li J-W, Zhao H, Wang G-Q. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents*. (2020) 20:533–4.
51. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. (2020) 20:533–4. doi: 10.1016/S1473-3099(20)30120-1
52. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. (2020) 323:2052–9. doi: 10.1001/jama.2020.6775
53. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. (2020) 395:1054–62. doi: 10.1016/S0140-6736(20)30566-3
54. Chen J, Qi T, Liu L, Ling Y, Qian Z, Li T, et al. Clinical progression of patients with COVID-19 in Shanghai, China. *J Infect*. (2020) 80:e1–6. doi: 10.1016/j.jinf.2020.03.004
55. Venkata C, Sampathkumar P, Afessa B, editors. Hospitalized patients with 2009 H1N1 influenza infection: the Mayo Clinic experience. *Mayo Clin Proc*. (2010) 85:798–805. doi: 10.4065/mcp.2010.0166
56. Morgan OW, Bramley A, Fowlkes A, Freedman DS, Taylor TH, Gargiullo P, et al. Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A (H1N1) disease. *PLoS ONE*. (2010) 5:e9694. doi: 10.1371/journal.pone.0009694

57. Lancet PSCJT. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. (2009) 373:1083–96. doi: 10.1016/S0140-6736(09)60318-4
58. Zheng W, McLerran DF, Rolland B, Zhang X, Inoue M, Matsuo K, et al. Association between body-mass index and risk of death in more than 1 million Asians. *N Engl J Med*. (2011) 364:719–29. doi: 10.1056/NEJMoa1010679
59. Murugan A, Sharma G. Obesity and respiratory diseases. *Chron Respir Dis*. (2008) 5:233–42. doi: 10.1177/1479972308096978
60. Steele RM, Finucane FM, Griffin SJ, Wareham NJ, Ekelund U. Obesity is associated with altered lung function independently of physical activity and fitness. *Obesity*. (2009) 17:578–84. doi: 10.1038/oby.2008.584
61. Falagas M, Athanasoulia A, Peppas G, Karageorgopoulos DE. Effect of body mass index on the outcome of infections: a systematic review. *Obes Rev*. (2009) 10:280–9. doi: 10.1111/j.1467-789X.2008.00546.x
62. Chang TH, Chou CC, Chang LYJOR. Effect of obesity and body mass index on coronavirus disease 2019 severity: a systematic review and meta-analysis. *Obes Rev*. (2020) 21:e13089. doi: 10.1111/obr.13089

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

COMMUNITY CASE STUDY
published: 18 March 2021
doi: 10.3389/fmed.2021.610100

Teamwork and Leadership Under Fire at the Epicenter of the COVID-19 Epidemic in the Bronx

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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Medicine

Received: *25 September 2020*
Accepted: *23 February 2021*
Published: *18 March 2021*

Citation:
Tomer Y, Ng Gong M, Keller MJ, Southern W, Kitsis EA, Kajita GR, Shapiro LI, Jariwala SP and Epstein EJ (2021) Teamwork and Leadership Under Fire at the Epicenter of the COVID-19 Epidemic in the Bronx. Front. Med. 8:610100. doi: 10.3389/fmed.2021.610100

The first Covid-19 patient was admitted to Montefiore Medical Center (MMC) on March 10, 2020. Soon thereafter there was a rapid and exponential surge of Covid-19 admissions to MMC that could have resulted in catastrophic consequences if MMC had been overwhelmed, as happened in Europe. To adjust to this crisis our institution, under the inspiring leadership of Dr. Philip Ozuah, President and CEO of Montefiore Medicine, adopted an "all hands on deck" approach, mobilizing our entire workforce to expand our units to accommodate the growing number of patients being admitted. Given that the internal medicine (IM) and ICU units are part of the department of medicine (DOM), the DOM was at the center of this mobilization. The DOM is the largest department at MMC and mobilizing it required careful planning, seamless teamwork, and strong leadership. To achieve that goal, we applied a framework that we designate the "**3C framework,**" denoting **C**oordination, **C**ommunication, and **C**ollaboration. In this report we describe the many initiatives the Montefiore Einstein DOM implemented during the Covid-19 pandemic using the **3C** framework. These included establishing the Medicine Covid-19 Taskforce to lead our efforts, starting a daily newsletter for up-to-date communications, rapidly expanding the ICU and IM units, converting most specialty inpatient consults to eConsults, coordinating research studies, and more. The goal of this report is to serve as a guide on how the 3C framework helped us organize, mobilize, and energize the department of medicine effectively and efficiently during this unprecedented crisis.

Keywords: COVID-19, department of medicine, pandemic, teamwork, leadership, telehealth, coordination, communication

INTRODUCTION

The first Covid-19 patient was admitted to the Montefiore Medical Center (MMC) intensive care unit (ICU) on March 10, 2020. Within 2 weeks, 345 Covid-19 patients were hospitalized at MMC (comprising 4 hospitals, Montefiore, Weiler, Children's Hospital, and Wakefield). As the rapid surge of Covid-19 admissions to MMC accelerated, predictive models were used to estimate the number of patients likely to be admitted in the coming days, and they all painted a grim picture. Three models (Montefiore Einstein Department of Epidemiology and Population Health model, New York City (NYC) Department of Health model, and Susceptible, Exposed, Infected, Resistant [SEIR] model) predicted that Montefiore would be overwhelmed with Covid-19 patients by early April, even after expanding bed capacity to its limits (**Figure 1**). This outcome could have resulted in catastrophic consequences, like the flooding of hospitals that was seen in Italy just a few weeks earlier (1, 2), where hospitals exhausted resources and personnel needed to care for the patients. To prevent this bioethical nightmare scenario (3) our institution, adopted an "all hands on deck" approach, mobilizing our entire workforce to expand our units to accommodate the growing number of patients being admitted. Given that the medical and ICU units are part of the department of medicine (DOM), the DOM was at the center of this mobilization.

With 15 divisions the Montefiore Einstein DOM is the largest department in our institution and mobilizing such a large department required careful planning, seamless teamwork, and strong leadership. To achieve that goal, we applied a framework for our efforts and initiatives during the crisis that we designate the "**3C framework**", an abbreviation for **C**oordination, **C**ommunication, and **C**ollaboration (**Figure 2**). In this report we describe the many initiatives the Montefiore Einstein DOM implemented during the Covid-19 pandemic using the **3C** framework. For a summary of our initiatives within the 3C framework see **Table 1**. The goal of our report is not to summarize the MMC Department of Medicine's experience during Covid-19 (such a summary would be beyond the scope of this manuscript), but to serve as a guide on how the 3C framework helped us organize, mobilize, and energize the department of medicine effectively and efficiently during this unprecedented crisis.

BACKGROUND: THE DEPARTMENT OF MEDICINE AT MONTEFIORE MEDICAL CENTER

The MHS includes 11 hospitals located in the Bronx, Westchester County, and the Hudson Valley in New York State. MMC comprises four MHS hospitals located in the Bronx and includes the Montefiore Hospital, Weiler Hospital, Children's Hospital at Montefiore, and Wakefield Hospital, which together have approximately 1,500 beds including 108 intensive care unit (ICU) and 30 intermediate care unit beds, 93,000 annual admissions, and more than 200 outpatient care sites. The current manuscript focuses on the implementation of the 3C framework by the DOM at the MMC.

The DOM is the largest department at MMC and includes 25 inpatient units, 3 medical and cardiac ICUs, and 754 beds, with approximately 47,000 discharges per year. The DOM comprises 15 divisions and has 1,293 providers (of them > 800 full time faculty). The DOM trains 429 residents and fellows in 3 residencies (Moses-Weiler IM residency training 168 residents, Wakefield IM residency training 77 residents, and Dermatology residency training 19 residents) and 15 fellowships (training a total of 165 fellows). Of note the Critical Care Division includes all 7 ICU's and 2 step-down units including the surgical ICU's.

The DOM is also the largest research department at Einstein and Montefiore with approximately $96 million in total grant money received, 150 grants, and 140 ongoing clinical trials (pre-Covid-19) in 2019.

THE CHALLENGES FACED BY THE MMC DEPARTMENT OF MEDICINE

Challenges faced by the Department of Medicine included: the need to rapidly deploy physician staffing to care for a rapidly expanding inpatient census, provide support for physicians newly deployed to the inpatient setting as well as non-IM physicians who were deployed, stay abreast of the rapidly expanding body of research on Covid-19 to develop and continuously update standardized care protocols, develop processes for the triage and appropriate care of patients being placed in expanded ICUs and non-traditional care spaces, develop and rapidly initiate Covid-19-related research, maintain real-time communication with all providers, and offer emotional and logistical support to physicians and physician assistants (PAs) who were delivering care in extremely challenging and distressing conditions. Residents were the primary providers of inpatient care during the epidemic. In addition to postponing their usual educational activities, all residents were also exposed to the unpredictability and grief associated with caring for Covid-19 patients, during a formative period in their careers.

COORDINATION, COMMUNICATION, AND COLLABORATION

Medicine Covid-19 Taskforce: The Key to Coordinating the DOM Efforts

To coordinate the deployment and activities of such a large workforce we established a unique task force to centralize and synchronize all DOM activities during the Covid-19 crisis. This task force, the **M**edicine **C**ovid-19 **T**askforce (**MCT**), was charged with seamless coordination and implementation of all initiatives and operations of the DOM. The MCT included 18 members representing all arms of the DOM (**Table 2**), and it convened every morning through a conference call. During these structured conference calls, every DOM leader and member of the MCT gave a detailed report updating all members on activities, challenges, and plans within their domain. At the end of each presentation we discussed what coordination and

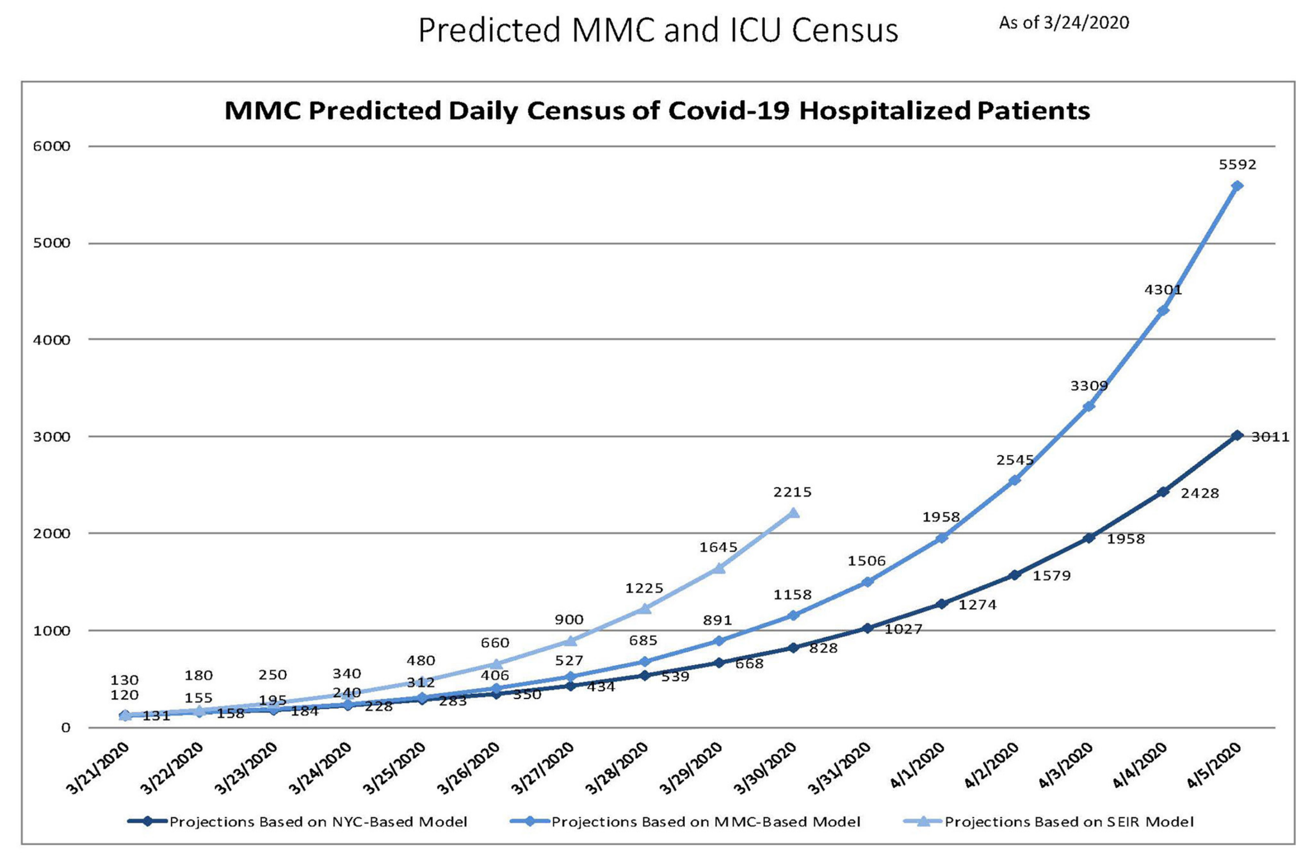

FIGURE 1 | Three predictive models generated on March 24, 2020 showing the expected exponential increase in daily Montefiore Medical Center census over the following 2 weeks.

synchronization of efforts and resources were needed to achieve our goals and implement our plans and how to communicate these to the entire department. The most important coordination of efforts involved deployment of faculty and trainees. The regular updates and discussions at the MCT ensured that all new ICU and medicine units that were being built and opened overnight were always properly staffed with attendings and trainees.

Another example in which coordination was important was the development and dissemination of Covid-19 treatment protocols. We were able not only to ensure that all Covid-19 patients admitted to MMC were treated consistently, but also to implement new protocols very rapidly and in many cases much earlier than at other Medical Centers. Moreover, our uniform protocols allowed us to study in real time the impact of our treatment protocols on outcomes. As an example, analysis of Montefiore patient data showed that treatment with steroids was associated with reduced mortality only when the C-reactive protein (CRP) levels were >20 mg/dl, but when CRP was lower than 10 mg/dL steroid treatment was associated with increased mortality (4). This study that was performed in real time contributed to a modification of the protocol to incorporate these new data.

Our coordinated efforts through the MCT enabled us to coordinate many other initiatives. To name a few: (1) The production of critical educational video lectures to train physicians not usually working in the ICU setting; (2) Solicitation, receipt, and distribution of donated personal protective equipment (PPE), and other essential supplies such as pulse oximeters and electronic tablets; (3) Teaching of the medical students; (4) Continuation of essential procedures; (5) Conversion of most activities to telehealth and more.

The key to the 3C framework success was that it operated at all levels of the DOM, not only at the leadership level, that is, within the divisions, as well as at each Covid-19 unit. To facilitate the implementation of the 3C framework within the divisions, the MCT met with all division chiefs twice a week to update them on DOM deployment and other efforts. This ensured that all departmental and divisional efforts were coordinated, that there was no duplication of efforts, and, most importantly, that every issue was immediately addressed in real time. Division Chiefs then held conference calls with their faculty coordinating and communicating with them and receiving communication from their faculty and feedback that was then communicated back to the MCT. To ensure that the 3C framework reached the individual Covid-19 units the chiefs of the Critical Care

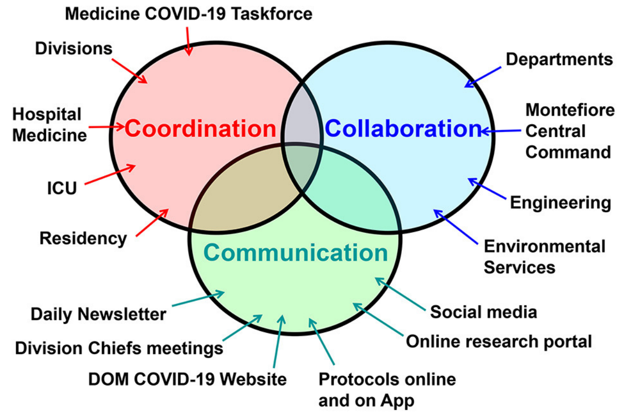

FIGURE 2 | The 3C framework consists of three elements: coordination between the department of medicine (DOM) divisions, ICU, Covid-19 units, residency training program, as well as other arms of the DOM. This was led by the Medicine Covid-19 Taskforce; Communication between all arms of the DOM was achieved via a daily newsletter, division chiefs meetings, online resources, and even social media; Collaboration with all arms of the institution, especially with Montefiore Medical Center administration and central command, was essential to ensure synergy and uniformity of efforts within the entire institution.

(MNG) and Hospital Medicine (WS) divisions held regular virtual meetings with the attendings in the ICU's and Covid-19 IM units. Thus, the 3C framework was successful because it was delegated from the DOM leadership to Divisional leadership and to attending physicians at the Covid-19 unit level, and because it was bi-directional.

The chair of medicine (YT) and chiefs of Critical Care Medicine (MNG) and Hospital Medicine (WS) also held regular meetings with hospital administration, nursing leadership, and other departments to ensure seamless collaboration.

The DOM Covid-19 Daily Newsletter: The Key to our Communication

Transparency is essential for ensuring that members of the department have full trust in departmental leadership and are willing to do whatever is requested of them. This is especially true in times of crisis. Early on the decision was made that with very few exceptions everyone in the department would know what the leadership knew. Therefore, we created a DOM Covid-19 Daily Update, an electronic newsletter that was sent to all members of the department which updated them on everything that was happening—from our hospital Covid-19 statistics, to new protocols, to new relevant publications, and even to discounts by companies to healthcare workers. To ensure that the content was relevant we monitored the number of views of different items and focused on popular items. In addition, we gave the readers an e-mail address to offer suggestions, provide comments, or ask questions. The newsletter was highly successful; it was distributed to > 6,500 people with a daily open rate of up to 65%.

ICU Expansion

During the Covid-19 crisis our ICU beds at MMC expanded from about 100 ICU beds to 306. This rapid expansion necessitated coordination of deployment between the ICU leadership, residency directors, division chiefs, other departments, and the Montefiore Command Center (which oversaw all ICU deployments). Critical Care not only expanded its ICU bed capacity but also responded to cardiac arrests and rapid emergency calls that increased 5-fold (from an average of 7–8 per day pre-Covid-19 to 33 per day). The Chief of the Critical Care Division (MNG) led and supervised the ICU expansion. The expansion followed specific steps that included: **(1)** Identification of suitable space for an ICU that had enough room for patients in isolation, on ventilators, and with bedside monitoring (e.g., OR recovery unit); **(2)** Coordination with engineering to convert each unit into an ICU, including construction, terminal cleaning, and procuring equipment, especially ventilators; **(3)** Coordination with DOM leadership as well as other department leaders to organize deployment of faculty to the new units; **(4)** Coordination with the program directors and Montefiore Command Center to organize deployment of residents and fellows to the new units; **(5)** Coordination with nursing for the deployment of nurses to the new units; **(6)** Communication to the Emergency Department, Hospital Medicine division, and all providers about the establishment of a new ICU and which patients could be admitted or transferred to the new ICU; **(7)** Development of a Critical Care Command Center to provide 24/7 critical care expertise, remote monitoring of expanded ICU's, deployment of emergency personnel and equipment, point of care ultrasounds, and coordination of transfers of patients, resources and personnel between ICUs and between MMC campuses, and from outside hospitals; **(8)** Development of protocols and procedures for emergency responses like intubation and cardiopulmonary resuscitation to minimize aerosolization and infection risk during the pandemic; **(9)** Development of infection control measures in coordination with respiratory therapy and hospital epidemiology for high risk respiratory procedures in the hospital.

Expansion of Internal Medicine Units

At the same time as the ICU's were expanding the Internal Medicine (IM) general units were rapidly expanding, too, from approximately 700 beds to ∼ 1,100 beds. To achieve this, space for the increased number of patients needed to be identified, and increased physician staffing needed to be mobilized. To provide the needed space, the Covid/Medicine service first expanded into virtually all inpatient spaces that do not traditionally accommodate Medicine patients including Neurology, Oncology and Surgical inpatient units. Next, many non-clinical spaces were rapidly renovated to accommodate inpatients including a large meeting space, unit day rooms, a cafeteria, and rehab gymnasiums. Finally, a large free-standing outpatient surgical center was converted into inpatient units. To provide physician staffing for the expanded service the DOM rapidly constructed novel 3-person inpatient care teams consisting of a Medicine attending, a Medicine resident and an "allied" (non-Medicine) resident. These teams could be constructed and deployed within

TABLE 1 | List of Department of Medicine (DOM)-led initiatives in which the 3C framework was implemented.

Initiative	Description	DOM participants	Coordination	Communication	Collaboration
MCT*	A taskforce charged with coordinating all operations of the DOM during the Covid-19 crisis.	The leadership of the DOM (18 members)	Every initiative or plan was reviewed and discussed by the MCT and coordinated by it	All MCT decisions were communicated to the entire DOM through the Daily Newsletter	All MCT initiatives or plans were in cooperation with Montefiore Command Center and with other departments. Different MCT members based on their area of responsibility in charge of collaboration.
ICU expansion	ICU beds expanded from ∼ 100 to ∼306; additional ∼100 patients on ventilators admitted to medicine units	Critical Care and Pulmonary divisions leadership	ICU staffing by residents and fellows was coordinated with PD's and Division chiefs	Deployment decisions were communicated to DC and program directors at DC meetings held twice a week, and directly to physicians deployed	Deployments were in cooperation with the Central Deployment command center of Montefiore and other department chairs
IM units' expansion	Medicine beds expanded from ∼700 to ∼ 1,100	Hospital medicine division leadership	Medicine unit staffing was coordinated with PD's and Division Chiefs	Deployment decisions were communicated to division chiefs, program directors and physicians deployed	Allied residents (from non-Medicine departments) were deployed in cooperation with other departments and Central Deployment command center.
Creating and disseminating unified Covid-19 treatment protocols	Departmental experts created protocols for treating Covid-19 disseminated to all providers (e.g., steroid, anti-coagulation, DKA, proning, end of life protocols, etc)	Led by the division of Hospital Medicine with participation of specialists with expertise in subject area of individual protocols	All protocols were reviewed by several experts and DOM leadership before being approved. Data supporting protocols were included in the protocol	Protocols are accessible via an online portal, smart phone Application (MedProtocols), and DOM Covid-19 website; Disseminated by text messages to all providers, in daily Newsletter, and through a nightly conference calls with all providers	Collaboration with legal department to add appropriate disclaimers; cooperation with other departments and dissemination to all departments participating in the care of Covid-19 patients
Inpatient eConsults	Converted the majority of inpatient consults to eConsults	DOM director of faculty practice, DOM QI co-director, DOM director of innovation, hospital medicine leadership	Director of DOM faculty practice coordinated all involved in development and implementation of inpatient eConsults	Daily Newsletter and at DC meetings	Creating of eConsults required collaboration with the EPIC team and all other departments since all departments participated
Tele-visits for outpatient	Converted nearly all outpatient visits to tele-visits	Project led by DOM faculty practice leadership and administration	Director of DOM faculty practice coordinated the efforts	Daily Newsletter and at DC meetings	DOM practice leadership rolled out tele-visits in cooperation with Montefiore FPG group, EPIC team and other departments
Education: Covid-19 training and education	Educational activities included: **(1)** Medicine Grand Rounds series on Covid-19 (via Zoom); **(2)** Production of 5 video lectures on treating Covid-19 patients with ARDS on a vent;	**(1)** Grand Rounds organized by VC for faculty affairs; speakers included DOM faculty & outside speakers; (2) Videos lectures given by Pulmonary & Critical Care faculty	**(1)** Grand Rounds were coordinated by Chair, VC for faculty affairs, and administration; **(2)** Videos production coordinated by DOM director of media and communications and Einstein department of communications	Grand Rounds and videos were communicated by special announcements and via Daily Newsletter	Grand Rounds organized in cooperation with other departments (e.g. Psychiatry, Family & Social Medicine) to include their experts as speakers; coordinated to have members of all departments and Einstein researchers attend the Zoom lectures
Research: Clinical Trials/Studies	Within < 2 weeks of the first Covid-19 patient admitted to Montefiore the DOM began participating in clinical trials. Altogether the DOM participated in 8 randomized clinical trials: 3 Remdesivir; 1 Sarilumab; 2 Leronlimab; 1 Convalescent Plasma; 1 HCQ; and a CDC surveillance of HCW	Pulmonary & CCM divisions, ID division, HM division, all deployed DOM physicians (participated in recruiting patients)	Trials vetted by VC for research (MK) and chair of Medicine (YT) and coordinated among Divisions and PI's	Communication about trials, inclusion/exclusion criteria disseminated via Daily Newsletter and DOM Covid-19 Website	All clinical trials performed in cooperation with EPIC team and other participating departments (e.g. surgery)

(Continued)

TABLE 1 | Continued

Initiative	Description	DOM participants	Coordination	Communication	Collaboration
Research: Retrospective analysis of Montefiore Covid-19 data	About 200 retrospective analyses of Montefiore Covid-19 data performed by DOM faculty	Faculty from all DOM divisions	Established a committee consisting of 10 division chiefs to review all research projects in the DOM to achieve the following goals: (1) have large and diverse collaborative groups for each project; (2) have appropriate expertise for each project; (3) have the proper tools and study design to achieve aims(4) ensure no overlap or duplication between projects; (4) engage junior faculty and trainees in projects.	All projects were uploaded to an online portal so they can be viewed by all DOM faculty, DC were updated at our meetings on progress in review and approval of projects by the committee	Cooperated with other departments on some projects (e.g. department of epidemiology and population health).
Innovation	Implemented innovative strategies to treat Covid-19 patients: **(1)** Cardiac telemetry patch; **(2)** CGM for Covid-19 inpatients; **(3)** Cellavision autoanalyzer for hematology; **(4)** IV lines and CRRT tubing outside patients' rooms in ICU's (**5**) Critical Care Command Center to provide 24/7 expertise, remote monitoring, and resource allocation to critically ill patients across all campuses (**6**) Portable bedside monitors with remote link to Critical Care Command Center to turn any hospital bed into a temporary high intensity monitored setting (**7**) Intubation drapes and boxes to minimize aerosolization of respiratory secretions during emergent intubations (**8**) Proning teams	Faculty from all divisions	Activities coordinated by MCT	Daily Newsletter	Collaboration with Montefiore Command Center and EPIC team as needed
Alumni volunteers	∼40 alumni physicians volunteered to come to Montefiore and help. Of them 9 were deployed.	Deployment of alumni efforts were led by VC for faculty affairs	Efforts coordinated by MCT	Daily Newsletter	Cooperated with Montefiore Command Center for logistics, Care Management Organization for credentialing, EPIC team for EPIC access
Donations	Using social medial and our Newsletter put out a call for donations both monetary and non-monetary (e.g., PPE, food, scrubs, pulse oximeters, and more).	Efforts to secure donations were led by the DOM senior administrator and her staff	Efforts coordinated by MCT	Daily Newsletter and social media	Collaboration with department of finance for establishing funds to hold monetary donations, and with procurement department for donations of supplies

(Continued)

TABLE 1 | Continued

Initiative	Description	DOM participants	Coordination	Communication	Collaboration
Community outreach	Launched a dynamic social media campaign calling for submissions of notes, photos, and videos from children (and adults) in our community supporting Montefiore healthcare heroes.	Efforts led by the DOM director of media and communications	Efforts coordinated by MCT	Daily Newsletter and social media	Cooperated with Montefiore marketing to expand campaign and produce and disseminate videos featuring submissions received from members of our community
Improving morale	Launched a large campaign dubbed #MontefioreProud on social media and at Montefiore. #MontefioreProud T-shirts, bumper magnets and buttons were distributed widely to HCW	Campaign led by DOM chair and senior administrator and their staff	Efforts coordinated by MCT	Daily Newsletter and social media	Cooperated with Montefiore marketing to produce and disseminate marketing materials and to promote #MontefioreProud on social media

**MCT, Medicine Covid-19 Taskforce; ICU, intensive care unit; DOM, department of medicine; ID, infectious diseases, HM, hospital medicine; PD, program director; HCW, healthcare workers; DC, division chiefs; FPG, faculty practice group; PI, principal investigator; HCQ, hydroxychloroquine; CGM, continuous glucose monitors; VC, vice chair.*

24 h of notification of a new staffing need. In addition, several non-Medicine services took over the care of Covid-19 patients including Neurology, Oncology and Pediatrics, and Family Medicine significantly increased their inpatient capacity.

In order to achieve this enormous expansion in a coordinated and organized way the Chief of the Division of Hospital Medicine (WS) implemented several key measures: **(1) Leadership** – with the exponential growth of the general medicine units a new divisional leadership structure was created appointing faculty to new leadership positions, such as director of the IM units at our outpatient facility; **(2) Standards of care** – Divisional leadership in consultation with specialists in different areas such as diabetes and coagulopathies, created uniform protocols for the treatment of Covid-19 patients, including an EPIC Covid-19 admission order set and note template; **(3) Mentoring** – several non-IM units (e.g., pediatrics, neurology) were converted into IM Covid-19 units that were staffed by the original department. Since the providers on these units did not have experience in adult hospital medicine and Covid-19 the Hospital Medicine division provided mentors that came daily and rounded with the providers on these units to help manage their service; **(4) Triaging** – the Division of Hospital Medicine developed criteria for transferring patients from acute Covid-19 units to post- acute areas (non-clinical areas converted into Covid-19 units). **(5) Deployment of physician assistants (PAs)** – PAs were essential on the IM Covid-19 units that did not have residents and the PA leadership at the Hospital Medicine division managed their deployment and training to take on new roles such as being on the code team.

Medicine Sub-specialty Inpatient Consults

The inpatient subspecialty consultation services had to resolve two main challenges: **(1)** Most consultants were deployed to ICU's or IM Covid-19 units and could not do inpatient consults; and **(2)** PPE was in short supply and consultants coming to do in-person consults would use a large amount of PPE. To resolve both issues the MCT initiated an eConsult service for all inpatient consultations except for a few that required procedures (**Table 1**).

Covid-19 Treatment Protocols and Education

One of the challenges our expansion created was that numerous providers with limited ICU or IM experience were deployed to ICU's and IM Covid-19 units. In order to ensure that they could perform their new roles well, we implemented two important initiatives: development and dissemination of detailed and uniform Covid-19 treatment protocols, and production and dissemination of educational Covid-19 video lectures. The Covid-19 treatment protocols were developed by experts in their fields together with the Hospital Medicine Division leadership and were based on the best available data. This approach resulted in very early adoption at Montefiore of life-saving Covid-19 protocols. To mention a few, the Montefiore steroid treatment protocol was rolled out and uniformly implemented on April 6 (4); our anti-coagulation protocol was rolled out on April 5; and the Montefiore subcutaneous (SQ) insulin diabetic ketoacidosis (DKA) protocol was rolled out on April 1. Some of these protocols were disseminated across the country (e.g., our DKA protocol was posted on the American Diabetes Association website and published in UpToDate) (5).

These protocols were easily accessible through an online portal and later through a free downloadable mobile application (MedProtocols, see below). In addition to making the protocols easily accessible from anywhere, any new protocols or modifications to existing protocols were communicated to every provider on the IM units through our daily newsletter, text messaging, and nightly briefs with the Chief of the division of Hospital Medicine. In addition, we converted our weekly Medicine Grand rounds to a virtual format, and held a special Covid-19 series that focused on Internal Medicine subspecialty manifestations of Covid-19.

TABLE 2 | Members of the medicine covid-19 taskforce and their roles in coordinating DOM efforts and initiatives.

Role in the DOM	Charge during Covid-19	Comments
Chair	Leading all IM departmental efforts and activities	Chaired the MCT
Chief of Pulmonary & Critical Care Divisions	Leading ICU expansion, ICU operations, protocols, staffing, ventilator management and protocols, critical care resource allocation, emergency responses, supervising all clinical trials performed in the ICU's	Either the Chief or her designee participate in all MCT meetings
Chief of the Division of Hospital Medicine	Leading Medicine Units expansion, Medicine Units operations, protocols, staffing, supervising allied (non-medicine) providers working on medicine or medicine-converted units, supervising all clinical trials performed in the medicine units	
Chief of the Division of Infectious Diseases (ID)* and Member of the Infection Control Team (ICT)	Leading all activities of the ID division operations and staffing, working with Hospital Epidemiologist and ICT on ID protocols for the hospital, leading major studies such as the Convalescent Plasma study	
Residency Program Directors for Moses-Weiler and Wakefield campuses	Leading and supervising all the residents including managing their deployment, quarantine, Covid-19 infections, protocols, as well as training and education during the Covid-19 crisis	Montefiore has 2 residency programs with a combined 243 residents
Vice Chair for Faculty Affairs	Overseeing faculty credentialing, deployment of alumni volunteering to work at Montefiore, communicating departmental updates to all faculty	About 40 alumni volunteered to come and be deployed at Montefiore
Vice Chair for Research	Overseeing all clinical trials in the department, vetting all proposals for clinical trials presented to the department to ensure adequate infrastructure and rapid implementation, overseeing the shutting down and re-opening of all wet-bench labs and clinical research, overseeing all retrospective analyses of Covid-19 data, overseeing all IRB submissions	Montefiore had numerous requests for participation in clinical trials, mostly from pharmaceutical companies, and numerous human studies requiring IRB approval (both clinical trials and retrospective analyses) during the Covid-19 crisis
Associate Chair for Undergraduate Medical Education	Overseeing all medical students Internal Medicine teaching during the Covid-19 deployment, all done remotely using virtual learning platforms	All medical students teaching continued during the Covid-19 epidemic including virtual teaching of Internal Medicine to third and fourth year students that were not allowed to continue bedside learning
DOM Senior administrator, Associate Chair and Director of the Faculty Practice and the Faculty Practice team (administrator, and nursing supervisor)	Overseeing and leading the conversion of all our outpatient activities into tele-health, overseeing all DOM outpatient activities, deploying DOM staff to Covid-19 testing sites and to the frontlines, converting most inpatient consults into e-Consults, overseeing requests and receipts of donations to the DOM	The DOM converted all outpatient visits into tele-visits within 3 days of shutting down our practices, most inpatient consults were also converted into eConsults within a week of the surge. The DOM received numerous donations including monetary donations, PPE, essential supplies such as pulse oximeters and WiFi tablets (to connect patients on the floors with their families), and food.
Associate Chair and Director of Innovation	Overseeing and leading all activities implementing new technology such as tele-health, eConsults, WiFi tablets and EPIC builds for tele-medicine	
Director of Media and Communications	Assisting the Chair with all communications to the DOM, including publishing a Daily Newsletter, and sending messages and information by e-mail and on Social Media	Our Social Media campaign was instrumental for engaging our community to support the DOM frontline health care workers, and in soliciting donations of PPE and other essential supplies.

**MCT, medicine covid-19 taskforce; IM, internal medicine; ID, infectious diseases; ICT, infection control team.*

Outpatient Deployment and Conversion to Telemedicine

Within 10 days of the first Covid-19 patient being admitted to MMC all but one outpatient practice were closed and many of their staff and providers deployed to Covid-19 units. However, MMC was able to continue most outpatient operations through a rapid conversion to telemedicine. The DOM implemented video visit platforms, and patients were called and instructed that their appointments would be done remotely. One of the challenges we faced in the Bronx was that many patients did not have the ability to do video visits (e.g., they did not have WiFi at home) and therefore only telephone visits were possible for them. The conversion of our outpatient practices to televisits required coordination and collaboration with the Faculty Practice Group, our call center, our Electronic Medical Record team, and our billing services in order to support billing for televisits. To ensure a smooth transition to televisits a DOM team trained and helped providers performing televisits.

Covid-19 Post-discharge Televisit Program

As large numbers of recovering Covid-19 patients began to be discharged home from Montefiore IM units, there was a need for follow-up care. Therefore, the DOM established a post-discharge follow-up program. Since most of our physicians were deployed we enlisted third year medical students to help with the program which included follow-up phone calls/video visits by physicians or medical students to address the following: **(1)** Ensure that patients were recovering; **(2)** For patients discharged home with pulse oximeters the oxygen saturation readings were evaluated; **(3)** If patients needed follow-up care with specialists, appointments were coordinated and scheduled; **(4)** Patients with financial and socio-economic challenges were assigned a care coordinator from the Montefiore Care Management Organization (the Montefiore accountable care organization) who contacted them to assist. These activities were coordinated with the Montefiore Primary Care group.

Infection Control and Prevention

Infection control procedures implemented at our institution included universal masking of patients and health care workers (6), appropriate PPE usage when caring for COVID-19 patients, conversion of in-person consults to telemedicine, universal PCR testing upon admission to the hospital, environmental disinfection, and education of staff *via* weekly lectures and the DOM newsletter. When we identified a suspected exposure, we activated an infection control team that performed the contact tracing and implemented isolation and quarantine measures (7). However, the DOM's infection control practices evolved over time in several ways: iterative approaches to PPE distribution were employed until all providers had easy access, and the infection control protocols were adjusted following changes in the CDC recommendations. To implement and disseminate these frequent protocol changes we used our 3C approach by coordinating the implementation of these changes through the MCT and communicating these changes to all providers through our various communication methods (see above). As a result of these efforts, resident sick calls returned to pre-COVID levels within weeks despite an ongoing rise in the number of COVID-19 patients hospitalized at our institution (8).

Mental Health Support

To address the stress and anxiety that the COVID-19 pandemic induced in healthcare workers the Psychiatry Department at Montefiore established several interventions. These included a support phone line, staff support centers, team support sessions, and more. For a review of these interventions see (9). An additional unique resource - the Montefiore Emotional Support Allies (MESA) – was also established, in which health care workers were individually assigned to a mental health professional (psychologist, psychiatrist, or social worker) who *actively* reached out to them and offered to help. The mental health professionals provided peer support and served as navigators to other emotional health resources. About 20% of those contacted opted for one or more peer support contacts; many finding them meaningfully helpful (Alpert, personal communication)."

Coordination of Research Studies

From the onset of the epidemic in NYC, clinical and laboratory investigator-initiated research studies aimed to better our understanding of Covid-19 and to improve the care of Covid-19 patients.

Clinical Trials

Performing clinical trials during an epidemic when an institution is overwhelmed with patients is challenging. Nevertheless, we decided that it was imperative that we participate in clinical trials aimed at finding new therapies for Covid-19. Our leadership received numerous requests for participation in clinical trials examining new treatments for Covid-19, and those had to be vetted by experts in the field. All clinical trial efforts were centralized and coordinated by the vice chair for research (MJK). In addition, the Albert Einstein College of Medicine established a committee of experts in different relevant fields that evaluated proposed trials to select those that were suitable for our institution. The criteria used to select trials that our institution joined were: **(1)** Convincing premise and rationale for the proposed study; **(2)** Rigorous prior research and preliminary data showing potential efficacy; **(3)** Feasibility of performing the study at Montefiore; **(4)** Adequate infrastructure and staff for rapid implementation. To meet the sheer demands of the pandemic and the urgency of launching new studies quickly, experienced clinical trials coordinators were supplemented with coordinators who volunteered their time when their outpatient studies were suspended. Data collection and entry were assigned to coordinators and volunteers who were based outside of the hospital because of health or infection control restrictions to allow for hospital-based coordinators to concentrate on enrollment and study procedures. With these criteria and strategies, we participated in eight randomized clinical trials during the pandemic: three Adaptive Covid-19 Treatment Trials (ACTT) of remdesivir; sarilumab trial; two leronlimab trials; convalescent plasma trial; an NHLBI-funded hydroxychloroquine trial; and a CDC surveillance study of healthcare workers. These studies helped establish the efficacy of remdesivir, the safety of convalescent plasma, and the lack of efficacy of hydroxychloroquine and sarilumab. The leronlimab trials are ongoing.

Retrospective Analysis of Our Covid-19 Cohort

More than 8,000 Covid-19 patients were admitted to MMC and the data collected during their hospitalization was critical to learning about Covid-19. Therefore, investigators and clinicians in the DOM designed protocols and obtained IRB approval for analyzing data collected from all Covid-19 patients cared for at MMC. As these research efforts intensified, it became clear that there was a need for a centralized review and approval process. A large number of retrospective studies were being done simultaneously by various groups within the DOM and it was possible that many of them could overlap. Therefore, we established a **R**esearch **C**ommittee on **C**ovid-19 (RCC) to coordinate all retrospective research efforts and to evaluate each study for premise, importance, feasibility, appropriate expertise, and overlap with other studies. The RCC evaluated approximately 200 projects. To assist the RCC in its work we built an online portal to which every new project was uploaded providing all the necessary information for the RCC to evaluate the project. At the time of the writing of this manuscript, 23 research studies from the DOM at Montefiore have been published. They include studies that had a huge impact on our understanding of Covid-19 (10–16) and on treatment protocols for Covid-19 (4).

Other Studies

Non-Covid-related clinical research continued remotely and transitioned to video visits when possible. Some projects used electronic consent (e-consent) to facilitate continued recruitment into studies. DOM investigators submitted 35 Covid-19-related applications for funding and 11 were awarded to implement high-impact trials, pursue multicenter observational studies, support underserved patients with diabetes, and implement artificial intelligence and machine learning to predict respiratory failure in patients with Covid-19.

New Technology and Innovation

The epidemic created many challenges that required innovative solutions. The DOM director of innovation (SPJ) led our efforts to use technology to overcome challenges the epidemic created. Some challenges that required innovative technological solutions included: **(1)** Converting most outpatient visits to video visits; this was achieved through several new platforms for video visits; **(2)** Connecting patients with their families as families were not allowed to visit; this was achieved by providing dozens of electronic tablets (donated to the department) to our inpatient floors and fitting them onto carts; **(3)** Rapid dissemination and updating of our treatment protocols; this was achieved by creating (with a developer) a free downloadable mobile App (MedProtocols, available on the iOS and Android App Stores) that stores all the Montefiore Covid-19 protocols.

Recruiting Alumni Volunteers and Outreach for Donations

We contacted physician alumni of Einstein and Montefiore asking for volunteers to work in our hospitals during the pandemic. These efforts were highly successful with many alumni volunteering to come to the Bronx and work in our hospitals (**Table 1**). We also solicited donations through an Amazon page where we listed items needed (e.g., pulse oximeters for patients, etc). Through our newsletter and social media outreach we received numerous donations that not only helped us cope with shortages of these items but also gave a strong morale boost to our providers.

Community Outreach and Efforts to Raise the Morale of Our Frontline Providers

Faced with a disease that had no treatment and caring for large numbers of patients decompensating and dying, the stress and heartbreak felt by our frontline providers cannot be overstated (17). We alleviated this stress through constant communication between leadership and the frontline providers (see above). We also collaborated with the Department of Psychiatry that established a strong mental health support program for the frontline providers at Montefiore. These measures were helpful, but we felt that we needed to do more. Therefore, we reached out to our Bronx, Westchester, and Hudson Valley communities through social media, and requested displays of support for the frontline providers at Montefiore. The response of the community was overwhelming and heartening. Hundreds of e-mails, letters, photos, videos, and artwork, mostly created by children, were sent to us and were shared with our frontline providers, energizing them and boosting their morale during these terrible times. We also launched a social media campaign under the hashtag **#MontefioreProud**. #MontefioreProud gear was distributed to DOM providers and staff and were highly popular and had a significant positive impact on morale and camaraderie at our institution.

THE DEPARTMENT OF MEDICINE POST-COVID

As of the writing of this manuscript the positive Covid-19 testing rate has declined significantly in New York City and the epidemic seems to be contained. However, our work is not finished as we have to address two main remaining challenges: **(1)** preparing for additional Covid-19 surges; **(2)** treating patients who recovered from Covid-19 and continue to suffer from its long-term consequences.

Preparing for Additional Surges

During the first Covid-19 wave at our institution we created an online database where we stored the information about all our deployed physicians. We have since updated this database with information about all physicians who may need to be deployed and where. Our approach is similar to military reserve preparedness where our central command can deploy physicians very quickly using this online database. Plans are in place for ICU expansion, IM units' expansion, and converting all our units into Covid-19 units, and rapid initiation of clinical trials.

Treating Patients With Chronic Consequences of Covid-19

It is becoming evident that a large number of patients who survived Covid-19, especially those that were admitted to the ICU, suffer from long-term consequences of Covid-19 including chronic fatigue, dyspnea, foggy thinking, chronic anosmia, memory loss, depression, as well as cardiac, renal, pulmonary, and brain complications from the disease (18, 19). To address these issues the Montefiore DOM established a Covid Recovery (CORE) clinic where a multi-disciplinary team of clinicians are following patients who recovered from Covid-19. The CORE clinic will also serve as a research platform to study the long-term consequences of Covid-19, their causes, and how they can be prevented and treated.

LESSONS LEARNED

During a crisis such as the Covid-19 pandemic effective leadership can be described by the abbreviation **A,B,C,D,E**:

Available – the leadership team should always be available and responsive to all communications and requests coming from the frontlines.

Back – the providers at the frontlines should know and be constantly reassured that the leadership team always has their back and will support them with all resources available.

Clear – communications coming from the leadership team should be clear and consistent.

Determined – the leadership team should show determination and decisiveness, and decisions have to be made promptly without delay.

Example – the leadership team should lead by example.

The DOM leadership team, comprising the Medicine Covid-19 Taskforce (MCT) and our division chiefs adhered to these five principles: Our leadership team was available all the time and communicated with frontline providers continuously; we supported our frontline providers with all our resources, and when resources were insufficient (e.g., PPE) we solicited donations to acquire them; communications were clear, consistent, and timely; decisions were made promptly and unambiguously; and all members of our leadership team who did not have medical/age exemptions worked at the frontline together with our providers.

The first important lesson is that the 3C framework was effective, but only when applied at all levels of the organization and in a bi-directional way, from leadership to frontlines but also from frontlines to leadership (**Figure 2**).

One of the key components of the 3C framework was the establishment of the Medicine Covid-19 Taskforce (MCT). An important lesson learned is that the MCT had to be large to encompass all arms of the department. The MCT had 18 members and while that lengthened our meetings it was critical for coordinating such a large department.

The 3C framework enabled us not only to coordinate all arms of the DOM but also to quickly implement creative, out of the box, solutions to the new challenges we were facing such as switching inpatients consults to eConsults, or making all our protocols available through a free downloadable mobile App.

Finally, one of the most important lessons learned is that while the main focus was on deployment and expansion of our ICU's and IM units to accommodate the rapid inflow of Covid-19 patients, our work did not end with deployment only. We had to devote time and effort to research, education, outpatient care, donations, community outreach and much more, while at the same time expanding our capacity to care for Covid-19 inpatients. Here again the 3C framework was very helpful.

CONCLUSIONS

The Covid-19 pandemic caused the most serious public health crisis of this century. No Medical Center in the US had experience with such a large-scale epidemic, and therefore hospitals had to adapt to the new situation and the many challenges it created overnight. Making things even worse, the lack of preparedness by government agencies for such a large-scale pandemic resulted in shortages of PPE, delayed testing for infection, and lack of clear and consistent treatment guidelines (20). Our medical center, located in the Bronx, was at the epicenter of the epidemic when it first hit the US during the months of March to May. In order to mobilize the DOM to handle the exponential increase in the number of patients with Covid-19 being admitted to our units we implemented a teamwork strategy that we dubbed the 3C framework. Using this framework, we were able to adapt quickly to the new situation in a coordinated and synergistic way, doubling our medicine units, deploying physicians, creating uniform and up-to-date treatment protocols, creating educational materials on treating Covid-19 for our frontline providers, converting inpatient consults and all outpatient activities into telemedicine, performing clinical trials, innovating and reaching out to our community through a large social media campaign. The main lesson from our experience is that the key to confronting such a challenging and stressful situation as the Covid-19 pandemic is to work in a cohesive leadership team that applies that 3C framework and functions in a coordinated and synergistic fashion. We believe that the same 3C framework can be effective not only within an individual Medical Center but when responding to a public health crisis at the regional and national level (3, 21, 22).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval were not required for the study since it did not involve human participants, in accordance with the local legislation and institutional requirements. Written informed consent was not required for the study since it did not involve human participants, in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YT: performed the work described in the manuscript for the Chair of Medicine, conceived the idea of the manuscript, and wrote the manuscript. MN: performed the work described in the manuscript for the Chief of Critical Care Medicine and wrote certain sections of the manuscript. MK: performed the work described in the manuscript for the Vice Chair of Medicine for Research and wrote certain sections of the manuscript. WS: performed the work described in the manuscript for the Chief of Hospital Medicine and wrote certain sections of the manuscript. EK: performed the work described in the manuscript for the Vice Chair for Faculty Affairs and wrote certain sections of the manuscript. GK: performed the work described in the manuscript for the Residency Program Director (Wakefield campus) and wrote certain sections of the manuscript. LS: performed the work described in the manuscript for the Residency Program Director (Moses-Weiler campuses) and wrote certain sections of the manuscript. SJ: performed the work described in the manuscript for the Department of Medicine Director of Innovation and wrote certain sections of the manuscript. EE: performed the work described in the manuscript for the Director of Medicine Faculty Practice and wrote certain sections of the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We wish to express our utmost gratitude to the tens of thousands of Montefiore Health System's health care providers, who worked selflessly, day and night, for many weeks, risking their lives and the welfare of their families, to care for Covid-19 patients. They all deserve our profound thanks and gratitude. These brave men and women saved thousands of lives and are the reason that MHS responded to the epidemic so effectively. Special thanks to the Montefiore-Einstein leadership, Drs. Philip Ozuah, Andrew Racine and Dean Gordon Tomaselli for their unwavering stewardship, for inspiring us, and serving as role models for all of us. We also wish to thank Dr. Silvie Colman, PhD and Dr. Mimi Kim, ScD for producing **Figure 1** of the manuscript.

REFERENCES

1. Zangrillo A, Beretta L, Silvani P, Colombo S, Scandroglio AM, Dell'Acqua A, et al. Fast reshaping of intensive care unit facilities in a large metropolitan hospital in Milan, Italy: facing the COVID-19 pandemic emergency. *Crit Care Resusc.* (2020) 22:91–4.
2. Ciceri F, Castagna A, Rovere-Querini P, De Cobelli F, Ruggeri A, Galli L, et al. Early predictors of clinical outcomes of COVID-19 outbreak in Milan, Italy. *Clin Immunol.* (2020) 217:108509. doi: 10.1016/j.clim.2020.108509
3. Emanuel EJ, Persad G, Upshur R, Thome B, Parker M, Glickman A, et al. Fair allocation of scarce medical resources in the time of covid-19. *N Engl J Med.* (2020) 382:2049–55. doi: 10.1056/NEJMsb2005114
4. Keller MJ, Kitsis EA, Arora S, Chen JT, Agarwal S, Ross MJ, et al. Effect of systemic glucocorticoids on mortality or mechanical ventilation in patients with covid-19. *J Hosp Med.* (2020) 15:489–93. doi: 10.12788/jhm.3497
5. Wexler DJ, Hirsch IB, Mulder JE. Coronavirus disease 2019 (COVID-19): issues related to diabetes mellitus in adults. *UpToDate.* (2020).
6. Richterman A, Meyerowitz EA, Cevik M. Hospital-acquired SARS-CoV-2 infection: lessons for public health. *JAMA.* (2020). doi: 10.1001/jama.2020.21399. [Epub ahead of print].
7. Spitzer Sverd S, Gardner LE, Cabassa JA, Schneider M, Noone RH, Jahdi MH, et al. A Bronx tale: exposure, containment and care on inpatient psychiatry units during COVID-19. *Gen Hosp Psychiatry.* (2020). doi: 10.1016/j.genhosppsych.2020.07.010. [Epub ahead of print].
8. Merken R, Kruger A, Bhardwaj G, Kajita GR, Shapiro LI. Internal medicine resident work absence during the COVID-19 pandemic at a large academic Medical Center in New York City. *J Grad Med Educ.* (2020) 12:682–5. doi: 10.4300/JGME-D-20-00657.1
9. Bernstein CA, Bhattacharyya S, Adler S, Alpert JE. Staff emotional support at montefiore Medical Center during the covid-19 pandemic. *Jt Comm J Qual Patient Saf.* (2020) 47:185–9. doi: 10.1016/j.jcjq.2020.11.009
10. Agarwal S, Schechter C, Southern W, Crandall JP, Tomer Y. Preadmission diabetes-specific risk factors for mortality in hospitalized patients with diabetes and coronavirus disease 2019. *Diabetes Care.* (2020) 43:2339–44. doi: 10.2337/dc20-1543
11. Reyes Gil M, Barouqa M, Szymanski J, Gonzalez-Lugo JD, Rahman S, Billett HH. Assessment of lupus anticoagulant positivity in patients with coronavirus disease 2019 (COVID-19). *JAMA Netw Open.* (2020) 3:e2017539. doi: 10.1001/jamanetworkopen.2020.17539
12. Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. *Metabolism.* (2020) 108:154262. doi: 10.1016/j.metabol.2020.154262
13. Fisher M, Neugarten J, Bellin E, Yunes M, Stahl L, Johns TS, et al. AKI in hospitalized patients with and without covid-19: a comparison study. *J Am Soc Nephrol.* (2020) 31:2145–57. doi: 10.1681/ASN.2020040509
14. Nori P, Cowman K, Chen V, Bartash R, Szymczak W, Madaline T, et al. Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City pandemic surge. *Infect Control Hosp Epidemiol.* (2020) 42:1–5. doi: 10.1017/ice.2020.368
15. Chand S, Kapoor S, Orsi D, Fazzari MJ, Tanner TG, Umeh GC, et al. COVID-19-associated critical illness-report of the first 300 patients admitted to intensive care units at a New York city Medical Center. *J Intensive Care Med.* (2020) 35:963–70. doi: 10.1177/0885066620946692
16. Sourial MY, Sourial MH, Dalsan R, Graham J, Ross M, Chen W, et al. Urgent peritoneal dialysis in patients with covid-19 and acute kidney injury: a single-center experience in a time of crisis in the United States. *Am J Kidney Dis.* (2020) 76:401–6. doi: 10.1053/j.ajkd.2020.06.001
17. Cunningham CO, Diaz C, Slawek DE. COVID-19: the worst days of our careers. *Ann Intern Med.* (2020) 172:764–5. doi: 10.7326/M20-1715
18. Carfì A, Bernabei R, Landi F, Gemelli against C-P-ACSG. Persistent symptoms in patients after acute COVID-19. *JAMA.* (2020) 324:603–5. doi: 10.1001/jama.2020.12603
19. Li Z, Zheng C, Duan C, Zhang Y, Li Q, Dou Z, et al. Rehabilitation needs of the first cohort of post-acute COVID-19 patients in Hubei, China. *Eur J Phys Rehabil Med.* (2020) 56:339–44. doi: 10.23736/S1973-9087.20.06298-X
20. Shapiro LI, Kajita GR, Arnsten JH, Tomer Y. Toward better preparedness for the next pandemic. *J Clin Invest.* (2020) 130:4543–45. doi: 10.1172/JCI140296
21. Schuchat A, Team CC-R. Public Health Response to the Initiation and Spread of Pandemic COVID-19 in the United States, February 24–April 21, 2020. *MMWR Morb Mortal Wkly Rep.* (2020) 69:551–6. doi: 10.15585/mmwr.mm6918e2
22. Haffajee RL, Mello MM. Thinking Globally, Acting Locally—The U.S. Response to Covid-19. *N Engl J Med.* (2020) 382:e75. doi: 10.1056/NEJMp2006740

Conflict of Interest: YT was previously (1/2015 – 6/2017) the PI on a basic research project jointly funded by the Juvenile Diabetes Research Foundation and Pfizer that is unrelated to the current manuscript. YT has two patent applications. (PCT/US2016/067775 & US provisional No: 61/883,062) that are not related to the current manuscript.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 19 March 2021
doi: 10.3389/fmed.2021.622541

Patient Provider Continuity and Prostate Specific Antigen Testing: Impact of Continuity on Receipt of a Non-recommended Test

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Background: Continuity of care with a regular physician has been associated with treatment adherence but it is unclear if continuity of care may lead to inappropriate treatments. We assessed the relationship between the receipt of prostate-specific antigen (PSA) screening, a non-recommended test, and having continuity with a single personal doctor.

Methods: We analyzed the 2016 and 2018 Behavioral Risk Factor Surveillance System (BRFSS). Responses from men aged 40 and older with no symptoms or family history of prostate cancer were analyzed (unweighted $n = 232{,}548$, representing 36,919,766 individuals). Continuity with one doctor was analyzed in relation to discussions of advantages and disadvantages of PSA tests, provider recommendation to receive a test and receipt of a PSA test.

Results: 39.5% of men received PSA screening during the time that the test was not recommended. Having a single personal doctor was associated with discussion of both advantages (53.3 vs. 29.7%, $p < 0.001$) and disadvantages (24.2 vs. 13.5%, $p < 0.001$) of PSA tests but also a recommendation to receive a PSA test (45.3 vs. 29.3%, $p < 0.001$). The adjusted odds of receiving a PSA test was higher among those with a single personal doctor compared to those without (OR 2.31; 95% CI, 2.17–2.46).

Conclusion: In a nationally representative sample during the time when PSA screening was not recommended by the US Preventive Services Taskforce, having a single personal doctor was associated with both recommendations for the test and receipt of the test. These findings emphasize the importance of the patient physician relationship and the need for evidence-based care.

Keywords: continuity, prostate, value, trust, patient–doctor relationship

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Specialty section:
This article was submitted to
Family Medicine and Primary Care,
a section of the journal
Frontiers in Medicine

Received: *28 October 2020*
Accepted: *23 February 2021*
Published: *19 March 2021*

Citation:
Mainous AG III, Rooks BJ, Mercado ES and Carek PJ (2021) Patient Provider Continuity and Prostate Specific Antigen Testing: Impact of Continuity on Receipt of a Non-recommended Test. Front. Med. 8:622541. doi: 10.3389/fmed.2021.622541

INTRODUCTION

Interpersonal continuity of care is the ongoing relationship between a patient and an individual physician. This patient physician dyad and the concomitant patient-physician relationship is a hallmark of primary care. There is evidence that having a regular physician is associated with decreased hospital admissions, emergency department visits and mortality risk (1–4).

The continuity between a patient and a physician is assumed to increase trust in the physician. This trust in the physician should therefore yield greater treatment adherence to treatments suggested by the physician. Several studies have indicated that having higher continuity is associated with greater treatment adherence in terms of medication use (5–7). There is even some evidence that continuity with a regular physician is associated with receipt of preventive services (8, 9).

Most studies focusing on continuity between a patient and a physician have centered on the receipt of needed preventive services and appropriate treatment adherence. What is unclear is an understanding of whether continuity has an impact on the receipt of low value or not universally recommended services. Low value testing is not benign and can have substantial negative impacts (10).

While differing recommendations were present based upon the specific organization, prostate specific antigen (PSA) testing was recommended by the USPSTF in 2012 as a level D, or a test that the task force recommends against (11). They concluded that there is moderate or high certainty that the test has no net benefit or that the harms outweigh the benefits. It remained as a level D recommendation until May, 2018 when it was reclassified as a C or one that is selectively offered based on professional judgement and patient preferences (12). Consequently, from 2012 until May, 2018, a PSA was a test that was recommended against by the USPSTF. Some data indicate that although prostate cancer screening significantly declined after the 2012 USPSTF guideline discouraging PSA-based screening a significant proportion of men continued to be screened (13).

The purpose of this study is to examine whether having a single personal doctor is associated with a recommendation for a test that is discouraged by the USPSTF and the receipt of such a test. Consequently, we undertook an investigation of a nationally representative survey of adult males aged 40 and older in the US to examine receipt of a PSA test.

METHODS

We analyzed the Behavioral Risk Factor Surveillance System (BRFSS) for 2016 and the first 4 months of 2018 (January–April). This time frame was chosen because it was far enough out from the last change in the USPSTF recommendations on prostate cancer screening in 2012 to ensure wide dissemination among physicians and we do not include any responses after the next change in the recommendations in May, 2018. Thus, during the time frame under study, the recommendation was a level D. The BRFSS is a nationally representative phone survey which includes both a core set of questions and optional modules that can be selected by each state or territory. Variables used in this study were obtained from the core modules of the combined landline and call phone data sets, which were sent to all 50 states, the District of Columbia, Guam, and Puerto Rico. The cohort for this study included men aged 40 and older who did not have a family history and were not symptomatic for prostate cancer so that the test was consistent with screening not case-finding.

Prostate Specific Antigen Test

The respondents were asked if they had ever received a PSA test. Because the question was phrased as having ever received a PSA test, we classified individuals as a YES on this variable to individuals who reported that their most recent test was within the past 3 years for those queried in 2016 and past 5 years for those queried in 2018, thereby making the test within the timeframe of the level D recommendation.

Having a Single Personal Doctor

The question on a regular source of care was asked "Do you have one person you think of as your personal doctor or health care provider?"

Advice and Recommendation From Health Care Providers on PSA Test

Several questions were asked about advice and recommendations related to PSA testing. The respondents were asked (a) whether a doctor, nurse, or other health professional ever talked with them about the advantages of the PSA test, (b) whether they talked with them about the disadvantages of the PSA test, and (c) whether a health professional ever recommended that they have a PSA test.

Covariates

We also included information on participant race/ethnicity, health insurance status, income, age, education, and location in the USA. Participants were classified into one of four regions in the US based off designations made by the US Census Bureau (14).

Analysis

All analyses were conducted in R version 3.6.3, and the complex survey design of the BRFSS survey was taken into account using the survey package to allow us to make population estimates of the US state and territorial population.

Chi-square tests were computed to assess potential differences in demographics and advice and recommendations for PSA tests and having a single personal doctor between those who received a PSA test and those who did not. Chi-square tests were also computed to assess differences in advice and recommendations concerning PSA testing between those who had one regular doctor and those who don't. Finally, the relationship between having a single personal doctor and receipt of a non-recommended PSA test while controlling for the potential confounding variables of race/ethnicity, health insurance status, education, income, and region in the USA was determined using multiple logistic regression.

RESULTS

Of the 232,548 men surveyed in our cohort (representing 36,919,766 individuals), 39.5% of them indicated they received a PSA test during a time frame where the USPSTF recommended the procedure as a level D. **Table 1** shows differences between those who did and did not receive a PSA test. Those who received PSA tests tended to be older, white, more educated, and married/cohabitating with a partner. The proportion of men

TABLE 1 | Characteristics of men who did and did not receive PSA screening.

	Received PSA Screen	Did Not Receive	*P*
Total	39.5%	60.5%	
Age 40–54	21.2%	70.0%	
55–69	50.9%	28.6%	
70+	27.9%	9.4%	<0.001
Race Non-Hispanic White	74.6%	63.8%	
Non-Hispanic Black	10.1%	10.3%	
Hispanic	10.2%	16.9%	
Other	5.0%	9.0%	<0.001
Income Less than $15,000	5.4%	11.3%	
$15,000–$24,999	10.7%	15.9%	
$25,000–$34,999	8.2%	10.2%	
$35,000–$49,999	13.2%	12.5%	
$50,000 or more	62.5%	50.1%	<0.001
Education High School or Less	33.4%	49.3%	
Some College	30.3%	26.8%	
College or Higher	36.3%	23.9%	<0.001
Marital Status Married/Cohabitate	75.0%	63.6%	
Never Married/ Separated/ Divorced	25.0%	36.4%	<0.001
Region West	20.8%	25.1%	
Midwest	20.8%	21.8%	
Northeast	17.1%	16.8%	
South East	39.6%	35.6%	<0.001
Have one regular doctor	86.0%	67.9%	<0.001
Discussed advantages to PSA	89.3%	20.3%	<0.001
Discussed disadvantages to PSA	40.4%	10.2%	<0.001
Doctor recommended PSA	87.5%	10.8%	<0.001

TABLE 2 | Discussion of PSA screening by continuity of care.

	Have a Regular Doctor	No Regular Doctor	*p*
Discussed advantages to PSA	53.3%	29.7%	<0.001
Discussed disadvantages to PSA	24.2%	13.5%	<0.001
Provider recommended Patient have a PSA	45.3%	25.3%	<0.001

who discussed either the advantages or disadvantages of PSA screening were substantially higher among those who received a PSA screening than those who did not, and discussing the advantages of the screening were twice as common as discussing the disadvantages. Similarly, the proportion of participants who reported receiving a PSA test reported that a doctor recommended they receive a PSA test at a much higher rate than those who did not receive a PSA test.

The results of Chi-square tests of independence between patients who have a single personal doctor and whether they discussed and advantages and disadvantages of PSA testing or were recommended PSA testing are shown in **Table 2**. Discussion of the merits of a PSA test and receiving a recommendation for a PSA test were both higher among those who reported having a single personal doctor.

The results of a logistic regression analysis on the association between having a single doctor and receiving a PSA test indicates a significant relationship even after controlling for potential confounding variables. The odds of receiving a PSA test is 2.90 (95% CI: 2.74–3.06) times higher among those with a single personal doctor than those who do not report having a single doctor. After adjustment, the odds of receiving a PSA test is 2.31 (95% CI: 2.17–2.46) times higher.

DISCUSSION

This study demonstrated that patients who received a non-recommended, low value preventive service (PSA testing) was strongly linked to patients having one person they think of as their personal doctor or health care provider. As noted previously, higher interpersonal continuity is associated with several factors associated with high quality of care, such as greater medication adherence and receipt of preventive services. Further, past research has shown that physician recommendations directly influences patient behavior and perceptions of risk (15, 16). This study extends the previous literature by examining recommendations and receipt of a test consistent with low quality of care and interpersonal continuity.

The finding that nearly 40% of patients received this level D recommendation test and the test was recommended by a large number of patients' regular physicians and health care providers is worrisome. A large number of patients are being tested inappropriately and a large number of physicians and health care providers are recommending a test whose results do not benefit and, in actuality, may harm these patients. In this instance, having a regular doctor appears to be associated with low value care that may lead to harmful additional testing and treatment.

The physicians ordering the test may have specific reasons for their recommendation and ordering of a low value test. One reason may be that they were unfamiliar with the USPSTF recommendations. However, our study design examined tests that were received during the time the PSA test was a level D and we limited the assessment of responses to a time frame that was at least 4 years after the recommendation was initially disseminated suggesting that the recommendation had been present in the community for a substantial amount of time. Other reasons for deviating from USPTF guideline may include personal reasons for deviating from guidelines, disagreement with guidelines and using other recommended guideline (such as the American Urological Association) in decision making. Between 2016 and 2018, the time of this study, the American Urological Association recommended no routine screening for men aged 40–54 but encouraged shared discussion between patients and physicians for men 55–69, advice not completely consistent with the USPSTF (17). Agreement with guidelines and behavior has been shown for recommended tests as well. Physician disagreement with guidelines has also been shown to be associated with the low level of screening for abnormal glucose, a USPSTF level B recommendation (18, 19).

The trust placed in a physician or other health care provider is paramount to a patient's decision-making regarding testing such as PSA. Patients will comply with recommendations from a physician. Our findings reinforce the importance of evidence-based guidelines in care. Evidence-based guidelines and standardization of practices are meant to minimize ordering of non-recommended testing. A variety of strategies have been used to try and minimize low value care. The case of imaging for low back pain provides some lessons (10, 20). For example, a best practice advisory or electronic medical record (EMR) alert is presented when a physician or other health care provider is attempting to order the test in question (21). Another possible strategy would be to restrict order placement within a health system without directly acknowledging the test is non-recommended.

An additional point that needs to be made is that these results have some implications for health equity. Even though these are low value, non-recommended tests, they are more likely to be recommended to White, high-income patients. This seems consistent with this patient population more likely to receive medical tests. The primary point here is that they are also more likely to receive inappropriate tests. Which has implications for both the distribution of healthcare resources but also the importance of evidence based medicine.

Several limitations to this study are present. Although we attempted to limit the length of time that respondents needed to remember to discuss the test, there still may have been somes recall bias. A second limitation is that we classified individuals who reported having more than one doctor as not having a regular doctor. It is possible that one physician among several seen by the patient may have had a strong continuous relationship with the patient. Third, we do not know the motivation or the knowledge base of the providers who recommended the tests. Fourth, it is possible that the patients suffer from hypochondriasis and pressured the physicians to order the test. This is possible but the prevalence of hypochondriasis is ∼5% and so this may have played a role but the prevalence is so low that it cannot explain the primary findings.

In conclusion, the results do not suggest that interpersonal continuity with one regular doctor is not important. Quite the contrary, these results reinforce the power of that relationship but the results also point to the impact, in a negative way, if the regular doctor does not follow evidence-based guideline consistent care. The patient physician relationship and trust in one's physician is critical in providing care but the concomitant responsibility that falls to physicians is to provide the best high quality care.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AM, BR, and PC: conceptualization. AM and BR: data analysis. AM, BR, EM, and PC: drafting of manuscript. All authors participated in the project and reviewed and approved the final submission.

REFERENCES

1. Mainous AG 3rd, Gill JM. The importance of continuity of care in the likelihood of future hospitalization: is site of care equivalent to a primary clinician? *Am J Public Health.* (1998) 88:1539–41. doi: 10.2105/AJPH.88.10.1539
2. Gill JM, Mainous AG 3rd. The role of provider continuity in preventing hospitalizations. *Arch Fam Med.* (1998) 7:352–7. doi: 10.1001/archfami.7.4.352
3. Gill JM, Mainous AG 3rd, Nsereko M. The effect of continuity of care on emergency department use. *Arch Fam Med.* (2000) 9:333–8. doi: 10.1001/archfami.9.4.333
4. Pereira Gray DJ, Sidaway-Lee K, White E, Thorne A, Evans PH. Continuity of care with doctors-a matter of life and death? A systematic review of continuity of care and mortality. *BMJ Open.* (2018) 8:e021161. doi: 10.1136/bmjopen-2017-021161
5. Chen CC, Cheng SH. Continuity of care and changes in medication adherence among patients with newly diagnosed diabetes. *Am J Manag Care.* (2016) 22:136–142.
6. Brookhart MA, Patrick AR, Schneeweiss S, Avorn J, Dormuth C, Shrank W, et al. Physician follow-up and provider continuity are associated with long-term medication adherence: a study of the dynamics of statin use. *Arch Intern Med.* (2007) 167:847–52. doi: 10.1001/archinte.167.8.847
7. Dossa AR, Moisan J, Guénette L, Lauzier S, Grégoire JP. Association between interpersonal continuity of care and medication adherence in type 2 diabetes: an observational cohort study. *CMAJ Open.* (2017) 5:E359–E64. doi: 10.9778/cmajo.20160063
8. Allen SM, Wieland S, Griffin J, Gozalo P. Continuity in provider and site of care and preventive services receipt in an adult Medicaid population with physical disabilities. *Disabil Health J.* (2009) 2:180–7. doi: 10.1016/j.dhjo.2009.06.004
9. Matulis JC 3rd, Schilling JJ, North F. Primary care provider continuity is associated with improved preventive service ordering during brief

visits for acute symptoms. *Health Serv Res Manag Epidemiol.* (2019) 6:1–5. doi: 10.1177/2333392819826262

10. Bouck Z, Calzavara AJ, Ivers NM, Kerr EA, Chu C, Ferguson J, et al. Association of low-value testing with subsequent health care use and clinical outcomes among low-risk primary care outpatients undergoing an annual health examination. *JAMA Intern Med.* (2020) 180:973–83. doi: 10.1001/jamainternmed.2020.1611
11. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* (2012) 157:120–34. doi: 10.7326/0003-4819-157-2-201207170-00459
12. US Preventive Services Task Force. Screening for prostate cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. (2018). 319:1901–13. doi: 10.1001/jama.2018.3710
13. Drazer MW, Huo D, Eggener SE. National prostate cancer screening rates after the 2012 US Preventive Services Task Force Recommendation discouraging prostate-specific antigen-based screening. *J Clin Oncol.* (2015) 33:2416–23. doi: 10.1200/JCO.2015.61.6532
14. National Center for Health Statistics (US). *Health, United States 2018*. Hyattsville, MD: National Center for Health Statistics (US) Figure, U.S. *Census Bureau: Four Geographic Regions and Nine Divisions of the United States*. Available online at: https://www.ncbi.nlm.nih.gov/books/NBK551093/figure/appii.fig1/
15. Post RE, Mainous AG 3rd, Gregorie SH, Knoll ME, Diaz VA, Saxena SK. The influence of physician acknowledgment of patients' weight status on patient perceptions of overweight and obesity in the United States. *Arch Intern Med.* (2011) 171:316–21. doi: 10.1001/archinternmed.2010.549
16. Mainous AG, Mansoor H, Rahmanian KP, Carek PJ. Perception of risk of developing diabetes among patients with undiagnosed prediabetes: the impact of health care provider advice. *Clin Diabetes.* (2019) 37:221–6. doi: 10.2337/cd18-0050
17. Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, et al. Early detection of prostate cancer: AUA Guideline. *J Urol.* (2013) 190:419–26. doi: 10.1016/j.juro.2013.04.119
18. Mainous AG 3rd, Tanner RJ, Scuderi CB, Porter M, Carek PJ. Prediabetes screening and treatment in diabetes prevention: the impact of physician attitudes. *J Am Board Fam Med.* (2016) 29:663–71. doi: 10.3122/jabfm.2016.06.160138
19. Mainous AG 3rd, Tanner RJ, Baker R. Prediabetes diagnosis and treatment in primary care. *J Am Board Fam Med.* (2016) 29:283–5. doi: 10.3122/jabfm.2016.02.150252
20. Morgan T, Wu J, Ovchinikova L, Lindner R, Blogg S, Moorin R. A national intervention to reduce imaging for low back pain by general practitioners: a retrospective economic program evaluation using Medicare Benefits Schedule data. *BMC Health Serv Res.* (2019) 19:983. doi: 10.1186/s12913-019-4773-y
21. Chen D, Bhambhvani HP, Hom J, Mahoney M, Wintermark M, Sharp C, et al. Effect of electronic clinical decision support on imaging for the evaluation of acute low back pain in the ambulatory care setting. *World Neurosurg.* (2020) 134:e874–e7. doi: 10.1016/j.wneu.2019.11.031

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

PERSPECTIVE
published: 31 March 2021
doi: 10.3389/fmed.2021.591201

A Brief Screening Tool for Opioid Use Disorder: EMPOWER Study Expert Consensus Protocol

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Specialty section:
This article was submitted to
Family Medicine and Primary Care,
a section of the journal
Frontiers in Medicine

Received: *04 August 2020*
Accepted: *23 February 2021*
Published: *31 March 2021*

Citation:
You DS, Mardian AS, Darnall BD, Chen C-YA, De Bruyne K, Flood PD, Kao M-C, Karnik AD, McNeely J, Porter JG, Schwartz RP, Stieg RL and Mackey SC (2021) A Brief Screening Tool for Opioid Use Disorder: EMPOWER Study Expert Consensus Protocol. Front. Med. 8:591201. doi: 10.3389/fmed.2021.591201

Growing concerns about the safety of long-term opioid therapy and its uncertain efficacy for non-cancer pain have led to relatively rapid opioid deprescribing in chronic pain patients who have been taking opioid for years. To date, empirically supported processes for safe and effective opioid tapering are lacking. Opioid tapering programs have shown high rates of dropouts and increases in patient distress and suicidal ideation. Therefore, safe strategies for opioid deprescribing that are more likely to succeed are urgently needed. In response to this demand, the EMPOWER study has been launched to examine the effectiveness of behavioral medicine strategies within the context of patient-centered opioid tapering in outpatient settings (https://empower.stanford.edu/). The EMPOWER protocol requires an efficient process for ensuring that collaborative opioid tapering would be offered to the most appropriate patients while identifying patients who should be offered alternate treatment pathways. As a first step, clinicians need a screening tool to identify patients with Opioid Use Disorder (OUD) and to assess for OUD severity. Because such a tool is not available, the study team composed of eight chronic pain and/or addiction experts has extended a validated screening instrument to develop a brief and novel consensus screening tool to identify OUD and assess for OUD severity for treatment stratification. Our screening tool has the potential to assist busy outpatient clinicians to assess OUD among patients receiving long-term opioid therapy for chronic pain.

Keywords: screening tool, opioid use disorder, long-term opioid use, opioid deprescribing, consensus protocol

Growing concerns about adverse effects and potential harms associated with long-term opioid use combined with lack of effectiveness data (1–3) have led national and state organizations to recommend reducing initiation of opioid medications for chronic pain (4, 5), and in some cases to impose mandated tapering (6, 7). To date, empirically supported processes for effective outpatient opioid tapering are lacking, potentially contributing to high rates of patient attrition (∼ 53.3%) (8, 9) and seeking other sources of opioids (10). While the literature remains nascent, a pilot study has demonstrated that prescribing physicians can help patients reduce opioid dose by about 50%, without an increase in pain intensity, by using a slow and individualized tapering method at outpatient settings (11). Intensive interdisciplinary programs (12) may be appropriate to reduce opioid medications for patients who have more medical or psychiatric complexity, although access to these programs is notably limited. Furthermore, clinical practice guidelines recommend that prescribing physicians routinely assess patients on long-term opioid therapy for opioid use disorder (OUD) (4). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5, OUD is defined as *a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems* (13) and exists on a continuum of severity (mild, moderate, and severe) (13). For patients with a diagnosis of OUD, particularly moderate-severe OUD, medication for addiction treatment (MAT) is recommended rather than opioid tapering (14, 15). Therefore, deprescribing approaches need to be tailored to an individual patient to optimize the likelihood of successful reduction.

One challenge in assessing OUD and its severity is that the American Psychiatric Association's DSM has modified various diagnostic terms over the years to define the spectrum of problematic opioid use. Historically, DSM-III (16) and DSM-IV (17) used two distinct diagnostic categories to describe problematic opioid use: *abuse* and *dependence*. The DSM-IV diagnostic term of *abuse* is defined by "a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of substances," and the definition of *dependence* is the same as that of OUD in DSM-5 (13). In contrast to the diagnoses of abuse and dependence in the DSM-IV, the DSM-5 has adopted a dimensional approach (18) in which OUD is now diagnosed along a continuum of mild, moderate and severe. This change requires clinicians to understand both the current and previous diagnostic classification systems as well as the degree of concordance between the two systems because cumulative data for evidence-based addiction treatment have been derived from the previous systems (19, 20) and new treatment studies and recommendations use the current version of DSM. Studies show that patients with DSM-5 moderate or severe OUD have a high degree of concordance with DSM-IV *opioid dependence*. Specifically, DSM-5 moderate to severe OUD yields 99% sensitivity and 99% positive predictive value (PPV) for DSM-IV opioid dependence (21). In contrast, only 18% of patients with mild OUD meet criteria for DSM-IV *opioid dependence* (21). As such, clinicians using a binary diagnostic approach (yes vs. no) for OUD will be limited in offering optimal treatments for diverse patients on long-term opioid therapy. Therefore, accurate and scalable systems to identify OUD and assess for OUD severity are critical for treatment stratification, but no such system or screening tool is currently available (22).

DEVELOPMENT OF THE EMPOWER STUDY EXPERT CONSENSUS PROTOCOL FOR OUD SCREENING

The EMPOWER study team first searched for a screening tool to identify OUD by severity categories when preparing to launch a study to investigate the effectiveness of behavioral medicine strategies within the context of patient-centered opioid tapering in outpatient settings (23). Our search yielded several self-report instruments that were validated and widely used to assess prescription opioid misuse and aberrant drug-taking behaviors such as the Current Opioid Misuse Measure (24), Pain Medication Questionnaire (25), and Prescription Opioid Misuse Index (26). There are also self-reports to screen for opioid abuse or dependence such as the NIDA-modified ASSIST (27), Drug Abuse Screening Test (28), Prescription Opioid Abuse Checklist (29), Prescription Drug Use Questionnaire (30), Addiction Behavior Checklist (31), and Rapid Opioid Dependence Screen (32). These existing tools intended for use in patients receiving long-term opioid therapy for chronic pain aim to identify opioid aberrant medication-related behavior, misuse, abuse, or dependence and either suffer from intolerably low sensitivity or are too lengthy for practical use in primary care settings with high patient volumes (33, 34). More importantly, these tools do not provide OUD severity for treatment stratification. After determining the lack of existing suitable tools, the EMPOWER study team decided to develop an efficient and scalable tool to assess OUD severity and identify the most appropriate care pathway.

When launching the EMPOWER study, the study team recognized that opioid tapering is not right for everyone. Patients with moderate or severe symptoms of OUD may be ill-suited to outpatient tapering and require different care pathways (14, 15). To identify OUD and assess OUD severity, the study team identified two candidate tools: the Tobacco, Alcohol, Prescription Medication, and Other Substance use (TAPS-1 and 2) (35) and DSM-5 OUD criteria (13). The TAPS-1 and−2 were developed to screen for a problematic use of alcohol, tobacco, and other substances in patients visiting primary care clinics. The TAPS uses a two-step screening process (35). In the first step, the four-item TAPS-1 is administered to all patients and screens for the use of four substance types in the past 12 months. Then, the appropriate items on TAPS-2 assessing the use of each substance in the past 3 months are administered to those who endorse other than "never" response on the TAPS-1 items. The TAPS has acceptable sensitivity (>0.70) and specificity (>0.85) when screening for problematic use of tobacco, alcohol and marijuana, but unacceptably low sensitivity (0.48) when screening for OUD specific to prescription opioid use (35). Alternatively, clinicians may use the 11 criteria for OUD defined by the DSM-5 OUD

TABLE 1 | The EMPOWER OUD screening protocol.

STEP 1:	**Administer the three items from the TAPS-2 Tool**: In the PAST 3 MONTHS,		
	1. Did you use a prescription opioid pain reliever (for example, Percocet, Vicodin) not as prescribed or that was not prescribed for you?	Yes	No
	2. Have you tried and failed to control, cut down or stop using opioid pain relievers?	Yes	No
	3. Has anyone expressed concern about your use of an opioid pain reliever?	Yes	No
If a patient marks YES to ANY of the 3 items, administer the Opioid Use Disorder Checklist below			
STEP 2:	**DSM-5 Opioid Use Disorder Checklist:** In the PAST 12 MONTHS,		
	1. Opioids are often taken in larger amounts or over a longer period than was intended.	Yes	No
	2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.	Yes	No
	3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.	Yes	No
	4. Craving, or a strong desire or urge to use opioids.	Yes	No
	5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.	Yes	No
	6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.	Yes	No
	7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.	Yes	No
	8. Recurrent opioid use in situations in which it is physically hazardous.	Yes	No
	9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.	Yes	No
	10. Tolerance, as defined by either of the following: • A need for markedly increased amounts of opioids to achieve intoxication or desired effect. • A markedly diminished effect with continued use of the same amount of an opioid. (**Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.**)	Yes	No
	11. Withdrawal, as manifested by either of the following: • The characteristic opioid withdrawal syndrome. • Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms. (**Note: This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.**)	Yes	No
	Sum the number of symptoms indicated above: SUM SCORE:		—————-
STEP 3:	**Interpretation of DSM-5 Opioid Use Disorder Checklist Results**		
	No OUD: Presence of 0-1 symptom.		
	• OK for outpatient opioid tapering		
	Mild: Presence of 2–3 symptoms. 305.50 (F11.10)		
	• OK to consider for outpatient opioid tapering, or intensive rehabilitation program for opioid tapering, or referral for OUD treatment		
	Moderate: Presence of 4–5 symptoms. 304.00 (F11.20)		
	• Referral for OUD treatment		
	Severe: Presence of 6 or more symptoms. 304.00 (F11.20)		
	• Referral for OUD treatment		

For the EMPOWER study, STEP 2 items are adapted into questions.

(13). Yet, the DSM-5 criteria are rarely used to assess OUD (36) because it is not practical to conduct the clinical interview for every patient on long-term opioid therapy in a busy clinic.

THE EMPOWER CONSENSUS PROTOCOL FOR OUD SCREENING AND TREATMENT STRATIFICATION

The EMPOWER study team composed of eight chronic pain and/or addiction experts developed a novel consensus protocol to identify OUD and assess for OUD severity in patients taking long-term prescription opioids for chronic pain. The study team modified the two-step process used in the TAPS. To increase sensitivity, the team, in collaboration with the authors of TAPS (35), decided to use all three opioid items in the TAPS-2 as initial screening items, instead of using the TAPS-1. Next, to optimize specificity and assess for OUD severity, the DSM-5 OUD criteria were used in the form of a checklist. Therefore, the EMPOWER consensus protocol for screening and distinguishing severity of OUD includes (**Table 1**): (Step 1) all three opioid items from the TAPS-2 and (Step 2) the DSM-5 Criteria Checklist for OUD to (Step 3) stratify the severity of OUD. Step 1 can be self-administered in a paper format to all patients on opioid therapy. Based on patients' responses on Step 1, a clinician completes the checklist during the in-person clinical interview only with those endorsing any of the 3 screening items (Step 2).

The opioid-prescribing clinician has historical knowledge of the opioid and other drug taking behavior of their patients; this, combined with the medical record and prescription drug monitoring databases, can serve as collateral information in determining a diagnosis and its corresponding severity. Clinicians are reminded of the caveat for tolerance and withdrawal symptoms in **Table 1**, Step 2. These two underlined items are not considered criteria for OUD when opioids are taken as prescribed; rather, tolerance and withdrawal symptoms are indices of expected normal physiologic adaptation to persistent opioid use, which is distinct from addiction or opioid use disorder.

STRENGTH AND LIMITATIONS OF THE EMPOWER STUDY EXPERT CONSENSUS PROTOCOL

In the absence of existing validated methods, we provide our consensus screening protocol in response to the urgent societal need for such tools so that (a) clinicians may offer appropriate treatments to a heterogeneous patient population receiving long-term opioid therapy for chronic pain (**Table 1**, Step 3), and (b) researchers can study characteristics and treatment outcomes of patients with appropriate opioid use and across the spectrum of OUD severity. Our screening protocol can also facilitate efficient evaluation of eligibility for our multi-site pragmatic study of patient-centered opioid tapering (23). We are currently investigating the validity and reliability of administrating our protocol in an electronic format using an open-source learning healthcare system (https://choir.stanford.edu/). Additionally, we will examine data for patients who are screened as having no or mild OUD severity using our two-step protocol and will characterize their opioid taper and pain reduction outcomes.

Achieving optimal results for prescription opioid tapering requires careful assessment of patients and their opioid-taking behaviors because such assessment ensures that effective individualized opioid tapering or opioid addiction treatments are delivered to patients according to their individual needs. The EMPOWER study team found a gap in existing approaches for practical, individualized opioid deprescribing due to the lack of a brief tool to identify OUD and stratify severity for patients with chronic pain receiving long-term opioid therapy. Our study team has developed a streamlined consensus protocol to identify OUD and assess for OUD severity for clinical and research use.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

DY: conceptualization, writing—original draft, review, and editing. AM: conceptualization, methodology, writing—original draft, and review and editing. BD: conceptualization, methodology, writing—review and editing, and project administration. C-YC, KD, PF, AK, JM, JP, RPS, and RLS: conceptualization, methodology, writing—review and editing. M-CK: conceptualization and methodology. SM: conceptualization, methodology, writing—review and editing, project administration, and supervision. All authors: contributed to the article and approved the submitted version.

FUNDING

This work was supported through a Patient-Centered Outcomes Research Institute (PCORI) Award (OPD-1610-37007) (PI, BD). All statements in this report are solely those of the authors and do not necessarily represent the views of the PCORI, its Board of Governors or Methodology Committee. DY (K23 DA048972) and SM (K24DA029262) received funding from the National Institute on Drug Abuse. SM also received Redlich Pain Endowment.

REFERENCES

1. Glanz JM, Binswanger IA, Shetterly SM, Narwaney KJ, Xu S. Association between opioid dose variability and opioid overdose among adults prescribed long-term opioid therapy. *JAMA Netw Open.* (2019) 2:e192613. doi: 10.1001/jamanetworkopen.2019.2613
2. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med.* (2015) 162:276–86. doi: 10.7326/M14-2559
3. Hoffman EM, Watson JC, St Sauver J, Staff NP, Klein CJ. Association of long-term opioid therapy with functional status, adverse outcomes, and mortality among patients with polyneuropathy. *JAMA Neurol.* (2017) 74:773–9. doi: 10.1001/jamaneurol.2017.0486
4. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain -United States, 2016. *JAMA.* (2016) 315:1624–45. doi: 10.1001/jama.2016.1464
5. U.S. Department of Health and Human Services. HHS guide for clinicians on the appropriate dosage reduction or discontinuation of long-term opioid analgesics. Available online at: https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf Published October (2019) (accessed June 25, 2020).
6. Oregon Health Authority. Guideline note 60: opioid prescribing for conditions of the back and spine. prioritized list of health services. Available online at: https://www.oregon.gov/oha/HPA/DSI-HERC/PrioritizedList/7-1-2016_Prioritized_List_of_Health_Services.pdf (accessed June 25, 2020).
7. Kertesz SG, Satel SL, DeMicco J, Dart RC, Alford DP. Opioid discontinuation as an institutional mandate: questions and answers on why we wrote to the Centers for Disease Control and Prevention. *Subst Abus.* (2019) 40:466–8. doi: 10.1080/08897077.2019.1635973
8. Kurita G, Højsted J, Sjøgren P. Tapering off long-term opioid therapy in chronic non-cancer pain patients: a randomized clinical trial. *Eur J Pain.* (2018) 22:1528–43. doi: 10.1002/ejp.1241

9. Fiellin DA, Schottenfeld RS, Cutter CJ, Moore BA, Barry DT, O'Connor PG. Primary care–based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. *JAMA Intern Med.* (2014) 174:1947–54. doi: 10.1001/jamainternmed.2014.5302
10. Manhapra A, Arias AJ, Ballantyne JC. The conundrum of opioid tapering in long-term opioid therapy for chronic pain: a commentary. *Subst Abus.* (2018) 39:152–61. doi: 10.1080/08897077.2017.1381663
11. Darnall BD, Ziadni MS, Stieg RL, Mackey IG, Kao M-C, Flood P. Patient-centered prescription opioid tapering in community outpatients with chronic pain. *JAMA Intern Med.* (2018) 178:707–8. doi: 10.1001/jamainternmed.2017.8709
12. Cunningham JL, Evans MM, King SM, Gehin JM, Loukianova LL. Opioid tapering in fibromyalgia patients: experience from an interdisciplinary pain rehabilitation program. *Pain Med.* (2016) 17:1676–85. doi: 10.1093/pm/pnv079
13. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association (2013).
14. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. *J Addict Med.* (2015) 9:358–67. doi: 10.1097/ADM.0000000000000166
15. Oesterle TS, Thusius NJ, Rummans TA, Gold MS. Medication-assisted treatment for opioid-use disorder. *Mayo Clin Proc.* (2019) 94:2072–86. doi: 10.1016/j.mayocp.2019.03.029
16. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed. Arlington, VA: American Psychiatric Association (1980).
17. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association (1994).
18. Narrow WE, Kuhl EA. Dimensional approaches to psychiatric diagnosis in DSM-5. *J Ment Health Policy Econ.* (2011) 14:197–200.
19. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev.* (2009) 3:CD002209. doi: 10.1002/14651858.CD002209.pub2
20. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev.* (2014) 2:CD002207. doi: 10.1002/14651858.CD002207.pub4
21. Peer K, Rennert L, Lynch KG, Farrer L, Gelernter J, Kranzler HR. Prevalence of DSM-IV and DSM-5 alcohol, cocaine, opioid, and cannabis use disorders in a largely substance dependent sample. *Drug Alcohol Depend.* (2013) 127:215–9. doi: 10.1016/j.drugalcdep.2012.07.009
22. Wakeman SE. Diagnosis and treatment of opioid use disorder in 2020. *JAMA.* (2020) 323:2082–3. doi: 10.1001/jama.2020.4104
23. Darnall BD, Mackey SC, Lorig K, Kao M-C, Mardian A, Stieg R, et al. Comparative effectiveness of cognitive behavioral therapy for chronic pain and chronic pain self-management within the context of voluntary patient-centered prescription opioid tapering: the empower study protocol. *Pain Med.* (2019) 21:1523–31. doi: 10.1093/pm/pnz285
24. Butler SF, Budman SH, Fernandez KC, Houle B, Benoit C, Katz N, et al. Development and validation of the current opioid misuse measure. *Pain.* (2007) 130:144–56. doi: 10.1016/j.pain.2007.01.014
25. Holmes CP, Gatchel RJ, Adams LL, Stowell AW, Hatten A, Noe C, et al. An opioid screening instrument: long-term evaluation of the utility of the pain medication questionnaire. *Pain Pract.* (2006) 6:74–88. doi: 10.1111/j.1533-2500.2006.00067.x
26. Knisely JS, Wunsch MJ, Cropsey KL, Campbell ED. Prescription Opioid Misuse Index: a brief questionnaire to assess misuse. *J Subst Abuse Treat.* (2008) 35:380–6. doi: 10.1016/j.jsat.2008.02.001
27. National Institute on Drug Abuse. NIDA-modified ASSIST V2.0. 2013. The survey is available online at: https://www.drugabuse.gov/sites/default/files/pdf/nmassist.pdf (accessed July 03, 2021).
28. Yudko E, Lozhkina O, Fouts A. A comprehensive review of the psychometric properties of the drug abuse screening test. *J Subst Abuse Treat.* (2007) 32:189–98. doi: 10.1016/j.jsat.2006.08.002
29. Chabal C, Erjavec MK, Jacobson L, Mariano A, Chaney E. Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors. *Clin J Pain.* (1997) 13:150–5. doi: 10.1097/00002508-199706000-00009
30. Compton PA, Wu SM, Schieffer B, Pham Q, Naliboff BD. Introduction of a self-report version of the Prescription Drug Use Questionnaire and relationship to medication agreement noncompliance. *J Pain Symptom Manage.* (2008) 36:383–95. doi: 10.1016/j.jpainsymman.2007.11.006
31. Wu SM, Compton P, Bolus R, Schieffer B, Pham Q, Baria A, et al. The addiction behaviors checklist: validation of a new clinician-based measure of inappropriate opioid use in chronic pain. *J Pain Symptom Manage.* (2006) 32:342–51. doi: 10.1016/j.jpainsymman.2006.05.010
32. Wickersham JA, Azar MM, Cannon CM, Altice FL, Springer SA. Validation of a brief measure of opioid dependence: the Rapid Opioid Dependence Screen (RODS). *J Correctional Health Care.* (2015) 21:12–26. doi: 10.1177/1078345814557513
33. Moore TM, Jones T, Browder JH, Daffron S, Passik SD. A comparison of common screening methods for predicting aberrant drug-related behavior among patients receiving opioids for chronic pain management. *Pain Med.* (2009) 10:1426–33. doi: 10.1111/j.1526-4637.2009.00743.x
34. Jones T, Moore T, Levy JL, Daffron S, Browder JH, Allen L, et al. A comparison of various risk screening methods in predicting discharge from opioid treatment. *Clin J Pain.* (2012) 28:93–100. doi: 10.1097/AJP.0b013e318225da9e
35. McNeely J, Wu L-T, Subramaniam G, Sharma G, Cathers LA, Svikis D, et al. Performance of the tobacco, alcohol, prescription medication, and other substance use (TAPS) tool for substance use screening in primary care patients. *Ann Intern Med.* (2016) 165:690–9. doi: 10.7326/M16-0317
36. Marsden J, Tai B, Ali R, Hu L, Rush AJ, Volkow N. Measurement-based care using DSM-5 for opioid use disorder: can we make opioid medication treatment more effective? *Addiction.* (2019) 114:1346–53. doi: 10.1111/add.14546

Conflict of Interest: RPS reports serving as a consultant to Verily Life Sciences, Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers
in Public Health

ORIGINAL RESEARCH
published: 31 May 2021
doi: 10.3389/fpubh.2021.504998

Performing Through Privatization: An Ecological Natural Experiment of the Impact of the Swedish Free Choice Reform on Ambulatory Care Sensitive Conditions

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OPEN ACCESS

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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Public Health

Received: *28 January 2021*
Accepted: *03 May 2021*
Published: *31 May 2021*

Citation:
Mosquera PA, San Sebastian M, Burström B, Hurtig AK and Gustafsson PE (2021) Performing Through Privatization: An Ecological Natural Experiment of the Impact of the Swedish Free Choice Reform on Ambulatory Care Sensitive Conditions. Front. Public Health 9:504998. doi: 10.3389/fpubh.2021.504998

Background: In 2010, Sweden opened up for establishment of privately owned primary health care providers, as part of a national Free Choice in Primary Health Care reform. The reform has been highly debated, and evidence on its effects is scarce. The present study therefore sought to evaluate whether the reform have impacted on primary health care service performance.

Methods: This ecological register-based study used a natural experimental approach through an interrupted time series design. Data comprised the total adult population of the 21 counties of Sweden 2001–2009 (pre-intervention period) and 2010–2016 (post-intervention period). Hospitalizations and emergency department visits for ambulatory care sensitive conditions (ACSC) were used as indicators of primary health care performance. Segmented regression analysis was used to assess the effects of the reform, in Sweden as a whole, as well as compared between counties grouped by (i) change in private provision pre- to post reform; (ii) the timing of the implementation; and (iii) sustained presence of private providers both pre- and post-reform.

Results: The results suggest that, following the introduction of the reform in Sweden as a whole, the trends in total hospitalizations rates were slowed down by 1.0% albeit acute emergency visits increased 1.1% more rapidly after the introduction of the reform. However, we found no evidence of more beneficial effects in counties where the reform had been implemented more ambitiously, specifically those with a larger increase in private primary care providers, or where the reform was introduced early and thus had longer time effects to emerge. Lastly, counties with a sustained high presence of private primary care providers displayed the least favorable development when it comes to ACSC.

Conclusion: Taken together, the present study does not support that the Swedish Free Choice reform has improved performance of the primary care delivery system in Sweden, and suggests that high degree of private provision may involve worse performance and higher care burden for specialized health care. Further evaluations of the consequences of the reform are dire needed to provide a comprehensive picture of its intended and unintended impact on health care provision, delivery and results.

Keywords: health system reform, ambulatory care sensitive conditions, natural experiment, interrupted time series analysis, Sweden

BACKGROUND

The Swedish health care system has historically been predominantly public, managed and provided by the 21 county councils, but has since the 1990s gradually increased its market-orientation, particularly within primary health care (1). In 2007–2009, a few counties introduced primary care choice models for patients and opened up the market for new establishment of private primary health care providers. On January 1st 2010, Sweden opened up for the establishment of privately owned primary health care (PHC) providers, as part of a national Free Choice in PHC (FCPHC) reform. The reform was implemented nationally in conjunction with a Health Care Guarantee law ensuring the promptness of access to health care [1]. While such notable changes in the health system can be expected to impact on health care access, quality and performance, the national effects of the reform, and particularly the results of the health care, have been poorly studied (1–3).

The FCPHC reform consisted of two main parts, directed at providers and patients, respectively. First, the reform allowed all PHC providers that met certain basic requirements to establish a health care center at a geographical location of their choice; and second, it allowed patients to choose their PHC provider, which in turn served as a basis for capitation payment to the providers (4). The reform thus involved a shift in the responsibility of the PHC centers; from the entire population in a catchment area, to only the patients listed at that specific center. The main motivations underlying the reform were to expand the PHC provision and to introduce competition between health care centers, and thereby improve efficiency and quality of services, which ostensibly would lead to increased access and stronger status for the patients (2, 5). An increased access and efficiency could in turn be expected to involve a shift of burden of care from secondary and tertiary to primary care.

The reform has been a matter of contention even since before its implementation. One reason for this is that the introduction of the reform embodies an underlying ideological shift from a more egalitarian to a more libertarian view of health care organization (5). Other concerns were also raised about reduced continuity, increased fragmentation and impaired equity in the provision of services (4, 6–8). Initial reports by public agencies indicated that implementation of the reform was coupled with increased new establishments of private health care providers, increased number of health care visits, and a maintained level of quality, but with an inconclusive and debated effect on the actual gains in terms of health care performance (3, 4, 8). Moreover, recent studies including those summarized in a scoping review in 2017 suggested that the increased number of PHC visits had been concentrated particularly to areas with a high patient-provider ratio and to socioeconomically advantaged groups (2, 9, 10). When it comes to quality and performance, one early assessment (up to 2013) found small improvements of patient' satisfaction with care but no significant effects on avoidable hospitalizations or satisfaction with access to care (9). Furthermore, it has also been suggested that the reform had negatively affected provision of services for patients with complex needs, which may in turn have lessened the impact of PHC on overall population health (2, 11).

The introduction of similar choice policies and market competition in other European health systems has, like in Sweden, been controversial. The accumulated evidence on the effects is so far insufficient and inconclusive, and has been limited to outcomes related to health service provision such as waiting times and patient satisfaction (4, 12–14). Therefore, knowledge about how PHC service delivery performance is affected by the reform is dearly needed for public health practice and policy-making. Particularly in light of the possible detrimental effects of the reform on equity provision, whether the reform has actually led to improvement in overall PHC performance is key evidence to make a comprehensive assessment of its impact.

While there are many alternative approaches to evaluate policies and interventions, there is a growing interest from epidemiologists and public health researchers in using natural experiments. Natural experiment is an approach referring to empirical studies that evaluate the effects of interventions through detailed comparisons of contrasting cases (e.g., exposed/non-exposed), where the intervention is not allocated by the researcher but naturally occurring (15–19). In the Swedish case, the FCPHC reform permitted and sought to stimulate—but did not enforce—increased establishment of private PHC providers. Its introduction indeed led to large shifts from public to private PHC provision in certain counties, but minimal changes in others. Moreover, a number of counties had already introduced free choice models for patients years before the FCPHC reform implementation, and some of them had had a sustained and continuous high presence of private providers over time. This unintended variation in the de facto implementation of the reform creates a design opportunity to detect and disentangle potential reform effects from underlying secular trends according to a natural experimental approach.

Abbreviations: ACSC, Ambulatory Care Sensitive Conditions; ACSC-H, Ambulatory Care Sensitive Conditions-Hospitalizations; ACSC-EV, Ambulatory Care Sensitive Conditions-Emergency Visits; FCPHC, Free Choice in Primary Health Care; ICD, International Classification of Disease; ITSA, Interrupted Time Series Analysis; PHC, Primary Health Care.

The present study sought to utilize a natural experiment design to evaluate whether the reform have impacted PHC service performance at the national level, and if the impact varied by regional differences in the de facto implementation of the reform. We measured ambulatory care sensitive conditions (ACSC), which are widely used to assess overall access, quality and performance of the primary care delivery system (20, 21). Hospitalizations for ACSCs are commonly divided into acute and chronic ACSCs, which reflect different aspect of PHC (20). While hospitalizations for acute conditions (e.g., ear infection) can reflect suboptimal timeliness of PHC and are potentially preventable by e.g., early diagnosis and prompt treatment, hospitalizations for chronic diseases (e.g., diabetic complications) can relate more to poor effectiveness of PHC, as it relies on continuous monitoring, patient education and control (20). We hypothesize that the reform has led to reduced rates of avoidable hospitalizations and emergency department visits for ACSC (for example through the increase of access and number of visits to primary care). We further hypothesize that the effects may show some regional variations in impact according to different levels of exposure in de facto implementation of the reform (i.e., greater improvements in counties with more marked and enduring implementation).

With these hypotheses as a point of departure, the present study aimed to examine: (1) whether the FCPHC reform has led to national decreased rates of avoidable hospitalizations and emergency visits in Sweden 2001–2016, and (2) whether the effects of the reform shows regional variations depending on (a) increase in public/private ratio (b) timing of implementation of the reform, and (c) sustained presence of private PHC providers.

MATERIALS AND METHODS

Design and Data

This ecological register-based study was based on data on the total adult population of the 21 counties of Sweden aged 20 years and older for the time period 2001–2016. As a majority of young Swedes still go to secondary school and lives with their parents up to the age of 19 years, 20 years was chosen as the youngest age. We employed a natural experimental approach to assess the effects of the FCPHC reform; specifically, an interrupted time series design with segmented regression analysis.

Interrupted time series analysis (ITSA) is the strongest quasi-experimental approach for evaluating longitudinal effect of public health policies introduced at a population level over a clearly defined period of time (16–19). A single-group ITSA estimates an intervention effect by the trends in the outcome over a period of time following the intervention, as compared to the trends before the intervention (19), whereas a multiple-group ITSA additionally compares the trends before and after the intervention between a treated group and one or more control groups (unexposed or less exposed) (19).

In the present study we used single-group ITSA to test the overall national reform effects, and a series of multiple-group ITSA comparing counties with different levels of the de facto implementation of the reform, in order to more specifically attribute any effects to the FCPHC reform.

Aggregated county-level data was collected for each year of observation 2001–2016. Outcome data stratified by sex and 5-year age groups was retrieved from the National Patient Register of the National Board of Health and Welfare. Total population numbers (for denominators) were retrieved from publicly available data from Statistics Sweden; and information on numbers of annual private and public PHC centers per county and hospital beds per 1,000 population were gathered from the Swedish Association of Local Authorities and Regions.

The studies involving human participants were reviewed and approved by The Regional Ethical Review Board in Umeå (approval ref. no. 2017/229-31). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Variables

Intervention Operationalization

To operationalize the FCPHC reform, contrasting groups of counties were created according to three characteristics of the de facto implementation of the reform (1, 8).

Magnitude of Implementation

While the reform covered the entire Sweden from January 1st 2010, the regional context varies when it comes to the attractiveness for private health care providers to establish (1). As a results, the de facto implementation of the reform as expressed in a relative shift from public to private providers remained very unevenly distributed across the country, with some counties experiencing large increase in the proportion of private providers, while in other counties the presence of private providers did not change noticeably.

A number of steps were conducted to operationalize the magnitude, with the purpose of identifying a population for whom the introduction of reform indeed involved a large increase in the exposure to private PHC provision (high magnitude of implementation), and a contrasting population for whom the reform has not involved any major change in this regard (low magnitude of implementation). First, the proportion of private PHC centers was calculated for each county (i.e., Number of private PHC centers/Number of private + Number of public PHC centers). Second, the change in the proportion of PHC from before to after the reform was calculated for each county, using the year before the implementation of the reform (i.e., 2009 for the majority of counties) as the baseline proportion, and the average proportion across the years following the reform (i.e., 2010–2016 for the majority of counties) as the post-reform proportion. As absolute and relative changes may capture different aspects of increased/decreased privatization, both the absolute (before – after) and relative (before/after) change in the proportion of private PHC centers from before to after the reform were calculated separately. Third, the 21 counties were ranked according to the absolute and relative changes, respectively, and then a mean of the two rankings was calculated. Fourth and last, the mean rank was divided into tertiles. The top tertile encompassing the seven counties with greatest increase in the private proportion from before to after the reform (>10% absolute increase and >60% relative increase) was categorized

TABLE 1 | Counties by groups of intervention exposure.

County	Number of health care providers		% Private providers		Classification		
	Before[a]	After[b]	Before[a]	After[b]	Magnitude	Time	Sustained presence before/after*
Jönköping	32	50	6.3	37.5	High	Late	Low/Low
Södermanland	21	26	9.5	33.7	High	Late	Low/Low
Dalarna	30	29	0.0	15.3	High	Late	Low/Low
Kronoberg	26	32	11.5	32.1	High	Early	Low/Low
Uppsala	41	42	24.4	48.5	High	Early	Low/High
Västra Götaland	157	202	25.5	43.7	High	Early	Low/High
Värmland	35	38	11.4	25.0	High	Late	Low/Low
Norrbotten	33	33	3.0	12.4	Middle	Late	Low/Low
Skåne	125	150	27.2	42.2	Middle	Early	Low/High
Gävleborg	37	40	18.9	33.2	Middle	Late	Low/Low
Stockholm	171	202	49.1	64.1	Middle	Early	High/High
Västernorrland	26	32	23.1	35.7	Middle	Late	Low/Low
Östergötland	42	43	14.3	20.4	Middle	Early	Low/Low
Västerbotten	36	38	11.1	17.1	Middle	Late	Low/Low
Blekinge	21	21	33.3	39.2	Low	Late	High/Low
Halland	44	47	43.2	48.6	Low	Early	High/High
Västmanland	30	30	53.3	58.3	Low	Early	High/High
Gotland	8	7	25.0	27.2	Low	Late	Low/Low
Jämtland	26	26	15.4	17.0	Low	Late	Low/Low
Örebro	29	29	13.8	13.7	Low	Late	Low/Low
Kalmar	46	39	41.3	31.9	Low	Late	High/Low
Total Sweden	1095	1163	28.5	41.4	N/A	N/A	N/A

[a]Year before implementation of the reform.
[b]Average across the years after implementation of the reform.
**Higher than Swedish average.*

as high magnitude (=1); the lowest tertile of the seven counties with the smallest increase (or even a decrease) in the private proportion (<6% absolute increase and <15% relative increase) was categorized as low magnitude (=0). To ensure a clear contrast for the comparison, the middle tertile consisting of counties with a moderate change in the private proportion was excluded of the comparison (see **Table 1**; counties by groups based on 2016 figures).

Timing of Implementation

A number of counties introduced a free choice model and opened up the market for new establishment of private health care providers before the national implementation of the FCPHC reform; in 2007 (Halland), 2008 (Stockholm and Västmanland) and 2009 (Uppsala, Kronoberg, Skåne, Östergötland and Västra Götaland) (22). The populations of these eight counties were thus exposed to free choice and private PHC provision before the rest of the Swedish population, and were categorized as early implementers (=1). The other 13 counties, which implemented in 2010 when the reform become national, were categorized as late implementers (=0).

Sustained Presence

A third group of counties was identified based on sustained high presence of private PHC providers over the entire observation period. These counties had in effect already exemplified a model prescribed by the reform. They were special in that they were highly exposed to private health care provision both in time and magnitude, but at the same time a saturated market may have diminished opportunities for incremental changes in the establishment of private providers following the reform. Three counties had a private/public proportion above the national mean both before (28.5%) and after (41.4%) the reform, and were therefore categorized as having a sustained presence (=1), while 13 counties with a lower than national average in private/public proportion both before and after the reform were categorized as having a low presence of private providers (=0). Counties that did not have consistently higher or lower proportions than national averages were excluded of the comparison.

Outcome

Hospitalizations and emergency department visits for ambulatory care sensitive conditions (ACSC) were used as outcomes. ACSC are a set of acute and chronic health conditions that potentially can be managed with timely and effective primary health care, reducing the need for or avoiding secondary care such as hospitalization and emergency department visits (20, 21). These outcomes were chosen as global and results-oriented indicators of PHC performance as they are widely used to assess access, quality and performance of the primary care delivery system (20, 23).

The identification of ACSC was done through International Classification of Disease (ICD-10) codes and categorized by the Swedish National Board of Health and Welfare classification of avoidable hospitalizations. This classification has been used for monitoring and research on primary care performance and quality in Sweden (24, 25) and is comparable to some other international classifications (26).

Chronic ACSC include diabetes complications, hypertension, heart failure, chronic obstructive pulmonary disease, angina, anemia and asthma. Acute ACSC include diarrhea, bleeding ulcers, epileptic seizures, pelvic inflammatory diseases, pyelonephritis and ear, nose and throat infection (20). Hospitalizations for ACSC (ACSC-H, "avoidable hospitalizations") were defined as all inpatient stays for any of the conditions listed above. Emergency department visits due to ACSC (ACSC-EV) were defined using as a proxy all ambulatory care visits to hospital that have not been scheduled in advance, and that have as diagnosis any of the conditions listed above. Acute and chronic avoidable hospitalizations and emergency department visits were analyzed separately as the temporal effects of the reform can be expected to differ for these groups of disease.

Analysis

Age-standardized hospitalization and emergency visits rates (per 100,000 inhabitants) were calculated across the period 2001–2016, using Swedish total population 2016 as standard.

Corresponding to the first aim, we first estimated the change in trends of ACSC-H and ACSC-EV in Sweden as a whole through single-group ITSA. Corresponding to the second aim we subsequently performed multiple-group ITSA for comparisons between contrasting groups of counties with different levels of the de facto implementation of the reform as follows: (a) High vs. low magnitude of implementation; (b) Early vs. late timing of implementation; and (c) High vs. low sustained presence of private providers. The pre-intervention period was defined as 2001–2009 and post-intervention period 2010–2016. Time series for each outcome (avoidable hospitalizations and emergency visits) were plotted by 6-month periods, giving 18 points before and 14 points after the reform implementation. Analysis for each outcome was done by total number of cases as well as separately by acute and chronic conditions, totaling six single-group and eighteen multiple-group ITSA models.

Preliminary analysis suggested that our data was moderately overdispersed, and we therefore fit our segmented regression analysis with negative binomial regression models, which is an approach that has been shown to be appropriate for modeling time series of counts data when there is evidence of overdispersion (27). The presence of autocorrelation within the data was examined by plotting the residuals and robust standard errors were calculated to control for mild violations of underlying assumptions. Rate ratios (RR) and the 95% confidence intervals (95% CI) were obtained using the Stata 15.0 software.

Since the number of available hospital beds could be a particularly important confounder for hospitalization rates (25), ACSC-H models were adjusted for number of hospital beds per 1,000 inhabitants. Additional confounders that were considered in the analysis were the median income, the percentage of people born outside Sweden and percentage of people who attained highest level of education per county. There were no significant differences among the groups for any of these characteristics so they were excluded from the main analysis.

Auxiliary Analyses

In addition to the six single-group ITSA and 18 multiple-group ITSA carried out as the main analyses, a number of additional analyses were run. First, the models were rerun stratified by sex (women and men; in total 48 analyses) and broad age groups (<65 and >65 years; 48 analyses), to explore whether the overall results were valid across gender and age.

Moreover, to explore the sensitivity of the results to the choice of cut-offs for the intervention operationalization and the time point to evaluate the reform, a series of analyses were carried out using alternative cut-offs. For the intervention operationalization, the cut-off for early implementation was changed to at least 1 year before 2010 (i.e., implemented before 2009 rather than before 2010; in total 24 analyses), and for the magnitude of implementation the cut-off was changed to the national average, including all counties (rather than comparing the highest and lowest tertile of counties; 24 analyses). For the time point to evaluate the reform, the year was changed to 2011 instead of 2010, allowing for a longer period of implementation (24 analyses).

Since the auxiliary analyses comprised a large set of models and led to similar conclusions as the main analyses, a summary of the results are reported in the Results section, and details are available on request.

RESULTS

Overall Impact of the Reform in Sweden

A summary of results of the single-group ITSA, corresponding to the first aim of estimating the overall impact of the FCPHC reform on ACSC outcomes in Sweden as a whole, are reported in **Table 2** and **Figure 1**.

The 9 years prior to the introduction of the reform (the "pre-trend"), saw a universal increase in ACSC outcomes, both for hospitalizations and emergency visits, and for chronic as well as acute ACSC. These trends were significant for all outcomes except for chronic ACSC hospitalization, and the largest increases were seen for acute ACSC hospitalizations and emergency visits, corresponding to an estimated 2.2 and 1.7% average semi-annual increase in the age-adjusted rates, respectively.

Upon the introduction of the reform in 2010, the trends changed for the different outcomes. The trend of total ACSC hospitalization flattened out after introducing the reform (2011–2016), as seen in insubstantial and non-significant 0.1% decrease (post-trend). This shift in trend from before to after the introduction of the reform was significant (pre-post trend), estimated at an average 1% lower increase in the semi-annual hospitalization rate, relative to the pre-intervention trend. This effect seemed to be driven by post-reform reductions in hospitalizations due to chronic, rather than acute, ACSC.

TABLE 2 | Segmented regression analysis of ACSC-H and ACSC-EV trends in Sweden before and after reform implementation.

Sweden	ACSC hospitalizations[a]			ACSC emergency visits		
	Total RR (95% CI)	Chronic RR (95% CI)	Acute RR (95% CI)	Total RR (95% CI)	Chronic RR (95% CI)	Acute RR (95% CI)
Pre-trend (2001–2009)	1.009 (1.003, 1.015)	1.004 (0.997, 1.011)	1.022 (1.015, 1.028)	1.013 (1.009, 1.017)	1.011 (1.006, 1.016)	1.017 (1.014, 1.020)
Post trend (2010–2016)	0.999 (0.990, 1.009)	0.987 (0.977, 0.998)	1.025 (1.012, 1.037)	1.014 (1.011, 1.018)	1.004 (0.999, 1.009)	1.029 (1.025, 1.032)
Pre-post trend (2001–2009 vs. 2010–2016)	0.990 (0.985, 0.995)	0.983 (0.977, 0.989)	1.003 (0.997, 1.009)	1.001 (0.996, 1.007)	0.993 (0.986, 1.001)	1.011 (1.007, 1.015)

[a] *Adjusted for No. of hospital beds per year and county.*

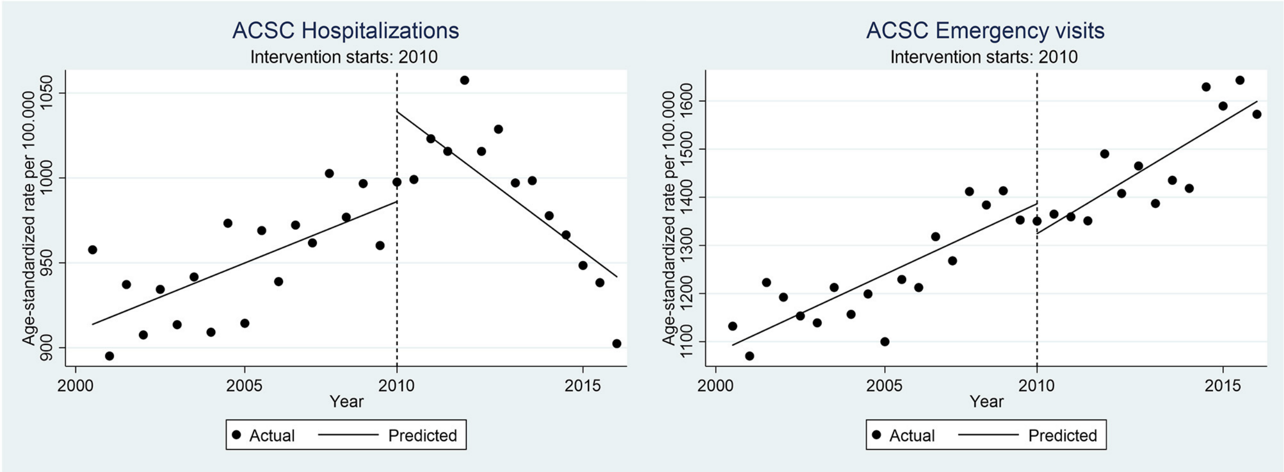

FIGURE 1 | Age-standardized ACSC-H and ACSC-EV rates (per 100,000 population) in Sweden before-after the reform implementation.

In contrast to hospitalization rates, the increasing trend in total ACSC emergency visits before the reform continued even after the introduction of the reform, at a comparable pace and with no significant break in the trend (post-trend). A similar pattern was seen specifically for chronic ACSC emergency visits. In contrast, the increasing trend of acute ACSC emergency visits rather accelerated after the reform, estimated at a significant 1.1% higher increase after compared to before the reform (pre-post trend).

Auxiliary analyses (results not shown; available on request) by age specific groups and stratified by sex, overall pointed in the same direction as in the total population. For example, there was a significant decrease pre-post trend in total ACSC hospitalizations (1.1% in women, 0.9% in men, 1.2% in >65 years and 0.6% in <65 years; compared to 1.0% in the total sample) and in chronic ACSC hospitalizations (1.6% in women, 1.7% in men, 1.8% in >65 and 1.3 in <65; compared to 1.7% in total population), and a significant increase in acute emergency visits (0.7% in women, 1.4% in men, 1% in >65 and 1.2% in <65; compared to 1.1% in the total population). In addition, pre-post trends were also significant for acute hospitalizations in men (0.8% increase; compared to non-significant increase of 0.3% in the total sample) and chronic emergency visits in men and <65 years (0.7 and 1% decrease compared to non-significant decrease of 0.7% in the total population).

Variation in Impact by Reform Implementation Characteristics

Based on the overall impact of the reform on ACSC outcomes in Sweden described above, the subsequent series of analyses report variations in the impact across counties who differed with respect to increases in the proportion of private PHC providers following the introduction of the reform (magnitude; aim 2a), the year of introduction of the reform (timing; aim 2b), and a long-term presence of private providers (sustained presence; aim 2c).

Magnitude of Implementation

Table 3 reports the results from multiple-groups ITSA, with magnitude of implementation of the reform as the between-groups contrast. The trends were similar in the two comparison groups for all outcomes, both before (pre-trend difference) and after (post-trend difference) the introduction of the reform in 2010 (**Figure 2**). This similarity in trends resulted in a small (0.4–0.7%) and non-significant pre-post trend difference, indicating no variation in impact of the reform between the group with

TABLE 3 | Segmented regression analysis of ACSC-H and ACSC-EV trends comparing counties by magnitude of implementation 2001–2016.

High vs. low implementers	Hospitalizations[a]			Emergency visits		
	Total RR (95% CI)	Chronic RR (95% CI)	Acute RR (95% CI)	Total RR (95% CI)	Chronic RR (95% CI)	Acute RR (95% CI)
Initial mean level difference	0.961 (0.917, 1.006)	0.953 (0.897, 1.013)	0.977 (0.938, 1.017)	1.034 (0.914, 1.170)	0.987 (0.865, 1.127)	1.133 (1.007, 1.273)
Pre-trend high implementation	1.005 (1.001, 1.009)	1.001 (0.996, 1.006)	1.014 (1.010, 1.019)	1.010 (1.003, 1.016)	1.004 (0.996, 1.012)	1.020 (1.014, 1.026)
Pre-trend low implementation	1.001 (0.997, 1.005)	0.999 (0.994, 1.004)	1.007 (1.004, 1.011)	1.005 (0.996, 1.013)	0.997 (0.988, 1.005)	1.020 (1.011, 1.029)
Pre-trend difference	1.003 (0.999, 1.008)	1.004 (0.998, 1.010)	1.001 (0.997, 1.005)	1.005 (0.994, 1.016)	1.008 (0.996, 1.019)	0.999 (0.088, 1.010)
Post-trend high implementation	0.998 (0.993, 1.002)	0.992 (0.988, 0.997)	1.009 (1.000, 1.018)	1.014 (1.011, 1.016)	1.005 (1.001, 1.009)	1.026 (1.024, 1.028)
Post-trend low implementation	0.998 (0.993, 1.003)	0.991 (0.985, 0.997)	1.012 (1.006, 1.018)	1.013 (0.999, 1.028)	1.000 (0.983, 1.017)	1.033 (1.020, 1.045)
Post-trend difference	1.000 (0.993, 1.006)	1.001 (0.995, 1.008)	0.997 (0.987, 1.007)	1.000 (0.986, 1.015)	1.005 (0.987, 1.022)	0.993 (0.981, 1.006)
Pre-post trend difference	0.996 (0.989, 1.004)	0.997 (0.988, 1.006)	0.996 (0.984, 1.006)	0.995 (0.977, 1.014)	0.997 (0.976, 1.018)	0.994 (0.978, 1.011)

[a] *Adjusted for No. of hospital beds per year and county.*

larger compared to smaller increase in the proportion of private PHC providers following the introduction of the reform.

Early Introduction of the Reform

The comparisons between counties which introduced the free choice earlier than the FCPHC reform was implemented nationally displayed a more complex pattern depending on the outcomes; see **Table 4** and **Figure 2**.

For all ACSC hospitalization outcomes (total, chronic, and acute), the early adopters of the reform showed a less promising development, with a significantly worse trends before the reform (pre-trend difference). The universal introduction of the reform in 2010 did however not change this pattern, with similarly sized but non-significantly worse trends among the early compared to late implementers (post-trend difference), and a non-significant pre-post trend difference as a result.

In contrast, the early implementers displayed a less pronounced increase in the acute ACSC emergency visits compared to the late implementers before the reform (pre-trend difference), but a similar increase after the reform (post-trend difference). This resulted in a significantly more unfavorable impact of the reform among the early implementers (pre-post trend difference), amounting to a 1.4% accelerated rates among early compared to late implementers. This overall pattern was in the same direction but non-significant for total and chronic ACSC emergency visits.

Sustained Presence of Private Providers

The impact of the reform on ACSC outcomes differed consistently between counties with a high-sustained presence of private providers compared to those with a consistently low presence, both before and after the introduction of the reform; see **Table 5** and **Figure 2**.

For hospitalizations outcomes, this was explained by significantly more steeply increasing pre-reform trends among the counties with high compared to low sustained presence of private providers (pre-trend difference), in combination with increasing trends after the reform (post-trend difference), which resulted in a significant 0.8–0.9% less favorable impact of the reform among the counties with sustained presence (pre-post trend difference).

A more sizable less favorable impact of the reform among the counties with high compared to low sustained presence of private providers was also seen for emergency visit outcomes amounting to a 2.2–2.4% difference (pre-post-trend difference). This was the result of less pronounced increasing trends before the implementation (pre-trend difference) in combination with steeper increasing trends after the reform in the counties with sustained presence of private providers (post-trend difference).

Sensitivity Analyses

Analyses stratified by sex and age (results available on request) led to the same overall conclusions as in the total population. Specifically, there were no variation in impact of the reform by magnitude of implementation either by gender or age; an unfavorable impact of the reform in acute emergency visits among the early compared to late implementers (1.5% in women, 1.3% in men, 1.% in <65 and 1.1% in >65; compared with 1.4% in the total population); and an overall negative impact of the reform in both, hospitalizations (0.8–0.9% in women and 0.8–1% in men; 1–1.1% in >65; compared with 0.8–0.9 in total population) and emergency visits (2.1–2.5% in women and 2.3–2.4% in men, 2.6–2.7 in <65 and 1.8–1.9% in >65; compared with 2.2–2.4% in total population) among the counties with high compared to low sustained presence of private providers.

The series of sensitivity analysis (results available on request) using different cut-off points for intervention operationalization

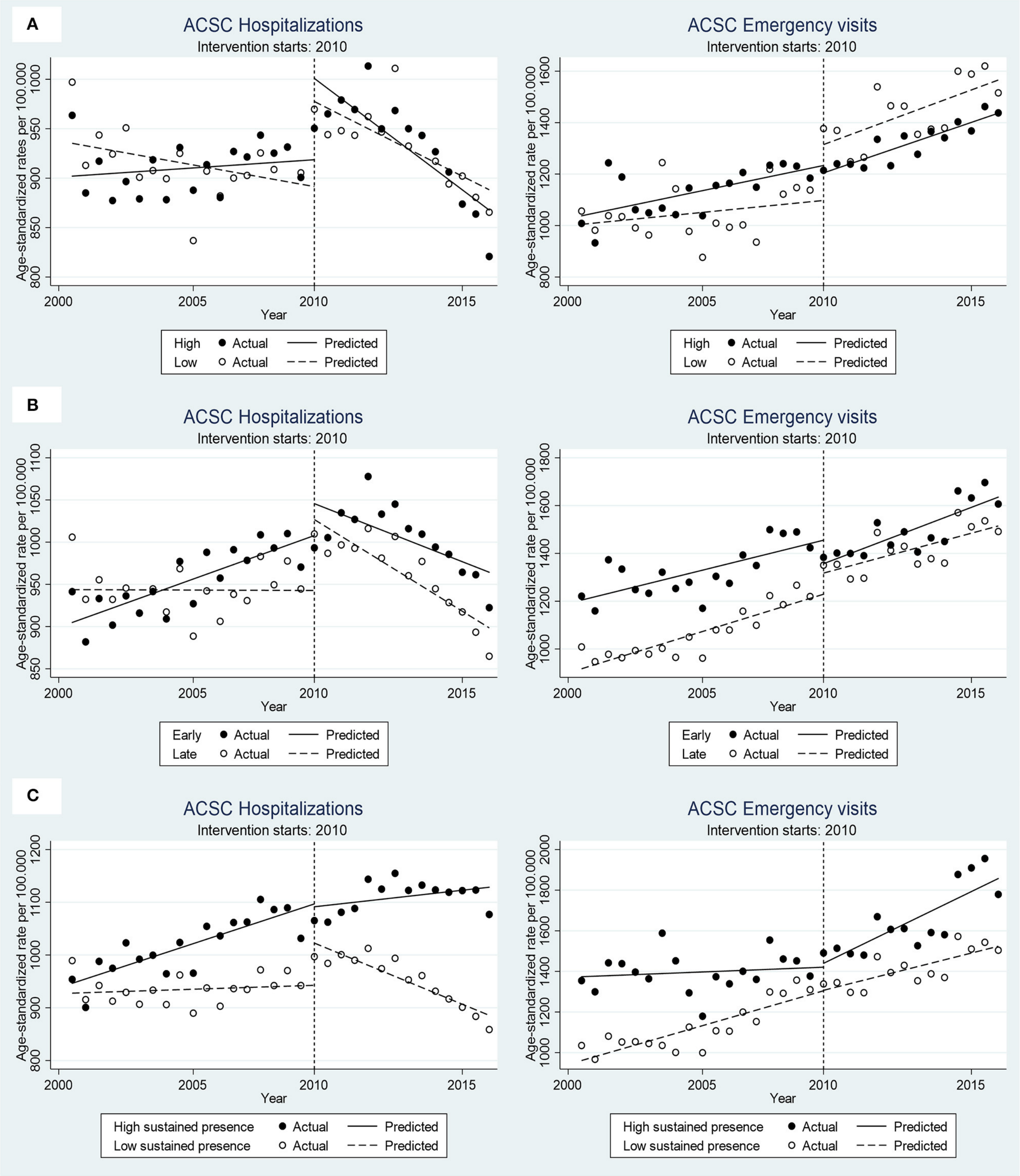

FIGURE 2 | Age-standardized ACSC-H and ACSC-EV rates (per 100,000 population) before-after the reform implementation by comparison groups. **(A)** High vs. low implementers, **(B)** Early vs. late implementers and **(C)** high vs. low sustained presence of private providers.

and timing of the intervention confirmed the inferences from the main analysis, only with slightly larger pre-post trend differences observed for certain comparisons when the time point to evaluate the reform was changed to 2011 instead of 2010, thereby allowing for a longer period of implementation. Specifically, the pre-post trend differences were more pronounced for hospitalizations in

TABLE 4 | Segmented regression analysis of ACSC-H and ACSC-EV trends comparing counties by timing of implementation 2001–2016.

Early vs. late implementers	**Hospitalizations**[a]			**Emergency visits**		
	Total RR (95% CI)	**Chronic RR (95% CI)**	**Acute RR (95% CI)**	**Total RR (95% CI)**	**Chronic RR (95% CI)**	**Acute RR (95% CI)**
Initial mean level difference	0.979 (0.946, 1.013)	0.996 (0.951, 1.044)	0.935 (0.909, 0.962)	1.306 (1.208, 1.411)	1.177 (1.080, 1.283)	1.573 (1.454, 1.702)
Pre-trend early implementation	1.009 (1.003, 1.015)	1.004 (0.996, 1.011)	1.022 (1.013, 1.030)	1.010 (1.006, 1.015)	1.009 (1.003, 1.015)	1.012 (1.008, 1.016)
Pre-trend late implementation	1.003 (1.001, 1.006)	1.001 (0.997, 1.004)	1.009 (1.007, 1.012)	1.016 (1.010, 1.021)	1.010 (1.004, 1.016)	1.027 (1.021, 1.034)
Pre-trend difference	1.006 (1.002, 1.009)	1.006 (1.002, 1.011)	1.005 (1.001, 1.008)	0.994 (0.987, 1.002)	0.999 (0.991, 1.007)	0.985 (0.978, 0.992)
Post-trend early implementation	0.998 (0.994, 1.002)	0.990 (0.986, 0.995)	1.014 (1.008, 1.021)	1.014 (1.010, 1.018)	1.004 (0.999. 1.010)	1.028 (1.024, 1.031)
Post-trend late implementation	0.993 (0.990, 0.997)	0.985 (0.980, 0.990)	1.009 (1.005, 1.013)	1.011 (1.002, 1.020)	0.998 (0.988, 1.008)	1.029 (1.021, 1.037)
Post-trend difference	1.005 (0.999, 1.010)	1.005 (0.999, 1.011)	1.005 (0.998, 1.013)	1.004 (0.994, 1.013)	1.006 (0.995, 1.018)	0.999 (0.991, 1.007)
Pre-post trend difference	0.999 (0.993, 1.006)	0.999 (0.991, 1.007)	1.001 (0.992, 1.009)	1.009 (0.997, 1.021)	1.007 (0.993, 1.021)	1.014 (1.003, 1.025)

[a] *Adjusted for No. of hospital beds per year and county.*

TABLE 5 | Segmented regression analysis of ACSC-H and ACSC-EV trends comparing counties by sustained presence of private providers.

High vs. low sustained presence of private providers	**Hospitalizations**[a]			**Emergency visits**		
	Total RR (95% CI)	**Chronic RR (95% CI)**	**Acute RR (95% CI)**	**Total RR (95% CI)**	**Chronic RR (95% CI)**	**Acute RR (95% CI)**
Initial mean level difference	1.081 (1.042, 1.120)	1.088 (1.039, 1.139)	1.062 (1.021, 1.105)	1.413 (1.315, 1.517)	1.232 (1.136, 1.336)	1.769 (1.631, 1.919)
Pre-trend H/H implementation	1.010 (1.005, 1.015)	1.006 (>1.000, 1.013)	1.018 (1.013, 1.023)	1.002 (0.998, 1.006)	1.002 (0.997, 1.007)	1.001 (0.997, 1.006)
Pre-trend L/L implementation	1.005 (1.003, 1.007)	1.003 (>1.000, 1.005)	1.009 (1.007, 1.012)	1.017 (1.011, 1.022)	1.012 (1.006, 1.018)	1.025 (1.019, 1.031)
Pre-trend difference	1.006 (1.002, 1.010)	1.008 (1.003, 1.012)	1.003 (0.999, 1.006)	0.985 (0.979, 0.992)	0.990 (0.983, 0.998)	0.977 (0.969, 0.984)
Post-trend H/H implementation	1.008 (1.005, 1.011)	1.002 (0.998, 1.006)	1.021 (1.017, 1.024)	1.019 (1.013, 1.026)	1.012 (1.003, 1.020)	1.030 (1.025, 1.035)
Post-trend L/L implementation	0.994 (0.991, 0.997)	0.986 (0.981, 0.990)	1.009 (1.006, 1.013)	1.012 (1.005, 1.018)	1.000 (0.992, 1.008)	1.029 (1.023, 1.035)
Post-trend difference	1.014 (1.010, 1.019)	1.017 (1.011, 1.023)	1.011 (1.007, 1.016)	1.008 (0.998, 1.016)	1.012 (1.001, 1.024)	1.001 (0.993, 1.008)
Pre-post trend difference	1.008 (1.002, 1.014)	1.009 (1.001, 1.017)	1.009 (1.003, 1.015)	1.022 (1.011, 1.034)	1.022 (1.008, 1.036)	1.024 (1.014, 1.035)

[a] *Adjusted for No. of hospital beds per year and county.*

the high compared to low sustained presence counties (1.1–1.3% increase; compared to 0.8–0.9%) and for emergency visits in the early compared to late implementers (1.2–1.5% increase; compared to 0.9–1.4%).

DISCUSSION

Summary of Main Findings

This study set out to evaluate the impact of the 2010 Swedish Free Choice in Primary Health Care reform on PHC performance as indicated by rates of hospital admissions and emergency visits for chronic and acute Ambulatory Care Sensitive Conditions. The results suggest that, following the introduction of the reform in Sweden as a whole, the trends in total hospitalizations rates were slowed down and for chronic conditions even turned to a downward trend, which marks a break from the pre-reform secular trend. On the other hand, acute emergency visits increased more rapidly after the introduction of the reform. However, we found no evidence of more beneficial effects in counties where the reform had been implemented more ambitiously, specifically those with a larger increase in private primary care providers, or where the reform was introduced early and thus had longer time effects to emerge. This suggests that the overall changes in Sweden as a whole are not to be attributed to the reform itself. Lastly, counties with a sustained high presence of private primary care providers displayed the least favorable development when it comes to ACSC. Taken together, our study does not provide evidence that the FCPHC reform has had the expected positive impact on ACSC, and instead tentatively suggests that widespread private PHC provision could, in the long run, negatively affect PHC performance.

Overall National Impact of the Reform

The pattern of slightly increasing trends in hospitalizations for chronic ACSC turning toward downward trend after 2010 have been noted before (28), and has been interpreted as reflecting improved interventions in outpatient care for diseases such as chronic heart failure and chronic obstructive lung disease. The fact that we were unable to attribute this change or the increase in emergency visits to features of the reform overall corresponds to findings from a preliminary study following avoidable hospitalizations up to 2013 (9), and warrants a comment on other possible causes of the observed changes. First, as noted above, the positive development seen for to chronic conditions hospitalizations could reflect universal improvements in the treatment and management of chronic conditions not restricted to primary care. Second, despite a Healthcare Guarantee Law serving to reduce waiting times in health care was introduced in 2010, waiting times in primary and secondary care have rather increased in the years after 2010 (29), a development that possibly could contribute to the increase in emergency care visits. Third, the reduced availability of hospital beds could be expected to impact the tendency to hospitalize patients (25); however, the results remained after adjustment for hospital beds, and this is thus an unlikely contributor to the findings.

Complementary interventions implemented together or as a consequence of the reform could have also played a role on the observed results. For example, it is possible that the reduction of hospitalizations would be a reflection of guideline adaptations made at county-level to improve quality indicators. i.e., the ACSC have been used as quality performance indicators (25) and therefore it is possible that hospital admission criteria for these conditions may have become stricter. Such a behavior could partly explain the combination of decreased chronic hospitalization but increased acute hospitalizations and emergency visits. Moreover, the overall trend of increased emergency visits also could be understood from the fact that stricter admission criteria would result in most of the acute ACSC situations being managed in the emergency rooms, with only very critical cases ending up in hospitalization. Identifying whether such interventions implemented at county-level actually have played a role would require a more deep exploration, e.g., through case studies, since counties have certain degree of autonomy to implement reforms.

Regional Differences in the Impact of the Reform

When it comes to the between-county comparisons, it is possible that other characteristics than changes in the proportion of private provision have led to the estimated effects of the reform. For example, whereas most of the county councils have a mixed reimbursement system largely based on capitation and a small part on fee-for-service (30), each county decide on their particular arrangements and adapt their system according to their own dynamics, with no national documentation of the various modifications. This makes it difficult to track and operationalize changes in reimbursement systems over time to measure their link to the effects of the reform. Nevertheless, it is well-known that funding mechanisms and reimbursement systems have the potential to create incentives to improve access and quality of care (31). Indeed, recent studies in southern Swedish counties, including Stockholm, whose reimbursement system has been unique up to 2015 [large fraction based on fee-for-service (60%) and the remaining (40%) unweighted capitation], found increases in the number of visits to health care centers associated with changes in the reimbursement system (7, 32). However, the changes did not particularly benefit those with greater health care needs (7). It is possible that changes in reimbursement system might have ended up incentivising short visits among otherwise healthy people, and therefore the group with chronic conditions may have been de-prioritized in primary care, ending up in emergency care instead. Further research exploring regional differences and changes in reimbursement systems, and their impact on ACSC would be needed to provide more insight into this issue.

The observation that counties with sustained presence of private providers showed the worst development when it comes to ACSC was a notable and surprising finding. This comparison does not directly reflect the impact of the 2010 national reform, but should instead be seen as an illustration of the possible long-term outcome of the reform in Sweden as a whole, if all counties were to develop a persistent dominance of private primary care providers. A lot of controversy surrounds the role of the private (for-profit) sector in health services delivery. Indeed previous research have cautioned policymakers of possible negative effects, such as the potential of the private sector to strip away the workforce from the public sector, and their tendency to focus on advantaged groups and over treat patients to generate more profits (33). Some evidence from low- and middle income countries indeed suggests that increasing private health care provision might not meet the promises of ending up in more efficient, accountable or medically effective provision (33, 34). In Sweden, the introduction of similar market-oriented reforms for other social services have also shown to be detrimental for care-takers (30). However, when it comes to health care in Europe, there is still an ongoing discussion and an open call for sound empirical analysis providing answers as to the rather silent question on the long-term consequences of privatization on health care performance (35). Therefore, robust evaluation and continuous learning and development are needed to ensure the current trend of public-private mix of health provision can fulfill its promise of a quality driven health care service model.

Whereas impact on equity in PHC performance was not part of the scope of the present report, it is important to note that failures to meet the needs of underserved population groups, as has been found in previous research in Sweden (2), could hamper a population-wide improvement in performance (11), and inequity in performance could thus be contributing to the lack of positive overall effect of the reform seen in our results. Considering the long-standing concerns about how the reform may negatively impact on equity, future evaluations are specifically needed to shed light on this issue.

Methodological Considerations

The main strengths of the present study are the longitudinal design spanning over 16 years of follow up; the use of a comprehensive set of outcomes retrieved from Swedish total population registers of good quality; and the interrupted time series designs, which is considered the best available mean of assessing an intervention impact (15, 36).

Some potential limitations should be considered when interpreting our results. First, the analyses were done using population-level rates and can therefore not be used to make individual-level inferences (17). Furthermore, unplanned hospital visits were used as proxy for emergency visits which may have led to an over or under estimation of the rates in these particular outcomes. While case ascertainment can be a matter of concern, a quality control of the Swedish registers is performed routinely to ensure accuracy and completeness (37). Nevertheless, the extent of measurement bias in this outcome is ultimately unknown.

Although the single-group ITSA does not require to have a comparison group to obtain association between an intervention and outcome (19, 38), it is well-known that having a comparison group to serve as the counterfactual is a superior approach to ascertain intervention effects (39). In that sense, further evaluations comparing Sweden with a truly unexposed group, e.g., using a "synthetic international comparator" (40), would be needed to better understand the effects of the FCPHC reform. Nevertheless, identifying truly comparable contexts for external control groups outside of Sweden will involve challenges by itself. It should also be noted that for some outcomes, control groups in the multiple-groups ITSA were not completely comparable to the treatment group when it comes to observed pre-intervention levels and trends, which could raise concerns about the ability of the analysis to draw causal inferences about the relationship between the intervention and the outcomes (19).

Moreover, it is possible that the lack of effect in counties where the reform had been implemented more ambitiously is due to the chosen operationalization of the reform, and that the results therefore also may conceal differential developments in specific sub-groups (e.g., persons with greater health care needs). However, in this paper, we tried various analyses stratified by sex and age subgroups with different cut-off points for magnitude and timing, yet none of them led to a different result. Nonetheless, it should be noted that using other aspects rather than the public/private proportions to operationalize the reform and other specific subgroups for the analysis could possibly yield different inferences.

It is also possible that the reform needs a longer time to produce an impact on PHC performance, perhaps beyond the period of this study. For example, in the shorter term, the reform would be expected primarily to increase the number of providers; while in the medium term, the benefit might be in access to primary care and only in the long term, a clearer benefit in reducing the burden of secondary and tertiary care would be seen. In this analysis, we included 18 observations points (9 years) before and 14 points (7 years) after the reform implementation, which would be considered sufficient to statistically evaluate changes (17). Nevertheless, the need of more time to observe effects in a long-term outcome cannot be ruled out, and we anticipate future research to explore the more long-term effects of the reform.

Lastly, it is difficult to isolate the independent impact of the reform in a dynamic ever-changing health system and society. In fact, to identify competing or complementary interventions to the reform that could be responsible for shifting the time series of the evaluated outcomes is challenging by itself, as there could be national preventive efforts and particular county level interventions, as well variations in reimbursement systems as discussed above, that could be expected to have a similar effect as the reform itself. Relatedly, considering the long study period over 16 years, a change in unconsidered population or health system characteristics could also potentially confound the analyses, as long as the change coincides with the introduction of the reform. Even though the ITS design is based on both within- and between-group comparisons of trends, and the threat to internal validity is considerably lower than for a weaker study design, confounding cannot be ruled out. In preliminary analyses, sociodemographic characteristics did not differ between the comparison groups, but other unobserved potential confounders include for example regional health system differences, such as variations in clinical practice, and also healthcare seeking behavior. Another potential confounder is the actual prevalence and incidence of chronic disease. There are unfortunately no national register data on disease prevalence in Sweden outside the patient registers that were used as outcomes in the study.

These considerations illustrate the inherent challenges of performing population-wide evaluations in real-world settings, which are relevant for future research on the impact of health system changes on PHC performance. The choice of evaluation design is a key methodological issue that may be restricted by the availability of appropriate data. Controlled designs are preferred but formulation of the comparison population requires careful consideration, which poses a challenge also for regionally implemented interventions [see e.g., (41)]. The issue of competing interventions and confounding is an ever-present threat particularly for weaker evaluation designs, e.g., in the absence of control group or with single pre-test and post-test observations rather than trends. Additional methodological considerations include the choice of outcome, e.g., summary indicators such as ACSC used in the present study, or indicators of more specific aspects of PHC performance (21), as well as the quality and coverage of outcome data; the expected temporality of intervention impact of the chosen outcome and follow-up time – e.g., immediate or delayed; and the possibilities of ecological and individual-level analysis. For future evaluations it would be particularly interesting to consider the possibility to conduct an ITSA with multiple treatment analysis or other design alternatives (19).

Conclusion

The present study contributes to evidence on the effects of a major health care reform, driven by libertarian goals rather than the egalitarian principles that traditionally have been central to Swedish health care system.

Taken together, the present study does not support that the Swedish Choice in PHC reform has improved the overall quality and performance of the primary care delivery system in Sweden, and suggests that high degree of private provision in PHC may lead to worse PHC performance and higher care burden for specialized health care.

The results illustrate the value of using population-level approaches and counterfactual evaluation designs to assess interventions through attributable impact. While evidence-based policy-making free from ideological or ethical guiding principles may neither be realistic nor desirable, rigorous evidence as provided by the present study represents an important aspect for assessing, tailoring and designing effective health policy. Further evaluations of the consequences of the reform are direly needed to provide a comprehensive picture of its intended and unintended impact on health care provision, delivery and results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon request, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Regional Ethical Review Board in Umeå (approval ref. no. 2017/229-31). The study is based on aggregated data on a large scale, and thus does not process any personal data. The Regional Ethical Review Board in Umeå waived the requirement for written informed consent for participants in this study in accordance with Swedish national regulations (Ethical Review Act 2003:460), as the study only retrieved and utilized secondary register data.

AUTHOR CONTRIBUTIONS

PM, PG, and MS conceived the study. PM conducted the data analysis, interpretation of the data and drafted the manuscript, with support from PG. PG and MS contributed to the analysis and interpretation of the data and revised the manuscript. BB and AKH participated in the interpretation of the data and revised the manuscript. All authors approved the final draft.

FUNDING

This work was supported by Forte - Swedish Research Council for Health, Working Life and Welfare (Grant Number 2016-00236 to PM). The funding body had no role in the design of the study, data collection, analysis, interpretation of data or in writing the manuscript.

REFERENCES

1. Andersson F, Janlöv N, Rehnberg C. *Konkurrens, kontrakt och kvalitet–hälso- och sjukvård i privat regi. Rapport till Expertgruppen för studier i offentlig ekonomi* Finansdepartementet, Regeringskansliet (2014).
2. Burstrom B, Burstrom K, Nilsson G, Tomson G, Whitehead M, Winblad U. Equity aspects of the primary health care choice reform in Sweden - a scoping review. *Int J Equity Health.* (2017) 16:29. doi: 10.1186/s12939-017-0524-z
3. Myndigheten för Vårdanalys. *Vårdval och jämlik vård inom primätvården: En jämförande studie mellan tre landsting före och efter vårdvalets införande*. Stockholm: Myndigheten för Vårdanalys (2015).
4. Winblad U, Isaksson D, Bergman P. *Effekter av valfrihet inom hälso-och sjukvård: en kartläggning av kunskapsläget*. Swedish Agency for Health and Care Services Analysis (2012).
5. Burstrom B. Market-oriented, demand-driven health care reforms and equity in health and health care utilization in Sweden. *Int J Health Serv Plan Admin Eval.* (2009) 39:271–85. doi: 10.2190/HS.39.2.c
6. Burstrom B. Will Swedish healthcare reforms affect equity? *BMJ.* (2009) 339:b4566. doi: 10.1136/bmj.b4566
7. Agerholm J, Bruce D, de Leon AP, Burström B. Equity impact of a choice reform and change in reimbursement system in primary care in Stockholm County Council. *BMC Health Serv Res.* (2015) 15:420. doi: 10.1186/s12913-015-1105-8
8. Riksrevisionen. *Primärvårdens styrning– efter behov eller efterfrågan*? *(RiR 2014:22). Riksrevisionen. Report No.: 978 91 7086 358 5*. Riksrevisionen (2014).
9. Dietrichson J, Ellegård LM, Kjellsson G. Patient choice, entry, and the quality of primary care: evidence from Swedish reforms. In: *Working Papers 2016:36, Lund University, Department of Economics* (2018).
10. Isaksson D, Blomqvist P, Winblad U. Free establishment of primary health care providers: effects on geographical equity. *BMC Health Serv Res.* (2016) 16:28. doi: 10.1186/s12913-016-1259-z
11. Stiernstedt G, Zetterberg D, Ingmanson A. *Effektiv vård. Statens Offentliga Utredningar*. Stockholm. (2016)
12. Dixon A, Le Grand J. Is greater patient choice consistent with equity? The case of the English NHS. *J Health Serv Res Policy*. (2006) 11:162–6. doi: 10.1258/135581906777641668
13. Fotaki M, Roland M, Boyd A, McDonald R, Scheaff R, Smith L. What benefits will choice bring to patients? Literature review and assessment of implications. *J Health Serv Res Policy.* (2008) 13:178–84. doi: 10.1258/jhsrp.2008.007163
14. Mendis D. Choosing choice? *Int J Health Plan Manage.* (2009) 24:266–75. doi: 10.1002/hpm.1015
15. Craig P, Cooper C, Gunnell D, Haw S, Lawson K, Macintyre S, et al. Using natural experiments to evaluate population health interventions: new Medical Research Council guidance. *J Epidemiol Comm Health.* (2012) 66:1182–6. doi: 10.1136/jech-2011-200375
16. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther.* (2002) 27:299–309. doi: 10.1046/j.1365-2710.2002.00430.x
17. Penfold RB, Zhang F. Use of interrupted time series analysis in evaluating health care quality improvements. *Acad Pediatr.* (2013) 13 (6 Suppl.):S38–44. doi: 10.1016/j.acap.2013.08.002
18. William RS, Cook TD, Donald TC. *Experimental and Quasi-Experimental Designs for Generalized Causal Inference*. Boston, MA: Houghton Mifflin Company (2002).
19. Linden A. Conducting interrupted time-series analysis for single-and multiple-group comparisons. *Stata J.* (2015) 15:480–500. doi: 10.1177/1536867X1501500208

20. AHRQ Quality Indicators. *Guide to Prevention Quality Indicators: Hospital Admission for Ambulatory Care Sensitive Conditions*. Rockville, MD: Agency for Health Care Research and Quality (2001).
21. OECD. *Health Care Quality Indicators - Primary Care: Organisation for Economic Cooperation and Development*. (2005). Available online at: http://www.oecd.org/els/health-systems/hcqi-primary-care.htm (accessed March 15, 2021).
22. Swedish Competition Authority. *Val av vårdcentral: Förutsättningar för kvalitets–konkurrens i vårdvalssystemen*. Stockholm (2012).
23. Oster A, Bindman AB. Emergency department visits for ambulatory care sensitive conditions: insights into preventable hospitalizations. *Med Care.* (2003) 41:198–207. doi: 10.1097/01.MLR.0000045021.70297.9F
24. Lofqvist T, Burstrom B, Walander A, Ljung R. Inequalities in avoidable hospitalisation by area income and the role of individual characteristics: a population-based register study in Stockholm County, Sweden. *BMJ Qual Saf.* (2014) 23:206–14. doi: 10.1136/bmjqs-2012-001715
25. The National Board of Health and Welfare and Swedish Association of Local Authorities and Regions. *Quality and Efficiency in Swedish Health Care - Regional Comparisons 2012*. Stockholm (2012).
26. National Health Performance Committee. *National Report on Health Sector Performance Indicators 2003*. Canberra: Australian Institute of Health and Welfare (2004).
27. Davis RA, Wu R. A negative binomial model for time series of counts. *Biometrika.* (2009) 96:735–49. doi: 10.1093/biomet/asp029
28. Swedish Association of Local Authorities and Regions. *Hälso- och sjukvårdsrapporten 2018*. Swedish Association of Local Authorities and Regions. Stockholm (2018).
29. Myndigheten för vård- och omsorgsanalys. *Löftesfri garanti*? *En uppföljning av den nationella vårdgarantin*. *Rapport 2017:6* (2017).
30. Burstrom B. Sweden–recent changes in welfare state arrangements. *Int J Health Services Plan Admin Eval.* (2015) 45:87–104. doi: 10.2190/HS.45.1.g
31. Tao W, Agerholm J, Burstrom B. The impact of reimbursement systems on equity in access and quality of primary care: a systematic literature review. *BMC Health Serv Res.* (2016) 16:542. doi: 10.1186/s12913-016-1805-8
32. Svereus S, Kjellsson G, Rehnberg C. Socioeconomic distribution of GP visits following patient choice reform and differences in reimbursement models: evidence from Sweden. *Health policy.* (2018) 122:949–56. doi: 10.1016/j.healthpol.2018.07.017
33. Wadge H, Roy R, Sripathy A, Prime M, Carter A, Fontana G, et al. *Evaluating the Impact of Private Providers on Health and Health Systems*. London, UK: Imperial College London (2017).
34. Basu S, Andrews J, Kishore S, Panjabi R, Stuckler D. Comparative performance of private and public healthcare systems in low- and middle-income countries: a systematic review. *PLoS Med.* (2012) 9:e1001244. doi: 10.1371/journal.pmed.1001244
35. Jeurissen PP, Maarse H. New provider models for sweden and spain: public, private or non-profit? Comment on "governance, government, and the search for new provider models". *Int J Health Policy Manage.* (2016) 5:721–3. doi: 10.15171/ijhpm.2016.87
36. Biglan A, Ary D, Wagenaar AC. The value of interrupted time-series experiments for community intervention research. *Prevent Sci.* (2000) 1:31–49. doi: 10.1023/A:1010024016308
37. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health.* (2011) 11:450. doi: 10.1186/1471-2458-11-450
38. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol.* (2017) 46:348–55. doi: 10.1093/ije/dyw098
39. Linden A. Challenges to validity in single-group interrupted time series analysis. *J Eval Clin Pract.* (2017) 23:413–8. doi: 10.1111/jep.12638
40. Abadie A, Diamond A, Hainmueller J. Comparative politics and the synthetic control method. *Am J Polit Sci.* (2015) 59:495–510. doi: 10.1111/ajps.12116
41. San Sebastian M, Mosquera PA, Gustafsson PE. Do cardiovascular disease prevention programs in northern Sweden impact on population health? An interrupted time series analysis. *BMC Public Health.* (2019) 19:202. doi: 10.1186/s12889-019-6514-x

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 21 July 2021
doi: 10.3389/fmed.2021.651925

Comparing Multimorbidity Patterns Among Discharged Middle-Aged and Older Inpatients Between Hong Kong and Zurich: A Hierarchical Agglomerative Clustering Analysis of Routine Hospital Records

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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Medicine

Received: *11 January 2021*
Accepted: *25 June 2021*
Published: *21 July 2021*

Citation:
Lai FTT, Beeler PE, Yip BHK, Cheetham M, Chau PYK, Chung RY, Wong ELY, Yeoh E-K, Battegay E and Wong SYS (2021) Comparing Multimorbidity Patterns Among Discharged Middle-Aged and Older Inpatients Between Hong Kong and Zurich: A Hierarchical Agglomerative Clustering Analysis of Routine Hospital Records. Front. Med. 8:651925. doi: 10.3389/fmed.2021.651925

Background: Multimorbidity, defined as the co-occurrence of $\geq$2 chronic conditions, is clinically diverse. Such complexity hinders the development of integrated/collaborative care for multimorbid patients. In addition, the universality of multimorbidity patterns is unclear given scarce research comparing multimorbidity profiles across populations. This study aims to derive and compare multimorbidity profiles in Hong Kong (HK, PRC) and Zurich (ZH, Switzerland).

Methods: Stratified by sites, hierarchical agglomerative clustering analysis (dissimilarity measured by Jaccard index) was conducted with the objective of grouping inpatients into clinically meaningful clusters based on age, sex, and 30 chronic conditions among 20,000 randomly selected discharged multimorbid inpatients (10,000 from each site) aged $\geq$ 45 years. The elbow point method based on average within-cluster dissimilarity, complemented with a qualitative clinical examination of disease prevalence, was used to determine the number of clusters.

Results: Nine clusters were derived for each site. Both similarities and dissimilarities of multimorbidity patterns were observed. There was one stroke-oriented cluster (3.9% in HK; 6.5% in ZH) and one chronic kidney disease-oriented cluster (13.1% in HK; 11.5% ZH) in each site. Examples of site-specific multimorbidity patterns, on the other hand, included a myocardial infarction-oriented cluster in ZH (2.3%) and several clusters in HK with high prevalence of heart failure (>65%) and chronic pain (>20%).

Conclusion: This is the first study using hierarchical agglomerative clustering analysis to profile multimorbid inpatients from two different populations to identify universalities and differences of multimorbidity patterns. Our findings may inform the coordination of integrated/collaborative healthcare services.

Keywords: comorbidity, machine learning, multiple chronic conditions, non-communicable disease, population aging

INTRODUCTION

Multimorbidity is commonly referred to as the co-occurrence of two or more chronic health conditions (1) and is consistently associated with poorer quality of life (2), more healthcare utilization (3), deteriorating mental health (4), and greater risk of mortality (5). Various models of care have been proposed and trialed to address this complexity in clinical practices (6, 7).

Multimorbid patients are clinically diverse (8) and may have markedly different prognoses due to different disease combinations (9). Such heterogeneity limits the provision of integrated or collaborative care in various healthcare settings (10, 11) as evidence-based clinical guidelines are inadequate (12) given the scarcity of randomized controlled trials conducted on multimorbid populations (13), even those with more prevalent disease combinations (14). This challenge is often further complicated by the need to manage multiple drug regimens (polypharmacy) (15) and the associated adverse effects (16).

Numerous attempts have thus been made to identify common patterns of multimorbidity to simplify the problem (8, 17). Prados-Torres et al. (17) identified 97 different combinations of two or more co-occurring chronic conditions, which were mostly represented as cardiometabolic, musculoskeletal, and mental patterns. In a more recent review, Ng et al. (8) updated the literature search and evaluated the methods by which multimorbidity patterns are identified. Clustering analysis has been found to be the commonest approach to identifying disease patterns: grouping together similar diseases that are found in the same individuals (8, 17). While this approach omits the possibility that one disease may belong with more than one cluster and that even individuals with the same disease may be clinically distinct from each other given other conditions, very few reviewed studies (18) adopted clustering analysis or other methods to group similar patients instead of similar diseases (8, 17). Furthermore, very few studies have compared multimorbidity patterns across countries using the same methods (19). Similarities and dissimilarities between multimorbidity patterns observed in different contexts, therefore, remain unexplored. In fact, the presence of universal patterns may strengthen the rationale for more randomized controlled trials to be conducted on multimorbid patients because results would confer cross-country implications.

This study aims to describe and compare the patterns of co-occurring chronic conditions among discharged multimorbid inpatients in Hong Kong and Zurich using a hierarchical agglomerative clustering analytic approach, which is typically used for grouping similar individuals based on predetermined ranges of characteristics. Since the healthcare system as well as the cultural and demographic characteristics differ drastically between the two sites, observations of similar multimorbidity patterns may potentially imply universal challenges facing clinicians globally.

MATERIALS AND METHODS

Study Design and Data Collection

We conducted a retrospective analysis of clinical records of discharged patients aged $\geq$ 45 from all public hospitals in Hong Kong (representing >90% of all inpatient services) during January 2010-December 2013 and from the University Hospital Zurich (general acute hospital, teaching hospital for University of Zurich) during August 2009-August 2017. The discrepancy of observation period was mainly due to the much smaller amount of data generated from Zurich as it is only one hospital compared with the whole public hospital system in Hong Kong.

The data contained information on patients' age, sex, the length of stay, and the first 15 clinical diagnoses made during the hospital stay coded with the International Classification of Diseases, Ninth Revision (ICD-9) for Hong Kong and with the Tenth Revision (ICD-10) for Zurich. Multimorbidity is defined as having two or more chronic conditions using a list of 30 diseases coded either by ICD-9 or ICD-10. The list of chronic conditions is based on validated coding algorithms summarized by Tonelli et al. (20) and included alcohol misuse, asthma, atrial fibrillation, chronic heart failure, chronic kidney disease, chronic pain, chronic pulmonary disease, chronic viral hepatitis B, cirrhosis, dementia, depression, diabetes, epilepsy, hypertension, hypothyroidism, inflammatory bowel disease, irritable bowel syndrome, lymphoma, metastatic cancer, multiple sclerosis, myocardial infarction, non-metastatic cancer (breast, cervical, colorectal, lung, and prostate), Parkinson's disease, peptic ulcer disease, peripheral vascular disease, psoriasis, rheumatoid arthritis, schizophrenia, severe constipation, and stroke or transient ischemic attack (TIA). These diseases are all convertible between ICD-9 and ICD-10 in accordance with the Tonelli algorithms and therefore diseases could be mapped between the sites. Ten thousand patients with two or more of these conditions from each site were randomly selected and included with the "sample" function according to approach described by Ripley (21) in R, version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). This sample size was approximately four times the minimum required number recommended for a clustering analysis of 32 variables (22).

30-day readmission and length of stay in hospital were measured to compare health care utilizations between clusters and sites. We considered only the first discharge of each patient during the data collection period to observe their clinical profiles and length of stay, then followed them up 30 days after their baseline discharge to observe any readmission.

Clustering Analysis

Stratified by sites (Hong Kong and Zurich), a hierarchical agglomerative clustering analysis implemented with R package "hclust" was conducted to form clusters of patients starting by grouping similar individuals in terms of age groups (categorized according to the World Health Organization's 5-year intervals: 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80+), sex, and the presence of listed chronic conditions with dissimilarity between patients measured by Jaccard index (23). Using the Ward's method, the pair of clusters or patients merged in each step was the one associated with the smallest increase in the total within-cluster dissimilarity. To inform our decision on the number of clusters to be specified, we first plotted the total within-cluster dissimilarity by number of specified clusters to look for an elbow point at which total within-cluster dissimilarity cease to decrease significantly, then we conducted a qualitative examination of the disease prevalence across clusters to eventually determine the optimal number of clusters from a clinical perspective, i.e., the balance between interpretability and meaningful clinical grouping of patients. Clustering of patients was then compared between sites.

We performed statistical analyses with R and there were no missing data in the anonymized hospital records. An ethics waiver has been granted by Cantonal Ethics Committee of Zurich for the analysis of Zurich inpatient data (Ref: NZ-B-Nr.2017-00882) while the analysis of Hong Kong inpatient data was approved by the Survey and Behavioral Ethics Committee of the Chinese University of Hong Kong (Project Code: Elderly Care – CUHK). As only secondary analysis of anonymized inpatient data was performed, no informed consent was required.

RESULTS

Over the corresponding study periods (see **Figure 1**), there were 1,015,225 inpatients aged ≥ 45 discharged from Hong Kong public hospitals among which 144,711 were multimorbid; and of the 102,936 discharged from the University Hospital Zurich, 37,574 were multimorbid. For each site, 10,000 patients were randomly selected for analysis.

Comparison of Disease Prevalence and Demographics

Table 1 shows the comparison of sample characteristics and disease prevalence between sites. First, the sample from Hong Kong had an older median age (75 vs. 70) and fewer males (51.2 vs. 57.6%) than the Zurich sample. Second, while 30-day readmission rate was similar, the median length of current stay is substantially greater in Zurich (7 vs. 4 days). Third, patients from Zurich had more diagnoses than those from Hong Kong, where only 1.4% of the sample had five or more diseases, compared with 5.0% in Zurich. There were notable differences in specific disease prevalence between the sites. Prevalence of alcohol misuse, epilepsy, and cancer prevalence among patients in Zurich was about triple that in Hong Kong. Much fewer Zurich patients had atrial fibrillation and heart failure compared with Hong Kong patients and there was a sharp contrast in peripheral vascular disease prevalence (0.0% in Hong Kong vs. 10.4% in Zurich).

Comparison of Disease Dyads

Figure 2 shows two chord diagrams which represent the frequencies of each disease dyad in both sites (represented by ribbon width). There were 54,052 co-occurring pairs of diseases

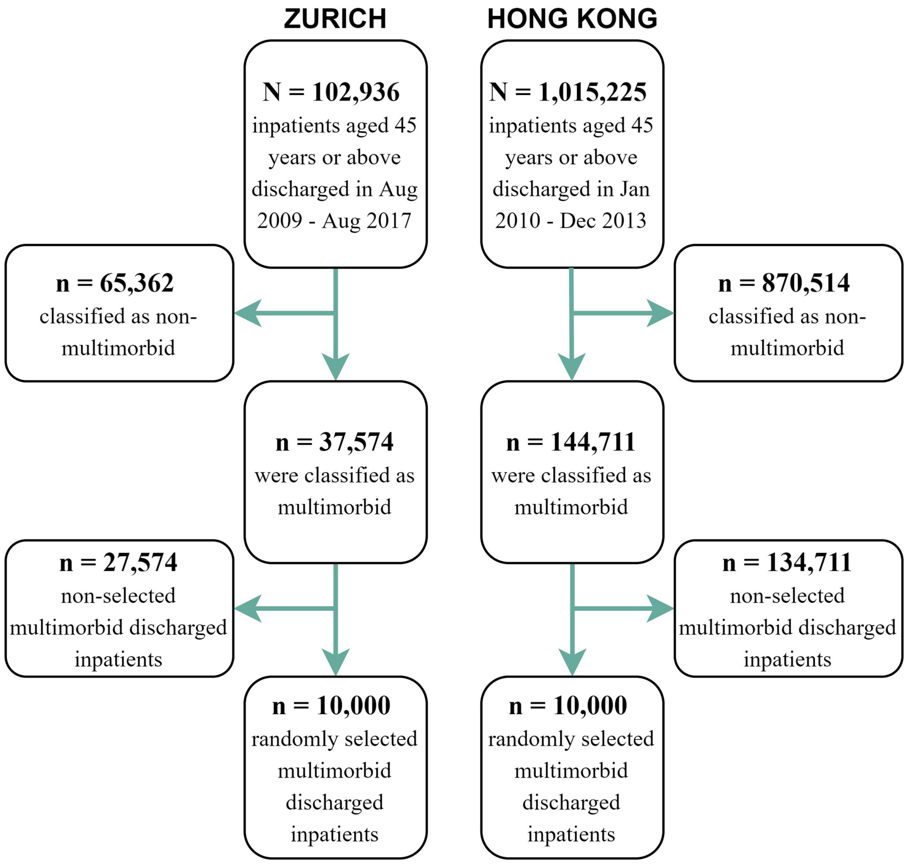


FIGURE 1 | Graphical representation of the sample selection for the analysis.

TABLE 1 | Comparison of demographics and disease prevalence between sites.

	Hong Kong	Zurich	
N	**10,000**	**10,000**	***P*-value**[a]
Age (median [IQR])	75 [64, 82]	70 [61, 78]	<0.001
Male (%)	5,125 (51.2)	5756 (57.6)	<0.001
Length of current stay (median [IQR])	4 [2, 9]	7 [3, 13]	<0.001
30-day readmission (%)	1,034 (10.3)	1,185 (11.8)	0.001
Number of chronic diseases (%)			<0.001
Two	6,727 (67.3)	5,461 (54.6)	
Three	2,503 (25.0)	2,865 (28.6)	
Four	635 (6.3)	1,171 (11.7)	
Five or more	135 (1.4)	503 (5.0)	
Chronic diseases (%)			
Alcohol misuse	176 (1.8)	650 (6.5)	<0.001
Asthma	314 (3.1)	220 (2.2)	<0.001
Atrial fibrillation	1,531 (15.3)	654 (6.5)	<0.001
Cancer, lymphoma	26 (0.3)	195 (1.9)	<0.001
Cancer, metastatic	200 (2.0)	768 (7.7)	<0.001
Cancer, non-metastatic	285 (2.8)	481 (4.8)	<0.001
Chronic kidney disease	1,499 (15.0)	1,721 (17.2)	<0.001
Chronic pain	1,614 (16.1)	2,764 (27.6)	<0.001
Chronic pulmonary disease	752 (7.5)	827 (8.3)	0.052
Cirrhosis	932 (9.3)	1,019 (10.2)	0.04
Dementia	237 (2.4)	44 (0.4)	<0.001
Depression	211 (2.1)	172 (1.7)	0.05
Diabetes	354 (3.5)	409 (4.1)	0.046
Epilepsy	307 (3.1)	943 (9.4)	<0.001
Heart failure	4,945 (49.5)	2,925 (29.2)	<0.001
Hepatitis B	166 (1.7)	496 (5.0)	<0.001
Hypertension	7,132 (71.3)	7,438 (74.4)	<0.001
Hypothyroidism	235 (2.4)	916 (9.2)	<0.001
Inflammatory bowel disease	8 (0.1)	72 (0.7)	<0.001
Irritable bowel syndrome	11 (0.1)	15 (0.1)	0.556
Multiple sclerosis	14 (0.1)	49 (0.5)	<0.001
Myocardial infarction	407 (4.1)	894 (8.9)	<0.001
Parkinson's disease	243 (2.4)	164 (1.6)	<0.001
Peptic Ulcer Disease	195 (1.9)	57 (0.6)	<0.001
Peripheral Vascular Disease	3 (0.0)	1,044 (10.4)	<0.001
Psoriasis	26 (0.3)	65 (0.6)	<0.001
Rheumatoid arthritis	177 (1.8)	346 (3.5)	<0.001
Schizophrenia	171 (1.7)	93 (0.9)	<0.001
Severe constipation	447 (4.5)	182 (1.8)	<0.001
Stroke	1,577 (15.8)	1,265 (12.6)	<0.001

[a] P-value indicates the statistical significance of chi-square test (or Fisher's exact test for frequencies smaller than five) comparing socio-demographics and disease prevalence between sites.

in the Zurich sample but only 38,964 in the Hong Kong sample, plausibly due to the fact that patients in Zurich had more diagnoses (see **Table 1**). In general, the patterns of disease dyads were fairly similar. Among all dyads in Hong Kong, 10,701 were related to hypertension, 7,815 to heart failure, and 2,967 to chronic pain. In Zurich, 13,294 were related to hypertension, 6,252 to chronic pain, and 6,166 to heart failure. Patients in Zurich had more different multimorbidity patterns (more narrow ribbons): based on the presence and absence of the 30 listed diseases, there were 1,799 configurations among patients in Zurich but only 982 in Hong Kong.

Comparison of Clusters Between Sites

Figure 3 shows the average within-cluster dissimilarity by number of specified clusters. Based on the elbow point method, at five clusters, within-cluster dissimilarity ceased to decline further significantly. Hence, we examined clustering schemes from 5 to 10 specified clusters in each site. This clinical review of clustering schemes indicated that at nine clusters, a balance between interpretability and meaningful categorization of patients was achieved. Thus, clustering patterns with nine specified clusters are presented. The order of clusters was in accordance with the size of the clusters (#1 being largest and #9 smallest).

Figures 4, **5** show the characterizing diseases by clusters (most prevalent diseases within clusters and diseases that were most prevalent compared with other clusters) in each site respectively, while **Tables 2**, **3** show exact disease prevalence, median age, median length of stay, and 30-day readmission rates of clusters.

Accordingly, each site had one stroke-oriented cluster (>90% prevalence), one among older adults in Hong Kong (Hong Kong: H9, see **Table 2**) and another among males in Zurich (Zurich: cluster Z8, see **Table 3**). In both clusters, hypertension and heart failure were relatively prevalent. **Figure 6** shows a comparison of the chord diagrams of these two clusters (H9 and Z8) representing all disease dyads in each site. Further, there was one chronic kidney disease-oriented cluster (>50% prevalence) in each site (H3 and Z3) and both clusters also featured atrial fibrillation (see **Figure 7** for chord diagram comparison). While 53% of patients in Z3 suffered from chronic pain, H3 showed the highest prevalence of myocardial infarction across clusters in Hong Kong. The only myocardial infarction-oriented cluster in the study was generated for Zurich among relatively young males (Z9). Zurich featured two additional unique clusters, i.e., epilepsy sometimes combined with chronic pulmonary disease in young patients (Z7), and hypothyroidism in older females (Z5). Several clusters in Hong Kong featured high heart failure prevalence (H2, H6, H8, H4), and chronic pain was also relatively prevalent in those clusters. Two clusters in Zurich (Z6, Z2) showed heart failure prevalence over 50%, but only Z6 had a high proportion of chronic pain. Z2 on the other hand featured the highest prevalence of peripheral vascular disease across all clusters, whereas that diagnosis was rare in Hong Kong. Some clusters in Hong Kong and Zurich had mixed features and were thus less clear, including chronic pulmonary disease with stroke and heart failure (H5), cirrhosis with severe constipation (H1), depression, dementia, and alcohol misuse (H7), chronic pain and diabetes (Z1), as well as metastatic cancer, cirrhosis, and hepatitis B (Z4).

DISCUSSION

Findings of this study provide an overview of the clustering patterns of multimorbidity based on which further investigations

FIGURE 2 | Chord diagrams showing the frequencies of disease dyads among inpatients from Hong Kong (38,964 disease dyads) and Zurich (54,052 disease dyads).

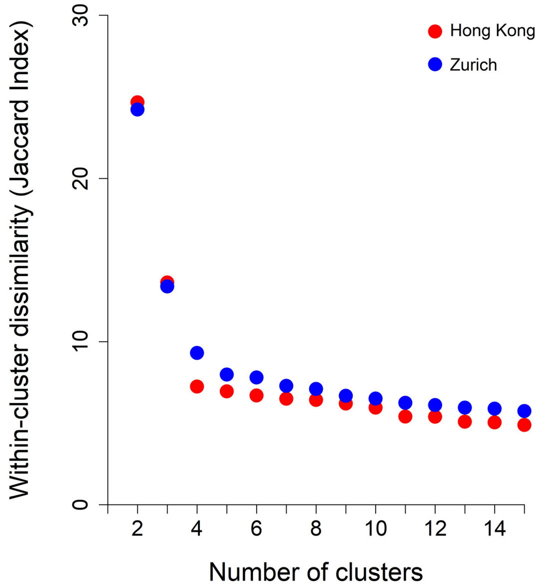


FIGURE 3 | Within-cluster dissimilarity index (measured by Jaccard Index) by number of clusters derived from hierarchical agglomerative clustering and by jurisdictions, i.e., Hong Kong and Zurich.

could be conducted to inform potential integration of services and collaboration between medical specialties. In addition, the comparison between patient records from Hong Kong and Zurich provide preliminary results on the degree of universality of multimorbidity patterns across world populations. Overall speaking, there were no striking similarities or dissimilarities of the identified clustering patterns beyond established disease relationships between the two sites, with the co-occurrence of known comorbidities being most frequently observed. Specifically, only two out of nine clusters were found to be common clusters across the two sites. In both sites, especially in Hong Kong where fewer diagnoses were recorded, disease dyads mostly fell within the same medical specialties, which may suggest the importance of integrated practices within the specialty relative to cross-specialty collaboration.

Interpretation and Implications

While a focused examination of disease prevalence within each cluster reflect only the previously identified disease relationships, the overall findings jointly represent the distribution of morbidity burden within and across clusters among multimorbid patients in a realistic healthcare setting. In other words, an overall clinical profile of multimorbid inpatients in terms of a variety of chronic conditions is presented. While the differences between the sites may be attributed to the different healthcare delivery and financing mechanisms as well as cultural and demographic factors, the identified similarities of multimorbidity patterns may suggest common specific segments of patients requiring further attention across populations, and the results convey important information on the management level for the planning and coordination of services for multimorbid patients in hospitals and other healthcare facilities. For instance, although it is commonly known that chronic kidney disease and atrial fibrillation are closely related diseases (24), our analysis further showed that patients having these two conditions constituted a significant proportion of multimorbid patients in both sites. Hence, the successful implementation of integrated care for these patients may alleviate the healthcare burden of multimorbidity significantly.

Likewise, the presence of stroke-oriented clusters which have been observed in both sites, despite having different demographics, suggest that stroke and associated morbidities (25, 26) represent a sizeable proportion of multimorbid patients in a hospital setting. While there are existing integrated services for stroke patients in typical healthcare systems of developed societies, it is also important to assess the degree to which these patients contribute to the total burden of multimorbidity.

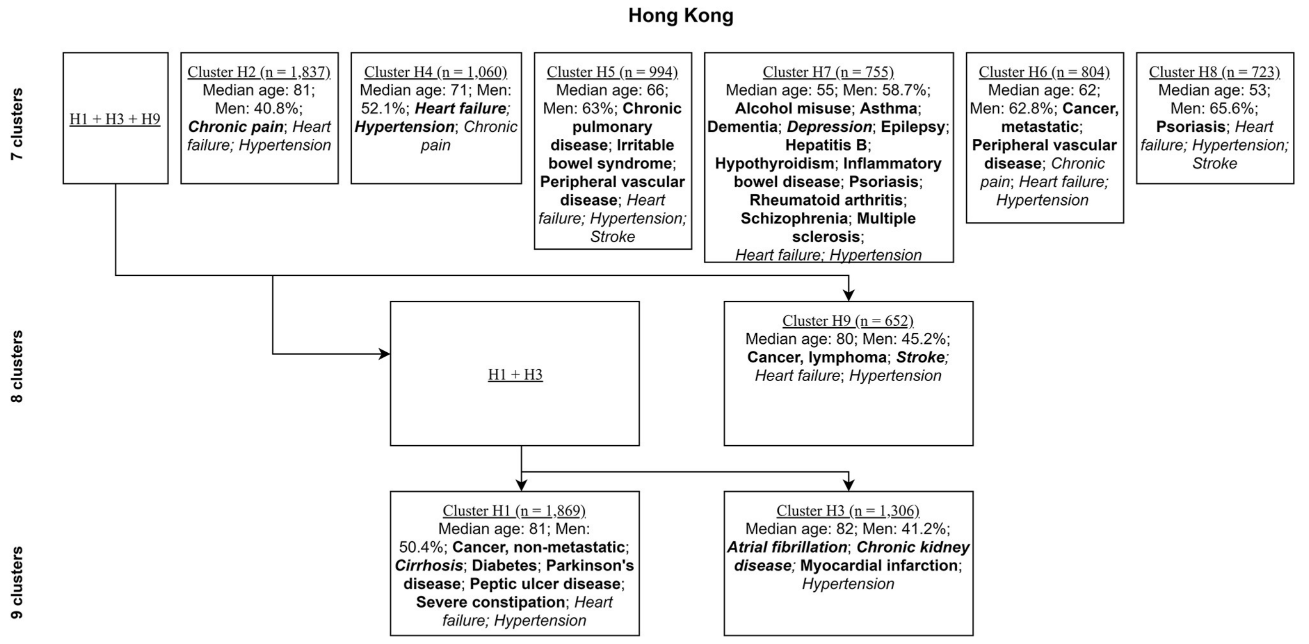
There are also unique clusters in each site which may be of clinical importance. Specifically, only in Zurich did we observe a myocardial infarction-oriented cluster (99% prevalence). Also, the prevalence of peripheral vascular disease is drastically higher in the sample of Zurich than that of Hong Kong. These results may suggest potentially different etiologies of cardiovascular diseases between Hong Kong and Zurich due to different lifestyles, living environments, and economic structures. Nevertheless, such difference may also be attributed to different specialization foci of the hospitals, different referral patterns, and other practices that may differ between sites. More observations are needed to investigate the underlying reasons.

In Hong Kong, the clusters featuring high prevalence (>65%) of heart failure also had relatively high prevalence of chronic pain, which was partially the case in Zurich. This may relate to the regular practice of hospital clinicians in the assessment of heart failure which include the report of pain (27, 28). If confirmed by further research, this begs the question whether chronic pain prevalence is currently being underestimated among patients with other diseases (without assessment of pain) and, hence, whether it is necessary to include the assessment of pain for them. In fact, the observed prevalence of heart failure is apparently higher compared with previous inpatient research in other populations, such as in Canada (29). Further research is recommended to examine the potentially underlying reasons for this difference.

In each of the two sites, there existed highly complex clusters (H7 and Z4) in which a wide variety of diseases was featured. However, as these clusters did not constitute a markedly large proportion of multimorbid patients, integrated or collaborative care for the rest of the clusters with obvious characterizing diseases should be the priority for alleviating the healthcare burden of multimorbidity.

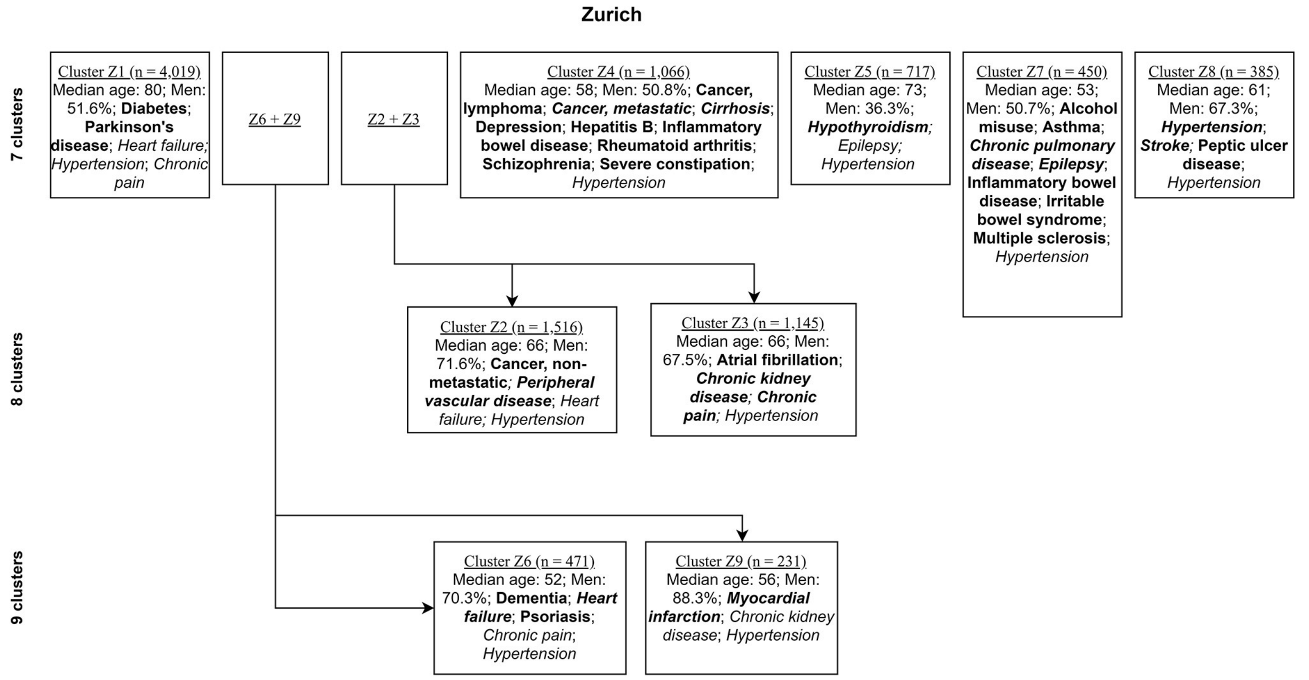
Relationship With the Literature

While the results of this study are context specific, it provides preliminary information on the replicability of multimorbidity profiling between populations. In the literature, there are at least two recent important systematic reviews on the results of multimorbidity profiling from previous research with a huge variety of statistical methods (8, 30). It has been suggested that



Bold font indicates disease prevalence that is highest in that cluster compared with other clusters
Italic font represents the three diseases with highest prevalence within that cluster

FIGURE 4 | Clustering process (from seven to nine clusters) of Hong Kong inpatients labeled with characterizing diseases.



Bold font indicates disease prevalence that is highest in that cluster compared with other clusters
Italic font represents the three diseases with highest prevalence within that cluster

FIGURE 5 | Clustering process (from seven to nine clusters) of Zurich inpatients labeled with characterizing diseases.

TABLE 2 | Prevalence of chronic conditions by cluster (Hong Kong)*.

Cluster	**H1**	**H2**	**H3**	**H4**	**H5**	**H6**	**H7**	**H8**	**H9**
N	1,869	1,837	1,306	1,060	994	804	755	723	652
Age (median [IQR])	81 [76, 86]	81 [78, 86]	82 [78, 87]	71 [68, 73]	66 [63, 69]	62 [59, 64]	55 [52, 59]	53 [50, 56]	80 [76, 84]
Length of stay (median [IQR])	5 [2, 11]	4 [2, 9]	5 [2, 9]	3 [1, 6]	4 [2, 10]	3 [2, 7]	3 [1, 7]	3 [2, 7]	11 [4, 28]
30-day readmission (%)	12.3	12.1	14.7	10.3	6.6	9.6	6.6	4.7	8.3
Male (%)	50.4	40.8	41.2	52.1	63	62.8	58.7	65.6	45.2
Chronic conditions (%)									
Alcohol misuse	2.3	0.2	0.2	0.3	1.7	0.6	**12.5**	0.6	0.8
Asthma	9.8	0.4	0.7	1.3	0.8	0.2	**10.7**	1	0.3
Atrial fibrillation	11.2	3.2	**55.8**	1.5	30.8	2.7	7.7	1.8	18.4
Cancer, lymphoma	0.1	0.3	0.1	0.1	0.2	0.1	0.7	0.4	**0.8**
Cancer, metastatic	4.8	0.4	0.5	0.4	1.9	**5.7**	3	0.1	0.5
Cancer, non-metastatic	**9.3**	1	1.1	1.2	1.2	1.2	4.8	0.4	0.6
Chronic kidney disease	12.3	6	**61.2**	6.9	9.2	20	4.2	0.3	0.2
Chronic pain	6.4	**33.8**	8.1	27.2	3.2	28.9	5	23.1	1.8
Chronic pulmonary disease	15.6	5.7	0.7	0.4	**20.7**	3.4	12.7	0.4	1.7
Cirrhosis	**34.7**	3.8	4	1	5.9	1.1	9.3	0.8	1.2
Dementia	1.1	0.7	0.8	4.3	1.7	1.6	**12.8**	2.1	0.8
Depression	2.8	0.5	0.8	2	0.2	0.6	**14.8**	0	0
Diabetes	**13**	3.6	1.1	0.5	1	0.6	0.4	0	0.9
Epilepsy	2.4	4.2	0.6	0.8	3.4	1	**13**	2.2	1.8
Heart failure	18.4	78.4	31.2	**87.4**	35.9	76.5	22.9	67.8	29.6
Hepatitis B	1	1.1	3.6	0.7	1	1.1	**4.9**	0.8	1.7
Hypertension	59.6	82.5	72.7	**84.2**	65.9	70.5	39.3	83.3	83
Hypothyroidism	5.9	0.3	1.1	0.7	1.4	0.2	**8.6**	0.7	1.7
Inflammatory bowel disease	0	0	0	0	0.4	0	**0.5**	0	0
Irritable bowel syndrome	0.2	0	0	0.1	**0.4**	0	0	0.1	0.2
Multiple sclerosis	0.1	0	0	0.1	0.1	0.4	**0.9**	0.1	0
Myocardial infarction	0.9	0.4	**14.5**	0.8	1.9	14.1	4.4	2.2	0.5
Parkinson's disease	**8.6**	0.8	1.1	0.3	4.3	0.4	0.4	0	0.2
Peptic ulcer disease	**4.9**	0.4	1.1	2.6	1.3	1.7	2.5	0.3	0.6
Peripheral vascular disease	0	0	0	**0.1**	**0.1**	**0.1**	0	0	0
Psoriasis	0.1	0.1	0	0.5	0.3	0.4	**0.7**	**0.7**	0.3
Rheumatoid arthritis	1	3.1	0.6	0.1	1.5	0.1	**9.8**	0.1	0.2
Schizophrenia	0.4	1.9	0.3	4.9	0.8	0.2	**7.3**	0.8	0.3
Severe constipation	**13.1**	1	1.5	0.8	6.7	2.5	7.3	0	2.1
Stroke	4.6	2	4.4	7.5	39.3	1.4	3.8	35.4	**96.8**

**Bold font denotes the cluster in which the corresponding disease is most prevalent (compared with all other clusters). Underscore denotes the most prevalent three diseases within each cluster.*

with the exceptions of mental and cardiovascular patterns, other patterns did not seem to show good evidence of universality across populations even when stratified by statistical methods of multimorbidity profiling (30). However, even with highly sophisticated meta-analytic approaches, it should be noted that across studies, different ranges of chronic conditions and specifications of statistical analyses were adopted. Therefore, evidence from analyses with the same methods on different populations is important to further our understanding. This study is one of the first attempts to narrow such a gap and as far as we are aware, this is the first study to adopt hierarchical agglomerative clustering analysis to compare multimorbid patient clustering patterns.

Strengths and Limitations

Despite this novelty and the methodological strength of the well-validated algorithms to define chronic conditions using ICD-9 and ICD-10, this study has several limitations that require caution in interpreting the results. First, while the Hong Kong data are highly representative of the inpatients of the public sector, we do not have access to patient records in the private sector which may specialize in certain different conditions from those found prevalent in our sample. Also, University Hospital Zurich was our only source of Zurich data; nevertheless, it is a well-established general acute hospital representing diverse patient intake and standard practices. Second, the validity and comprehensiveness of diagnostic codes may differ between sites

TABLE 3 | Prevalence of chronic conditions by cluster (Zurich)*.

Cluster	Z1	Z2	Z3	Z4	Z5	Z6	Z7	Z8	Z9
N	4,019	1,516	1,145	1,066	717	471	450	385	231
Age (median [IQR])	80 [75, 84]	66 [61, 69]	66 [62, 70]	58 [53, 63]	73 [68, 80]	52 [49, 54]	53 [49, 57]	61 [54, 66]	56 [52, 61]
Length of stay (median [IQR])	8 [3, 14]	5 [2, 10]	7 [3, 13]	9 [4, 15]	8 [4, 14]	7 [3, 13]	8 [4, 16]	11 [7, 17]	5 [2, 9]
30-day readmission (%)	11	11.6	15.5	16	10.6	11	9.1	7	9.5
Male (%)	51.6	71.6	67.5	50.8	36.3	70.3	50.7	67.3	88.3
Chronic conditions (%)									
Alcohol misuse	2.3	14.6	2.5	12.2	2.5	11	**16.4**	7	3
Asthma	1.8	3.3	1.4	2.1	1.5	2.8	**6.9**	0.3	0.9
Atrial fibrillation	7.6	2.1	**20.2**	1.5	6	1.9	1.1	1.6	3
Cancer, lymphoma	1.7	0.6	1.3	**7.1**	1.5	1.5	2.2	0	0
Cancer, metastatic	7.7	1.6	1.6	**35.6**	2.8	0.6	2.2	1	0
Cancer, non-metastatic	3.6	**15.8**	1.7	3.5	4.9	0.4	0.4	0.3	0
Chronic kidney disease	19.1	3.4	**53**	2.7	10.3	25.3	3.6	4.2	18.6
Chronic pain	35.2	9.4	**50.2**	16.8	24.4	49.7	7.1	1.6	2.6
Chronic pulmonary disease	10.1	2.9	3.6	6.4	6.7	1.9	**46.9**	0.3	0.4
Cirrhosis	11.3	10.1	11.7	**19.8**	3.5	3	3.3	2.1	1.7
Dementia	0.1	0.8	0.3	0.8	0	**1.9**	1.1	0.3	0.9
Depression	0.6	3.8	0.2	**6.6**	0.4	2.1	1.1	0.3	0
Diabetes	**8.6**	0.5	1.4	0.8	3.6	0.6	0.2	0.5	0
Epilepsy	2.6	1.8	3.1	9.1	45.6	5.3	**68.7**	2.9	2.6
Heart failure	29.2	51.1	26.7	7.4	22.9	**54.8**	14.7	19	14.3
Hepatitis B	5.4	1.1	1.1	**18.3**	2	1.7	4	2.3	2.6
Hypertension	81.1	81.3	73.7	46.4	71.7	77.9	48.9	**86.2**	74.9
Hypothyroidism	4.2	1.4	3.3	17.7	**59.1**	2.5	8.7	5.2	1.7
Inflammatory bowel disease	0.5	0.6	0.9	**1.3**	0.8	0.4	**1.3**	1	0
Irritable bowel syndrome	0.1	0.1	0	0.3	0.3	0	**1.1**	0	0
Multiple sclerosis	0.2	0.4	1	0.8	0	0.2	**3.1**	0.3	0
Myocardial infarction	8.7	11.9	6.2	1.3	1.5	5.7	1.1	1.6	**98.7**
Parkinson's disease	**3.3**	0.1	0.6	0.5	2	0.4	0.4	0	0.4
Peptic ulcer disease	0.4	0.8	0.4	0.8	0.8	0.2	0.2	**1.6**	0
Peripheral vascular disease	12.8	**26.2**	5	1.9	4.3	3.6	0.4	1	0.9
Psoriasis	0.4	1.4	0.5	0.5	0.7	**1.5**	1.1	0	0.4
Rheumatoid arthritis	4.1	2.2	1.6	**8**	1.7	1.5	3.8	2.6	0
Schizophrenia	0.3	0.7	0.6	**4.1**	1.3	1.1	0.7	0.8	0
Severe constipation	1.5	0.7	0.9	**6.6**	2.2	1.1	0.9	1.3	0.4
Stroke	17.1	1.8	4.3	7.6	3.6	0.6	2.2	**98.7**	0.4

**Bold font denotes the cluster in which the corresponding disease is most prevalent (compared with all other clusters). Underscore denotes the most prevalent three diseases within each cluster.*

and may not be sufficiently reflective of the comparison of the true prevalence, especially considering the different healthcare financing mechanisms (social insurance in Zurich and taxation in Hong Kong), infrastructures, medical training, and practice culture, which might have considerable influence on disease coding practices (31). That might also have contributed to the rare coding of peripheral vascular disease in Hong Kong. Also, the codes were based on only one admission instead of a longitudinal assessment. Nevertheless, disease diagnoses were made by registered clinicians in each of the sites, then complemented by ICD codes given by professional teams and can therefore be reasonably considered a reliable source of disease codes in the given settings of this study. Third, inpatient data are limited to those who have already been admitted due to acute symptoms, and therefore do not represent community prevalence. For example, despite higher screening prevalence of hepatitis B in Hong Kong than Zurich (32), the observed prevalence in our Hong Kong sample is lower than that in our Zurich sample. Therefore, the findings are not readily generalizable to the outpatient populations in which multimorbid patients requiring chronic care and medications are typically better represented. Future studies are recommended to include outpatient samples with well-maintained data coding consistency and quality. Fourth, there may be under-coding of diagnoses for which no specific screening is in place upon hospital admission in general, such as mental disorders. Fifth, we only adopted

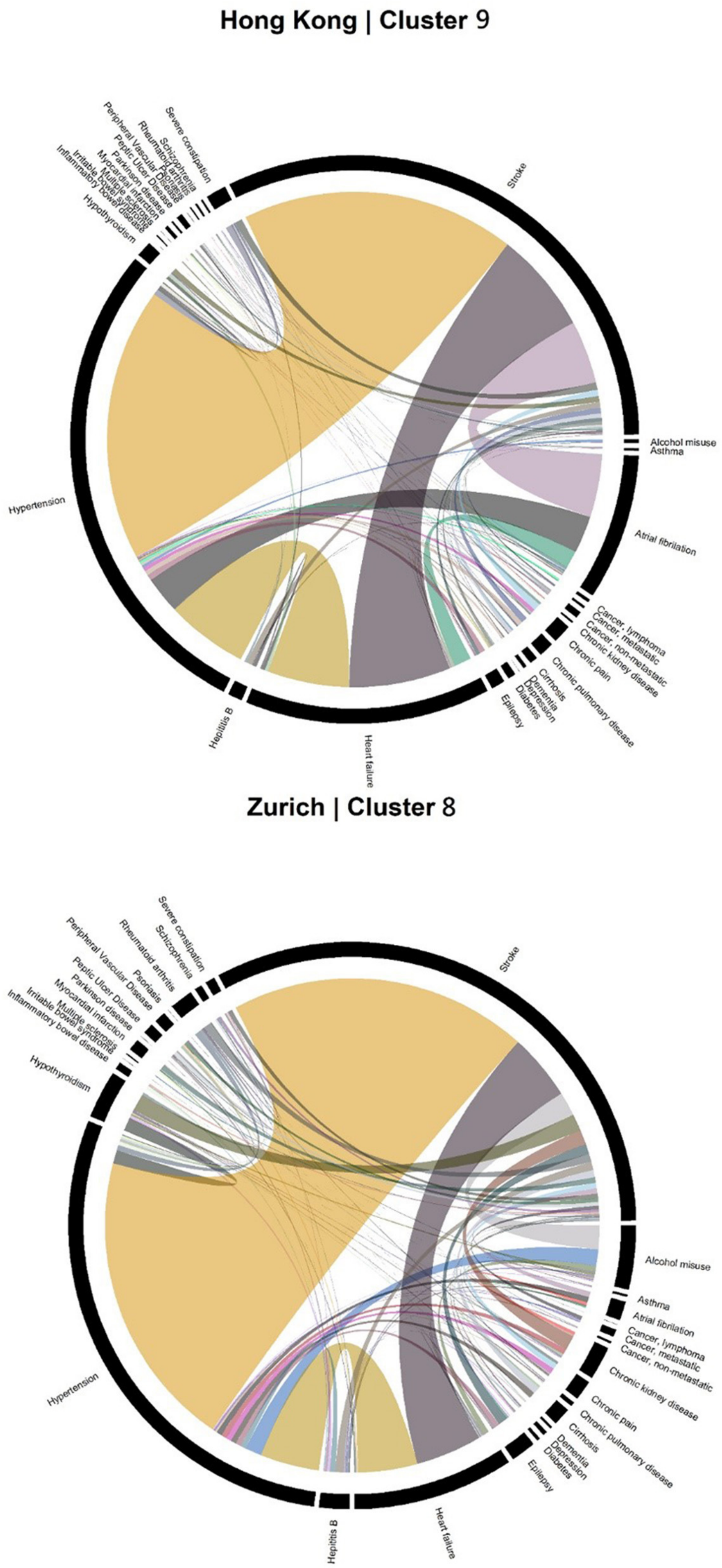


FIGURE 6 | Chord diagrams showing the frequencies of disease dyads among inpatients from Cluster H9 of Hong Kong and Cluster Z8 of Zurich (stroke clusters).

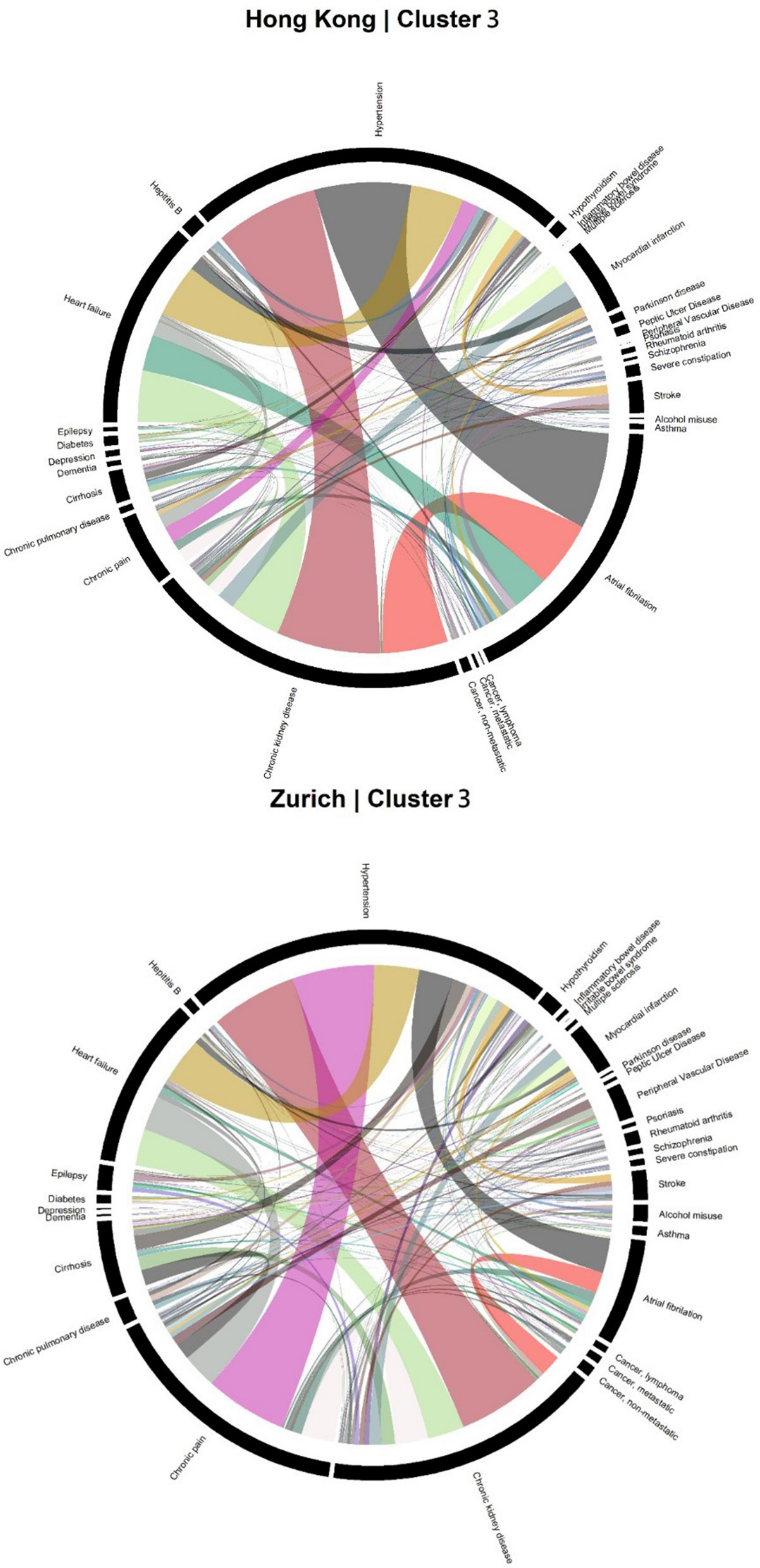


FIGURE 7 | Chord diagrams showing the frequencies of disease dyads among inpatients from Cluster H3 of Hong Kong and Cluster Z3 of Zurich (chronic kidney disease clusters).

a limited predetermined list of 30 diseases for the clustering analysis. Diseases not included in the list were not used for multimorbidity profiling. However, this approach allowed us to use well-validated algorithms (20) that enable first insight into the question of universality without having to validate these algorithms for the specific settings. Importantly, the present study provides preliminary evidence of some degree of universality across populations. Sixth, the comparison between the sites were mainly qualitative and no statistical tests were applied to quantitatively summarize the differences of the clustering patterns. However, our approach was a combination of clinical reasoning and exploratory machine learning methods in addressing the problem, which may facilitate future research with similar purposes. Last but not least, as the sample were randomly drawn from the Hong Kong and Zurich populations only, external generalizability is limited and the analysis should be replicated in other populations to verify the results.

To conclude, we conducted a hierarchical agglomerative clustering analysis on discharged inpatients from Hong Kong and Zurich based on a list of 30 diseases and provided findings on the universality of multimorbidity patterns across inpatient populations from the two places. Results should be facilitative of the experimentation and development of integrated or collaborative care for multimorbid patients in the healthcare systems of both populations. Future research should adopt more representative samples, longitudinal disease coding, and comprehensive lists of chronic conditions to verify results of this study and make recommendations on the care planning and coordination of services for multimorbid inpatients.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Authorization to access the data may be considered by the Hospital Authority of Hong Kong upon reasonable requests. Requests to access these datasets should be directed to Hospital Authority of Hong Kong, hacpaaedr@ha.org.hk.

ETHICS STATEMENT

An ethics waiver has been granted by Cantonal Ethics Committee of Zurich for the analysis of Zurich inpatient data (Ref: NZ-B-Nr.2017-00882) while the analysis of Hong Kong inpatient data was approved by the Survey and Behavioral Ethics Committee of the Chinese University of Hong Kong (Project Code: Elderly Care – CUHK). As only secondary analysis of anonymized inpatient data was performed, no informed consent was required.

AUTHOR CONTRIBUTIONS

FL and PB conceptualized the study design, conducted the analysis, and drafted the manuscript. EB and SW supervised the analysis and result interpretation and critically commented on the manuscript drafts. All authors contributed to the interpretation of results and helped revise the manuscript.

FUNDING

This work was partially supported by a commissioned grant from the Health and Medical Research Fund (HMRF) of the Food and Health Bureau of the Government of the Hong Kong Special Administrative Region (Project Code: Elderly Care – CUHK). FL was supported by the RGC Postdoctoral Fellowship 2020/21 (inaugural exercise) under the Research Grants Council, University Grants Committee, Hong Kong SAR (Ref: PDFS2021-4H03).

ACKNOWLEDGMENTS

The authors gratefully acknowledge the Hospital Authority of Hong Kong and University Hospital Zurich for the generous provision of data.

REFERENCES

1. Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. Defining and measuring multimorbidity: a systematic review of systematic reviews. *Eur J Public Health.* (2018) 29:182-9. doi: 10.1093/eurpub/cky098
2. Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. *Health Qual Life Outcomes.* (2004) 2:51. doi: 10.1186/1477-7525-2-51
3. Mondor L, Maxwell CJ, Hogan DB, Bronskill SE, Gruneir A, Lane NE, et al. Multimorbidity and healthcare utilization among home care clients with dementia in Ontario, Canada: a retrospective analysis of a population-based cohort. *PLoS Med.* (2017) 14:e1002249. doi: 10.1371/journal.pmed.1002249
4. Lai FTT, Ma TW, Hou WK. Multimorbidity is associated with more subsequent depressive symptoms in three months: a prospective study of community-dwelling adults in Hong Kong. *Int Psychogeriatr.* (2019) 31:1367–71. doi: 10.1017/S1041610218001916
5. Lai FTT, Wong SYS, Yip BHK, Guthrie B, Mercer SW, Chung RY, et al. Multimorbidity in middle age predicts more subsequent hospital admissions than in older age: a nine-year retrospective cohort study of 121,188 discharged in-patients. *Eur J Intern Med.* (2019) 61:103–11. doi: 10.1016/j.ejim.2018.12.001
6. Salisbury C, Man MS, Bower P, Guthrie B, Chaplin K, Gaunt DM, et al. Management of multimorbidity using a patient-centred care model: a pragmatic cluster-randomised trial of the 3D approach. *Lancet.* (2018) 41–50. doi: 10.1016/S0140-6736(18)31308-4
7. Gunn J. Designing care for people with mixed mental and physical multimorbidity. *BMJ.* (2015) 350:h712. doi: 10.1136/bmj.h712
8. Ng SK, Tawiah R, Sawyer M, Scuffham P. Patterns of multimorbid health conditions: a systematic review of analytical methods and comparison analysis. *Int J Epidemiol.* (2018) 47:1687-704. doi: 10.1093/ije/dyy134
9. Schiltz NK, Warner DF, Sun J, Bakaki PM, Dor A, Given CW, et al. Identifying specific combinations of multimorbidity that contribute to health care resource utilization: an analytic approach. *Med Care.* (2017) 55:276-84. doi: 10.1097/MLR.0000000000000660
10. Smith SM, O'Kelly S, O'Dowd T. GPs' and pharmacists' experiences of managing multimorbidity: a "Pandora's box." *Br J Gen Pract.* (2010) 60:285-94. doi: 10.3399/bjgp10X514756

11. Kamerow D. How can we treat multiple chronic conditions? *BMJ.* (2012) 344:e1487. doi: 10.1136/bmj.e1487
12. Uhlig K, Leff B, Kent D, Dy S, Brunnhuber K, Burgers JS, et al. A framework for crafting clinical practice guidelines that are relevant to the care and management of people with multimorbidity. *J Gen Intern Med.* (2014) 29:670–9. doi: 10.1007/s11606-013-2659-y
13. Smith SM, Soubhi H, Fortin M, Hudon C, O'Dowd T. Managing patients with multimorbidity: systematic review of interventions in primary care and community settings. *BMJ.* (2012) 345:e5205. doi: 10.1136/bmj.e5205
14. Muth C, Kirchner H, van den Akker M, Scherer M, Glasziou PP. Current guidelines poorly address multimorbidity: pilot of the interaction matrix method. *J Clin Epidemiol.* (2014) 67:1242–50. doi: 10.1016/j.jclinepi.2014.07.004
15. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet.* (2012) 380:37–43. doi: 10.1016/S0140-6736(12)60240-2
16. Tinetti ME, Bogardus STJ, Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *N Engl J Med.* (2004) 351:2870–4. doi: 10.1056/NEJMsb042458
17. Prados-Torres A, Calderon-Larranaga A, Hancco-Saavedra J, Poblador-Plou B, van den Akker M. Multimorbidity patterns: a systematic review. *J Clin Epidemiol.* (2014) 67:254–66. doi: 10.1016/j.jclinepi.2013.09.021
18. Newcomer SR, Steiner JF, Bayliss EA. Identifying subgroups of complex patients with cluster analysis. *Am J Manag Care.* (2011) 17:e324-32. Available online at: https://cdn.sanity.io/files/0vv8moc6/ajmc/dd33b539149a32222aa8c483eeebf720a0b7bb5d.pdf/948a54555554eb134cf52e6662520b33.pdf
19. Garin N, Koyanagi A, Chatterji S, Tyrovolas S, Olaya B, Leonardi M, et al. Global multimorbidity patterns: a cross-sectional, population-based, multi-country study. *J Gerontol A Biol Sci Med Sci.* (2016) 71:205–14. doi: 10.1093/gerona/glv128
20. Tonelli M, Wiebe N, Fortin M, Guthrie B, Hemmelgarn BR, James MT, et al. Methods for identifying 30 chronic conditions: application to administrative data. *BMC Med Inform Decis Mak.* (2015) 15:1–11. doi: 10.1186/s12911-015-0155-5
21. Ripley BD. *Stochastic Simulation*. New York, NY: Wiley (2009).
22. Dolnicar S, Grün B, Leisch F, Schmidt K. Required sample sizes for data-driven market segmentation analyses in tourism. *J Travel Res.* (2013) 53:296–306. doi: 10.1177/0047287513496475
23. Milligan GW, Cooper MC. A study of the comparability of external criteria for hierarchical cluster analysis. *Multivariate Behav Res.* (1986) 21:441–58. doi: 10.1207/s15327906mbr2104_5
24. Soliman EZ, Prineas RJ, Go AS, Xie D, Lash JP, Rahman M, et al. Chronic kidney disease and prevalent atrial fibrillation: the chronic renal insufficiency cohort (CRIC). *Am Heart J.* (2010) 159:1102–7. doi: 10.1016/j.ahj.2010.03.027
25. Lai FTT, Mercer SW, Guthrie B, Yip BHK, Chung GKK, Zou D, et al. Sociodemographic moderation of the association between depression and stroke incidence in a retrospective cohort of 0.4 million primary care recipients with hypertension. *Psychol Med.* (2020) 1–9. doi: 10.1017/S0033291720001920
26. Kitzman PH, Sutton KM, Wolfe M, Bellamy L, Dobbs MR. The prevalence of multiple comorbidities in stroke survivors in rural appalachia and the clinical care implications. *J Stroke Cerebrovasc Dis.* (2019) 28:104358. doi: 10.1016/j.jstrokecerebrovasdis.2019.104358
27. Goodlin SJ, Wingate S, Albert NM, Pressler SJ, Houser J, Kwon J, et al. Investigating pain in heart failure patients: the pain assessment, incidence, and nature in heart failure (PAIN-HF) study. *J Card Fail.* (2012) 18:776–83. doi: 10.1016/j.cardfail.2012.07.007
28. Yu DS, Chan HY, Leung DY, Hui E, Sit JW. Symptom clusters and quality of life among patients with advanced heart failure. *J Geriatr Cardiol.* (2016) 13:408–14. doi: 10.11909/j.issn.1671-5411.2016.05.014
29. Verma AA, Guo Y, Kwan JL, Lapointe-Shaw L, Rawal S, Tang T, et al. Prevalence and costs of discharge diagnoses in inpatient general internal medicine: a multi-center cross-sectional study. *J Gen Intern Med.* (2018) 33:1899–904. doi: 10.1007/s11606-018-4591-7
30. Busija L, Lim K, Szoeke C, Sanders KM, McCabe MP. Do replicable profiles of multimorbidity exist? Systematic review and synthesis. *Eur J Epidemiol.* (2019) 34:1025–53. doi: 10.1007/s10654-019-00568-5
31. Fiedler BA, Greathouse LJ. "Chapter 12 - Evaluating reimbursement strategies in the US," In: Fiedler BA, editor. *Managing Medical Devices Within a Regulatory Framework*. Oxford: Elsevier (2016). p. 203–24.
32. Razavi-Shearer D, Gamkrelidze I, Nguyen MH, Chen D-S, Van Damme P, Abbas Z, et al. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol.* (2018) 3:383–403. doi: 10.1016/S2468-1253(18)30199-7

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 01 December 2021
doi: 10.3389/fmed.2021.778434

COVID-19 Post-acute Sequelae Among Adults: 12 Month Mortality Risk

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Background: There are concerns regarding post-acute sequelae of COVID-19, but it is unclear whether COVID-19 poses a significant downstream mortality risk. The objective was to determine the relationship between COVID-19 infection and 12-month mortality after recovery from the initial episode of COVID-19 in adult patients.

Methods: An analysis of electronic health records (EHR) was performed for a cohort of 13,638 patients, including COVID-19 positive and a comparison group of COVID-19 negative patients, who were followed for 12 months post COVID-19 episode at one health system. Both COVID-19 positive patients and COVID-19 negative patients were PCR validated. COVID-19 positive patients were classified as severe if they were hospitalized within the first 30 days of the date of their initial positive test. The 12-month risk of mortality was assessed in unadjusted Cox regressions and those adjusted for age, sex, race and comorbidities. Separate subgroup analyses were conducted for (a) patients aged 65 and older and (b) those <65 years.

Results: Of the 13,638 patients included in this cohort, 178 had severe COVID-19, 246 had mild/moderate COVID-19, and 13,214 were COVID-19 negative. In the cohort, 2,686 died in the 12-month period. The 12-month adjusted all-cause mortality risk was significantly higher for patients with severe COVID-19 compared to both COVID-19 negative patients (HR 2.50; 95% CI 2.02, 3.09) and mild COVID-19 patients (HR 1.87; 95% CI 1.28, 2.74). The vast majority of deaths (79.5%) were for causes other than respiratory or cardiovascular conditions. Among patients aged <65 years, the pattern was similar but the mortality risk for patients with severe COVID-19 was increased compared to both COVID-19 negative patients (HR 3.33; 95% CI 2.35, 4.73) and mild COVID-19 patients (HR 2.83; 95% CI 1.59, 5.04). Patients aged 65 and older with severe COVID-19 were also at increased 12-month mortality risk compared to COVID-19 negative patients (HR 2.17; 95% CI 1.66, 2.84) but not mild COVID-19 patients (HR 1.41; 95% CI 0.84, 2.34).

Discussion: Patients with a COVID-19 hospitalization were at significantly increased risk for future mortality. In a time when nearly all COVID-19 hospitalizations are preventable this study points to an important and under-investigated sequela of COVID-19 and the corresponding need for prevention.

Keywords: COVID-19, mortality, cohort, adult, post COVID

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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Medicine

Received: *16 September 2021*
Accepted: *01 November 2021*
Published: *01 December 2021*

Citation:
Mainous III AG, Rooks BJ, Wu V and Orlando FA (2021) COVID-19 Post-acute Sequelae Among Adults: 12 Month Mortality Risk. Front. Med. 8:778434. doi: 10.3389/fmed.2021.778434

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has had devastating consequences on the global population. In terms of directly measured outcomes, by August 2021, COVID-19 has resulted in more than 4.2 million direct deaths worldwide, and more than 600,000 direct deaths in the United States alone (1). Millions of people globally have recovered from the illness, and there has been significant interest into the impacts of a COVID-19 infection on patients after the patient has recovered.

Post-acute sequelae of COVID-19 is not well understood. For some patients, the post-acute complications can affect multiple organ systems and persist for many months affecting quality of life (2–7). Severe complications like post-acute thrombosis, respiratory failure, and cardiac and vascular damage may increase the likelihood of future morbidity and mortality in recovered COVID-19 patients (8–10). The data from cohort studies investigating these long-term complications post COVID-19 infection is quite limited, and studies mainly focus on complications leading to re-admission rather than post-acute complications (11–14). One study suggested that COVID-19 infection carries an increased 6-month mortality risk (15).

A recent study focusing on hospitalizations for post-acute sequelae of COVID-19 suggested that severe COVID-19 (defined as a COVID-19 hospitalization) confers a greater risk of downstream hospitalization than either COVID-19 negative patients or even mild COVID-19 (16). It is unclear, however, whether a severe COVID-19 infection places patients at a greater 12-month mortality risk beyond the initial episode of infection. Moreover, little research has focused on post-acute COVID-19 sequelae for younger vs. older patients.

The purpose of this study was to examine the post-acute COVID-19 sequelae on 12-month mortality, specifically examining differences in risk between patients with severe COVID-19, mild COVID-19 and no COVID-19. This 12-month risk was examined in a longitudinal cohort of patients who tested either positive or negative for COVID-19 as determined by Polymerase Chain Reaction (PCR) testing within in a large healthcare system.

METHODS

The data for this project comes from a de-identified research databank containing electronic health records (EHR) of patients tested for or diagnosed with COVID-19 in any setting in the University of Florida (UF) Health system. The dataset compiles line-level diagnosis, treatment, resource utilization and outcome information on UF Health patients with COVID-19-like symptoms or who have undergone COVID-19 clinical testing as recorded in the UF Health Epic EHR. The data include qualifying patients seen at UF Health locations in Gainesville and Jacksonville since Jan 1, 2020. Usage of the databank for research is not considered human subjects research, and IRB review was not required to conduct this study.

Definition of Cohort

The cohort for this study consisted of all adult patients aged 18 and older who were tested for COVID-19 between 01/01/2020 and 06/30/2020 within the UF Health system, in any encounter type (ambulatory, Emergency Department, inpatient, etc.). The databank contained EHR data for all patients in the cohort current through 06/30/2021. COVID-19 diagnosis was validated by PCR. Baseline dates for COVID-19 positive patients were established at the date of their earliest recorded PCR-confirmed positive COVID-19 test, and baseline for COVID-19 negative patients was assessed at the earliest recorded negative COVID-19 test. Each patient was only included once in the analysis. For patients with multiple COVID-19 tests, if at least one test gave a positive result, the patient was classified as COVID-19 positive, and the date of their earliest positive COVID-19 test result was used as their baseline date. For patients with multiple COVID-19 tests which were all negative, the patient was classified as COVID-19 negative, and the date of their earliest negative COVID-19 test results was used as their baseline date. Patients were tested in the context of seeking care for COVID-19; the tests were not part of general screening and surveillance.

Only patients with at least 365 days of follow-up time after their baseline date were retained in the cohort. Patients with more than 365 days of follow-up were censored at 365 days. COVID-19 positive patients were also categorized as having had either a severe or mild/moderate COVID-19. Patients seen only in an outpatient setting were classified as having mild/moderate COVID-19, while those who were hospitalized for any reason during their first 30 days of follow-up were classified as severe.

Our analysis was undertaken including patients early in the pandemic with the understanding that the International Classification of Diseases-10 (ICD-10) code for a confirmed COVID-19 diagnosis was not issued until April 1, 2020, yet our sample included patients beginning in January 1, 2020, a time frame that included hospitalizations before the ICD-10 code existed (17). We attempted to validate if the primary diagnosis for the hospital encounter was for COVID-19 by examining if the COVID-19 positive patient who was hospitalized was diagnosed with COVID-19 according to the ICD-10 code of U07.1.

The cohort was also censored for 30 days post-baseline in the COVID-19 negative patients or until 30 days post hospital discharge for the severe COVID-19 patients to ensure that health care utilization was post-acute and not part of the initial COVID-19 episode of care (e.g., not a readmission). For COVID-19 negative patients, both patients who were and were not hospitalized within the first 30 days of follow-up were included in the analysis. This left-hand censoring allows us to consider the outcome to be a post-acute sequelae distinct from the initial COVID-19 episode.

Outcome Variables

The primary outcome investigated in this study was the 365-day all-cause mortality rate. Mortality data was sourced both from EHR data and the Social Security Death Index (SSDI), allowing for the assessment of deaths which occurred outside of UF's healthcare system. When conflicting dates of death were observed between the EHR and SSDI, the date recorded in the

TABLE 1 | Diagnosis codes for analyzed outcomes and comorbidities.

Outcome conditions	ICD-10/ICD-9 codes
Cardiovascular diagnoses	
Heart failure	I21
Myocardial infarction	I50, I11.0, I13.0, I13.2
Stroke	G46, I63, I69
Respiratory diagnoses	
Pneumonia	J12, J13, J15, J16, J17, J18, J82, J84
Acute respiratory distress syndrome	J80, J96
Hypoxemia	R09.02

patient's medical record was used. Patients who died within their 365-day follow-up window were censored at the date of their recorded death. Patients who died within the first 30 days of their baseline COVID-19 test were excluded from the analysis as well patients whose mortality status was unknown. Based on previous literature regarding organ systems affected by COVID-19 and likely complications, additional analyses on condition-specific mortality were performed for cardiovascular or respiratory-related causes of death (8–10). As the cause of death was not directly recorded in the either the SSDI or EHR, causes of death were estimated algorithmically. For patients who were hospitalized within the 30 days preceding their death, a patient was considered to have died of a cardiovascular, or respiratory-related condition if an ICD-10 code corresponding to one of these conditions was associated with an inpatient encounter. The targeted conditions investigated as cardiovascular outcomes were myocardial infarction, heart failure, and stroke. The respiratory conditions were pneumonia, hypoxemia, and acute respiratory distress syndrome. The ICD-10 codes used to define these outcomes are given in **Table 1**.

Comorbidities

Comorbidities and demographic variables which could potentially confound the associations between mild/moderate COVID-19, severe COVID-19, and no COVID-19 and mortality for post-acute COVID-19 complications were collected at baseline for each member of the cohort. Demographic variables included patient age, race, ethnicity, and sex. The Charlson Comorbidity Index was also calculated, accounting for the conditions present for each patient at their baseline. The Charlson was designed to be used to predict 1 year mortality and is a widely used measure to account for comorbidities.

Analysis

Hazard ratios for the risk of death for post-acute COVID-19 complications by COVID-19 status were determined using Cox proportional hazard models. We obtained hazard ratios for mortality based on COVID-19 diagnosis category, using COVID-19 negative status as the reference. These analyses were then modified to control for age, sex, race, ethnicity, and the Charlson Comorbidity Index.

Additional analyses stratified by age (above/below age 65) were performed to compare the strength of the association between COVID-19 status and mortality between the two subgroups. The proportional hazards assumption was confirmed by inspection of the Schoenfeld residual plots for each variable included in the models and testing of the time-dependent beta coefficients. Analyses were conducted using the survival package in R v4.0.5.

RESULTS

A total of 13,638 patients were included in the final cohort, of whom 178 (1.31%) were classified as severe COVID-19, 246 (1.80%) as moderate/mild COVID-19, and 13,214 (96.9%) as no COVID-19 patients. The characteristics of the sample split into the three groups of (a) mild/moderate COVID-19, (b) severe COVID-19 and (c) negative COVID-19 is shown in **Table 2**. Among COVID-19 PCR positive patients who were hospitalized beginning January 1, 2020, 86.5% of the patients had the ICD-10 code (U07.1) released in April, 2020 for a confirmed COVID-19 diagnosis. **Figure 1** presents the Kaplan-Meier curves comparing the risk of mortality for all conditions by COVID-19 severity. The risk of mortality post COVID-19 infection is presented in **Table 3**. In both unadjusted and adjusted analyses, severe COVID-19 infection has a significantly increased risk compared to those with no COVID-19. In addition to the greater mortality risk relative to no COVID-19, the severe COVID-19 group had a significantly increased risk of death compared to the mild/moderate COVID-19 group in adjusted analyses. The mild/moderate COVID-19 patients were not at increased risk of death compared to the COVID-19 negative group.

Age-specific hazard ratios for all-cause mortality were also determined. Among patients 65 and older, a significantly increased risk of death was observed between patients with severe COVID-19 and no COVID-19. Among patients under 65, a greater significantly increased risk of death between severe COVID-19 and no COVID-19 was observed. The ratio of hazard ratios derived from the interaction between age-grouping and severe COVID-19 was statistically significant (HRR = 1.62; 95% CI: 1.05, 2.51), suggesting that patients under 65 with severe COVID-19 have a higher mortality risk than patients aged 65 and older with severe COVID-19 relative to patients with no COVID-19. No effect between mild/moderate COVID-19 and mortality was observed in either subgroup.

The number of deaths when attempting to classify them by cause of death indicated the majority of patients who had COVID-19 died of other causes than respiratory or cardiovascular. Only 20.5% of the post-acute COVID-19 deaths were for respiratory or cardiovascular causes. Among the total cohort, the risk of mortality because of respiratory disease for severe COVID vs. no COVID was HR 4.58 (2.58, 8.13). Similarly, among the total cohort, the risk of cardiovascular mortality for severe COVID vs. no COVID was HR 3.13 (95% CI 1.64, 5.97).

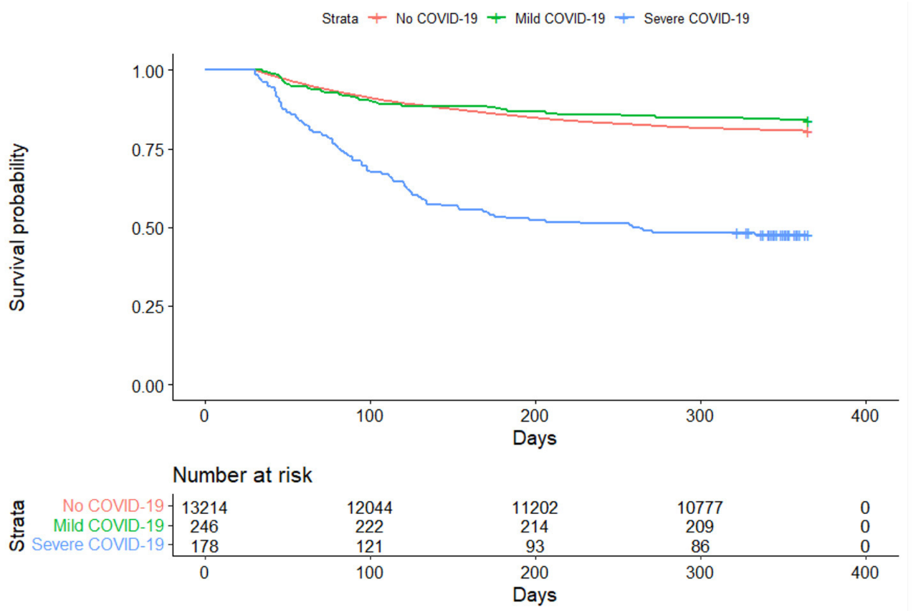

FIGURE 1 | Kaplan-Meier curve comparing all-cause mortality between COVID-19 positive and COVID-19 negative patients.

TABLE 2 | Characteristics of the COVID-19 positive and COVID-19 negative patients in the cohort.

	Total (*n* = 13,638)	**Severe COVID-19 (*n* = 178)**	**Mild/Moderate COVID-19 (*n* = 246)**	**No COVID-19 (*n* = 13,214)**
No. (%) with data				
All-cause deaths	2,686 (19.7%)	93 (52.2%)	39 (15.9%)	2,554 (19.3%)
Cardiovascular deaths	191 (1.4%)	11 (6.2%)	1 (0.04%)	179 (1.4%)
Respiratory deaths	181 (1.3%)	13 (7.3%)	2 (0.8%)	166 (1.3%)
Male	5,674 (41.6%)	75 (42.1%)	87 (35.4%)	5,512 (41.7%)
Non-Hispanic White	8,706 (63.8%)	86 (48.3%)	113 (45.9%)	8,507 (64.4%)
Non-Hispanic Black	3,379 (24.7%)	76 (42.7%)	80 (32.5%)	3,223 (24.3%)
Hispanic	764 (5.6%)	5 (2.8%)	32 (13.0%)	727 (5.5%)
Age				
Under 65	8,801 (64.5%)	81 (45.5%)	196 (79.7%)	8,524 (64.5%)
65+	4,837 (35.5%)	97 (54.5%)	50 (20.3%)	4,690 (35.5%)
Charlson Comorbidity Index score	6,753 (49.5%)	46 (25.8%)	181 (73.6%)	6,526 (49.4%)
0–1				
2–3	2,856 (20.9%)	48 (27.0%)	23 (9.3%)	2,980 (22.6%)
4+	3,834 (28.1%)	84 (47.2%)	42 (17.1%)	3,708 (28.1%)

DISCUSSION

These results support previous findings indicating that there is a substantial impact on the likelihood of severe post-acute COVID-19 sequelae depending on the severity of the initial COVID-19 episode (16). This study provides evidence that the increased risk of death from COVID-19 is not limited to the initial episode of COVID-19, but a severe episode of COVID-19 carries with it a substantially increased risk of death in the following 12 months. In fact, the risk of 12-month mortality among adults under 65 who are hospitalized with COVID-19 is increased by 233% over those who are COVID-19 negative. Nearly 80% of the downstream deaths among patients with COVID-19 were for causes other than respiratory or cardiovascular. Since these deaths were not for a direct COVID-19 cause of death among these patients who have recovered from the initial episode of COVID-19, this data suggests that the biological insult from COVID-19 and physiological stress from COVID-19 is significant.

TABLE 3 | All-cause mortality hazard ratios by COVID-19 status for conditions other than COVID-19.

	Hazard ratios (95% CI)					
	Unadjusted			Adjusted^{a}		
	Mild/moderate vs. no COVID-19	Severe vs. no COVID-19	Severe vs. mild/moderate COVID-19	Mild/moderate vs. no COVID-19	Severe vs. no COVID-19	Severe vs. mild/moderate COVID-19
Full cohort	0.81 (0.59, 1.12)	3.61 (2.93, 4.44)	4.43 (3.05, 6.44)	1.34 (0.97, 1.84)	2.50 (2.02, 3.09)	1.87 (1.28, 2.74)
Under 65	0.80 (0.50, 1.28)	4.54 (3.22, 6.39)	5.66 (3.20, 10.0)	1.17 (0.74, 1.88)	3.33 (2.35, 4.73)	2.83 (1.59, 5.04)
65 and Older	1.36 (0.88, 2.09)	2.49 (1.92, 3.23)	1.84 (1.12, 3.02)	1.54 (0.99, 2.40)	2.17 (1.66, 2.84)	1.41 (0.84, 2.34)

[a] *Models were adjusted for age, race/ethnicity, sex, and the Charlson Comorbidity Index. Models which were stratified by age above/below 65 were further adjusted for age as a continuous variable to adjust for the presence of residual confounding.*

This study adds to the accumulating literature of post-acute sequelae following a COVID-19 infection. While those 65 and older are more likely to be hospitalized and die from COVID-19 than those under 65 (18), we found the 12-month mortality of those under 65 hospitalized with COVID-19 to be increased more than their older counterparts when compared to the COVID-19 negative group. Even though we focused primarily on all cause mortality we were able to determine the impact of COVID-19 on both downstream respiratory and cardiovascular death risk. The vast majority of deaths did not fall into these categories. These novel findings identify critical areas for future research and demonstrate the pervasive nature of COVID-19 sequelae. They also suggest that individuals are dying of a variety of conditions.

Based on the evidence that contracting severe COVID-19 infection increases the risk of death after surviving the episode, it is clear that prevention of significant COVID-19 infection is the most effective way to decrease the risk of death following COVID-19. Mitigation strategies like masking, physical distancing and improved ventilation are useful strategies to prevent a COVID-19 infection. Vaccination is a measure that can both prevent and substantially decrease the risk of a severe COVID-19 infection, as it has been shown that breakthrough infections are mild-moderate in severity (19). There were no significant differences in mortality risk between patients with mild/moderate infection and the COVID-19 negatives, suggesting the value of vaccinations at preventing death from the downstream complications of COVID-19.

There are several strengths and limitations to this study. A strength to this study is that the study has a PCR validated COVID-19 negative comparison group. Rather than simply treating patients in the residual category who weren't diagnosed with COVID-19 as negative this study has a PCR validation of their status. A second strength of this study is that this is the first study, to our knowledge, to follow COVID-19 patients out 12 months post-acute COVID-19. This allows us to have an even better idea of downstream significant outcomes of COVID-19.

In terms of limitations, the first that needs to be considered is that the analysis was based on patients seen in one health system with a regional catchment area. Although more than 13,000 PCR based COVID-19 diagnoses were included in the analysis, and the cohort was followed for 12 months, the study cohort may not be representative of the patient population in other areas of the USA. Second, we are not able to determine the reasons that patients chose to interact with our health system. It is possible that asymptomatic patients who had not been exposed to the virus sought a COVID-19 test prior to traveling and were included in the analysis. Third, this study involved patients from the initial wave of the COVID-19 pandemic. Our data collection began in January, 1, 2020 and the ICD-10 code for a confirmed COVID-19 diagnosis wasn't even issued until April 1, 2020. Complete compliance with the new diagnosis code may have lagged. Our knowledge of effective management of COVID-19 has increased considerably since then, and the results identified in this analysis may be mitigated if repeated at a later date. Fourth, we had hoped to examine the causes of death of these patients in more specific categories than what we reported. As we indicated in the results, importantly, the patients died from a wide variety of causes. We examined a variety of causes of death that may have been expected to follow from COVID-19 but most had few deaths because mortality was dispersed across many causes. Even causes we might have predicted like clotting disorders had few deaths. We examined clotting disorders defined as deep vein thrombosis, venous thromboembolism, and pulmonary embolism and their associated ICD-10 codes (16). Only one patient with COVID-19 (1 in severe group and 0 in mild group) ended up dying of a clotting disorder over the next 12 months. The survival analysis was unreliable based on so few deaths with this type of condition. This reinforces that we may need to reconceptualize the impact of COVID-19 on patients.

In conclusion, this study demonstrates a previously undocumented risk to infection with COVID-19, particularly for patients who are hospitalized for COVID-19. These patients have a substantially increased risk for mortality over the next 12 months. The benefits of preventing severe COVID-19 goes beyond flattening the curve for overwhelming the health system with hospitalized patients but extends to decreased 12-month mortality risk for conditions other than COVID-19 directly.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: individuals must apply to the University of Florida Integrated Data Repository. Requests to access these datasets should be directed to https://idr.ufhealth.org/.

AUTHOR CONTRIBUTIONS

AM conceptualized the study and oversaw the drafting of the manuscript. BR participated in conceptualizing the study and oversaw the data analysis. VW and FO participated in the data analysis and writing of the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We acknowledge the University of Florida Integrated Data Repository (IDR) and the UF Health Office of the Chief Data Officer for providing the analytic data set for this project.

REFERENCES

1. JHU. *COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)*. (2020). Available online at: https://coronavirus.jhu.edu/map.html (accessed August 9, 2021).
2. Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect.* (2020) 81:e4–6. doi: 10.1016/j.jinf.2020.08.029
3. Del Rio C, Collins LF, Malani P. Long-term health consequences of COVID-19. *JAMA.* (2020) 324:1723–4. doi: 10.1001/jama.2020.19719
4. Logue JK, Franko NM, McCulloch DJ, McDonald D, Magedson A, Wolf CR, et al. Sequelae in adults at 6 months after COVID-19 infection. *JAMA Netw Open.* (2021) 4:e210830. doi: 10.1001/jamanetworkopen.2021.0830
5. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet.* (2021) 397:220–32. doi: 10.1016/S0140-6736(20)32656-8
6. Cortinovis M, Perico N, Remuzzi G. Long-term follow-up of recovered patients with COVID-19. *Lancet.* (2021) 397:173–5. doi: 10.1016/S0140-6736(21)00039-8
7. Janiri D, Carfì A, Kotzalidis GD, Bernabei R, Landi F, Sani G. Posttraumatic stress disorder in patients after severe COVID-19 infection. *JAMA Psychiatry.* (2021) 78:567–9. doi: 10.1001/jamapsychiatry.2021.0109
8. Zuin M, Rigatelli G, Zuliani G, Roncon L. The risk of thrombosis after acute-COVID-19 infection. *QJM.* (2021) 2021:hcab054. doi: 10.1093/qjmed/hcab054
9. Umbrajkar S, Stankowski RV, Rezkalla S, Kloner RA. Cardiovascular health and disease in the context of COVID-19. *Cardiol Res.* (2021) 12:67–79. doi: 10.14740/cr1199
10. Brosnahan SB, Jonkman AH, Kugler MC, Munger JS, Kaufman DA. COVID-19 and Respiratory system disorders: current knowledge, future clinical and translational research questions. *Arterioscler Thromb Vasc Biol.* (2020) 40:2586–97. doi: 10.1161/ATVBAHA.120.314515
11. Lavery AM, Preston LE, Ko JY, Chevinsky JR, DeSisto CL, Pennington AF. Characteristics of hospitalized COVID-19 patients discharged and experiencing same-hospital readmission—United States, March–August 2020. *MMWR Morb Mortal Wkly Rep.* (2020) 69:1695–9. doi: 10.15585/mmwr.mm6945e2
12. Parra LM, Cantero M, Morrás I, Vallejo A, Diego I, Jiménez-Tejero E, et al. Hospital readmissions of discharged patients with COVID-19. *Int J Gen Med.* (2020) 13:1359–66. doi: 10.2147/IJGM.S275775
13. Rokadiya S, Gil E, Stubbs C, Bell D, Herbert R. COVID-19: Outcomes of patients with confirmed COVID-19 re-admitted to hospital. *J Infect.* (2020) 81:e18–9. doi: 10.1016/j.jinf.2020.07.007
14. Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. *BMJ.* (2021) 372:n693. doi: 10.1136/bmj.n693
15. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature.* (2021) 594:259–64. doi: 10.1038/s41586-021-03553-9
16. Mainous AG. 3rd, Rooks BJ, Orlando FA. Risk of new hospitalization post COVID-19 infection for non-COVID-19 conditions. *J Am Board Fam Med.* (2021) 34:907–13. doi: 10.3122/jabfm.2021.05.210170
17. Centers for Disease Control and Prevention. *ICD-10-CM Official Coding and Reporting Guidelines April 1, 2020 through September 30, 2020*. Available online at: https://www.cdc.gov/nchs/data/icd/COVID-19-guidelines-final.pdf (accessed September 20, 2021).
18. Centers for Disease Control and Prevention. *Risk for COVID-19 Infection, Hospitalization, and Death By Age Group*. Available online at: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html (accessed August 12, 2021).
19. Moline HL, Whitaker M, Deng L, Rhodes JC, Milucky J, Pham H, et al. Effectiveness of COVID-19 vaccines in preventing hospitalization among adults aged ≥65 years—COVID-NET, 13 States, February–April 2021. *MMWR Morb Mortal Wkly Rep.* (2021) 70:1088–93. doi: 10.15585/mmwr.mm7032e3

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 10 January 2022
doi: 10.3389/fmed.2021.771313

Dual Burden of Malnutrition Among Adolescents With Hunger Aged 12–15 Years in 41 Countries: Findings From the Global School-Based Student Health Survey

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Background: Hunger is a pandemic among adolescents, resulting in both underweight and obesity, and posing a substantial health challenge.

Objective: To estimate the dual burden of malnutrition among adolescents with hunger.

Design: Data were from the Global school-based Student Health Survey (GSHS). In total, data from 26,986 adolescents with hunger across 5 regions and 41 countries between 2010 and 2015 were analyzed in this study. Weighted prevalence and mean estimates of underweight, overweight, and obesity were calculated by gender, age, and country. Prevalence and 95% confidence intervals (CI) were calculated for regional and country-level income.

Results: The total prevalence of underweight, overweight and obesity among young adolescents with hunger was 6.2% (95% CI: 4.4–8.0%), 25.1% (95% CI: 20.3–29.9%) and 8.9% (95% CI: 6.5–11.3%), respectively. Southeast Asia had the highest prevalence of underweight (17.2%; 95% CI: 7.3–27.0%). America had the highest regional prevalence of obesity (11.1%; 95% CI: 7.2–15.1%) and overweight (28.9%; 95% CI: 21.9–35.9%). Low income countries had relatively high prevalence of underweight (11.5%; 95% CI: 3.2–19.9%). High income countries had the highest prevalence of obesity (17.4%; 95% CI: 14.9–19.9%) and overweight (38.7%; 95% CI: 32.0–45.4%). The co-existence of underweight and overweight among adolescents with hunger was highest in the Eastern Mediterranean region, and in upper-middle and high-income countries.

Conclusions: There is a dual burden of underweight and obesity among adolescents with hunger aged 12–15 years, which differs between geographical regions. The integration of targeted interventions and policies is required to simultaneously address both underweight and increasing rates of obesity among adolescents with hunger in different regions.

Keywords: hunger, obesity, adolescent, malnutrition, underweight, overweight

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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Medicine

Received: *06 September 2021*
Accepted: *15 December 2021*
Published: *10 January 2022*

Citation:
Liu H, Zhang M, Fu P, Chen Y and Zhou C (2022) Dual Burden of Malnutrition Among Adolescents With Hunger Aged 12–15 Years in 41 Countries: Findings From the Global School-Based Student Health Survey. Front. Med. 8:771313. doi: 10.3389/fmed.2021.771313

INTRODUCTION

The number of hungry people worldwide has been slowly rising since 2014, with more than 840 million people projected to experience hunger by 2030 (1); this issue is most acute among adolescents, with about 30% experiencing moderate or severe hunger, which is more than triple the global average for the total population of 8.9%. Hunger among adolescents is therefore a serious global public health issue. Adolescence is a critical period of rapid growth, in which the foundations for future health are established. Adolescents therefore have higher nutritional requirements, placing them at greater risk of malnutrition. Generally, hunger increases the risk of being underweight, which is a primary cause of poor health, and compromises the socio-economic development, ability to learn, and productivity of an individual (2).

Pediatric obesity is also increasing rapidly worldwide, with the global prevalence of obesity or overweight children and adolescents aged 5–19 years increasing more than four-fold from 4 to 18% from 1975 to 2016 (3). Overweight or obesity in adolescence is also likely to give rise to lifelong overweight or obesity (4), which is associated with an increased risk of developing chronic non-communicable diseases (such as type 2 diabetes, hypertension, and cardiovascular disease) at an earlier stage, as well as early death (5, 6).

Obesity is often a consequence of over-eating. A recent study indicated that hedonic hunger, defined as eating food for pleasure, is positively associated with obesity among women (7). Several studies have reported a positive association between hedonic hunger and eating unhealthy foods (8, 9) among young people, which increases the risk of childhood obesity (10). Among overweight or obese people, reducing hunger may improve weight loss (11).

Overweight or obesity and underweight may co-exist in a population (12, 13), referred to as the "dual burden" of hunger, which is a great challenge for public health that has negative economic impacts. This dual burden (14) was originally reported in adults, but is also known to affect young adolescents (2, 15); however, to date, there is a dearth of studies aiming to characterize the dual burden among hungry adolescents. Hunger may not only increase the risk of underweight, but may also be linked with obesity, posing complex and substantial challenges to adolescent health. In this study, we characterize the burden of underweight, overweight and obesity among young adolescents with hunger aged 12–15 years worldwide, using data from the World Health Organization (WHO) Global school-based Student Health Survey (GSHS). Describing the dual burden of hunger among adolescents will enable policymakers to identify and implement targeted actions to achieve the United Nations (UN) Sustainable Development Goal of ending malnutrition in all its forms by 2030.

MATERIALS AND METHODS

Data and Participants

The data used in this study came from the GSHS, which is a global collaborative surveillance project designed to obtain and assess health behavioral risks and protective factors among young adolescents worldwide. It was developed by the World Health Organization in association with the United States Centers for Disease Control and Prevention, the United Nations Children Fund, the United Nations Educational, Scientific and Cultural Organization, and the Joint United Nations Programme on HIV/AIDS. The GSHS was approved in each country by a national government administration (most often the ministry of health or education) and an institutional review board or ethics committee. Verbal or written consent was obtained from participants and their parents in all countries. More details about the GSHS can be found at https://www.who.int/ncds/surveillance/gshs/en.

A two-stage cluster sampling strategy was used in each participating country. All schools were selected with a probability proportional to their enrolment sizes, then classes in which all students were eligible to participate in the survey were randomly chosen from these schools. The GSHS questionnaire was self-administered and anonymously completed by students. In total, 29,941 young adolescents with hunger aged 12–15 years from 5 regions and 41 countries completed the survey between 2010 and 2015. From these, 26,986 individuals were included in our study, after excluding participants with missing information on sex, age, height, weight, and hunger, and surveys in which response rates were $<60\%$.

Measures

Weight and height were self-reported in the GSHS, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Overweight, obesity and underweight were defined as BMI-for-age >1 standard deviation (SD), >2 SD, and <2 SD from the WHO growth reference values for 5–19 years (16, 17), respectively. Hunger was measured using the question "during the past 30 days, how often did you go hungry because there was not enough food in your home?" The possible responses were "never," "rarely," "sometimes," "most of the time," and "always." In this study, respondents were categorized as hungry if the answer was "sometimes," "most of the time," or "always." National incomes were stratified into four levels for analysis ("low income," "lower-middle income," "upper-middle income," and "high income") according to World Bank Analytical classifications based on gross national income per capita for the corresponding survey year (18).

Statistical Analysis

All data were weighted using the cluster sampling design of the surveys, with stratification and primary sampling at the national level, to give nationally-representative samples. The weighted prevalence of underweight, overweight, and obesity were calculated for each country. The pooled prevalence and 95% confidence intervals (CI) for underweight, overweight, and obesity among all included individuals, boys, girls, those aged 12–13 years, and those aged 14–15 years, according to WHO region and national income, were calculated using Stata v16.0 (Stata Corporation, College Station, TX, USA). Differences with non-overlapping 95% CIs were considered statistically significant; which is a relatively conservative estimate. In addition, the chi-square test of independence was conducted for sex, age, WHO region, and national income against underweight, overweight, and obesity indices. A *P*-value of <0.05 was considered statistically significant in this analysis.

RESULTS

Participants

The characteristics of the individuals included in this study from the GSHS are described in **Table 1**. In total, 41 countries from five WHO regions had complete BMI and hunger data between 2010 and 2015 [Africa: 4; Western Pacific: 12; Southeast Asia: 2; Eastern Mediterranean: 10; and America (Central and South America): 13]. A total of 26,986 adolescents with hunger (46.7% of whom were male) aged 12–15 years were included in this study. The overall response rate was 90.1%, ranging from 70.5% (Timor Leste) to 97.5% (Brunei). The size of the samples varied from 87 (Chile) to 4,945 (Malaysia).

Prevalence of Underweight, Overweight and Obesity by Country

The prevalence of underweight, overweight, and obesity in the 41 countries included in our study is shown in **Figure 1**. There were considerable variations in the prevalence of underweight, overweight, and obesity across countries. Overall, 48.8% (20/41) countries had a prevalence of underweight ≥5.0%, with prevalences exceeding 15.0% in Vietnam, Timor Leste, and Cambodia. The prevalence of underweight was high in many countries in Southeast Asia. Conversely, the prevalence of underweight was <1.0% in the Cook Islands, Kiribati, Nauru, Tonga, Chile, and Peru. The prevalence of overweight varied from 2.8% in Vietnam to 61.4% in the Cook Islands. The prevalence of obesity was highest in Kuwait, Chile, Bahamas, Tonga, and Cook Islands (≥20%) and lowest in Cambodia, Vietnam, Bangladesh, and Timor Leste (<1.0%).

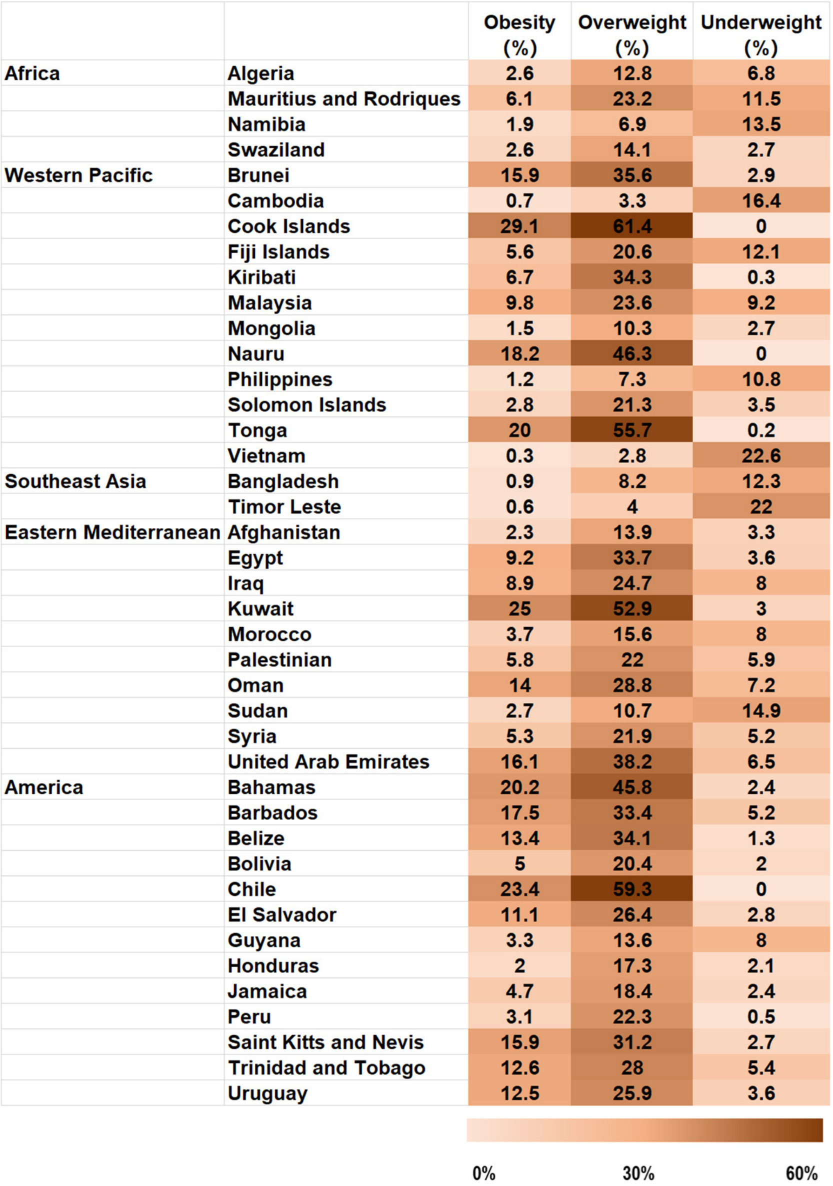
Prevalence of Underweight, Overweight and Obesity by Region, Sex and Age

As shown in **Table 2**, the total prevalence of underweight, overweight and obesity among young adolescents across all 41 countries was 6.2% (95% CI: 4.4–8.0%), 25.1% (95% CI: 20.3–29.9%) and 8.9% (95% CI: 6.5% 95% CI: 11.3%), respectively. Southeast Asia had the highest prevalence of underweight, at 17.2% (95% CI: 7.3–27.0%), followed by Africa, at 8.6% (95% CI: 3.7–13.5%). America had the highest regional prevalence of obesity, at 11.1% (95% CI: 7.2–15.1%) and overweight, at 28.9% (95% CI: 21.9–35.9%). Sex, age and regional differences in the prevalence of obesity and underweight were calculated using the chi-square test. Regional differences were still apparent when the data were stratified by sex and age group; however, the total and regional prevalence values for obesity and underweight did not differ significantly between boys and girls, or between adolescents

TABLE 1 | Characteristics of the global school-based student health surveys by region and country (2010–2015).

	Survey year	Response rate (%)	Sample size	Boys (%)
Africa (*n* = 4)				
Algeria	2011	93.0	995	48.3
Mauritius and Rodriques	2011	92.3	493	45.2
Namibia	2013	92.6	873	42.0
Swaziland	2013	95.4	523	38.0
Western pacific (*n* = 12)				
Brunei	2014	97.5	553	43.8
Cambodia	2013	91.1	509	40.5
Cook Islands	2011	94.0	374	49.7
Fiji Islands	2010	91.9	778	43.2
Kiribati	2011	90.5	516	43.0
Malaysia	2012	95.7	4,945	50.6
Mongolia	2013	95.0	471	50.3
Nauru	2011	87.7	213	48.8
Philippines	2011	89.9	1,356	44.9
Solomon Islands	2011	81.9	569	50.3
Tonga	2010	95.5	1,030	43.7
Vietnam	2013	94.3	332	44.6
Southeast asia (*n* = 2)				
Bangladesh	2014	88.3	1,359	34.7
Timor leste	2015	70.5	409	35.9
Eastern mediterranean (*n* = 10)				
Afghanistan	2014	79.2	423	34.3
Egypt	2011	76.5	378	59.0
Iraq	2012	89.8	228	50.9
Kuwait	2015	85.9	468	42.1
Morocco	2010	91.9	491	51.5
Occupied palestinian territory	2010	83.9	2,225	52.4
Oman	2015	85.4	264	47.3
Sudan	2012	89.8	254	41.7
Syria	2010	91.1	855	43.0
United arab emirates	2010	87.5	287	39.7
America (*n* = 13)				
Bahamas	2013	89.4	353	44.5
Barbados	2011	84.2	294	49.3
Belize	2011	87.2	355	43.9
Bolivia	2012	92.9	706	52.5
Chile	2013	89.7	87	50.6
El salvador	2013	90.2	212	52.4
Guyana	2010	94.7	642	45.3
Honduras	2012	90.5	182	50.5
Jamaica	2010	94.9	517	50.7
Peru	2010	89.7	391	50.6
Saint kitts and nevis	2011	86.3	334	48.8
Trinidad and tobago	2011	82.5	564	54.1
Uruguay	2012	89.4	178	50.0

Data are proportion (95% confidence interval).



		Obesity (%)	Overweight (%)	Underweight (%)
Africa	Algeria	2.6	12.8	6.8
	Mauritius and Rodriques	6.1	23.2	11.5
	Namibia	1.9	6.9	13.5
	Swaziland	2.6	14.1	2.7
Western Pacific	Brunei	15.9	35.6	2.9
	Cambodia	0.7	3.3	16.4
	Cook Islands	29.1	61.4	0
	Fiji Islands	5.6	20.6	12.1
	Kiribati	6.7	34.3	0.3
	Malaysia	9.8	23.6	9.2
	Mongolia	1.5	10.3	2.7
	Nauru	18.2	46.3	0
	Philippines	1.2	7.3	10.8
	Solomon Islands	2.8	21.3	3.5
	Tonga	20	55.7	0.2
	Vietnam	0.3	2.8	22.6
Southeast Asia	Bangladesh	0.9	8.2	12.3
	Timor Leste	0.6	4	22
Eastern Mediterranean	Afghanistan	2.3	13.9	3.3
	Egypt	9.2	33.7	3.6
	Iraq	8.9	24.7	8
	Kuwait	25	52.9	3
	Morocco	3.7	15.6	8
	Palestinian	5.8	22	5.9
	Oman	14	28.8	7.2
	Sudan	2.7	10.7	14.9
	Syria	5.3	21.9	5.2
	United Arab Emirates	16.1	38.2	6.5
America	Bahamas	20.2	45.8	2.4
	Barbados	17.5	33.4	5.2
	Belize	13.4	34.1	1.3
	Bolivia	5	20.4	2
	Chile	23.4	59.3	0
	El Salvador	11.1	26.4	2.8
	Guyana	3.3	13.6	8
	Honduras	2	17.3	2.1
	Jamaica	4.7	18.4	2.4
	Peru	3.1	22.3	0.5
	Saint Kitts and Nevis	15.9	31.2	2.7
	Trinidad and Tobago	12.6	28	5.4
	Uruguay	12.5	25.9	3.6

FIGURE 1 | Proportions of obese, overweight and underweight adolescents with hunger aged 12–15 years, organized by country.

aged 12–13 and 14–15 years, as indicated by non-overlapping 95% CIs.

Prevalence of Underweight, Overweight and Obesity by Income, Sex and Age

Table 3 shows the prevalence of obesity, overweight, and underweight among adolescents with hunger by national income, sex, and age. Compared with high income countries (3.5%; 95% CI: 2.1–5.0%), low income countries had a significantly higher prevalence of underweight (11.5%; 95% CI: 3.2–19.9%). High income countries had the highest prevalence of obesity, at 17.4 % (95% CI: 14.9–19.9%) and overweight, at 38.7% (95% CI: 32.0–45.4%). This relationship was still observed in the data when stratified by sex and age group. We found significant differences in the prevalence of obesity, overweight, and underweight across different national income levels.

Relationship Between Prevalence of Overweight and Prevalence of Underweight

Figure 2 shows the relationship between prevalence of overweight and that of underweight by among adolescents with hunger by country. 17.1% (7/41) countries had a prevalence of overweight and underweight greater than the median prevalence estimates for overweight and underweight, respectively, with the highest values observed in the Eastern Mediterranean

TABLE 2 | Prevalence of obese, overweight and underweight adolescents with hunger by region, sex and age.

	Obesity	Overweight	Underweight
All	8.9% (6.5–11.3%)	25.1% (20.3–29.9%)	6.2% (4.4–8.0%)
Gender			
Boys	9.4% (6.8–12.1%)	24.3% (19.4–29.2%)	7.4% (5.4–9.4%)
Girls	8.3% (6.0–10.6%)	25.9% (20.9–30.9%)	5.1% (3.3–6.8%)
χ^2	34.837	0.006	96.301
P	<0.001	0.937	<0.001
Age group			
12–13 years	10.4% (7.7–13.0%)	28.0% (23.1–32.8%)	5.9% (4.1–7.7%)
14–15 years	8.1% (5.7–10.5%)	23.8% (19.0–28.6%)	6.3% (4.4–8.2%)
χ^2	68.277	91.809	19.240
P	<0.001	<0.001	<0.001
All			
Africa	3.3% (1.4–5.2%)	14.3% (7.5–21.1%)	8.6% (3.7–13.5%)
Western pacific	9.3% (3.8–14.8%)	26.9% (15.2–38.6%)	6.7% (2.4–11.1%)
Southeast Asia	0.8% (0.4–1.1%)	6.1% (1.9–10.3%)	17.2% (7.3–27.0%)
Eastern mediterranean	9.3% (4.7–13.9%)	26.2% (18.1–34.4%)	6.6% (4.3–8.8%)
America	11.1% (7.2–15.1%)	28.9% (21.9–35.9%)	3.0% (1.7–4.2%)
χ^2	278.054	572.279	231.950
P	<0.001	<0.001	<0.001
Boys			
Africa	2.4% (−0.3–5.1%)	10.5% (5.2–15.8%)	12.1% (6.6–17.7%)
Western pacific	10.3% (4.4–16.3%)	25.5% (14.5–36.5%)	8.2% (3.1–13.3%)
Southeast Asia	0.5% (0.3–0.6%)	6.5% (1.5–11.4%)	17.5% (10.7–24.2%)
Eastern mediterranean	10.7% (6.0–15.8%)	27.6% (18.9–36.2%)	7.7% (5.6–9.8%)
America	11.2% (6.9–15.5%)	27.7% (19.7–35.6%)	3.4% (2.0–4.7%)
χ^2	168.220	282.603	152.151
P	<0.001	<0.001	<0.001
Girls			
Africa	4.0% (2.6–5.4%)	17.5% (8.8–26.2%)	5.7% (1.5–10.0%)
Western pacific	8.3% (3.2–13.4%)	28.3% (15.7–41.0%)	5.3% (1.6–9.0%)
Southeast Asia	1.2% (0.2–2.2%)	5.6% (2.6–8.6%)	16.2% (2.7–29.6%)
Eastern mediterranean	7.9% (3.4–12.3%)	24.9% (16.9–32.9%)	5.5% (2.5–8.6%)
America	11.0% (6.9–15.1%)	30.2% (23.4–37.1%)	2.5% (1.3–3.8%)
χ^2	126.151	320.705	117.875
P	<0.001	<0.001	<0.001
12–13 years			
Africa	5.1% (3.3–6.8%)	17.1% (10.4–23.7%)	8.5% (5.5–11.4%)
Western pacific	9.6% (4.1–15.2%)	28.3% (18.0–38.7%)	7.4% (3.0–11.8%)
Southeast Asia	2.1% (1.7–2.4%)	8.0% (6.4–9.6%)	17.3% (9.7–24.8%)
Eastern mediterranean	11.8% (5.5–18.2%)	31.1% (21.4–40.8%)	5.2% (3.4–7.0%)
America	12.9% (8.9–16.8%)	31.6% (23.8–39.5%)	2.6% (1.2–4.0%)
χ^2	94.411	180.353	77.491
P	<0.001	<0.001	<0.001
14–15 years			
Africa	2.5% (0.5–4.5%)	12.9% (5.9–19.9%)	9.0% (3.1–14.8%)
Western pacific	9.2% (3.7–14.7%)	27.0% (15.1–39.0%)	6.5% (2.0–10.9%)
Southeast Asia	0.4% (0.2–0.6%)	5.6% (0.6–10.5%)	17.1% (6.4–27.7%)
Eastern mediterranean	7.8% (3.6–12.0%)	23.5% (15.8–31.1%)	7.1% (4.6–9.5%)
America	10.2% (6.0–14.4%)	27.3% (20.6–34.1%)	3.1% (1.9–4.3%)
χ^2	188.054	390.197	154.872
P	<0.001	<0.001	<0.001

Data are proportion (95% confidence interval).

TABLE 3 | Prevalence of obese, overweight and underweight adolescents with hunger by national income, sex and age.

Income group	Obesity	Overweight	Underweight
All			
Low income	1.9% (0.7–3.1%)	9.3% (2.9–15.7%)	11.5% (3.2–19.9%)
Lower middle income	5.3% (2.8–7.8%)	20.1% (13.8–26.4%)	6.8% (3.5–10.0%)
Upper middle income	5.3% (2.9–7.7%)	18.8% (13.7–23.9%)	7.4% (3.8–11.0%)
High income	17.4% (14.9–19.9%)	38.7% (32.0–45.4%)	3.5% (2.1–5.0%)
χ^2	669.760	696.021	125.137
P	<0.001	<0.001	<0.001
Boys			
Low income	2.9% (0.8–5.0%)	10.2% (3.5–16.8%)	11.5% (2.7–20.3%)
Lower middle income	5.2% (2.8–7.5%)	18.3% (12.3–24.2%)	7.9% (4.3–11.4%)
Upper middle income	5.5% (2.0–8.9%)	17.1% (10.7–23.4%)	9.7% (4.9–14.6%)
High income	18.9% (16.1–21.7%)	39.9% (33.2–46.4%)	4.6% (2.7–6.4%)
χ^2	311.322	329.579	66.835
P	<0.001	<0.001	<0.001
Girls			
Low income	0.7% (0.3–1.2%)	8.3% (1.3–15.2%)	11.8% (2.4–21.2%)
Lower middle income	5.3% (2.5–8.1%)	21.6% (14.7–28.5%)	5.7% (2.7–8.8%)
Upper middle income	5.2% (3.7–6.6%)	20.7% (15.5–25.9%)	5.2% (2.6–7.9%)
High income	16.1% (13.1–19.1%)	37.8% (30.3–45.3%)	2.6% (1.2–4.1%)
χ^2	361.998	370.617	68.989
P	<0.001	<0.001	<0.001
12–13 years			
Low income	1.8% (−1.0–4.5%)	11.4% (4.4–18.8%)	8.6% (2.4–14.7%)
Lower middle income	6.3% (3.7–8.9%)	22.6% (16.9–28.4%)	7.1% (3.7–10.5%)
Upper middle income	7.5% (4.4–10.6%)	21.6% (15.2–28.0%)	6.9% (3.2–10.5%)
High income	20.0% (16.7–23.3%)	42.8% (35.3–50.2%)	3.3% (1.8–4.7%)
χ^2	223.694	206.968	45.597
P	<0.001	<0.001	<0.001
14–15 years			
Low income	1.8% (0.2–3.4%)	8.7% (2.6–14.8%)	12.2% (3.1–21.3%)
Lower middle income	4.7% (2.3–7.1%)	19.0% (12.7–25.3%)	6.8% (3.5–10.1%)
Upper middle income	4.1% (2.0–6.2%)	17.1% (12.3–21.9%)	7.5% (3.6–11.4%)
High income	16.1% (12.9–19.3%)	36.9% (30.2–43.5%)	3.6% (2.1–5.2%)
χ^2	433.345	325.758	79.963
P	<0.001	<0.001	<0.001

Data are proportion (95% confidence interval).

region (30.0%; 3/10), and in the upper-middle and high-income countries (38.9%; 7/18).

DISCUSSION

In this study, we estimated the dual burden of malnutrition among adolescents with hunger at the population level from 41 countries around the world. We found that 1 in 15 adolescents with hunger was underweight, and 1 in 4 were overweight or obese. Adolescent populations with hunger contained those who were underweight and those who were overweight or obese.

Our findings showed a high prevalence of underweight, overweight, and obesity among young adolescents with hunger; however, there were also substantial differences between regions and countries. The prevalence of underweight was higher in Southeast Asia, while the prevalence of obesity was higher in Central and South America, which is comparable with findings from other studies (3, 19). More adolescents with hunger were underweight than obese in the low and lower-middle income countries, as well as all countries across Southeast Asia and Africa. However, pediatric obesity has surpassed underweight in Central and South America, in which most countries are high income. Obesity is often associated with high income countries or high socio-economic status (20, 21). The co-existence of underweight and overweight among adolescents with hunger at the national level was highest among Eastern Mediterranean countries and those with upper-middle and high incomes. Despite the increasing prevalence of overweight and obesity worldwide, our finding that young adolescents with hunger who were underweight outnumbered those with obesity

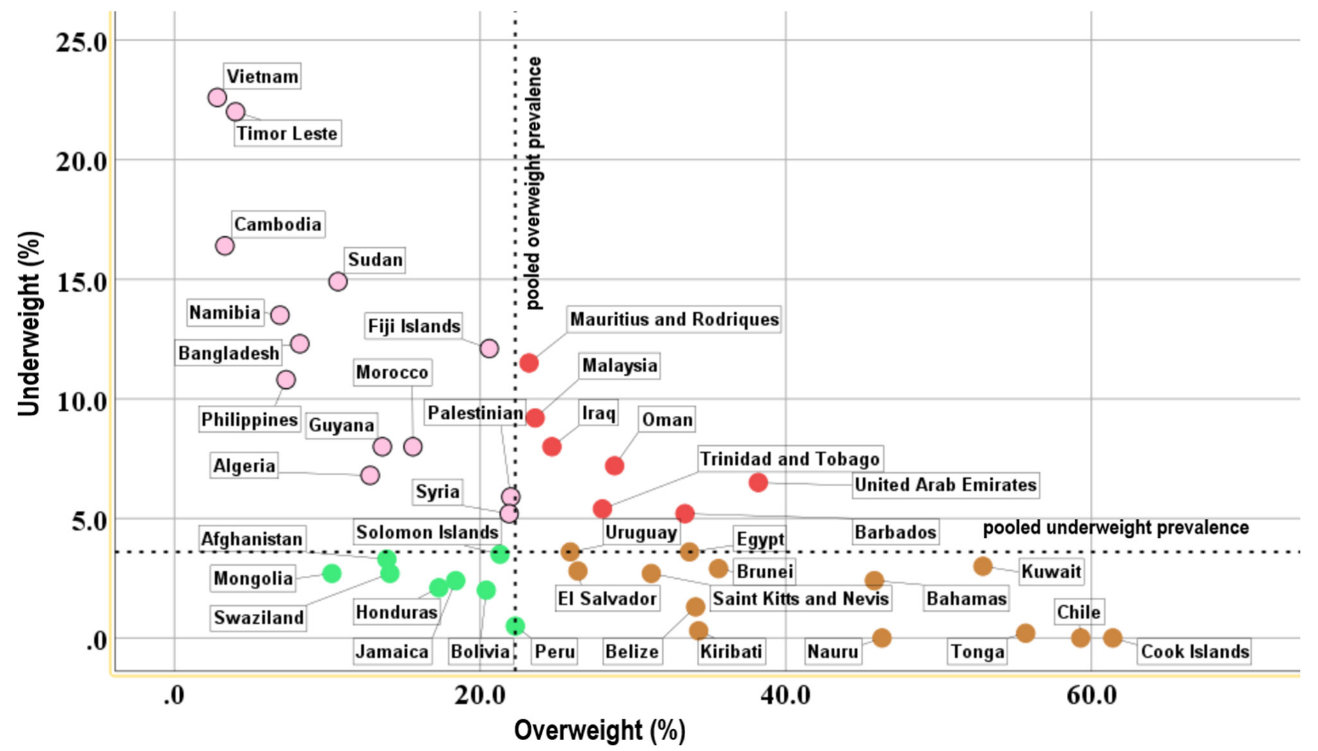


FIGURE 2 | Scatterplot showing the relationship between the proportion of overweight and underweight adolescents with hunger aged 12–15 years, organized by country.

in most countries indicated that underweight remains a primary health issue in young adolescents with hunger; there is thus a continued need for policies that enhance food security, especially in Southeast Asia, Africa, and low-income countries.

The prevalence of adolescents with hunger who were underweight in this study (7.6%) was greater than that of young adolescents in a previous study by Yang and colleagues (4.7%) (19). Adolescents with hunger due to food insufficiency at home were more likely to be underweight when faced with additional food shortages or food poverty. However, adolescents with hunger who are exposed to obesogenic environments (available and affordable food outside the home, especially foods that are high in fat or sugar, low in vitamins, minerals and protein, and relatively inexpensive) are more likely to become overweight or obese (22). Previous research has shown that greater degrees of hunger lead to the consumption of greater amounts of food, owing to increasing meal size or frequency (23). Furthermore, hunger may cause food deprivation, which leads to stress, anxiety, and emotional distress (24, 25), which may result in stress eating or over-eating (26), and visceral fat accumulation (27). Thus, adolescents with hunger may actually be more likely to become obese than those without hunger (12, 28). Levels of overweight among adolescents with hunger in this study were comparable with those reported in other studies (29).

It is remarkable that middle-income countries may have the greatest dual burden of malnutrition. One recent study (30) showed that the prevalence of obesity is highest among poor individuals in high income countries, and among wealthy individuals in low income countries. The relatively rapid transition from underweight to overweight and obesity has been noted in low and middle income countries (31, 32). Increasing economic development may lead to greater availability of nutrient-poor, energy-dense foods and thus a transition from underweight to overweight and obese among young adolescents; strategies targeting this phenomenon may therefore help to reduce levels of malnutrition in developing countries. Notably, the transition from underweight to overweight or obese among adolescents has accelerated in Southeast Asia (15), indicating that a strategy to combat malnutrition in this region should focus on attenuating this transition while simultaneously resolving hunger issues leading individuals to become or stay underweight.

The dual burden of malnutrition poses serious resource allocation challenges for governments in order to address the dual burden of underweight and overweight or obesity simultaneously (33, 34). Policies that target overweight and obesity in adolescents involve using taxes on "unhealthy" foods high in fat, sugar and/or salt to reduce their consumption, particularly in high income countries. Evidence from Central America indicates that tariff removal has had a positive effect on the affordability of healthy balanced diets and helped improve nutrition in a region characterized by the coexistence of underweight and obesity (35). Price subsidies or food vouchers that target whole grains and fresh fruits and vegetables could also be adopted to make nutritionally dense food more affordable. In addition, supply-side reforms in the food industry such as tax cuts could help to stimulate the production and supply of healthier food. The unaffordability of "healthy" food leads to economic inequalities in levels of overweight and obesity, and also limits the impact of policies targeting unhealthy foods.

To our knowledge, this study is the first to assess the dual burden of malnutrition in adolescents with hunger from a global perspective. However, there are some limitations to our study. First, weight and height were self-reported, which may lead to underestimation of the actual number of overweight or obese individuals (36–38). Second, the GSHS has a wide time frame of data collection (from 2010 to 2015) limiting the comparability of data across countries or regions.

CONCLUSIONS

The nutritional landscape among adolescents with hunger is becoming more complex. We found a dual burden of malnutrition (underweight and overweight or obese) among adolescents with hunger aged 12–15 years, which varied by geographical region. Our findings highlighted that regionally-targeted, integrative interventions and policies are needed to simultaneously address underweight and increasing levels of obesity among adolescents with hunger.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the GSHS was approved, in each country, by both a national government administration (most often the ministry of health or education) and an institutional review board or ethics committee. Verbal or written consent was obtained from participants and their parents in all countries. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

HL conceptualized and designed the study, drafted the initial manuscript, and revised the manuscript. MZ, PF, and YC collated the data, carried out the initial analyses, and reviewed and revised the manuscript. CZ conceptualized and designed the study and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

FUNDING

This study was supported by the National Natural Science Foundation of China (71974117), the Natural Science Research Project of Anhui Educational Committee (KJ2019A0302), and the 512 Talent training Project of Bengbu Medical College (BY51201203). The funding bodies had no role in designing this study, collecting, analyzing, or interpreting the data, producing the draft manuscript, or deciding to publish the results of this study.

ACKNOWLEDGMENTS

We thank the World Health Organization and US Centers for Disease Control and Prevention for compiling the datasets for the GSHS in all participating countries and making them publicly available on their website. We also thank the country survey coordinators for supplying the data.

REFERENCES

1. FAO, IFAD, UNICEF, WFP and WHO. *In Brief to The State of Food Security and Nutrition in the World 2020. Transforming Food Systems for Affordable Healthy Diets*. Rome: FAO (2020).
2. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet.* (2013) 382:427–51. doi: 10.1016/S0140-6736(13)60937-X
3. NCD Risk Factor Collaboration. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet*. (2017) 390:2627–42. doi: 10.1016/S0140-6736(17)32129-3
4. Wells JC, Sawaya AL, Wibaek R, Mwangome M, Poullas MS, Yajnik CS & Demaio A. The double burden of malnutrition: aetiological pathways and consequences for health. *Lancet.* (2020) 395:75–88. doi: 10.1016/S0140-6736(19)32472-9
5. Reilly JJ, Kelly J. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. *Int J Obes (Lond).* (2011) 35:891–8. doi: 10.1038/ijo.2010.222
6. Twig G, Yaniv G, Levine H, Leiba A, Goldberger N, Derazne E, et al. Body-mass index in 2.3 million adolescents and cardiovascular death in adulthood. *N Engl J Med.* (2016) 374:2430–40. doi: 10.1056/NEJMoa1503840
7. Rabiei S, Sedaghat F, Rastmanesh R. Is the hedonic hunger score associated with obesity in women? A brief communication. *BMC Res Notes.* (2019) 12:330. doi: 10.1186/s13104-019-4351-8
8. Stok FM, De Vet E, Wardle J, Chu MT, De Wit J, De Ridder DT. Navigating the obesogenic environment: How psychological sensitivity to the food environment and self-regulatory competence are associated with adolescent unhealthy snacking. *Eat Behav.* (2015) 17:19–22. doi: 10.1016/j.eatbeh.2014.12.003
9. Bejarano CM, Cushing CC. Dietary motivation and hedonic hunger predict palatable food consumption: an intensive longitudinal study of adolescents. *Ann Behav Med.* (2018) 52:773–86. doi: 10.1093/abm/kax051

10. Duan R, Wang X, Shan S, Zhao L, Xiong J, Libuda L, et al. The Chinese adolescent cohort study: design, implementation, and major findings. *Front Nutr.* (2021) 8:747088. doi: 10.3389/fnut.2021.747088
11. Hansen TT, Andersen SV, Astrup A, Blundell J, Sjödin A. Is reducing appetite beneficial for body weight management in the context of overweight and obesity? A systematic review and meta-analysis from clinical trials assessing body weight management after exposure to satiety enhancing and/or hunger reducing products. *Obes Rev.* (2019) 20:983–97. doi: 10.1111/obr.12854
12. Scheier LM. What is the hunger-obesity paradox? *J Am Diet Assoc.* (2005) 105:883–4. doi: 10.1016/j.jada.2005.04.013
13. Koh KA, Hoy JS, O'Connell JJ, Montgomery P. The hunger-obesity paradox: obesity in the homeless. *J Urban Health.* (2012) 89:952–64. doi: 10.1007/s11524-012-9708-4
14. Nugent R, Levin C, Hale J, Hutchinson B. Economic effects of the double burden of malnutrition. *Lancet.* (2020) 395:156–64. doi: 10.1016/S0140-6736(19)32473-0
15. Tzioumis E, Adair LS. Childhood dual burden of under- and overnutrition in low- and middle-income countries: a critical review. *Food Nutr Bull.* (2014) 35:230–43. doi: 10.1177/156482651403500210
16. World Health Organization. *World Health Organization*. (2020). Available online at: https://www.who.int/growthref/who2007_bmi_for_age/en/ (accessed December 21, 2021).
17. de Onis M, Lobstein T. Defining obesity risk status in the general childhood population: which cut-offs should we use? *Int J Pediatr Obes.* (2010) 5:458–60. doi: 10.3109/17477161003615583
18. The World Bank. *How Does the World Bank Classify Countries?* Available online at: https://datahelpdesk.worldbank.org/knowledgebase/articles/378834-how-does-the-world-bank-classify-countries (accessed December 21, 2021).
19. Yang L, Bovet P, Ma C, Zhao M, Liang Y, Xi B. Prevalence of underweight and overweight among young adolescents aged 12-15 years in 58 low-income and middle-income countries. *Pediatr Obes.* (2019) 14:e12468. doi: 10.1111/ijpo.12468
20. Fruhstorfer BH, Mousoulis C, Uthman OA, Robertson W. Socio-economic status and overweight or obesity among school-age children in sub-Saharan Africa - a systematic review. *Clin Obes.* (2016) 6:19–32. doi: 10.1111/cob.12130
21. Wang Y, Lim H. The global childhood obesity epidemic and the association between socio-economic status and childhood obesity. *Int Rev Psychiatry.* (2012) 24:176–88. doi: 10.3109/09540261.2012.688195
22. Drewnowski A, Darmon N. Food choices and diet costs: an economic analysis. *J Nutr*. (2005) 135:900–4. doi: 10.1093/jn/135.4.900
23. Latawitz T, Spielau U, Lipek T, Gausche R, Lück M, Kiess W, et al. Neighbourhood deprivation and community nutrition environment: associations between the social and built environment and food availability. *Gesundheitswesen.* (2019) 81:405–12. doi: 10.1055/a-0602-4382
24. Laraia B, Vinikoor-Imler LC, Siega-Riz AM. Food insecurity during pregnancy leads to stress, disordered eating, and greater postpartum weight among overweight women. *Obesity.* (2015) 23:1303–11. doi: 10.1002/oby.21075
25. Leung CW, Epel ES, Willett WC, Rimm EB, Laraia BA. Household food insecurity is positively associated with depression among low-income supplemental nutrition assistance program participants and income-eligible nonparticipants. *J Nutr*. (2015) 145:622–7. doi: 10.3945/jn.114.199414
26. Torres SJ, Nowson CA. Relationship between stress, eating behavior, and obesity. *Nutrition*. (2007) 23:887–94. doi: 10.1016/j.nut.2007.08.008
27. Laraia BA. Food insecurity and chronic disease. *Adv Nutr*. (2013) 4:203–12. doi: 10.3945/an.112.003277
28. Caballero B. A nutrition paradox—underweight and obesity in developing countries. *N Engl J Med.* (2005) 352:1514–6. doi: 10.1056/NEJMp048310
29. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the global burden of disease study 2013. *Lancet.* (2014) 384:766–81. doi: 10.1016/S0140-6736(14)60460-8
30. Templin T, Cravo Oliveira Hashiguchi T, Thomson B, Dieleman J, Bendavid E. The overweight and obesity transition from the wealthy to the poor in low- and middle-income countries: a survey of household data from 103 countries. *PLoS Med.* (2019) 16:e1002968. doi: 10.1371/journal.pmed.1002968
31. Muthuri SK, Francis CE, Wachira L-JM, et al. Evidence of an overweight/obesity transition among school-aged children and youth in Sub-Saharan Africa: a systematic review. *PLoS One.* (2014) 9:e92846. doi: 10.1371/journal.pone.0092846
32. Rivera JÁ, de Cossío TG, Pedraza LS, Aburto TC, Sánchez TG, Martorell R. Childhood and adolescent overweight and obesity in Latin America: a systematic review. *Lancet Diab Endocrinol.* (2014) 2:321–32. doi: 10.1016/S2213-8587(13)70173-6
33. WHO. *Double-Duty Actions for Nutrition.* Geneva: Policy Brief (2017).
34. Hawkes C, Ruel MT, Salm L, Sinclair B & Branca F. Double-duty actions: seizing programme and policy opportunities to address malnutrition in all its forms. *Lancet.* (2020) 395:142–55. doi: 10.1016/S0140-6736(19)32506-1
35. Development Initiatives. *Central America Nutrition Profile*. Bristol: Global Nutrition Report (2020).
36. Aasvee K, Rasmussen M, Kelly C, Kurvinen E, Giacchi MV, Ahluwalia N. Validity of self-reported height and weight for estimating prevalence of overweight among Estonian adolescents: the health behaviour in school-aged children study. *BMC Res Notes.* (2015) 8:606. doi: 10.1186/s13104-015-1587-9
37. Perez A, Gabriel K, Nehme EK, Mandell DJ, Hoelscher DM. Measuring the bias, precision, accuracy, and validity of self-reported height and weight in assessing overweight and obesity status among adolescents using a surveillance system. *Int J Behav Nutr Phys Act.* (2015) 12(Suppl. 1):S2. doi: 10.1186/1479-5868-12-S1-S2
38. Brener ND, McManus T, Galuska DA, Lowry R,Wechsler H. Reliability and validity of self-reported height and weight among high school students. *J Adolesc Health.* (2003) 32:281–7. doi: 10.1016/S1054-139X(02)00708-5

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

OPINION
published: 31 January 2022
doi: 10.3389/fpubh.2022.815825

Family Medicine at the Forefront: Lessons Learnt From the COVID-19 Vaccine Rollout in Crete, Greece

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Keywords: vaccination, COVID-19, primary care, family medicine, Greece

OPEN ACCESS

Edited by:
Arch Mainous,
University of Florida, United States

Reviewed by:
Jenny Flagler-George,
University of Waterloo, Canada

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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Public Health

Received: *15 November 2021*
Accepted: *04 January 2022*
Published: *31 January 2022*

Citation:
Lionis C, Anastasaki M, Petelos E, Souliotis K and Tsiligianni I (2022) Family Medicine at the Forefront: Lessons Learnt From the COVID-19 Vaccine Rollout in Crete, Greece. Front. Public Health 10:815825. doi: 10.3389/fpubh.2022.815825

INTRODUCTION

With the world being amidst the global coronavirus pandemic, the development of vaccines to prevent further transmission was urgently needed, and the response to address this need has been unprecedented. On 21 December 2020, the European Commission (EC), upon a positive scientific recommendation of the European Medicines Agency (EMA), granted the first Conditional Marketing Authorization (CMA) to a vaccine against SARS-CoV-2 (Comirnaty of BioNTech and Pfizer) (1). The CMA was granted for preventing coronavirus disease 2019 (COVID-19) in people from 16 years of age.

On December 27, the COVID-19 vaccination rollouts started across the European Union (EU) Member-States with healthcare and other frontline workers; older adults were identified as priority groups across jurisdictions, while different priority groups were established across different countries. In Greece, January 16 was the first day for the vaccine administration to adults from 85 years of age. Greece introduced a staggered vaccination rollout based on age and exposures. The University Hospital of Heraklion (PAGNI) in Crete was amongst the first healthcare units to participate in this effort. The task was assigned to the PAGNI's Department of Public Health, under the coordination of three university professors and with the participation of 17 residents trained in General Practice/Family Medicine (GP/FM).

This perspective article aims to snapshot observations and experiences gathered from the COVID-19 Vaccination Centre (VC) established at the University Hospital of Heraklion in Crete. We also seek to discuss how key practice aspects could be used to inform future interventions and to translate the experiences gained into concrete proposals to improve the role of healthcare practitioners in GP/FM and in primary health care (PHC), to improve the efficiency and effectiveness of future rollouts, as well as to combat similar crises in the future. Finally, We share the first experiences and observations made to date. Furthermore, we formulate our experiences into recommendations aiming to inform the transformation PHC urgently requires in Greece needs to enhance the resilience of the healthcare system, increase preparedness, and improve response.

EXPERIENCES GAINED

To date (October 1st, 2021), adults, and children from 13 years of age, have been presenting for vaccination to the VC of PAGNI in Crete. During the pre-vaccination consultation, a brief medical history, regarding comorbidities and medications was obtained, along with information on recent episodes of flu or other infections, recent vaccination uptake, and history of contact with any confirmed or suspected COVID-19 case. The first and last author have involved in the providing the services at the VC and supervised the whole process upon the endorsement of the administrative authorities of the University Hospital. Although, it is an audit paper that it has been written as an opinion, the Hospital leaders have fully approved it.

To facilitate the flow of the information in this report, we classified the experiences gained from the VC in three time slots and specifically:

- the first one corresponds to the first 4 months (January–April 2021), i.e., the vaccination of older adults;
- the second (after April 2021–now) corresponds to the period of the first adverse reactions and hesitancy emerging and resulting in a sustained effect against the COVID-19 vaccination attributed to the reported adverse reactions of Vaxzevria (Astra Zeneca);
- the third period one corresponds to the period of indication extension and subsequent vaccination rollout to pediatric population following the approval for ages 12–15. https://www.ema.europa.eu/en/news/first-covid-19-vaccine-approved-children-aged-12-15-eu). All persons vaccinated were provided with clear instructions about which side effects to expect and how to report them to the VC. According to the available protocol, vaccinated people were advised to stay in the hospital, under close observation for 15 min after the administration of the vaccine. The critical comments are shortly outlined below and, where possible, patients' quotes have been used to vividly support the experiences gained vividly.

First Period: Vaccination of the Elderly

(a) Physical function was limited in many of the presenting people and the majority needed assistance. Almost half of them were on wheelchairs, while the presence of frailty was quite apparent in several.

(b) Although almost all older people were living with or close to their children, they frequently expressed feeling isolated, potentially because of the measures taken by their children to protect their parents. One lady mentioned: *"It is very frustrating to live in the same building with my six grandchildren and not to be able to see them. I wish this vaccine will end this torture."*

GPs involved in the vaccination rollout set up a plan prior to its initiation so that, apart from vaccination, an empathetic and compassionate approach would be adopted independently of time limitations. If necessary, GPs would provide further consultations. Almost all elderly reacted positively to the empathetic approach of the healthcare professionals and expressed their gratitude for the warm and friendly services they were receiving. A man said: *"I wish there were no other people in the waiting room so I could stay more with you and discuss. I felt so lonely, and you are so welcoming.... I wish I knew where to find you when all this ends."*

Many people also shared stories from when they were younger and more active. A well-known retired medical doctor of 89 years who presented for vaccination said: *"I am glad that you made us feel so welcome; you remind me the days I was young, and I felt so close to my patients."*

The overall experience confirmed that time should be dedicated to really connecting with patients, even presents certain concrete challenges given the limitations in terms of time available for the encounters in the context of vaccine administration at the VC.

(c) Older people were almost always accompanied by their children, who were present during consultations. These caregivers asked a lot of questions regarding possible vaccination side effects. Discussions in the context of the encounters at the VC revealed that there might be plenty of room for interventions regarding their own vaccination coverage and several other issues related to disease prevention. This underlined the strong bonds between family members, —a valid characteristic of the Greek society, which has primarily contributed to counteracting the effects of previous crises- and highlighted the need to support family cohesion during the strenuous times of the pandemic.

d) The most challenging task was approaching older people with severe mental disorders and dementia, because of the inability to clearly communicate feelings and any potential side effects and given issues of addressing decision-making and autonomy. This challenge had to be managed through close contact with patient caregivers and family, to which GPs explained how to recognize and report side effects.

Second Period: The First Negative Reactions and Vaccination Hesitancy

In the second period, an increased hesitancy to the vaccinations was reported, as captured in the Pharmacovigilance Risk Assessment Committee (PRAC) regarding the sporadic cases of unusual blood clots with low blood platelets with Vaxzevria (AstraZeneca's COVID-19 vaccine) (https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-6-9-april-2021). This resulted in a high level of anxiety and uncertainty to the local populations, affecting the vaccination rate, especially in many rural areas where these two vaccines were the only ones available. Furthermore, The lack of active and personal involvement of GPs and PHC professionals in communicating the explicit messages and information as the frontline physicians, with a sporadic role in the vaccination rollout, enhanced the hesitancy, and increased the existing confusion. Several proposals were put forth to local stakeholders and presented in the local media but were not implemented. Among them, the following have been mentioned:

- Establishing a telephone line to facilitate effective communication with people experiencing high fear and anxiety;
- Engaging local stakeholders and key local actors to communicate the key messages in a more effectively way, in addition to the centrally delivered by TV and the social media messages.

One major challenge that Greece faces is the fact that PHC is still nascent despite some progress in the past few years (2). Across the world, the role of PHC during this pandemic was considered crucial, representing the epicenter of service delivery (3). In Greece the pandemic revealed existing issues and this large gap, as people didn't have a "doctor" to trust and to discuss their concerns in case they needed more information or were hesitant (4).

Third Period: Pediatric Populations

In the last period, the contact with children and families revealed the need for closer focus on the family and the adaptation of all the measures to the expectations, wishes, and needs of both the children and their parents, and for key messages to communicate soundly the benefits and soundly. Again, the need of primary care transformation and need for involvement of GP/FM was evident given how trust relationships can contribute to quality service delivery and outcomes.

DISCUSSION

The observations presented in this paper should be discussed in the light of efforts that current healthcare systems undertake to make health and social care services more resilient. It is a general agreement that strengthening PHC is the key to achieve it, while OECD and EC Expert Panel on Effective Ways of Investing in Health underlines the need to strength PHC with a focus on multidisciplinary teams, integrated with community health services, and equipped with digital technologies (5, 6).

Our second observation and especially the first quote, is also an indicates of the perception of what complete full vaccination signaled to them in terms of ending the pandemic.

An observation deserving further attention, especially when GP/FM meets older people with cognitive impairment, is the role of autonomy in the decision-making process, as well as the role of the GP/FM in reporting side effects, pharmacovigilance, and early safety signal identification. Specific recommendations regarding these aspects can be found in the framework of the European guidelines for good pharmacovigilance practices (GVP). Furthermore, safeguarding mobility and autonomy for these people in Greece may be an important area of focus. According to the 2019 OECD report *"In 2017, life expectancy at age 65 was 20.1 years, slightly higher than in EU countries. However, people in Greece can expect to live only about 40 % of these years without disability, compared to about 50 % in the EU, which translates into two healthy life years less"* (7). This highlights the need for public health and PHC measures to support this part of the population and their families. In addition, frailty has been proven to be a relatively good independent predictor/prognostic factor for COVID-19 outcomes, so this was an opportunity to map and inform on population-level characteristics (8, 9).

Equally, our observations point out to the impact of social isolation and the need for strong vital networking for people of this age group (over 85 years). In Greece, the role of family is crucial, and it seemed that, in our setting, there was good support provided to the elderly. However, loneliness was very prevalent and the need to see able to see their grandchildren was amongst the people's first wishes and perhaps a reason that motivated them to be vaccinated. We propose that vaccination programmes can be used for opportunistic screening of those elderly that need support in the form of mental and social care interventions, by easily identifying people without family or support/members or those that face other difficulties in accessing healthcare services. In line with the recommendations of the EC Expert Panel on effective ways to invest in health (10), the need to focus more on a comprehensive approach to old and vulnerable people including those who have a mental health condition and are socially and economically marginalized, by visiting them at home; assessing their health status, meeting their care and health needs seems to be an urgent priority; and current challenge for the Greek GP/FM and PHC.

To that direction, new healthcare models to respond to the current challenges should be discussed for example. The Italian healthcare system invested locally during the pandemic, and the idea is to keep patients near their families and friends who can take care of them (11). GP/FPs have the chance to work in teams with nurses and other specialists, including psychologists and dieticians to provide care close to patients. Although in Greece models based on such a decentralized form have still not been largely tested, in Greece, community-oriented care could potentially be one of the most successful stories shortly. GP/FM should take the lead toward the establishment of new organizational models.

In parallel, the role of compassion and empathy has received a prompt attention during the past years, and its impact has been assessed during the pandemic. A Lancet perspective article stated that *"Our empathy, our capacity to envision that we too could be affected, has been a powerful tool in the public health arsenal"* (12). However, this remains another challenge for the Greek healthcare system and its reform.

Health technology has been used in the fight against this pandemic; for example, remote consultations have been extensively used (13, 14). However, this is also a challenge as not all healthcare professionals have adequate digital literacy, whereas not everyone has access to new technologies. Furthermore, evaluation and assessment of these technologies to optimize their delivery and harvest their potential lags. Williams and Tsiligianni (3) report that health information and technology should follow the equity rules. They must be provided for the estimated 40% of the world not yet online. Health Technology Assessment International (HTAi) has also developed two position statements as a response to the COVID-19, emphasizing both the need of ensuring high evidentiary standards, and the need to have sound value propositions with early vaccine assessment for communication with the public (https://htai.org/hta-support-for-covid-19/position-statements-and-hta-reads).

The high hesitancy to COVID-19 vaccination observed during the second period calls for an effective communication strategy to recover from the pandemic, based on sound evidence and with aligned messages across jurisdictions, communities and, even, across borders. Such a strategy needs to involve and engage stakeholders and community leaders. PHC seems to be the suitable ground to achieve it and there are several positive examples gained from Crete that they can be used as best practices (15). To that direction, GP/FPs and PHC practitioners need to be equipped with skills of risk communication and to be able to provide appropriate management based on rational approaches and a clear understanding of people's risk perceptions (16–18). In addition, according to a recent publication (18), risk perception, motivation, and health literacy, all important predictors of health-seeking behavior and adherence to measures, needed to be addressed.

Finally, the vaccination to children and adolescents in the third period highlights the importance the role of the family-oriented PHC and underlines the needs for further training of GP/FPs in the field of child care.

CONCLUSION

The COVID-19 pandemic has placed health systems under pressure and has led to the introduction of extraordinary, if necessary, measures in Greece and across the world. Older people and patients with pre-existing medical conditions and, in general, with vulnerability are at higher risk of infection and worse outcomes (19). Integrated care can help address the public health challenges brought to the fore by the pandemic, and several responses at the European level (20), including nested integrated care approaches, can be used by health systems toward this direction. Rethinking PHC and the care of older and vulnerable people within the public health context is known to be essential for non-communicable diseases (21) and our preliminary observations suggest that this also holds true for COVID-19. GP/FM should approach the persons and the families by taking into consideration their health's biological, environmental, social, and psychological determinants of their health.

Taking into consideration the critical stage of the pandemic and the PHC reforms lately unfolding in Greece (22), our experiences although they were based on personal observations from one VC, can provide ground for further research and support the efforts toward upgrading the country's PHC system toward its integration with public health and substantial involvement of PHC in the design and delivery of efficient and effective vaccination strategies (15). Strengthening PHC is the core message of a recent OECD report (5); Greece should urgently invest in community and family-oriented PHC as a key priority to ensure a resilient health system, increased preparedness and improved response. It could be considered as an important step toward strategic and evidence-informed planning to overcome hesitancy and improve the vaccination rollout in terms of efficiency and effectiveness, improving the overall uptake in across population groups in Greece (23).

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

ACKNOWLEDGMENTS

The authors need to thank Assistant Prof. Emmanouil Symboulakis, Prof. Emmanouil Galanakis, and Associate Prof. Chrissoula Perdikoyanni, the residents in general practice, and as well as all physicians, nurses, and administrative employees who contributed to the successful operation of the vaccination center in the University Hospital (PAGNI). Many thanks also to the Manager Prof. George Chalkiadakis and Deputy Manager Dr. Stelios Kteniadakis, to Members of the Executive Board of this Hospital, as well as to the General Medical Prof. Nikos Tzanakis for continuous support.

REFERENCES

1. European Commission. *European Commission Authorises First Safe and Effective Vaccine Against COVID-19*. (2020). Available online at: https://ec.europa.eu/commission/presscorner/detail/en/IP_20_2466 (accessed january 15, 2022).
2. Lionis C, Symvoulakis EK, Markaki A, Vardavas C, Papadakaki M, Daniilidou N, et al. Integrated primary health care in Greece, a missing issue in the current health policy agenda: a systematic review. *Int J Integr Care.* (2009) 9:e88. doi: 10.5334/ijic.322
3. Williams S, Tsiligianni I. COVID-19 poses novel challenges for global primary care. *NPJ Prim Care Respir Med.* (2020) 30:30. doi: 10.1038/s41533-020-0187-x
4. Gountas I., Hillas G., Souliotis K. Act early, save lives: managing COVID-19 in Greece. *Public Health*. (2020) 187:136–9. doi: 10.1016/j.puhe.2020.08.016
5. OECD. *Strengthening the Frontline: How Primary Health Care Helps Health Systems Adapt During the COVID 19 Pandemic*. (2021). Available online at: https://www.oecd.org/coronavirus/policy-responses/strengthening-the-frontline-how-primary-health-care-helps-health-systems-adapt-during-the-covid-19-pandemic-9a5ae6da/ (accessed january 15, 2022).
6. EC Expert Panel on Effective Ways of Investing in Health. *The Organisation of Resilient Health and Social Care Following the COVID-19 Pandemic*. Available online at: Panelhttps://ec.europa.eu/health/sites/default/files/expert_panel/docs/026_health_socialcare_covid19_en.pdf (accessed january 15, 2022).
7. OECD. *State of Health in the EU Greece Country Health Profile*. Available online at: https://www.oecd.org/greece/greece-country-health-profile-2019-d87da56a-en.htm (accessed january 15, 2022).
8. Zhang XM, Jiao J, Cao J, Huo X-P, Zhu C, Wu XJ, et al. Frailty as a predictor of mortality among patients with COVID-19: a systematic review and meta-analysis. *BMC Geriatr*. (2021) 21:186. doi: 10.1186/s12877-021-02138-5
9. Hewitt J, Carter B, Vilches-Moraga A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. *Lancet Public Health.* (2020) 5:e444–51. doi: 10.1016/S2468-2667(20)30146-8
10. Barros P. Introduction to the Expert Panel on Effective ways of investing in health (EXPH) and its mandate. *Eur J Public Health*. (2021) 31(Suppl. 3):ckab164.147. doi: 10.1093/eurpub/ckab164.147
11. Politico. *When Smaller Is Better: Italian Health Care Goes Local After Pandemic*. (2021). Available online at: https://www.politico.eu/article/italy-health-care-hospital-local-coronavirus-pandemic/ (accessed january 15, 2022).
12. Galea S. The art of medicine: compassion in a time of COVID-19. *Lancet*. (2020) 395:1897–8. doi: 10.1016/S0140-6736(20)31202-2
13. van der Velden AW, Bax EA, Bongard E, Munck Aabenhus R, Anastasaki M, Anthierens S, et al. Primary care for patients with respiratory tract infection before and early on in the COVID-19 pandemic: an

observational study in 16 European countries. *BMJ Open.* (2021) 11:e049257. doi: 10.1136/bmjopen-2021-049257

14. Wanat M, Hoste M, Gobat N, Anastasaki M, Böhmer F, Chlabicz S, et al. Transformation of primary care during the COVID-19 pandemic: experiences of healthcare professionals in eight European countries. *Br J Gen Pract.* (2021) 71:e634–42. doi: 10.3399/BJGP.2020.1112
15. Lionis C, Petelos E, Papadakis S, Tsiligianni I, Anastasaki M, Angelaki A, et al. Towards evidence-informed integration of public health and primary health care: experiences from Crete. *Public Health Panorama.* (2018) 4:699–713. Available online at: https://tiems.info/dmdocuments/events/TIEMS_2008_Bernd_Rohrmann_Keynote.pdf
16. Rohrmann B. Risk perception, risk attitude, risk communication, risk management: a conceptual appraisal. In: *Proceedings of the International Emergency Management Society Annual Conference.* Prague (2008). Available online at: https://tiems.info/dmdocuments/events/TIEMS_2008_Bernd_Rohrmann_Keynote.pdf
17. Rohrmann, B.; Renn, O. Risk perception research. An introduction. In: *Cross-cultural Risk Perception. A Survey of Empirical Studies*. Berlin: Springer (2000). p. 11–53.
18. Priesemann V, Balling R, Bauer S, Beutels P, Valdez AC, Cuschieri S, et al. Towards a European strategy to address the COVID-19 pandemic. *Lancet.* (2021) 398:838–9. doi: 10.1016/S0140-6736(21)01808-0
19. World Health Organization. *Q&A on Coronaviruses (COVID-19)*. Available online at: https://www.who.int/news-room/q-a-detail/q-a-coronaviruses (accessed january 15, 2022).
20. Lindner S, Kubitschke L, Lionis C, Anastasaki M, Kirchmayer U, Giacomini S, et al. Can Integrated Care Help in Meeting the Challenges Posed on Our Health Care Systems by COVID-19? Some Preliminary Lessons Learned from the European VIGOUR Project. *Int J Integr Care.* (2020) 20:4. doi: 10.5334/ijic.5596
21. Tziraki C, Grimes C, Ventura F, O'Caoimh R, Santana S, Zavagli V, et al. Rethinking palliative care in a public health context: addressing the needs of persons with non-communicable chronic diseases. *Prim Health Care Res Dev.* (2020) 21:e32. doi: 10.1017/S1463423620000328
22. World Health Organization. *Greek Health Reform: Opening of New Primary Health Care Units*. (2017). Available online at: http://www.euro.who.int/en/countries/greece/news/news/2017/12/greek-health-reform-opening-of-new-primary-health-care-units (accessed january 15, 2022).
23. *European Centre for Disease Prevention and Control Overview of the Implementation of COVID-19 Vaccination Strategies and Deployment Plans in the EU/EEA*. Technical report (2021). Available online at: https://www.ecdc.europa.eu/en/publications-data/overview-implementation-covid-19-vaccination-strategies-and-deployment-plans (accessed january 15, 2022).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers
in Public Health

ORIGINAL RESEARCH
published: 09 February 2022
doi: 10.3389/fpubh.2022.810348

Relationships Between Diagnosis, Bacterial Isolation, and Antibiotic Prescription in Out Patients With Respiratory Tract Infection Symptoms in Rural Anhui, China

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Objectives: This paper aims to explore the direct associations of antibiotics prescription with clinical diagnosis and bacterial detection. It also analyses the relations of clinical diagnosis with symptoms and bacterial detection, with a hope of revealing indirect links to antibiotic prescription.

Methods: The study was implemented in one village clinic and one township health center in each of four rural residential areas in Anhui Province, China. Observations were conducted to record clinical diagnosis and antibiotic prescription. A semi-structured questionnaire survey was used to collected patients' sociodemographic information and reported symptoms. Sputum and throat swabs were collected for bacterial culture.

Results: Among 1,068 patients presenting in the study settings who received a diagnosis of respiratory tract infection (RTI), 87.8% of prescriptions included an antibiotic and 35.8% included two or more antibiotics. Symptomatic RTI patients to the site clinics were diagnosed mainly as having upper respiratory tract infection (32.0%), bronchitis/tracheitis (23.4%), others (16.6%), pharyngitis (11.1%), common cold (8.0%), pneumonia/bronchopneumonia (4.6%) and tonsillitis (4.3%). These clinical diagnosis were associated with symptoms to a varied degree especially for upper respiratory tract infection and bronchitis/tracheitis. Prescription of any antibiotics was positively associated with diagnosis of bronchitis/tracheitis (OR: 5.00, 95% CI: 2.63–9.51), tonsillitis (OR: 4.63, 95% CI: 1.48–14.46), pneumonia/bronchopneumonia (OR: 4.28, 95% CI: 1.40–13.04), pharyngitis (OR: 3.22, 95% CI: 1.57–6.59) and upper respiratory tract infection (OR: 3.04, 95% CI: 1.75–5.27). Prescription of two or more antibiotics was statistically significant related to diagnosis of bronchitis/ tracheitis (OR: 2.20, 95% CI: 1.44–3.35) or tonsillitis (OR: 2.97, 95% CI: 1.47–6.00). About 30% of the patients were identified with some type of bacteria. Bacteria detection was linked with pharyngitis (OR: 0.50, 95% CI: 0.28–0.88) but not prescription of antibiotics.

Edited by:
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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Public Health

Received: *06 November 2021*
Accepted: *03 January 2022*
Published: *09 February 2022*

Citation:
Xingrong S, Rui F, Jing C, Jing C, Oliver I, Lambert H and Wang D (2022) Relationships Between Diagnosis, Bacterial Isolation, and Antibiotic Prescription in Out Patients With Respiratory Tract Infection Symptoms in Rural Anhui, China. Front. Public Health 10:810348. doi: 10.3389/fpubh.2022.810348

Conclusions: Antibiotics prescription were found with a strong relation to diagnosis of RTIs given by the clinician but was not associated with the presence of bacteria in patient samples. Part of the diagnosis may have been given by the clinician to justify their antibiotics prescription. There is clear need to use additional measures (e.g., symptoms) in conjunction with diagnosis to supervise or audit excessive antibiotics use.

Keywords: antibiotic, respiratory tract infection, primary care, diagnosis, bacterial isolation

INTRODUCTION

Antimicrobial resistance (AMR) is a global public health problem, which contributes to increased morbidity, mortality, and economic costs associated with infections (1, 2). AMR is caused primarily by over or inappropriate use of antibiotics (3–5). The bulk of human antibiotic use happens in primary care settings, with respiratory tract infections (RTI) accounting for over 80% of antibiotic prescriptions (6). The equivalent of primary care facilities in western countries, township health centers and village clinics in China, provide most outpatient care in rural areas, but antibiotic stewardship programs in these settings are much less developed than in higher level settings such as county, prefecture and provincial level hospitals (7, 8). Data from the National Center for Health Statistics of the United States shows that between 20 and 50% of outpatient antibiotic prescribing in the US is estimated to be unnecessary, which translates into nearly 47 million unnecessary antibiotic prescriptions each year (9). Excessive antibiotic use may be even more prevalent in China. Our previous study conducted in primary care settings of Anhui Province in China revealed that 88.0% of symptomatic RTI patients were prescribed antibiotics (6).

AMR containment depends heavily upon thorough understanding of drivers of antibiotic prescribing. Ideally, prescribing decisions should be evidence-based and information on bacterial presence together with antibiotic sensitivity can help. However, as in most countries, in China, microbiological tests are not available in primary care settings and patient samples are rarely sent to referral laboratories for testing (10). In consequence, existing studies in rural China have seldom investigated relationships between microbiological and clinical diagnoses in the treatment of RTI.

Another way of optimizing antibiotic prescribing is addressing clinical drivers. Several studies have found that symptoms reported by patients, diagnosis given by physicians and the social-demographic background of patients are all linked to antibiotic prescribing patterns (11–13). Other studies have reported that antibiotic prescribing rates are higher in rural (vs. urban) practices, among patients with longer illness duration or acute bronchitis, and when providers experience greater diagnostic uncertainty (14, 15). However, contemporary studies on determinants of antibiotic prescription in rural China suffer from two major shortcomings. First, they rely primarily on retrospective reports or review of patient records (16, 17). Retrospective reports are prone to biases, and this is especially true for rural residents many of whom are illiterate and may not be capable of distinguishing antibiotic from non-antibiotic medications; while in a previous study we found that electronic patient records do not match actual prescriptions to a large extent in rural China (18).

Funded jointly by the National Natural Science Foundation of China (NSFC) and UK Research and Innovation (UKRI) through the Newton Fund, we carried out a 3-year project titled "Pathways to optimizing antibiotic use in rural Anhui province, China" that aimed to investigate the magnitude and drivers of antibiotic use and antibiotic resistance in rural areas in China. The project adopted a mixed methodology making innovative use of non-participant observation, qualitative interviews, structured questionnaire surveys, microbiological testing and record review. The overall study protocol and results from other study components are published elsewhere (19, 20). This part of the study explores the direct associations of antibiotics prescription with clinical diagnosis and bacterial detection. It also analyses the relations of clinical diagnosis with symptoms and bacterial detection, with a hope of revealing indirect links to antibiotic prescription.

MATERIALS AND METHODS

Recruitment Criteria

The study took place in one village clinic and one township health center in each of four counties in Anhui Province, China. Participants were male or female outpatients who were: (a) 18 years or older and able to give consent to participate in the study; (b) presenting to the recruitment site for the first time for the current illness; and (c) observed as having exacerbation of chronic obstructive pulmonary disease (COPD), upper respiratory tract infection with productive cough or sore throat.

These conditions were selected because they are common clinical presentations that can be associated with bacterial infection and where an organism may be identified through laboratory testing.

Sampling and Sample Size

The clinics/centers in each county were selected randomly from a list provided by the provincial health board of all potential facilities fulfilling set criteria (population size, location, transport links, patient footfall). The participant patients were selected *via* a "consecutive sampling" in which, when a start date had been determined for a site, the recruitment continued daily (7 days a week) thereafter, until the target numbers had been reached. All presenting patients to the site village clinics and township health centers who met the inclusion criteria during any study day were invited to participate.

The sample size used for this study was calculated based on the microbiological sub-study aims. We estimate that at least 1,000 RTIs patients this will yield 100 *Streptococcus pneumoniae* isolates which should provide sufficient power to allow us to estimate key antibiotic susceptibilities. The detailed description and calculation of the sample size for this study has been reported in the published study protocol (19).

Questionnaire and Data Collection Procedures

Data were collected from semi-structured observations, exit survey, specimen collection and testing (**Figure 1**). The observation focused on daily operational routine including test ordering, prescribing, patient recall and other standard procedures using a pre-designed worksheet (19). The exit survey was a brief face-to-face questionnaire consisting of structured and semi-structured questions and completed by all patients consented by the attending clinicians at clinics and health centers and recruited into the study. The questionnaire was informed by open-ended interviews undertaken in the study's pilot phase and included information on social demographics, symptoms and diseases history (**Supplementary File 1**). A trained researcher was sent to each participating clinics and health centers to perform semi-structured observations.

Sputum and throat swabs for bacterial culture, identification and susceptibility testing were collected. Sputum was collected from patients presenting with productive cough and throat swabs from patients with sore throat. The specimens were collected by the attending doctor using a sterilized container and according to a standard protocol. The specimens were transported and tested at the Central Laboratory of Anhui Medical University (AMU). For details are included in the published protocol (19).

Data Management and Analysis

Questionnaire responses were double-entered into a database using EPI DATA 3.1, then exported and analyzed using SPSS. The analysis consisted of two parts. Part one centered on descriptive analysis using 2-sided x^2, of null hypothesis, of the power of differences ($P < 0.05$) in the groups of education year (s), days since onset, symptoms, diagnosis, antibiotic use and bacterial detected between different sex and age groups.

Part two built 2 sets of multivariable logistic regression models aimed to derive the two kinds of associations as specified in the study purposes. More specifically, the first set of models used "any antibiotic prescription," "combined antibiotic prescription," and "bacterial isolation" as the dependent variable, respectively, and diagnosis, days since onset and social demographics as the independent variables. The second set of models used 7 categories diagnosis (including bronchitis/tracheitis, upper respiratory tract infection, pharyngitis, common cold, pneumonia/bronchopneumonia, tonsillitis, others diagnosis) as the dependent variable, respectively, and symptoms, days since onset and social demographics as the independent variables. **Supplementary File 2** lists details of values assigned to variables used. The P (<0.05) and OR value was used to judge whether a given variable is and to what extent linked to antibiotic prescription or bacterial isolation or clinical diagnosis. Any missing data were excluded from the analysis.

RESULTS

Descriptive Characteristics of the Study Population

As shown in **Table 1**, a total of 1,068 patients aged 17–89 (51.0% males and 49.0% females) completed the exit survey and provided specimens, accounting for 99.5% of all the symptomatic RTI patients who met the inclusion criteria. Male and younger participants had more years of education than female and older ones ($P = 0.000$). Younger patients' visits to the clinics or health center showed a shorter time interval since onset of symptoms than older ones ($P = 0.000$). For the RTI patients, the proportion of antibiotic prescription, combined antibiotic prescription and bacterial detection was 87.8, 35.8, and 30.8%, respectively. Antibiotic prescription rate showed no statistical differences between sex and age subgroups, but men and older patients were more likely to get prescriptions containing two or more antibiotics than women and younger patients. There was a significant difference in the percentage of samples from which a bacterial pathogen was isolated by sex [higher in males (33.8%) than females (27.7%), $P = 0.033$] and age [older (39.6%) than younger (23.5%) patients, $P = 0.001$].

Among all the patients, the most frequently reported symptoms were sore throat (561, 52.5%), followed by cough with white sputum (525, 49.2%) and breathing difficulties (365, 34.2%). Compared with female patients, male patients were less likely to report snotty nose (4.6 vs. 8.6%), dry cough (10.8 vs. 14.9%), sore throat (43.3 vs. 62.1%) and headache (15.4 vs. 22.4%) but more likely to report cough with white sputum (55.4 vs. 42.6%) and itchy throat (27.2 vs. 21.0%). Compared with older patients, younger ones were more likely to report blocked nose, dry cough, cough with green sputum, sore throat and headache, while being less likely to report cough with white sputum and breathing difficulties. The top diagnoses given by the attending doctors were upper respiratory tract infection (342, 32.0%) and, bronchitis/tracheitis (250, 23.4%).

Factors Associated With Antibiotic Prescription

Model 1 and Model 2 in **Table 2** describes the statistics from the logistic regression modeling of "any antibiotic prescription" and "combined antibiotic prescription". Any antibiotic prescription was positively associated with diagnosis of bronchitis/tracheitis (OR: 5.00, 95% CI: 2.63–9.51), tonsillitis (OR: 4.63, 95% CI: 1.48–14.46), RTI (OR: 3.04, 95% CI: 1.75–5.27), pharyngitis (OR: 3.22, 95% CI: 1.57–6.59) and pneumonia/bronchopneumonia (OR: 4.28, 95% CI: 1.40–13.04) but negatively linked with patients reporting illness duration of over seven days as compared with those reporting an illness duration of 2 days or less (OR: 0.27, 95% CI: 0.16–0.46). Combined antibiotic prescription was more likely to be given to patients aged 40 years older and in patients diagnosed with bronchitis/tracheitis

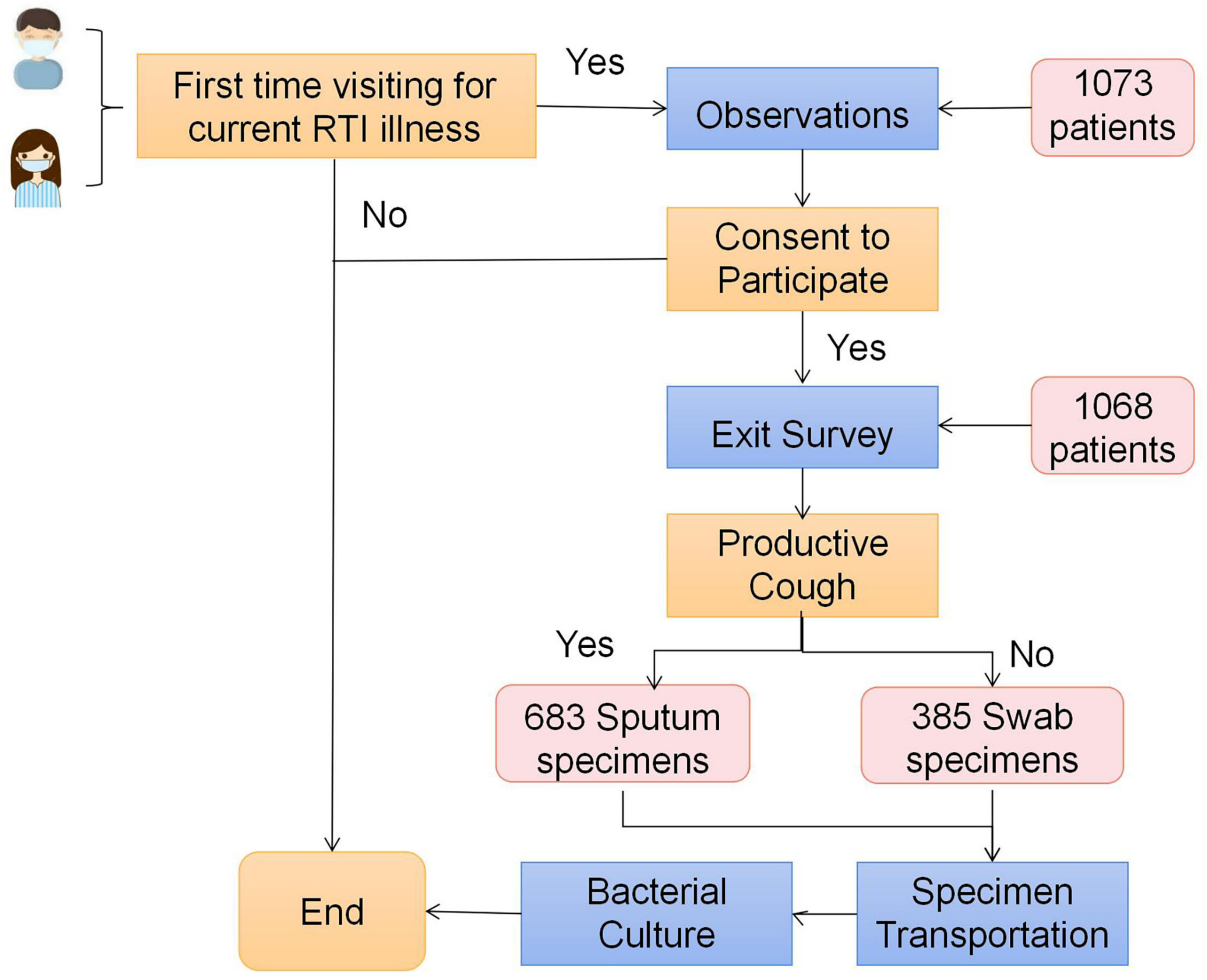

FIGURE 1 | Flow chart of participant recruitment.

(OR: 2.20, 95% CI: 1.44–3.35) or tonsillitis (OR: 2.97, 95% CI: 1.47–6.00). But less likely to be given to patients reporting longer illness duration (more than 7 days) (OR: 0.62, 95% CI: 0.41–0.94).

Factors Associated With Bacterial Isolation

Model 3 in **Table 2** provides the statistics from the logistic regression modeling of "bacterial detected". The likelihood of detecting a bacterial isolate was higher in biological samples from patients aged 65 years or older than from those under 40 years (OR: 1.72, 95% CI: 1.05–2.81) and also from patients who presented at the health facility 3.5–7 days (OR: 1.55, 95% CI: 1.05–2.77) or more than 7 days (OR: 1.83, 95% CI: 1.22–2.74) since onset of infection than from those who presented within 2 days but was lower in patients diagnosed with pharyngitis (OR: 0.50, 95% CI: 0.28–0.88). No statistical association was observed between bacteria detection and prescription of antibiotics.

Relationships Between Symptoms and Diagnosis

Table 3 summarizes results from the logistic regression analysis undertaken to explore possible symptom determinants for the range of clinical diagnoses assigned by the participating doctors in our study. After controlling for sex, age and education, diagnosis of "bronchitis/tracheitis" was found to be positively linked to symptoms of breathing difficulties (OR: 1.94, 95% CI: 1.40–2.68) and to a longer duration (3.5–7 days) since onset of infection compared with ≤2 days (OR: 2.51, 95% CI: 1.62–3.89), while negatively linked to sore throat (OR: 0.53, 95% CI: 0.38–0.75). "RTI" witnessed a positive association with blocked nose (OR: 1.68, 95% CI: 1.22–2.32), runny nose (OR: 1.57, 95% CI: 1.15–2.15), snotty nose (OR: 1.86, 95% CI: 1.07–3.23), sore throat (OR: 1.40, 95% CI: 1.04–1.88) and headache (OR: 1.48, 95% CI: 1.03–2.12), while a negative association with breathing difficulties (OR: 0.63, 95% CI: 0.46–0.87) and days since infection onset (vs. ≤2 days). "Common cold" showed positive link

TABLE 1 | Descriptive statistics of antibiotics prescription, symptoms, diagnosis and common socio-demographics, *N* (%).

	Sex		***P***	**Age**				***P***	**Total**
	Male	**Female**		**≤39**	**40–53**	**54–64**	**≥65**		
Year(s) of education									
0	89 (16.3)	187 (35.8)	0.000	2 (0.7)	53 (18.7)	101 (40.1)	120 (46.2)	0.000	276 (26.0)
1–5	157 (28.8)	149 (28.5)		32 (11.8)	115 (40.5)	72 (28.6)	87 (33.5)		306 (28.8)
6–8	155 (28.4)	74 (14.1)		68 (25.0)	82 (28.9)	45 (17.9)	34 (13.1)		229 (21.6)
>8	141 (25.9)	109 (20.8)		167 (61.4)	33 (11.6)	33 (13.1)	17 (6.5)		250 (23.6)
Missing	3 (0.6)	4 (0.8)		3 (1.1)	1 (0.4)	1 (0.4)	2 (0.8)		
Days since onset									
≤2 days	163 (29.9)	171 (32.7)	0.758	102 (37.5)	98 (34.5)	65 (25.8)	69 (26.5)	0.000	334 (31.5)
2–3.5 days	155 (28.4)	137 (26.2)		85 (31.3)	84 (29.6)	59 (23.4)	64 (24.6)		292 (27.5)
3.5–7 days	118 (21.7)	112 (21.4)		50 (18.4)	58 (20.4)	63 (25.0)	59 (22.7)		230 (21.7)
>7 days	105 (19.3)	99 (18.9)		33 (12.1)	43 (15.1)	62 (24.6)	66 (25.4)		204 (19.2)
Missing	4 (0.7)	4 (0.8)		2 (0.7)	1 (0.4)	3 (1.2)	2 (0.8)		
Symptoms									
Blocked nose	118 (21.7)	139 (26.6)	0.060	95 (34.9)	72 (25.4)	53 (21.0)	37 (14.2)	0.000	257 (24.1)
Runny nose	140 (25.7)	137 (26.2)	0.850	62 (22.8)	69 (24.3)	63 (25.0)	83 (31.9)	0.080	277 (25.9)
Snotty nose	25 (4.6)	45 (8.6)	0.008	20 (7.4)	20 (7.0)	17 (6.7)	13 (5.0)	0.698	70 (6.6)
Dry cough	59 (10.8)	78 (14.9)	0.046	45 (16.5)	43 (15.1)	28 (11.1)	21 (8.1)	0.014	137 (12.8)
Cough with green sputum	120 (22.0)	130 (24.9)	0.273	82 (30.1)	70 (24.6)	61 (24.2)	37 (14.2)	0.000	250 (23.4)
Cough with white sputum	302 (55.4)	223 (42.6)	0.000	92 (33.8)	120 (42.3)	135 (53.6)	178 (68.5)	0.000	525 (49.2)
Dry/burning throat	120 (22.0)	138 (26.4)	0.096	70 (25.7)	79 (27.8)	51 (20.2)	58 (22.3)	0.169	258 (24.2)
Itchy throat	148 (27.2)	110 (21.0)	0.019	71 (26.1)	73 (25.9)	54 (21.4)	60 (23.1)	0.547	258 (24.2)
Sore throat	236 (43.3)	325 (62.1)	0.000	182 (66.9)	157 (55.3)	121 (48.0)	101 (38.8)	0.000	561 (52.5)
Breathing difficulties	179 (32.8)	186 (35.6)	0.349	59 (21.7)	84 (29.6)	95 (37.7)	127 (48.8)	0.000	365 (34.2)
Headache	84 (15.4)	117 (22.4)	0.004	67 (24.6)	48 (16.9)	48 (19.0)	38 (14.6)	0.021	201 (18.8)
Weakness	65 (11.9)	74 (14.1)	0.281	40 (14.7)	37 (13.0)	31 (12.3)	31 (11.9)	0.783	139 (13.0)
Fever	77 (14.1)	69 (13.2)	0.656	47 (17.3)	36 (12.7)	30 (11.9)	33 (12.7)	0.249	146 (13.7)
Other symptoms	98 (18.0)	115 (22.0)	0.101	45 (16.5)	53 (18.7)	59 (23.4)	56 (21.5)	0.206	213 (19.9)
Diagnosis									
D1	144 (26.4)	106 (20.3)	0.018	36 (13.2)	62 (21.8)	66 (26.2)	86 (33.1)	0.000	250 (23.4)
D2	166 (30.5)	176 (33.7)	0.264	98 (36.0)	99 (34.9)	91 (36.1)	54 (20.8)	0.000	342 (32.0)
D3	47 (8.6)	72 (13.8)	0.008	51 (18.8)	40 (14.2)	17 (6.7)	11 (4.2)	0.000	119 (11.1)
D4	48 (8.8)	37 (7.1)	0.296	18 (6.6)	25 (8.8)	16 (6.3)	26 (10.0)	0.346	85 (8.0)
D5	26 (4.8)	23 (4.4)	0.771	4 (1.5)	7 (2.5)	19 (7.5)	19 (7.3)	0.000	49 (4.6)
D6	22 (4.0)	24 (4.6)	0.657	25 (9.2)	12 (4.2)	4 (1.6)	5 (1.9)	0.000	46 (4.3)
D7	92 (16.9)	85 (16.3)	0.783	40 (14.7)	39 (13.7)	39 (15.5)	59 (22.7)	0.022	177 (16.6)
Antibiotic use	483 (88.6)	455 (87.0)	0.417	232 (85.3)	255 (89.8)	219 (86.9)	232 (89.2)	0.343	938 (87.8)
Combined antibiotic use	219 (40.2)	163 (31.2)	0.002	64 (23.5)	107 (37.7)	102 (40.5)	109 (41.9)	0.000	382 (35.8)
Bacterial detected	184 (33.8)	145 (27.7)	0.033	64 (23.5)	81 (28.5)	81 (32.1)	103 (39.6)	0.001	329 (30.8)
Total	545 (51.0)	523 (49.0)		272 (25.5)	284 (26.6)	252 (23.6)	260 (24.3)		1,068

D1, Bronchitis/tracheitis; D2, upper respiratory tract infection; D3, Pharyngitis; D4, Common cold; D5, Pneumonia/bronchopneumonia; D6, Tonsillitis; D7, Others.

with blocked nose (OR: 2.29, 95% CI: 1.37–3.83), runny nose (OR: 1.90, 95% CI: 1.17–3.11), cough with white sputum (OR: 2.22, 95% CI: 1.21–4.08) and itchy throat (OR: 1.83, 95% CI: 1.10–3.04), while negative link with breathing difficulties (OR: 0.29, 95% CI: 0.16–0.54) and > 7 days since onset (OR: 0.36, 95% CI: 0.15–0.86). Patients with other diagnoses were most frequently among patients with cough with green sputum (OR: 2.49, 95% CI: 1.61–3.86) and with longer duration of symptoms (>3.5 days).

DISCUSSION

The study found that 87.8% of prescriptions for patients presenting with symptoms associated with RTIs contained an antibiotic, which is substantially higher than that found at similar settings in the United States (14.7%), Africa region (46.8%), the United Kingdom (42.0%) and that recommended by the World Health Organization (15). In addition, more than one in three (35.8%) of prescriptions contained two or more antibiotics. These

TABLE 2 | Multivariable logistic regression statistics between diagnosis and antibiotic prescription or bacterial isolation.

Independent variables	Model1: any antibiotic prescription				Model2: combined antibiotic prescription				Model3: bacterial detected			
	OR	95% C.I		P	OR	95% C.I		P	OR	95% C.I		P
		Lower	Upper			Lower	Upper			Lower	Upper	
Sex (female as ref.)	0.80	0.52	1.23	0.300	0.70	0.52	0.94	0.017	0.78	0.58	1.05	0.100
Age												
≤39	**Ref.**		0.632	**Ref.**	0.008	**Ref.**	0.191					
40–53	1.26	0.67	2.35	0.471	1.94	1.26	3.00	0.003	1.33	0.86	2.07	0.200
54–64	1.01	0.52	1.93	0.985	2.09	1.32	3.31	0.002	1.34	0.84	2.14	0.214
≥65	1.42	0.69	2.94	0.346	2.11	1.29	3.45	0.003	1.72	1.05	2.81	0.031
Year (s) of education												
0	**Ref.**		0.215	**Ref.**	0.812	**Ref.**	0.382					
1–5	0.88	0.49	1.57	0.669	1.05	0.72	1.51	0.815	0.74	0.51	1.07	0.106
6–8	1.02	0.51	2.05	0.946	1.04	0.67	1.60	0.867	0.78	0.50	1.20	0.253
≥9	0.56	0.28	1.12	0.102	0.86	0.53	1.39	0.537	0.89	0.55	1.45	0.646
Days since onset												
≤2 days	**Ref.**		0.000	**Ref.**	0.064	**Ref.**	0.024					
2–3.5 days	0.80	0.46	1.39	0.429	1.00	0.71	1.42	0.991	1.43	0.99	2.05	0.054
3.5–7 days	1.24	0.65	2.38	0.518	1.03	0.71	1.51	0.861	1.55	1.05	2.27	0.027
>7 days	0.27	0.16	0.46	0.000	0.62	0.41	0.94	0.023	1.83	1.22	2.74	0.004
Bacterial detected/antibiotic prescription	1.17	0.75	1.81	0.487	0.92	0.69	1.23	0.590	1.19	0.77	1.84	0.437
Diagnosis												
Bronchitis/tracheitis	5.00	2.63	9.51	0.000	2.20	1.44	3.35	0.000	0.73	0.48	1.11	0.136
Upper respiratory tract infection	3.04	1.75	5.27	0.000	1.46	0.96	2.21	0.079	0.71	0.47	1.07	0.100
Pharyngitis	3.22	1.57	6.59	0.001	0.58	0.31	1.05	0.073	0.50	0.28	0.88	0.016
Common cold	1.09	0.55	2.16	0.799	0.35	0.17	0.71	0.004	0.64	0.36	1.15	0.138
Pneumonia/bronchopneumonia	4.28	1.40	13.04	0.011	1.81	0.93	3.52	0.081	0.97	0.50	1.88	0.931
Tonsillitis	4.63	1.48	14.46	0.008	2.97	1.47	6.00	0.002	0.96	0.47	1.98	0.914
Constant	6.33				0.46				0.48			

results suggest that excessive antibiotic use in primary health care settings in rural China is still very prevalent and there is a clear need for a better understanding of the issue.

Our study revealed that most of the clinical diagnoses except common cold were strong predictors of antibiotics use. Treatment should be based on diagnosis, however, the study shows that the antibiotic prescriptions were not necessarily based on the etiology/pathology. According to China national guidelines on rational medicine use for frontier medical care givers (21), antibiotics use is recommended only for pneumonia/bronchopneumonia but not for bronchitis/tracheitis, upper respiratory tract infection, pharyngitis and tonsillitis unless there are clear indications of bacterial infection. However, in our study, a diagnosis of any of these RTIs was a strong predictors of antibiotic prescription. Studies have documented only marginal effects of antibiotic use for these diagnoses, resulting in above a half-day reduction in cough but no reduction of functional impairment compared to placebo treatment (22). For some physicians, diagnosis was given for satisfying record keeping requirement rather than clinical purposes.

Prescription of combined (two or more) antibiotics demonstrated different relationships with diagnosis and symptoms. In terms of diagnosis, it was only positively linked to tonsillitis and bronchitis/tracheitis but negatively related to common cold. These findings may partly be explained, according to our qualitative interviews, by the beliefs that: (a) "common cold is generally, as indicated by its name, common, mild and self-limiting" and therefore "does not need antibiotics treatment"; (b) tonsillitis and bronchitis/tracheitis are "often caused by and/or accompanied with bacterial infections," "are difficult to treat" and thus "need adequate, potent and broad-spectrum antibiotics".

The evidence shows that the relationship between diagnosis and symptoms were consistent with national guidelines (21). However, a substantial proportion of patients (13.5%) were not given any diagnosis. This may be explained by the fact that it is difficult to reach a precise RTI diagnosis, especially in primary care settings where lab tests and sophisticated examinations are generally lacking and that consequently, doctors may be accustomed to providing presumptive treatment in the face of diagnostic uncertainty (23). One of the strengths of this study is the collection of clinical samples. However, bacterial detection was negatively linked only to the diagnostic category of pharyngitis. Another interesting and counterintuitive finding relates to duration of illness. Patients with longer than 3.5 days of illness duration were more likely to provide samples which produced positive bacterial cultures but less likely to be prescribed with antibiotics. This suggests that antibiotics may

TABLE 3 | Multivariable logistic regression statistics between diagnosis and common factors.

	D1		D2		D3		D4		D5		D6		D7	
	OR	**95% C.I.**	**OR**	**95% C.I.**	**OR**	**95% C.I.**	**OR**	**95% C.I.**	**OR**	**95% C.I.**	**OR**	**95% C.I.**	**OR**	**95% C.I.**
Sex (female as ref.)	0.85	(0.60, 1.21)	0.91	(0.67, 1.23)	1.53	(0.96, 2.42)	0.97	(0.57, 1.65)	1.33	(0.65, 2.70)	1.12	(0.56, 2.24)	1.02	(0.69, 1.50)
Age														
≤39	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.							
40–53	1.49	(0.88, 2.52)	1.20	(0.78, 1.84)	0.61	(0.34, 1.10)	1.72	(0.83, 3.60)	1.15	(0.30, 4.41)	0.68	(0.29, 1.63)	0.74	(0.42, 1.30)
54–64	1.49	(0.86, 2.58)	1.53	(0.96, 2.43)	0.34*	(0.17, 0.72)	1.30	(0.57, 2.93)	3.41	(0.96, 12.06)	0.39	(0.11, 1.35)	0.70	(0.38, 1.29)
≥65	1.66	(0.92, 3.00)	0.76	(0.45, 1.30)	0.20*	(0.08, 0.48)	2.31	(0.99, 5.38)	2.85	(0.74, 11.02)	0.59	(0.17, 2.10)	1.28	(0.67, 2.43)
Year (s) of education														
0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.							
1–5	0.72	(0.47, 1.10)	0.97	(0.65, 1.45)	2.20*	(1.10, 4.42)	0.76	(0.38, 1.51)	1.19	(0.56, 2.53)	1.11	(0.29, 4.29)	1.00	(0.62, 1.61)
6–8	0.96	(0.59, 1.57)	0.91	(0.57, 1.45)	1.14	(0.50, 2.60)	1.26	(0.58, 2.73)	0.91	(0.31, 2.65)	2.63	(0.71, 9.77)	0.93	(0.52, 1.65)
≥9	0.84	(0.48, 1.45)	0.94	(0.57, 1.57)	1.69	(0.73, 3.92)	1.16	(0.51, 2.63)	0.63	(0.19, 2.13)	2.79	(0.71, 10.92)	0.70	(0.37, 1.34)
Days since onset														
≤2 days	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.							
2–3.5 days	1.41	(0.91, 2.19)	0.68*	(0.48, 0.96)	1.11	(0.65, 1.89)	0.87	(0.49, 1.55)	1.86	(0.76, 4.58)	1.18	(0.55, 2.53)	1.21	(0.72, 2.04)
3.5–7 days	2.51*	(1.62, 3.89)	0.48*	(0.33, 0.72)	0.61	(0.31, 1.19)	0.70	(0.37, 1.35)	1.10	(0.40, 3.01)	0.26	(0.06, 1.18)	2.09*	(1.25, 3.52)
>7 days	1.56	(0.98, 2.49)	0.27*	(0.17, 0.42)	1.38	(0.75, 2.55)	0.36*	(0.15, 0.86)	1.83	(0.72, 4.61)	1.71	(0.70, 4.19)	3.17*	(1.89, 5.33)
Blocked nose	0.72	(0.48, 1.07)	1.68*	(1.22, 2.32)	0.37*	(0.20, 0.68)	2.29*	(1.37, 3.83)	0.41	(0.16, 1.04)	0.50	(0.21, 1.18)	1.09	(0.72, 1.64)
Runny nose	0.99	(0.70, 1.41)	1.57*	(1.15, 2.15)	0.40*	(0.22, 0.72)	1.90*	(1.17, 3.11)	0.45	(0.20, 1.01)	0.87	(0.39, 1.95)	0.73	(0.48, 1.11)
Snotty nose	0.96	(0.52, 1.77)	1.86*	(1.07, 3.23)	0.31	(0.09, 1.07)	0.24	(0.03, 1.82)	1.24	(0.42, 3.65)	1.41	(0.37, 5.45)	0.98	(0.52, 1.87)
Dry cough	1.02	(0.58, 1.79)	1.46	(0.93, 2.31)	1.00	(0.55, 1.81)	0.52	(0.17, 1.64)	/	/	0.88	(0.40, 1.96)	0.88	(0.44, 1.76)
Cough with green sputum	0.74	(0.48, 1.15)	1.07	(0.74, 1.55)	0.39*	(0.21, 0.73)	1.67	(0.88, 3.18)	1.88	(0.85, 4.15)	0.17*	(0.05, 0.57)	2.49*	(1.61, 3.86)
Cough with white sputum	1.37	(0.92, 2.02)	0.83	(0.59, 1.17)	0.56*	(0.33, 0.95)	2.22*	(1.21, 4.08)	1.55	(0.72, 3.37)	0.21*	(0.08, 0.52)	1.40	(0.91, 2.14)
Dry/burning throat	0.81	(0.56, 1.18)	0.87	(0.63, 1.22)	1.39	(0.87, 2.21)	0.87	(0.49, 1.55)	1.11	(0.55, 2.22)	1.21	(0.59, 2.45)	1.08	(0.72, 1.61)
Itchy throat	0.93	(0.65, 1.34)	0.87	(0.62, 1.23)	0.85	(0.50, 1.44)	1.83*	(1.10, 3.04)	1.27	(0.61, 2.62)	1.71	(0.77, 3.78)	0.92	(0.60, 1.40)
Sore throat	0.53*	(0.38, 0.75)	1.40*	(1.04, 1.88)	1.33	(0.84, 2.12)	0.96	(0.58, 1.59)	0.77	(0.39, 1.50)	2.62*	(1.18, 5.84)	1.00	(0.68, 1.45)
Breathing difficulties	1.94*	(1.40, 2.68)	0.63*	(0.46, 0.87)	0.85	(0.51, 1.42)	0.29*	(0.16, 0.54)	1.65	(0.87, 3.11)	0.74	(0.32, 1.74)	1.24	(0.86, 1.80)
Headache	0.96	(0.62, 1.50)	1.48*	(1.03, 2.12)	0.68	(0.36, 1.27)	1.19	(0.63, 2.25)	0.21*	(0.06, 0.78)	0.69	(0.28, 1.66)	1.01	(0.63, 1.62)
Weakness	0.77	(0.47, 1.27)	1.06	(0.69, 1.60)	0.50	(0.23, 1.08)	1.02	(0.49, 2.14)	1.79	(0.77, 4.20)	1.03	(0.41, 2.62)	1.58	(0.97, 2.56)
Fever	0.93	(0.56, 1.55)	0.92	(0.61, 1.40)	0.71	(0.34, 1.45)	0.63	(0.27, 1.44)	2.59	(1.08, 6.25)	1.28	(0.53, 3.08)	1.42	(0.84, 2.39)
Constant	0.20		0.55		0.28		0.04		0.01		0.04		0.08	

D1, Bronchitis/tracheitis; D2, upper respiratory tract infection; D3, Pharyngitis; D4, Common cold; D5, Pneumonia/bronchopneumonia; D6, Tonsillitis; D7, Others.

sometimes have been used as a "preventive" action rather than to treat existing bacterial infection or even simply to meet perceived demand since symptoms in the earlier the stage of RTI, can be more extensive thus the greater the perceived demand for a "quick cure" (24, 25). In addition, patients aged 65+ were more likely to provide samples from which bacteria could be grown. This may be partly attributable to reduced immunity and more comorbidities in the elderly population who are therefore, more prone to bacterial infection (26, 27). Finally, it is important to note that bacteria isolation was not associated with prescription of antibiotics.

Implications for Research and Practice

Our study not only calls for additional attention to the excessive use of antibiotics in rural China but also sheds new lights on how to better understand and address the problem. In particular, future efforts should include: (a) research into determinants of antibiotics use for specific diagnoses, especially bronchitis/tracheitis, upper respiratory tract infection, pharyngitis and tonsillitis; (b) training of primary care doctors on compliance with management guidelines of commonly diagnosed RTIs, misapprehensions about these infections and the effectiveness of antibiotics in treating these infections, understanding patients' real demand and reassuring patients without antibiotics; (c) introducing microbiological tests into rural primary care in China and leveraging the test results into rational use of antibiotics, for example, using the results of regular microbiological surveillance surveys to inform local selection of narrow spectrum antibiotics or to reassure patients about the safety of not using an antibiotic; (d) educating patients/residents about disbenefits of unnecessary antibiotics and about clearly communicating their expectations of the consultation.

Strengths and Limitations

This study has both strengths and limitations. It is the first study to collect data from healthcare providers and users through direct (non-participative) observation, whilst most existing research on antibiotic use in China relies on data from medical records or reports by health care professionals, who may be inclined to omit recording overuse or misuse of antibiotics so as to meet relevant policy requirements. It is also the first study to perform both microbiological testing and clinical data collection in rural and township care settings, thus enabling cross-linking of data from different sources. However, the study covered only either sites (village clinics or health centers) within a single province, so caution is warranted in generalizing our findings to other parts of China, although the social, cultural and economic background of Anhui is similar to the majority of areas in the nation. The use of observational methods may also have influenced, to some extent, the routine encounters between the patients and doctors and the prescription behaviors being observed, although we instituted a 2-week preparation period for each site clinic before starting data collection to allow the field researchers to build trust with the doctors and the research team is confident that doctors' prescribing practices were not unduly affected by their presence.

Conclusions

Excessive use of antibiotics is still prevalent in rural Anhui, China. Most of the commonly diagnosed RTIs (bronchitis/tracheitis, pneumonia/bronchopneumonia, tonsillitis, pharyngitis and upper respiratory tract infection) were strong predictors of antibiotic prescription but common cold was not. Prescribing behavior was not associated with microbiological detection of bacteria in patient samples. Part of the diagnosis may have been given by the clinician to justify their antibiotics prescription. Therefore, there is clear need to use additional measures (e.g., symptoms) in conjunction with diagnosis to supervise or audit excessive antibiotics use.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Biomedical Ethics Committee of Anhui Medical University (reference number: 20170271). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SX directed study implementation and data collection, conducted data analysis, and drafted the manuscript. DW and HL conceptualized and supervised the study and revised the manuscript together with IO. FR, ChaJ, and CheJ developed data collection materials and collected data together with SX. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Newton Fund [UK Research and Innovation (UKRI)] and the National Natural Science Foundation of China (NSFC, Grant Number 81661138001 and 81861138049) under the UK-China Antimicrobial resistance Partnership Initiative, Grant Number MR/P00756/1.

ACKNOWLEDGMENTS

We would like to thank all the doctors who helped in patient recruitment and specimen collection and all the graduate students who contributed to conducting exit surveys, specimen transportation and data input and cleaning.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.810348/full#supplementary-material

REFERENCES

1. O'Connor R, O'Doherty J, O'Regan A, Dunne C. Antibiotic use for acute respiratory tract infections (ARTI) in primary care; what factors affect prescribing and why is it important? A narrative review. *Ir J Med Sci.* (2018) 187:969–86. doi: 10.1007/s11845-018-1774-5
2. WHO. *Antimicrobial Resistance. Global Report on Surveillance*. Geneva: WHO (2014).
3. O'Neill J. *Review on Antimicrobial Resistance: Tackling Drugresistant Infections Globally: Final Report and Recommendations*. London: Wellcome Trust and UK Government (2016).
4. Otávio BP, Eduardo MK, Eulalia S, Olavo M, José RGT, Fabrizio RR, et al. How to avoid the inappropriate use of antibiotics in upper respiratory tract infections? A position statement from an expert panel. *Braz J Otorhinolaryngol.* (2018) 84:265–79. doi: 10.1016/j.bjorl.2018.02.001
5. António TR, João CFN, Marta E, Adolfo F, Fátima R, Maria TH, et al. comparing hospital and primary care physicians' attitudes and knowledge regarding antibiotic prescribing: a survey within the Centre Region of Portugal. *Antibiotics.* (2021) 10:629. doi: 10.3390/antibiotics10060629
6. Shen X, Lu M, Feng R, Cheng J, Chai J, Xie M, et al. Web-based just-in-time information and feedback on antibiotic use for village doctors in rural Anhui, China: randomized controlled trial. *J Med Internet Res.* (2018) 20:e53. doi: 10.2196/jmir.8922
7. National Bureau of Statistics of China. *National data. National Bureau of Statistics of China.* (2018). Available online at: http://data.stats.gov.cn/ (accessed December 11, 2020).
8. Liu C, Liu C, Wang D, Deng Z, Tang Y, Zhang X. Determinants of antibiotic prescribing behaviors of primary care physicians in Hubei of China: a structural equation model based on the theory of planned behavior. *Antimicrob Resist Infect Control.* (2019) 8:23. doi: 10.1186/s13756-019-0478-6
9. Shaver AL, Jacobs DM, LaMonte MJ, Noyes K. Antibiotic prescribing for acute respiratory tract infections in the United States outpatient setting. *BMC Fam Pract.* (2019) 20:91. doi: 10.1186/s12875-019-0980-1
10. Xue H, Shi Y, Huang L, Yi H, Zhou H, Zhou C, et al. Diagnostic ability and inappropriate antibiotic prescriptions: a quasi-experimental study of primary care providers in rural China. *J Antimicrob Chemother.* (2019) 74:256–63. doi: 10.1093/jac/dky390
11. Wei X, Zhang Z, Walley JD, Hicks JP, Zeng J, Deng S, et al. Effect of a training and educational intervention for physicians and caregivers on antibiotic prescribing for upper respiratory tract infections in children at primary care facilities in rural China: a cluster-randomised controlled trial. *Lancet Glob Health.* (2017) 5:e1258–67. doi: 10.1016/S2214-109X(17)30383-2
12. Diao M, Shen X, Cheng J, Chai J, Feng R, Zhang P, et al. How patients' experiences of respiratory tract infections affect healthcare-seeking and antibiotic use: insights from a cross-sectional survey in rural Anhui, China. *BMJ Open.* (2018) 8:e019492. doi: 10.1136/bmjopen-2017-019492
13. Wu Y, Xu S, Shen X, Cheng J, Chai J, Feng R, et al. Trajectories of symptoms and healthcare use following respiratory tract infections in rural Anhui, China: a cross-sectional study. *J Infect Public Health.* (2020) 13:1939–45. doi: 10.1016/j.jiph.2020.09.022
14. Morley VJ, Firgens EP, Vanderbilt RR, Zhou Y, Zook M, Read AF, et al. Factors associated with antibiotic prescribing for acute bronchitis at a university health center. *BMC Infect Dis.* (2020) 20:177. doi: 10.1186/s12879-020-4825-2
15. Chem ED, Anong DN, Akoachere JKT. Prescribing patterns and associated factors of antibiotic prescription in primary health care facilities of Kumbo East and Kumbo West Health Districts, North West Cameroon. *PLoS ONE.* (2018) 13:e0193353. doi: 10.1371/journal.pone.0193353
16. McKay R, Mah A, Law MR, McGrail K, Patrick DM. Systematic review of factors associated with antibiotic prescribing for respiratory tract infections. *Antimicrob Agents Chemother.* (2016) 60:4106–18. doi: 10.1128/AAC.00209-16
17. Palin V, Mölter A, Belmonte M, Ashcroft DM, White A, Welfare W, et al. Antibiotic prescribing for common infections in UK general practice: variability and drivers. *J Antimicrob Chemother.* (2019) 74:2440–50. doi: 10.1093/jac/dkz163
18. Kwiatkowska R, Shen X, Lu M, Cheng J, Hickman M, Lambert H, et al. Patients without records and records without patients: review of patient records in primary care and implications for surveillance of antibiotic prescribing in rural China. *BMC Health Serv Res.* (2020) 20:564. doi: 10.1186/s12913-020-05308-0
19. Zhao L, Kwiatkowska RM, Chai J, Cabral C, Chen M, Bowker K, et al. Pathways to optimising antibiotic use in rural China: identifying key determinants in community and clinical settings, a mixed methods study protocol. *BMJ Open.* (2019) 9:e027819. doi: 10.1136/bmjopen-2018-027819
20. Shen X, Shen J, Pan Y, Cheng J, Chai J, Bowker K, et al. Clinical diagnosis and treatment of common respiratory tract infections in relation to microbiological profiles in rural health facilities in China: implications for antibiotic stewardship. *BMC Fam Pract.* (2021) 22:87. doi: 10.1186/s12875-021-01448-2
21. Chinese Medical Association, Journal of Chinese Medical Association, general practice branch of Chinese Medical Association, et al. Guidelines for primary diagnosis and treatment of acute upper respiratory tract infection. *Chin J Gen Pract.* (2020) 19:689–97. doi: 10.3760/cma.j.cn114798-20200520-00603
22. Spurling GK, Mar C, Dooley L, Foxlee R, Farley R. Delayed antibiotic prescriptions for respiratory infections. *Cochrane Database Syst Rev.* (2017) 9:CD004417. doi: 10.1002/14651858.CD004417.pub5
23. Harris AM, Hicks LA, Qaseem A, High Value Care Task Force of the American College of Physicians and for the Centers for Disease Control and Prevention. Appropriate antibiotic use for acute respiratory tract infection in adults: advice for high-value care from the American College of Physicians and the Centers for Disease Control and Prevention. *Ann Intern Med.* (2016) 164:425–34. doi: 10.7326/M15-1840
24. Fletcher-Lartey S, Yee M, Gaarslev C, Khan R. Why do general practitioners prescribe antibiotics for upper respiratory tract infections to meet patient expectations: a mixed methods study. *BMJ Open.* (2016) 6:e012244. doi: 10.1136/bmjopen-2016-012244
25. Claus M, Christian JL, Kim T, Tom H, Jens S, Peter J, et al. Antibiotic therapy as personalized medicine - general considerations and complicating factors. *APMIS.* (2019) 127:361–71. doi: 10.1111/apm.12951
26. Rachel MZ, Andrea S, Brian AS, David YH. Outpatient antibiotic use and the need for increased antibiotic stewardship efforts. *Pediatrics.* (2018) 141:e20174124. doi: 10.1542/peds.2017-4124
27. Steeper M, Plebanski M, Flanagan KL. The global challenge and future strategies for keeping the world's aging population healthy by vaccination. *Trans R Soc Trop Med Hyg.* (2016) 110:427–31. doi: 10.1093/trstmh/trw054

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

ORIGINAL RESEARCH
published: 10 February 2022
doi: 10.3389/fpubh.2022.800042

Do Residents and Healthcare Providers Differ in Preference for Family Doctor Contract Service? Evidence From a Discrete Choice Experiment

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Edited by:
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University of Florida, United States

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University of Sassari, Italy

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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Public Health

Received: *22 October 2021*
Accepted: *10 January 2022*
Published: *10 February 2022*

Citation:
Zhang J, Xu L, Qin W and Xu A (2022) Do Residents and Healthcare Providers Differ in Preference for Family Doctor Contract Service? Evidence From a Discrete Choice Experiment. Front. Public Health 10:800042. doi: 10.3389/fpubh.2022.800042

Objective: Few are known on how and to what extent residents and healthcare providers have different preferences for family doctor contract service (FDCS). This study aimed to elicit and compare the residents' and healthcare providers' preferences for FDCS through a discrete choice experiment (DCE).

Methods: Residents and healthcare providers recruited for the DCE were asked to choose repeatedly between two hypothetical service plans, which differed in six attributes: cost, service package, service delivery, type of service, accessibility of medicine, and level of healthcare team. We use mixed logit regression models to determine preferences for potential attributes.

Results: A total of 2,159 residents and 729 healthcare providers completed valid DCE questionnaires. The mixed logit model results suggested that cost, service package, service delivery, type of service, accessibility of medicine, and level of healthcare team all had a significant impact on residents' and healthcare providers' preference. The level of healthcare team was the most important characteristic of FDCS to both residents and healthcare providers, followed by types of service. They have different preferences on the cost and way of service delivery.

Conclusions: This study provides new evidence on how and to what extent residents and healthcare providers have different preferences for FDCS by determining their perception of various service attributes. These findings suggested that the optimal design and improvement of FDCS plans should consider not only residents but also healthcare providers' preferences to maximize contract service uptake.

Keywords: family doctor contract service, discrete choice experiment, preference, resident, healthcare provider

INTRODUCTION

General practice is regarded by the World Health Organization as the most economical and appropriate healthcare service model. International experience has proved that the promotion of family doctors contract service (FDCS) is an important way to strengthen the primary healthcare system and protect and maintain people health. The Chinese government has piloted the FDCS project since 2016 (1) and proposed that FDCS is healthcare services provided by signing service contract with family doctors (FDs) in the community healthcare centers, and signing service contract with FDs to use FDCS is voluntary. After years of practice, China has initially established a FDCS system and formed some service models with local characteristics; for example, Shanghai "1 + 1 + 1" contract service model (2), Hangzhou "integrated medical treatment and nursing care system" contracted service model (3). Previous studies have shown that the implementation of FDCS has generally improved the effectiveness of self-management in health (4) and primary care quality (5). But at the same time, there are some problems that restrict the progress of FDCSs in China. More recently, some researchers have noted that both the actual signing rate and utilization rate of FDCS are far from the national target in China and need to be improved. A meta-analysis study from Li et al. (6), for example, showed that the signing rate of FDCS for Chinese residents was 46.2% (95%CI: 35.5–56.9%). Further, Deng et al. (7) found that the overall utilization rate of FDCS was 6.9%. In addition to improve the supporting measures and guarantee mechanism at national level, optimizing the design of FDCS plans is also considered as a key determinant to comprehensively promote the quality and efficiency of FDCSs (8). The important prerequisite for this is to clarify the preferences for FDCS from the perspective of residents (demander) and healthcare providers (supplier) (9). However, evidence is unclear cut on how and to what extent residents and healthcare providers have different preferences.

Discrete choice experiments (DCEs) have been used to measure patient and healthcare providers preferences in a range of settings internationally (10). A DCE can be conducted to measure preferences for attributes of treatment by eliciting choices between hypothetical treatment profiles with systematic differences in their attributes (11). Using DCEs in primary care is valuable for determining how to improve rational shared decision-making. Including patient preferences when designing and evaluating healthcare programs can prove beneficial and help broaden the perspective on new or existing technologies. Therefore, this approach has been widely used in healthcare and health economic studies to quantify preferences for treatment attributes (12).

Prior researches have already estimated preferences using DCEs since the implement of FDCS in China. However, most of these studies focused on the view of the demander (residents/patients). For instance, Fu et al. (13) conducted a DCE in Chinese rural population and suggested residents valued the FDs' competence most. Zhu et al. (14) found that the most valued attribute in general practitioner (GP) care for patients was the organizational factors related to whether the provider had sufficient medicine and equipment to provide capable primary care service. Only one study to data measured the supply preferences from the perspective of healthcare providers (15). Meanwhile, similar studies have been conducted in other countries (16–20); nevertheless, considering that patients and healthcare providers references may be subjected to cultural and policy differences, the applicability of research from overseas to China mainland may be limited. More importantly, given the asymmetry of information between consumer and provider, it is not always clear that observed healthcare consumption is based on consumers' preferences and choice alone (21). It is important to understand that the value residents and healthcare providers place on different attributes of FDCS and how these preferences differ. To date, however, no study has been conducted to compare the demand and supply preferences of residents and healthcare providers for FDCS.

To make up for the research gap, the aim of this study is, therefore, to elicit and quantify residents and healthcare providers preferences for various attributes of FDCS by conducting DCEs and to explore the commonalities and differences between the demander and the supplier. We also examine the relative importance (RI) that patients and healthcare providers place on different treatment attributes. Results of this study could provide scientific evidences for the optimal design and strategic improvement in FDCS plans.

MATERIALS AND METHODS

According to the clear guidance on how to conduct DCEs proposed in previous literature (11, 22, 23), we developed and conducted the DCE in 4 main steps: (1) establishing attributes and levels for the experiment, (2) generating the experimental design and questionnaire, (3) collecting data, and (4) analyzing data.

Establishing Attributes and Levels for the DCE

Identifying the attributes and levels that adequately describe the good or service of interest is the key step in DCE study. In our study, the service of interest was FDCS. The selected attributes and levels should be realistic and credible to residents and healthcare providers. We used a stepwise qualitative approach to establish attributes and levels for the DCE. First, we conducted a rapid literature review of existing DCE studies in primary healthcare and FDCS to select a preliminary list of attributes and levels. Combined with requirements of relevant policy documents of the FDCS in China, 10 important attributes were considered: content of service, the level of medical team, types of service, cost of contract, distance to practice, shared-decision making, insurance reimbursement rate, accessibility of medicine, ways of service, and attitude of service. Subsequently, we conducted semistructured interviews with five experts from research and practice (two researchers on FDCS, two GPs in primary healthcare institutions, and one DCE experts) and used the insights gained from these to validate and refine our selection of attributes and levels. Finally, six attributes that impact

TABLE 1 | Attributes and levels used in the DCE.

Attributes	Levels	Description
1. Cost	CNY10 ($65); CNY50 ($325); CNY100 ($650)	Annual out-of-pocket expenses for contracted services incurred by an individual resident
2. Service package	Basic package; Individualized package	The basic package includes national basic public health services and health management services; The individualized package includes basic package and personalized paid services for different groups of people
3. Service delivery	Outpatient visit; Telephone follow-up; Home visit	The ways of service provided by the contract medical team
4. Type of service	Chinese Medicine (CM); Western Medicine (WM); Integrated Chinese and Western Medicine (ICWM)	The types of service provided by the contract medical team
5. Accessibility of medicine	Low; Medium; High	The accessibility of medicine provided by the contract medical team.
6. Level of healthcare team	Level-I; Level-II; Level-III	Level-I refers to a core team composed of general practitioners or village doctors, community nurses, and public health personnel; Level-II is a horizontal combined team composed of the level-I team and specialists (assistants) in primary health institutions; Level-III is a vertical combined team composed of level-II team and experts from secondary and above medical institutions.

residents' and healthcare providers' decision-making the most were selected: cost of contract, content of service, types of service, ways of service, accessibility of medicine, and the level of medical team. The next step was to refine the terminology that described the attributes and levels. We chose levels for the cost attribute based on the spread of current prices for FDCS in China. The attributes 2, 3, 4, 5, and 6 were designed at 2 or 3 levels each to include the most common specifications of FDCS and capturing a realistic range within China's primary healthcare system. The final experimental design included six attributes with 2 or 3 levels each (see **Table 1**).

Generating the Experimental Design and Questionnaire

Based on the attributes and levels we set, a large number of choice tasks will be generated (five attributes at three levels and one attributes at two levels = $3^5{*}2^1$). To reduce the choice tasks to a manageable number, we used a fractional factorial design with 16 choice sets with two alternatives. We generated the experimental design using Stata 14.0 software, which chose a design based on optimal D-efficiency that allowed for the optimization of design efficiency, level balance, and the number of choice tasks. The DCE tasks were then divided into two blocks of eight choice sets each. Additionally, we included one repeated choice task as consistency test to ensure that each respondent made realistic trade-offs and to check internal validity. To reduce cognitive burden, respondents were randomly assigned to one of the blocks. To avoid larger numbers of respondents who choose the opt-out option to prevent making challenging choices, we did not leave respondents an opt-out option. This is also consistent with the policy background of our study: with the implementation of the policy of full coverage of FDCS, residents and healthcare providers must make their choice when they are assumed to participate in the FDCS. Previous study suggested that pictures were useful to explain attributes in a low-or middle-income country context where literacy cannot be assumed (24). Thus, we added visual elements into the questionnaire to reduce potential boredom and help respondents engage. To check the respondents' understanding of the questionnaire, a pilot survey was undertaken among 30 voluntary community residents and 10 healthcare providers in Tai'an city. We made minor changes to the format and layout, and our questionnaire was thought to be appropriated in length and understood easily by respondents through the pilot study. **Table 2** shows an example choice task for residents and healthcare providers. The DCE choice tasks faced by residents and healthcare providers were exactly the same, whereas they had to choose between two services 1 and 2 from their different perspectives (demander and supplier).

TABLE 2 | Example of a DCE choice task.

	Service 1	Service 2
Cost	50 CNY	10 CNY
Service package	Basic	Individualized
Service delivery	Outpatient visit	Home visit
Type of service	CM	WM
Accessibility of medicine	Low	High
Level of healthcare team	Level-III	Level-I
Which one would you prefer?	☐	☐

In addition to the DCE part, the questionnaire for residents also included a series of questions concerning respondents' sociodemographic characteristics and current health situation, and the questionnaire for healthcare providers consisted of questions regarding sociodemographic characteristics, present work situation, and current health situation. All questionnaires included an explanation of the attributes and levels.

Sampling and Data Collection

The survey was conducted in Tai'an city, Shandong Province, China. Multistage random sampling was used to choose the

TABLE 3 | Characteristics of participants.

Residents ($n = 2,159$)		**Healthcare providers ($n = 729$)**	
Variables	***n* (%)**	**Variables**	***n* (%)**
Female	1,253 (58.04)	Female	345 (47.33)
Age, Mean±SD	63.06 ± 10.76	Age, Mean±SD	42.78 ± 8.55
Residence		Residence	
Rural	1,432 (66.33)	Rural	419 (57.48)
Urban	727 (33.67)	Urban	310 (42.52)
Marital status		Marital status	
Couple	1,800 (83.37)	Couple	670 (91.91)
Single	359 (16.63)	Single	59 (8.09)
Education		Education (year)	
Primary school and below	1,138 (52.71)	≤12	256 (35.12)
Junior school	666 (30.85)	13∼15	310 (42.52)
Senior school and above	355 (16.44)	≥16	163 (22.36)
Annual household income (yuan)		Annual personal income (yuan)	
≤10,000	572 (26.49)	≤15,000	160 (21.95)
10,001∼25,000	491 (22.74)	15,001∼20,000	131 (17.97)
25,001∼45,000	390 (18.06)	20,001∼30,000	151 (20.71)
45,001∼70,000	337 (15.61)	30,001∼40,000	125 (17.15)
>70,000	369 (17.09)	>40,000	162 (22.22)
Chronic conditions		Workplace	
Yes	1,727 (79.99)	Community health center	127 (17.42)
No	432 (20.01)	Community health station	68 (9.33)
Self-rated health		Township health center	95 (13.03)
Good	1,230 (56.97)	Village clinic	439 (60.22)
Medium	31.08 (31.08)	Professional title	
Poor	11.95 (11.95)	None	283 (38.82)
		Junior	309 (42.39)
		Intermediate and above	137 (18.79)
		Chronic conditions	
		Yes	144 (19.75)
		No	585 (80.25)

TABLE 4 | Results of mixed logit model of residents and healthcare providers.

Attribute levels	**Residents**		**Healthcare providers**	
	OR	**95%CI**	**OR**	**95%CI**
Cost (per yuan ¥)	0.997***	(0.996, 0.998)	1.003***	(1.001, 1.004)
Service package (basic package ^{a})				
Individualized package	0.927**	(0.884, 0.972)	0.887***	(0.832, 0.946)
Service delivery (home visit ^{a})				
Outpatient visit	0.522***	(0.488, 0.559)	1.129**	(1.035, 1.231)
Telephone follow-up	0.540***	(0.511, 0.571)	1.019	(0.935, 1.111)
Type of service (CM ^{a})				
WM	1.067	(1.000, 1.138)	1.159**	(1.054, 1.275)
ICWM	1.711***	(1.621, 1.806)	1.386***	(1.275, 1.508)
Accessibility of medicine (low ^{a})				
High	1.465***	(1.383, 1.552)	1.135**	(1.043, 1.235)
Medium	1.577***	(1.477, 1.684)	1.073	(0.981, 1.173)
Level of healthcare team (level-I ^{a})				
Level-III	4.188***	(3.863, 4.540)	1.350***	(1.216, 1.499)
Level-II	2.522***	(2.374, 2.680)	1.408***	(1.285, 1.542)
ASC	1.039	(0.981, 1.101)	0.986	(0.909, 1.070)
No. of observations	34,544		11,664	
No. of respondents	2159		729	
Log likelihood	−9,764.399		−3,913.567	

*a, reference level; OR, odds ratio; CI, confidence interval; ASC, alternative special constant; CM, Chinese Medicine; WM, Western Medicine, ICWM, Integrated Chinese and Western Medicine; ***$p < 0.001$; **$p < 0.01$.*

representative sample of residents and healthcare providers. First, three or four townships were randomly selected from each district (county) in Tai'an city; second, eight villages (communities) were randomly selected from each township, with a total of 160 villages (communities); third, residents were randomly selected from each village (community), and healthcare providers were enrolled from the selected primary health institutions. The inclusion criteria of residents were the key populations covered by FDCS: pregnant women, patients with chronic diseases, and the elderly aged 60 years and above. The inclusion criteria of healthcare providers were as follows: GPs, village doctors, nurses, public health workers, and other members of FDs team. We collected explicit and written consent from respondents after providing them with a detailed explanation of how their personal data would be used. To ensure the quality of the residents' responses, about 40 min of one-to-one, face-to-face interview for every participant was conducted using the questionnaire by the trained enumerator. Since most healthcare providers had high levels of educational attainment, a centralized self-filling questionnaire method was adopted, but two research assistants accompanied participants from commencement to the completion of the survey with assistance on any queries they may have.

The minimum required sample size for DCE, based on the method suggested by Orme (25), was 84 ($500 \times 3 \div 9 \div 2$) respondents in this study. To increase precision of estimates, 2,226 residents and 816 healthcare providers were enrolled in DCE study, of which 67 residents and 87 healthcare providers were eliminated for failing consistency test, respectively. Finally, a total sample of 2,159 residents and 729 healthcare providers were included the statistical analysis.

Data Analysis

We analyzed the choice observations from residents and healthcare providers separately using mixed logit model, which is a commonly used method for examining DCEs (26). In our model, expected overall utility U of respondent i from service plan *j* in the choice set *t* was given by:

$$\begin{aligned} U_{ijt} \ = \ & \beta_{1i}Cost_{itj} + \beta_{2i}Package_{itj} + \beta_{3i}ServiceDelivery_{itj} \\ & + \beta_{4i}Type_{itj} + \beta_{5i}Medicine_{itj} \\ & + \beta_{6i}HealthcareTeam_{itj} + \varepsilon_{ijt} \end{aligned}$$

A significant coefficient (β) indicates that the attribute (level) is important for the participants' decision for FDCS. The utilities were converted into odds ratios (ORs) and a statistically significant OR ($p < 0.05$) indicated that the attribute level had an impact on the choice process of the participants. We calculated the RI of each attribute by computing the difference in the utility of the highest and lowest level of that attribute, divided by the sum of differences of all attributes. We additionally calculated the willingness to pay (WTP) of residents and willingness to supply (WTS) of healthcare providers by taking the ratio of the preference weight of the attribute to the preference weight of the cost of service. We carried out the entire data analysis using Stata 14.0 software.

RESULTS

Characteristics of Participants

Characteristics of residents ($n = 2{,}159$) are reported in **Table 3**. The residents had a mean age of 63.06 years (SD = 10.76), the majority of them were women (58.04%), and 66.33% lived in rural area. A total of 79.99% have been diagnosed with one or more chronic diseases, and more than half of residents (56.97%) reported good health. **Table 3** also shows the profile of healthcare providers ($n = 729$). The mean age of healthcare providers was 42.78 years, 47.33% of them were women, and 57.48% lived in rural area. More than half of them were worked in the village clinic (60.22%), <20% had the intermediate title or above, and 144 (19.75%) reported having chronic conditions.

Discrete Choice Experiment Results

Table 4 presents the preferences of residents and healthcare providers. In general, all ORs were statistically significant, which suggests that all attributes played a role in their decision for demand and supply of FDCS. As expected, residents preferred to choose service with lower costs, and healthcare provider preferred to supply service with higher costs. Regarding the way of service delivery, healthcare providers preferred outpatient service instead of home visit, whereas residents were more likely to select home visit service. In addition, Integrated Chinese and Western Medicine (ICWM), a higher accessibility of medicine and higher level of healthcare team were preferred by residents and healthcare providers compared with the respective reference categories. However, neither residents nor healthcare providers preferred to pick individualized package. An analysis that includes participants who failed the consistency test provided highly similar results, which indicated that the preferences of residents and healthcare providers for FDCS was robust (see **Supplementary File**).

Figure 1 shows the RI of the attributes. Level of healthcare team was most important for both residents (37.2%) and healthcare providers (29.6%), followed by type of service. Moreover, healthcare providers placed more importance on cost (20.6%) and way of service delivery (11.5%). In contrast, residents valued way of service delivery (20.5%) and accessibility of medicine (14.5%). It was also noted that the service package was least important for both residents and healthcare providers, relative to all other attributes.

Willingness to Pay and Willingness to Supply

Table 5 reports the WTP and WTS estimates based on the mixed logit model results. Residents were willing to pay CNY 490.44 (95%CI, 374.56–606.32) for their preferred highest level of healthcare team (yuan). This is higher than what they were willing to pay for the other attributes: Residents were willing to pay CNY 130.94 for high accessibility of medicine and CNY 183.95 to get ICWM service. The negative (–) results indicate theoretically to what extent the residents would be willing to be compensated for an attribute level. A subsidy of CNY 25.71 was required for residents to accept individualized package services. Meanwhile, the results showed that healthcare providers were willing to sacrifice certain service costs for the preferred attributes and levels: healthcare providers were willingness to sacrifice CNY 112.97 to supply the service by higher level of healthcare team, CNY 123.93 to provide ICWM service, and CNY 45.82 for outpatient service delivery. On the contrary, they would charge CNY 45.53 to provide individualized package service for contracted residents, instead of basic package service.

DISCUSSION

To the best of our knowledge, this is the first study using a DCE to reveal the residents' and healthcare providers' preferences for FDCS and compare the difference in preferences between the demander and the supplier in China. Our study showed that cost of service, service package, way of service delivery, type of service, accessibility of medicine, and level of healthcare team all influenced residents' and healthcare providers' preferences for FDCS, which provides new insights on how residents and healthcare providers value attributes associated with FDCS from their different perspective.

Understanding the residents' preferences for FDCS could contribute to better service communication and quality to enhance uptake and adherence of FDCS. We found that residents were mostly driven by high level of healthcare team, and they had the highest WTP for the level-III healthcare team when choosing to sign up for the FDCS. This is not surprising, and the level of healthcare team is generally considered as representing appropriateness and quality of primary care, which could be linked with desired effect of care for patients. In line with this research, previous studies conducted in China revealed that respondents had a strong preference for the healthcare providers with high competence (13, 27, 28). However, recent evidence showed that the low competency of FDs was still one of the notable barriers to implement FDCS in China (8). FDs and team members are the flagbearers of FDCS, and their service capabilities, willingness, and attitudes all influence the quality of primary care. At the same time, the DCE results showed that healthcare providers also valued the higher level of healthcare

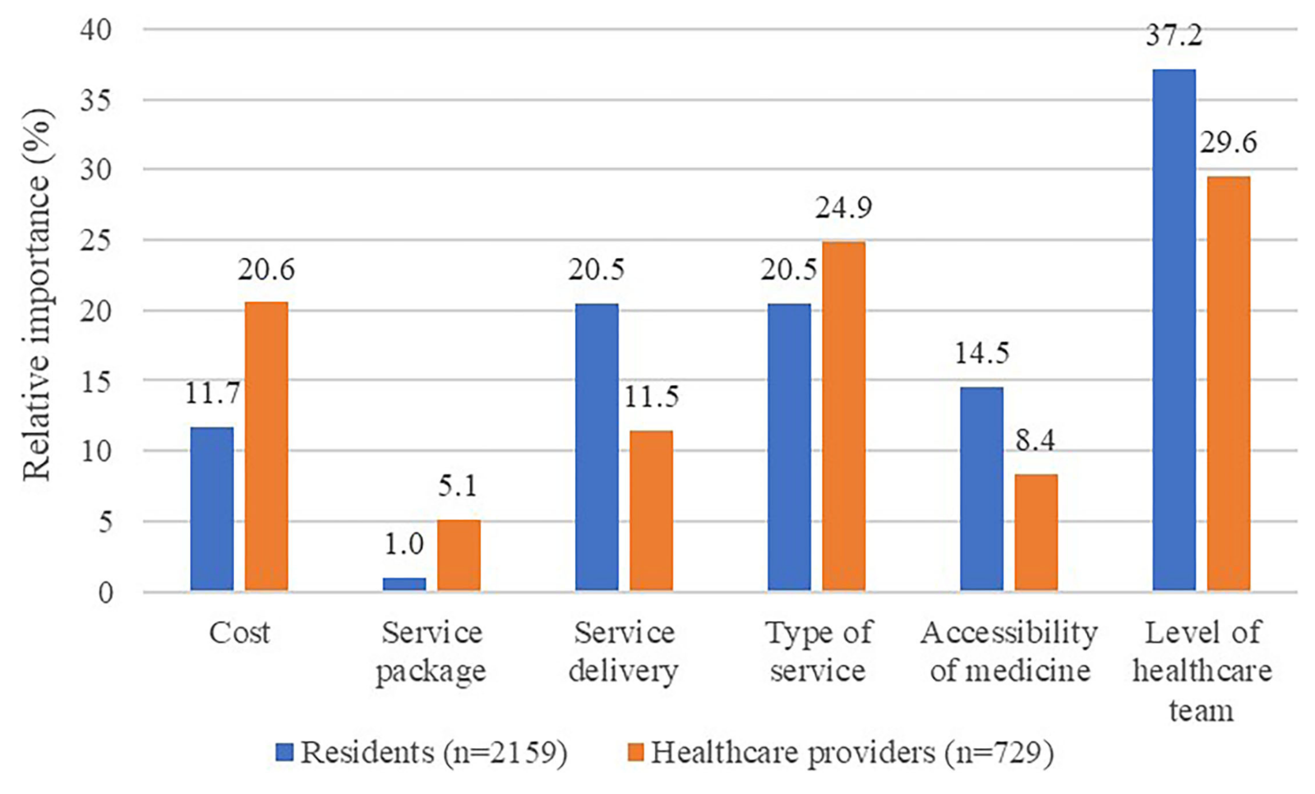

FIGURE 1 | RI of the FDCS attributes for residents and healthcare providers. RI, relative importance; FDCS, family doctor contract service.

team. Except the professional nature, which determines their instinct to provide better services to residents, altruistic behavior that has been proven in the previous studies may also explain these preference choices (29, 30). Moreover, results from previous studies have suggested FDs' role as perfect agent for their patients can be strengthened in the presence of an effective governance and operating environment (20, 31). Our results may contribute to the development of future policies taking into account the common preferences of residents and healthcare providers. Therefore, we recommend that more attention should be paid to not only the talent team construction of FDs and regular training, but also the general governance structure and regulation environment.

The type of ICWM service was another important driver of both residents' and healthcare providers' positive decision on FDCS plans. It has been proved that traditional Chinese medicine (TCM) can meet the needs for public health and primary medical care, improve health equity, and realize the great goal that everyone will get access to the basic medical and health services (32). Meanwhile, the ICWM theory for the prevention and treatment of chronic and infectious diseases is more widely accepted in China (33, 34). These highlight the need to promote ICWM services in the implementation and improvement of the FDCS.

Further, we also found different preferences in the way of service delivery between residents and healthcare providers. Similar to results from previous studies (16), our findings revealed that home visits significantly influenced the residents' preference for FDCS. The residents included in our study were key population, such as the elderly people, who generally have high healthcare needs and desire more home visit service. However, the characteristic of FDCS in China is that home visit services are provided by FDs only for those vulnerable group of old, multimorbid, and immobile persons who have specific needs

TABLE 5 | WTP of residents and WTS of healthcare providers (yuan ¥).

	WTP	(95%CI)	WTS	(95%CI)
Service package				
Individualized package	-25.71^{**}	(−42.68, −8.74)	45.53^{**}	(73.62, 17.44)
Service delivery				
Outpatient visit	-222.26^{***}	(−278.93, −165.59)	-45.82^{*}	(−8.99, −82.64)
Telephone follow-up	-210.66^{***}	(−262.98, −158.34)	−7.25	(−39.22, 24.72)
Type of service				
WM	22.12	(−0.22, 44.46)	-55.82^{**}	(−90.11, −21.53)
ICWM	183.95^{***}	(134.48, 233.41)	-123.93^{***}	(−177.78, −70.08)
Accessibility of medicine				
High	130.94^{***}	(93.67, 168.01)	-48.27^{*}	(−87.49, −69.04)
Medium	156.16^{***}	(115.81, 196.51)	−26.72	(−64.57, 11.14)
Level of healthcare team				
Level-III	490.44^{***}	(374.56, 606.32)	-112.97^{**}	(−180.76, −45.18)
Level-II	316.66^{***}	(240.92, 392.41)	-130.02^{***}	(−190.17, −69.86)

WTP, willingness to pay; WTS, willingness to supply; $^{***}p < 0.001$; $^{**}p < 0.01$; $^{*}p < 0.05$.

(35). On the other hand, the reality is that the current number of primary healthcare providers is not inadequate (36), and the related laws and operating specifications for home visit services are not insufficient in China, which may explain why healthcare providers preferred the outpatient visit service generally. Policy interventions are needed to address these serious problems in the primary care system (e.g., shortage of FDs).

In general, choosing a service package that suits an individual's needs should be an important factor for signing up the FDCS program. However, our results showed that the service package, while relevant, was of the least importance to the residents and healthcare providers. These can partly be explained by the setting of attribute level in the DCE task. The way of the service package attribute was presented by only two levels, which may not have been as tangible as the difference between other attributes. This may have resulted in the small preference estimates we observed for the service package levels. In spite of this, we found both residents and healthcare providers preferred the basic package service instead of individualized package. This is probably owing to the current characteristics and status quo of Chinese FDCS implementation. The Chinese government has basically achieved full coverage of FDCS for key population; nevertheless, most residents instinctively and voluntarily signed up free basic package service, and the acceptance and uptake of paid individualized packages service among residents was still not high. This gives insight into the importance of improving the service package programs and strengthening the policy publicity to further promote the FDCS in China.

Our study findings and interpretations are subjected to certain limitations. As with other DCE studies, this study is subject to hypothetical bias, as respondents had to make choices between hypothetical service options. Second, only a limited number of attributes can be included in the DCEs. Nevertheless, we have attempted to present real-world decision-making environments by extensive literature review and qualitative interviews to ensure the relevance on FDCS. A third limitation of this study is that we did not provide respondents with an opt-out option, which may lead to parameter estimation bias, but this also requires more research to test. Finally, this DCE study was conducted in one city, which may limit the generalization of the findings to the whole country, and the follow-up study could expand the scope of sampling to verified the findings of this study.

CONCLUSIONS

In this study, we identified residents' preferences for choosing FDCS plans, but also those of healthcare providers' preferences for supplying services. The high level of healthcare team, ICWM service, high accessibility of medicine, and basic package services were common preferences of residents and healthcare providers. Meanwhile, they have different preferences in the cost and way of service delivery. This information could help decision makers to set up appropriate FDCS programs to fit with residents' and healthcare providers' preferences. With the further advancement of China's FDCS programs, it is more important to consider the benefit-risk preferences that residents and healthcare providers have for different service attributes to optimize FDCS programs that can ultimately improve residents' health outcomes and healthcare providers' job satisfaction.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

LX, JZ, and WQ: concept and design and acquisition of data. JZ and WQ: analysis and interpretation of data. JZ: drafting of the manuscript and statistical analysis. LX and AX: critical revision of the paper for important intellectual content, obtaining funding, and supervision. LX and JZ: provision of study materials or patients. LX and WQ: administrative, technical, or logistic support. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported by the grants of National Natural Science Foundation of China (71974118) and National Social Science Foundation of China (No. 2018VJX065).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.800042/full#supplementary-material

REFERENCES

1. National Health Commission of the People's Republic of China. Guidance on promoting general practitioners' contract service. Available online at: http://www.gov.cn/xinwen/2016-06/06/content_5079984.htm. (accessed July 2, 2021).
2. Liu S, Wang L, Zhang T et al. Factors affecting the work competency and stability of family doctors in Shanghai: a tracking study. *Bmc Fam Pract.* (2019) 20:95. doi: 10.1186/s12875-019-0988-6
3. Shao L, Ning XU. Analysis of problems in the process of contracting services with community doctors team under integrated medical treatment and nursing care system and corresponding countermeasures. *Chinese General Practice.* (2017) 20:4096–9.
4. Jiaoling, Huang, Tao et al. The effect of family doctor–contracted services on noncommunicable disease self-management in Shanghai, China. *The International Journal of Health Planning and Management*. (2019). 34:935–46 doi: 10.1002/hpm.2865

5. Feng S, Cheng A, Luo Z, Xiao Y, Zhang L. Effect of family doctor contract services on patient perceived quality of primary care in southern China. *Bmc Fam Pract.* (2020) 21:218. doi: 10.1186/s12875-020-01287-7
6. Li X, Zhang R, Dan H et al. Research on the current situation of family doctor contract service in China:Based on field re-search in 4 provinces. *Chinese Journal of Health Policy.* (2020) 13:39–44. doi: 10.3969/.issn.1674-2982.2020.05.006
7. Deng Y, Wang C, Gan Y, Lu Z. The current status of family doctors' contracting service utilization and its influencing factors:Based on a survey of 31 provinces and cities in China. *Chinese Journal of Health Policy.* (2020) 13:47–54. doi: 10.3969/j.issn.1674-2982.2020.09.008
8. Yuan S, Wang F, Li X, Jia M, Tian M. Facilitators and barriers to implement the family doctor contracting services in China: findings from a qualitative study. *BMJ Open.* (2019) 9:e032444. doi: 10.1136/bmjopen-2019-032444
9. Wang H, Shi L, Han X et al. Factors associated with contracted services of Chinese family doctors from the perspective of medical staff and consumers: a cross-sectional study. *Bmc Health Serv Res.* (2019) 19:986. doi: 10.1186/s12913-019-4801-y
10. Clark MD, Determann D, Petrou S, Moro D, de Bekker-Grob EW. Discrete choice experiments in health economics: a review of the literature. *Pharmacoeconomics.* (2014) 32:883–902. doi: 10.1007/s40273-014-0170-x
11. Reed Johnson F, Lancsar E, Marshall D et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR conjoint analysis experimental design good research practices task force. *Value Health.* (2013) 16:3–13. doi: 10.1016/j.jval.2012.08.2223
12. Bekker-Grob EWD, Ryan M, Gerard K. Discrete choice experiments in health economics: a review of the literature. *Health Econ.* (2012) 21:145–72. doi: 10.1002/hec.1697
13. Fu P, Wang Y, Liu S, Li J, Gao Q, Zhou C et al. Analysing the preferences for family doctor contract services in rural China: a study using a discrete choice experiment. *Bmc Fam Pract*. (2020). 21. doi: 10.1186/s12875-020-01223-9
14. Zhu J, Li J, Zhang Z, Li H. Patients' choice and preference for common disease diagnosis and diabetes care: A discrete choice experiment. *The International Journal of Health Planning and Management*. (2019) 34. doi: 10.1002/hpm.2841
15. Zhang H. Analysis general practitioners' provide preferences and influencing factors. [master's thesis]. [Wuhan (CHN)]: Huazhong University of Science and Technology (2019).
16. Krinke KS, Tangermann U, Amelung VE, Krauth C. Public preferences for primary care provision in Germany – a discrete choice experiment. *Bmc Fam Pract.* (2019) 20:80. doi: 10.1186/s12875-019-0967-y
17. Hjelmgren J, Anell A. Population preferences and choice of primary care models: A discrete choice experiment in Sweden. *Health Policy.* (2007) 83:314–22. doi: 10.1016/j.healthpol.2007.02.006
18. Seghieri C, Mengoni A. Applying discrete choice modelling in a priority setting: an investigation of public preferences for primary care models. *Eur J Health Econ.* (2014) 15:773–85. doi: 10.1007/s10198-013-0542-8
19. Ezatabadi MR, Rashidian A, Shariati M, Foroushani AR, Sari AA. Using Conjoint Analysis to Elicit GPs' Preferences for Family Physician Contracts: A Case Study in Iran. *Iran Red Crescent Me.* (2016) 18:e29194. doi: 10.5812/ircmj.29194
20. Riise J, Hole AR, Gyrd-Hansen D, Skatun D. GPs' implicit prioritization through clinical choices – evidence from three national health services. *J Health Econ.* (2016) 49:169–83. doi: 10.1016/j.jhealeco.2016.07.001
21. Victoor A, Delnoij DM, Friele RD, Rademakers JJ. Determinants of patient choice of healthcare providers: a scoping review. *Bmc Health Serv Res.* (2012) 12:272. doi: 10.1186/1472-6963-12-272
22. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making. *Pharmacoeconomics.* (2008) 26:661–77. doi: 10.2165/00019053-200826080-00004
23. Mühlbacher A, Johnson FR. Choice experiments to quantify preferences for health and healthcare: state of the practice. *Applied Health Economics & Health Policy.* (2016) 14:1–14. doi: 10.1007/s40258-016-0232-7
24. Mangham LJ, Kara H, Barbara M. How to do (or not to do) … Designing a discrete choice experiment for application in a low-income country. *Health Policy & Planning.* (2009) 24:151–8. doi: 10.1093/heapol/czn047
25. Orme BK. Getting started with conjoint analysis: strategies for product design and pricing research second edition. Madison: Research Publishers LLC (2010).
26. Lancsar E, Fiebig DG, Hole AR. Discrete Choice Experiments: A Guide to Model Specification, Estimation and Software. *Pharmacoeconomics.* (2017) 35:697–716. doi: 10.1007/s40273-017-0506-4
27. Sun H, Wang M, Luo Y, Jin C, Wang H. Preferred Family Doctor Services in Contracted Chronic Disease Patients in Shanghai. *Chinese General Practice.* (2020) 23:5. doi: 10.12114/.issn.1007-9572.2020.00.295
28. Jiang MZ, Fu Q, Xiong JY Li XL, Shen X. Preferences heterogeneity of health care utilization of community residents in China: A stated preference discrete choice experiment. *Bmc Health Serv Res.* (2020) 20:430. doi: 10.1186/s12913-020-05134-4
29. Olivella P, Siciliani L. Reputational concerns with altruistic providers. *J Health Econ*. (2017). 55:1–13 doi: 10.1016/j.jhealeco.2017.05.003
30. Godager G, Wiesen D. Profit or patients' health benefit? Exploring the heterogeneity in physician altruism. *J Health Econ.* (2013) 32:1105–16. doi: 10.1016/j.jhealeco.2013.08.008
31. Pedersen LB, Riise J, Hole AR, Gyrd-Hansen D. GPs' shifting agencies in choice of treatment. *Appl Econ.* (2014) 46:750–61. doi: 10.1080/00036846.2013.854305
32. Li B, Ma X, Yu Y, Wang G, Fu W. Letting traditional chinese medicine play its unique role. (2020) 2020:113–21. doi: 10.1007/978-981-32-9603-9_10
33. Chen X, Gong D, Huang H et al. Expert consensus and operational guidelines on exercise rehabilitation of chronic obstructive pulmonary disease with integrating traditional Chinese medicine and Western medicine. *J Thorac Dis*. (2021) 13:3323. doi: 10.21037/jtd-21-431
34. Liu M, Gao Y, Yuan Y et al. Efficacy and Safety of Integrated Traditional Chinese and Western Medicine for Corona Virus Disease (2019). (COVID-19): a systematic review and meta-analysis. *Pharmacol Res*. (2020) 158. doi: 10.1016/j.phrs.2020.104896
35. General Office of the National Health Commission. Notice on completing Family Doctor Contract Services in (2019). Available online at: http://www.gov.cn/xinwen/2019-04/26/content_5386470.htm. (accessed by August 26, 2021).
36. Xi L, Lu J, Shuang H, Cheng KK, Hu S. The primary health-care system in China. *Lancet.* (2017) 390:2584–94. doi: 10.1016/S0140-6736(17)33109-4

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 15 February 2022
doi: 10.3389/fmed.2022.796955

Health Behavior, Level of Hemoglobin A1c, and Quality of Life Among Agricultural Workers of Various Ethnicities in Thai Border Communities

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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Medicine

Received: 18 October 2021
Accepted: 13 January 2022
Published: 15 February 2022

Citation:
Boonyathee S, Ong-Artborirak P, Seangpraw K, Tonchoy P, Kantow S, Bootsikeaw S, Auttama N, Choowanthanapakorn M, Dokpuang D and Panta P (2022) Health Behavior, Level of Hemoglobin A1c, and Quality of Life Among Agricultural Workers of Various Ethnicities in Thai Border Communities. Front. Med. 9:796955. doi: 10.3389/fmed.2022.796955

Background: Little is known about the glycated hemoglobin (HbA1c) levels and quality of life (QoL) in ethnic minority agricultural workers. We investigated the links among health behaviors, HbA1c levels, and QoL ethnic agricultural workers living in rural areas.

Methods: A cross-sectional study was conducted in three northern Provinces of Thailand. Agricultural workers of Indigenous, Hmong, Karen, and Lua communities were recruited. The number of 468 samples were selected using multistage sampling. Data collection was done from interviews using questionnaires, and blood samples were taken.

Results: We revealed 56.8% of participants to be female, with an average age of 49.6 years. Also, 56.0 and 34.8% of participants had low and moderate levels of knowledge on non-communicable diseases, respectively. In addition, 56.8 and 30.6% of participants had moderate and low health behaviors, respectively. Also, 51.5% had a HbA1c level ($\geq$6.5%). We found that 64.7, 22.9, and 12.4% had moderate, low, and high QoL, respectively. Multiple linear regression analysis revealed that having an underlying disease and knowledge score were both significantly related to the health behaviors score ($p < 0.05$), accounting for 68.6% of the variance. Five variables (ethnicity, BMI, having an underlying disease, smoking, and health behaviors) were significantly related to the HbA1c level ($p < 0.05$), accounting for 24.6% of the variance. Education, health behaviors, and HbA1c level were significantly associated with QoL ($p < 0.05$). These three factors could explain 79.4% of the variance in QoL among ethnic agricultural workers.

Conclusion: Health behaviors of ethnic minority agricultural workers influenced their HbA1c level and QoL. Effective health behaviors modification programs should be developed in accordance with the problems and needs among ethnic minority agricultural workers to enhance their QoL.

Keywords: healthcare behavioral, quality of life, hemoglobin A1c, agricultural workers, ethnicities

INTRODUCTION

Agriculture has the largest proportion of informal employment, which is estimated to be more than 90% (1). Most developing countries, like Thailand, have a significant informal sector. According to the formal employment survey 2020, more than half of Thai workers were informal workers (53.8%), with 55.6% working in the agricultural sector (2). Agricultural workers in the informal sector often have low wages and working conditions (3–5). In addition, the majority of Thailand's informal workers are ethnic minority groups residing in rural areas. These ethnic minorities have migrated from neighboring countries. They are distributed in the north provinces, such as Chiang Rai, Phayao, Lamphun, Nan, and Tak (6, 7). Thailand has an estimated population of over 4 million migrants, but no valid population-based data on their health status exists (8).

Most of these individuals are living in poor economic conditions (7–10). For most of their lives, they are engaged in agricultural activities. Some are employed as "general labor" on the highlands, such as growing rice, and planting local vegetables along the hillside. According to one survey, most of these ethnic minorities are informal workers without a Thai national identification card, so they cannot apply for better-paid jobs in the lowlands or cities (11, 12). Some of these ethnic minorities must live in a forest to find rare products to sell for a living. Previously, their lives were unstable because they had to migrate to a better place to live and to obtain better-paid employment (11, 12). They continue to experience problems in daily life, such as having poor access to health services, or being unable to access to certain public services and/or education (11). The neglect of ethnic minorities could create health consequences for them especially epidemics and chronic non-communicable diseases (11–13) which, ultimately, will affect the economy, society, and public-health system of Thailand (13).

Ethnic minorities are designated "vulnerable populations" with a range of health concerns, including non-communicable diseases (NCDs) (e.g., hypertension, diabetes mellitus (DM), hyperlipidemia) due to their specific lifestyles, cultures and diets (9–11). One prospective study indicated that a group of farmers exposed to certain pesticides carried a higher risk of developing DM (14). One study indicated that DM incidence among Thai farmers was associated with pesticide exposure from their working environment (15). Several studies have found that hazardous substances from pesticides can affect insulin secretion, glucose homeostasis, and other related symptoms such physiological, stress, and oxidative (16–19). These factors, which include health behaviors and agricultural activities, may have an impact on the health and quality of life (QoL) of ethnic minority agricultural workers, who contribute economic value for a country. In this study, we focused on their HbA1C levels, which can be useful for people with undiagnosed type 2 diabetes.

QoL studies have been conducted extensively in the field of medicine and public health (20). Those studies have explored the factors influencing the QoL and impact of certain diseases and treatment on the QoL among patients and health-risk groups (9, 10, 20, 21). The Quality of Life Report mentioned that QoL quantifies health status as a component related to physical functioning as well as mental, emotional, and social conditions (21). The concept goes beyond direct measures of population health, life expectancy, and causes of death, and focuses on the impact that health status has on the QoL (21). An individual's life experience is dependent upon the goals, expectations, standards, and concerns in different cultures and value systems (20, 21).

The literature suggests that the QoL among agricultural workers should be improved, and that attention must be given to all dimensions of QoL components, especially for workers in rural areas (21). Health and QoL among informal workers differ on the basis of knowledge and experience that affects their lifestyles (22). Some studies have suggested that personal characteristics, suffering from DM, and self-care behaviors can affect (directly or indirectly) the level of HbA1c and QoL of informal workers (23). One literature review showed that the key factors influencing levels of blood sugar and lipids were age, sex, knowledge and perception of health status, and health behaviors (e.g., diet, exercise, and emotional management); all of these factors could determine good health and QoL among people (15, 24, 25). Research that links DM and ethnic minority agriculture workers is relatively rare (23–25). Few studies have used this method to assess the QoL and health status among ethnic minorities in northern Thailand (23–25). We were interested in examining knowledge, health behaviors, HbA1c levels, and QoL among ethnic minority agriculture workers in the upper and rural areas of northern Thailand, as well as the relationships among these factors. In concept, health behaviors are considered to influence both HbA1c levels and quality of life, and HbA1c levels may also play a role in quality of life. The results of this study could be used to initiate health-promotion programs to control an abnormality of blood glucose levels and to prevent non-communicable diseases and health complications. However, the programs should be appropriated in the context of local rural communities and ethnic minorities.

METHODS

This research was a cross-sectional study under the Unit of Excellence "Health Promotion and Quality of Life." Data were collected from November 2020 to April 2021 in the northern border provinces where highland and lowland ethnic minority groups live, which comprises the provinces of Lamphun, Phayao, and Nan. Nan Province is a highly mountainous area located in the easternmost part of northern Thailand, near the Laos border. Phayao Province is a plateau area surrounded by mountains, and is adjacent to Nan Province and Laos (26). Lamphun Province is the smallest province located in the north. The geographical area is flat and it is far from the capital city (26). Previously, many ethnic minority groups migrated from Myanmar and Laos to settle in large numbers in northern Thailand (27). Large populations of ethnic minorities were living in the three Provinces we selected. The study areas are about 30–40 km from city centers, and access to public services (including primary care centers and Tambon Health Promoting Hospitals) is difficult. The study cohorts from each Province were selected using a multistage sampling method

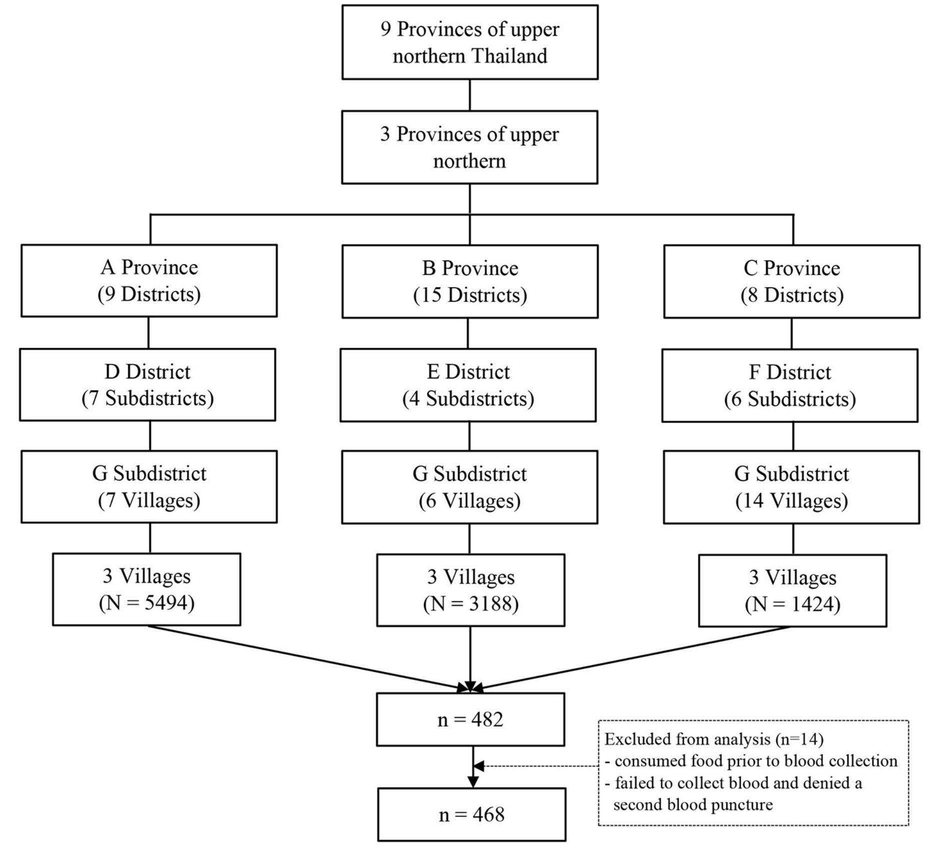

FIGURE 1 | Flow diagram of participants.

(**Figure 1**). First, the three Provinces were selected. Second, we selected districts using a simple random sampling method by lottery, resulting in one district per province. Third, three sub-districts were chosen randomly from each district. Each of the three villages in each sub-district was selected randomly. Then, the recruitment of volunteers to participate in our study was announced through public relations using health volunteers, the head of the village, and health workers in the primary care unit as the main communication channels. The samples were selected using simple random sampling. The sample size was calculated using Cochran's formula with a proportion of 50% (assuming maximum variability), precision of 5%, and 95% confidence level (28). We allowed for a dropout prevalence among participants of 25%. We enlisted the participation of 482 people.

The inclusion criteria were females and males: (a) aged ≥20 years; (b) being an ethnic minority registered with the Health Center of Ethnic Group Migrant Peoples, and Migrant Workers, Department of Health, Ministry of Public Health and municipalities in the area; (c) residing in the area for ≥2 years to avoid enlisting temporary migrant workers; (d) able to communicate in the local language; (e) who provided written informed consent before study initiation. People with cognitive and/or psychological disorders, or with gestational diabetes, were excluded from the study, as determined by a research assistant who was familiar with the local population.

Most potential recruits did not speak Thai. Therefore, to obtain correct data, we recruited research assistants from the study area to communicate appropriately and correctly. Before study initiation, an announcement was made, and we recruited 15 research assistants from each sub-district: three public-health scholars, two nurses, and 10 health volunteers from the village. They were able to communicate in the local language and to access study participants (hereafter termed "participants") rapidly and conveniently.

Before data collection, a meeting for research assistants in each area was held to clarify the objectives of the research, data-collection process, understanding of questionnaires, and the privacy of participants. We aimed to ensure that all research assistants understood the process, interview method, and research details. The study was conducted during the "second wave" of coronavirus disease 2019 (COVID-19) epidemic, so the procedure was authorized by the local government agency and head of the village. All procedures for data collection followed the government measures for COVID-19 prevention which was announced in each community area. The head of the village announced a review of the research to clarify the objectives and necessary background information through the village radio broadcast in the morning using the local dialect.

After receiving the signed consent forms, a blood specimen (3 ml) was taken for HbA1c analysis. The latter were interviewed face-to-face from 9 am to noon in a private room in the village with the help of a research assistant. The latter interviewed and allowed the participants to respond to questions. Each interview lasted approximately 15–20 min per person. Trained physicians and family care teams undertook the initial physical examinations of all participants in an appropriate room provided by the community. A small gift was given to each participant after completing the survey.

The research instrument used to collect quantitative data was developed to be suitable for people living in rural areas, and comprised four parts. Part 1 focused on general demographic characteristics: sex, age, ethnicity, marital status, education, and income. The health assessment comprised underlying disease, body mass index (BMI), alcohol intake, and tobacco smoking. Part 2 centered on a knowledge questionnaire on NCDs. It comprised 10 items adapted to be suitable for people living in rural areas (29). The questions were multiple-choice and allowed the participant to respond with a correct or incorrect answer. The total score was in the range 0–10 points. The total score was divided into three levels: "high" ($\geq$8 points), "moderate" (6–7 points), and "low" ($\leq$5 points). Part 3 focused on a questionnaire on health behaviors applicable for research in rural areas (29). It consisted of questions on general health behaviors, such as food consumption and exercise. The questionnaire comprised 12 items. The questionnaire was a rating scale with three levels: "never practiced," "rarely practiced" (1–3 times/week), and "regularly practiced" (4–6 times/week). They were divided into three levels: "high" (score $\geq$80%, i.e., $\geq$28 points); "moderate" (score of 60–79%, i.e., 21–27 points), and "low" (score <60%, i.e., $\leq$20 points). Part 4 centered on the World Health Organization Quality of Life: Brief Version (WHOQOL–BREF) (30). We employed the version developed by the WHO translated for Thailand in a short form (WHOQOL–BREF–THAI) (31, 32). The latter consisted of 26 items divided into four domains: Physical Health with seven items (DOM1); Psychological Health with six items (DOM2); Social Relationships with three items (DOM3); Environmental Health with eight items (DOM4). Each item of WHOQOL–BREF (30) is scored from 1 to 5 on a response scale. The scores were divided into three levels: a score of 26–60 denoted a "poor" QoL; a score of 61–95 reflected a "moderate" QoL; a score of 96–130 indicated a "good" QoL.

An analyzer was used to measure the HbA1c level among participants. A medical technician from the School of Allied Health Sciences within the University of Phayao (Thailand) undertook the collection and analyses of blood, and interpretation of results. The laboratory equipment passed the quality inspection required.

All questionnaires were developed based on the literature. After completing the first draft of the questionnaires, they were checked for accuracy using the Item Objective Congruence (IOC) method. Then, they were checked by external experts in their respective fields (internal medicine, behavioral health, public health). A question with a score <0.5 was eliminated from the set of questions. A question with a score 0.5–0.69 was revised based on feedback from experts. A question with a score >0.7 was considered to be acceptable for use in data collection. The questionnaire was tested on 30 participants with similar characteristics. For the knowledge questionnaire (Part 2 of the research instrument), the Kuder Richardson formula (KR20) = 0.80. Part 3 and Part 4 of the research instrument were carried out to check the reliability of the questionnaire using Cronbach's alpha coefficient: the value was 0.79 and 0.84, respectively.

Statistical Analysis

Statistical analyses were undertaken using SPSS 17 (IBM, Armonk, IL, USA) licensed from Chiang Mai University (Thailand). General information was described using mean, standard deviation (SD), minimum (Min), and maximum (Max) values, as well as frequencies and percentages. We used linear regression analysis to examine the factors related to health behaviors, HbA1c level, and QoL in ethnic minority agricultural workers. After the univariable analysis, variables with a $p < 0.15$ were analyzed together in a multivariable model using the enter technique. The final model in which all predictors were found to be significant at $p < 0.05$ is presented. The unstandardized coefficient (B) and standardized coefficient (Beta) are reported.

RESULTS

Sociodemographic Characteristics

Table 1 presents the sociodemographic characteristics of participants categorized based on minority group. The mean age of the participants was 49.6 years (SD = 13.8). Ethnic minorities were classified as Hmong (50.6%), Lua (23.0%), Indigenous (15.2%), and Karen (11.2%). We found that 56.8% of participants were female, 52.1% did not have an educational background, and 49.6% were financially insufficient. We discovered that 50.6% consumed alcohol and 73.1% did not smoke cigarettes. We revealed that 58.5% had an underlying disease diagnosed by a doctor, such as hypertension (39.7%), hyperlipidemia (7.6%), DM (5.8%), stroke (3.0%), heart disease (1.7%), or kidney disease (0.4%). The average BMI of the study was 24.7 kg/m^2 (SD = 4.5).

Knowledge, Health Behaviors, HbA1c Level, and Quality of Life Among Participants

The score for knowledge ranged from 3 to 9, with a mean of 5.4 (SD = 1.2) (**Table 2**). We discovered that 56.0% of participants had a low level of knowledge, followed by 34.8% who had a moderate level, and 9.2% had a high level of knowledge. The highest mean scores for knowledge were found in Lua, followed by Hmong, Karen, and Indigenous people. Another interesting variable about the scores of health behavioral ranged from 18 to 30 (mean = 22.7, SD = 2.9). With regard to health behavioral, 56.8% had a moderate level, 30.6% had a low level, and 12.6% had a high level. The highest mean scores for health behaviors were found in Lua, followed by Hmong, Karen, and Indigenous people. Results revealed that 51.5% of participants had HbA1c $\geq$6.5, which was interpreted as an abnormality. Indigenous people had the highest mean HbA1c levels, followed by Lua, Hmong, and

TABLE 1 | Sociodemographic of participants categorized based on minority groups.

Variables	Overall ($n = 468$) n (%)	Indigenous ($n = 71$) n (%)	Hmong ($n = 237$) n (%)	Karen ($n = 52$) n (%)	Lua ($n = 108$) n (%)
Gender					
Male	200 (43.2)	29 (40.8)	112 (47.3)	26 (50.0)	35 (32.4)
Female	266 (56.8)	42 (59.2)	125 (52.7)	26 (50.0)	73 (67.6)
Age (years)					
Mean ± SD	49.6 ± 13.8	59.8 ± 10.5	46.8 ± 12.9	59.1 ± 13.2	44.2 ± 12.0
Min–Max	20–89	36–88	20–89	20–79	22–89
Marital status					
Single/widowed/separated	142 (30.3)	36 (50.7)	49 (20.7)	13 (25.0)	44 (70.0)
Married	326 (69.7)	35 (49.3)	188 (79.3)	39 (75.0)	64 (59.3)
Education					
No	244 (52.1)	50 (70.4)	129 (50.4)	24 (46.2)	41 (38.0)
Yes	224 (47.9)	21 (29.6)	108 (45.6)	28 (53.8)	67 (62.0)
Financial status					
Insufficient	232 (49.6)	42 (59.2)	120 (50.6)	34 (65.4)	36 (33.3)
Sufficient	236 (50.4)	29 (40.8)	117 (49.4)	18 (34.6)	72 (66.7)
Alcohol consumption					
No	231 (49.4)	51 (71.8)	117(49.4)	26 (50.0)	37 (34.3)
Yes	237 (50.6)	20 (28.2)	120(50.6)	26 (50.0)	71 (65.7)
Smoking status					
Non-smoker	342 (73.1)	51 (71.8)	164 (69.2)	39 (75.0)	88 (81.5)
Smoker	126 (26.9)	20 (28.2)	73 (30.8)	13 (25.0)	20 (18.5)
Body mass index (kg/m^2)					
Mean ± SD	24.7 ± 4.5	22.8 ± 3.7	24.3 ± 3.7	30.7 ± 4.2	23.8 ± 4.3
Min–Max	15.2–42.0	16.6–36.8	16.0–36.2	22.2–42.0	15.2–37.8
Current disease					
No	194 (41.5)	19 (26.8)	117 (49.4)	21 (40.4)	37 (34.3)
Yes	274 (58.5)	52 (73.2)	120 (50.6)	31 (59.6)	71 (65.7)
Type of disease					
Hypertension	186 (39.7)	39 (54.9)	77 (32.5)	21 (40.4)	49 (45.4)
DM	27 (5.8)	2 (2.8)	12 (5.1)	6 (11.5)	7 (6.4)
Stroke	14 (3.0)	5 (7.0)	4 (1.7)	3 (5.8)	2 (1.9)
Hyperlipidemias	36 (7.6)	6 (8.5)	19 (8.0)	1 (1.9)	10 (9.2)
Kidney	4 (0.9)	0 (0.0)	2 (0.8)	0 (0.0)	2 (1.9)
Heart	7 (1.5)	0 (0.0)	6 (2.5)	0 (0.0)	1 (0.9)

Karen. The QoL score among participants was 56–103 (mean = 72.3, SD = 12.5). We discovered that 64.7% of participants had a moderate level of QoL, 22.9% had a low level, and 12.4% had a high level. The highest mean scores for QoL were found in Lua, followed by Hmong, Karen, and Indigenous people.

Factors Associated With the Health Behaviors, HbA1c Level, and Quality of Life of Ethnic Minority Agricultural Workers

A strong positive correlation was observed between the score for knowledge on NCDs and health behaviors among ethnic minority agricultural workers (beta = 0.818), which accounted for 66.8% of the variance (**Table 3**). Multivariable analysis revealed that having an underlying disease and a score of knowledge about NCDs were both significantly related to the score for health behaviors ($p < 0.05$, $R^2 = 68.6\%$). The HbA1c level was inversely correlated with the score for knowledge (beta = −0.191) and score for health behaviors (beta = −0.305) (**Table 4**). The final model showed five variables (ethnicity, BMI, having an underlying disease, smoking, health behaviors) to be significantly related to the HbA1c level ($p < 0.05$, $R^2 = 24.6\%$). Health behaviors could explain 9.1% of the variance in the HbA1c level. The factors influencing the QoL in ethnic minority agricultural workers are shown in **Table 5**. In the multivariable model, education, health behaviors, and HbA1c level were significantly related to QoL ($p < 0.05$). These three factors accounted for 79.4% of the variance in the QoL. The single factors of health behaviors and HbA1c level accounted for 78.5 and 11.1% of the variance in the QoL, respectively.

TABLE 2 | Descriptive analysis of knowledge, healthcare behaviors, HbA1c, and quality of life among participants.

Variables	**Overall** (*n* = 468) *n* (%)	**Indigenous** (*n* = 71) *n* (%)	**Hmong** (*n* = 237) *n* (%)	**Karen** (*n* = 52) *n* (%)	**Lua** (*n* = 108) *n* (%)
Knowledge					
Low level (scores ≤5)	262 (56.0)	54 (76.1)	140 (59.1)	31 (59.6)	37 (34.3)
Moderate level (scores 6–7)	163 (34.8)	16 (22.5)	73 (30.8)	15 (28.8)	59 (54.6)
High level (scores ≥8)	43 (9.2)	1 (1.4)	24 (10.1)	6 (11.5)	12 (11.1)
Mean ± SD	5.4 ± 1.2	4.9 ± 0.9	5.39 ± 1.2	5.2 ± 1.4	5.9 ± 1.2
Min–Max	3–9	3–8	3–9	3–8	3–9
Health behavior					
Low level (scores ≤20)	143 (30.6)	30 (42.3)	77 (32.5)	26 (50.0)	10 (9.3)
Moderate level (scores 21–27)	266 (56.8)	38 (53.5)	128 (54.0)	18 (34.6)	82 (75.9)
High level (scores ≥28)	59 (12.6)	3 (4.2)	32 (13.5)	8 (15.4)	16 (14.8)
Mean ± SD	22.7 ± 2.9	21.5 ± 2.0	22.7 ± 3.0	22.3 ± 3.3	23.8 ± 2.5
Min–Max	18–30	19–29	19–31	18–30	19–30
HbA1c (%)					
Normal (<6.5)	227 (48.5)	37 (52.1)	109 (46.0)	31 (59.6)	50 (46.3)
Abnormal (≥6.5)	241 (51.5)	34 (47.9)	128 (54.0)	21 (40.4)	58 (53.7)
Mean ± SD	6.6 ± 1.3	6.8 ± 1.7	6.6 ± 1.1	6.4 ± 1.1	6.6 ± 1.2
Min–Max	3.9–13.8	4.0–13.8	3.9–11.9	4.8–10.6	3.9–11.4
Quality of life					
Low level (scores 26–60)	107 (22.9)	21 (29.6)	61 (25.7)	17 (32.7)	8 (7.4)
Moderate level (scores 61–95)	303 (64.7)	49 (69.0)	142 (59.9)	28 (53.8)	84 (77.8)
High level (scores 96–130)	58 (12.4)	1 (1.4)	34 (14.3)	7 (13.5)	16 (14.8)
Mean ± SD	72.3 ± 12.5	67.2 ± 8.0	72.0 ± 12.9	71.8 ± 13.4	76.8 ± 12.2
Min - Max	56–103	58–100	56–102	56–102	59–103
Physical health					
Mean ± SD	18.7 ± 2.7	18.1 ± 2.1	18.6 ± 2.7	18.5 ± 2.7	19.7 ± 2.8
Min–Max	13.0–30.0	14.0–25.0	13.0–30.0	14.0–26.0	15.0–27.0
Psychological health					
Mean ± SD	16.1 ± 3.2	15.9 ± 2.2	15.7 ± 3.6	15.7 ± 3.2	17.2 ± 2.4
Min–Max	8.0–28.0	11.0–24.0	8.0–27.0	12.0–27.0	13.0–28.0
Social relationships					
Mean ± SD	8.4 ± 2.2	7.6 ± 1.7	8.5 ± 2.4	7.9 ± 2.2	8.7 ± 2.0
Min–Max	3.0–16.0	3.0–12.0	3.0–16.0	5.0–13.0	6.0–15.0
Environmental health					
Mean ± SD	32.0 ± 5.8	20.1 ± 4.2	23.1 ± 5.3	22.6 ± 7.0	24.9 ± 6.4
Min–Max	13.0–40.0	16.0–30.0	15.0–40.0	13.0–40.0	16.0–40.0

In addition, the ethnic groups of Lua and Hmong are analyzed separately. In the ethnic group of Lua, the final model revealed that having an underlying disease and a score of knowledge about NCDs were both significantly related to the score for health behaviors ($p < 0.05$, $R^2 = 47.5\%$). BMI and health behaviors were related to the HbA1c level ($p < 0.05$, $R^2 = 19.8\%$). Alcohol consumption, health behaviors, and HbA1c level were significantly related to QoL ($p < 0.05$, $R^2 = 68.9\%$). In the ethnic group of Hmong, not only having an underlying disease and a score of knowledge about NCDs, but also smoking were significantly associated with the score for health behaviors ($p < 0.05$, $R^2 = 79.6\%$). Four variables - BMI, having an underlying disease, smoking, and health behaviors - were associated with the HbA1c level ($p < 0.05$, $R^2 = 23.2\%$). Sex, age, financial status, health behaviors, and HbA1c level were all found to have a significant association with QoL ($p < 0.05$, $R^2 = 83.4\%$). Due to the small sample size, the association was not examined in Karen and Indigenous people.

DISCUSSION

This is the first study to link the health behaviors, HbA1c level, and QoL of ethnic minority agricultural workers. We discovered that 51.5% of participants had a high level of HbA1c (>6.5). The effects of poor regulation of the HbA1c level on the body

TABLE 3 | Factors associated with health behaviors in agricultural workers by linear regression ($n = 468$).

Factors	Univariable			Multivariable		
	B	**Beta**	***P*-value**	**B**	**Beta**	***P*-value**
Constant				13.38		<0.001*
Ethnics						
- Indigenous	Ref.					
- Hmong	1.27	0.218	0.001*			
- Karen	0.88	0.095	0.089			
- Lua	2.40	0.346	<0.001*			
Gender (female)	0.75	0.127	0.006*			
Age (years)	−0.10	−0.467	<0.001*			
Education (yes)	3.05	0.523	<0.001*			
Marital status (married)	0.42	0.067	0.148			
Financial status (sufficient)	1.73	0.297	<0.001*			
BMI (kg/m^2)	0.01	0.011	0.819			
Current disease (yes)	−1.97	−0.332	<0.001*	−0.81	−0.136	<0.001*
Alcohol drinking (yes)	0.19	0.033	0.473			
Smoking (yes)	−0.77	−0.117	0.011*			
Knowledge (scores)	1.89	0.818	<0.001*	1.81	0.783	<0.001*
					R^2 = 68.6%	

B, Unstandardized coefficient; Beta, Standardized coefficients.
**Significance at the 0.05 level (2-tailed).*

TABLE 4 | Factors associated with HbA1c in agricultural workers by linear regression ($n = 468$).

Factors	Univariable			Multivariable		
	B	**Beta**	***P*-value**	**B**	**Beta**	***P*-value**
Constant				6.78		<0.001*
Ethnics						
- Indigenous	Ref.			Ref.		
- Hmong	−0.17	−0.069	0.311	−0.05	−0.020	0.739
- Karen	−0.41	−0.102	0.075	−0.83	−0.206	<0.001*
- Lua	−0.15	−0.051	0.429	0.11	0.037	0.528
Gender (female)	0.02	0.009	0.840			
Age (years)	0.01	0.053	0.251			
Education (yes)	−0.27	−0.105	0.023*			
Marital status (married)	−0.27	−0.099	0.033*			
Financial status (sufficient)	−0.10	−0.040	0.388			
BMI (kg/m^2)	0.05	0.186	<0.001*	0.08	0.269	<0.001*
Current disease (yes)	0.88	0.343	<0.001*	0.52	0.204	<0.001*
Alcohol drinking (yes)	0.48	0.191	<0.001*			
Smoking (yes)	0.64	0.224	<0.001*	0.50	0.177	<0.001*
Knowledge (scores)	−0.19	−0.191	<0.001*			
Health behaviors (scores)	−0.13	−0.305	<0.001*	−0.10	−0.238	<0.001*
					R^2 = 24.6%	

**Significance at the 0.05 level (2-tailed).*

have been discussed extensively (23, 33, 34). Most participants in our study had a low educational level and insufficient income, which may have had a negative impact on their health behaviors. Interestingly, the participants with high HbA1C did not report a history of diabetes because they had not previously or for many years undergone medical examinations and/or health assessments. This phenomenon is similar to that described, who mentioned that uninformed people can make inappropriate judgments toward healthcare behaviors (33). Consistent with the results of a study, we found that participants had limited access to health services which prevented them from being aware of their health status (34). However, such participants were living in a traditional way of life (9, 33). They are unaware of making the correct food choices, which resulted in inappropriate healthcare behaviors in terms of diet. Furthermore, most of their cooking recipes were derived from China and cultural traditions, so some dishes were unhealthy because of extensive use of salt, monosodium glutamate, and oils from animals (33, 35). Similar to a previous showed that hill tribes had a higher prevalence of abnormal HbA1c level (33). One study focusing on African Americans and Latinos showed that both groups had a higher average HbA1c level than that of other ethnic groups; Hispanics had the highest HbA1c level (8.5%) (36). Consistent with the previous studies showed that ethnic minority participants had a high mean level of HbA1c (7.39 ± 1.11%) (23) and some studies showed that participants in Taiwan had a higher mean level of HbA1c (7.8 ± 1.5%) (37).

We found that 56.0% had a low and 34.8% had a moderate level of knowledge. These findings can be explained by the low level of education of participants. In addition, communication between personnel in health departments of hospitals and ethnic minority agricultural workers in each area may be the cause. Most participants used the local dialect, so language could have been a barrier in healthcare communication. This explanation is consistent with a study which stated that language differences are major problems for accessing health services (9). A previous study showed that people who obtained incorrect knowledge toward diabetes did so due to language differences (38). It is consistent with the study which showed one group of people did not have sufficient knowledge to take care of their own health due to lack of communication skills, which prevented them from accessing healthcare information and managing their diabetes (35).

We showed that 64.7% of participants had a moderate QoL score and 22.9% had a low QoL score. During our study, the second wave of the COVID-19 epidemic arose, which impacted on the physical and mental health of participants (2), including anxiety due to reduced income from a lack of work. Quality of life is determined by an individual's satisfaction toward domains such as social relationships, environmental health, and mental health (39). Similar to the concept of Pender's, in which perception of individual toward health status are according to their experience and perception of one's health; which all of these are linked to self-inflicted illnesses (40). Almost half of participants had an underlying disease, which could further reduce their QoL. Some studies have shown that having high blood sugar levels have a significant effect on the QoL of study participants (41). Distress and dissatisfaction with life due to diabetes have been significantly associated with QoL (42).

TABLE 5 | Factors associated with QoL in agricultural workers by linear regression (*n* = 468).

Factors	**Univariable**			**Multivariable**		
	B	**Beta**	***P*-value**	**B**	**Beta**	***P*-value**
Constant				−3.67		0.245
Ethnics						
- Indigenous	Ref.					
- Hmong	4.83	0.194	0.004*			
- Karen	4.64	0.117	0.038*			
- Lua	9.64	0.325	<0.001*			
Gender (female)	3.52	0.140	0.002*			
Age (years)	−0.36	−0.399	<0.001*			
Education (yes)	12.88	0.515	<0.001*	1.92	0.077	0.002*
Marital status (married)	1.58	0.058	0.208			
Financial status (sufficient)	6.40	0.256	<0.001*			
BMI (kg/m^2)	−0.02	−0.008	0.856			
Current disease (yes)	−8.27	−0.326	<0.001*			
Alcohol drinking (yes)	0.82	0.033	0.476			
Smoking (yes)	−3.30	−0.117	0.011*			
Knowledge (scores)	7.63	0.770	<0.001*			
Health behaviors (scores)	3.79	0.886	<0.001*	3.52	0.822	<0.001*
HbA1c (%)	−3.31	0.336	<0.001*	−0.76	−0.077	0.001*
					R^2 = 79.4%	

**Significance at the 0.05 level (2-tailed).*

We discovered that 56.8% had moderate and 30.6% had low health behaviors, which may have been due to most of the participants being uneducated and middle-aged. Pender stated that people with a high level of education are more likely to seek health benefits than those with a low level of education (40). Moreover, the main motivating factor for behavior modification is cognitive, such as specific feelings toward self-care behavior (40). The way a person can change toward healthier healthcare behaviors is due to his/her experiences and perceptions (40). In addition, the literature suggests that healthcare behaviors among ethnic groups are derived from indigenous knowledge, social factors, cultural adherence to self-care plans, self-treatment by "folk" and herbal formulations, and worship of sacred deities to help them heal from their illness (9, 43). In addition, occupational risk-based health conditions are important (44). Similar with the previous study, it was found health behaviors among ethnic minorities to be in accordance with the beliefs, traditions, cultures, and lifestyles of each ethnic group (9). Perceived health status has been shown to be positively correlated with health behaviors at 0.01 level (45). Procedural multiple regression analysis showed that perceptions of health status and attitudes were significant for predicting health-enhancing behaviors among older workers (46).

When analyzing the many variables related to health behaviors, we showed that Hmong and Lua communities had better health behaviors than those of Indigenous people. This was because the health behaviors and practices of each ethnicity were culturally different (9). The Hmong and Lua ethnic groups live in the highlands, and their healthcare behaviors are based on their ancestors. Therefore, these ethnic groups gained experiences from culture, traditions, beliefs, local rituals, and illness to practice in self-care (47). The Indigenous group inhabited flat, plain areas. They began to harmonize the values, social and economic changes in the context of that area (47).

Sex, age, education, income sufficiency, underlying diseases, smoking, and knowledge were significantly associated with health behaviors. Multivariable analysis showed that participants with underlying disease and knowledge on NCDs could predict health behaviors. This finding is consistent with work indicating that poorly literacy can lead to a reduction in health behaviors and healthcare practices; and ethnic minorities are more likely to suffer health complications and to have limited access to healthcare services, which impacts on the quality of their healthcare (48). It is consistent with the study which found that sex, education, economic status, and health status were major predictors associated with deterioration of health and QoL among patients (49). One systematic review showed that several factors contributing to health inequalities among ethnic minorities (including low health literacy and low socioeconomic status) could lead to a higher incidence of illness (50). Similar to a previous study, we found that self-care behavior was an important factor associated with QoL among older ethnic minorities (9).

Studies have suggested that a high blood sugar level is an independent predictor of cardiovascular disease regardless of the diagnosis of DM (50–52). One study suggested that the perception of disease and self-care behaviors were predictive factors significantly associated with the HbA1c level (36). A study from India reported people with a low education level to be at greater risk of having hypertriglyceridemia than those with a higher level of education (53). They also pointed out that smoking is a risk factor for cardiovascular disease (53). We showed that the Karen community had lower levels of HbA1c compared with those of the Indigenous group, which is similar to a study showing that racial/ethnic differences can result in higher triglyceride levels (35). Studies have shown that certain tribes from Lua and Hmong communities carried a significantly higher risk of coronary artery disease compared with that of other ethnic groups, which suggests that differences in racial/ethnic backgrounds can affect triglyceride levels (33). One study undertaken in a large sample in the USA in 2014, it showed that the samples aged 35 and older of different ethnicities had a significantly higher rates of hypertriglyceridemia differently (54).

Multivariable analyses showed that ethnicity, BMI, underlying disease, smoking, and health behaviors were significantly related to the HbA1c level. These data indicated that lifestyle factors, such as obesity, congenital disease, and smoking, were predictors of health problems (55). Several studies have shown that a poor lifestyle and inappropriate healthcare behaviors have direct effects on blood sugar levels (23, 54). Some studies have found that farmers with underlying diseases and exposure to certain chemicals are significantly associated with adult-onset diabetes (56).

Ethnicity, sex, age, education level, financial status, underlying disease, smoking, knowledge, health behaviors, and the HbA1c level were significantly associated with the QoL. Multivariable analysis showed a high positive correlation between knowledge and health behaviors and QoL (beta = 0.770 and 0.886, respectively). These findings are consistent with the concept of health awareness leading to improvement in self-care behaviors (40). The American Diabetes Association reported that the QoL is an indicator of psychosocial outcomes in DM control (57). Previous research had also indicated that people with DM had a lower QoL than those not suffering from DM (58). Some studies have suggested that people with good QoL may have high motivation to control blood sugar levels, which would result in lower HbA1c levels (23).

Those studies have also pointed out that control of HbA1c levels in DM patients requires knowledge that would enable them to have better self-care and behavioral modifications (23). Cross-sectional studies have shown that self-care behaviors influence QoL directly (59, 60). Several cross-sectional and longitudinal studies have indicated self-care behaviors to be significantly negatively associated with the HbA1c level (61, 62). The QoL of ethnic minority agricultural workers is essential to their wellbeing in terms of undertaking high-quality work and generating income for them (4, 43).

The perception of the person under the ethnic culture are associated with awareness of the individual in term of four components: physical, mental, social relationships, and environment, which these elements are interrelated (63). Each ethnic group has different backgrounds and lifestyles, and they are unique in each area. Ethnic minorities show their identity through culture, traditions, lifestyles, and beliefs which may be associated with their QoL (9, 10). One longitudinal study demonstrated that self-care behaviors may affect QoL directly among ethnic minorities during the first 6-months of study, and that self-care behaviors are significant for subsequent QoL (23). Some studies have suggested that health and QoL are linked to lifestyle and social factors (20).

According to the findings, both HbA1c levels and quality of life are considered to be influenced by health behaviors. HbA1c levels may play a role in mediating the link between health behavior and quality of life. Normally, HbA1C is used as a sugar control monitor and a quality-of-life indicator in diabetic patients. In this study, it is also used as a marker of undiagnosed DM. Poor health behaviors such as eating habits and exercising in different ethnic minorities are considered to produce health problems such as high HbA1C levels, hypertension, and dyslipidemia which then affect quality of life. Individuals should be encouraged to recognize their commitment to health behaviors. They would be able to control HbA1c levels if they focused on appropriate health behavior modifications as well as avoiding health risk factors. The importance of an abnormal HbA1C level and the need to access health services for diagnosis and treatment should be emphasized in particular for the risk group. Furthermore, there should be information available in ethnic dialects that allows them to quickly access health information in a format that is appropriate for them. This may improve the quality of life for ethnic minority agricultural workers in rural areas.

There were some limitations to our research. First, due to the second wave of the COVID-19 epidemic and an announcement by the Thailand government to limit the number of people gathering in an area, some people refused to participate in our study. Second, causal inferences are impossible to draw from a cross-sectional study. Third, because of the difficulty of communicating in a local language and the large number of research assistants conducting face-to-face conversations, the information obtained may not be comprehensive and may affect the quality of data. This study did not take into account occupational factors such as working environments. Further research should also examine if there is a correlation between agricultural workers use of pesticides and HbA1c level and health. Additional types of blood lipids should be studied to develop a model for modifying healthcare behaviors among ethnic minorities. Blood pressure and other variables together with physical examination should also be considered.

CONCLUSION

BMI, having an underlying disease, smoking, and health behaviors were related to the HbA1c level, accounting for 24.6% of the variance. Education, health behaviors, and HbA1c level were associated with QoL. These three factors could explain 79.4% of the variance in QoL among ethnic minority agricultural workers. An intervention programs should be tailored to the local context, focusing on eating behaviors such as cooking and eating local foods, eating beliefs, unhealthy lifestyles, and avoiding risk factors that contribute to health problems. In this case, improving health behaviors is helpful for increasing HbA1C control and overall quality of life.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Phayao Human Ethics Committee, Thailand (UP-HEC-1.2/023/64). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SK and SBoon contributed to the conception and design of the work. SBoot, NA, MC, DD, and PP contributed the data acquisition. PO-A and KS contributed the analysis and interpretation of data for the work. SK, SBoon, and PO-A contributed drafting the work. SK and PO-A contributed revising the work for important intellectual content. All authors approved of the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING

The authors are grateful to the research project was supported by School of Medicine (MD-65-04) and the Thailand Science Research and Innovation fund and the University of Phayao the Unit of Excellence.

ACKNOWLEDGMENTS

The author's gratitude and appreciation goes to administration of the Health Promoting Hospitals Sub-District (Ban Pang Kha, Pa Lao, and Phu Fa), Pong district, Phayao Province, Mae Tha District, Lamphun Province, and Bo Kluea district, Nan Province. We thank the participants of the ethnicities in border community for their continued cooperation and participation in our research project.

REFERENCES

1. International Labour Organization. *Informal Economy*. (2018). Available online at: https://www.ilo.org/global/about-the-ilo/newsroom/news/WCMS_627189/lang--en/index.htm (accessed September 1, 2021).
2. National Statistical Office, Labor Statistics Group. *The Informal Employment Survey 2020*. Bangkok, Thailand; Ministry of Digital Economy and Society (2020).
3. Buddhari A, Rugpenthum P. *A Better Understanding of Thailand's Informal Sector*. (2019). Available online at: https://www.bot.or.th/Thai/MonetaryPolicy/ArticleAndResearch/FAQ/FAQ_156.pdf (accessed September 1, 2021).
4. Thanapop C, Thanapop S, Keam-Kan S. Health status and occupational health and safety access among informal workers in the rural community, Southern Thailand. *J Prim Care Community Health*. (2021) 12:1–7. doi: 10.1177/21501327211015884
5. Chanprasit C, Jongrungrotsakul W, Kaewthummanukul T, Indratula R. Working behaviors and lifestyle among informal workers: corn farmers. *Nurs J*. (2020) 47:50–63.
6. Young G. *The Hill Tribes of Northern Thailand*. Bangkok, Thailand: Thai-American Audiovisual (1962).
7. Sutinyamanee V. Factors determining migration among hill tribe people in Northern Thailand: a case study of karen people in Pateung Community, Chiangmai Province, Thailand. *Kasem Bundit J*. (2016) 17:150–63. Available online at: https://so04.tci-thaijo.org/index.php/jkbu (accessed September 1, 2021).
8. World Health Organization (WHO). WHO Country Cooperation Strategy, Thailand: 2017–2021. World Health Organization. Regional Office for South-East Asia. (2017). Available online at: https://apps.who.int/iris/handle/10665/255510
9. Ong-Artborirak P, Seangpraw K. Association between self-care behaviors and quality of life among elderly minority groups on the border of Thailand. *J Multidiscip Healthc*. (2019) 12:1049–59. doi: 10.2147/JMDH.S227617
10. Kantow S, Seangpraw K, Ong-Artborirak P, Tonchoy P, Auttama N, Bootsikeaw S, et al. Risk factors associated with fall awareness, falls, and quality of life among ethnic minority older adults in upper Northern Thailand. *Clin Interv Aging*. (2021) 16:1777–88. doi: 10.2147/CIA.S328912
11. Singkorn O, Apidechkul T, Putsa B, Detpetukyon S, Sunsern R, Thutsanti P, et al. Factor associated with alcohol use among Lahu and Akha hill tribe youths, northern Thailand. *Subst Abuse Treat Prev Policy*. (2019)14:5. doi: 10.1186/s13011-019-0193-6
12. Jakae O, Tanpichai P, Jai-aree A. Construction of social space in Thai hill tribe ethnic groups in Kamphaeng Phet province Kasetsart. *J Soc Sci*. (2020) 41:329–35. Available online at: https://so04.tci-thaijo.org/index.php/kjss/article/view/232598 (accessed September 1, 2021).
13. Prapasuchat N. Accessibility system of health services and mechanisms of health service rights for the stateless persons (Thai). *MFU Connexion: J Humanit Soc Sci*. (2016) 5:178–94. Available online at: https://so05.tci-thaijo.org/index.php/MFUconnexion/article/view/241326 (accessed September 1, 2021).
14. Montgomery MP, Kamel F, Saldana TM, Alavanja MCR, Sandler DP. Incident diabetes and pesticide exposure among licensed pesticide applicators: agricultural health study, 1993–2003. *Am J Epidemiol*. (2008) 167:1235–46. doi: 10.1093/aje/kwn028
15. Juntarawijit C, Juntarawijit Y. Association between diabetes and pesticides: a case-control study among Thai farmers. *Environ Health Prev Med*. (2018) 23:3. doi: 10.1186/s12199-018-0692-5
16. Sargis RM. The hijacking of cellular signaling and the diabetes epidemic: mechanisms of environmental disruption of insulin action and glucose homeostasis. *Diabetes Metab*. (2014) 28:13–24. doi: 10.4093/dmj.2014.38.1.13
17. Rahimi R, Abdollahi M. A review on the mechanisms involved in hyperglycemia induced by organophosphorus pesticides. *Pestic Biochem Physiol*. (2007) 88:115–21. doi: 10.1016/j.pestbp.2006.10.003
18. Hectors TLM, Vanparys C, Van Der Ven K, Martens GA, Jorens PG, Van Gaal LF, et al. Environmental pollutants and type 2 diabetes: a review of mechanisms that can disrupt beta cell function. *Diabetologia*. (2011) 54:1273–90. doi: 10.1007/s00125-011-2109-5
19. Park WH, Kang YC, Piao Y, Pak DH, Pak YK. Causal effects of synthetic chemicals on mitochondrial deficits and diabetes pandemic. *Arch Pharm Res*. (2013) 36:178–88. doi: 10.1007/s12272-013-0022-9
20. Liu X, Gu S, Duan S, Wu Y, Ye C, Wang J, et al. Comparative study on health-related quality of life of farmers and workers. *Value Health Reg Issues*. (2017) 12:123–9. doi: 10.1016/j.vhri.2017.03.006
21. Zhou W, Ke J, Chen J. Health-related quality of life and factors among rural residents in China. *Acta Universitatis Medicinalis Nanjing*. (2011) 11:189–93. Available online at: https://en.cnki.com.cn/Article_en/CJFDTotal-YKNS201103009.htm (accessed September 1, 2021).
22. Innamma S. Working and social life of informal workers and impacts on health: a case study of the sewing group of ban meng subdistrict, Nong Ruea District, Khon Kaen Province (Thai). *J Health Syst Res*. (2010) 4:379–92. Available online at: http://hdl.handle.net/11228/3054 (accessed September 1, 2021).
23. Hsu HC, Lee YJ, Wang RH. Influencing pathways to quality of life and HbA1c in patients with diabetes: a longitudinal study that inform evidence-based practice. *Worldviews Evid Based Nurs*. (2018) 15:104–12. doi: 10.1111/wvn.12275
24. Ariyanti R, Besral B. Dyslipidemia associated with hypertension increases the risks for coronary heart disease: a case-control study in Harapan Kita Hospital, National Cardiovascular Center, Jakarta. *J Lipids*. (2019) 2019:1–6. doi: 10.1155/2019/2517013
25. Opoku S, Gan Y, Fu W, Chen D, Addo-Yobo E, Trofimovitch D, et al. Prevalence and risk factors for dyslipidemia among adults in rural and urban China: findings from the China National Stroke Screening and prevention project (CNSSPP). *BMC Public Health*. (2019) 19:1500. doi: 10.1186/s12889-019-7827-5
26. Vivattanaseth P. Cultural identity of ethnic group in tailue's ritual of life, Phayao Province (Thai). *Payap University J*. (2018) 28:173–89. doi: 10.14456/pyuj.2018.29
27. Phonprasoet B. The space of people in Phrathat (Stupa) Hariphunchai Water Blessing Ceremony before 1957 A.D (Thai). *J Hum Sci*. (2018) 19:11–32. Available online at: https://so03.tci-thaijo.org/index.php/JHUMANS/article/view/131339 (accessed September 1, 2021).
28. Cochran WG. *Sampling Techniques*. New York: John Wiley & Sons Inc Book (1977).
29. Department of health Service. *Family Volunteer Guide and Caring for Patients With Non-Communicable Diseases (Thai)*. Ministry of Public health (2017). Available online at: http://phc.moph.go.th/www_hss/data_center/dyn_mod/NCDs.pdf (accessed September 1, 2021).

30. Development of the World Health Organization WHOQOL-BREF quality of life assessment. *Psychol Med.* (1998) 28:551–8. doi: 10.1017/S0033291798006667
31. Mahatnirunkul S, Tuntipivatanaskul W, Pumpisanchai W. Comparison of the WHOQOL-100 and the WHOQOLBREF (26 items). *J Ment Health Thai.* (1998) 5:4–15.
32. Mahatnirunkul S, WHOQOL. – BREF – THAI. *Department of Mental Health, Ministry of Public Health Thailand*. (2002). Available online at: https://www.dmh.go.th/test/download/files/whoqol.pdf (accessed September 1, 2021).
33. Upala P, Apidechkul T, Wongfu C, Khunthason S, Kullawong N, Keawdounglek V, et al. Factors associated with hypertriglyceridemia among the hill tribe people aged 30 years and over, Thailand: a cross-sectional study. *BMC Public Health.* (2021) 21:581. doi: 10.1186/s12889-021-10632-z
34. Straw S, Spry E, Yanawana L, Matsumoto V, Cox D, Cox E, et al. Understanding lived experiences of Aboriginal people with type 2 diabetes living in remote Kimberley communities: diabetes, it don't come and go, it stays! *Aust J Prim Health.* (2019) 25:486–94. doi: 10.1071/PY19021
35. Kullawong N, Apidechkul T, Upala P, Tamornpark R, Keawdounglek V, Wongfu C, et al. Factors associated with elevated low-density lipoprotein cholesterol levels among hill tribe people aged 30 years and over in Thailand: a cross-sectional study. *BMC Public Health.* (2021) 21:498. doi: 10.1186/s12889-021-10577-3
36. Heisler M, Piette JD, Spencer M, Kieffer E, Vijan S. The relationship between knowledge of recent HbA1c values and diabetes care understanding and self-management. *Diabetes Care.* (2005) 28:816–22. doi: 10.2337/diacare.28.4.816
37. Ouyang CM, Dwyer JT, Jacques PF, Chuang LM, Haas CF, Weinger K. Diabetes self-care behaviours and clinical outcomes among Taiwanese patients with type 2 diabetes. *Asia Pac J Clin Nutr.* (2015) 24:438–43. doi: 10.6133/apjcn.2015.24.3.03
38. Pitchalard K, Rattanasuwan P. Caring experience for ethnics elderly with type 2 diabetes mellitus of healthcare professionals (Thai). *JOPN.* (2012) 13:24–33. Available online at: https://he01.tci-thaijo.org/index.php/policenurse/article/view/247349 (accessed September 1, 2021).
39. Sharma RC. *Population Trends Resources and Environment Hand Book on Population Education*. New Delhi: Tata McGraw-Hill (1975).
40. Pender NJ. Health Promotion in Nursing Pratice (3rd ed.). Stamford, CT: Appleton & Lange (1996).
41. Gilbert TR, Noar A, Blalock O, Polonsky WH. Change in hemoglobin A1c and quality of life with real-time continuous glucose monitoring use by people with insulin-treated diabetes in the landmark study. *Diabetes Technol Ther.* (2021) 23:S35–39. doi: 10.1089/dia.2020.0666
42. Vigen CLP, Carandang K, Blanchard J, Sequeira PA, Wood JR, Spruijt-Metz D, et al. Psychosocial and behavioral correlates of A1C and quality of life among young adults with diabetes. *Diabetes Educ.* (2018) 44:489–500. doi: 10.1177/0145721718804170
43. Health Center of Ethnic group, Migrant Peoples and Migrant Workers. *Health Promotion and Environmental Management of the Lua Hill Tribe People*. Department of Health Ministry of Public Health. Thailand (2015). Available online at: http://hhdc.anamai.moph.go.th/database/admin/research/file/200814102014.pdf (accessed September 1, 2021).
44. Rogers B. *Occupational and Environmental Health Nursing: Concepts and Practice*. 4th ed. Philadelphia, PA: W.B. Saunders (2003).
45. Phopa Y, Prasertsong C, Durongritichai V. Factors associated health behaviors of uncontrolled dysllpidemia (Thai). *J Royal Thai Army Nurses.* (2018) 16:123–30. Available online at: https://he01.tci-thaijo.org/index.php/JRTAN/article/view/36175 (accessed September 1, 2021).
46. Kaewpan W, Kalampakorn S. Health status and health promoting behaviors among aging workers in Thailand. *J Med Assoc Thai.* (2012) 96:S16–30. Available online at: http://jmatonline.com/index.php/jmat/article/view/2506# (accessed September 1, 2021).
47. Department of Social Development and Welfare. *Highland Communities Within 20 Provinces of Thailand 2002*. Bangkok Thailand; Ministry of Social Development and Human Security (2002). Available online at: http://hhdc.anamai.moph.go.th/ewt_dl_link.php?nid=1707&filename=download (accessed September 1, 2021).
48. Szczepura A. Access to health care for ethnic minority populations. *Postgrad Med J.* (2005) 81:141–7. doi: 10.1136/pgmj.2004.026237
49. Sze M, Butow P, Bell M, Vaccaro L, Dong S, Eisenbruch M, et al. Psycho-oncology co-operative research group culturally and linguistically diverse (CALD) TEAM. Migrant health in cancer: outcome disparities and the determinant role of migrant-specific variables. *Oncologist.* (2015) 20:523–31. doi: 10.1634/theoncologist.2014-0274
50. Chauhan A, Walton M, Manias E, Walpola RL, Seale H, Latanik M, et al. The safety of health care for ethnic minority patients: a systematic review. *Int J Equity Health.* (2020) 19:118. doi: 10.1186/s12939-020-01223-2
51. Clement KC, Suarez-Pierre A, Sebestyen K, Alejo D, DiNatale J, Whitman GJR, et al. Increased glucose variability is associated with major adverse events after coronary artery bypass. *Ann Thorac Surg.* (2019) 108:1307–13. doi: 10.1016/j.athoracsur.2019.06.046
52. Abu Tailakh M, Ishay SY, Awesat J, Poupko L, Sahar G, Novack V. Hemoglobin A1c in patients with diabetes predict long-term mortality following coronary artery surgery. *J Clin Med.* (2021) 10:2739. doi: 10.3390/jcm10122739
53. Gupta R, Deedwania PC, Sharma K, Gupta A, Guptha S, Achari V, et al. Association of educational, occupational and socioeconomic status with cardiovascular risk factors in Asian Indians: a cross-sectional study. *PLoS ONE.* (2012) 7:e44098. doi: 10.1371/journal.pone.0044098
54. Frank AT, Zhao B, Jose PO, Azar KM, Fortmann SP, Palaniappan LP. Racial/ethnic differences in dyslipidemia patterns. *Circulation.* (2014) 129:570–9. doi: 10.1161/CIRCULATIONAHA.113.005757
55. Marmot M, Wilkinson RG. *Social Determinants of Health*. Oxford: Oxford University Press (1999).
56. Starling AP, Umbach DM, Kamel F, Long S, Sandler DP, Hoppin JA. Pesticide use and incident diabetes among wives of farmers in the agricultural health study. *Occup Environ Med.* (2014) 71:629–35. doi: 10.1136/oemed-2013-101659
57. American Diabetes Association (ADA). Standards of medical care in diabetes-2017: summary of revisions. *Diabetes Care*. (2017) 40:S4–5. doi: 10.2337/dc17-S003
58. Kiadaliri AA, Najafi B, Mirmalek-Sani M. Quality of life in people with diabetes: a systematic review of studies in Iran. *J Diabetes Metab Disord.* (2013) 12:54. doi: 10.1186/2251-6581-12-54
59. Lee EH, Lee YW, Moon SH. A structural equation model linking health literacy to self-efficacy, self-care activities, and health-related quality of life in patients with type 2 diabetes. *Asian Nurs Res.* (2016) 10:82–7. doi: 10.1016/j.anr.2016.01.005
60. Wang RH, Wu LC, Hsu HY. A path model of health-related quality of life in type 2 diabetic patients: a cross-sectional study in Taiwan. *J Adv Nurs.* (2011) 67:2658–67. doi: 10.1111/j.1365-2648.2011.05701.x
61. Egede LE, Gebregziabher M, Echols C, Lynch CP. Longitudinal effects of medication nonadherence on glycemic control. *Ann Pharmacother.* (2014) 48:562–70. doi: 10.1177/1060028014526362
62. Kamuhabwa AR, Charles E. Predictors of poor glycemic control in type 2 diabetic patients attending public hospitals in Dar es Salaam. *Drug Healthc Patient Saf.* (2014) 6:155–65. doi: 10.2147/DHPS.S68786
63. World Health Organization. *Programme on Mental Health: WHOQOL Measuring Quality of Life*. Geneva; WHO (1997).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

MINI REVIEW
published: 24 February 2022
doi: 10.3389/fmed.2022.815783

Challenges in Multimorbidity Research: Lessons Learned From the Most Recent Randomized Controlled Trials in Primary Care

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Multimorbidity has received much attention and there is a growing number of original studies. However, randomized controlled trials (RCTs) have failed to demonstrate effectiveness of interventions aimed at improving outcomes for patient with multimorbidity in primary care. The purpose of this article is to synthesize and analyze the most recent RCTs to identify the factors that may have contribute to the success or lack of success in order to draw lessons to inform further development in intervention research. A scoping review was conducted to include current up-to-date state-of-the-art studies in primary care published from 2019. Nine articles reporting on six RCTs studies were included in the review. The findings were mixed, with primary outcomes showing no differences between intervention and control groups in four of the six but differences in secondary outcomes in all six. All studies involved family practice patients but interventions took place at different sites, and the time between the beginning of the intervention and the time of evaluation of outcomes varied across studies. Authors reported issues regarding the need for training of care teams, the roles and composition of the teams, the selection of patients and implementation barriers of the complex interventions in trying contexts with not enough time for the changes required. The randomized controlled design may not be the best evaluation design given the complexity of the interventions, and alternative designs should be considered in which qualitative components are included. Further attention to outcome measures and to equity issues is recommended.

Keywords: multimorbidity, primary care, randomized controlled trials, interventions, review

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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Medicine

Received: *15 November 2021*
Accepted: *31 January 2022*
Published: *24 February 2022*

Citation:
Fortin M, Stewart M, Almirall J and Beaupré P (2022) Challenges in Multimorbidity Research: Lessons Learned From the Most Recent Randomized Controlled Trials in Primary Care. Front. Med. 9:815783. doi: 10.3389/fmed.2022.815783

INTRODUCTION

Multimorbidity, the presence of two or more long-term conditions, has received much attention among decision makers, researchers and clinicians in the recent years (1). Despite a growing number of original studies, randomized trials have failed to demonstrate effectiveness of interventions aimed at improving outcomes for patient with multimorbidity in primary care (2). Most of them have reported neutral effects or mixed results. These studies however offer a valuable source of information to learn from in order to pave the way for future research in this area in primary care. Which are the best interventions to manage these patients? It is a question to which primary care providers are trying to respond. Research is needed to answer it correctly.

The purpose of this article was to synthesize and analyze the most recent randomized trials of interventions aimed at improving outcomes for patients with multimorbidity to identify the factors that may have contributed to the success or lack of success and to inform further developments in intervention research. Special attention will be given to four elements of the intervention: (1) its description and content; (2) the context in which it was deployed; (3) the evaluation design chosen to test the effectiveness, and (4) the intervention's implementation.

METHODS

In order to synthesize and analyze the publications, a scoping review was conducted following the five stage approach suggested by Arksey and O'Malley's (3). We felt that a scoping review was adequate to address our research question. The central research question of this scoping review was: which factors may have contributed to the success or lack of success in randomized trials of interventions aimed at improving outcomes for patients with multimorbidity?

To identify relevant studies, we used a collection of publications on multimorbidity from the International Research Community on Multimorbidity website (4). The reference list of articles on multimorbidity that we call "Library of publications on multimorbidity" is a document that has carefully and gradually been built for more than 10 years by the Research Community which comprises 71 international researchers as contributors. The articles that have been included in the repository over the years come from different sources that include the databases MEDLINE, SCOPUS, and CINAHL, articles found in the reference lists of published papers, and work communicated by colleagues and other authors. In recent years, it has been regularly updated with searches in MEDLINE three times a year. It was quoted as a source of information in a systematic review (5) and in a large study on multimorbidity (6). It is therefore considered a comprehensive collection of articles on the subject but, as in any collection or review, the absence of some articles is possible. At the time of conducting the search, the collection covered articles published until August 2021. For this review, relevant studies were randomized controlled trials (RCTs) of clinical interventions aimed at improving outcomes for patients with multimorbidity and review articles on the same subject. Review articles were used to identify publications that might have escaped our search of randomized trials.

Our scoping review was not intended to be exhaustive, but we wanted to include enough research papers to answer robustly the research question and to analyze the papers in a way that goes beyond the conclusion of a systematic review by reflecting on the process and mechanisms associated with the effect or absence of effect of the individual trials included. Our intention was more exploratory and explanatory. Ultimately we wanted to generate hypotheses for use in future research.

We included in our review current up-to-date state-of-the-art studies published from 2019. We limited to the last 2 years on the premise that the most recent studies must have already integrated some lessons from the previous ones. For the study selection, two authors (JA and PB) independently assessed the eligibility of publications. In the screening process, the title and the abstract were first reviewed and, if necessary, the complete article. To be included in the process of charting the data, studies had to be conducted in primary care and report at least the following elements: a description of the intervention in context, the design of the evaluation including the choice of outcomes and issues related to implementation.

For charting the data, two authors (JA and PB) conducted separately a comprehensive reading of the articles and extracted the data into a template generated for this purpose following the guide of Arskey and O'Malley (3). The template included the following main items which were described under the item heading: intervention characteristics, context, evaluation design and results, implementation issues and other relevant information. Main items within the template were further subdivided into sub items. Findings from each article were represented twice within the template as both authors conducted their analysis independently. Meetings were held to compare and adjust the data extracted from each article and, after reaching agreement, findings were merged. For collating, summarizing and reporting the results, co-interpretation of different elements of interventions was conducted by all authors. Two senior authors (MF and MS) took the lead in synthesizing and reporting the results.

RESULTS

We identified 13 potential articles published since 2019 (**Figure 1**). Seven articles were rejected for not fulfilling the inclusion criteria. Six articles reporting RCTs studies were included in the review. These six articles were considered the "main" articles of the RCTs studies but, while processing the information from the articles, we learned about another three articles related to these six RCTs, and we included them in the review for a total of nine articles. All reviewed articles are shown in **Table 1** grouped by RCT. Summary descriptions of the clinical interventions tested in the included studies are provided in **Table 2**.

The findings of the six studies were mixed, with primary outcomes showing no differences between intervention and control groups in four of the six. The effects that were found in primary outcomes were: in health related quality of life post intervention (12, 14); and number of health problems (14). Positive impacts of interventions were found in secondary outcomes as follows: in occupational satisfaction and self-reported hospital appointments (12); in mental health outcomes for patients who had depression as well as physical health problems (6); self-reported physical activity (7, 13); healthy eating (7); mental health outcomes in the subgroup with $\geq$\$50K Canadian dollars annual income (with authors highlighting the issue of lack of equity of the intervention) (9); and total number of long-term medications (14).

Context

All studies involved primary care patients in affiliation with family practices but interventions took place at different sites,

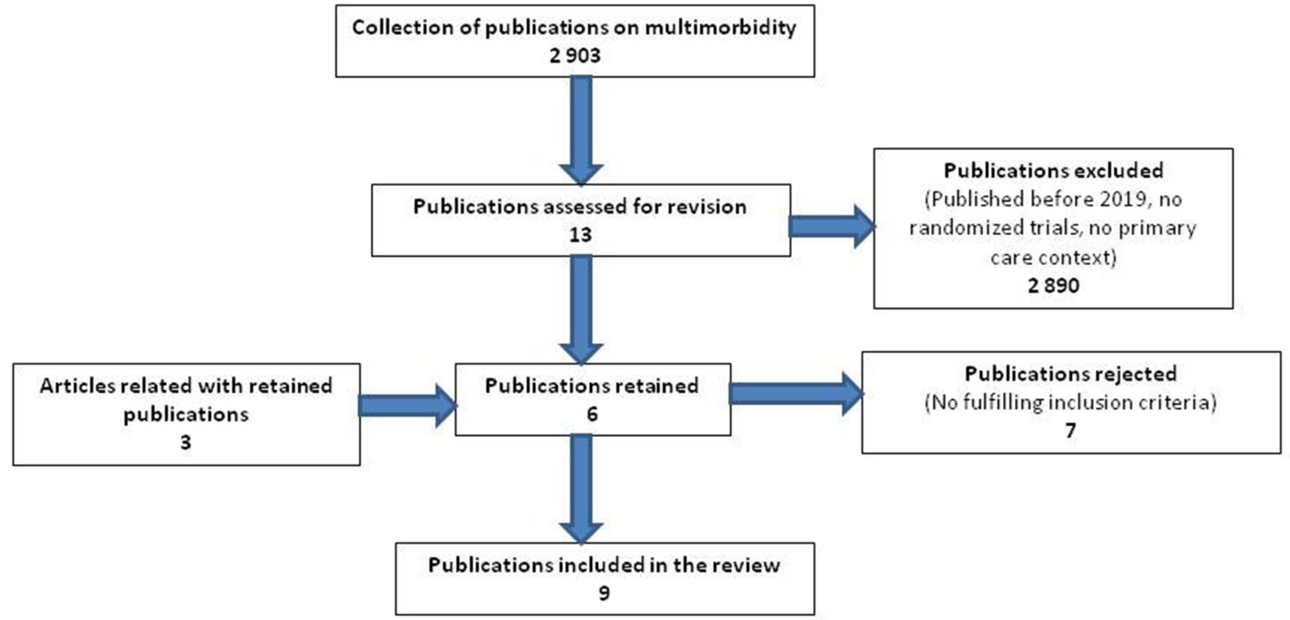

FIGURE 1 | Flow diagram for the selection of publications.

which included the family physician's practice (6, 7), face to face or video meetings (9), patients' home (13), and a center where the intervention was delivered (12). They spanned these countries: Canada (7, 8, 10, 15), the United Kingdom (6, 11), Ireland (12), Finland (13), and the Netherlands (14). The wider health policy contexts showed the following features. Some interventions aligned with interests of the Ministries of Health (15); others arose from the interests of local practitioners (13, 14); one had both influences (9). Among the studies, four (6, 7, 9, 12) described in their report a particular context that could have had some influence in the conduct of the intervention. In Quebec, Canada, which has universal health coverage, there was a major reform of healthcare organizations and governance at the time of the intervention, that may have impeded the deployment of the intervention by slowing the decision processes. Several movements of professionals from one site to another and changes of role among managers also challenged and delayed the implementation. In Ontario, Canada, which also has universal health coverage, there was variable access to interprofessional teams to assist with complex health issues; <1-fourth of the population had access to team-based primary care (9, 10), implying a variety of contexts in which the intervention was implemented. However, the policy context in Ontario supported the roll-out of the intervention because of its focus on high users of the health system (the complex, multimorbid patients). In the United Kingdom, which has universal health coverage, the trial was conducted at a time when many practices were under huge strain and struggling to provide essential care, practices were facing other organizational changes, and several of the practices in the trial were facing problems with recruiting physicians (6, 11). Ireland has a mixed public and private primary healthcare system, with one-third of the population entitled to free primary care based on low income; primary care remains underdeveloped and fragmented (12). In summary, the wider practice and health policy context has had positive and detrimental impacts on the research reviewed.

Evaluation Design

All studies had in common that they were randomized trials. However, the time between the beginning of the intervention and the time of evaluation of outcomes varied across studies. Two studies (7, 9) collected outcome data at baseline and 4 months after the intervention. In one study, outcomes were collected at baseline and 9 and 15 months after recruitment (6). In another, assessments were conducted at baseline, immediately post-intervention at 6 weeks, and after a 6-month follow-up (12). In one of the studies outcome measures were collected at baseline, 3 and 6 months (14). The longest follow-up occurred in a study with assessments at baseline, after 1 and 2-year follow-up (13).

Primary outcomes used in all studies were generic, namely, quality of life (assessed with EuroQol-5 Dimensions; EQ-Visual Analog Scale, EQ-VAS; or the 36-Item Short-Form Health Survey, SF-36) (6, 12–14), health education impact (assessed with the Health Education Impact Questionnaire, heiQ) (7, 9), self-efficacy (assessed with Self-Efficacy for Managing Chronic Diseases, SE-CD) (7, 9), and number of health problems (14). Results in primary outcomes in the studies were neutral, except in one study in which modest improvements were observed in EQ-VAS and the number of health problems (14). Authors suggested that outcome measures aligned neither with goals of the intervention nor patient expectations of the intervention, which authors suggested were mental health, function and

TABLE 1 | Articles of RCTs studies of interventions for patients with multimorbidity in primary care settings included in the review.

References	Country	Control group		Intervention group		Methods		Results of primary outcomes
		Number of patients	**Mean age, y**	**Number of patients**	**Mean age, y**	**Intervention**	**Primary outcomes**†	
Main article: Fortin et al. (7) **Related article:** Ngangue et al. (8)	Canada	140	61.1	144	60.8	Pragmatic randomized controlled trial	heiQ SE-CD	Neutral
Main article: Stewart et al. (9) **Related article:** Pariser et al. (10)	Canada	77	63.1	86	61.9	Pragmatic randomized controlled trial	heiQ SE-CD	Neutral
Main article: Salisbury et al. (6) **Related article:** Salisbury et al. (11)	UK	749	70.7	797	71.0	Pragmatic randomized controlled trial	EQ-5D-5L	Neutral
O'Toole et al. (12)	Ireland	71	65.9	78	65.5	Pragmatic randomized controlled trial	EQ-5D-3L EQ-VAS	Improvement in EQ-VAS in those aged <65 years
Kari et al. (13)	Finland	126	81.4	151	81.0	Randomized controlled trial	SF-36	Neutral
Verdoorn et al. (14)	Netherlands	314	78*	315	80*	Pragmatic randomized controlled trial	EQ-5D-5L EQ-VAS No. health problems	Improvement in EQ-VAS and No. health problems

**Median age. †heiQ, Health Education Impact Questionnaire; SE-CD, Self-Efficacy for Managing Chronic Diseases; EQ-5D, EuroQol-5Dimensions; EQ-VAS, EuroQol Visual Analog Scale; SF-36, 36-Item Short-Form Health Survey.*

TABLE 2 | Description of included studies.

References	Intervention	Change in care delivery	Process goal	Target patients	Setting	Theoritical framework
Fortin et al. (7)	Multifaceted intervention including nurse interview and, consultations with other professionals and individualized care plan.	Professionals were added to existing family medicine teams	To enhance patient self-management	3 or more chronic conditions	7 family medicine groups (FMGs) in Quebec, Canada	Patient Centered Clinical Method (17), Chronic Care Model (16), and Self-management support (18)
Stewart et al. (9)	Multifaceted patient-centered care including a nurse interview at home, a team meeting, a care plan and nurse follow-up	Professionals were added and the team meeting was added	To improve patient engagement in their care and to reduce emergency room visits	3 or more chronic conditions	9 team-based family practices familiar with the intervention in Toronto, Ontario, Canada	Patient Centered Clinical Method (17), Chronic Care Model (16), and Self-management support (18)
Salisbury et al. (6)	Two appointments with a nurse and a named responsible physician, a medication review by a pharmacist, and a collaborative health plan with the patient	Replacing disease-focused reviews of each health condition by a comprehensive 3D multidisciplinary review	To improve continuity, coordination, and efficiency of care	Patients with at least 3 types of chronic conditions	33 practices in England and Scotland	Patient Centered Clinical Method (17), and Chronic Care Model (16)
O'Toole et al. (12)	Professionally-led 6-week group self-management support program	Introducing educational and goal-setting components that included participant interaction and discussion	Self-management support aimed to have a specific focus on function and issues relevant to multimorbidity	2 or more chronic conditions	8 primary care teams in Eastern Ireland	Self-management support (18)
Kari et al. (13)	At-home patient interviews, an interprofessional team meetings (nurse, pharmacist and genral practitionner) to create a care plan	To include in-depth clinical medication and health reviews which are not present within the existing health system	To encourage patient active role in collaborative goal setting and empower them to live well with long-term conditions	Multimorbid patients with 7 or more prescribed medicines	Primary care settings in Tornio, Finland	People Centered Care Model (10), and Chronic Care Model (16)
Verdoorn et al. (14)	Clinical medication reviews (CMRs) with the availability of all clinical data and an extensive patient interview	A CMR review focused on personal goals which is not offered to all patients in usual care	Building on patients' health-related goals and preferences	Community-living multimorbid patients with 7 or more long-term medications	35 community pharmacies in the Netherlands	Patient Centered Approach in Clinical Medication Review (8)

feeling validated (9). Studies chose a large number of secondary outcomes which may lead to false positive findings (6, 11).

Some studies used mixed-methods, triangulating a quantitative trial with views of patients, family members and health professionals (6, 7, 9). Two studies also included in their evaluation a qualitative assessment of patients' experience (7, 9).

Selection of patients was an issue in all studies. There were different methods for the selection of patients and for applying inclusion and exclusion criteria before randomization. Four of the studies reported that patients were referred by the family physicians based on their clinical judgement (6, 7, 9, 12). The authors of these studies discussed some limitations associated with this method of selecting patients: (1) as the recruitment was under the control of the primary care providers within the practices, some may have selected patients with lower needs for an intervention on the basis of their motivation leading to baseline scores with little room for improvement (7); (2) only a third of invited patients agreed to participate and this raises the possibility of recruitment bias (6, 11); (3) the sample was unrepresentative of the general population (9). In one study (13), patients were selected at random from a health center database; the response rate was 39%, and this probably led to a selection bias toward older people more willing and able to participate. Another study recognized its failure to include the needy, the avoiders and those with low health literacy (14) implying a lack of equity in the conduct of the research; and (4) the original power calculation was revised downwards because of recruitment difficulties (12).

The comparison group to the intervention was typically usual care. Authors noted that usual care may have been particularly strong, including strategies in the intervention and showing positive effects on outcome (6, 9). Blinding was not possible in these trials with the possibility of professional contamination in small town locations (13) and patient susceptibility to change behavior due to exposure to the consent process (14).

Implementation of the Intervention

All authors reported some issues with implementation of the interventions. Fortin et al. used formal training at the beginning but found obstacles such as the complexity of the intervention, the health system reorganization in the province at the time of the intervention, the internal organization of the practices, the lack of compatibility of the intervention principles with some family physicians' philosophy and practice (7, 8).

Stewart et al. reported that patients appreciated receiving a summary of the recommendations from the consultation; however, having ≥6 providers in the case conference was linked to negative outcomes (9). Also, having ≥3 h (vs. fewer hours) of nurse follow-up work within 4 months of the case conference was related to statistically significantly less improvement in primary outcomes from baseline to 4-month follow-up (9). These findings imply that the intervention was varied in its implementation and that these variations made a difference to outcomes.

Salisbury et al. described that the staff was familiar with existing disease-specific templates that they had used for many years, and some found it difficult to adapt to the new 3D template; their unfamiliarity with the template required more of their attention and influenced their consultation style in a way which mitigated against the patient-centered approach intended (6). They also mentioned that in some practices, not all general practitioners agreed to take part in the trial, and some participating patients had to consult a different doctor from the one they usually saw, affecting the continuity of care for some patients (6). Although three-quarters of patients received at least one 3D review during the 15-month follow-up period, only about half received the two reviews that were planned (6). Furthermore, an important issue that affected implementation was the wide variation between practices in the roles and competencies of the practice nurses. Some nurses were trained to work only with specific long-term conditions and did not feel confident working with patients with other conditions (6).

Kari et al. discussed that implementation of the people-centered care model into primary care organizations (in order to provide comprehensive, preventive and demand-oriented care for patients), required a shift from providing disease-specific care to people-centered care, which may have been time-consuming (13). Also, probably, it would have been necessary to better identify patients most likely to benefit from this kind of care intervention. They noted that usual care may also have changed during the trial (13).

Verdoorn et al. (14) mentioned the inclusion of training at all stages. They also raised the possibility that patients in the control group could have been prompted to consider obtaining advice about their medication, health problems, or goals by participating in this study (14). In addition, they discussed that when unrealistic or unsolvable goals are proposed by the patient, this may have led to disappointment and a reduction in quality of life. One cannot exclude the possibility that some of the goals may not have been realistic (14). It remained difficult to demonstrate which part of the complex intervention contributed to the observed positive effects (14).

Synthesis of Results

A synthesis of these six studies revealed four key issues that facilitated implementation or were barriers. First, the importance of training at the beginning of the project was stressed (7) as was the need for ongoing further education (14). Second, the roles and composition of the interdisciplinary care team can be a facilitator to implementation or a barrier. The opportunity for team members to focus on their roles was seen as an asset (7). The wide variation in team members' roles from one practice to another impeded the smooth roll-out of the intervention (6) and a large number of professionals was a detriment to effectiveness (9).

Third, the interventions were complex but personalized which was an asset (14). The personalized aspect aligned with provider values and the coordination in combination with the personalized aspect was appreciated by patients (9). The integration of care models [such as the Chronic Care Model (16) and the Patient-Centered Clinical Method (17)] with specific therapeutic approaches [such as self-management (18) and motivational interviewing (19)] was considered a facilitator of successful implementation (7). However, on the other hand, the new way of practice contrasted with the traditional disease-specific guidelines and that contrast was a potential barrier to speedy change (6).

Finally, several reasons were proposed for inadequate intervention delivery. The context of widespread stress and change in the health care system affected intervention fidelity (6, 7). The short duration of time to mount the intervention and change primary care practice (typically ∼4 months) may have been a barrier (6, 7). Health care professionals' values and current practices were an asset if they aligned with the intervention (7, 9) but were not an asset to the intervention roll-out if they conflicted with the intervention, e.g., Salisbury (6) posited that the intervention may have interfered with the previous patient-centered approach of the health professionals and Verdoorn (14) posited that intervention goals may have been considered "risky" and "unrealistic."

DISCUSSION

In this review, we sought to identify the factors that may have contributed to the success or lack of success of trials for multimorbidity in primary care in order to draw lessons and to inform further developments in intervention research. The field is indeed heterogeneous, and our intention was humble in writing this paper. Our contribution is to stimulate the conversation and generate new ideas about the research and about the clinical care. The six studies included represent a variety of interventions with enough substance to inspire such conversation.

All multifaceted interdisciplinary interventions involved multiple primary care providers from various disciplines. Evidence supporting such interventions for multimorbidity is scarce, as typically, interventions have shown mixed results (2). But interdisciplinary interventions are in line with the most recent recommendations from NICE (20). However, building such interventions requires close discussion with high level decision makers in order to keep the intervention aligned with policies already in place in order to prepare for scaling-up effective interventions. There are ongoing primary care reforms in many jurisdictions focusing on interdisciplinary work on which it is possible to capitalize and test innovative interventions while embracing the reform.

Implementation and sustainability of intervention deemed to be effective represent a challenge especially when the intervention implies a change in care delivery by a team. We already discussed the importance of aligning the intervention to the policy context to avoid navigating countercurrents. Organizing teamwork in primary care goes beyond having different disciplines working in the same environment. In a previous paper, we suggested an evidence-based framework for effective interventions for multimorbidity in primary care (Patient centered Innovations for Persons with Multimorbidity Framework for effective intervention or PACE in MM Framework) (15). The framework encompasses five components: (1) shared philosophy among the team members; (2) a special attention to the internal relations among the team members including the patient; (3) building on existing external relations within the health care system and the community; (4) professional training of the team members in order to develop integrated care skills; and (5) probably the most important component of enhanced relationship with patients. This framework supplements the classical Chronic Care Model, that was inspirational for most of the studies included in this scoping review, by identifying the processes to create productive interactions between the providers and the patient leading to improve outcomes. It was not clear if all components of this evidence-based framework were enacted in the studies included in this review, but future interventions should consider using this framework in addition to those guiding the specific interventions.

Randomized controlled trials are classically considered the best evaluation design for testing interventions in medical sciences (21). Given the complexity of the interventions within an already complex primary care system, is RCT the best design or is it somewhat limited? Is an RCT appropriate for an intervention that varies from one patient to the other, as opposed to a standard clinical trial looking at a simple intervention for example testing the efficacy of a drug in a specific condition? Most RCT focus on disease-oriented outcomes which is not appropriate in interventions for multimorbidity. In this review, Quality of Life (QofL) was a primary outcome in most studies. This really make sense given the strong association between multimorbidity and low QofL (22). But are the measures of QofL enough sensitive to change to be useful in trial on multimorbidity? This is questionable particularly in trials that are limited in time (6). Authors have suggested a core set of outcomes for interventions in multimorbidity (23). The majority of the studies, included in our review, have used some of these outcomes and reported neutral effects. It is possible that health interventions generate benefits that fall outside the outcomes measured and therefore were not captured in the studies. Qualitative assessment conducted in some of the studies may support this hypothesis (7, 9). New measures are needed to reflect outcomes that are important to patients and sensitive to change to detect benefit from interventions in primary care (6, 7, 24); authors suggest that these include patient function and mental health. Even when the goals of patient are elicited, which is expected for patient-centered interventions, there are no means to ensure that this will be captured in the outcomes given that all patients do not share the same goals. Valid measures of goal attainment to be used on an individual basis are lacking.

A quasi-experimental design with repeated measures where the patients are their own controls may offer an interesting alternative that is more inclusive and a robust enough design that could be included in a systematic review (25). Stepped wedge design could also be considered if the intervention cannot be implemented in all practices at the same time and a control group is not acceptable (25). Researchers have expanded their evaluation designs to include other components in addition to the RCT like qualitative research, process evaluation that could generate explanations and new hypotheses (6, 7, 9).

Selection of patients is of special concern and is prone to bias. Patients who could have most to gain from interventions may be under-represented in participants particularly if the recruitment involves a decision from the primary care provider. Offering patients with high needs to take the risk of not receiving an innovative intervention (thought to be effective) if randomized to the control group, may explain some reluctance from the primary care providers to even offer the intervention. This could explain the low rate of referral or participation in some studies (6, 7, 14). However, this bias also has implications for equity in multimorbidity research.

Conducting a trial in primary care where natural patient-centered interventions are already occurring may reduce the chance of obtaining an effect. It may be that the usual care is already good enough and that enhancing the care may not result in better outcomes. Some of the trials where the baseline evaluation showed already acceptable measures may support this potential explanation (6, 7, 12). None of the studies included in this review specifically included patients with low scores of any outcome measured at baseline.

Implementing changes and conducting pragmatic trial in real world environment may be a bit disruptive for the primary care teams as shown in studies where the fidelity of the intervention was questioned (6, 7). Primary care practices are complex organizations where things could get out of control easily in many circumstances: sick leave of primary care providers, outbreak of infectious diseases, changes in governance, or just the chaos of normal days working with sick peoples with high needs. Studies in which the practices which had contributed to the intervention seemed to have fewer implementation issues than when the intervention was suggested by researchers or others outside the practices.

The question of equity is of special concern. Two indications of lack of equity deserve attention: one in the effect of the intervention only for higher income groups of patients (9); and a second in the selection of patients by inadvertently failing to include the needy, the avoiders and those with low health literacy (14). Our interventions and our research must thoughtfully address equity issues raised here.

This scoping review has limitations. The search was limited to the most recent years which, while a limitation, could also be considered an asset as these recent studies were seen to have learned from the previous ones and represent the most current state-of-the-art studies. The goal of this scoping review was never to be exhaustive in the identification of studies but to include enough papers to be able to make suggestions for the future of interventional research on multimorbidity in primary care. There were enough commonalities among the studies to support this idea.

CONCLUSION

This scoping review identified several lessons on planning for future intervention studies on multimorbidity in primary care. Interdisciplinary teams as the basis for most interventions, while recommended, may need more support by policy and practice leadership to be successfully deployed and evaluated. The randomized controlled design may not be the best evaluation design given the complexity of the interventions; alternative designs should be considered in which qualitative components are included. Special attention should be given to outcome measures ensuring that they are better aligned to patient goals. Selection of patients prone to bias toward the less needy, hampers the ability to document effectiveness and raises question about equity in research. Implementation of the interventions needs special attention and enough time to gel.

AUTHOR CONTRIBUTIONS

MF and MS contributed to conception, design of the study, and took the lead in synthesizing and reporting the results. JA and PB conducted the study selection and extracted the data. JA wrote the first draft of the manuscript and co-interpretation of different elements of studies was conducted by all authors. All authors contributed to the article and approved the submitted version.

FUNDING

Funding for this review was from the Patient-Centered Innovations for Persons with Multimorbidity in Primary Care, Canadian Institute of Health Research Community-based Signature Initiative. MF was funded by the Research Chair on Chronic Diseases in Primary Care, Université de Sherbrooke, (2007–2020). MS was funded by the Dr. Brian W. Gilbert Canada Research Chair (Tier 1) in Primary Health Care Research (2003–2017).

REFERENCES

1. Whitty CJM, MacEwen C, Goddard A, Alderson D, Marshall M, Calderwood C, et al. Rising to the challenge of multimorbidity. *BMJ.* (2020) 368:l6964. doi: 10.1136/bmj.l6964
2. Smith SM, Wallace E, Clyne B, Boland F, Fortin M. Interventions for improving outcomes in patients with multimorbidity in primary care and community setting: a systematic review. *Syst Rev.* (2021) 10:271. doi: 10.1186/s13643-021-01817-z
3. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Social Res Methodol.* (2005) 8:19–32. doi: 10.1080/1364557032000119616
4. *International Research Community on Multimorbidity*. Available online at: https://crmcspl-blog.recherche.usherbrooke.ca/ (accessed November 3, 2021).
5. Smith SM, Wallace E, O'Dowd T, Fortin M. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *Cochrane Database Syst Rev.* (2016) 3:CD006560. doi: 10.1002/14651858.CD006560.pub3
6. Salisbury C, Man MS, Chaplin K, Mann C, Bower P, Brookes S, et al. A patient-centred intervention to improve the management of multimorbidity in general practice: the 3D RCT. *Health Serv Deliv Res.* (2019) 7. doi: 10.3310/hsdr07050
7. Fortin M, Stewart M, Ngangue P, Almirall J, Belanger M, Brown JB, et al. Scaling up patient-centered interdisciplinary care for multimorbidity: a pragmatic mixed-methods randomized controlled trial. *Ann Fam Med.* (2021) 19:126–34. doi: 10.1370/afm.2650
8. Ngangue P, Brown JB, Forgues C, Ag Ahmed MA, Nguyen TN, Sasseville M, et al. Evaluating the implementation of interdisciplinary patient-centred care

intervention for people with multimorbidity in primary care: a qualitative study. *BMJ Open.* (2021) 11:e046914. doi: 10.1136/bmjopen-2020-046914

9. Stewart M, Fortin M, Brown JB, Ryan BL, Pariser P, Charles J, et al. Patient-centred innovation for multimorbidity care: a mixed-methods, randomised trial and qualitative study of the patients' experience. *Br J Gen Pract.* (2021) 71:e320–30. doi: 10.3399/bjgp21X714293
10. Pariser P, Pham TT, Brown JB, Stewart M, Charles J. Connecting people with multimorbidity to interprofessional teams using telemedicine. *Ann Fam Med.* (2019) 17(Suppl. 1):S57–62. doi: 10.1370/afm.2379
11. Salisbury C, Man MS, Bower P, Guthrie B, Chaplin K, Gaunt DM, et al. Management of multimorbidity using a patient-centred care model: a pragmatic cluster-randomised trial of the 3D approach. *Lancet.* (2018) 392:41–50. doi: 10.1016/S0140-6736(18)31308-4
12. O'Toole L, Connolly D, Boland F, Smith SM. Effect of the OPTIMAL programme on self-management of multimorbidity in primary care: a randomised controlled trial. *Br J Gen Pract.* (2021) 71:e303–e11. doi: 10.3399/bjgp20X714185
13. Kari H, Aijo-Jensen N, Kortejarvi H, Ronkainen J, Yliperttula M, Laaksonen R, et al. Effectiveness and cost-effectiveness of a people-centred care model for community-living older people versus usual care horizontal line a randomised controlled trial. *Res Social Adm Pharm.* (2021). doi: 10.1016/j.sapharm.2021.07.025. [Epub ahead of print].
14. Verdoorn S, Kwint HF, Blom JW, Gussekloo J, Bouvy ML. Effects of a clinical medication review focused on personal goals, quality of life, and health problems in older persons with polypharmacy: a randomised controlled trial (DREAMeR-study). *PLoS Med.* (2019) 16:e1002798. doi: 10.1371/journal.pmed.1002798
15. Fortin M, Stewart M. Implementing patient-centred integrated care for multiple chronic conditions: evidence-informed framework. *Can Fam Physician.* (2021) 67:235–8. doi: 10.46747/cfp.6704235
16. Wagner EH, Austin BT, Von Korff M. Improving outcomes in chronic illness. *Manag Care Q.* (1996) 4:12–25.
17. Stewart MA, Brown JB, Weston WW, McWhinney IR, McWilliam CL, Freeman TR. *Patient-Centered Medicine: Transforming the Clinical Method.* 3e ed. Cornwall: Radcliffe Medical Press Ltd (2013).
18. Lorig KR, Holman H. Self-management education: history, definition, outcomes, and mechanisms. *Ann Behav Med.* (2003) 26:1–7. doi: 10.1207/S15324796ABM2601_01
19. Resnicow K, McMaster F. Motivational interviewing: moving from why to how with autonomy support. *Int J Behav Nutr Phys Act.* (2012) 9:19. doi: 10.1186/1479-5868-9-19
20. Kernick D, Chew-Graham CA, O'Flynn N. Clinical assessment and management of multimorbidity: NICE guideline. *Br J Gen Pract.* (2017) 67:235–6. doi: 10.3399/bjgp17X690857
21. Oakley A, Strange V, Bonell C, Allen E, Stephenson J, Team RS. Process evaluation in randomised controlled trials of complex interventions. *BMJ.* (2006) 332:413–6. doi: 10.1136/bmj.332.7538.413
22. Makovski TT, Le Coroller G, Putrik P, Choi YH, Zeegers MP, Stranges S, et al. Role of clinical, functional and social factors in the association between multimorbidity and quality of life: findings from the survey of health, ageing and retirement in Europe (SHARE). *PLoS ONE.* (2020) 15:e0240024. doi: 10.1371/journal.pone.0240024
23. Smith SM, Wallace E, Salisbury C, Sasseville M, Bayliss E, Fortin M. A core outcome set for multimorbidity research (COSmm). *Ann Fam Med.* (2018) 16:132–8. doi: 10.1370/afm.2178
24. Sasseville M, Chouinard MC, Fortin M. Evaluating the content of a patient-reported outcome measure for people with multimorbidity: a Delphi consensus. *Qual Life Res.* (2021) 30:2951–60. doi: 10.1007/s11136-021-02888-0
25. Smith SM, Bayliss EA, Mercer SW, Gunn J, Vestergaard M, Wyke S, et al. How to design and evaluate interventions to improve outcomes for patients with multimorbidity. *J Comorb.* (2013) 3:10–7. doi: 10.15256/joc.2013.3.21

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

ORIGINAL RESEARCH
published: 28 February 2022
doi: 10.3389/fpubh.2022.810216

A Mixed-Method Analysis of Inequalities Associated With Adverse Sexual and Reproductive Health Outcomes and the Requisite Interventions Among Young Women in Durban Informal Settlements, South Africa

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OPEN ACCESS

Edited by:
Arch Mainous,
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Reviewed by:
Larry K. Olsen,
Logan University, United States
Robert Drury,
ReThink Health, United States

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Specialty section:
This article was submitted to
Family Medicine and Primary Care,
a section of the journal
Frontiers in Public Health

Received: *06 November 2021*
Accepted: *03 February 2022*
Published: *28 February 2022*

Citation:
Bolarinwa OA and Boikhutso T (2022)
A Mixed-Method Analysis of Inequalities Associated With Adverse Sexual and Reproductive Health Outcomes and the Requisite Interventions Among Young Women in Durban Informal Settlements, South Africa.
Front. Public Health 10:810216.
doi: 10.3389/fpubh.2022.810216

Background: Over the years, positive sexual and reproductive health (SRH) outcomes have been made possible by a series of policies such as the Sustainable Development Goals, targeted toward different aspects of young women's SRH needs. Nevertheless, inequalities in the levels and trends of adverse SRH outcomes still exist in sub-Saharan Africa (SSA), including South Africa. Thus, this study examines the inequalities associated with adverse SRH outcomes among young women in Durban informal settlements, South Africa, using a mixed-method analysis and suggested requisite interventions to reduce or eliminate the disparity.

Methods: A mixed-method sequential explanatory design was used to address the research question. First, a quantitative cross-sectional survey was conducted among 547 young women aged 18 to 24 years in four informal settlements in Durban, South Africa, between April and July 2021. Thereafter, twenty (20) key informant interviews were conducted among different participants but with the same study characteristics. The study's outcome variable was adverse SRH outcomes, including HIV, STIs and unintended pregnancy, while the independent variable was inequality. The quantitative analysis employed binary and multivariable analysis to determine the association between the outcome and explanatory variables, using an alpha level of $p < 0.05$ to determine significance, while the qualitative analysis was done thematically.

Results: At the quantitative level, the prevalence of adverse SRH outcomes among young women dwelling in Durban informal settlements was 82.45%, 90.86% and 81.90% for STIs, HIV and unintended pregnancy, respectively. The adjusted odds ratio showed that young women who ever discussed sexual matters with their parents had a lower likelihood of reporting having STIs [aOR = 0.20; 95% (CI = 0.15–1.01)], HIV [aOR = 0.20; 95% (CI = 0.15–1.01)] and unintended pregnancy [aOR = 0.20; 95% (CI = 0.15–1.01)] compared to young women who never had a sexual discussion with their parents. Almost all the key informant interview participants shared the same perspective and proffered possible solutions in the qualitative results.

Conclusion: There are disparities in the factors associated with adverse SRH outcomes in Durban's informal settlements. Healthcare proximity, child support grants, cigarette smoking, alcohol consumption, polygamous family structures and gender based violence were associated with higher odds of reporting adverse SRH outcomes.

Keywords: mixed-method analysis, inequality, adverse sexual and reproductive health outcomes, informal settlements, South Africa

BACKGROUND

Sub-Saharan Africa (SSA) has made significant progress in sexual and reproductive health (SRH) outcomes among adolescents and young women over the last few years. Evidence has shown that contraceptive prevalence among single young women (i.e., 15–24 years old) increased by 10%, reflecting an increase from 23% in 1996–2000 to 33% in 2011–2015 (1). In addition, there has been a substantial decline in child marriage incidence across the region (2). Melesse et al. (3) also argued that the HIV epidemic among young people appears to be stalled in most SSA countries, although this is not universal. Positive SRH outcomes over the years have been made possible by a series of policies such as the International Conference on Population and Development's Programme of Action (ICPD-PoA), the Millennium Development Goals (MDGs) and the Sustainable Development Goals (SDGs), targeted toward a different aspect of young women's SRH needs (4).

Nevertheless, there are still inequalities in the levels and trends of adverse SRH outcomes in SSA. For instance, while the highest rate of child marriages is reported in West African countries, the burden of HIV infections abounds in Southern African countries (5, 6), thus raising research interest in exploring the inequalities in SRH outcomes in SSA.

It is important to note that inequalities in SRH outcomes exist at the regional level and within the individual country level. In this study, the focus is centered on informal settlements in South Africa and the inequalities in SRH outcomes in these settlements. Generally, SRH outcomes in South Africa are not homogeneous. The country is overwhelmed with HIV infections and remains the global epicenter of the HIV pandemic (7). Moreover, the 2016 South Africa Demographic and Health Survey (SADHS) revealed that most women aged <22 years had unwanted pregnancies (8). Similarly, Haffejee et al. (9) also reported that the prevalence of unintended pregnancies in South Africa stood at 63%. This shows the heterogeneity in SRH outcomes among young women in South Africa.

Informal settlements in South Africa are continuously growing, with one out-of-seven households in South Africa living in informal settlements (10). Most informal settlements are characterized by high levels of poverty and relative deprivation, with women who find themselves in such settlements being at high risk of adverse SRH outcomes, including HIV infection and STIs, as well as unintended pregnancies (11, 12). However, it is important to note that adverse SRH outcomes are not homogenous within informal settlements. Some young women in informal settlements are more likely than others to have adverse SRH outcomes. For instance, a study in two informal settlements in Nairobi, Kenya, showed that adolescent girls and young women (AGYW) who experienced some form of sexual and gender-based violence or lacked parental support were most likely to report having unintended pregnancies (12). This is consistent with another study conducted in Malawi that also revealed that young women in informal settlements are at high risk of unintended pregnancies (13).

Since 2015, South Africa government and United Nations (UN) member states have signed the 17 SDGs. The SDGs propose to leave no one behind in any of the 17 SDG targets (3). It is imperative to identify and understand the inequalities in term of adverse SRH outcomes (i.e., HIV infection, STIs and unintended pregnancies). However, this subject has not received the attention it requires in South Africa, especially in informal settlements within the country. The question remains: to what extent do inequalities relating to contextual factors, social inequality and parental connectedness influence adverse SRH outcomes? And what are the required social and behavioral interventions to reduce the inequality of adverse SRH outcomes among young women in Durban informal settlements, South Africa? To address these questions, the current study explores adverse SRH outcomes inequality among young women in Durban informal settlements, South Africa, while suggesting requisite social and behavioral interventions to reduce the disparity.

METHODS

Study Population and Research Design

This study was conducted in four informal settlements in Durban, eThekwini Municipality, KwaZulu-Natal. Durban is the third-most populous city in South Africa with over three million residents, and it is the largest city in KwaZulu-Natal, South Africa. Located on the east coast of South Africa, Durban is the busiest port in the country (14). In the KwaZulu-Natal province,

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Abbreviations: AGYW, Adolescent girls and young women; aOR, Adjusted odds ratio; cOR, crude odds ratio; GBV, Gender-based violence; HIV, Human immunodeficiency virus; ICPD-PoA, International Conference on Population and Development's Programme of Action; SDG, Sustainable development goal; SRH, Sexual and Reproductive Health; STIs, Sexually transmitted infections; SSA, Sub-Saharan Africa; MDGs, Millennium Development Goals; SADHS, South Africa Demographic and Health Survey; UN, United Nations.

about 239,000 households live in informal settlements. Moreover, over 500 informal settlements are in the eThekwini District, with 20 informal settlements in Durban (15). The study setting was purposively chosen because of available evidence on the high prevalence of adverse SRH outcomes, including STIs, HIV and unintended pregnancy, in KwaZulu-Natal (16).

A mixed-method sequential explanatory design was used to address the research question. First, a quantitative cross-sectional survey was conducted in four informal settlements in Durban in the eThekwini Municipality of the KwaZulu-Natal province, South Africa. After that, key informant interviews were conducted among the same category of respondents but with different participants in order to seek solutions to the SRH outcomes inequalities facing their age group dwelling in informal settlements (17). Living in urban slums or informal settlements has been reported as one of the factors associated with limited access to SRH services (18), with several adverse SRH outcomes being reportedly high among young women residing in informal settlements in South Africa (19–21).

Umgudulu and Banana City informal settlements have 560 and 455 households, respectively, with single-room houses, alongside shacks. These settlements are located 3 km apart from each other, which is ∼15 min' drive to the center of Durban. Basic amenities are lacking, and there are no inside toilets or playgrounds for children. The Quarry Road and New Germany informal settlements have 1,200 and 980 households, respectively. They are both located along the main road and are significantly larger than the Umgudulu and Banana City informal settlements in landmass. Pathways are not well-defined or tarred, with the central toilet and laundry washing system being practiced with the shack housing clustered together.

Quantitative Data Collection and Sample Size Determination

Two research assistants with at least a college certificate were recruited at each informal settlement for this study, these two research assistants were trained explicitly for 1 week on a self-administered questionnaire using the Android version of the Open Data Kit (ODK) mobile application. They were also briefed on the study's objectives. The research assistants were fluent in the widely spoken local language (isiZulu), and all data collection was done under the supervision of the principal investigator. The ODK mobile application simultaneously allows multi-users, ensures privacy, and collects data (22). Android mobile telephones were given to the research assistants by the principal investigator, and these telephones were retrieved after the daily debriefing sessions. The respondents' responses were archived to the server database daily and were deleted from the mobile device before returning the telephone to the research assistants the following day to continue the data collection until the last day of the survey. The data collection was conducted between April–July 2021.

A multi-stage sampling method was employed in the study settings (23). First, all informal settlements in Durban were counted and listed. Thereafter, all the informal settlements' names were written on a different piece of paper, and a simple random sampling technique was used in selecting four informal settlements through ballot (24). At the end of the exercise, the four informal settlements selected were Banana City, Umgudulu, New Germany and Quarry Road.

The researchers employed a systematic random sampling method in selecting the study participants. A list of all shacks/houses was accessed at each study setting through the community leader. Each shack is usually occupied by one household. All households were listed, and the first household was automatically selected as the first eligible household, followed by the next two households, i.e., $k = 2$ (This is derived by dividing the minimum number of households in a settlement by the desired sample size [i.e. = 455/200]). All eligible young women aged 18–24 years in all the selected households in each informal settlement were interviewed (25).

The minimum sample size should be 420 participants, using Yamane's formula sample size estimation technique at a ±5% precision level and a 95% confidence level (26). However, the study sample size was increased to 800 participants to enable the authors to account for non-response or oversampling errors (27, 28). After considering respondents who are sexually active in line with the study's objective, 547 potential respondents were eligible for this study. As such, the data analysis for this study was limited to the 547 eligible respondents, with 178, 120, 104, 145 respondents from Quarry Road, New Germany, Umgudulu and Banana City, respectively. Prior to data collection, the data collection instrument (a questionnaire scripted on the ODK mobile application) was administered to 20 young women between the ages of 18–24 years old residing in Durban and purposively chosen for the pilot survey/pre-test exercise to validate the instrument.

Quantitative Analysis and Measures

Outcome Variable

The study outcome variable was adverse SRH outcomes measured by HIV, STIs, and unintended pregnancy (29–31). To determine if a participant has ever had HIV/STIs or unintended pregnancy, questions about whether the respondent has ever used medications to treat STIs/tested positive for HIV or whether the respondent has ever had an unintended pregnancy were asked. A binary response of "No" or "Yes" was used to categorize participants' responses. To ensure that the responses supplied by the respondents were correct, a retrospective question was asked as a follow-up question during the interview.

Independent Variables

The key independent variables were inequalities derived from contextual factors, including GBV; proximity to a healthcare facility; social inequalities including child support grants and the household or relative wealth index; patterns of behavior, including alcohol intake and smoking of cigarettes; parental connectedness, including parental living arrangements and the discussion of sexual matters with the parent. Other included explanatory variables were family structure, place of settlement, and ethnicity.

GBV was determined by asking if the respondent had ever experienced intimate partner violence, household violence, or any other physical violence exhibited by someone else (32); while healthcare facility proximity was determined by asking the distance of the closest government-owned healthcare facility to the participant's informal settlement (33). GBV was categorized as binary responses "No" or "Yes," while responses for healthcare facility proximity were category as "<5 km", "5 to 9 km," "10 to 19 km and 20 km and above" (34, 35). The child support grant was determined by asking if the respondent currently receives any grant support toward the upkeep of her child(ren) (36), while the household/relative wealth index was determined by using the household items available in each participant household. The index was constructed in line with demographic health survey (DHS) metrics by assigning a generic number of "1" to each household item such as "electricity, radio, television, mobile telephone, non-mobile telephone, refrigerator, cable TV, generating set, air conditioner, computer, electric iron, fan" listed on the questionnaire. If a respondent did not have any of the listed household items, then it was coded "0." Based on the household items each respondent had, the researchers then re-categorized the response as "Lower quintile" "Middle quintile" and "Upper quintile" (37). Child support grant responses were categorized as binary "No" or "Yes," while pattern of behavior was measured by whether the respondent ever drinks alcohol and ever smokes cigarettes, while parental connectedness was measured by whether the respondent ever had a discussion about sexual matters with either of the parents, and whether the respondent was currently living with either of the parents or somewhere else. All the responses for the four variables were categorized in a binary form of "No" or "Yes" (38–41).

Other independent variables included in this study were family type/structure, place of settlement and ethnic group. Family type/structure responses were categorized as either "Monogamous" or "Polygamous." The place of settlement was the respondent's current informal settlement name, which could be either "Umgudulu," "Banana City," "Quarry Road," or "New Germany." This was followed by ethnic groups, categorized as "isiZulu," "Xhosa," "Sesotho," and "Siswati." All selected covariates were based on existing literature (19, 42).

Quantitative Statistical Analysis

The analysis started with all the 800 young women interviewed. However, after dropping 253 respondents who were not sexually active, the sample size was reduced to 547 sexually active young women. Therefore, this current study's analysis included 547 sexually active young women. First, descriptive statistics were calculated for all the variables included in this study, followed by a chi-square to test the association between the key independent variables, the covariates and outcome variables. Furthermore, a-two logistic regression models were fitted to determine the likelihood of association between selected inequalities such as GBV; proximity to a healthcare facility; social inequalities; patterns of behavior; and parental connectedness. and other independent variables such as family structure, place of settlement, and ethnicity, and the outcome variable (adverse SRH outcomes). The first model (Model I) is a binary logistic regression model, which is an estimate of unadjusted odds ratios of the association between child grant support, wealth index (social inequalities), covariates and HIV/STIs and unintended pregnancy (adverse SRH outcomes). The second model (Model II) is a multivariable model, which included all the covariates, key independent variables and outcome variables considered in this study. The precision level of Alpha <0.05 was considered statistically significant. The multicollinearity test, which used the variance inflation factor (VIF), revealed no evidence of collinearity among the key independent variables and covariates. All the analyses were carried out using Stata version 17.0 (Stata Corporation, College Station, TX, USA).

Qualitative Interviews

Sample Size and Thematic Analysis

Five key informant interviews were conducted in each informal settlement after the quantitative data collection was analyzed and SRH outcomes inequality was determined. Five participants who did not participate in the quantitative research data collection were interviewed in English from each of the four informal settlements, giving a total of 20 participants who suggested interventions that would reduce or eliminate the SRH outcomes inequality discovered in the quantitative data analysis.

The participants were purposively chosen at random. Furthermore, the only criteria observed were that they must not have participated in the earlier quantitative data collection. The interview lasted 20–30 min per participant. A tape recorder and question guide were used during the interviews, conducted by the principal investigator in a private room. All recorded interviews were transcribed thematically using NVivo software. All participants were assigned a unique reference code that has a combination of their informal settlement name and serial number. These unique reference codes were articulated before each interview (43).

Thematic Analysis followed six steps (familiarization, coding, generating, reviewing, naming, defining, and finally, writing up the data analysis). The audiotaped transcripts from the interviews were transcribed verbatim by the principal investigator, and these were read and validated by the academic supervisor. All coding was carried out by highlighting relevant words using sentences or phrases from the transcripts. Each selected inequality was discussed, and suggested solutions were thematically summarized to tackle the variables associated with the inequality of adverse SRH outcomes among young women in Durban informal settlements. The variables include gender-based violence, healthcare proximity, grant child support, pattern of behavior and parental connectedness. The interview exercise, the reporting and transcription follow the approved Consolidated Criteria for Reporting Qualitative Research (COREQ) (44).

RESULTS

Quantitative Analysis

Descriptive Statistics and Tests of Chi-Square of the Independent and Dependent Variables

The prevalence of adverse SRH outcomes among young women dwelling in Durban informal settlements was 82.45, 90.86, and 81.90% for STIs, HIV and unintended pregnancy, respectively.

TABLE 1 | Distribution of selected inequalities and adverse sexual and reproductive health outcomes of young women in Durban informal settlements.

Variables $n = 547$	**Frequency**	**Percentage**	**Adverse sexual and reproductive health outcomes**					
Inequalities			**STIs**		**HIV**		**Unintended pregnancy**	
			No	**Yes**	**No**	**Yes**	**No**	**Yes**
Contextual factors								
Experienced GBV			p (χ^2) <0.001		p (χ^2) <0.001		p (χ^2) <0.001	
No	404	73.86	90.59	9.41	95.79	90.59	9.41	95.79
Yes	143	26.14	59.44	40.56	76.92	59.44	40.56	76.92
Healthcare proximity			p (χ^2) <0.001		p (χ^2) <0.001		p (χ^2) <0.001	
Less than 5 km	310	56.67	91.94	8.06	98.39	91.94	8.06	98.39
5 to 9 km	208	38.03	68.75	31.25	79.33	68.75	31.25	79.33
10 to 19 km	24	4.39	83.33	16.67	95.83	83.33	16.67	95.83
20 km and above	5	0.91	60.00	40.00	80.00	20.00	80.00	20.00
Social inequalities								
Child support grant			p (χ^2) <0.001		p (χ^2) <0.001		p (χ^2) <0.001	
No	439	80.26	95.44	4.56	94.76	95.44	4.56	94.76
Yes	108	19.74	29.63	70.37	75.00	29.63	70.37	75.00
Wealth index			p (χ^2) <0.001		p (χ^2) <0.001		p (χ^2) <0.001	
Lower quintile	310	56.67	88.52	11.48	93.39	88.52	11.48	93.39
Middle quintile	208	38.03	80.43	19.57	89.32	80.43	19.57	89.32
Upper quintile	24	4.39	75.90	24.10	89.16	75.90	24.10	89.16
Pattern of behavior								
Drink alcohol			p (χ^2) <0.01		p (χ^2) <0.01		p (χ^2) <0.05	
No	362	66.18	85.64	14.36	93.37	85.64	14.36	93.37
Yes	185	33.82	76.22	23.78	85.95	76.22	23.78	85.95
Smoke cigarettes			p (χ^2) <0.001		p (χ^2) <0.001		p (χ^2) <0.001	
No	478	87.39	85.36	14.64	92.68	85.36	14.64	92.68
Yes	69	12.61	62.32	37.68	78.26	21.74	62.32	37.68
Parental connectedness								
Discuss sexual matter			p (χ^2) <0.05		p (χ^2) <0.01		p (χ^2)=0.09	
No	328	59.96	85.06	14.94	88.41	85.06	14.94	88.41
Yes	219	40.04	78.54	21.46	94.52	78.54	21.46	94.52
Living arrangement			p (χ^2) <0.01		p (χ^2) = 0.13		p (χ^2) <0.01	
Not together	339	61.97	79.06	20.94	89.38	79.06	20.94	89.38
Living together	208	38.03	87.98	12.02	93.27	87.98	12.02	93.27
Family structure			p (χ^2) <0.001		p (χ^2) <0.001		p (χ^2) <0.001	
Monogamous	497	90.86	85.31	14.69	93.56	6.44	85.71	14.29
Polygamous	50	9.14	54.00	46.00	64.00	36.00	44.00	56.00
Place of settlement			p (χ^2) <0.001		p (χ^2) <0.001		p (χ^2) <0.001	
Umgudulu	104	19.01	87.50	12.50	95.19	4.81	90.38	9.62
Banana City	145	26.51	59.31	40.69	72.41	27.59	57.24	42.76
Quarry road	178	32.54	87.64	12.36	98.88	1.12	87.64	12.36
New Germany	120	21.94	98.33	1.67	97.50	2.50	95.83	4.17
Ethnicity			p (χ^2) = 0.29		p (χ^2) <0.05		p (χ^2) <0.05	
isiZulu	265	48.45	85.66	14.34	94.34	5.66	86.79	13.21
Xhosa	255	46.62	79.22	20.78	87.06	12.94	76.86	23.14
Sesotho	22	4.02	81.82	18.18	95.45	4.55	81.82	18.18
Siswati	5	0.91	80.00	20.00	80.00	20.00	80.00	20.00
Overall			**82.45**	**17.55**	**90.86**	**9.14**	**81.90**	**18.10**

p (χ^2) = chi-square p-value.

Young women who had ever experienced GBV; those who lived within 10 to 19 km proximity to a healthcare clinic; and those who received child support grants had a 76.92, 83.33, and 70.37% prevalence of unintended pregnancy, HIV, and STIs, respectively. In the same vein, young women dwelling in Durban informal settlements within the Upper quintile; those who drink alcohol; and smoke cigarettes, had a 24.10, 76.22, and 37.68% prevalence of STIs, HIV, and unintended pregnancy.

The test of chi-square showed an association between all selected inequalities and adverse SRH outcomes (STIs, HIV and unintended pregnancy) as $p(x^2) < 0.05$, except sexual discussion and unintended pregnancy and ethnicity affiliation and STIs (**Table 1**).

Binary and Multivariable Logistics Regression Analyses

Table 2 below shows the significant association between selected inequalities and adverse SRH outcomes (STIs, HIV, and unintended pregnancy). All the selected inequalities variables, except the wealth index, showed a significant association with at least one adverse SRH outcome (Model II). The associated inequalities to SRH outcomes included contextual factors (GBV and healthcare proximity), social inequality (child support grant), the pattern of behavior (drink alcohol and smoke cigarettes), parental connectedness (discuss sexual matters and living together with parent) and others (including family structure, place of settlement, and ethnicity).

The results from the adjusted model (Model II) show that young women dwelling in Durban informal settlements with healthcare proximity between 5 and 9 km [aOR = 43.19; 95% (CI = 3.24–456.38)] who receive child support grants [aOR = 54.45; 95% (CI = 25.01–118.51)], smoke cigarettes [aOR = 2.07; 95% (CI = 0.71–5.99)] and reside in Banana City [aOR = 5.99; 95% (CI = 1.94–18.44)] were more likely to report ever having had STIs compared to those residing <5 km from a healthcare clinic; those who are not receiving child support grants, those who are not smoking; and young women residing in Umgudulu. Similarly, young women with healthcare proximity between 5 and 9 km [aOR = 26.92; 95% (CI = 1.41–513.05)] who receive child support grants [aOR = 2.94; 95% (CI = 1.34–6.42)], drink alcohol [aOR = 1.07; 95% (CI = 0.49–2.34)], are from polygamous family structures [aOR = 2.41; 95% (CI = 1.02–5.69)], reside in Banana City [aOR = 3.32; 95% (CI = 1.12–9.81)] and are affiliated with the Xhosa tribe [aOR = 2.92; 95% (CI = 1.34–6.32)] were more likely to report having HIV compared to those residing <5 km from a healthcare clinic; young women who never receive child support grants; those who never drank alcohol; young women from monogamous family structures; young women residing in Umgudulu; and those who are affiliated with the isiZulu tribe. In the same vein, young women who had ever experienced GBV [aOR = 2.58; 95% (CI = 1.05–6.33)], who receive child support grants [aOR = 24.35; 95% (CI = 12.22–48.67)], those from polygamous family structures [aOR = 3.55; 95% (CI = 1.34–9.42)], young women residing in Banana City [aOR = 5.91; 95% (CI = 2.05–17.04)], and those affiliated with the Xhosa tribe [aOR = 1.97; 95% (CI = 0.98–3.98)] were more likely to have ever had an unintended pregnancy, compared to those who never experienced GBV, who never receive child support grants, those from monogamous family structures, those residing in Umgudulu and those affiliated with the isiZulu tribe.

On the other hand, young women dwelling in Durban informal settlements who discuss sexual matters with their parents were less likely to report having STIs [aOR = 0.18; 95% (CI = 0.10–2.74)] [aOR = 0.40; 95% (CI = 0.17–0.97)] or ever having had an unintended pregnancy [aOR = 0.03; 95% (CI = 0.01–2.11)] compared to those who never discussed sexual matters with their parents. In the same vein, young women living with their parents were less likely to report having STIs [aOR = 0.22; 95% (CI = 0.09–0.57)] or ever having had unintended pregnancy [aOR = 0.26; 95% (CI = 0.11–0.59)] compared to those not living with parents.

Key Informant Interviews

The quantitative analysis results showed inequalities associated with adverse SRH outcomes among young women in Durban informal settlements. However, the researchers conducted key informant interviews to determine the desired interventions or solutions that the same population feels are required to bridge these inequalities. The authors thematically categorized the participants' responses in line with the quantitative study results as interventions required to reduce or eliminate the influence of (i) contextual factors, (ii) social inequality, (iii) patterns of behavior, and (iv)parental connectedness on adverse SRH outcomes among young women dwelling in Durban informal settlements.

Characteristics of Participants

Key informant interviews were conducted with 20 key young women dwelling in the same informal settlements where the quantitative study was conducted. Five (5) participants were selected from each settlement.

The participants' mean age was 21.80 years, with a standard deviation of 2.17 years and age ranging from 18 to 24 years. All the participants were young women and were literate.

Contextual Factors and Adverse Sexual and Reproductive Health Outcomes

Contextual factors were measured by gender-based violence and healthcare proximity. Both measures were associated with either of the adverse SRH outcomes.

Gender-Based Violence

- Yes, I have been raped. I was 11 years, and I was raped (Umgudulu, Participant 2).
- No, I have never been raped. However, when some guys come for me and ask for sex, I will give them willingly because I don't want them to force me to do it so I wouldn't call that rape (Umgudulu, Participant 4).

Suggested Solutions

- To stop the rape of young girls is for young girls to speak when they feel uncomfortable with their uncles, brothers and fathers, and some of the young girls should not wear short clothes around. Some young girls wear short clothes when

TABLE 2 | Binary and Multivariable logistic regression analysis of selected inequalities and adverse Sexual and Reproductive Health outcomes.

Variables $n = 547$	**Adverse sexual and reproductive health outcomes**					
Inequalities	**STIs**		**HIV**		**Unintended pregnancy**	
	Model I cOR [95% CI]	**Model II aOR [95% CI]**	**Model I cOR [95% CI]**	**Model II aOR [95% CI]**	**Model I cOR [95% CI]**	**Model II aOR [95% CI]**
Contextual factors						
Experienced GBV						
No	1	1	1	1	1	1
Yes	6.57*** [4.10–10.54]	2.26 [0.85–6.02]	6.83*** [3.67–12.72]	1.24 [0.50–3.06]	6.39*** [4.01–10.19]	2.58* [1.05–6.33]
Healthcare proximity						
Less than 5 km	1	1	1	1	1	1
5 to 9 km	5.18*** [3.13–8.57]	1.74 [0.39–7.78]	15.90*** [6.18–40.91]	7.10* [1.29–39.06]	4.89*** [3.01–7.94]	1.66 [0.41–6.76]
10 to 19 km	2.28 [0.72–7.19]	1.06 [0.14–7.85]	2.65 [0.30–23.66]	1.41 [0.96–20.79]	0.91 [0.20–4.10]	0.29 [0.03–3.08]
20 km and above	7.6* [1.21–47.63]	43.19** [3.24–56.38]	15.25* [1.43–161.96]	26.92* [1.41–513.05]	2.52 [0.27–23.31]	6.85 [0.41–114.61]
Social inequalities						
Child support grant						
No	1	1	1	1	1	1
Yes	49.76*** [27.04–91.55]	54.45*** [25.01–118.51]	6.03*** [3.29–11.04]	2.94** [1.34–6.42]	26.04*** [15.09–44.95]	24.39*** [12.22–48.67]
Wealth index						
Lower quintile	1	1	1	1	1	1
Middle quintile	1.88* [1.09–3.23]	1.20 [0.49–2.94]	1.87 [0.91–3.83]	1.06 [0.42–2.69]	1.86* [1.09–3.17]	1.19 [0.52–2.69]
Upper quintile	2.45* [1.24–4.82]	2.23 [0.76–6.50]	1.90 [0.76–4.78]	1.21 [0.39–3.75]	2.32* [1.19–4.55]	2.28 [0.85–6.09]
Pattern of behavior						
Drink alcohol						
No	1	1	1	1	1	1
	1.86** [1.19–2.91]	1.01 [0.39–2.59]	2.30** [1.28–4.14]	1.07* [0.49–2.34]	1.74* [1.12–2.71]	0.75 [0.32–1.73]
Smoke cigarettes						
No	1	1	1	1	1	1
Yes	3.52*** [2.03–6.10]	2.07* [0.71–5.99]	3.51*** [1.80–6.85]	1.47 [0.60–3.57]	3.35*** [1.94–5.80]	1.72 [0.65–4.56]
Parental connectedness						
Discuss sexual matter						
No	1	1	1	1	1	1
Yes	0.42*** [0.10–1.50]	0.18* [0.10–2.74]	0.44* [0.22–0.87]	0.40* [0.17–0.97]	0.45** [0.39–1.25]	0.03* [0.01–2.11]
Living arrangement						
Not together	1	1	1	1	1	1
Living together	0.51** [0.31–0.84]	0.22** [0.09–0.57]	0.61 [0.32–1.15]	0.63 [0.26–1.52]	0.52** [0.32–0.85]	0.26** [0.11–0.59]
Family structure						
Monogamous	1	1	1	1	1	1
Polygamous	4.95*** [2.69–9.10]	1.53 [0.51–4.59]	8.17*** [4.14–16.13]	2.41* [1.02–5.69]	7.63*** [4.14–14.09]	3.55* [1.34–9.42]
Place of settlement						
Umgudulu	1	1	1	1	1	1
Banana City	4.80*** [2.46–9.37]	5.99** [1.94–18.44]	7.54*** [2.86–19.88]	3.32* [1.12–9.81]	7.02*** [3.38–14.57]	5.91** [2.05–17.04]
Quarry road	0.99 [0.47–2.05]	4.02 [0.60–27.12]	0.22 [0.04–1.18]	0.91 [0.09–8.96]	1.33 [0.60–2.92]	3.47 [0.58–20.78]
New Germany	0.12** [0.03–0.54]	0.79 [0.07–8.45]	0.51 [0.12–2.18]	2.83 [0.33–23.92]	0.41 [0.13–1.24]	3.37 [0.51–22.32]
Ethnicity						
isiZulu	1	1	1	1	1	1
Xhosa	1.23 [0.15–10.16]	1.26 [0.58–2.75]	0.42 [005–3.58]	2.92** [1.34–6.32]	1.25 [0.15–10.33]	1.97* [0.98–3.98]
Sesotho	3.58 [0.41–30.97]	3.52 [0.73–16.91]	2.1 [0.24–18.45]	1.35 [0.14–12.67]	3.83 [0.44–33.11]	2.63 [0.57–12.01]
Siswati	2.50 [0.24–25.72]	0.58 [0.00–144.94]	5.09 [0.52–50.00]	2.04 [0.07–56.66]	3.23 [0.32–32.48]	0.70 [0.00–195.56]

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; 1, reference category; cOR, crude odds ratio; aOR, adjusted odds ratio; Model I, unadjusted logistic model; Model II, adjusted logistic model of all the selected inequalities; STIs, sexually transmitted infections; HIV, human immunodeficiency virus.*

their parents are not around, and they will be gallivanting around in short clothes. This could invite rape (Umgudulu, Participant 2).

- Young girls must speak up and allow them so that they wouldn't injure you or kill you, then report later (Umgudulu, Participant 4).

Healthcare Proximity

- There is no clinic around Banana City informal settlement. Family planning and other sexual and reproductive health services are gotten at Reservoir Hill clinic, which is around 10 min drive (Banana City, Participant 1).
- There is no clinic for family planning service here, we get it at Reddit Avenue at Reservoir Hill, and it's very far from here. Whenever I want to go, I get discouraged because of the distance (Umgudulu, Participant 2).

Suggested Solutions

- Having health clinic centers closer to the informal settlement, like mobile health facilities where required services and information on sexual education will be shared. Health experts should tell us what we need to do and what we are not doing right about contraception sexual and reproductive health, and the services should be free (Banana City, Participant 1).
- More mobile clinics should be established in places like informal settlements where Nurses should be routinely sent here, which will help us a lot (Umgudulu, Participant 2).

Social Inequality and Adverse Sexual and Reproductive Health Outcomes

Social inequality was measured by the child support grant and wealth index. Only the child support grant was associated with SRH outcomes.

Social Inequalities Identified and Suggested Solutions

- Well, for me, the social grant shouldn't be given to children because there should be an age where a grant should be given to a baby. After all, you see a girl <16 years with a baby and then get the social grant, she will get another pregnant and get another money, but she will give these children to her parent and be using the money anyhow. I think it should be stopped (New Germany, Participant 1).
- Aahh! Yes, the social grant makes young girls to make more children, and if they increased it, it would make girls to have more children as well because they are having sex without a condom. I feel the government should stop it (Quarry Road, Participant 1).
- Some of them get pregnant because they want more money, and it's not right because R460 is not enough to raise a child, especially when the father impregnates the girl and runs away. Some of the young girls want to give birth to more children so that they can have a lot of money from the social grant, and it is not helping (Banana City, Participant 1).

The Pattern of Behavior and Adverse Sexual and Reproductive Health Outcomes

The pattern of behavior was measured by alcohol intake and cigarette smoking.

Pattern of Behavior

- Let me make an instance for me. If I have taken alcohol, I won't use my brain; when a man makes a move, I won't think about it, and we will have sex without a condom or protection. It's the same thing when I am high on smokes or narcotics (Banana City, Participant 4).
- I don't think people who smoke or drink alcohol will have time to think of contraception or condom. A lot of times, it usually turns to one-night stands. I don't think they will think about condoms. Who cares about condoms in one-night stands? (New Germany, Participant 1).
- I don't think those who were drunk on high on smoke will use a condom because when I was drunk, I didn't use condoms because when a person is drunk, her mind is not working properly (Quarry Road, Participant 2).

Suggested Solution

- The government should work on limiting the use of alcohol and smoke among young women. If these can be reduced, it will reduce the non-use of condoms and other sexual and reproductive health services (Banana City, Participant 1).

Parental Connectedness and Adverse Sexual and Reproductive Health Outcomes

Parental Connectedness

- Yes, if my parent had talked to me about puberty, sex, HIV/STIs, I would have used condoms, maybe I would do better, and maybe I wouldn't even have this child, but they don't talk to me about it (Quarry Road, Participant 5).
- If my parent had not told me about sexual health or puberty, I might still have used a condom because I learned these things from school, but I know that the information from school is not enough. However, if my parents talked to me about this, I would use a condom more consistently (Quarry Road, Participant 3).
- Because the girls don't have much information from their parents, they wouldn't want to use a condom (New Germany, Participant 5).
- Living with your parent helps make decisions about good sexual and reproductive health, such as using condoms, contraception, and unintended pregnancy. Many children here don't stay with their parents, and some of their parents drink a lot and do not attend to the young girl's needs or questions about sexual health (Banana City, Participant 1).

Suggested Solution

- I think when parents talk to their girls more, it will help them in their decision to use condoms or family planning. So, the parent should talk to their girls more and ensure they live together (New Germany, participant 4).

DISCUSSION

Accelerating the attainment of SDG target 3.7 requires evidence-based interventions. As such, the present study explored adverse SRH outcomes inequality among young women in Durban informal settlements, South Africa, while suggesting the required social and behavioral interventions to reduce the disparity. The quantitative analysis indicates that healthcare proximity, child support grants, cigarette smoking, alcohol consumption, polygamous family structures, GBV and residing in Banana City or belonging to the Xhosa tribe were associated with higher odds of reporting STIs HIV and unplanned pregnancies. However, these factors were associated with adverse SRH outcomes in varied ways.

Access to child support grants emerged as a significantly associated factor in relation to adverse SRH outcomes. The child support grant in South Africa was introduced in the late 1990s as an initiative to improve the quality of life of young women who become mothers through monthly state-funded cash transfers (45). In order for the young woman to be eligible for this grant, the child must be below age 18 and living with the biological parent(s) or primary caregiver. The study results indicate that young women who had access to child support grants reported higher odds of STIs, HIV, and unplanned pregnancies than those who did not have access. This result aligns with that of Jordan et al. (46), who reported that South African young women are getting pregnant in order to access child support grants. A plausible explanation for this observation could be that young women perceive the child support grant as an opportunity to make money. As such, instead of this intervention to reduce their sexual behaviors, it rather encourages them to engage in unprotected sex, thereby raising their risk of unplanned pregnancies, STIs, and HIV.

The findings also show that residing in Banana City was associated with higher odds of STIs, HIV and unplanned pregnancies. This result reflects the high level of poverty and deprivation in Banana City, as compared to Umgudulu. For instance, Phoku (47) reported that food insecurity and poverty are high in Banana City. Hence, young women will place less priority on having protected sex, thereby exacerbating their risk of STIs, HIV and unplanned pregnancies. Findings from the qualitative analysis support this association by linking the higher level of adverse SRH outcomes to the absence of clinic and family planning services in Banana City. Relatedly, the results suggest that young women who identified with the Xhosa tribe were more likely to have HIV or unplanned pregnancies than those who identified with isiZulu. This association could be linked to the Xhosa culture about contraception norms. In the Xhosa culture, public conversations about conception and family planning are taboo (48). As such, young women are denied accurate information about contraception, condom use and family planning. This inadvertently increases the risk of unprotected sex, which can exacerbate the risk of HIV and unplanned pregnancies.

Results from the quantitative analysis suggest that young women who smoked cigarettes and consumed alcohol were more likely to experience STIs and HIV, respectively, compared to those who did neither. This is in line with findings from the qualitative analysis where respondents revealed that people who smoke or drink alcohol do not have time to think of contraception or condoms. Hence, these women are more likely to engage in risky sexual behaviors, including concurrent multiple sexual partnerships, transactional sex and unprotected sex, elevating their odds of contracting STIs and HIV (48). Our findings also highlight the need to improve healthcare proximity in Durban informal settlements, as longer proximity to healthcare was associated with a greater risk of STIs and HIV.

The researchers also observed that young women in the polygamous family structure were more likely to experience unplanned pregnancy or HIV. The findings can be explained from the perspective that, in a polygamous family structure, there is heightened competition for scarce resources and insufficient parental control (49). Given that the family is the primary agency for the socialization of its members, these deficiencies associated with the polygamous family structure is likely to reduce women's capacity to make informed decisions such as practicing protected sex, negotiating for safe sex, etc., thereby contributing to an elevated risk of unplanned pregnancies and HIV among young women in this family structure. Women who had experienced GBV were at higher risk of unplanned pregnancy, which aligns with related studies conducted in South Africa (50–52). GBV that manifests through sexual abuse prevents young women from practicing or negotiating for safe sex, thereby putting them at higher risk of unplanned pregnancy.

Concerning parental connectedness and adverse SRH outcomes, our findings revealed that living with parents and communicating with parents about SRH issues was a significant protective factor that limited the risk of STIs and unplanned pregnancy. This result corroborates a related study that showed that the quality of parental connectedness significantly influenced condom and contraceptive use, which is necessary for reducing the risk of STIs and unplanned pregnancy among young women in informal settlements (38).

Policy Implications

The findings from our study underscore the need for targeted interventions that focus primarily on young women who are at higher risk of adverse SRH outcomes. More specifically, the results highlight the urgency for the government to prioritize the SRH needs of informal settlements in Durban, particularly in Banana City. More social and health infrastructure (i.e., family planning service centers, clinics, etc.) would have to be developed in Durban's informal settlements, especially in Banana City. Public health educational promotions should be expanded to informal settlements in order to break socio-cultural norms that fuel GBV, which has proven to be significantly associated with adverse SRH outcomes. Our findings also iterate the need for the government to develop down strong policies and ensure the enforcement of already existing policies that control cigarette smoking and alcohol consumption among young people in South Africa.

Research Implication

Our study has some implications for future research. In the future, researcher should consider a longitudinal design in order to be able to establish causal inferences between the various factors considered in this analysis and their relationship with adverse SRH outcomes overtime, researcher should also consider including young men in the future in order to give better view of how young men contributes to young women adverse SRH outcomes.

Strengths and Limitations

The use of mixed methods in this study helped complement the shortcomings of both qualitative and quantitative methods. The researchers triangulated the data from the qualitative and quantitative study appropriately, ensuring the validity and reliability of the findings. However, there are some noteworthy limitations. Since the results of this study were self-reportedby the young women during the interview, there is possiblity of recall due to biases from the information supplied.

CONCLUSION

Based on our findings, it is clear that there are disparities in the factors associated with adverse SRH outcomes in Durban's informal settlements. Healthcare proximity, child support grants, cigarette smoking, alcohol consumption, polygamous family structures, GBV, and residing in Banana City or belonging to the Xhosa tribe was associated with higher odds of reporting STIs, HIV and unplanned pregnancies. Living with a parent and communicating with parents about SRH issues were associated with a lower risk of adverse SRH outcomes.

CORONAVIRUS RULE AND GUIDELINE COMPLIANCES

Since data collection took place during the coronavirus disease (COVID-19) pandemic, the principal investigator ensured that all COVID-19 rules and guidelines were complied with as recommended by South Africa and the World Health Organization. Coronavirus adherence prescribed recommendations such as social distancing, wearing of face masks, frequent washing of both hands, and using alcohol-based sanitizer was highly upheld during the data collection and while having physical engagement or contact with any person.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The University of KwaZulu-Natal's Ethical Review Body approved this study with Reference number: HSSREC/00002192/2020 before the questionnaire administration. The principal investigators and research assistants endeavored to provide participants with information on the purpose of the study, the process and how the findings will be used. The principle of voluntary participation guided the study, and, as such, each participant was required to sign an informed consent form. The participants were also promised that all ethical research considerations such as anonymity and confidentiality of the information provided would be upheld. All the institutional review board's guidelines for research using human subjects were also considered in this study.

AUTHOR CONTRIBUTIONS

OB developed the study's concept, conducted the primary data collection and key informant interviews, drafted the abstract, introduction, methodology, discussion, and conclusion sections, and analyzed the study. TB supervised the study at every stage and contributed substantially to the overall development of this study. All authors proofread the first draft of the manuscript and approved the final version for submission.

ACKNOWLEDGMENTS

The authors acknowledge and thank the College of Health Sciences for giving the authors all the required support at all stages of the manuscript development.

REFERENCES

1. Ali MM, Cleland J. Long term trends in behaviour to protect against adverse reproductive and sexual health outcomes among young single African women. *Reprod Health.* (2018) 15:1–10. doi: 10.1186/s12978-018-0576-6
2. UNICEF. *Child Marriage: Latest Trends and Future Prospects*. New York, NY: UNICEF (2018).
3. Melesse D, Mutua M, Choudhury A, Wado Y, Faye C, Neal S, et al. Adolescent sexual and reproductive health in sub-Saharan Africa: who is left behind? *BMJ Glob Health.* (2020) 5:e002231. doi: 10.1136/bmjgh-2019-002231
4. Chandra-Mouli V, Neal S, Moller A-B. *Adolescent Sexual and Reproductive Health for All in Sub-Saharan Africa: A Spotlight on Inequalities*. Springer (2021).
5. UNAIDS. *Trends of New HIV Infections*. (2020). Available online at: http://aidsinfo.unaids.org (accessed October 25, 2021).
6. UNICEF. *Child Marriage in West and Central Africa*. (2018). Available online at: https://www.unicef.org/wca/media/2596/fle (accessed October 22, 2021).
7. Coleman JN, Milford C, Mosery N, Choi KW, Greener LR, Matthews LT, et al. "I did not plan… that is what hurts": Pregnancy intentions and contraceptive use among pregnant young women in KwaZulu-Natal, South Africa. *Afr J AIDS Res*. (2021) 20:149–57. doi: 10.2989/16085906.2021.1914693
8. National Department of Health SSA, South African Medical Research Council, ICF. *South Africa Demographic and Health Survey 2016*. Pretoria; Rockville, MD (2019).
9. Haffejee F, Govender N, Reddy P, Sibiya MN, Ghuman S, Ngxongo T, et al. Factors associated with unintended pregnancy among women attending a public health facility in KwaZulu-Natal, South Africa. *South Afr Fam Pract.* (2018) 60:79–83. doi: 10.1080/20786190.2017.1396790

10. Selebalo H, Webster D. Monitoring the right of access to adequate housing in South Africa. *Studies in Poverty and Inequality Institute Working Paper*. Johannesburg: Studies in Poverty and Inequality Institute (SPII) (2017).
11. Kabiru CW, Beguy D, Undie C-C, Zulu EM, Ezeh AC. Transition into first sex among adolescents in slum and non-slum communities in Nairobi, Kenya. *J Youth Stud.* (2010) 13:453–71. doi: 10.1080/13676261003801754
12. Mumah JN, Beguy D, Wawire S. *Contraceptive Use Among Youth: A Comprehensive Account of Associated Individual-Level Factors in Two Informal Settlements in Kenya*. Available online at: https://iussp.org/sites/default/files/event_call_for_papers/Contraceptive%20use%20among%20youth_IUSSP%202013.pdf (accessed October 26, 2021).
13. Kamndaya M, Kazembe LN, Vearey J, Kabiru CW, Thomas L. Material deprivation and unemployment affect coercive sex among young people in the urban slums of Blantyre, Malawi: A multi-level approach. *Health Place.* (2015) 33:90–100. doi: 10.1016/j.healthplace.2015.03.001
14. Marx C, Charlton S. *The Case of Durban, South Africa. Global Report on Human Settlements*. UN-HABITAT (Hg) (2003). pp. 195–223.
15. Ngyende A. *KwaZulu-Natal: Informal Settlements Status 2013*. Johannesburg: Housing Development Agency (2013).
16. Statistics South Africa (STATS SA). *South Africa Demographic and Health Survey 2016: Key Indicators Report*. Pretoria: Stats SA (2017).
17. Andrew S, Halcomb EJ. *Mixed Methods Research for Nursing and the Health Sciences*. New Jersey: John Wiley & Sons; Wiley-Blackwell (2009).
18. Mberu B, Mumah J, Kabiru C, Brinton J. Bringing sexual and reproductive health in the urban contexts to the forefront of the development agenda: the case for prioritizing the urban poor. *Matern Child Health J.* (2014) 18:1572–7. doi: 10.1007/s10995-013-1414-7
19. Ajayi AI, Ezegbe HC. Association between sexual violence and unintended pregnancy among adolescent girls and young women in South Africa. *BMC Public Health.* (2020) 20:1–10. doi: 10.1186/s12889-020-09488-6
20. Waldman L, Stevens M. *Sexual and Reproductive Health Rights and Information and Communications Technologies: A Policy Review and Case Study From South Africa*. Brighton: Institute of Development Studies (IDS) (2015).
21. Kheswa J. Conditions and challenges associated with women's risk sexual behaviour in informal settlements across South Africa. *J Hum Ecol.* (2020) 70:124–31. doi: 10.31901/24566608.2020/70.1-3.3230
22. Bokonda PL, Ouazzani-Touhami K, Souissi N. Open data kit: mobile data collection framework for developing countries. *Int J Innov Technol Explor Eng.* (2019) 8:4749–54. doi: 10.35940/ijitee.L3583.1081219
23. Etikan I, Bala K. Sampling and sampling methods. *Biometr Biostat Int J.* (2017) 5:00149. doi: 10.15406/bbij.2017.05.00149
24. Meng X, editor. Scalable simple random sampling and stratified sampling. In: *International Conference on Machine Learning.* Mountain View: MLResearchPress (2013).
25. Singh D, Singh P. New systematic sampling. *J Stat Plan Inference.* (1977) 1:163–77. doi: 10.1016/0378-3758(77)90021-0
26. Glenn I. *Determining Sample Size. Fact Sheet PEOD-6, A Series of the Program Evaluation and Organizational Development.* Florida Cooperative Extension Service, Institute of Food and Agricultural Sciences, University of Florida (1992).
27. Lenth RV. Some practical guidelines for effective sample size determination. *Am Stat.* (2001) 55:187–93. doi: 10.1198/000313001317098149
28. Fox N, Hunn A, Mathers N. *Sampling and Sample Size Calculation*. East Midlands/Yorkshire: the National Institutes for Health Research Design Service for the East Midlands/Yorkshire & the Humber (2009).
29. World Health Organization (WHO). *Integrating Sexual and Reproductive Health Into Health Emergency and Disaster Risk Management*. Geneva: Switzerland (2012).
30. Hlongwa M, Mashamba-Thompson T, Makhunga S, Hlongwana K. Evidence on factors influencing contraceptive use and sexual behavior among women in South Africa: a scoping review. *Medicine.* (2020) 99:e19490. doi: 10.1097/MD.0000000000019490
31. Simbayi L, Zuma K, Zungu N, Moyo S, Marinda E, Jooste S, et al. *South African national HIV prevalence, incidence, behaviour and communication survey, 2017: Towards achieving the UNAIDS 90-90-90 targets*. Available online at: https://www.hsrcpress.ac.za/books/south-african-national-hiv-prevalence-incidence-behaviour-and-communication-survey-2017
32. Cooper LB, Paluck EL, Fletcher EK, Ryan IM, Branscombe N, Center TJ. Reducing gender-based violence. In: Ryan MK, Branscombe NR, editors. *The Sage Handbook of Gender and Psychology*. London: Sage Publications (2013). pp. 359–78.
33. Tomita A, Vandormael AM, Cuadros D, Slotow R, Tanser F, Burns JK. Proximity to healthcare clinic and depression risk in South Africa: geospatial evidence from a nationally representative longitudinal study. *Soc Psychiatry Psychiatr Epidemiol.* (2017) 52:1023–30. doi: 10.1007/s00127-017-1369-x
34. Peven K, Taylor C, Pursell E, Mallick L, Burgert-Brucker CR, Day LT, et al. Distance to available services for newborns at facilities in Malawi: A secondary analysis of survey and health facility data. *PLoS ONE.* (2021) 16:e0254083. doi: 10.1371/journal.pone.0254083
35. Karra M, Fink G, Canning D. Facility distance and child mortality: a multi-country study of health facility access, service utilization, and child health outcomes. *Int J Epidemiol.* (2017) 46:817–26. doi: 10.1093/ije/dyw062
36. Triegaardt JD. The Child Support Grant in South Africa: a social policy for poverty alleviation? *Int J Soc Welf.* (2005) 14:249–55. doi: 10.1111/j.1369-6866.2005.00367.x
37. Rutstein SO. *Steps to Constructing the New DHS Wealth Index*. Rockville, MD: ICF International (2015).
38. Sidze EM, Elungata'a P, Maina BW, Mutua MM. Does the quality of parent–child connectedness matter for adolescents' sexual behaviors in Nairobi informal settlements? *Arch Sex Behav.* (2015) 44:631–8. doi: 10.1007/s10508-014-0402-3
39. Negeri EL. Assessment of risky sexual behaviors and risk perception among youths in Western Ethiopia: the influences of family and peers: a comparative cross-sectional study. *BMC Public Health.* (2014) 14:1–12. doi: 10.1186/1471-2458-14-301
40. O'Leary CM, Bower C. Guidelines for pregnancy: what's an acceptable risk, and how is the evidence (finally) shaping up? *Drug Alcohol Rev.* (2012) 31:170–83. doi: 10.1111/j.1465-3362.2011.00331.x
41. Seggie J. Alcohol and South Africa's youth. *South Afr Med J.* (2012) 102:587. doi: 10.7196/SAMJ.6003
42. Bolarinwa O. Knowledge of sexually transmitted infections and socio-demographic factors affecting high-risk sex among unmarried youths in Nigeria. *Int J Glob Health.* (2019) 2:23–8.
43. Braun V, Clarke V. Thematic analysis. In: Cooper H, Camic PM, Long DL, Panter AT, Rindskopf D, Sher KJ, editors. *APA Handbook of Research Methods in Psychology, Vol. 2. Research Designs: Quantitative, Qualitative, Neuropsychological, and Biological*. Washington, DC: American Psychological Association (2012). pp. 57–71.
44. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care.* (2007) 19:349–57. doi: 10.1093/intqhc/mzm042
45. Lund F, A. step in the wrong direction: linking the South Africa Child Support Grant to school attendance. *J Poverty Soc Just.* (2011) 19:5–14. doi: 10.1332/175982711X559118
46. Jordan N, Patel L, Hochfeld T. Early motherhood in Soweto: the nexus between the child support grant and developmental social work services. *Soc Work.* (2014) 50:392–409. doi: 10.15270/50-3-406
47. Phoku ML. *Can recipients of the child social grants in Banana City informal settlement generate an adequate standard of living form the grant?* (Doctoral dissertation). Available online at: https://researchspace.ukzn.ac.za/bitstream/handle/10413/10388/Phoku_Mathapelo_L_2009.pdf?sequence=1&isAllowed=y
48. Zuma T, Seeley J, Mdluli S, Chimbindi N, Mcgrath N, Floyd S, et al. Young people's experiences of sexual and reproductive health interventions in rural KwaZulu-Natal, South Africa. *Int J Adolesc Youth.* (2020) 25:1058–75. doi: 10.1080/02673843.2020.1831558
49. Odimegwu C, Adedini SA. Do family structure and poverty affect sexual risk behaviors of undergraduate students in Nigeria? *Afr J Reprod Health.* (2013) 17:137–49.
50. Karim QA, Baxter C. The dual burden of gender-based violence and HIV in adolescent girls and young women in South Africa: guest editorial. *South Afr Med J.* (2016) 106:1151–3. doi: 10.7196/SAMJ.2017.v106i12.12126

51. Christofides NJ, Jewkes RK, Dunkle KL, McCarty F, Shai NJ, Nduna M, et al. Risk factors for unplanned and unwanted teenage pregnancies occurring over two years of follow-up among a cohort of young South African women. *Glob Health Action.* (2014) 7:23719. doi: 10.3402/gha.v7.23719
52. Bolarinwa OA, Boikhutso T. Mapping evidence on predictors of adverse sexual and reproductive health outcomes among young women in South Africa: A scoping review. *Afr J Prim Health Care Fam Med.* (2021) 13:e1–10. doi: 10.4102/phcfm.v13i1.3091

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Public Health

ORIGINAL RESEARCH
published: 01 April 2022
doi: 10.3389/fpubh.2022.842950

Patients' Willingness of First Visit in Primary Medical Institutions and Policy Implications: A National Cross-Sectional Survey in China

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Background: The Chinese hierarchical treatment system expects patients to first visit primary medical institutions (PMIs), and patients' willingness determined their utilization of primary health care. The aim of this study was to explore the factors associated with patients' willingness to make their first visit to PMIs.

Methods: We employed multistage stratified sampling and convenience sampling to administer questionnaires to 1,507 patients in Beijing, Qinghai, and Fujian. Patients' willingness of first visit in PMIs was analyzed using Chi-square test and binary logistic regression.

Results: Of the 1,507 participants in the survey, 55.1% were willing to make their first visit in PMIs. Fewer patients in Beijing (17.6%) are willing to make their first visit in PMIs than those in Qinghai (71.9%) and Fujian provinces (72.0%). Binary logistic regression analysis revealed that higher recognition of the community first visit policy and higher satisfaction with the medical technology of PMIs are associated with patients' willingness of first visit in PMIs.

Conclusions: Due to differences in local economic conditions, medical resources, and policy formulation, there are differences among provinces in patients' willingness of first visit in PMIs. To increase patients' rate of visits in PMIs, it is important to improve service capacity and quality of PMIs and change residents' attitudes for PMIs.

Keywords: primary medical institutions, first visit, hierarchical medical system, patient willingness, China

Edited by:
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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Public Health

Received: *24 December 2021*
Accepted: *11 March 2022*
Published: *01 April 2022*

Citation:
Li J, Zhao N, Zhang H, Yang H and Yang J (2022) Patients' Willingness of First Visit in Primary Medical Institutions and Policy Implications: A National Cross-Sectional Survey in China.
Front. Public Health 10:842950.
doi: 10.3389/fpubh.2022.842950

INTRODUCTION

The World Health Organization issued the Alma-Ata Declaration in 1978. The document identifies primary healthcare as the core of integrated health services and regards primary healthcare as the basis for a sustainable development of healthcare systems (1). There is presently a three-tier health care system in China (primary, secondary, and tertiary medical facilities), and different levels of facilities have different functions and positions (2). Medical institutions of higher levels have more medical resources and can provide more comprehensive health services (3). Primary medical institutions (PMIs), including community health service centers /stations, township health centers and village clinics, mainly provide basic public health services and primary care, such as disease prevention, chronic disease management, health education and the treatment of common and frequent diseases (4). By the end of 2020, there are 35,365 community health service centers/stations, 35,762 township health centers, and 608,828 village health clinics in China (5). Due to lack of trust of patients for PMIs and the demand for quality healthcare services, the majority of patients prefer to bypass primary care and go to high-level hospitals (6–8).

It is very common for patients to overutilize high-level hospitals healthcare services but underutilize primary healthcare services in China (9). In 2017, outpatient visits of tertiary hospitals accounted for 45.17% of the total number of outpatient visits, compared to 15.93% for community health centers (10). Over 70% of patients with general and chronic diseases choose to consult doctors at tertiary hospitals (11). To improve the utilization efficiency of medical resources in PMIs and relieve the pressure of high-level hospitals, the Chinese government has formulated a series of policies such as hierarchical medical system and medical insurance differentiated reimbursement policy (12, 13). The purpose is to guide residents to make their first visit in PMIs. Hierarchical medical system aims to require patients to choose PMIs as their first site of treatment, then transfer to high-level hospitals for further treatment based on their condition. Meanwhile, high-level hospitals transfer inpatients in stable conditions to PMIs for rehabilitation (14). But this policy did not strictly constrain community-based first visit, and residents are still free to choose their ideal health care facility for consultation. Medical insurance differential reimbursement policy guides patients to seek medical treatment in an orderly manner by appropriately raising the proportion of medical insurance reimbursement in PMIs. The Chinese government expects to adjust the layout of the medical service system and rationalize the allocation and utilization of medical resources through relevant policies to finally solve the problem of "difficult and expensive medical treatment." But the community first visit system is not really working and exists in name only (15). Medical resources are more abundant in urban areas, and thus regardless of the severity of the disease, urban patients prefer to access secondary and tertiary hospitals instead of PMIs (16, 17). According to data from the *2020 China Statistical Yearbook of Health*, the number of consultations in PMIs accounted for 61.87% of total consultations in 2010, but decreased to 53.17% in 2020 (18).

Patients' willingness determines their utilization of primary health care. Previous researches focused on the people's preference for primary health care and influencing factors. For example, models of service, medical costs, satisfaction, family income, characteristics of provider and medical experience would influence patients' choice of medical institutions (19–23). First, most studies are limited by geographic areas, and the scope of the studies is in one province or one city, lacking cross-provincial studies (3, 20, 22–24). Second, few studies have studied whether residents' knowledge of the policy influences their willingness or choice to seek treatment (25, 26). Cross-provincial studies are useful for the formulation of relevant medical policies. It is essential for policymakers to understand the impact of policies on patients' choice of medical institutions. However, there has not been a study on patients' willingness of first visit in PMIs, and the impact of policy awareness on first visits. Therefore, this study selected the three provinces based on regional distribution and economic development level for analysis. The study has two objectives: (1) to investigate patients' willingness of first visit in PMIs; and (2) to explore the variables that are associated with patients' willingness of first visit in PMIs, especially the relevant policy variables. Based on the results of this study, we discuss how to improve patients' willingness of first visit in PMIs, in order to provide reference for the government to develop a hierarchical medical system.

MATERIALS AND METHODS

Study Design and Data Sources

The study is a cross-sectional survey, and multi-stage stratified sampling and convenience sampling were used to choose research subjects. Firstly, according to the geographical location and economic development level, three provinces were chosen (Beijing, Fujian and Qinghai provinces). Secondly, according to the progress of the implementation of the hierarchical medical system and economic development level, two cities were selected from each province, and a total of six cities were selected. The formula for calculating the sample size for each city patient is $n = \frac{Z^2P(1-P)}{E^2}$, $Z = 1.96$. E is the error value, $E = 5\%$; P is the ratio of visits at community health centers to total visits in 2020, $P = 26\%$; $n = 296$. Therefore, we planned to select 300 patients in each city. Third, with the support of the Chinese Hospital Association, each city selected two tertiary hospitals, two secondary hospitals, and two community healthcare centers. The sample size of tertiary hospitals, secondary hospitals and community health centers in each city was 100. Fourth, convenience sampling was used to survey patients. 50 patients in each medical institution were selected for the investigation. In total, 1,807 questionnaires were distributed. Based on previous experience, there are very few inpatients in PMIs, so only outpatients were analyzed in this study. After excluding inpatients and invalid questionnaires s, a total of 1,507 outpatients were included in the research sample, and the valid response rate was 83.40%. The sample size selection process was showed in **Figure 1**.

The questionnaire was self-designed on the basis of literature research and expert consultation. After designing the questionnaire, we looked for respondents to conduct a pre-investigation to test the reliability and validity of the questionnaire and revised it based on the survey results. After several revisions, the contents and structure of the questionnaire were determined. Finally, the questionnaire was converted into an electronic questionnaire to survey. Data were collected via face-to-face interviews with trained interviewers, and respondents were given a survey incentive to ensure the response rate and validity of the data. Meanwhile, to ensure the quality of the data, only patients over 18 years old were included. Before handing out the questionnaire, we stated the study purpose and content to all respondents, obtained their informed consent, and committed that their privacy was protected. This study was

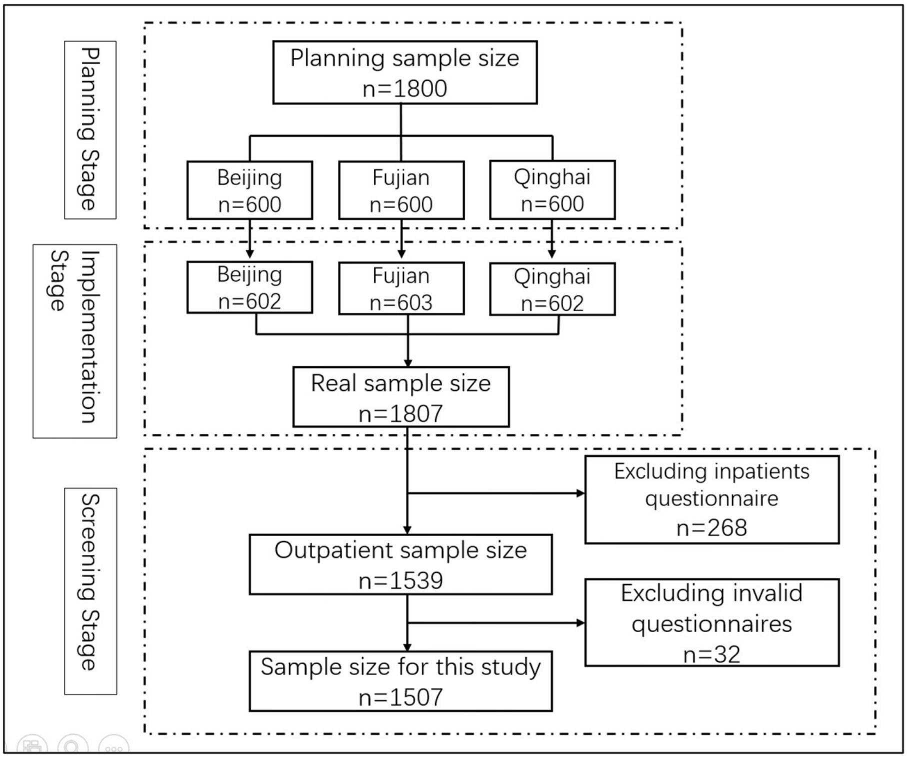

FIGURE 1 | Flow chart of the selection of respondents.

conducted from March to May 2019. According to the study design, only parts of the questions in the questionnaire were included as variables.

Dependent Variable

In this study, the dependent variable is the patients' willingness of first visit in PMIs (In this questionnaire, community health service centers/stations refer to PMIs). It was measured by a question: "are you willing to make your first visit in the community and then be referred to a higher-level hospital via the community health center/station?" The response was divided into 5 options: a. very unwilling; b. more unwilling; c. indifferent; d. more willing; e. very willing. We converted the five-dimensional ordered variables to binary variables based on published studies (12, 27–29). Options a, b, and c were combined into "unwilling"; options d and e were combined into "willing."

Independent Variables

The independent variables were divided into three parts. Part 1 is the sociodemographic characteristics, including province, gender, age, education, registered permanent residence, chronic disease status, length of residence in the city, household annual income and average monthly medical expense. Part 2 is the attitude toward PMIs, including experience of PMIs visits in the past year, degree of satisfaction with the medical technology of PMIs and degree of satisfaction with the service attitude of PMIs. Part 3 is the level of understanding of relevant policies, including understanding of the first visit policy, recognition of the community first visit policy, understanding of the medical insurance differential reimbursement policy, and influence of the medical insurance differential reimbursement policy (see **Supplementary File 1**).

Statistical Analysis

The software SPSS 26.0 was used to analyze data. Descriptive statistics (frequency and percentage) were used to describe the sociodemographic characteristics of patients, and the Chi-square test was used to analyze patients' willingness of first visit in PMIs. Those statistically significant variables in the Chi-square test were included as independent variables in the logistic regression model, and the factors associated with first visit willingness were further analyzed. The differences were regarded as to be statistically significant when *P*-value <0.05.

RESULTS

Sociodemographic Characteristics and Willingness of First Visit in PMIs of All the Participants

After excluding outliers, a total of 1,507 patients were included in this study (83.40% valid rate). **Table 1** presents the sociodemographic distribution characteristics of the patients. Of the 1,507 patients, 523 (34.7%) patients were interviewed in Qinghai, among whom 54.7% were females. The majority

TABLE 1 | Patients' sociodemographic characteristics and univariate analysis of patients' willingness of first visit in PMIs.

Variables	**The willingness of first visit to PMIs *N* (%)**				
	Unwilling *N* = 677 (44.9)	**Willing *N* = 830 (55.1)**	**Total *N* = 1,507, *N* (%)**	χ^2	***P***
Part 1 Sociodemographic					
Province				384.967	**<0.001**
Beijing	385 (82.4)	82 (17.6)	467 (31.0)		
Fujian	145 (28.0)	372 (72.0)	517 (34.3)		
Qinghai	147 (28.1)	376 (71.9)	523 (34.7)		
Gender				2.491	0.115
Male	322 (47.1)	361 (52.9)	683 (45.3)		
Female	355 (43.1)	469 (56.9)	824 (54.7)		
Age (years)				3.816	0.282
<45	392 (46.9)	443 (53.1)	835 (55.4)		
45–54	158 (41.5)	223 (58.5)	381 (25.3)		
55–64	87 (42.4)	118 (57.6)	205 (13.6)		
≥65	40 (46.5)	46 (53.5)	86 (5.7)		
Education				0.473	0.789
Junior or below	41 (45.6)	49 (54.4)	90 (6.0)		
Senior high school	209 (43.6)	270 (56.4)	479 (31.8)		
Bachelor or above	427 (45.5)	511 (54.5)	938 (62.2)		
Registered permanent residence				5.688	0.058
The city's downtown	190 (43.4)	248 (56.6)	438 (29.1)		
The city's suburbs	164 (50.8)	159 (49.2)	323 (21.4)		
Out-of-town	323 (43.3)	423 (56.7)	746 (49.5)		
Length of residence in the city (years)				3.331	0.189
<1	66	61	127 (8.4)		
1–2	125	170	295 (19.6)		
≥2	486	599	1,085 (72.0)		
Household annual income (yuan)				6.301	**0.043**
<80,000	298 (41.7)	417 (58.3)	715 (47.4)		
80,000–150,000	334 (48.3)	357 (51.7)	691 (45.9)		
≥150,000	45 (44.6)	56 (55.4)	66 (4.4)		
Average monthly medical expense (yuan)				11.461	**0.003**
≤300	100 (35.8)	179 (64.2)	279 (18.5)		
301–800	455 (47.2)	510 (52.8)	965 (64.0)		
>800	122 (46.4)	141 (53.6)	263 (17.5)		
Chronic disease status				15.324	**<0.001**
Yes	641 (44.0)	816 (56.0)	1,457 (96.7)		
No	36 (72.0)	14 (28.0)	50 (3.3)		
Part 2 Attitude toward PMIs					
Degree of satisfaction with the medical technology of PMIs				69.461	**<0.001**
Not satisfied	20 (35.7)	36 (64.3)	56 (3.7)		

(Continued)

TABLE 1 | Continued

Variables	**The willingness of first visit to PMIs *N* (%)**				
	Unwilling *N* = 677 (44.9)	**Willing *N* = 830 (55.1)**	**Total *N* = 1,507, *N* (%)**	χ^2	***P***
Less satisfied	268 (36.5)	466 (63.5)	734 (48.7)		
Generally	257 (61.2)	163 (38.8)	420 (27.9)		
More satisfied	84 (47.5)	93 (52.5)	177 (11.7)		
Very satisfied	48 (40.0)	72 (60.0)	120 (8.0)		
Degree of satisfaction with the service attitude of PMIs				24.083	**<0.001**
Not satisfied	32 (39.5)	49 (60.5)	81 (5.4)		
Less satisfied	114 (40.3)	169 (59.7)	283 (18.8)		
Generally	220 (40.4)	325 (59.6)	545 (36.2)		
More satisfied	240 (54.4)	201 (45.6)	441 (29.3)		
Very satisfied	71 (45.2)	86 (54.8)	157 (10.4)		
Experience of PMIs visits in the past year				1.245	0.264
Yes	565 (44.3)	710 (55.7)	1,275 (84.6)		
No	112 (48.3)	120 (51.7)	232 (15.4)		
Part 3 Level of understanding of relevant policies					
Understanding of the community first visit policy				0.497	0.481
Yes	71 (47.7)	78 (52.3)	149 (9.9)		
No	606 (44.6)	752 (55.4)	1,358 (90.1)		
Recognition of the community first visit policy				110.397	**<0.001**
Not recognize	224 (34.3)	429 (65.7)	653 (43.3)		
Mildly recognize	135 (40.8)	196 (59.2)	331 (22.0)		
Moderate	213 (61.4)	134 (38.6)	347 (23.0)		
Partly recognize	89 (71.8)	35 (28.2)	124 (8.2)		
Completely recognize	16 (30.8)	36 (69.2)	52 (3.5)		
Understanding of the medical insurance differential reimbursement policy				15.088	**<0.001**
Yes	131 (36.1)	232 (63.9)	363 (24.1)		
No	526 (47.7)	598 (52.3)	1,144 (75.9)		
Influence of the medical insurance differential reimbursement policy				52.499	**<0.001**
No impact	10 (20.8)	38 (79.2)	48 (3.2)		
Less impact	115 (37.0)	196 (63.0)	311 (20.6)		
Moderate	217 (39.8)	328 (60.2)	545 (36.2)		
More impact	235 (55.7)	187 (44.3)	422 (28.0)		
Greatest impact	100 (55.2)	81 (44.8)	181 (12.0)		

The bold P values indicates that the difference is statistically significant.

(55.4%) of patients were under 45 years old. Almost half (49.5%) of the patient's household registration were out-of-town. The great majority of patients are well-educated: 31.8% of patients have a high school degree and 62.2% have a college degree or above. Most patients (72.0%) lived in the city for more than 2 years. The largest proportion of respondents have a household annual income of <80,000 yuan, and 64.0% of respondents have average monthly medical expenditures between 301 and 800 yuan. For chronic disease status, 96.7% of respondents have chronic diseases.

This study found that 830 (55.1%) of the 1,507 respondents were willing to first visit in PMIs and be referred to secondary or tertiary hospital through PMIs if necessary. 90.1% of respondents were understanding of the first visit policy and 43.3% of respondents said they cannot recognize it. 24.1% of patients were aware of the medical insurance differential reimbursement policy. In the past year, 84.6% of patients had experience in PMIs. 19.7% of patients were satisfied with the technology of PMIs and 39.7% of patients were satisfied with the service attitude (more satisfied and very satisfied were defined as satisfied).

Sociodemographic Characteristics, Attitude, and Understanding of Relevant Policies and Their Relationships With Patients' Willingness of First Visit in PMIs

The Chi-square test was applied to check the relationship between all variables and willingness of first visit in PMIs. The results showed that there were statistically significant differences in the willingness of patients to first visit PMIs for province ($P < 0.001$), household annual income ($P = 0.043$), chronic disease status ($P < 0.001$), average monthly medical expense ($P = 0.003$), recognition of the community first visit policy ($P < 0.001$), understanding of the medical insurance differential reimbursement policy ($P < 0.001$), influence of the medical insurance differential reimbursement policy ($P < 0.001$), degree of satisfaction with the medical technology of PMIs ($P < 0.001$), and degree of satisfaction with the service attitude of PMIs ($P < 0.001$).

Predictors of Patients' Willingness of First Visit in PMIs

Firstly, binary logistic regression model was tested for goodness-of-fit. The results of Hosmer–Lemeshow tests showed $P > 0.10$; binary logistic regression model was considered to be good fitting. The results of binary logistic regression analysis are presented in **Table 2**. Compared with patients in Qinghai, patients in Beijing were more unwilling to first visit in PMIs (OR = 0.097, $P < 0.001$). Recognition of the community first visit policy is associated with patients' willingness of first visit in PMIs. Compared with patients who completely recognize the community first visit policy, patients who partly (OR = 0.292, $P = 0.004$), moderately (OR = 0.334, $P = 0.004$), mildly (OR = 0.407, $P = 0.019$), and not recognize (OR = 0.421, $P = 0.021$) the policy were more unwilling to first visit PMIs. It means that other groups of patients had a lower willingness to first visit PMIs compared to those who strongly recognized of the community first visit policy. Compared with patients who were very satisfied with the medical technology of the PMIs, patients with general satisfaction were more unwilling to first visit PMIs (OR =0 .593, $P = 0.034$).

Patients' Sociodemographic Characteristics, Attitude, and Understanding of Relevant Policies and Their Relationships With Different Provinces

To further explore the disparities in other aspects among patients from different provinces, we conducted the univariate analysis (**Table 3**). The results showed that there were statistical significance among patients from different provinces for age ($P = 0.008$), education ($P = 0.011$), registered permanent residence ($P = 0.016$), household annual income ($P < 0.001$), chronic disease status ($P < 0.001$), degree of satisfaction with the medical technology of PMIs ($P < 0.001$), degree of satisfaction with the service attitude of PMIs ($P < 0.001$), understanding of the community first visit policy ($P = 0.004$), recognition of the community first visit policy ($P < 0.001$), understanding of the medical insurance differential reimbursement policy ($P < 0.001$), and influence of the medical insurance differential reimbursement policy ($P < 0.001$).

Figures 2, **3** shows the reasons why patients were willing/unwilling to make their first visit in PMIs. Higher medical insurance reimbursement rate (66.5%), closer to home (63.1%), and treatment environment fit for recovery (47.6%) are top 3 reasons for patients' willingness to go to PMIs. Distrust of the medical skills of PMIs (63.1%), the referral process wastes time (56.7%), and fewer checkup items (41.7%) are top 3 reasons for patients' unwillingness to go to PMIs.

DISCUSSION

To the best of our knowledge, this is the first study examining the willingness of outpatients in multiple provinces to make their first visit to PMIs. We found that patients with high recognition of the first visit policy and high satisfaction with the medical technology of PMIs were more willing to make their first visit in PMIs, and that patients in Beijing were more unwilling to make their first visit in PMIs. In this study, 55.1% of the patients were willing to make their first visit in PMIs and be referred to higher level hospitals if necessary. This result has not reached the expected goal of policy formulated by Chinese government in 2015 (≥70%) (30), and is similar to the results of a study conducted in Hubei in 2021 (55.22%) (31), and higher than that of a study conducted in nine tertiary hospitals in Shanghai in 2019 (48.4%) (32). Fewer patients are willing to first visit PMIs, which leads to low utilization of medical resources in PMIs and overutilization of medical resources in high level hospitals. There are several studies from other countries that have reached similar conclusions (33–36). A study from the United States showed that rural patients also bypass rural hospitals and choose large urban hospitals for consultations (33). A study from India found that most patients (especially hypertensive patients) bypassed

TABLE 2 | Binary logistic regression analysis of patients' willingness of first visit in PMIs.

Variables	*β*	*P*	OR	95%CI	
				Lower limit	Upper limit
Province (Ref: Qinghai)					
Beijing	−2.334	**<0.001**	0.097	0.067	0.140
Fujian	−0.024	0.880	0.977	0.718	1.328
Household annual income (yuan) (Ref: >150,000)					
<80,000	−0.324	0.220	0.723	0.431	1.214
80,000–150,000	−0.223	0.401	0.800	0.475	1.347
Chronic disease status (Ref: No)					
Yes	−0.217	0.569	0.805	0.381	1.700
Average monthly medical expense (yuan) (Ref: >800)					
≤300	0.386	0.076	1.471	0.960	2.253
301–800	−0.100	0.555	0.905	0.648	1.262
Recognition of the community first visit policy (Ref: completely recognize)					
Not recognize	−0.865	**0.021**	0.421	0.202	0.879
Mildly recognize	−0.899	**0.019**	0.407	0.191	0.865
Moderate	−1.096	**0.004**	0.334	0.158	0.709
Partly recognize	−1.229	**0.004**	0.292	0.127	0.674
Understanding of the medical insurance differential reimbursement policy (Ref: No)					
Yes	0.119	0.449	1.127	0.827	1.534
Influence of the medical insurance differential reimbursement policy (Ref: Greatest impact)					
No impact	0.541	0.195	1.718	0.757	3.901
Less impact	−0.177	0.450	0.838	0.529	1.326
Moderate	0.108	0.615	1.115	0.730	1.701
More impact	−0.060	0.784	0.941	0.611	1.450
Degree of satisfaction with the medical technology of PMIs (Ref: Very satisfied)					
Not satisfied	−0.160	0.674	0.852	0.405	1.794
Less satisfied	−0.063	0.788	0.939	0.595	1.483
Generally	−0.523	**0.034**	0.593	0.365	0.962
More satisfied	−0.065	0.817	0.937	0.539	1.628
Degree of satisfaction with the service attitude of PMIs (Ref: Very satisfied)					
Not satisfied	0.073	0.818	1.075	0.580	1.995
Less satisfied	0.185	0.429	1.203	0.760	1.904
Generally	0.196	0.353	1.217	0.804	1.841
More satisfied	0.194	0.384	1.214	0.785	1.877

The bold P values indicates that the difference is statistically significant.

primary health care and chose private medical facilities for usual care because of the low quality of primary health care (35). Our analysis shows the major reasons for patients' willingness of first visit in PMIs are higher reimbursement rate of health insurance and closer distance to home. This is consistent with the results of previous studies (20, 31, 37). For example, the policy of Qinghai Province stipulated that patients who are referred to secondary or higher hospitals through PMIs can enjoy higher reimbursement rate of medical insurance.

The results showed that patients in Qinghai Province were more willing to choose PMIs for their first visit than patients in Beijing. 17.6% of patients in Beijing are willing to choose PMIs for consultation, as compared to 71.9% in Qinghai Province. This finding is significantly lower than that of the 2019 study in Beijing by Song et al. (17.6 vs. 60.44%) (38). After preliminary analysis, we suggest that the large difference in the proportion of patients' willingness of first visit in PMIs is probably due to the different sources of research subjects in the two studies. All the samples of Song et al. were from community health service centers/stations, while those of this article were from tertiary, secondary hospitals and community health service centers. Many studies have shown that medical resource availability, transportation convenience, medical care quality, and socioeconomic factors significantly influence on patients' choice of medical institutions (39–41). Beijing is a developed economic city with a lot of high-quality medical resources, while Qinghai Province is an undeveloped economic city with fewer medical resources. The 2020 data have shown that the Gross Domestic Product Per Capita (GDPPC) in Beijing was 164,889 yuan, while Qinghai Province was 50,819 yuan (42). There were 106 tertiary hospitals and 158 secondary

TABLE 3 | Univariate analysis of patients' sociodemographic, attitudes and understanding of relevant policies in different provinces.

Variables	**Provinces *N* (%)**					
	Beijing *N* = 467 (31.0)	**Fujian *N* = 517 (34.3)**	**Qinghai *N* = 523 (34.7)**	**Total *N* = 1,507, *N* (%)**	χ^2	***P***
Gender					0.630	0.730
Male	218 (31.9)	234 (34.3)	231 (33.8)	683 (45.3)		
Female	249 (30.2)	283 (34.3)	292 (35.2)	824 (54.7)		
Age (years)					17.340	**0.008**
<45	276 (33.1)	263 (31.5)	296 (35.4)	835 (55.4)		
45–54	113 (29.7)	144 (37.8)	124 (32.5)	381 (25.3)		
55–64	44 (21.5)	82 (40.0)	79 (38.5)	205 (13.6)		
≥65	34 (39.5)	28 (32.6)	24 (27.9)	86 (5.7)		
Education					12.981	**0.011**
Junior or below	20 (22.2)	25 (27.8)	45 (50.0)	90 (6.0)		
Senior high school	137 (28.6)	172 (35.9)	170 (35.5)	479 (31.8)		
Bachelor or above	310 (33.0)	320 (43.1)	308 (32.8)	938 (62.2)		
Registered permanent residence					12.234	**0.016**
The city's downtown	148 (33.8)	146 (33.3)	144 (32.9)	438 (29.1)		
The city's suburbs	116 (35.9)	111 (34.4)	96 (29.7)	323 (21.4)		
Out-of-town	203 (27.2)	260 (34.9)	283 (37.9)	746 (49.5)		
Length of residence in the city (years)					5.630	0.229
<1	41 (32.3)	44 (34.6)	42 (33.1)	127 (8.4)		
1–2	75 (25.4)	106 (35.9)	114 (38.6)	295 (19.6)		
≥2	351 (32.4)	367 (33.8)	367 (33.8)	1,085 (72.0)		
Household annual income (yuan)					44.866	**<0.001**
<80,000	164 (22.9)	262 (36.6)	289 (40.4)	715 (47.4)		
80,000–150,000	264 (38.2)	218 (31.5)	209 (30.2)	691 (45.9)		
≥150,000	39 (38.6)	37 (36.6)	25 (24.8)	101 (6.7)		
Average monthly medical expense (yuan)					9.085	0.059
≤300	72 (25.8)	102 (36.6)	105 (37.6)	279 (18.5)		
301–800	304 (31.5)	341 (35.3)	320 (33.2)	965 (64.0)		
>800	91 (34.6)	74 (28.1)	98 (37.3)	263 (17.5)		
Chronic disease status					58.202	**<0.001**
Yes	427 (29.3)	513 (35.2)	517 (35.5)	1,457 (96.7)		
No	40 (80.0)	4 (8.0)	6 (12.0)	50 (3.3)		
Degree of satisfaction with the medical technology of PMIs						144.844
<0.001 Not satisfied	9 (16.1)	14 (25.0)	33 (58.9)	56 (3.7)		
Less satisfied	144 (19.6)	315 (42.9)	275 (37.5)	734 (48.7)		
Generally	209 (49.8)	105 (25.0)	106 (25.2)	420 (27.9)		
More satisfied	72 (40.7)	41 (23.2)	64 (36.2)	177 (11.7)		
Very satisfied	33 (27.5)	42 (35.0)	45 (37.5)	120 (8.0)		
Degree of satisfaction with the service attitude of PMIs					121.854	**<0.001**
Not satisfied	12 (14.8)	39 (48.1)	30 (37.0)	81 (5.4)		
Less satisfied	64 (22.6)	104 (36.7)	115 (40.6)	283 (18.8)		
Generally	128 (23.5)	201 (36.9)	216 (39.6)	545 (36.2)		
More satisfied	222 (50.3)	125 (28.3)	94 (21.3)	441 (29.3)		
Very satisfied	41 (26.1)	48 (30.6)	68 (43.3)	157 (10.4)		

(Continued)

TABLE 3 | Continued

Variables	Provinces *N* (%)					
	Beijing *N* = 467 (31.0)	**Fujian *N* = 517 (34.3)**	**Qinghai *N* = 523 (34.7)**	**Total *N* = 1,507, *N* (%)**	χ^2	***P***
Experience of PMIs visits in the past year					3.538	0.171
Yes	400 (31.4)	445 (34.9)	430 (33.7)	1,275 (84.6)		
No	67 (28.9)	72 (31.0)	93 (40.1)	232 (15.4)		
Understanding of the community first visit policy					10.844	**0.004**
Yes	58 (38.9)	57 (38.3)	34 (22.8)	149 (9.9)		
No	409 (30.1)	460 (33.9)	489 (36.0)	1,358 (90.1)		
Recognition of the community first visit policy					309.511	**<0.001**
Not recognize	84 (12.9)	274 (42.0)	295 (45.2)	653 (43.3)		
Mildly recognize	81 (24.5)	130 (39.3)	120 (36.3)	331 (22.0)		
Moderate	194 (55.9)	70 (20.2)	83 (23.9)	347 (23.0)		
Partly recognize	89 (71.8)	24 (19.4)	11 (8.9)	124 (8.2)		
Completely recognize	19 (36.5)	19 (36.5)	14 (26.9)	52 (3.5)		
Understanding of the medical insurance differential reimbursement policy					263.684	**<0.001**
Yes	62 (17.1)	252 (69.4)	49 (13.5)	363 (24.1)		
No	405 (35.4)	265 (23.2)	474 (41.4)	1,144 (75.9)		
Influence of the medical insurance differential reimbursement policy					237.757	**<0.001**
No impact	2 (4.2)	19 (39.6)	27 (56.3)	48 (3.2)		
Less impact	32 (10.3)	183 (58.8)	96 (30.9)	311 (20.6)		
Moderate	134 (24.6)	192 (35.2)	219 (40.2)	545 (36.2)		
More impact	205 (48.6)	80 (19.0)	137 (32.5)	422 (28.0)		
Greatest impact	94 (51.9)	43 (23.8)	44 (24.3)	181 (12.0)		

The bold P values indicates that the difference is statistically significant.

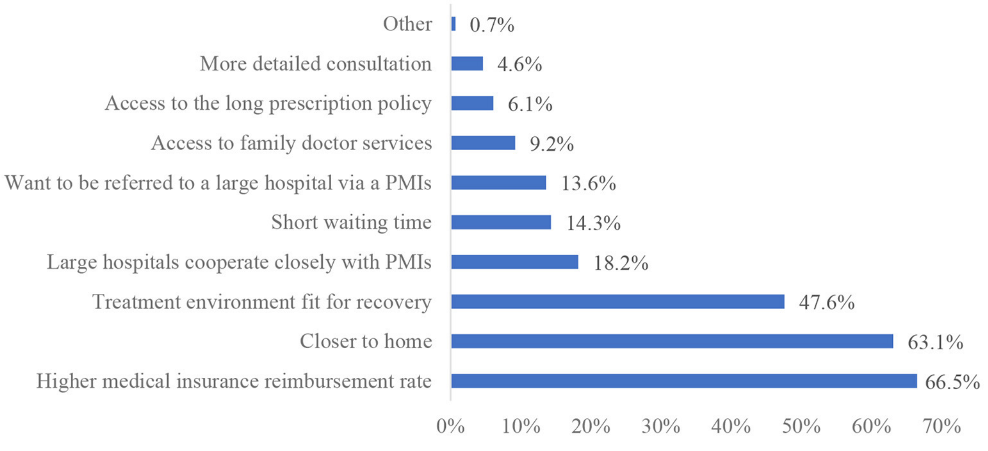

FIGURE 2 | Reasons for patients' willingness for first visit in PMIs.

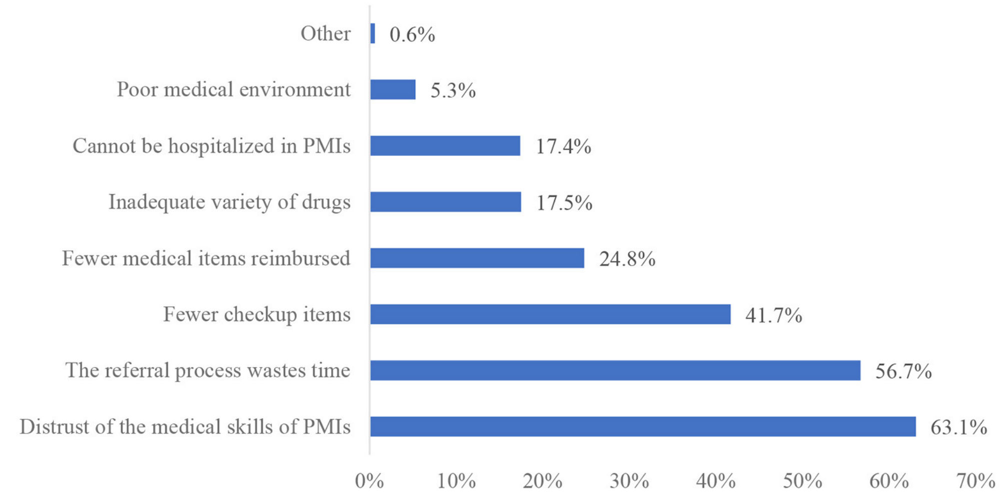

FIGURE 3 | Reasons for patients' unwillingness for first visit in PMIs.

hospitals in Beijing, while only 24 tertiary hospitals and 88 secondary hospitals in Qinghai Province (18). Hence, patients' willingness of first visit in PMIs is influenced by economic development and medical resources in different provinces. In some economically developed provinces in eastern China, the inequality in medical resource allocation between urban hospitals and PMIs has led to an "inverted triangle" phenomenon in the layout of medical resources, which indirectly affected patients' evaluation and preference for PMIs (43, 44). A reason is the different strength of policy implementation in the two provinces. Qinghai Province strictly controls the referral rate; for example, it is stipulated that the referral rate of general township health centers does not exceed 60%. Residents must be first visited in PMIs and hold the "Qinghai Province Employees and Urban and Rural Residents Medical Insurance Tiered Treatment Referral Approval Form" before they can be referred to higher level hospitals, otherwise medical expenses will not be reimbursed (45). Beijing did not explicitly control the referral rate of PMIs, while only the elderly and residents of working age were first visited in PMIs, and the referral process is more flexible (46). Another reason is the different policy of family doctor contract services. Beijing adopts flexible contracting service period of 1, 2, and 3 years, and the contracting service fee is no <100 yuan per year. Qinghai Province is contracted once a year and the contracting service fee is 70 yuan per year.

There was no statistically significant differences for patients' willingness of first visit in PMIs in Qinghai and Fujian. According to our research, two main reasons were found. First, Fujian and Qinghai have a higher number of PMIs per capita. Fujian has 6.25 PMIs per 10,000 people, and Qinghai has 9.94 PMIs per 10,000 people. Second, Fujian's family doctor contracting service is an important initiative to realize community-based first visit. For example, Xiamen City has introduced the "three doctors co-manage patients" (general practitioner, health manager and specialist) family doctor service model. The primary healthcare reform in Xiamen has led patients to visit the PMIs more frequently (22, 47). In Qinghai, economic constraints and accessibility of PMIs have prompted patients to choose PMIs for their first visit (48). The per capita income of residents in Qinghai Province is low. When residents experience illnesses, they may prefer to seek treatment in less costly PMIs. So these reasons lead to high and similar willingness of patients in Fujian and Qinghai provinces to make their first visit in PMIs.

Our study found that recognition of the community first visit policy was associated with patients' willingness of first visit in PMIs. This is consistent with findings of previous study that the higher patients' recognition of the community first visit policy, the greater possibility of patients' willingness to make their first visit in PMIs (49). The results showed that only 11.7% patients recognized the community first visit policy ("completely recognize" and "partly recognize" were regarded as recognize), and the majority of patients were not. This finding was much lower than previous studies conducted in Shenzhen (72.03%), Wuhan (43.06%), Nanjing (59.5%), China (37, 50, 51). Compared with previous studies, there are two major reasons for this difference: First, there is a correlation between understanding of the policy and recognition of the policy for patients. Patients who are more understanding of the policy are more willing to recognize it. Second, sample variability leads to different results. This study's sample was drawn from tertiary and secondary hospitals and community health centers, whereas the samples of previous studies were all drawn from community health centers. Wenya Yu et al. found that patients who supported the community first visit policy were more willing to refer downward to community health centers (52). This study and Wenya Yu's study combined indicate that patients' recognition of the community first visit policy indirectly impacted the utilization of primary health care services. Although there was no statistical difference between understanding of the community first visit policy and patients' willingness of first visit in PMIs, only 9.9% patients know to the community first visit policy. Hence, besides improving the construction of the hierarchical medical treatment system, it is necessary to strengthen the promotion and interpretation of relevant policies for residents.

The influence of the medical insurance differential reimbursement policy was not associated with patients' willingness of first visit in PMIs. However, the medical insurance differential reimbursement policy is one of the main reasons why patients were willing to first visit PMIs. There are three possible reasons for this situation: First, patient' s recognition and trust of service capability of PMIs is an important driver for patients to first visit PMIs. Under the premise that service capacity of PMIs can meet patients' medical needs, and the government implements the medical insurance differential reimbursement policy, patients will be willing to first visit PMIs. However, the current service capacity of PMIs in China is uneven and cannot meet the growing needs of patients (8). When the gap in service quality between PMIs and large hospitals is obvious, the medical insurance differential reimbursement policy cannot effectively guide patients to make their first visits in PMIs. Hence, the precondition for moderating effect of the differential reimbursement policy is the homogenization of quality of medical services. Second, medical services are a rigid demand, and patients' demand for medical services is less affected by price. In order to maximize health benefits, patients will choose better medical care. Third, the influence of the medical insurance differential reimbursement policy is influenced by many factors, such as family financial status, severity of illness, and education (53). Thus, the influence of the medical insurance differential reimbursement policy in this study was not associated with patients' willingness of first visit in PMIs, probably because of the influence of other variables in the model.

Binary logistic regression results showed that patients who were very satisfied with medical technology of PMIs were more willing to make their first visit in PMIs than those who were generally satisfied. However, few patients (19.7%) were satisfied with the medical technology of PMIs. Previous studies have shown that the medical technology of PMIs plays a decisive role for patients' willingness to make first visits (31, 54). This study also found that the major reason for patients' unwillingness of first visit in PMIs was distrust of the medical skills of PMIs. Patients may compare the medical technology of PMIs with that of large hospitals. However, compared with large hospitals, PMIs do not have advantages in medical equipment, medical personnel, and medical environment. Another reason may be that the medical service capacity of PMIs cannot meet patients' medical needs. The Chinese government proposed the Medical Alliance Policy in 2017 (5), which aims to promote the downward transfer of focus and sinking of resources in health care and enhance the capacity of primary care services through establishing partnerships among PMIs, secondary, and tertiary hospitals. Secondary, tertiary hospitals supervise and guide medical work of primary health care institutions, and regularly provide targeted training and exercise for primary care staff. However, it seems that implementation of the Medical Alliance Policy has not achieved the expected effects, and patients' preference for primary care providers has not significantly changed. Since launching the health care reform plan in 2009, the Chinese government has formulated several policies, and increased funding for primary care, from 19 billion yuan in 2008 to 197 billion yuan in 2018 (55). A series of plans to strengthen the construction of the primary health care team, to alleviate the residents "difficult and expensive medical treatment" played an important role.

Strengths and Limitations

This study is a multi-province investigation study with a large sample, which increases the generalizability in the Chinese setting. One of this article's outstanding strengths is understanding the impact of policies on patients' willingness of first visit in PMIs, and provided preliminary evidence to enhance the utilization of primary health care. Meanwhile, there are several limitations in this study. First, only partial factors were included in this study, but there are many factors associated with patients' willingness of first visit in PMIs (severity of illness, doctor-patient relationship) (56, 57). Second, this study only included the community first visit policy and health insurance reimbursement policy, but not the family doctor contracting policy. Third, all data were obtained from questionnaires, which might cause response bias. Fourth, this study used convenience sampling to select patients to administer questionnaires, so selection bias was unavoidable.

CONCLUSIONS

Patients' willingness of first visit in PMIs is associated with different provinces, recognition of the community first visit policy, and satisfaction with the medical technology of PMIs. As influenced by factors such as local economic conditions, distribution of health resources, and differences in policy formulation, there are certain regional differences in patients' willingness of first visit in PMIs. This study explored the factors associated with patients' willingness of first visit in PMIs, and provided preliminary evidence to enhance the utilization of primary health care. To increase patient' rate of visits in PMIs, it is important to improve service capacity and quality of PMIs and change residents' attitudes for PMIs. Meanwhile, it is recommended that different provinces have to develop appropriate relevant health policies based on the actual situation. Using easy-to-understand language to publicize the advantages of relevant health policies in the community, strengthening residents' understanding and recognition of relevant health policies and guiding them to seek medical treatment in PMIs are important. The aim of all these measures is to achieve community-based first visit via guidance, considering that mandatory community-based first visit in China cannot be achieved overnight. In the background of the Health China strategy, the Chinese government is exploring health management-oriented primary health service policies by bundling medical treatment, medicine and health insurance through implementing outpatient capitation payment. Therefore, in the future, it is necessary to explore whether capitation payments for outpatient can promote patient visits to PMIs. This is also the essential way to promote community-based first visit, two-way referral and hierarchical treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Capital Medical University. The patients/participants provided their written informed consent to participate in this study (NO.Z2020SY117).

AUTHOR CONTRIBUTIONS

JL and JY contributed to conception and design of the study, and manuscript revision. NZ, HY, and HZ collected data and organized the database. JL wrote the first draft of the manuscript. NZ and HZ performed the statistical analysis. All authors contributed to reading the manuscript and approved the submitted version.

FUNDING

This study was supported by the National Natural Science Foundation of China (grant number: 71603175).

ACKNOWLEDGMENTS

We thank all the participants, experts and researchers who participated in this study. We also appreciate Tao Xin from the Department of Applied Linguistics, School of Medical Humanities, Capital Medical University, for the language editing assistance.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.842950/full#supplementary-material

REFERENCES

1. WHO. *Declaration of Alma-Ata*. USSR: World Health Organization (1978). Available online at: http://www.who.int/publications/almaata_declaration_en.pdf (accessed December 06, 2021).
2. Eggleston K, Ling L, Qingyue M, Lindelow M, Wagstaff A. Health service delivery in China: a literature review. *Health Econ.* (2008) 17:149–65. doi: 10.1002/hec.1306
3. Jing X, Xu L, Qin W, Zhang J, Lu L, Wang Y, et al. The willingness for downward referral and its influencing factors: a cross-sectional study among older adults in Shandong, China. *Int J Environ Res Public Health.* (2020) 17:369. doi: 10.3390/ijerph17010369
4. Shi ML. Status quo and institutional arrangement of primary health care system based on integrated perspective in China. *Chin J Health Policy.* (2012) 5:28–33. doi: 10.3969/j.issn.1674-2982.2012.09.005
5. *General Office of the State Council on Promoting the Medical Union Guiding Opinions on Construction and Development.* (2017). Available online at: http://www.gov.cn/zhengce/content/2017-04/26/content_5189071.htm (accessed December 08, 2021).
6. Dong X, Liu L, Cao S, Yang H, Song F, Yang C, et al. Focus on vulnerable populations and promoting equity in health service utilization–an analysis of visitor characteristics and service utilization of the Chinese community health service. *BMC Public Health.* (2014) 14:503. doi: 10.1186/1471-2458-14-503
7. Jin YZ, Zhu YM, Zhang YG, Xu L, Meng QY. Impact of healthcare system development on healthcare seeking behavior among patients in China. *Chin Health Econ.* (2017) 36:67–70. doi: 10.7664/CHE20170619
8. Li X, Lu J, Hu S, Cheng KK, De Maeseneer J, Meng Q, et al. The primary health-care system in China. *Lancet.* (2017) 390:2584–94. doi: 10.1016/S0140-6736(17)33109-4
9. Xiao Y, Qiu QM, Huang YX, Zhu SY. Patients gather in large hospitals: the current situation of Chinese hospitals and the direction of medical reform. *Postgrad Med J.* (2021). doi: 10.1136/postgradmedj-2021-140147. [Epub ahead of print].
10. Li Y, Xing YY. Emperical study on the choice behavior of medical treatment in outpatients in China under the back-ground of hierarchical diagnosis and treatment. *Chin Hosp Manag.* (2020) 40:50–4. doi: 10.1093/oso/9780190061081.003.0003
11. Liu GG, Vortherms SA, Hong X. China's health reform update. *Annu Rev Public Health.* (2017) 38:431–48. doi: 10.1146/annurev-publhealth-031816-044247
12. Niu Y, Zhang L, Ye T, Yan Y, Zhang Y. Can unsuccessful treatment in primary medical institutions influence patients' choice? A retrospective cluster sample study from China. *BMJ Open.* (2019) 9:e022304. doi: 10.1136/bmjopen-2018-022304
13. Zhou Z, Zhao Y, Shen C, Lai S, Nawaz R, Gao J. Evaluating the effect of hierarchical medical system on health seeking behavior: a difference-in-differences analysis in China. *Soc Sci Med.* (2021) 268:113372. doi: 10.1016/j.socscimed.2020.113372
14. *Guiding Opinions of the Central Committee of the CPC and the State Council on Promoting the Construction of Hierarchical Medical System.* (2015). Available online at: http://www.gov.cn/zhengce/content/2015-09/11/content_10158.htm (accessed October 09, 2021)
15. Xiao Y, Wu XH, Chen J, Xie FF. Challenges in establishing a graded diagnosis and treatment system in China. *Fam Pract.* (2021) 39:214–6. doi: 10.1093/fampra/cmab089
16. Wu D, Lam TP, Lam KF, Zhou XD, Sun KS. Health reforms in china: the public's choices for first-contact care in urban areas. *Fam Pract.* (2017) 34:194–200. doi: 10.1093/fampra/cmw133
17. Yip W, Hsiao W. Harnessing the privatisation of China's fragmented health-care delivery. *Lancet.* (2014) 384:805–18. doi: 10.1016/S0140-6736(14)61120-X
18. China NHCotPsRo, editor. *2020 China Health Statistics Yearbook*. Beijing: China Union Medical University Press (2021).
19. Jiang MZ, Fu Q, Xiong JY, Li XL, Jia EP, Peng YY, et al. Preferences heterogeneity of health care utilization of community residents in China: a stated preference discrete choice experiment. *BMC Health Serv Res.* (2020) 20:430. doi: 10.1186/s12913-020-05134-4
20. Liu Y, Kong Q, Wang S, Zhong L, van de Klundert J. The impact of hospital attributes on patient choice for first visit: evidence from a discrete choice experiment in Shanghai, China. *Health Policy Plan.* (2020) 35:267–78. doi: 10.1093/heapol/czz159
21. Shen M, He W, Li L. Incentives to use primary care and their impact on healthcare utilization: evidence using a public health insurance dataset in China. *Soc Sci Med.* (2020) 255:112981. doi: 10.1016/j.socscimed.2020.112981

22. Zeng Y, Xu W, Chen L, Chen F, Fang Y. The influencing factors of health-seeking preference and community health service utilization among patients in primary care reform in Xiamen, China. *Patient Prefer Adher.* (2020) 14:653–62. doi: 10.2147/PPA.S242141
23. Zhang L, Li J, Ma T, Zhang R, Zhang Q. Usual source of care and experiences with primary care among community health service centre patients in Changchun, China: a cross-sectional survey. *Health Soc Care Community.* (2020) 28:1979–88. doi: 10.1111/hsc.13009
24. Jia E, Gu Y, Peng Y, Li X, Shen X, Jiang M, et al. Preferences of patients with non-communicable diseases for primary healthcare facilities: a discrete choice experiment in Wuhan, China. *Int J Environ Res Public Health.* (2020) 17:3987. doi: 10.3390/ijerph17113987
25. Yan YH, Kung CM, Yeh HM. The impacts of the hierarchical medical system on national health insurance on the resident's health seeking behavior in Taiwan: a case study on the policy to reduce hospital visits. *Int J Environ Res Public Health.* (2019) 16:3167. doi: 10.3390/ijerph16173167
26. Zhou S, Xu J, Ma X, Yuan B, Liu X, Fang H, et al. How Can One Strengthen a Tiered Healthcare System through Health System Reform? Lessons Learnt from Beijing, China. *Int J Environ Res Public Health.* (2020) 17:8040. doi: 10.3390/ijerph17218040
27. Feng D, Zhang D, Li B, Zhang Y, Serrano R, Shi D, et al. Does having a usual primary care provider reduce patient self-referrals in rural China's rural multi-tiered medical system? A retrospective study in Qianjiang District, China. *BMC Health Serv Res.* (2017) 17:778. doi: 10.1186/s12913-017-2673-6
28. Liu J, Yin H, Zheng T, Ilia B, Wang X, Chen R, et al. Primary health institutions preference by hypertensive patients: effect of distance, trust and quality of management in the rural Heilongjiang province of China. *BMC Health Serv Res.* (2019) 19:852. doi: 10.1186/s12913-019-4465-7
29. Liu Z, Tan Y, Liang H, Gu Y, Wang X, Hao Y, et al. Factors influencing residents' willingness to contract with general practitioners in Guangzhou, China, during the GP policy trial phase: a cross-sectional study based on andersen's behavioral model of health services use. *Inquiry.* (2019) 56:46958019845484. doi: 10.1177/0046958019845484
30. *State Council of the People's Republic of China Opinions on Promoting the Construction of Hierarchical Medical System.* (2015). Available online at: http://www.gov.cn/zhengce/content/2015-09/11/content_10158.htm (accessed December 01, 2021).
31. Li X, Zhang L, Li Z, Tang W. Patient choice and willingness toward gatekeepers as first-contact medical institutions in Chinese Tiered healthcare delivery system: a cross-sectional study. *Front Public Health.* (2021) 9:665282. doi: 10.3389/fpubh.2021.665282
32. Bai G, Zhou Y, Luo L, Wang Z. Resource allocation for chronic diseases based on a patient willingness survey. *Int J Health Plann Manage.* (2019) 34:926–34. doi: 10.1002/hpm.2864
33. Escarce JJ, Kapur K. Do patients bypass rural hospitals? Determinants of inpatient hospital choice in rural California. *J Health Care Poor Underserved.* (2009) 20:625–44. doi: 10.1353/hpu.0.0178
34. Kruk ME, Hermosilla S, Larson E, Mbaruku GM. Bypassing primary care clinics for childbirth: a cross-sectional study in the Pwani region, United Republic of Tanzania. *Bull World Health Organ.* (2014) 92:246–53. doi: 10.2471/BLT.13.126417
35. Kujawski SA, Leslie HH, Prabhakaran D, Singh K, Kruk ME. Reasons for low utilisation of public facilities among households with hypertension: analysis of a population-based survey in India. *BMJ Glob Health.* (2018) 3:e001002. doi: 10.1136/bmjgh-2018-001002
36. Macinko J, Guanais FC, Mullachery P, Jimenez G. Gaps in primary care and health system performance in six Latin American and Caribbean countries. *Health Aff.* (2016) 35:1513–21. doi: 10.1377/hlthaff.2015.1366
37. Gan Y, Li W, Cao S, Dong X, Li L, Mkandawire N, et al. Patients' willingness on community health centers as gatekeepers and associated factors in Shenzhen, China: a cross-sectional study. *Medicine.* (2016) 95:e3261. doi: 10.1097/MD.0000000000003261
38. Song HY, Zuo X, Cui CS, Meng K. The willingness of patients to make the first visit to primary care institutions and its influencing factors in Beijing medical alliances: a comparative study of Beijing's medical resource-rich and scarce regions. *BMC Health Serv Res.* (2019) 19:361. doi: 10.1186/s12913-019-4184-0
39. Borah BJ. A mixed logit model of health care provider choice: analysis of NSS data for rural India. *Health Econ.* (2006) 15:915–32. doi: 10.1002/hec.1166
40. Cao Y, Zhen F, Wu H. Public transportation environment and medical choice for chronic disease: a case study of Gaoyou, China. *Int J Environ Res Public Health.* (2019) 16:1612. doi: 10.3390/ijerph16091612
41. Liu Y, Zhong L, Yuan S, van de Klundert J. Why patients prefer high-level healthcare facilities: a qualitative study using focus groups in rural and urban China. *BMJ Glob Health.* (2018) 3:e000854. doi: 10.1136/bmjgh-2018-000854
42. Statistics NBo. *2020 China Statistical Yearbook*. Beijing: China Statistics Press (2021).
43. Dong E, Liu S, Chen M, Wang H, Chen LW, Xu T, et al. Differences in regional distribution and inequality in health-resource allocation at hospital and primary health centre levels: a longitudinal study in Shanghai, China. *BMJ Open.* (2020) 10:e035635. doi: 10.1136/bmjopen-2019-035635
44. Wan G, Wei X, Yin H, Qian Z, Wang T, Wang L. The trend in primary health care preference in China: a cohort study of 12,508 residents from 2012 to 2018. *BMC Health Serv Res.* (2021) 21:768. doi: 10.1186/s12913-021-06790-w
45. *Notice on the Further Improvement of the Opinion of Reasonable Expenditure on Medical Expenses.* General Office of the People' s Government of Qinghai Province (2015). Available online at: https://wsjkw.qinghai.gov.cn/zwgk/xxgkml/tzgg/2015/06/09/1433814013521.html (accessed December 15, 2021).
46. *Rules for the Implementation of the Basic Medical Insurance Scheme for Urban and Rural Residents in Beijing*. Beijing Municipal Human Resources and Social Security Bureau (2017). Available online at: http://www.beijing.gov.cn/zhengce/zhengcefagui/201905/t20190522_60735.html (accessed December 15, 2021).
47. Zeng Y, Yuan Z, Chen L, Wu J, Chen F, Fang Y. Primary care reforms in managing chronic diseases in Xiamen, China: a tentative assessment. *Int J Health Plann Manage.* (2019) 34:e1609–20. doi: 10.1002/hpm.2854
48. Hu X, Zhang H, Sun X, Gu Y, Zhen X, Gu S, et al. Older adults' choices of first-contact care and related factors in Zhejiang and Qinghai Province, China. *Geriatr Gerontol Int.* (2019) 19:938–44. doi: 10.1111/ggi.13746
49. Wang LJ, Lu ZH, Li YW. Willingness and its influential factors for initial medication-seeking at grassroots institution and referral among urban and rural residents with medical insurance in Shandong province. *Chinese Journal of Public Health.* (2021) 37:465–9.
50. Li W, Wang D, Gan Y, Zhou Y, Chen Y, Li J, et al. Factors influencing government insurance scheme beneficiary acceptance of the gatekeeper policy: a cross-sectional study in Wuhan, China. *BMC Health Serv Res.* (2018) 18:241. doi: 10.1186/s12913-018-3010-4
51. Li WZ, Gan Y, Zhou YF, Chen YW, Li J, Kkandawire N, et al. Factors affecting patient satisfaction with community health service under the gatekeeper system: a cross-sectional study in Nanjing, China. *Biomed Environ Sci.* (2017) 30:685–90. doi: 10.3967/bes2017.092
52. Yu W, Li M, Nong X, Ding T, Ye F, Liu J, et al. Practices and attitudes of doctors and patients to downward referral in Shanghai, China. *BMJ Open.* (2017) 7:e012565. doi: 10.1136/bmjopen-2016-012565
53. Qiu C, Wu X. The effect of medical insurance on outpatient visits by the elderly: an empirical study with china health and retirement longitudinal study data. *Appl Health Econ Health Policy.* (2019) 17:175–87. doi: 10.1007/s40258-018-0443-1
54. Wu D, Lam TP. Underuse of primary care in China: the scale, causes, and solutions. *J Am Board Fam Med.* (2016) 29:240–7. doi: 10.3122/jabfm.2016.02.150159
55. Li X, Krumholz HM, Yip W, Cheng KK, De Maeseneer J, Meng Q, et al. Quality of primary health care in China: challenges and recommendations. *Lancet.* (2020) 395:1802–12. doi: 10.1016/S0140-6736(20)30122-7
56. Victoor A, Delnoij DM, Friele RD, Rademakers JJ. Determinants of patient choice of healthcare providers: a scoping review. *BMC Health Serv Res.* (2012) 12:272. doi: 10.1186/1472-6963-12-272
57. Zhu J, Li J, Zhang Z, Li H. Patients' choice and preference for common disease diagnosis and diabetes care: a discrete choice experiment.

Int J Health Plann Manage. (2019) 34:e1544–55. doi: 10.1002/hpm.2841

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

PERSPECTIVE
published: 04 April 2022
doi: 10.3389/fmed.2022.826776

Embedding the Community and Individuals in Disease Prevention

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The primary prevention of non-communicable diseases is one of the most challenging and exciting aspects of medicine and primary care this century. For cancer, it is an urgent matter in light of the increasing burden of the disease among younger people and the higher frequency of more aggressive forms of the disease for all ages. Most chronic disorders result from the influence of the environment on the expression of genes within an individual. The environment at-large encompasses lifestyle (including nutrition), and chemical/physical and social exposures. In cancer, the interaction between the (epi)genetic makeup of an individual and a multiplicity of environmental risk and protecting factors is considered key to disease onset. Thus, like for precision therapy developed for patients, personalized or precision prevention is envisioned for individuals at risk. Prevention means identifying people at higher risk and intervening to reduce the risk. It requires biological markers of risk and non-aggressive preventive actions for the individual, but it also involves acting on the environment and the community. Social scientists are considering micro (individual/family), meso (community), and macro (country population) levels of care to illustrate that problems and solutions exist on different scales. Ideally, the design of interventions in prevention should integrate all these levels. In this perspective article, using the example of breast cancer, we are discussing challenges and possible solutions for a multidisciplinary community of scientists, primary health care practitioners and citizens to develop a holistic approach of primary prevention, keeping in mind equitable access to care.

Keywords: non-communicable disease, primary prevention, environment, primary healthcare, risk reduction, breast cancer, epigenome, social determinant

Edited by:
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Specialty section:
This article was submitted to
Family Medicine and Primary Care,
a section of the journal
Frontiers in Medicine

Received: *01 December 2021*
Accepted: *10 March 2022*
Published: *04 April 2022*

Citation:
Bellanger MM, Zhou K and
Lelièvre SA (2022) Embedding
the Community and Individuals
in Disease Prevention.
Front. Med. 9:826776.
doi: 10.3389/fmed.2022.826776

INTRODUCTION

Progress has been made globally to improve the health of populations. However, non-communicable diseases (NCDs) continue to impose a burden on individuals and communities as well as on economies in countries of all income levels. According to the World Health Organization (WHO), more than 80% of premature deaths related to NCDs are due to cardiovascular diseases (CVD) (44%), cancers (23%), chronic respiratory diseases (CRD) (10%), and diabetes (4%) (1). In addition, NCDs may contribute to disability. Between 1990 and 2019, there was a marked decline in disability–adjusted-life-years (DALYs) rates for CVD, and to a lesser extent for CRD (2). However, diabetes related DALYs were on the rise both in younger and older populations; alarmingly, DALYs related to cancers have been increasing since 2015 in people aged 15–49 (**Figure 1**).

In 2019, the global burden of cancer in adolescents and young adults (AYA), encompassing populations aged 15–39, was 1.2 million incident cancer cases and 0.4 million cancer-related deaths, which caused 23.5 million DALYs lost (3). Western Europe was the region with the highest age-standardized incidence rate of AYA cancers in the world (75.3 for women and 67.4 for men per 100,000 person-years) (3). Strikingly, for some cancers (i.e., breast, lung, and thyroid), the burden of incidence has been shifting from advanced-aged populations to AYA for whom it might represent the most significant increase in coming years (4–6). Particularly worrisome, breast cancer mortality among AYA has ceased decreasing because of the increasing proportion of "distant diseases" (5, 7). Thus, not only cancer is more frequent in AYA, but also certain forms of the disease are very aggressive. There is a sense of urgency to harness prevention of NCDs and notably, cancers.

Prevention of the first onset of a disease in an individual (i.e., primary prevention) is one of the three pillars of medicine, along with detection and treatment. Preventing NCDs requires to know individual and environmental factors contributing to disease emergence and develop the means to act. Policies focused on "removing the cause," as it is case with tobacco, become complex to establish when many NCDs are triggered by a combination of factors. Communication is currently centered on maintaining health with statements related to exercise and nutrition, and possibly lifestyle; but messages mostly target the general population. Epidemiology is at the forefront of primary prevention by proposing links between specific diseases and potential individual, social and environmental factors. However, the development of preventive interventions will require knowing the mechanisms that translate risk factors at the cellular level.

Individual factors contributing to NCDs may be anatomical and functional, and can often be related to genetic and epigenetic alterations (8). The epigenetic nature of NCDs directly links individuals to the lifelong impact of their environment. In health, the environment may be defined as any external factor that has an impact on an organism. Environmental risk factors may trigger global as well as specific biochemical alterations of the DNA and histone proteins that constitute the chromatin (9). Environmental elements acting on the epigenome may be categorized as modifiable risk factors, firstly because they might be changed via external actions (e.g., behavior, policies), but also because the malleable nature of the epigenome renders their epigenetic impact reversible.

The environment to which an individual is exposed during lifespan is complex. The exposome includes chemical and physical factors, nutrition and socioeconomic conditions (10). If chemical and physical factors are detrimental to the organism, they are considered pollutants. These factors have been involved in neurological disorders (11, 12), CVDs (13), respiratory disorders (14), thyroid diseases (15), allergies (16), diabetes (17), congenital disorders (18), and cancers (19). Exposure may be linked to lifestyle, but most of the time, it is imposed on people due to agricultural, industrial and urban activities. Nutrition may also increase the risk of NCDs. It may seem that risk is based on individual or family choices (20). However, food preservation and processing are also imposed on consumers (21). In contrast to other elements of the exposome, nutrition is always present and thus, it may be regarded as a positive or negative modulator of risk. Food insecurity has been linked with a risk of CVD, highlighting the importance of considering socioeconomic aspects of the environment (22).

Socioeconomic factors have an impact on NCDs globally, locally and individually (23). The NCDs unevenly affect countries depending on income level. According to the 2019 WHO global burden of disease, more than three quarters of NCD deaths occur in low-and middle-income countries (LMICs) and mostly in people 30–69 years old (1). For instance, in the poorest countries, women younger than 50 bear a higher burden of breast cancer mortality (24). Within a given country, the socioeconomically disadvantaged children and adults often suffer disproportionally from NCDs due to cumulative exposures to detrimental factors in their living areas and social stressors that prevent them from adopting a healthy lifestyle (25, 26). New evidence of the impact of the "*biological embodiment of social disadvantage*" on NCDs, beyond behavioral risk factors, has been brought based on large cohort studies in different countries and contexts (27).

Understanding the mechanisms or the causal pathways leading to the onset of NCDs is required to implement effective prevention strategies that will rely on clear connections between cumulative risks, social determinants and the body (25). In this perspective article, we report some of the most commonly used methods for primary prevention, before proposing an ecological model or a holistic approach inclusive of a multidisciplinary community of researchers, citizens, and healthcare practitioners to design interactive risk reduction programs.

SHEDDING LIGHT ON SOME PRIMARY PREVENTION STRATEGIES

Prevention strategies and policy-based interventions for NCDs have mainly targeted modifiable behavioral risk factors. Most strategies are nationwide or regional. Plans including taxation and smoking ban in public places along with education campaigns and targeted programs for populations of low socioeconomic status, have helped improve population health, especially in high- and upper-middle-income countries (HUMICs). There is now evidence of a decrease in mortality from lung cancer and other NCDs associated with smoking cessation (28). The 2013 WHO 25 × 25 Global Action Plan to reduce NCD-related premature mortality by 25% by 2025 aims to strengthen health systems and reinforce prevention policies for a decrease in incidence of the top four NCDs (CVD, cancers, CRD, and diabetes). This plan recommends efforts to be placed worldwide on risk factors, such as "tobacco use, physical inactivity, unhealthy diet, and harmful use of alcohol" (1). Priority is heightened since LMICs that have been under socioeconomic and epidemiological transitions, are facing the consequences of lifestyle changes (29) while the burden of infection-related diseases remains high (23).

Following the WHO recommendations on "fiscal policies for diet and prevention of NCDs," a growing number of countries

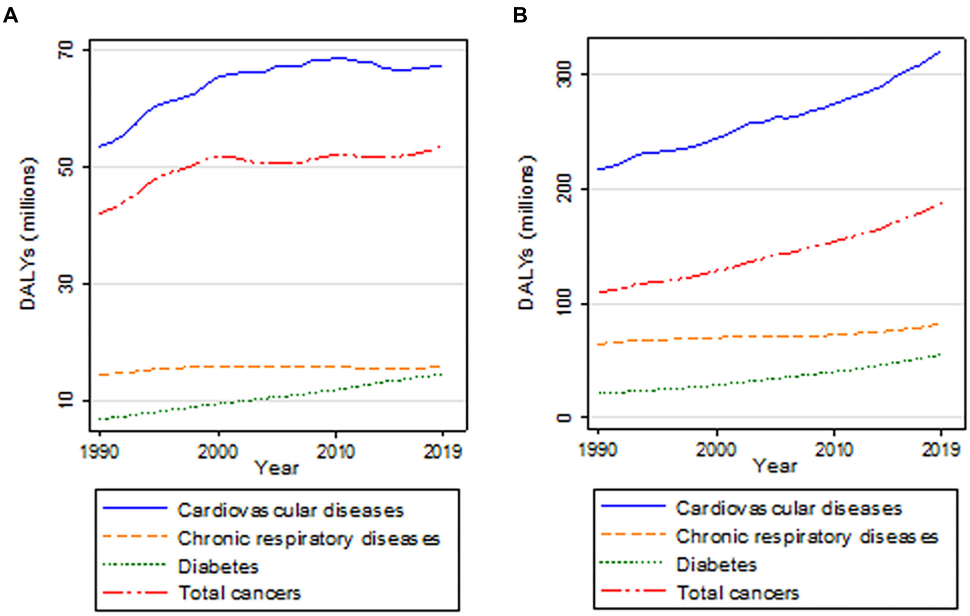

FIGURE 1 | Trends in DALYs for the four major NCDs, for people aged 15–49 years **(A)** and for people aged 50 years and above **(B)**. Source: Institute for Health Metrics and Evaluation (3).

have introduced taxations on sugar-sweetened beverages. These policies influence households and individuals' revenue and consumption while acting as potential levers to reduce diet-related risk factors (30). Implemented in few countries, like Denmark, economic incentives, such as selective taxations on foods to favor fruits, vegetables, and fiber consumption and decrease fat and saturated fat intake were effective to alter dietary behavior, leading to a reduction of the burden of ischemic heart disease and stroke, and to a lesser extent colorectal cancer (31). Fiscal policies such as tax on junk food and subsidy on fruit and vegetables in New Zealand resulted in larger health gain estimates than the 10% projected annual increase in tobacco tax over 15 years, with similar outcomes to those resulting from alcohol taxes (32). However, despite overall progress in prevention of NCDs through population-wide programs, disparities remain within and between countries. A study performed in 194 countries during the last five years reveals a huge gap between plans with policies targeting behavioral risks, such as use of tobacco, alcohol and unhealthy food, and actual implementations, particularly in countries where corporate interests may be in conflict with the health of their populations (33, 34).

Prevention through vaccination programs appear to be effective for human papillomavirus (HPV). Most of the HUMICs that allocated resources to such programs have observed a reduction in cervical cancer risk. The WHO identifies HPV and screening of women aged 30–49 as "best buys," i.e., effective prevention interventions with cost-effectiveness ratio $\leq \$_{International}$ 100 per DALY averted in LMICs (35). This endeavor has been reinforced via the 2020 WHO global strategy to accelerate the elimination of cervical cancer as a public health problem. Importantly, successful interventions were most often associated with schools and community involvements (23).

There is recent evidence of the cost-effectiveness of interventions performed at the community level and focused on diet for breast and ovarian cancers or on physical activity for NCDs including breast cancer in high income countries (36). Yet, several countries have invested in drug therapies and surgical procedures for breast cancer risk reduction. Efforts are necessary in lifestyle-related interventions for which the impact is likely to be higher since it will reduce the risk of other NCDs.

Disease prevention may require identifying the populations in which risk is highly confined. This method called risk stratification in epidemiology is most effective if quantitative assessment or biomarkers are available. The detection of mutations and single nucleotide polymorphisms has been in place for certain disorders, notably cancers (37). However, this approach is not sufficient to identify high-risk levels. For the most prevalent breast cancer for instance, the handful of well-established germline mutations only accounts for 5–10% of cases. Additional markers are being determined based on established links between the environmental or individual factors that they represent and a higher rate of disease onset. Because most of the risk factors for NCDs have been linked to epigenetic changes, a great deal of progress in risk stratification is expected to come from the identification of markers related to epigenetic alterations and thus, gene transcription products such as miRNAs that are stable in blood (9).

Risk stratification might lead to risk assessment on a per individual basis and be viewed as a key step toward individualized prevention; however, biomarkers would need to bring sufficient discrimination between risk levels (38).

Individualized prevention should consider not only the level of risk of an individual but also the nature of exposure. This concept is based on findings from mechanistic investigations revealing that different types of epigenetic pathways or modifications are affected depending on the nature of the risk (9). Additionally, the method used to prevent risk-mediated epigenetic modifications needs to target the epigenetic pathway that was specifically modified by risk exposure, as shown for instance for breast tumor onset (39). To act at the individual or micro level, lifestyle and nutritional changes might be envisioned, as well as therapies. Some epigenetic changes might be temporary and easily modified, by simply removing exposure. If exposure is strong enough or long enough, epigenetic modifications might ultimately become "permanent." Such situation would call for the use of targeted epigenetic modifiers, the nature of which remains to be clearly defined since the notion of benefit/risk is particularly stringent when treating people who have not yet developed the targeted disease.

Primary prevention cannot solely be performed at the individual level. The multifactorial risk stratification that is necessary to identify individuals at highest risk has shifted personalized prevention toward precision prevention that encompasses large numbers of participants to identify meaningful combinations of factors and their related biomarkers (40). Yet, there is an essential intermediate level in prevention between the individual and the population that would still empower the individual within the local community. In light of the social determinants of NCDs and the powerful effect of interventions at the community level mentioned above, the community at large or meso level is essential to include.

INTEGRATION OF MESO WITH MICRO AND MACRO LEVELS IN RISK MITIGATION

Social and environmental factors are affecting health and well-being. Exposure occurs throughout the lifespan and at individual, community and population levels. Acting on the social determinants of health is essential to reduce the risk and burden of NCDs and relies on an integrated approach (41) involving primary healthcare. Evidence shows that the distribution of DALYs from NCDs is largely dependent on social determinants of health embedded in behavioral risk factors (1). This finding is reflected in both HUMICs and LMICs in which social inequities intertwine with behavioral and strictly environmental risk factors (e.g., air pollution and chemical exposures), usually occurring from early childhood to late adulthood (41). In its updated global action plan, WHO urges to "*strengthen and orient health systems to address the prevention and control of NCDs and the underlying social determinants through people-centered primary health care and universal health coverage*" (42).

Integrated approaches at the community and primary health care levels can stimulate synergies in service delivery and help identify individuals and groups at highest risk, before delivering interventions to mitigate risks (43). Prevention and care must go hand-in-hand, especially for family and primary care (23) and rely on the micro-, meso-, and macro-level framework. Broadly speaking, this framework refers to interactions with individuals, primary care organization for the community and national, federal and local policies, depending upon systems and targeted populations. Embedding integrated actions across different levels and across sectors as a consistent "social determinant" approach to mitigate the risk of NCDs requires the necessary policies to align priorities across sectors and to define the assessment of key outcomes. In addition, building an integrated approach of services and interventions that profiles the risks of NCDs has several advantages. While supporting individuals as essential players of their health and well-being, it empowers them to have broader impacts by involving their community and endorsing key messages otherwise hindered in large prevention campaigns or inaccessible. In return, the community is associated with other stakeholders who are able to improve conditions across the life course, and ultimately reduce social inequalities (41). This approach entails working in close partnership with public and private sectors outside the healthcare system, such as schools and colleges, food industries and environmental agencies, toward a sustainable community. Effective public health policies implemented where people live and work help tackling the root of

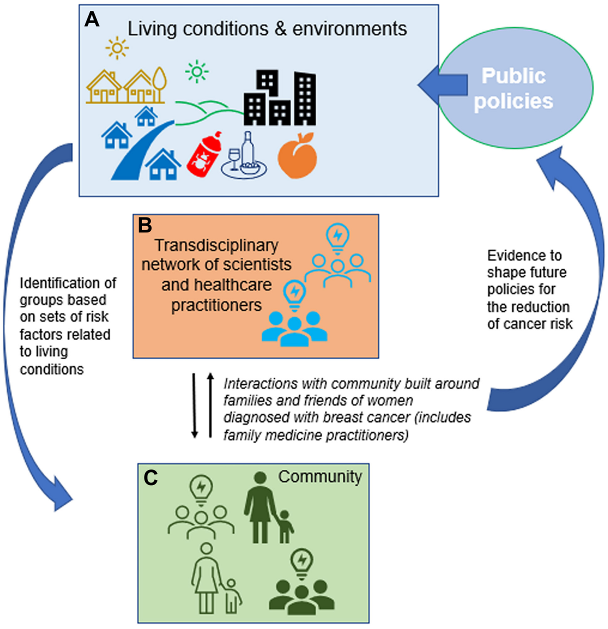

FIGURE 2 | Building communities for research on primary prevention of breast cancer. **(A)** Public health policies shape most of our environment by regulating pollutants, nutrition and the recreational use of potentially harmful substances, in addition to healthcare access and delivery. Along with lifestyle and social determinants of health, chemical and physical environmental factors influence the risk of developing breast cancer. **(B)** The transdisciplinary network of IBCN scientists and healthcare practitioners aims to recruit cancer free people (friends, family members) from within the community of women who develop breast cancer to run projects focused on communities representing different sets of risk factors **(C)**. Outcomes are expected to be the design of interventions to reduce breast cancer risk and an impact on public policies.

inequality that people face in the risks of NCDs. Outcomes will be new prevention priorities, as we illustrate below with the cancer prevention strategy for AYA.

Conventional passive cancer detection (44) should be shifted toward an active targeting of modifiable environmental risk factors during windows of susceptibility occurring in young age (45). The challenge of shifting to this new approach with AYA is undeniable. The conventional approach requires working and investing within the health system. However, to target environmental risks, holistic solutions with meso- and macro-level efforts are necessary to develop effective interventions that bear sustained coverage (46, 47).

The AYA population requires new preventive strategies. For example, conventional prevention strategies for breast cancer concentrate on middle-aged and older people and rely on the early detection of incident cases, which has led to a lack of priority to focus on primary prevention to decrease breast cancer risk. This is not an effective choice for AYA due to the poor sensitivity and specificity of screening techniques among young women (44). Accumulating evidence indicates that risk is often established during windows of susceptibility and that it might then take two decades prior disease diagnosis (46). There is room to act on environmental risk exposure; lifestyle, nutrition and chemical substances have become important targets for prevention efforts (45, 48).

Community engagement is emerging as a central node in identifying and reducing the risk of NCDs. Epidemiologists and clinicians know the importance of working with the community already with patients who participate in clinical research on detection and treatment. For primary prevention research, the strong impact of the environment on disease onset has compelled investigators to define communities based on their way of life or geographical situation. A study that focused on women with a metabolic syndrome, a strong breast cancer risk factor linked to overweight and obesity, using anthropometric measurement of the breast revealed an impact of metformin in reducing adiposity (49). By focusing on a community with a metabolic risk factor for breast cancer, this work provides initial clinical evidence that more research is worth investing to further understand the mechanism of action of metformin in risk reduction. Research outcomes resulting from community-oriented investigations instead of large population cohorts are likely to rapidly benefit individuals within a community and possibly influence public policies.

Other approaches might include citizen science that bridges scientists and the public through collaborative scientific enquiry. Australian women were asked to participate in data collection to capture and classify images of alcohol advertising in a breast cancer prevention project. According to the authors, the combination of datasets from the scientists and the population brought higher levels of validity compared to existing literature solely based on investigator-driven data collection (50).

The community is waking up to the fact that prevention of most NCDs lacks progress and people's involvement is necessary to speed up research development and implementation. The California Breast Cancer Research Program (CBCRP) initiated a first phase called "Californians Linking Action with Science for Prevention of Breast Cancer" with the aim to build coalitions and capacity through community engagement (51). This engagement is primarily in community-based participatory research since research in primary prevention is missing. The other focus of this program is research training via dissemination and implementation. This goal is similar to that of the International Breast Cancer and Nutrition (IBCN) network that aims to develop research on the link between environmental exposure and the epigenome of the breast and propose interventions to reduce cancer risk (52) (**Figure 2**). Here, engagement from the community will come from women who have had breast cancer and wish to help create groups from their family and friends to participate in research. For each project, scientists will define the environmental exposures to be studied and age range for cancer risk in order to target the community belonging to defined risk categories. Education on scientific aspects of the proposed research will be essential to entail informed decision to participate from the community (53).

Transdisciplinary efforts in primary prevention with participation from the community require policy plans for funding focused on communities that are particularly at risk for the onset of NCDs. These plans may be at the regional level in a particular country, like the CBCRP funding program for which phase 2 of funding support is on risk factors of "*disadvantaged, high risk communities with unmet social needs*" (54). On a global level, the European Union (EU) has made NCDs a main part of their action plans for health. Some of their Horizon Europe funding calls focus on adolescents in light of the report from the Lancet commission on adolescent health and well-being (55). This effort is paramount since it will enable scientists to work with a population that represents a main window of susceptibility to risk factors for NCDs, as it is the case for breast cancer for instance. Adolescents are particularly vulnerable for the setting of NCDs later in life both from biological and behavioral standpoints. Indeed, this period of life is highly malleable epigenetically and for establishing durable lifestyles and habits.

Research advocates from the community should be present from the start of new projects to help strategize and alleviate potential obstacles inherent to developing research with a group that is free of the disease being targeted. However, as highlighted in a thoughtful study of the strategies for genetic testing linked to cancer risk, new investigations on the ethical consequences of primary prevention research are warranted (56).

CONCLUSION

Scientists and health care practitioners are pillars to accompany and guide a community of individuals involved in risk reduction. This community is likely to encompass families since windows of susceptibility are prominent during childhood. Family medicine will have to be integrated in such efforts. One possible direction to involve the community of family medicine practitioners is via medical education programs and participation in translational research networks.

Our research perspective supports the core concept of community and individuals' engagement in the process of research, from its inception, and the process of using research findings to design NCD risk reduction programs. The foundations of our promising approach have their roots in the capability of the community members to define their healthcare and prevention commons and manage them collaboratively to create their own favorable individual and collective conditions of healthy environment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SL and MB wrote and edited the manuscript. KZ participated in writing and editing the manuscript, and prepared **Figure 1**. All authors contributed to the article and approved the submitted version.

FUNDING

SL is a Connect Talent Scholar from the Pays de la Loire Region.

ACKNOWLEDGMENTS

MB and SL are members of the International Breast Cancer and Nutrition (IBCN) network.

REFERENCES

1. World Health Organization [WHO]. *Fact Sheets: Non communicable Diseases*. (2021). Available online at: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases (Accessed November 25, 2021)
2. Gbd 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet.* (2020) 396:1204–22. doi: 10.1016/S0140-6736(20)30925-9
3. Wen YF, Chen MX, Yin G, Lin R, Zhong YJ, Dong QQ, et al. The global, regional, and national burden of cancer among adolescents and young adults in 204 countries and territories, 1990–2019: a population-based study. *J Hematol Oncol.* (2021) 14:89. doi: 10.1186/s13045-021-01093-3
4. Cheng F, Xiao J, Shao C, Huang F, Wang L, Ju Y, et al. Burden of thyroid cancer from 1990 to 2019 and projections of incidence and mortality until 2039 in China: findings from global burden of disease study. *Front Endocrinol (Lausanne).* (2021) 12:738213. doi: 10.3389/fendo.2021.738213
5. Hendrick RE, Helvie MA, Monticciolo DL. Breast cancer mortality rates have stopped declining in U.S. women younger than 40 years. *Radiology.* (2021) 299:143–9. doi: 10.1148/radiol.2021203476
6. Heer EV, Harper AS, Sung H, Jemal A, Fidler-Benaoudia MM. Emerging cancer incidence trends in Canada: the growing burden of young adult cancers. *Cancer.* (2020) 126:4553–62. doi: 10.1002/cncr.33050
7. Johnson RH, Anders CK, Litton JK, Ruddy KJ, Bleyer A. Breast cancer in adolescents and young adults. *Pediatr Blood Cancer.* (2018) 65:e27397. doi: 10.1002/pbc.27397
8. Cronjé HT, Elliott HR, Nienaber-Rousseau C, Pieters M. Leveraging the urban–rural divide for epigenetic research. *Epigenomics.* (2020) 12:1071–81. doi: 10.2217/epi-2020-0049
9. Lelièvre SA. Can the epigenome contribute to risk stratification for cancer onset? *NAR Cancer.* (2021) 3:zcab043. doi: 10.1093/narcan/zcab043
10. Wild CP. The exposome: from concept to utility. *Int J Epidemiol.* (2012) 41:24–32. doi: 10.1093/ije/dyr236
11. De Miranda BR, Goldman SM, Miller GW, Greenamyre JT, Dorsey ER. Preventing parkinson's disease: an environmental agenda. *J Parkinsons Dis.* (2021) 12:1–24. doi: 10.3233/JPD-212922
12. Panesar HK, Kennedy CL, Keil Stietz KP, Lein PJ. Polychlorinated biphenyls (PCBs): risk factors for autism spectrum disorder? *Toxics.* (2020) 8:70. doi: 10.3390/toxics8030070
13. Shams P, Hussain M, Karani S, Mahmood S, Hasan A, Siddiqi S, et al. Can sound public health policies stem the tide of burgeoning epidemic of cardiovascular disease in South Asians? *Curr Cardiol Rep.* (2021) 23:181. doi: 10.1007/s11886-021-01612-1
14. Verma A, Gudi N, Yadav UN, Roy MP, Mahmood A, Nagaraja R, et al. Prevalence of COPD among population above 30 years in India: a systematic review and meta-analysis. *J Glob Health.* (2021) 11:04038. doi: 10.7189/jogh.11.04038
15. Ciaula AD, Portincasa P. Relationships between emissions of toxic airborne molecules and type 1 diabetes incidence in children: an ecologic study. *World J Diabetes.* (2021) 12:673–84. doi: 10.4239/wjd.v12.i5.673
16. Pierau M, Arra A, Brunner-Weinzierl MC. Preventing atopic diseases during childhood – early exposure matters. *Front Immunol.* (2021) 12:231. doi: 10.3389/fimmu.2021.617731
17. Beulens JWJ, Pinho MGM, Abreu TC, den Braver NR, Lam TM, Huss A, et al. Environmental risk factors of type 2 diabetes-an exposome approach. *Diabetologia.* (2022) 65:263–74. doi: 10.1007/s00125-021-05618-w
18. Taruscio D, Bermejo-Sánchez E, Salerno P, Mantovani A. Primary prevention as an essential factor ensuring sustainability of health systems: the example of congenital anomalies. *Ann Ist Super Sanita.* (2019) 55:258–64. doi: 10.4415/ANN_19_03_11
19. Kripke M, Brody JG, Hawk E, Hernandez AB, Hoppin PJ, Jacobs MM, et al. Rethinking environmental carcinogenesis. *Cancer Epidemiol Biomarkers Prev.* (2020) 29:1870–5. doi: 10.1158/1055-9965.EPI-20-0541
20. Schnermann ME, Schulz C-A, Herder C, Alexy U, Nöthlings U. A lifestyle pattern during adolescence is associated with cardiovascular risk markers in young adults: results from the DONALD cohort study. *J Nutr Sci.* (2021) 10:e92. doi: 10.1017/jns.2021.84
21. Zhang Z, Jackson SL, Steele EM, Gillespie C, Yang Q. Relationship between ultraprocessed food intake and cardiovascular health among U.S. adolescents: results from the national health and nutrition examination survey 2007–2018. *J Adolesc Health.* (2021) 70:249–57. doi: 10.1016/j.jadohealth.2021.09.031
22. Palakshappa D, Ip EH, Berkowitz SA, Bertoni AG, Foley KL, Miller DP, et al. Pathways by which food insecurity is associated with atherosclerotic cardiovascular disease risk. *J Am Heart Assoc.* (2021) 10:e021901. doi: 10.1161/JAHA.121.021901
23. Bray F, Jemal A, Torre LA, Forman D, Vineis P. Long-term realism and cost-effectiveness: primary prevention in combatting cancer and associated inequalities worldwide. *J Natl Cancer Inst.* (2015) 107:djv273–273. doi: 10.1093/jnci/djv273
24. Bellanger M, Zeinomar N, Tehranifar P, Terry MB. Are global breast cancer incidence and mortality patterns related to country-specific economic development and prevention strategies? *J Glob Oncol.* (2018) 4:1–16. doi: 10.1200/JGO.17.00207
25. Palmer RC, Ismond D, Rodriquez EJ, Kaufman JS. Social determinants of health: future directions for health disparities research. *Am J Public Health.* (2019) 109:S70–1. doi: 10.2105/AJPH.2019.304964
26. Prescott SL, Logan AC. Each meal matters in the exposome: biological and community considerations in fast-food-socioeconomic associations. *Econ Hum Biol.* (2017) 27:328–35. doi: 10.1016/j.ehb.2017.09.004

27. Vineis P, Delpierre C, Castagné R, Fiorito G, McCrory C, Kivimaki M, et al. Health inequalities: embodied evidence across biological layers. *Soc Sci Med.* (2020) 246:112781. doi: 10.1016/j.socscimed.2019.112781
28. Colditz GA, Emmons KM. Accelerating the pace of cancer prevention- right now. *Cancer Prev Res (Phila).* (2018) 11:171. doi: 10.1158/1940-6207.CAPR-17-0282
29. Reitsma MB, Kendrick PJ, Ababneh E, Abbafati C, Abbasi-Kangevari M, Abdoli A, et al. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990–2019: a systematic analysis from the global burden of disease study 2019. *Lancet.* (2021) 397:2337–60. doi: 10.1016/S0140-6736(21)01169-7
30. World Health Organization. *Fiscal Policies For Diet And Prevention Of Noncommunicable Diseases: Technical Meeting Report, 5-6 May 2015*. Geneva: World Health Organization (2016).
31. Holm AL, Laursen M-B, Koch M, Jensen JD, Diderichsen F. The health benefits of selective taxation as an economic instrument in relation to IHD and nutrition-related cancers. *Public Health Nutr.* (2013) 16:2124–31. doi: 10.1017/S1368980013000153
32. Blakely T, Cleghorn C, Mizdrak A, Waterlander W, Nghiem N, Swinburn B, et al. The effect of food taxes and subsidies on population health and health costs: a modelling study. *Lancet Public Health.* (2020) 5:e404–13. doi: 10.1016/S2468-2667(20)30116-X
33. Allen LN, Wigley S, Holmer H. Implementation of non-communicable disease policies from 2015 to 2020: a geopolitical analysis of 194 countries. *Lancet Glob Health.* (2021) 9:e1528–38. doi: 10.1016/S2214-109X(21)00359-4
34. Madureira Lima J, Galea S. The corporate permeation index - a tool to study the macrosocial determinants of non-communicable disease. *SSM Popul Health.* (2019) 7:100361. doi: 10.1016/j.ssmph.2019.100361
35. WHO. *Tackling NCDs: "Best Buys" And Other Recommended Interventions For The Prevention And Control Of Non-Communicable Diseases. World Health Organization*. (2017). 25 p. Available online at: https://apps.who.int/iris/handle/10665/259232 (Accessed November 25, 2021).
36. Bellanger M, Barry K, Rana J, Regnaux J-P. Cost-effectiveness of lifestyle-related interventions for the primary prevention of breast cancer: a rapid review. *Front Med (Lausanne).* (2020) 6:325. doi: 10.3389/fmed.2019.00325
37. Mavaddat N, Pharoah PDP, Michailidou K, Tyrer J, Brook MN, Bolla MK, et al. Prediction of breast cancer risk based on profiling with common genetic variants. *J Natl Cancer Inst.* (2015) 107:djv036. doi: 10.1093/jnci/djv036
38. Pharoah PDP, Antoniou AC, Easton DF, Ponder BAJ. Polygenes, Risk prediction, and targeted prevention of breast cancer. *N Engl J Med.* (2008) 358:2796–03. doi: 10.1056/NEJMsa0708739
39. Duforestel M, Nadaradjane A, Bougras-Cartron G, Briand J, Olivier C, Frenel J-S, et al. Glyphosate primes mammary cells for tumorigenesis by reprogramming the epigenome in a TET3-dependent manner. *Front Genet.* (2019) 10:885. doi: 10.3389/fgene.2019.00885
40. Juengst ET, McGowan ML. Why does the shift from "Personalized Medicine" to "Precision Health" and "Wellness Genomics" matter? *AMA J Ethics.* (2018) 20:E881–90. doi: 10.1001/amajethics.2018.881
41. Marmot M, Bell R. Social determinants and non-communicable diseases: time for integrated action. *BMJ.* (2019) 364:l251. doi: 10.1136/bmj.l251
42. Who. *WHO Global NCD Action Plan 2013-2020*. Geneva: World Health Organizatio (WHO) (2018).
43. Atun R, Jaffar S, Nishtar S, Knaul FM, Barreto ML, Nyirenda M, et al. Improving responsiveness of health systems to non-communicable diseases. *Lancet.* (2013) 381:690–7. doi: 10.1016/S0140-6736(13)60063-X
44. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. *Br J Cancer.* (2013) 108:2205–40. doi: 10.1038/bjc.2013.177
45. Daly AA, Rolph R, Cutress RI, Copson ERA. Review of modifiable risk factors in young women for the prevention of breast cancer. *Breast Cancer (Dove Med Press).* (2021) 13:241–57. doi: 10.2147/BCTT.S268401
46. Terry MB, Michels KB, Brody JG, Byrne C, Chen S, Jerry DJ, et al. Environmental exposures during windows of susceptibility for breast cancer: a framework for prevention research. *Breast Cancer Res.* (2019) 21:96. doi: 10.1186/s13058-019-1168-2
47. Coughlin SS, Smith SA. The impact of the natural, social, built, and policy environments on breast cancer. *J Environ Health Sci.* (2015) 1:1–4. doi: 10.15436/2378-6841.15.020
48. Giulivo M, Lopez de Alda M, Capri E, Barceló D. Human exposure to endocrine disrupting compounds: their role in reproductive systems, metabolic syndrome and breast cancer. a review. *Environ Res.* (2016) 151:251–64. doi: 10.1016/j.envres.2016.07.011
49. Tapia E, Villa-Guillen DE, Chalasani P, Centuori S, Roe DJ, Guillen-Rodriguez J, et al. A randomized controlled trial of metformin in women with components of metabolic syndrome: intervention feasibility and effects on adiposity and breast density. *Breast Cancer Res Treat.* (2021) 190:69–78. doi: 10.1007/s10549-021-06355-9
50. Thomas JA, Trigg J, Morris J, Miller E, Ward PR. Exploring the potential of citizen science for public health through an alcohol advertising case study. *Health Promot Int.* (2021) daab139. doi: 10.1093/heapro/daab139 [Epub ahead of print].
51. Kerner JF, Kavanaugh-Lynch MHE, Baezconde-Garbanati L, Politis C, Prager A, Brownson RC. Doing what we know, knowing what to do: Californians linking action with science for prevention of breast cancer (CLASP-BC). *Int J Environ Res Public Health.* (2020) 17:5050. doi: 10.3390/ijerph17145050
52. Lelièvre SA, Weaver CM. Global nutrition research: nutrition and breast cancer prevention as a model. *Nutr Rev.* (2013) 71:742–52. doi: 10.1111/nure.12075
53. Perrault EK, Hildenbrand GM, Nyaga RG. Epigeneti-what? Approaches on translating research for primary breast cancer prevention. *Front Oncol.* (2019) 9:267. doi: 10.3389/fonc.2019.00267
54. Kerner JF, Kavanaugh-Lynch MH, Politis C, Baezconde-Garbanati L, Prager A, Brownson RC. Californians linking action with science for prevention of breast cancer (CLASP-BC)—phase 2. *Int J Environ Res Public Health.* (2020) 17:8863. doi: 10.3390/ijerph17238863
55. Patton GC, Sawyer SM, Santelli JS, Ross DA, Afifi R, Allen NB, et al. Our future: a lancet commission on adolescent health and wellbeing. *Lancet.* (2016) 387:2423–78.
56. Evans O, Gaba F, Manchanda R. Population-based genetic testing for women's cancer prevention. *Best Pract Res Clin Obstet Gynaecol.* (2020) 65:139–53. doi: 10.1016/j.bpobgyn.2020.02.007

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Public Health

ORIGINAL RESEARCH
published: 05 April 2022
doi: 10.3389/fpubh.2022.794309

Strengthening Primary Healthcare in Kosovo Requires Tailoring Primary, Secondary and Tertiary Prevention Interventions and Consideration of Mental Health

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Objectives: Kosovo has the lowest life expectancy in the Balkans. Primary healthcare (PHC) plays an essential role in non-communicable disease (NCD) prevention. We described primary, secondary and tertiary prevention indicators in Kosovo and assessed their association with depressive symptoms.

Methods: PHC users ($n = 977$) from the Kosovo NCD cohort baseline study were included. Depressive symptoms were assessed using the Depressive Anxiety Stress Scale-21. Cross-sectional associations between depressive symptoms and prevention indicators were quantified with mixed logistic regression models.

Results: Poor nutrition (85%), physical inactivity (70%), obesity (53%), and smoking (21%) were common NCD risk factors. Many cases of hypertension (19%), diabetes (16%) and Chronic Obstructive Pulmonary Disease (COPD) (45%) remained undetected by a PHC professional. Uncontrolled hypertension (28%), diabetes (79%), and COPD (76%) were also common. Depressive symptoms were positively associated with physical inactivity (OR 1.02; 95% CI 1.00–1.05 per 1-point increase in DASS-21) and undetected COPD (OR 1.07; 95% CI 1.00–1.15), but inversely with undetected diabetes (OR 0.95; 95% CI 0.91–1.00).

Conclusions: Continued attention and tailored modifications to primary, secondary and tertiary prevention in Kosovo are needed to narrow the Balkan health gap.

Keywords: depressive symptoms, hypertension, diabetes, COPD, prevention, public health

Edited by:
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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Public Health

Received: *13 October 2021*
Accepted: *28 February 2022*
Published: *05 April 2022*

Citation:
Obas KA, Bytyci-Katanolli A, Kwiatkowski M, Ramadani Q, Fota N, Jerliu N, Statovci S, Gerold J, Zahorka M and Probst-Hensch N (2022) Strengthening Primary Healthcare in Kosovo Requires Tailoring Primary, Secondary and Tertiary Prevention Interventions and Consideration of Mental Health. Front. Public Health 10:794309. doi: 10.3389/fpubh.2022.794309

INTRODUCTION

Over the last 30 years, there has been a discernible shift toward a greater proportion of the global disease burden (GBD) caused by non-communicable diseases (NCDs) (1). In 2019, NCDs accounted for 1,620,165,811 Disability Adjusted Life-Years (DALYs) or 64% of all DALYs globally, up from 43% in 1990 (2). Although the NCD burden in Kosovo is not well documented in part due to a health information system that is not yet fully functional (3), a heavy disease burden is evident from the considerably lower life expectancy (72.5 years) compared to neighboring countries such as Albania (78.6 years), Montenegro (76.9 years), North Macedonia (75.5 years), and Serbia (75.7 years) (4).

NCD management interventions are essential for achieving the SDG target of a one-third reduction in premature deaths from NCDs by 2030. The World Health Organization supports efforts toward achieving the 2030 Sustainable Development Goal 3 aimed at reducing NCD-related premature deaths by one-third by 2030. In fact, a Global Action Plan for the Prevention and Control of NCDs (5) was developed to help states reduce the burden of NCDs. Primary healthcare (PHC) plays an important role in NCD prevention and control (6). The Accessible Quality Healthcare (AQH) is a prominent project in Kosovo which is funded by the Swiss Agency for Development and Cooperation (SDC) and has been working with local stakeholders since 2016 to improve the quality of PHC in the public sector through a health system strengthening approach and with a focus on NCDs.

PHC has interventions at each stage of disease: Primary prevention aims to prevent the onset of disease through health promotion, secondary prevention aims to detect diseases early in an asymptomatic stage so that treatment can delay or block the occurrence of symptoms, and tertiary prevention attempts to deter adverse consequences of existing clinical disease (7, 8).

A rapid assessment of the PHC system in Kosovo conducted by the World Health Organisation (WHO) in 2019 (9) found that hospitalizations related to hypertension and diabetes decreased rapidly between 2012 and 2016, indicating major improvements in disease management in general (tertiary prevention). However, the life expectancy gap between Kosovo and its neighbors still exists in 2021. Equivalent data for chronic respiratory disease, and especially chronic obstructive pulmonary disease (COPD) is lacking. Identifying areas for improvement along the chain of care for common NCDs, i.e., in primary, secondary and tertiary prevention, can facilitate evidence-informed policymaking for PHC stakeholders in Kosovo and AQH project interventions.

A potentially important barrier to NCD prevention and control in Kosovo is poor mental health. as a post-conflict outcome. Depressive symptoms among PHC users were reported to be about 10% worldwide (10), while the prevalence of depressive symptoms reported in Kosovo far exceeds this, ranging from 30 to 67% (11–15). Depression has been linked to unhealthy behaviors such as smoking, physical inactivity, poor nutrition and alcohol consumption (16, 17). Depression has also been linked with uncontrolled hypertension (18–20) and poor glycemic control among diabetics (21) in other settings. Given the high prevalence of depressive symptoms reported in Kosovo, it is important to investigate its role in NCD management in the specific context.

Figure 1 depicts the study's conceptual framework. Primary care participants represent different stages of a disease continuum, from a healthy person to disease onset, to disease progression. Primary healthcare aims to prevent people from moving forward along the continuum. Primary, secondary and tertiary prevention strategies target people at different stages of the disease continuum. Our study assessed the distribution of negative cross-sectional indicators to identify gaps at the different prevention stages which may hinder NCD control in the Kosovo primary health care system. Specifically, it describes the prevalence of NCD risk factors (targets of primary prevention), as well as the prevalence of undetected hypertension, diabetes and chronic obstructive pulmonary disease (COPD) (targets of secondary prevention) and uncontrolled hypertension, diabetes and COPD (targets of tertiary prevention) among Kosovo public PHC users. It further assesses the association between depressive symptoms and these indicators to evaluate whether depressive symptoms act as a barrier to disease prevention and control.

MATERIALS AND METHODS

Study Design

The current cross-sectional study uses baseline data of the KOSovo NCD COhort (KOSCO), which began in March 2019. Details of the study protocol are described elsewhere (22). In brief, the overarching goal of the KOSCO study was to contribute epidemiological evidence to the prevention and control of NCDs in the Kosovo public primary health care system as the basis for policy and decision-making. Initially, 1,011 consecutive PHC users aged 40 years and above were recruited from 12 PHC facilities in Kosovo. The data collected through interviews and health examinations included: socio-demographic characteristics, social and environmental factors, comorbidities, health system, lifestyle, psychological factors, and clinical attributes (blood pressure, height, weight, waist/hip/neck circumferences, peak expiratory flow and HbA1c measurements). Cohort data were collected annually in two phases, approximately 6 months apart, with an projected total follow-up time of 5 years. The current study is based on cross-sectional data from the baseline assessment.

Setting

The study was conducted in Kosovo, which is situated in the middle of the Western Balkans and has a population of ∼1.8 million. In Kosovo, the public PHC system is divided into three tiers: each municipality has one main family medicine centre (MFMC), several family medicine centres (FMC) and several family medicine ambulantas (FMA). MFMCs are the largest facilities at the highest level of PHC, which offer more services, employ more staff and have more medical equipment and therefore have a higher patient flow compared with the second-level FMCs and third-level FMAs. There is also the private PHC sector with only one tier consisting of private clinics.

Study sites include the MFMCs from the following 12 municipalities: Gračanica, Drenas, Skënderaj, Malishevë, Rahovec, Gjakovë, Junik, Fushë Kosovë, Vushtrri, Mitrovicë, Lipjan, and Obiliq.

Participants

Recruitment and baesline data collection were conducted between March and November 2019. A total of 1,011 consecutive and consenting PHC users were included in the cohort. Ethical approvals were obtained from the Ethics Committee Northwest

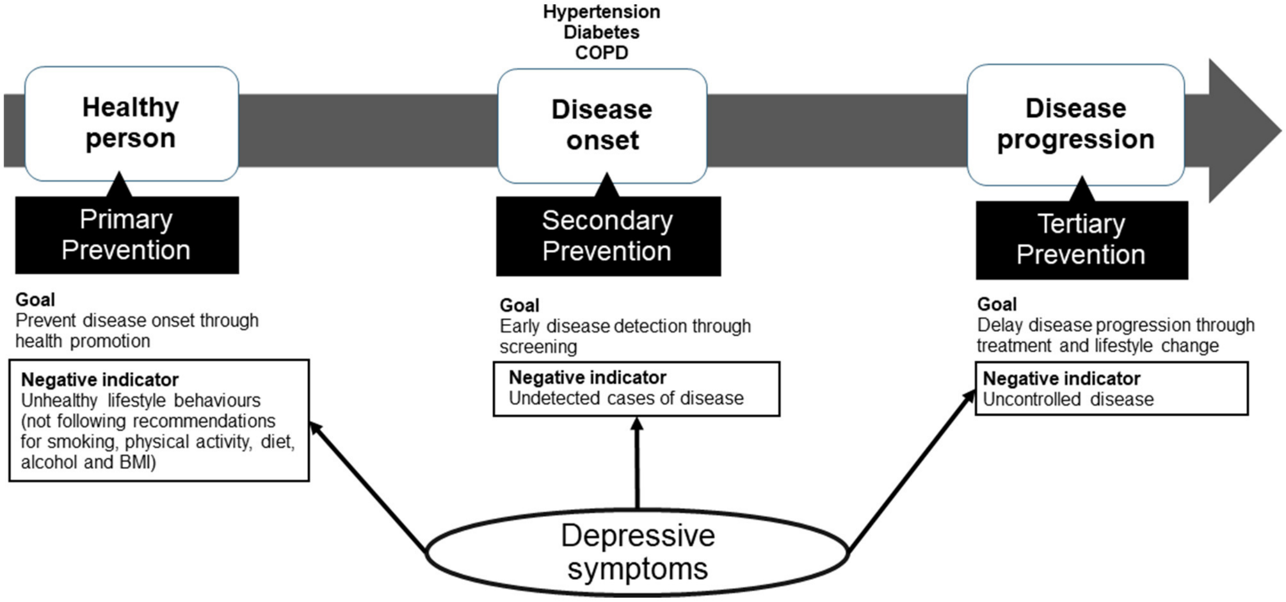

FIGURE 1 | Conceptual framework. Primary care participants exist on a disease continuum, from a healthy person to disease onset, to disease progression. Primary healthcare aims to prevent people from moving forward along the continuum. Primary, secondary and tertiary prevention strategies target people at different stages of the disease continuum. To evaluate gaps in primary, secondary and tertiary prevention in Kosovo's PHC system, our study assesses negative indicators of each stage of prevention. Specifically, it describes the prevalence of lifestyle risk factors (targets if primary prevention), as well as undetected hypertension, diabetes and chronic obstructive pulmonary disease (COPD) (targets of secondary prevention) and uncontrolled hypertension, diabetes and COPD (targets of tertiary prevention) among Kosovo PHC users. It further assesses the association between depressive symptoms and these indicators to evaluate whether depressive symptoms act as a barrier to disease prevention.

and Central Switzerland (Ref. 2018-00994) and the Kosovo Doctors Chamber (Ref. 11/2019).

Participants were included in the cohort if they were aged 40 years or older and consulted healthcare services irrespective of the reason on the day of recruitment. Participants were excluded from the cohort if they had a terminal illness, were not able to understand or respond to screening questions, did not live in one of the 12 study municipalities, or lived abroad for more than 6 months of the year.

Baselien participants who had complete data on confounders (age, sex, work status, highest level of education achieved, living in a rural or urban setting, and ethnicity), smoking status, physical activity, nutrition, alcohol, height, weight, blood pressure, glycated hemoglobin (HbA1c), peak expiratory flow (PEF), depressive symptoms score, and status of hypertension, diabetes and COPD diagnoses were included in the current study ($n = 977$). We excluded 34 participants due to incomplete data.

Variables and Data Sources

NCD Risk Factors

Participants answered questions during an in-person interview with a trained study nurse regarding lifestyle and mental health symptoms. Height (in meters) and weight (in kilograms) were measured, body mass index (BMI) was derived (weight/height^2). The following indicator variables for NCD risk factors were defined as follows:

- smoking status (current smoker).
- physical inactivity (<150 min of moderate-intensity physical activity per week, <75 min of vigorous-intensity physical activity per week, and less than an equivalent combination of moderate-intensity and vigorous-intensity activity).
- Poor nutrition (<5 fruit and/or vegetable portions per day).
- Alcohol consumption (any alcohol consumed in the last 30 days).
- Obesity (BMI ≥ 30).

A lifestyle index was equally derived by taking the sum of the indicators above, where one point was given for each criterion met.

Undetected and Uncontrolled Disease

Participants answered questions about physician-diagnosed hypertension, diabetes and COPD. Blood pressure, HbA1c and PEF were measured at the end of the interview. Systolic and diastolic blood pressures (in mmHg) were measured three times, at least 3 min apart, after sitting quietly for about 10 min, using an M3 model Omron blood pressure monitor (Omron Healthcare, Switzerland). The research nurses placed the blood pressure cuff 2 cm above the elbow on the bare left upper arm (in the case of arteriovenous fistula, radiotherapy or removal of lymph nodes in the armpit of the left arm, the right arm was used) of the seated participant and elevated the arm on the table to the level of the fourth intercostal space. The non-invasive (finger-prick blood sample) HbA1c test was performed by the MFMC staffed laboratory technician who received training from the supplier on how to use the SUPER ID clinchem device (Dr. Müller Gerätebau GmbH, Germany). In the absence of sufficient funds for the conduct of spirometry to assess irreversible obstruction to air flow for COPD assessment, PEF (L/min) was measured 3 times with a 30-second pause between attempts, using the OMRON Peak Flow Meter PFM20 (Omron Healthcare, Switzerland). PEF predicted (%) was calculated as the ratio of the estimated (measured) PEF to the expected PEF. The expected PEF values were derived based on age, gender and height using the regression equation developed by Hankinson et al. (23). From these data sources, indicator variables of undetected and uncontrolled hypertension, diabetes and COPD variables were defined as follows:

- Undetected hypertension: no self-reported physician diagnosis of hypertension as well as systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg.
- Undetected diabetes: no self-reported physician diagnosis of diabetes and HbA1c $\geq$ 6.5%.
- Undetected COPD: no self-reported physician diagnosis of COPD as well as PEF <80% Predicted (24) with breathlessness for 6 months or longer or cough for at least 3 months.
- Uncontrolled hypertension: self-reported physician diagnosis of hypertension as well as systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg.
- Uncontrolled diabetes: self-reported physician diagnosis of diabetes and HbA1c $\geq$ 6.5%.
- Uncontrolled COPD: self-reported physician diagnosis of COPD and PEF <80% Predicted.

Undetected and uncontrolled diseases were further stratified by stage of the disease:

- Hypertension: Stage 1 is systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg and stage 2 is systolic blood pressure $\geq$160 mmHg or diastolic blood pressure $\geq$100, according to the international society of hypertension (25).
- Diabetes: Level 1 is an HbA1c 6.5–7.4%, level 2 is an HbA1c 7.5–9.0%, level 3 is an HbA1c 9.1–11%, and level 4 is an HbA1c > 11% (26).
- COPD: level 1 is a PEF 50–79% Predicted, level 2 is a PEF < 50% predicted.

Depressive Symptoms

Depressive symptoms were measured using the Depressive Anxiety Stress Scale (DASS-21) (27), a 21-item questionnaire consisting of subscales for depressive, anxiety and stress symptoms, each containing seven items scored on a 4-point Likert scale ranging from 0 (did not apply to me at all) to 3 (applied to me very much). The sum of scores from the depressive symptoms subscale was then multiplied by 2. The depressive symptoms scores range from 0 to 42.

Statistical Analyses

Sociodemographic factors among PHC users were presented as frequency and percentages for categorical variables and as the median and interquartile range for non-normal distributed continuous variables.

The prevalence of NCD risk factors (smoking, physical inactivity, poor nutrition, alcohol consumption, obesity and lifestyle index) among PHC users were described as frequencies and percentages for the total study population and were stratified by sex (male, female) and highest education level attained (primary school, secondary school, university). The prevalences of undetected and uncontrolled hypertension, diabetes and COPD among PHC users were presented as frequency and percentages of the relevant subsample, and also stratified by sex and highest education level attained. For the outcome of undetected disease, participants were included in the subsample if they had either a diagnosis for the disease or pathological clinical findings for that disease (systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg for hypertension; HbA1c $\geq$ 6.5% for diabetes; PEF < 80% Predicted with breathlessness for 6 months or longer or cough for at least 3 months for COPD). For the outcome of uncontrolled disease, only those with a self-reported doctor's diagnosis of the disease were included in the subsample.

The adjusted cross-sectional associations between depressive symptoms as a continuous predictor variable and outcomes of smoking, physical inactivity, alcohol consumption, poor nutrition, and obesity, undetected hypertension, diabetes and COPD as well with uncontrolled hypertension and diabetes were quantified using mixed logistic regression models, while mixed ordinal logistic regression was used for the association between depressive symptoms and lifestyle index. Municipality (Gračanica, Drenas, Skënderaj, Malishevë, Rahovec, Gjakovë, Junik, Fushë Kosovë, Vushtrri, Mitrovicë, Lipjan, and Obiliq) was included as a random effect in all models. We selected potential confounders for inclusion in these models based on prior knowledge: age (years), sex (male, female), work status (currently working, house person, retired or disabled, unemployed), highest level of education achieved (primary school, secondary school, university), living in a rural or urban setting (rural, urban), and ethnicity (Albanian, Serbian, Roma or Ashkali or Egyptian or Other). Due to few observed cases of alcohol consumption in the last 30 days, the model of the association between depressive symptoms and alcohol was reduced to include only age, sex and ethnicity as confounders. Due to even fewer cases of uncontrolled COPD, a regression model for the association between depression and uncontrolled COPD was not interpretable. The same subsamples of undetected and uncontrolled disease apply to the regression models as the descriptive outcomes. The same methods were applied with depressive symptoms as a binary predictor variable and are available (moderate to very severe depressive symptoms equate to a DASS-21 depressive symptoms score $\geq$14) in the supplementary data (**Supplementary Table 1**).

Analyses were performed with Stata statistical software, release 16.

RESULTS

Sociodemographic Characteristics

We included 977 participants from KOSCO in this study. The participant characteristics are described in **Table 1**. There were more women than men in the study, and most had attained

TABLE 1 | Participant characteristics (Kosovo Non-Communicable Disease Cohort, Kosovo, 2019).

Sociodemographic factors	All participants ($n = 977$)
Age, median (IQR)	60 (53–67)
Sex, frequency (%)	
Male	402 (41.2)
Female	575 (58.8)
Education, frequency (%)	
Primary school or less	618 (63.3)
Secondary school	300 (30.7)
University/College	59 (6.0)
Work status, frequency (%)	
Currently working	162 (16.6)
House person	467 (47.8)
Retired or disabled	314 (32.1)
Unemployed	34 (3.5)
Residence, frequency (%)	
Rural	549 (56.2)
Urban	428 (43.8)
Municipality, frequency (%)	
Drenas	96 (9.8)
Fushe Kosova	109 (11.2)
Gjakova	72 (7.4)
Gracanica	52 (5.3)
Junik	21 (2.2)
Lipjan	171 (17.5)
Malisheva	77 (7.9)
Mitrovica	81 (8.3)
Obiliq	70 (7.2)
Rahovec	77 (7.9)
Skenderaj	93 (9.5)
Vushtrri	58 (5.9)
Ethnicity, frequency (%)	
Albanian	890 (91.1)
Serbian	48 (4.9)
Roma, Ashkali, Egyptian, Other	39 (4.0)
Clinical measurements	
Blood pressure (mmHg),	
Systolic, median (IQR)	133 (123–146)
Diastolic, median (IQR)	86 (80–93)
HbA1c (%), median (IQR)	6.5 (5.7–7.7)
PEF (L/min), median (IQR)	260 (187–350)
BMI, median (IQR)	30.3 (27.4–34.1)
Disease	
Diagnosed hypertension, freq (%)	605 (61.9)
Diagnosed Diabetes, freq (%)	506 (51.8)
Diagnosed COPD, freq (%)	59 (6.0)
Depressive symptoms score (median, IQR)	2 (0–6)
Depressive symptoms severity (freq, %)	
Normal (DASS depression score 0–9)	792 (81.1)
Mild (DASS depression score 10–13)	66 (6.8)
Moderate (DASS depression score 14–20)	84 (8.6)
Severe (DASS depression score 21–27)	17 (1.7)
Very severe (DASS depression score 28–42)	18 (1.8)

IQR, Interquartile range; mmHg, millimeters of mercury; HbA1c, glycated hemoglobin; PEF, Peak Expiratory Flow; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DASS, Depression Anxiety Stress Scale.

primary school education or less. Most participants were not working. The majority of participants identified as ethnic-Albanian and living in rural settings.

Primary Prevention

Table 2 describes the prevalence of NCD risk factors in the PHC users. More than 40% of participants reported 3 or more unhealthy lifestyle factors. Prevalence was highest for poor nutrition, with 85.1% reporting insufficient fruit and vegetable consumption, followed by 70.3% reporting physical inactivity, and 52.7% being obese. There existed important gender differences for smoking, alcohol consumption and obesity. Obesity and multiple unhealthy lifestyles were common among participants of low socioeconomic status, while higher socioeconomic status privileged smoking.

Secondary and Tertiary Prevention

Table 3 describes the prevalence of undetected (secondary prevention) and uncontrolled (tertiary prevention) diseases. Many cases of hypertension (19%), diabetes (16%) and COPD (45%) remained undetected by a healthcare professional in PHC facilities. Uncontrolled disease was also very common in diabetes patients (79%) and COPD patients (76%). Most undetected cases of hypertension and diabetes were within the lower stages of the disease, but at higher stages of disease for uncontrolled hypertension and diabetes. There were important sex differences in the detection and control of COPD. Highly educated people tended to have higher undetected hypertension and people with less education had a higher prevalence of uncontrolled COPD.

Association Between Depressive Symptoms Score and Primary, Secondary and Tertiary Prevention Indicators

Figure 2 shows the adjusted associations between depressive symptoms score and NCD risk factors (smoking, physical, inactivity, poor nutrition, alcohol consumption, obesity, and unhealthy lifestyle index), undetected and uncontrolled hypertension, diabetes and COPD. Per one-point increase in depressive symptoms, we found the following trends: increase in odds of physical inactivity (OR 1.02; 95% CI 1.00–1.05), a decrease in odds for undetected diabetes (OR 0.95; 95% CI 0.91–1.00), and an increase in odds for undetected COPD (OR 1.07; 95% CI 1.00–1.15). The coefficients represented in **Figure 2**

TABLE 2 | Prevalence of non-communicable disease risk factors, stratified by sex and highest level of education attained (Kosovo Non-Communicable Disease Cohort, Kosovo, 2019).

Risk factor	All participants ($n = 977$)	Sex			Highest level of education attained			
		Male ($n = 402$)	Female ($n = 575$)	*p*-value	Primary ($n = 618$)	Secondary ($n = 300$)	University ($n = 59$)	*p*-value
Current smoker	201 (20.6)	110 (27.4)	91 (15.8)	<0.001*[a]	106 (17.2)	77 (25.7)	18 (30.5)	0.002* [a]
Physical inactivity	687 (70.3)	250 (62.2)	437 (76.0)	<0.001*[a]	482 (78.0)	165 (55.0)	40 (67.8)	<0.001*[a]
Poor nutrition	831 (85.1)	340 (84.6)	491 (85.4)	0.725 [a]	537 (86.9)	246 (82.0)	48 (81.4)	0.106[a]
Alcohol consumption	44 (4.5)	43 (10.7)	1 (0.2)	<0.001*[a]	14 (2.3)	26 (8.7)	4 (6.8)	<0.001*[a]
Obesity	515 (52.7)	151 (37.6)	364 (63.3)	<0.001*[a]	381 (61.7)	111 (37.0)	23 (39.0)	<0.001*[a]
Lifestyle index [b]				<0.001*[c]				<0.001*[c]
0	16 (1.6)	13 (3.2)	3 (0.5)		2 (0.3)	11 (3.7)	3 (5.1)	
1	155 (15.9)	81 (20.2)	74 (12.9)		69 (11.2)	77 (25.7)	9 (15.3)	
2	379 (38.8)	156 (38.8)	223 (38.8)		240 (38.8)	115 (38.3)	24 (40.7)	
3	348 (35.6)	112 (27.9)	236 (41.0)		259 (41.9)	72 (24.0)	17 (28.8)	
4	74 (7.6)	35 (8.7)	39 (6.8)		46 (7.4)	23 (7.7)	5 (8.5)	
5	5 (0.5)	5 (1.2)	0 (0.0)		2 (0.3)	2 (0.7)	1 (1.7)	

*[a] Chi^2 test. [b] Lifesyle index is the sum of indicators for current smoker, physical inactivity, poor nutrition, alcohol consumption and obesity. [c] Kruskal-Wallis test. *$p < 0.05$.*

TABLE 3 | Prevalence of undetected and uncontrolled hypertension, diabetes and COPD, also disaggregated by disease severity and stratified by sex and educational level (Kosovo Non-Communicable Disease Cohort, Kosovo, 2019).

Category	All participants of subsample	Sex			Highest level of education attained			
		Male	Female	*P*-value[a]	Primary	Secondary	University	*P*-value[a]
Undetected hypertension ($n = 743$)	138 (18.6)	70 (24.0)	68 (15.1)	0.002*	75 (15.3)	51 (23.6)	12 (31.6)	0.004*
SBP 140–159 or DBP 90–99	111 (14.9)							
SBP ≥ 160 or DBP ≥ 100	27 (3.6)							
Undetected diabetes ($n = 601$)	95 (15.8)	36 (14.7)	59 (16.7)	0.478	62 (16.3)	27 (14.5)	6 (17.7)	0.826
Hba1c 6.5–7.4%	67 (11.2)							
Hba1c 7.5–9.0%	22 (3.7)							
Hba1c 9.1–11.0%	4 (0.7)							
Hba1c >11.0%	2 (0.3)							
Undetected COPD ($n = 108$)	49 (45.4)	13 (36.1)	36 (50.0)	0.172	35 (46.7)	13 (43.3)	1 (33.3)	0.870
PEF predicted 50–70%	25 (23.2)							
PEF predicted <50%	24 (22.2)							
Uncontrolled hypertension ($n = 605$)	171 (28.3)	74 (33.3)	97 (25.3)	0.350	114 (27.5)	49 (29.7)	8 (30.8)	0.837
SBP 140–159 or DBP 90-99	73 (12.1)							
SBP ≥160 or DBP ≥100	98 (16.2)							
Uncontrolled diabetes ($n = 506$)	400 (79.1)	170 (80.6)	230 (78.0)	0.478	258 (80.9)	121 (76.1)	21 (75.0)	0.416
Hba1c 6.5–7.4%	150 (29.6)							
Hba1c 7.5–9.0%	146 (28.9)							
Hba1c 9.1–11.0%	86 (17.0)							
Hba1c >11.0%	18 (3.6)							
Uncontrolled COPD ($n = 59$)	45 (76.3)	15 (65.2)	30 (83.3)	0.111	32 (80.0)	12 (70.6)	1 (50.0)	0.503
PEF predicted 50–70%	29 (49.2)							
PEF predicted < 50%	16 (27.1)							

*[a] Chi^2 test, *$p < 0.05$. SBP, systolic blood pressure in mmHg; DBP, diastolic blood pressure in mmHg; HbA1c, glycated hemoglobin; PEF, peak expiratory flow; COPD, chronic obstructive pulmonary disease. Subsamples for undetected hypertension, diabetes and COPD included all participants with a self-reported physician diagnosis or pathological findings for the given disease (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg for hypertension; HbA1c ≥ 6.5% for diabetes; PEF < 80% Predicted with breathlessness for 6 months or longer or cough for at least 3 months for COPD). Subsamples for uncontrolled disease included all participants with a self-reported physician diagnosis for the given disease. The vertical red line indicates the limit of the odds ratio of one. *$p < 0.05$.*

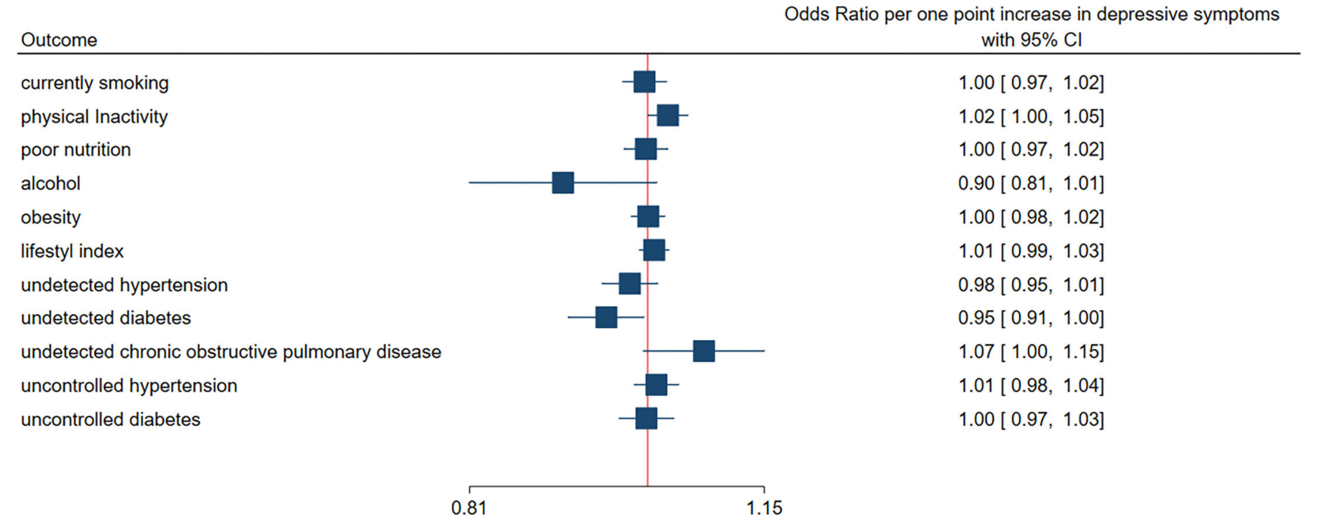

FIGURE 2 | Association between depressive symptoms (continuous score) and primary, secondary and tertiary prevention negative indicators. Squares indicate the odds ratio per one-point increase in depressive symptoms. Lines indicate the 95% confidence interval. Depressive symptoms were assessed using the Depression, Anxiety, Stress Scale-21. Mixed ordinal logistic regression models quantified the association between depressive symptoms and lifestyle index. The associations between depressive symptoms and all other outcomes were quantified with mixed logistic regression models. All models included municipality as a random effect and were adjusted for age, sex, work status, education level, living in a rural or urban setting, and ethnicity with exception of alcohol, which was reduced to adjustment for only age, sex and ethnicity.

are also available in table format available in the supplementary data (**Supplementary Table 2**).

DISCUSSION

The results of this study in Kosovo indicate that the need for improving NCD prevention and control in PHC remains high along the chain of care for disease prevention. NCD risk factors were common among PHC users. Many cases of hypertension, diabetes and possibly COPD remained undetected and also poorly controlled after their diagnosis. Depressive symptoms occurring at a high prevalence and being associated in particular with low levels of physical activity are an important control target and a potential barrier to the control or other NCDs.

Primary Prevention

Smoking

In a national STEPS population-based survey ($n = 6{,}117$) conducted in 2010, it was found that 28.4% were smokers, where the prevalence was nearly double among men compared to women. The age group with the highest prevalence was between 35 and 44 years (28). We found a lower prevalence of smokers in our sample of PHC users aged 40 years and older in 2019. The finding that smoking was more prevalent among those with higher education level was surprising, but may indicate socioeconomic mechanisms, as a symbol of status. Our findings may point toward success in smoking cessation among adult smokers, but they may also reflect the generally lower smoking rates in older persons. Given the increasing concern about smoking among younger people in Kosovo (29) and a general concerning increase in popularity of electronic cigarettes (vaping) among adolescents worldwide (30), careful planning of interventions to prevent the onset of smoking at an early age must continue to avoid a future health burden due to tobacco in the coming decades.

Physical Inactivity

Our findings point toward very low adherence to WHO recommended guidelines for physical activity. A study comparing elderly populations in European countries found that Kosovo performed the worst among 28 countries (31). One national survey in Kosovo conducted in 2015 (32) among people aged 65 and older found that only 14.3% were practicing regular physical activity, where males (20.2%) reported regular physical activity more often than women (9.2%). Our study indicates that nearly 30% of PHC users aged 40 years and older are physically active. Although our sample is younger than the 2015 survey, it is still promising that progress is being made toward improving physical activity. Nevertheless, 70% of PHC users are still physically inactive and thus interventions promoting regular exercise should remain in the focus of PHC interventions. Furthermore, additional research needs to identify personal and structural barriers to physical acitivity in the specific context of Kosovo.

Depression has been associated with physical inactivity (16) and our study supports these findings in the Kosovo setting. This relationship suggests that depression may play a role as a barrier to interventions aimed at physical activity. Therefore, adequately treating depressive symptoms may improve physical activity interventions in itself and thereby propagating a positive feedback loop as physical activity interventions have a beneficial effect on depressive symptoms (33).

Poor Nutrition

We found that poor nutrition was very common (85%), meaning that most participants did not consume at least 5 servings of fruit and/or vegetables per day. There were no differences between sex and education level.

Alcohol Consumption

We found a very low prevalence of alcohol consumers in the last 30 days. These findings were unsurprising given that our sample includes older adults who may be more inclined toward traditional practices in a country that has a Muslim majority. Yet, the fact that both, alcohol consumption and smoking were more prevalent among more educated participants suggests that adults in Kosovo are adopting a Western European lifestyle. A shift toward unhealthy lifestyles that parallels the economic development of the country should be prevented at all costs.

Obesity

Over 50% of PHC users were obese and the prevalence was higher among people with lower levels of education. More women were obese compared to men. A previous small study ($n = 423$) conducted in two Kosovar communities in 2010 had only 30% obesity (34). Interventions in PHC targeting obesity should pay special attention to tailor to women and those of lower socioeconomic status.

Lifestyle Index

Women and those with lower education levels tended to have more unhealthy lifestyles overall compared to men and higher education levels respectively. There was no association between depressive symptoms and the number of unhealthy lifestyle factors after adjusting for confounders. This was unexpected given that depression has been associated with a cluster of unhealthy lifestyles (16). The results of this study point to physical inactivity as a central aspect of an unhealthy lifestyle in persons with signs of depression.

Secondary Prevention

We found that nearly one in five PHC users with hypertension were unaware of it, nearly one in six with diabetes were not aware of it and nearly half with potential COPD were not aware of it. The diagnostic gap is scarcely studied in Kosovo. One study conducted in 2006 in adults 18 years and older ($n = 423$) found that over 1 in 3 people with pathological fasting glucose were not diagnosed with diabetes (34).

All of our participants received medical care for various reasons on the day of baseline data collection. Since 2019, the AQH project supports PHC with the implementation of WHO Package of Essential Non-Communicable Disease (PEN) Protocols (35) in five municipalities of Kosovo (Fushe Kosovo, Mitrovica, Malisheva, Gjakova and Vushtrri). The PEN protocol is used for the assessment and management of cardiovascular risk using hypertension, diabetes mellitus and tobacco use as entry points. It outlines screening recommendations for hypertension and diabetes in target groups through blood pressure and blood glucose measurement, which include people aged 40 years and over. Our findings highlight the importance of continuing and adapting the AQH efforts in implementing the PEN protocol and support its expansion to other municipalities and scaling up.

We found a high prevalence of potentially undetected COPD. In the absence of post-bronchodilation spirometry, though, the differentiation between COPD and/or asthma remains imperfect. But the results point to the importance of airflow obstruction. Although PEN protocols are available from the WHO for COPD, they were not yet implemented in Kosovo by AQH at the time of writing this paper. The MFMC directors requested that the study protocol include lung function testing for assessing respiratory disease. The stakeholder's clinical observations indicated that respiratory disease was a concern in their communities, and this study supports these observations. Further research on COPD with spirometric testing and considering also environmental factors is warranted. In Kosovo, Coal remains a common method to heat homes in the winter at a lower cost (36). The indoor air pollution from coal may be an important contributor to exacerbated respiratory disease.

Depressive symptoms were associated with lower odds of undetected diabetes in our adjusted models. This can be explained through increased healthcare utilization among people with depression (37). Underlying diabetes may be more likely to be diagnosed in people with depression since they are assessed and screened more often by a healthcare professional. A longitudinal study assessing healthcare utilization as a mediator of the association is warranted.

Tertiary Prevention

Uncontrolled disease was very common among PHC users. Over a quarter of people with diagnosed hypertension still had high blood pressure. Even more troubling was that the majority, over three in every four PHC users with diagnosed diabetes or what we considered as potential COPD, had their disease uncontrolled. Men had more difficulty controlling their blood pressure and women had more trouble controlling their lung function, while no marked differences in sex were observed for diabetes control. There were no marked differences for control of hypertension and diabetes by education level, but less-educated participants were more likely to have uncontrolled COPD, possibly due to a combination of less access to care and poorer indoor environments, favoring disease progression.

Strengths and Limitations

Our study comprehensively assesses the chain of care in the PHC system to identify specific areas for improvement. Given the current limited epidemiological data situation in the country, our findings provide evidence for stakeholders and decision-makers. Our study sample of PHC patients aged 40 years or more is not representative of the general population of Kosovo. However, the alarming prevalences of unhealthy lifestyle behaviors and poor detection and control of NCDs in our sample suggest that the current society-wide NCD prevention strategies are in urgent need of strengthening. While the prevalence estimates for unhealthy lifestyles might be an overestimation of the prevalence in the general population, given that we assessed PHC users, the fact that even in PHC users we observe a high rate of underdiagnosis and poor disease control could point to even higher rates in the general population with groups of people having very poor access to care.

Our findings brought to light the urgent need for further research on respiratory disease in Kosovo. We found that nearly half of people with problematic lung function were never diagnosed with COPD. Yet, peak flow measurements have limitations concerning detecting irreversible obstruction to airflow and cannot differentiate between COPD and asthma with high accuracy. It is foreseen for future cohort follow-ups to include pre- and post-bronchodilation spirometry as part of the health examinations.

Our study may be subject to response bias for the topics of alcohol and depression. In Kosovo, it is not generally well viewed to drink alcohol, especially among older adults and therefore participants may not have answered truthfully about alcohol intake. As most areas in the world, mental health is still a stigmatized topic in the country and similarly, participants may not have responded truthfully about their depressive symptoms. The prevalence of depression may therefore be an underestimation, which is particulary worrisome in the light of the recent COVID-19 pandemic, which may have increased the prevalence further. Although questions on alcohol were worded as per the WHO STEPS survey and we did not feel they needed to be changed, we decided to preface DASS questions with an introductory statement to frame the questions about wellbeing, which is a more socially acceptable topic.

The study is cross-sectional in nature and does not allow differentiating cause and effect in the association between depression and NCD control. The follow-up of the cohort will provide an opportunity in the future to address these associations longitudinally.

CONCLUSION

An unhealthy lifestyle, undetected and uncontrolled hypertension, diabetes and possibly COPD are common in Kosovo, contributing to the heavy disease burden in the country. Disease prevention in Kosovo is improving, but still needs continued attention and tailored modifications to primary, secondary and tertiary prevention to narrow the health gap between Kosovo and other Balkan countries.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the corresponding author upon reasonable request.

ETHICS STATEMENT

The study involving human participants were reviewed and approved by Ethics Committee Northwest and Central Switzerland (Ref. 2018-00994) and Kosovo Doctors Chamber (Ref. 11/2019). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KO co-developed and implemented the study protocol, coordinated and supervised data collection, carried out the data analysis, interpreted results, and wrote the manuscript. NJ contributed to study objectives related to non-communicable diseases in Kosovo. SS contributed to study objectives related to mental health in Kosovo. MK supervised data analysis. MZ, QR, AB-K, and JG contributed to the study objectives related to the evaluation of health service provision and to the integration of the study protocol within the AQH framework. NP-H developed the KOSCO cohort concept, study objectives and protocol, directed the implementation, data analysis, and result interpretation. All authors have read and approved the final protocol.

FUNDING

This study was funded by the Swiss Agency for Development and Cooperation.

ACKNOWLEDGMENTS

The implementation of the cohort study protocol and prioritization of study objectives would not be possible without the support of the Project Implementation Unit of the AQH project. Staff from 12 participating Main Family Medicine Centers (MFMCs) supported the study along with MFMC directors in the following municipalities: Fushë Kosovë, Gjakovë, Drenas, Gračanica, Junik, Lipjan, Malishevë, Mitrovicë, Obiliq, Rahovec, Skenderaj, and Vushtrri. The KOSCO research nurses were instrumental in the success of recruitment and data collection: Tevide Bllaca, Arizona Igrishta, Selvete Zyberaj, Shqipe Agushi, Alma Stojanović, and Fatime Zeneli.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.794309/full#supplementary-material

REFERENCES

1. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet.* (2020) 396:1204–22.
2. Institute for Health Metrics and Evaluation (IHME). GBD Results Tool (2019). Available online at: http://ghdx.healthdata.org/gbd-results-tool (accessed September 8, 2021).
3. Ahmeti M, Gashi M, Sadiku L, Mala E. Efficiency and effectiveness in implemention of unified and integrated health information system. 2017 Dec;50.

4. World Bank. *Life Expectancy At Birth, Total (years)*. (2017). Available online at: https://data.worldbank.org/indicator/SP.DYN.LE00.IN?locations=XK-RS-AL-MK-ME (accessed September 22, 2019).
5. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases: 2013-2020 (2013). Available online at: http://apps.who.int/iris/bitstream/10665/94384/1/9789241506236_eng.pdf (accessed October 23, 2020).
6. International Conference on Primary Health Care. *Declaration of Alma-Ata*. (1978). Available online at: http://link.springer.com/10.1057/palgrave.development.1100047 (accessed July 24, 2018).
7. Baumann LC, Karel A. Prevention: Primary, Secondary, Tertiary. In: Gellman MD, Turner JR, editors. *Encyclopedia of Behavioral Medicine*. New York, NY: Springer (2013). p. 1532–4. doi: 10.1007/978-1-4419-1005-9_135
8. Hensrud DD. Clinical preventive medicine in primary care: background and practice: 1. rationale and current preventive practices. *Mayo Clin Proc*. (2000) 75:165–72. doi: 10.1016/S0025-6196(11)64189-X
9. WHO Regional Office for Europe. *Primary health care in Kosovo: rapid assessment* (2019).
10. Craven MA, Bland R. Depression in primary care: current and future challenges. *Can J Psychiatry*. (2013) 58:442–8. doi: 10.1177/070674371305800802
11. Eytan A, Gex-Fabry M. Use of healthcare services 8 years after the war in Kosovo: role of post-traumatic stress disorder and depression. *Eur J Public Health*. (2012) 22:638–43. doi: 10.1093/eurpub/ckr096
12. Kashdan TB, Morina N, Priebe S. Post-traumatic stress disorder, social anxiety disorder, and depression in survivors of the Kosovo War: experiential avoidance as a contributor to distress and quality of life. *J Anxiety Disord.* (2009) 23:185–96. doi: 10.1016/j.janxdis.2008.06.006
13. Nakayama R, Koyanagi A, Stickley A, Kondo T, Gilmour S, Arenliu A, et al. Social networks and mental health in post-conflict Mitrovica, Kosova. *BMC Public Health*. (2014) 14:1169. doi: 10.1186/1471-2458-14-1169
14. Shkcmbi F, Melonashi E, Fanaj N. Personal and public attitudes regarding help-seeking for mental problems among kosovo students. *Proc Soc Behav Sci*. (2015) 205:151–6. doi: 10.1016/j.sbspro.2015.09.045
15. Wenzel T, Rushiti F, Aghani F, Diaconu G, Maxhuni B, Zitterl W. Suicidal ideation, post-traumatic stress and suicide statistics in Kosovo. *Torture*. (2009) 19:10.
16. Bonnet F, Irving K, Terra J-L, Nony P, Berthezène F, Moulin P. Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. *Atherosclerosis*. (2005) 178:339–44. doi: 10.1016/j.atherosclerosis.2004.08.035
17. Hartka E, Johnstone B, Leino EV, Motoyoshi M, Temple MT, Fillmore KM, et al. meta-analysis of depressive symptomatology and alcohol consumption over time*. *Br J Addict*. (1991) 86:1283–98. doi: 10.1111/j.1360-0443.1991.tb01704.x
18. Almas A, Patel J, Ghori U, Ali A, Edhi AI, Khan MA. Depression is linked to uncontrolled hypertension: a case–control study from Karachi, Pakistan. *J Ment Health.* (2014) 23:292–6. doi: 10.3109/09638237.2014.924047
19. Elperin DT, Pelter MA, Deamer RL, Burchette RJ, A. Large cohort study evaluating risk factors associated with uncontrolled hypertension. *J Clin Hypertens.* (2014) 16:149–54. doi: 10.1111/jch.12259
20. Rubio-Guerra AF, Rodriguez-Lopez L, Vargas-Ayala G, Huerta-Ramirez S, Serna DC, Lozano-Nuevo JJ. Depression increases the risk for uncontrolled hypertension. *Exp Clin Cardiol.* (2013) 18:10–2.
21. Lustman PJ, Anderson RJ, Freedland KE, Groot M de, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care*. (2000) 23:934–42. doi: 10.2337/diacare.23.7.934
22. Obas KA, Gerold J, Bytyçi-Katanolli A, Jerliu N, Kwiatkowski M, Ramadani Q, et al. Study protocol: a prospective cohort on non-communicable diseases among primary healthcare users living in Kosovo (KOSCO). *BMJ Open*. (2020) 10:e038889. doi: 10.1136/bmjopen-2020-038889
23. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med.* (1999) 159:179–87. doi: 10.1164/ajrccm.159.1.9712108
24. Thorat YT, Salvi SS, Kodgule RR. Peak flow meter with a questionnaire and mini-spirometer to help detect asthma and COPD in real-life clinical practice: a cross-sectional study. *NPJ Prim Care Respir Med.* (2017) 27:1–7. doi: 10.1038/s41533-017-0036-8
25. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 international society of hypertension global hypertension practice guidelines. *Hypertension*. (2020) 75:1334–57. doi: 10.1161/HYPERTENSIONAHA.120.15026
26. Nielsen ABS, Gannik D, Siersma V, de Fine Olivarius N. The relationship between HbA1c level, symptoms and self-rated health in type 2 diabetic patients. *Scand J Prim Health Care.* (2011) 29:157–64. doi: 10.3109/02813432.2011.585542
27. Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the depression anxiety stress scales (DASS) with the beck depression and anxiety inventories. *Behav Res Ther*. (1995) 33:335–43. doi: 10.1016/0005-7967(94)00075-U
28. Gashi S, Berisha M, Ramadani N, Gashi M, Kern J, Dzakula A, et al. Smoking behaviors in Kosova: Results of steps survey. *Slovenian J Public Health.* (2017) 56:158–65. doi: 10.1515/sjph-2017-0021
29. Ramadani N, Berisha M, Thaçi A, Gashi-Luci L, Koçinaj D, Jerliu N. Tobacco use among Kosovar schoolchildren: a cross-sectional study. *Med Arh.* (2009) 63:44–7.
30. Miech R, Johnston L, O'Malley PM, Bachman JG, Patrick ME. Trends in Adolescent Vaping, 2017–2019. *N Eng J Med.* (2019) 381:1490–1. doi: 10.1056/NEJMc1910739
31. Peralta M, Martins J, Guedes DP, Sarmento H, Marques A. Socio-demographic correlates of physical activity among European older people. *Eur J Ageing.* (2017) 15:5–13. doi: 10.1007/s10433-017-0430-7
32. Jerliu N, Krasniqi P, Berisha M, Ramadani N. Regular physical activity of older people in Kosovo: a population-based surveyNaim Jerliu. *Eur J Public Health.* (2015) 25:3. doi: 10.1093/eurpub/ckv175.216
33. Hu MX, Turner D, Generaal E, Bos D, Ikram MK, Ikram MA, et al. Exercise interventions for the prevention of depression: a systematic review of meta-analyses. *BMC Public Health.* (2020) 20:1255. doi: 10.1186/s12889-020-09323-y
34. Šubarić Gorgieva G, Stašević Z, Vasić S, Ristić S, LeŽaić V, Djukanović L. Screening of chronic diseases and chronic disease risk factors in two rural communities in Kosovo. *Cent Eur J Public Health*. (2010) 18:81–6. doi: 10.21101/cejph.a3582
35. World Health Organization. *WHO Package of Essential Noncommunicable (PEN) Disease Interventions For Primary Health Care*. Geneva: World Health Organization (2020). Available online at: https://apps.who.int/iris/handle/10665/334186 (accessed August 22, 2021).
36. Bajcinovci B. Environmental and climate dilemma: coal for heating or clean air for breathing: a case of Prishtina. *Environ Climate Technol.* (2019) 23:41–51. doi: 10.2478/rtuect-2019-0003
37. Tusa N, Koponen H, Kautiainen H, Korniloff K, Raatikainen I, Elfving P, et al. The profiles of health care utilization among a non-depressed population and patients with depressive symptoms with and without clinical depression. *Scand J Prim Health Care*. (2019) 37:312–8. doi: 10.1080/02813432.2019.1639904

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Frontiers in Public Health

ORIGINAL RESEARCH
published: 02 May 2022
doi: 10.3389/fpubh.2022.800612

Policy Goals of Contract Arrangements in Primary Care in Jeopardy: A Cross-Sectional Consumer Satisfaction Survey of Community Residents in Hangzhou, China

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Objective: China is attempting to establish a voluntary contracting system in primary care. This study aimed to determine the degree of consumer satisfaction with the entitlements of contract arrangements and its associated factors.

Methods: A stratified cluster sampling strategy was adopted to recruit study participants from three administrative districts of Hangzhou municipality, each containing six residential communities. In each community, 50 households were recruited. A questionnaire was administered through face-to-face interviews with members of the households who signed a contract with community health centers, to collect data regarding their sociodemographic characteristics, health conditions, and knowledge of and attitudes toward the contract entitlements. Consumer satisfaction was measured using six items rated on a five-point Likert scale ranging from "1=very dissatisfied" to "5=very satisfied" and a summed score was calculated. A mixed linear regression model was established to identify individual predictors of consumer satisfaction after adjustment of the random (intercept) effect of household clusters.

Results: Overall, the respondents reported low levels of awareness and understanding of the contract entitlements, with an average knowledge score of 8.21 (SD = 3.74) out of a maximum possible of 19. The respondents had relatively lower levels of satisfaction (satisfied or very satisfied) with their prioritized entitlements (51.5%) and hospitals at home and telemedicine services (31.3%), compared with the contract and insurance policies (85.5%) and medical services provided (87.0%). Female gender, older age, chronic conditions, and perceived better health were associated with higher levels of satisfaction, while poor awareness and knowledge were associated with lower levels of satisfaction.

Conclusion: The study participants perceived limited benefits from the contract arrangements in primary care, which may jeopardize the policy purpose of the arrangements to encourage patients to use primary care as the first contact point in

Edited by:
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Specialty section:
This article was submitted to
Family Medicine and Primary Care,
a section of the journal
Frontiers in Public Health

Received: 23 October 2021
Accepted: 12 April 2022
Published: 02 May 2022

Citation:
Ren L, Ren J, Liu C, He M and Qiu X
(2022) Policy Goals of Contract
Arrangements in Primary Care in
Jeopardy: A Cross-Sectional
Consumer Satisfaction Survey of
Community Residents in Hangzhou,
China.
Front. Public Health 10:800612.
doi: 10.3389/fpubh.2022.800612

accessing health care services. It is evident that consumer satisfaction with the contract entitlements varies by healthcare needs. Lower levels of satisfaction are associated with poor awareness and knowledge of the entitlements.

Keywords: primary care, consumer satisfaction, care contract, general practitioners, healthcare needs

BACKGROUND

Internationally, there is consensus that 90% of health problems can be appropriately managed in primary care settings, while the rest require specialist consultations (1). Since the 1960s, the important role and functions of general practitioners (also known as family doctors in some countries) in the development of an efficient and quality health system have been increasingly recognized. They are the backbone of the primary care sector, aiming at maintaining and promoting both individual and population health. Empirical evidence shows that a primary-care-dominant health system outperforms the others in population health outcomes (2).

In a primary-care-dominated health care system, general practice is usually a predominant stream of medical specialization. General practitioners (GPs) are often assigned a gate-keeping role and serve as the first contact point for consumers to access health care services. Some countries even go further by introducing contract arrangements to ensure that GPs also look after the entire group of patients, not just individuals. The UK national health system (NHS) is deemed an exemplar (3). It is a publicly-funded system in which each GP is responsible for managing about 2,000 contracted patients. Specialist consultations and hospital services except for emergency care require a referral from the GPs (4). Contract arrangements have the advantage of promoting continuity and coordination of patient care despite some compromise to patient freedom of choice (2). Evidence shows that the UK system is characterized by a relatively low investment with high returns (5). Under such a system, GPs attach great importance to preventive services (6). Despite the stark contrast with the UK system, in the largely market-driven health system in the US, contract arrangements have also demonstrated their potential to reduce hospitalization and readmission of hospital patients (7), although it is often considered as a cost containment measure (8, 9).

Many countries have not introduced a contract system for various reasons. Germany, for example, has a strong tradition of corporatism and consumers enjoy freedom in choosing their first contact doctors, as well as in negotiating referred doctors (8). Contract arrangements are usually absent in low- and middle-income countries simply because they do not have enough skilled primary care professionals. This has resulted in a serious shortage of research into the potential effects of contract arrangements in low- and middle-income countries (10).

China is an upper middle-income country. Over the past two decades, China has been attempting to establish a GP-led health system. However, general practice is still in its early stage of development. Despite a serious shortage of GPs, there is both an under-use of primary care facilities and an over-use of hospital facilities in China (11, 12). The freedom of patients to bypass primary care in seeking hospital services is often blamed for the irrational distribution of health resources and services. For historical reasons, primary care facilities in China employ a large number of physicians without a university medical degree. Concerns over quality have deterred the Chinese government from introducing a gate-keeping and referral mechanism similar to the UK and several other countries (13). As an alternative option, a voluntary contracting system was introduced (14). In May 2016, the national government issued guidelines to promote primary care contract arrangements. Local governments were also encouraged to develop and use contract entitlements to incentivize patients to increase their use of primary care facilities (15). These may involve certain free services, prioritized medical appointments and referrals, and favorable policies for social health insurance programs (16). Although the contract is usually signed between a GP and a patient, the entitlements go beyond the scope of the services delivered by the GP (14).

The existing studies on China have focused on documenting the coverage of the contract arrangements (14), with a prior assumption that such arrangements are beneficial to the patients and the health care system. However, little is known about the experience of the community residents who enter into the contracts. This study contributes to the literature by measuring the satisfaction of those who signed a contract with their local community health centers. Internationally, measuring consumer satisfaction has become an important step for quality improvement (17).

METHODS

A cross-sectional questionnaire survey of community residents was conducted in Hangzhou. Ethics approval was obtained from Hangzhou Normal University (Reference number 20190070). The survey was anonymous and oral informed consent was sought from the study participants prior to the survey.

Study Setting

Hangzhou is the capital city of Zhejiang province, one of the most developed regions in China. More than 10 million people reside in Hangzhou permanently and about 23% are older than 60 years. There are 5,925 health institutions in Hangzhou, including 2,626 community health centers (CHCs) (18). Community health services are available to all Hangzhou residents, including voluntary contract arrangements with local CHCs. Hangzhou started the voluntary contract initiative in 2014 and scaled it up across all CHCs in 2016. A total of 40.551 million patient visits to CHCs were recorded in Hangzhou in 2019 (18).

Sampling and Data Collection

A multi-stage stratified sampling strategy was adopted. Administrative districts were sorted in order according to their local gross domestic products and evenly divided into high-, middle-, and low-income districts. One district in each category was selected: Xiacheng (high income), Jianggan (middle income), and Gongshu (low income). Six residential communities were then conveniently selected from each participating district. In each residential community, 50 households were randomly selected. All adult (>18 years) household members were eligible to participate in the study. The households that rejected invitations or were not approachable were replaced by neighboring households.

Data were collected through household visits and face-to-face interviews in November 2018. Interviewers were recruited from local CHC health workers. A total of 36 interviewers were trained and grouped into six teams. Each team visited one residential community at a time. Each eligible household member was interviewed separately and completed the questionnaire independently. Those who were absent or refused to give informed consent were excluded. This resulted in a final sample of 2,315 individuals from 906 households. After excluding those who did not enter into a contract arrangement with local CHCs, 1,304 (56.33%) respondents from 673 households were included in data analyses for the purpose of this study. This sample size was at least 25 times the number of independent variables for regression modeling, far exceeding the minimal requirement (19).

Measurements

Satisfaction was defined as a subjective perception, reflecting the gap between one's expectation and actual experience (20). It was measured using a six-item scale in this study, covering six aspects of the contract entitlements, namely (1) favorable contract and insurance policies; (2) free services covered by the contract; (3) free personal inquiries and appointments; (4) prioritized consultations and referral; (5) hospitals at home and telemedicine; and (6) free prescription services for chronic diseases. The participants were asked to rate their degree of satisfaction with each of the six items on a five-point Likert scale, ranging from 1 (very dissatisfied) to 5 (very satisfied). Satisfaction ratings on the six items were summed for each respondent. The respondents were then divided into two groups using a cut-off point of 24 (exceeding the neutral total): low satisfaction (<24) and high satisfaction (≥24).

Knowledge has a significant impact on individual expectations (21). In this study, an eleven-item scale was developed to measure awareness of the respondents about their contracting institution (item 1) and GPs (item 2), and the benefits they were entitled to in line with the contract policy, which included discounts in out-of-pocket payments for insurance-covered services delivered in the contracting institution (300 Yuan reduction in deductibles–item three; 3% increase in reimbursement rates–item four); prioritized (free of charge) medical appointments (item five), consultations (item six) and referrals (item seven); free access to inquiries on personal records (item eight); and free prescribing services for chronic diseases (item nine). A score of one was assigned to a correct answer or a recognized benefit; 0 was recorded otherwise (including answer of unsure). The respondents were then asked to rate their overall understanding of the contract arrangements (item 10) and their entitlement to free prescribing services for chronic diseases (item 11) on a five-point Likert scale, ranging from 1 (very poorly) to 5 (very well). A summed

TABLE 1 | Characteristics of study participants.

Characteristics	Number (Person)	Percentage (%)
Sex		
Male	596	46.0
Female	701	54.0
Age (years)		
<18	90	6.9
18–40	126	9.7
41–60	290	24.0
>60	791	61.0
Educational attainment		
≤ Primary school	375	31.0
Middle school	372	30.8
High school	271	22.4
≥ University	191	15.8
Employment		
Employed	272	22.4
Retired	862	71.0
Unemployed	80	6.6
Occupation		
Management	188	16.9
Professional	195	17.5
Office clerical staff	202	18.1
Company sales and services	123	11.0
Self-employed	55	4.9
Industrial workers	171	15.3
Farming	80	7.2
Others	101	9.1
Marital status		
Unmarried	63	5.3
Married	1,028	86.1
Widowed	103	8.6
Basic medical insurance for employees		
Yes	614	47.4
No	682	52.6
Basic medical insurance for residents		
Yes	661	51.0
No	635	49.0
Chronic disease		
Yes	699	56.4
No	541	43.6
Self-rating on health		
Poor	216	23.3
Good	456	49.2
Excellent	255	27.5

TABLE 2 | Knowledge of study participants about contract arrangements.

Study participants	Knowledge about contract arrangements					
	($\bar{x}$±SD)	***p***	***% Low***	***% Medium***	***% High***	***p***
Sex		0.216				0.509
Male	8.05 ± 3.78		46.9	43.6	42.8	
Female	8.34 ± 3.72		53.1	56.4	57.2	
Age (years)		<0.001				<0.001
<18	3.41 ± 2.76		10.1	1.1	0.3	
18–40	7.37 ± 4.23		12.7	4.8	7.9	
41–60	8.16 ± 3.70		23.5	21.1	22.1	
>60	8.64 ± 3.50		53.7	72.9	69.6	
Educational attainment		0.015				<0.001
≤ Primary school	7.79 ± 3.23		36.7	34.0	21.1	
Middle school	8.93 ± 3.56		22.3	33.8	35.3	
High school	8.61 ± 3.81		23.3	19.1	27.7	
≥ University	8.34 ± 4.18		17.5	13.1	15.8	
Employment		<0.001				<0.001
Employed	7.74 ± 4.19		27.9	14.9	20.0	
Retired	8.68 ± 3.47		63.4	80.5	76.4	
Unemployed	7.26 ± 3.33		8.7	4.7	3.6	
Occupation		0.030				<0.001
Management	8.96 ± 3.84		16.2	16.5	21.7	
Professional	8.61 ± 3.88		16.9	17.0	19.3	
Office clerical staff	8.52 ± 3.94		18.9	15.6	22.4	
Company sales and services	8.01 ± 3.73		12.6	7.9	11.2	
Self-employed	7.40 ± 3.08		4.0	4.7	1.4	
Industrial workers	8.51 ± 3.44		12.9	19.5	15.6	
Farming	7.30 ± 2.89		8.9	9.4	2.7	
Others	8.15 ± 3.70		9.6	9.4	5.8	
Marital status		0.026				0.003
Unmarried	6.98 ± 4.14		8.3	2.6	3.9	
Married	8.38 ± 3.72		82.4	87.6	89.2	
Widowed	8.03 ± 3.48		9.2	9.7	6.9	
Basic medical insurance for employees		<0.001				<0.001
Yes	9.07 ± 3.60		38.1	48.3	65.0	
No	7.45 ± 3.67		61.9	51.7	35.0	
Basic medical insurance for residents		<0.001				<0.001
Yes	7.39 ± 3.63		60.3	51.3	31.7	
No	9.07 ± 3.63		39.7	48.7	68.3	
Chronic disease		<0.001				<0.001
Yes	9.17 ± 3.37		42.9	65.7	71.1	
No	7.30 ± 3.71		57.1	34.3	28.9	
Self-rating on health		0.023				0.010
Poor	9.29 ± 2.84		20.2	25.9	21.7	
Good	9.50 ± 3.12		43.4	48.0	54.7	
Excellent	8.85 ± 3.02		36.4	26.1	23.7	

score (ranging from 2 to 19) for each respondent was calculated. The respondents were subsequently divided into three knowledge groups: low (2–6, the lowest one quarter of the score range), medium (7–10, the lower middle range of score) and high (11–19, the higher middle and upper range of score), for the purpose of regression analyses since no linear correlation between knowledge and satisfaction could be assumed.

Health insurance benefits are an important component of the contract entitlement package. Although China has achieved almost universal coverage of social health insurance, multiple

TABLE 3 | Consumer satisfaction with contract arrangements.

Contract entitlement	Satisfaction rating		
	Mean ± SD	% of satisfied (≥4)	Ranking
(1) Favorable contract and insurance policies	4.25 ± 0.77	85.5	2
(2) Fee discounts for medical services provided	4.32 ± 0.76	87.0	1
(3) Free personal inquiry and appointments	4.00 ± 0.82	70.9	4
(4) Prioritized consultations and referrals	3.71 ± 0.84	51.5	5
(5) Hospitals at home and telemedicine	3.41 ± 0.72	31.3	6
(6) Free prescriptions for chronic diseases	4.09 ± 0.81	79.0	3

insurance programs with great disparities exist (22). In this study, we asked the respondents to report their membership of the two major social insurance programs: basic medical insurance for urban employees (BMIUE) and basic medical insurance for urban/rural residents (BMIUR). Both insurance programs require individual monetary contributions through premiums and copayments. The BMIUE usually has a larger funding pool and offers more generous financial benefits to enrollees than the BMIUR (23).

Previous research shows that consumer satisfaction with health care services often varies by sociodemographic characteristics of the consumers (20). In this study, we collected data in relation to the respondents' age (years), gender (male, female), marital status (unmarried, married, widowed), education (≤primary school, middle school, high school, ≥university), employment status (employed, retired, unemployed), and occupation (management, professional, office clerical staff, company sales and services, self-employed, industrial worker, farming, other). We also asked the respondents to report their health status measured by chronic diseases (yes, no) and self-rated general health (poor, good, excellent).

Data Analyses

The characteristics of the study participants were described through frequency distributions. Their knowledge of the contract arrangements (with a normal distribution) was described using mean scores and standard deviations, as well as percentage distributions across the high, medium and low knowledge groups.

Consumer satisfaction was described using mean and standard deviation of the satisfaction score (with a normal distribution), and the percentage of high satisfaction. Student *t*-tests (or ANOVA) and chi-squared tests were performed to identify the differences in the satisfaction score and the level of satisfaction, respectively, among respondents with different characteristics. The household cluster effect on consumer satisfaction was significant (ICC > 0.8). Therefore, a mixed linear regression model was established to determine individual predictors of patient satisfaction after adjustment of the random effect (intercept) of the family clusters. Independent variables were entered into the model in a block (enter approach) and all were coded as categorical measurements.

Data were managed using Epidata 3.1. Double data entry was conducted to ensure the accuracy of the data. Statistical analyses were performed using SPSS 21.0 software. A $p < 0.05$ was considered statistically significant.

RESULTS

Characteristics of Respondents

Slightly over half (54%) of the study participants were women. The respondents had a mean age of 59 years: more than 60% were older than 60 years. The majority had not completed high school (62%), were married (86%) and retired (71%) at the time of the survey. More than 53% of respondents reported chronic diseases, but most self-rated their health as good (49%) or excellent (28%) (**Table 1**).

Knowledge About Contract Entitlements

The respondents had low levels of knowledge about their contract entitlements (**Table 2**). More than 72.8% fell into the low (34.0%) and medium (38.7%) knowledge groups, resulting in an average score of 8.21 (SD = 3.74) out of a maximum possible of 19. Less than half of the respondents could name their contracting doctors (38.2%) or institutions (34.5%) correctly. About 59.4% only identified one or two benefits to which they were entitled. The most noticeable benefit was the 300 Yuan (US$50) reduction in deductibles for insurance-covered outpatient services (54.4%), followed by prioritized medical appointments (29.6%), 3% increase in insurance reimbursement rates (26.1%), and free access to inquiries on personal records (26.1%). Most respondents (56%) were not aware of the free prescribing services for chronic diseases.

Consumer Satisfaction With Contract Arrangements

Overall, the respondents had a mean satisfaction score of 22.24 (SD = 3.98), falling short of the cut-off point of 24. Variations in satisfaction with the different aspects of contract arrangements were evident. The respondents reported relatively lower levels of satisfaction with prioritized entitlements (51.5%, $p < 0.001$) and hospitals at home and telemedicine services (31.3%, $p < 0.001$), compared with favorable contract and insurance policies (85.5%) and fee discounts in the medical services provided (87.0%). The mean scores on prioritized entitlements and hospitals at home and telemedicine services fell below 4 (satisfied) (**Table 3**).

Factors Associated With Consumer Satisfaction With Contract Arrangements

The respondents who were older, retired, reported chronic conditions, and had a higher knowledge score on contract entitlements reported significantly ($p < 0.001$) higher degrees of satisfaction than the others. Similarly, those respondents were also more likely to fall into the high satisfaction group. Women were more likely to report higher satisfaction than men (**Table 4**).

TABLE 4 | Satisfaction with contract arrangements of respondents with different characteristics.

Characteristics	Satisfaction score			High satisfaction (≥24)	
	$\bar{x}$±SD	*F*	*p*	%	*p*
Gender		1.451	0.229		0.016
Male	19.79 ± 5.812			36.0	
Female	20.25 ± 6.228			64.0	
Age (years)		10.283	<0.001		0.006
<18	19.50 ± 3.082			0.4	
18–40	20.12 ± 3.384			4.1	
41–60	21.24 ± 4.033			17.8	
>60	22.84 ± 3.875			77.6	
Educational attainment		1.128	0.337		0.781
≤Primary school	22.75 ± 3.724			33.6	
Middle school	22.27 ± 4.148			30.7	
High school	21.98 ± 4.235			21.2	
≥University	21.78 ± 3.640			14.5	
Employment		8.294	<0.001		0.021
Employed	20.65 ± 3.789			12.8	
Retired	22.72 ± 3.912			83.5	
Unemployed	21.55 ± 4.123			3.7	
Occupation		1.052	0.393		0.396
Management	19.00 ± 6.218			19.7	
Professional	19.25 ± 5.806			17.5	
Office clerical staff	18.19 ± 6.251			15.4	
Company sales and services	17.51 ± 6.861			8.1	
Self-employed	18.93 ± 6.353			4.3	
Industrial workers	19.22 ± 5.520			15.4	
Farming	18.31 ± 5.563			9.0	
Others	18.93 ± 6.439			10.7	
Marital status		2.279	0.103		0.071
Unmarried	20.67 ± 3.247			1.3	
Married	22.31 ± 4.019			89.2	
Widowed	22.87 ± 3.672			9.6	
Basic medical insurance for urban employees		1.225	0.269		0.381
Yes	22.25 ± 4.097			49.8	
No	22.23 ± 3.857			50.2	
Basic medical insurance for residents		0.613	0.434		0.836
Yes	22.18 ± 3.748			46.5	
No	22.29 ± 4.174			53.5	
Chronic disease		131.035	<0.001		<0.001
Yes	23.84 ± 3.425			84.0	
No	19.44 ± 3.288			16.0	
Self-rating on health		0.128	0.880		0.698
Poor	22.27 ± 3.814			23.9	
Good	22.44 ± 4.058			50.8	
Excellent	22.00 ± 3.843			25.2	
Knowledge score about contract arrangements		56.856	<0.001		<0.001
Low (1–6)	19.48 ± 3.578			8.2	
Medium (7–10)	22.13 ± 3.863			44.9	
High (≥11)	23.72 ± 3.604			46.9	
Total	22.24 ± 3.98			26.7	

TABLE 5 | Multivariate linear regression analysis on factors associated with consumer satisfaction.

Predictor	Null model	Fixed effect model ($R^2 = 0.231$)		Mixed effect model	
		β	95% CI	β	95% CI
Gender (reference=Male)					
Female		0.803	(0.015, 1.592)	0.354	(−0.016, 0.725)
Age (reference = 0–40 years)					
41–60		−0.762	(−2.714, 1.190)	−0.436	(−1.718, 0.846)
>60		0.558	(−1.682, 2.798)	0.270	(−1.363, 1.903)
Educational attainment (reference= ≤Primary school)					
Middle school		0.140	(−0.862, 1.141)	0.089	(−0.566, 0.743)
High school		−0.453	(−1.583, 0.676)	−0.492	(−1.278, 0.293)
≥University		0.666	(−0.798, 2.131)	0.076	(−0.923, 1.075)
Employment (reference=Employed)					
Retired		−0.572	(−2.062, 0.918)	−0.065	(−1.056, 0.926)
Unemployed		0.527	(−3.630, 4.684)	0.670	(−1.802, 3.142)
Occupation (reference=Management)					
Professionals		0.596	(−0.650, 1.842)	−0.497	(−1.409, 0.416)
Office clerical		0.017	(−1.236, 1.270)	−0.598	(−1.519, 0.324)
Commercial/services		−0.263	(−1.769, 1.243)	−0.502	(−1.523, 0.519)
Self employed		1.662	(−0.579, 3.904)	−0.368	(−2.094, 1.358)
Industrial workers		0.894	(−0.380, 2.169)	−0.044	(−1.015, 0.926)
Farmer		0.076	(−1.644, 1.795)	−0.192	(−1.655, 1.272)
Others		1.385	(−0.180, 2.949)	0.632	(−0.567, 1.832)
Marital status (reference=Unmarried)					
Married		0.765	(−1.305, 2.835)	−0.036	(−1.339, 1.267)
Widowed		0.102	(−2.341, 2.545)	0.034	(−1.606, 1.674)
Basic medical insurance for urban employees (reference=Yes)					
No		0.283	(−1.463, 2.029)	0.496	(−1.114, 2.106)
Baisc medical insurance for residents (reference=Yes)					
No		−1.183	(−2.945, 0.579)	−0.698	(−2.344, 0.947)
Chronic conditions (reference=Yes)					
No		−4.426	(−5.326, −3.525)	−4.034	(−4.598, −3.469)
Self-assessment of health (reference=Poor)					
Good		0.335	(−0.589, 1.259)	0.190	(−0.447, 0.827)
Excellent		1.561	(0.469, 2.653)	0.980	(0.183, 1.776)
Knowledge about contract arrangements (reference=Low)					
Medium		2.656	(1.623, 3.688)	2.184	(1.232, 3.137)
High		5.353	(4.228, 6.477)	4.858	(3.815, 5.901)
intra-level correlation coefficient (ICC)	0.80			0.88	
Akaike Information Criterion (AIC)	5,621			4,732	
Schwarz's Bayesian Criterion (BIC)	5,635			4,741	

The high ICC values of the null model indicated a significant cluster effect of households on consumer satisfaction. The two-level mixed effect linear model generated consistent results after adjustment for variations in the random effect of family clusters ($p < 0.001$) as compared with those of the individual-level fixed effect model. High levels of knowledge on contract entitlements ($\beta = 2.184$–4.858, $p < 0.01$) and self-rated excellent health ($\beta = 0.980$, $p = 0.016$) were associated with higher levels of satisfaction with contract arrangements, while the absence of chronic conditions ($\beta = -4.034$, $p < 0.001$) was associated with lower levels of satisfaction with contract arrangements (**Table 5**).

DISCUSSION

The level of awareness and knowledge of contract entitlements of the study participants was very low, although they had all entered into a contract arrangement with their local CHC and the system has been fully implemented since 2016 (24). Less than half of the respondents could correctly identify two or more entitlements. The satisfaction rates with the contract entitlements ranged from 31 to 87%. Higher awareness, better perceived health, and living with chronic conditions are significant predictors of higher levels of satisfaction after adjustment for variations in other variables and the random effect of family clusters.

The low level of awareness and knowledge of the contract entitlements is concerning as it can jeopardize the attainment of the intended goals. We found that the financial benefit of discounts in out-of-pocket payments was most acknowledged, with 54.4% of respondents noticing the sizable 300 Yuan reduction in deductibles. Similar financial benefits are widely available across China despite variations in policy designs. In Shanghai, for example, contracted patients could be prescribed up to 2 months of medications for chronic conditions which saves costs on medical appointments and consultation fees, a benefit which is not readily available to non-contracted patients (25). However, it is not clear whether these financial benefits provide sufficient incentives to encourage consumers to seek medical attention from primary care facilities. Over the past decade, the volume of patient visits to primary care facilities has increased significantly; but patient visits to primary care as a proportion of the total volume of outpatient services has actually been declining in China (26). It appears that a lack of trust in primary care imposes a great barrier to diverting hospital patients to primary care. The perceived quality of medical services in primary care is often deemed inferior to those provided in hospitals (27). Although primary care has the advantage of maintaining continuous relationships with patients and GPs are well positioned to coordinate care on behalf of their patients (2), these benefits are not well endorsed by the patients, according to the findings of this study. Indeed, < 30% of the participants in our study realized the benefits of prioritized medical appointments and referrals and free access to inquiries on personal records. Previous studies showed that many people do not trust the competency of primary care providers in disease diagnosis and management. The legacy of the barefoot doctors led them to believe that primary care doctors nowadays are still inferior to hospital specialists (28).

In this study, we found that 56.33% of Hangzhou residents entered into contract arrangements with local CHCs, which is slightly higher than the average of 50.43% in China (29). Although Hangzhou did not lead in the contract rate (30), it outperformed some other developed regions in China such as Shanghai Changning District (52.8%) (31) and Guangdong province (52.9%) (32). Perceived financial benefits may be a major contributor to encourage consumers to sign a contract with CHCs in China. We found that the contracted patients were predominantly elderly and retirees. It is important to note that consumers do not need to pay a fee to enter into a contract arrangement. The contract arrangement system operates as part of the essential public health package funded by the government. Those who enter into contract arrangements still maintain freedom in their choice of providers. They are not obligated to abide by any conditions imposed by the contracts. Because "contract coverage" is one of the performance indicators of the essential public health package, CHCs often implement very aggressive strategies to incentivize residents to sign contracts. From the perspective of consumers, there is little to lose from entering into a contract with a CHC (29).

Our study revealed that consumer satisfaction with the contract arrangements fell short of expectations. We found that only 26.7% of the study participants obtained a summed satisfaction score of higher than 24, exceeding the neutral total. Although over 85% of the respondents were satisfied with the financial benefits of discounts in medical services, only slightly more than half of our study participants were satisfied with their entitlements for prioritized medical appointments and referrals and less than one third were satisfied with hospitals at home and telemedicine services. Specialist and hospital services can become more efficient and more effective by liaising with primary care workers (28). However, it is not possible for GPs to fulfill such a role without the trust and acceptance of consumers.

However, there are some positive signs. We found in this study that 79% of respondents were satisfied with the free prescription services for chronic diseases under the contract arrangements. This may ease some of the burdens on overcrowded hospitals (33). Further evidence needs to be gathered to support such a claim. In theory, the better management of chronic conditions through primary care is critical, not only to improve the quality of life of patients but also to reduce preventable hospital admissions (28). GPs are best positioned to manage chronic conditions as they can establish a long-term continuing relationship with their patients and they understand the multiple needs of their patients best (34). Interestingly, less than half the respondents in our study could name their contracting doctors. Liu et al. (35) found that patients in China favor a concept of continuity centered around team efforts facilitated by information technologies.

The Chinese government is determined to continue to expand the initiative of contract arrangements with primary care. Our study shows that consumers' lack of awareness and understanding of contract entitlements may jeopardize such an effort. The findings have some policy implications. Firstly, the CHC approach to entering into contracts with community residents does not provide any mechanism or incentives to ensure the effective provision and materialization of contract entitlements. Secondly, contracting by itself is not the ultimate goal. A systems approach is needed to enable contract arrangements to serve as an instrument to improve the continuity and coordination of patient care. Thirdly, more radical system restructuring in China, such as the introduction of a gatekeeping mechanism through primary care, can be hindered by the low confidence from the government and trust from the public (27). Finally, the fragmentations in policy development across sectors in China need to be addressed (36) so that various incentives can be better aligned (37) and public trust in primary care can be regained (15). Unlike many developed countries, where a "gatekeeper" role has been assigned to GPs through social health insurance policies (38, 39), the Chinese system currently depends on voluntary contract arrangements. A systems approach is needed to achieve the policy goals of the contract arrangement system. These will include, but are not limited to, a strong commitment from the government, better aligned policies across sectors, the strong capacity of GPs, and public endorsement and support (40, 41).

There are several limitations in this study. We assessed patient satisfaction with the contract entitlements, but did not evaluate its impacts on the entire healthcare delivery system. Further studies are needed to systematically examine the impacts of the contracting system. The study adopted a cross-sectional design, which prevents causal conclusions. The study sample was drawn from Hangzhou, one of the most developed regions in China. Any attempts to extrapolate the findings need to be cautious.

CONCLUSIONS

Contract arrangements for community residents with local primary care institutions represent the Chinese government's effort to reverse the hospital-dominant system in healthcare service delivery. Despite the rapid expansion of contracting rates, consumer awareness and understanding of contract entitlements is low, according to the findings of this study. Higher awareness, better perceived health, and living with chronic conditions are significant predictors of higher levels of satisfaction with the contract arrangements. Although the current system may bring certain benefits to consumers living with chronic conditions, a better design of contract arrangements, if not a fundamental change in the health care system, will be required to further advance the contracting system. Improving consumers' awareness and understanding of contract entitlements may help, but alone it is not enough.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethics approval for the study protocol was obtained from the Hangzhou Normal University (Reference Number 20190070). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JR and CL contributed to the conceptualization and methodological design. LR, MH, and XQ contributed to the collection and analysis of data. LR, JR, and CL contributed to the interpretation of the results and the drafting of the manuscript. All authors mentioned contributed to technical enrichment, the writing and also reviewed, and then approved the final manuscript.

FUNDING

This work was supported by National Natural Science Foundation of China (71874047) and Basic Public Welfare Research Program of Zhejiang Province (LGF21G030003).

REFERENCES

1. Liu Z, Tan Y, Liang H, Gu Y, Wang X, Hao Y, et al. Factors influencing residents' willingness to contract with general practitioners in Guangzhou, China, during the GP policy trial phase: a cross-sectional study based on Andersen's behavioral model of health services use. *Inquiry*. (2019) 56:46958019845484. doi: 10.1177/0046958019845484
2. Shi L, Lee D-C, Liang H, Zhang L, Makinen M, Blanchet N, et al. Community health centers and primary care access and quality for chronically-ill patients - a case-comparison study of urban Guangdong Province, China. *Int J Equity Health.* (2015) 14:90. doi: 10.1186/s12939-015-0222-7
3. Koperski M. The state of primary care in the United States of America and lessons for primary care groups in the United Kingdom. *Br J Gen Pract.* (2000) 50:319–22.
4. Ting S, Ou-min S, HW. Foreign family physician service model and its enlightenment on China. *Heilongjiang Med.* (2015) 39:852–3. doi: 10.3969/j.issn.1004-5775.2015.07.059
5. Yuan-yuan T, Xiao-yao W, DG. Foreign Family Doctor Service Mode. *Chinese Prim Heal Care*. (2015) 29:9–11. doi: 10.3969/j.issn.1001-568X.2015.02.0004
6. Peckham S. The new general practice contract and reform of primary care in the United Kingdom. *Health Policy.* (2007) 2:34–48. doi: 10.12927/hcpol.2007.18873
7. Gilfillan RJ, Tomcavage J, Rosenthal MB, Davis DE, Graham J, Roy JA, et al. Value and the medical home: effects of transformed primary care. *Am J Manag Care.* (2010) 16:607–14.
8. Yuxin S, Tangshui S, Ling B, QY. Experience and inspiration of contracting services of foreign family doctors. *Chinese Foreign Entrep*. (2019) 8:218–9.
9. Zwar N. Family medicine in the USA-an Australian perspective. *Aust Fam Physician.* (2010) 39:360–1.
10. Munge K, Mulupi S, Barasa E, Chuma J, A. critical analysis of purchasing arrangements in Kenya: the case of micro health insurance. *BMC Health Serv Res.* (2019) 19:45. doi: 10.1186/s12913-018-3863-6
11. Wu D, Lam TP, Lam KF, Zhou XD, Sun KS. Health reforms in china: the public's choices for first-contact care in urban areas. *Fam Pract.* (2017) 34:194–200. doi: 10.1093/fampra/cmw133
12. Wu D, Lam TP. Underuse of primary care in China: the scale, causes, and solutions. *J Am Board Fam Med.* (2016) 29:240–7. doi: 10.3122/jabfm.2016.02.150159
13. Luo Z, Bai X, Min R, Tang C, Fang P. Factors influencing the work passion of Chinese community health service workers: an investigation in five provinces. *BMC Fam Pract.* (2014) 15:77. doi: 10.1186/1471-2296-15-77
14. Wang H, Shi L, Han X, Zhang J, Ma Y, Yang X, et al. Factors associated with contracted services of Chinese family doctors from the perspective of medical staff and consumers: a cross-sectional study. *BMC Health Serv Res.* (2019) 19:986. doi: 10.1186/s12913-019-4801-y
15. Yuan S, Wang F, Li X, Jia M, Tian M. Facilitators and barriers to implement the family doctor contracting services in China: findings from a qualitative study. *BMJ Open.* (2019) 9:e032444. doi: 10.1136/bmjopen-2019-032444
16. Lieber SR, Kim SY, Volk ML. Power and control: contracts and the patient-physician relationship. *Int J Clin Pract.* (2011) 65:1214–7. doi: 10.1111/j.1742-1241.2011.02762.x
17. Harris LE, Swindle RW, Mungai SM, Weinberger M, Tierney WM. Measuring patient satisfaction for quality improvement. *Med Care.* (1999) 37:1207–13. doi: 10.1097/00005650-199912000-00004
18. *Hangzhou Statistical Yearbook*. Available online at: http://tjj.hangzhou.gov.cn/art/2020/10/29/art_1229453592_3819709.html
19. Stoltzfus JC. Logistic regression: a brief primer. *Acad Emerg Med.* (2011) 18:1099–104. doi: 10.1111/j.1553-2712.2011.01185.x

20. Manzoor F, Wei L, Hussain A, Asif M, Shah SIA. Patient satisfaction with health care services; an application of physician's behavior as a moderator. *Int J Environ Res Public Health*. (2019) 16:3318. doi: 10.3390/ijerph16183318
21. Walker RC, Tong A, Howard K, Palmer SC. Patient expectations and experiences of remote monitoring for chronic diseases: systematic review and thematic synthesis of qualitative studies. *Int J Med Inform*. (2019) 124:78–85. doi: 10.1016/j.ijmedinf.2019.01.013
22. Wang Z, Li X, Chen M, Si L. Social health insurance, healthcare utilization, and costs in middle-aged and elderly community-dwelling adults in China. *Int J Equity Health*. (2018) 17:17. doi: 10.1186/s12939-018-0733-0
23. Choi WI, Shi H, Bian Y, Hu H. Development of commercial health insurance in China: a systematic literature review. *Biomed Res Int*. (2018) 2018:3163746. doi: 10.1155/2018/3163746
24. Notice of the General Office of the Hangzhou Municipal People's Government on Issuing the Implementation Plan (Trial) for the Integrated Contracted Services of Medical Care in Hangzhou. Available online at: http://wsjkw.hangzhou.gov.cn/art/2015/3/16/art_1671470_37097008.html
25. Wei X, Li H, Yang N, Wong SYS, Owolabi O, Xu J, et al. Comparing quality of public primary care between Hong Kong and Shanghai using validated patient assessment tools. *PLoS ONE*. (2015) 10:e0121269. doi: 10.1371/journal.pone.0121269
26. Xu J, Powell-Jackson T, Mills A. Effectiveness of primary care gatekeeping: difference-in-differences evaluation of a pilot scheme in China. *BMJ Glob Heal*. (2020) 5:e002792. doi: 10.1136/bmjgh-2020-002792
27. Chen W, Feng Y, Fang J, Wu J, Huang X, Wang X, et al. Effect of trust in primary care physicians on patient satisfaction: a cross-sectional study among patients with hypertension in rural China. *BMC Fam Pract*. (2020) 21:196. doi: 10.1186/s12875-020-01268-w
28. Wu D, Lam TP, Lam KF, Zhou XD, Sun KS. Public views towards community health and hospital-based outpatient services and their utilisation in Zhejiang, China: a mixed methods study. *BMJ Open*. (2017) 7:e017611. doi: 10.1136/bmjopen-2017-017611
29. Shang X, Huang Y, Li B, Yang Q, Zhao Y, Wang W, et al.. Residents' awareness of family doctor contract services, status of contract with a family doctor, and contract service needs in Zhejiang Province, China: a cross-sectional study. *Int J Environ Res Public Health*. (2019) 16:3312. doi: 10.3390/ijerph16183312
30. Jiaoling H, Hong L, Weisheng Z, Jianmin Z, Chao W, Xiang C, et al. Influencing factor analysis of signing a contract with a family doctor among residents in Hongkou district. *Chinese Gen Pract*. (2019) 22:687–91. doi: 10.12114/j.issn.1007-9572.2018.00.340
31. Yuan L, Zhou C, Jiang P, Xu L, Zhang Q, Xu B. Community residents' demand for family physician service in Changning Districe, Shanghai. *Chinese Gen Pract*. (2014) 17:3860–4. doi: 10.3969/j.issn.1007-9572.2014.32.020
32. MH. Study on the status of family doctor signing service in different areas of guangdong province and it's countermeasure proposal. *Guangzhou Guangzhou Med Univ*. (2017).
33. Chen L, Horton R, Summerskill W. A call for research papers from China. *Lancet*. (2009) 373:1324. doi: 10.1016/S0140-6736(09)60754-6
34. Silina V, Kalda R. Challenges for clinical practice and research in family medicine in reducing the risk of chronic diseases. Notes on the EGPRN Spring Conference 2017 in Riga. *Eur J Gen Pract*. (2018) 24:112–7. doi: 10.1080/13814788.2018.1429594
35. Liu C, Wu Y, Chi X. Relationship preferences and experience of primary care patients in continuity of care: a case study in Beijing, China. *BMC Health Serv Res*. (2017) 17:585. doi: 10.1186/s12913-017-2536-1
36. Chen S, Chen Y, Feng Z, Chen X, Wang Z, Zhu J, et al. Barriers of effective health insurance coverage for rural-to-urban migrant workers in China: a systematic review and policy gap analysis. *BMC Public Health*. (2020) 20:408. doi: 10.1186/s12889-020-8448-8
37. Ma X, Wang H, Yang L, Shi L, Liu X. Realigning the incentive system for China's primary healthcare providers. *BMJ*. (2019) 365:l2406. doi: 10.1136/bmj.l2406
38. Farmer J, Iversen L, Campbell NC, Guest C, Chesson R, Deans G, et al. Rural/urban differences in accounts of patients' initial decisions to consult primary care. *Health Place*. (2006) 12:210–21. doi: 10.1016/j.healthplace.2004.11.007
39. Peckham S, Falconer J, Gillam S, Hann A, Kendall S, Nanchahal K, et al. The organisation and delivery of health improvement in general practice and primary care: a scoping study. *Health Serv Deliv Res*. (2015) 3:5. doi: 10.3310/hsdr03290
40. Li X, Krumholz HM, Yip W, Cheng KK, De Maeseneer J, Meng Q, et al. Quality of primary health care in China: challenges and recommendations. *Lancet*. (2020) 395:1802–12. doi: 10.1016/S0140-6736(20)30122-7
41. Jiao F, YX. Status and research progress of contracted services of family doctors in the western region. *China Prim Heal Care*. (2019) 33:16–9. doi: 10.3969/j.issn.1001-568X.2019.05.0006

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Public Health

ORIGINAL RESEARCH
published: 13 May 2022
doi: 10.3389/fpubh.2022.830181

Influence of Work Values on the Prescribing Behavioral Intentions Regarding Antibiotic Use Among Primary Physicians in Hubei, China

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Objective: Primary physicians have been an important cause of global antibiotic resistance. The aim of this study is to identify the influence of primary physicians' work values on prescribing behavioral intentions regarding antibiotic use (behavioral intentions).

Methods: A total of 656 primary physicians' work values and behavioral intentions were collected by a stratified cluster sampling from 67 primary care facilities in Hubei Province of China. Work values included 5 dimensions, namely intrinsic values, extrinsic values, reward values, social values and altruistic values. Behavioral intentions included 2 dimensions of the intentions to reduce antibiotic prescriptions and the intentions to prescribe antibiotics. A Likert five-point scale was used and higher scores meant greater intentions to prescribe antibiotics. A hierarchical multiple regression analysis was employed to model the influence of work values on behavioral intentions.

Results: Primary physicians' behavioral intention was 2.01 averagely. Intrinsic values negatively influenced overall intentions to prescribe more antibiotics ($\beta = -0.098$, $P = 0.010$). Whereas lower social values perception ($\beta = 0.248$, $P < 0.001$), less pursuit of reward values ($\beta = 0.194$, $P < 0.001$), and less emphasis on altruistic values ($\beta = 0.180$, $P < 0.001$) positively influenced lower overall intentions to prescribe antibiotic prescriptions. Besides, extrinsic values were not found influencing the behavioral intentions ($\beta = 0.001$, $P = 0.961$).

Conclusions: Primary physicians' work values influenced their behavioral intentions regarding antibiotic use. Training and education of work values may be an entry point for intervention on improving antibiotic prescribing.

Keywords: antibiotic prescribing, work values, behavioral intentions, primary physicians, China

Edited by:
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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Public Health

Received: *06 December 2021*
Accepted: *31 March 2022*
Published: *13 May 2022*

Citation:
Lu J, Liu C, Wang D and Zhang X (2022) Influence of Work Values on the Prescribing Behavioral Intentions Regarding Antibiotic Use Among Primary Physicians in Hubei, China. Front. Public Health 10:830181. doi: 10.3389/fpubh.2022.830181

INTRODUCTION

The emergence and increase of antibiotic resistance has become a significant public health threat, with a series of serious consequences, for example, it was estimated that 10 million people worldwide would die of antibiotic resistant infections in 2050, and infection caused by antibiotic resistance resulted in prolonged hospital stays, increased mortality and high health care costs (1–7). One of the important causes of antibiotic resistance is physicians' inappropriate prescription, which has been a severe problem in primary care facilities (8, 9). For instance, the proportion of outpatients encountered antibiotic prescriptions reached 53.4% in primary care facilities in China, seriously exceeding the proportion recommended by WHO (30%) (3). Therefore, many researches have been done to find the reasons and strategies for inappropriate use of antibiotics in primary care facilities (10, 11).

Recently, researchers have attempted to identify work values as important determinants of individual work-related behaviors (12, 13). Although physicians' pivotal role has been explored for in-depth understanding why they prescribe antibiotics inappropriately from the perspective of values mapping such as working environment, patient requirements and reward incentives, studies that systematically measure physicians' work values regarding antibiotic prescribing behaviors are still insufficient (11, 14–16).

As a vocational concept, work values emerge from the projection of general values onto the work setting (17), and show a perception of preference for certain aspects of individuals' work behaviors. Work values play important roles in work-related motivations and the establishment of goals that individuals intend to achieve, which lead an individual toward a particular role (13, 18). Most researchers have explored three or four types of work values: (1) intrinsic or cognitive values, pertaining to intrinsic personal orientation that affects work, such as independence and use of abilities; (2) extrinsic or instrumental values, pertaining to material aspects of work, such as work conditions; (3) social or affective values, pertaining to interaction with work-related people, such as co-workers and patients; (4) reward or prestige values, pertaining to a sense of personal superiority gained from work, such as advancement, achievement, and a prestigious, highly valued work (18–21). Besides, altruistic values related to the desire to make contributions to society and help others, were incorporated into work values, with the significance that workers would pay more attention to helping others especially in medical field (18, 21–23).

The research of influence of work values on behavior were mainly limited in the fields of post-retirement work intentions, entrepreneurial intentions, profession choices and turnover intentions (24–29). For example, workers expressed more post-retirement work intentions if they perceived the value of work to fit their personal value orientation (25). Entrepreneurial intentions were influenced by some dimensions of work values (24, 26). Besides, nurses' profession choices and turnover intentions were also found to be associated with work values (27–29). However, we did not find studies on the influence of work values on primary physicians' medical behaviors, especially the behaviors regarding antibiotic use.

The objectives of this study were to explore the influence of primary physicians' work values on their behavioral intentions regarding antibiotic use, in order to make contribution to the improvement on public health and antibiotic stewardship.

METHODS

Data Collection

A stratified cluster sampling method was used to collect data. The clusters were primary care facilities covering urban community health centers (UCHCs) and rural township health centers (RTHCs)in Hubei Province, which is geographically divided into western, central, and eastern regions. Based on the strategies developed by Dhand and Khatkar (the expected deviation < 6, precision $= 1$, level of confidence $= 95\%$, correlation coefficient within the group < 0.02 and cluster size $= 10$) (30), we estimated that each region required at least 17 clusters. In each region, one urban city and two rural counties were randomly selected. Eight primary care facilities (UCHCs or RTHCs) were then randomly selected in each selected city or county. To ensure sample size, more than 70 primary physicians were interviewed in each city/county. If the number of respondents in the selected city/county was < 70, an additional primary care facility was added to the sample. This sampling method was also used in other studies by our team (31, 32). Finally, a total of 67 primary care facilities, including 19 UCHCs and 48 RTHCs were enrolled in this study.

A structured self-administered questionnaire was applied to a cross-sectional survey from 23 April 2018 to 6 June 2018. Based on the composition of departments in primary care facilities in China, all primary physicians on duty with antibiotic prescribing authority from general practice, internal medicine, pediatrics, surgery, gynecology and Chinese medicine departments were invited to participate in this study. The investigators were trained strictly for the survey quality and distributed 712 questionnaires to the primary physicians, who were asked to submit informed consents and then complete the questionnaires independently. The incomplete questionnaires were returned to the physicians for recompletion. Eventually, a valid sample size was 656.

The Measurement

Work Values

Work values were measured from the following 5 dimensions, with a total of 16 items, based on the work value scales established (18–21, 33). Intrinsic values covered 2 items as the independence and use of abilities in work, in which higher score, more independently and freely that primary physicians could prescribe antibiotics and use of their professional abilities in work (19, 20). Extrinsic values covered 3 items as the work condition on bacterial identifications, drug sensitivity tests and general work condition, in which higher score, worse work condition that primary physicians perceived (19, 21). Reward values covered 3 items as the correlation between career promotion and prescription behavior, continuous learning and gain of prestige, in which higher score, higher rewards that primary physicians pursued (18, 21). Social values covered 4 items as the social pressures, consisting of recognition, trust, requests from patients and interaction with co-workers, in which higher score, more social pressures primary physicians perceived (18, 20, 21). Altruistic values covered 4 items as the contribution to patients, help patients appropriately, no harm to patients and do a responsible work, in which higher score, more likely physicians perceive altruistic from their prescribing behaviors (18, 19). For each item, primary physicians were asked to rate the agreement on a Likert five-point scale from 1 (strongly disagree) to 5 (strongly agree).

A pilot survey was conducted to assess the reliability and validity of the questionnaire on work values. The Kaiser–Meyer–Olkin value = 0.723 (KMO > 0.70, acceptable), and the Bartlett test $P < 0.001$ ($P < 0.05$, acceptable) (34), verified the feasibility of the exploratory factor analysis. The reliability of responses was further assessed using Cronbach's alpha. Coefficients of 0.62 or better were obtained in each sector for each of the 5 dimensions of items. Spearman rank correlation value was to evaluate the correlation between items and their corresponding dimensions, ranged from 0.55 to 0.91, with $P < 0.001$ (< 0.05, acceptable). Regarding to the confirmatory factor analysis, a good fitness of the questionnaire was found: Tucker-Lewis index = 0.96 (TLI > 0.90, acceptable), comparative fit index = 0.96 (CFI > 0.90, acceptable) and the root mean square error of approximation = 0.04 (RMSEA < 0.08, acceptable) (35).

Behavioral Intentions

The Theory of Planned Behavior proposes a model about how human action is guided. It predicts the occurrence of a specific behavior and regards intention as the precursor of action (36). Although there is a certain deviation between the behavioral intention and the actual behavior, intention can be used as an approximate measure of behavior when the measure of actual behavior is not readily available (35, 36). In this study, behavioral intentions represented the degree that primary physicians felt like to prescribe antibiotics and was computed by the averaging of next 4 items. The first three items reflected the behavioral intentions of primary physicians toward "expect", "want" and "intend" to reduce antibiotic prescriptions. The rating was performed on a five-point Likert scale from strongly agree (score = 1) to strongly disagree (score = 5). The last item was the intention to prescribe antibiotics to patients, which was measured by the number of patients (from 0 to 10) that would be prescribed with antibiotics. And the behavioral intentions were classified into 5 categories: patients ≤ 2 were defined as 1 point; others were equally divided into 4 groups, with a score of 2 ∼ 5 points according to the rational use rate (< 30%) of antibiotic prescriptions in primary care facilities recommended by WHO (37). The lower the scores, the better behavioral intentions.

A pilot survey was conducted to assess the reliability and validity of the questionnaire on behavioral intentions. The Cronbach's alpha coefficients was 0.90, with good internal consistency.

Statistical Analysis

The mean and standard deviation of each item were to describe work values and behavioral intentions. Hierarchical multiple regression analysis was conducted to determine the influences of work values on the intentions to reduce antibiotic prescriptions (Model 1), on the intentions to prescribe antibiotics to patients (Model 2) and on the overall behavioral intentions regarding antibiotic use (Model 3). The three models were designed respectively as 2 kinds of models. In the first kind of models as M11, M21, and M31, gender, age, education, working experience and department were entered as controlled variables; in the second kind of models as M12, M22, and M32, both the controlled variables and work value dimensions' measures were entered into the models. The standardized regression coefficient (β) of each variable and the corresponding *P*-values were calculated for multivariate analyses. The proportion of variance in behavioral intentions that could be explained by work values was assessed by the coefficient of determination (R^2) (38). Significance was considered at 2-sided $P < 0.05$.

The statistical analysis was performed using SPSS (version 24.0) and Amos (version 24.0).

RESULTS

Characteristics of Primary Physicians

Characteristics of primary physicians are presented in **Table 1**. The average age was 43.26 years (SD = 10.41), and males occupied the majority (69.36%). The years of working experience on average was 16.66 (SD = 11.06). Most of the physicians came from RTHCs (77.90%).

Work Values and Behavioral Intentions

Table 2 presents the levels of 5 dimensions of work values and 2 dimensions of behavioral intentions. The primary physicians displayed variations in work values. Extrinsic values (Mean=4.41, SD=0.83) presented the highest mean scores across all dimensions. Intrinsic values (Mean=3.46, SD=0.78), altruistic values (Mean = 3.22, SD = 0.81) and reward values (Mean =

TABLE 1 | Characteristics of primary physicians.

Characteristics	Sampled visits	*N* (%)	Mean±SD[a]
Age (years)			43.26 ± 10.41
Gender			
Male	455	69.36	
Female	201	30.64	
Facility			
Urban community health center	145	22.10	
Rural township health center	511	77.90	
Education			
Associate degree and below	404	61.59	
Bachelor degree	250	38.11	
Master degree	2	0.30	
Department			
General practitioner	264	40.24	
Internist/pediatrician	160	24.39	
Surgeon	92	14.02	
Gynecologist	90	13.72	
Chinese medical practitioner	50	7.62	
Professional title			
Junior doctor	341	51.98	
Attending doctor	250	38.11	
Associate senior doctor	61	9.30	
Senior doctor	4	0.61	
Working experience (years)			16.66 ± 11.06

[a] *SD, Standard deviation.*

TABLE 2 | Work values regarding antibiotic use and behavioral intentions.

Work values/Behavioral intentions	Mean	SD[a]	Cronbach's alpha	r[b]	P[c]
Work values	3.26	0.35			
Intrinsic values	3.46	0.78	0.60		
Independence in prescribing antibiotics	3.24	1.06		0.91	<0.001
Being able to use of abilities	3.69	0.79		0.75	<0.001
Extrinsic values	4.41	0.83	0.68		
Hard to receive bacterial identifications	4.59	1.09		0.60	<0.001
Hard to receive drug sensitivity tests	4.45	1.29		0.67	<0.001
Bad work condition in primary care facilities	4.19	0.76		0.80	<0.001
Reward values	3.11	0.77	0.58		
Low correlation between career promotion and prescription behavior	2.43	0.94		0.60	<0.001
Few opportunities for continuous learning	2.83	0.98		0.55	<0.001
A prestigious, highly valued work	4.09	1.64		0.70	<0.001
Social values	2.08	0.59	0.67		
Work for recognition	1.62	0.81		0.70	<0.001
Work for trust	1.38	0.70		0.71	<0.001
Work at requests of patients	2.70	1.07		0.63	<0.001
Work after interacting with co-workers	2.63	0.89		0.62	<0.001
Altruistic values	3.22	0.81	0.92		
Contribution to patients	3.37	0.86		0.86	<0.001
Help patients appropriately	3.24	0.92		0.89	<0.001
No harm to patients	3.20	0.98		0.86	<0.001
A responsible work	3.06	0.90		0.90	<0.001
Behavioral intentions	2.01	0.61			
Intentions to reduce antibiotic prescriptions	1.70	0.54	0.90		
I expect to reduce antibiotic prescriptions to patients	1.66	0.58		0.91	<0.001
I want to reduce antibiotic prescriptions to patients	1.65	0.57		0.90	<0.001
I intend to reduce antibiotic prescriptions to patients	1.80	0.61		0.92	<0.001
Intentions to prescribe antibiotics to patients[d]	2.32	1.02	N/A		

[a] *SD, Standard deviation;*

[b] *r, Spearman rank correlation value;*

[c] *P, $P < 0.05$ indicates statistical significance;*

[d] *Intentions to prescribe antibiotics to patients, The average prescription was 3.98, with an average score of 2.32 in 5 categories.*

3.11, SD = 0.77) presented slightly high scores. However, the scores of social values were the lowest (Mean = 2.08, SD = 0.59).

The average score of behavioral intentions was 2.01 (SD = 0.61). Primary physicians intended to prescribe antibiotics to nearly 40% of patients (3.98 patients, Mean = 2.32, SD = 1.02), and they showed intentions to reduce antibiotic prescriptions (Mean = 1.70, SD = 0.54).

Influence of Work Values on Behavioral Intentions

The influence of work values on primary physicians' behavioral intentions regarding antibiotic use were better explained by M12, M22, and M32, because the R^2 values in the M12, M22, and M32 were considerably higher than those in M11, M21, and M31.

According to the hierarchical multiple regression analysis, four dimensions of work values were statistically associated with behavioral intentions. Intrinsic values negatively influenced overall intentions to prescribe more antibiotics ($\beta = -0.098$, $P = 0.010$), while social values perception ($\beta = 0.248$, $P < 0.001$), reward values ($\beta = 0.194$, $P < 0.001$), and altruistic values ($\beta = 0.180$, $P < 0.001$) positively influenced overall intentions to prescribe more antibiotics. Besides, extrinsic values were not found to influence the behavioral intentions ($\beta = 0.001$, $P = 0.961$). The detailed results are summarized in **Table 3**.

In summary, we found that primary physicians showed intentions to reduce antibiotic use, and the influence of work values on behavioral intentions of primary physicians were significant. Primary physicians intended to prescribe fewer antibiotics when perceiving higher intrinsic values, but they showed higher intentions to prescribe antibiotics when perceiving higher social values, more pursuit of reward values and greater emphasis on altruistic values.

DISCUSSION

The increasing frequency of antibiotic resistance has become a major health crisis. To our knowledge, this is the first study

TABLE 3 | Influencing factors of work values toward behavioral intentions.

variables	Model 1		Model 2		Model 3	
	Reduce antibiotic prescriptions		Prescribe antibiotics to patients		Overall behavioral intentions	
	M11^a β (*P*)	M12^b β (*P*)	M21^a β (*P*)	M22^b β (*P*)	M31^a β (*P*)	M32^b β (*P*)
Gender	0.030 (0.538)	−0.043 (0.381)	−0.077 (0.121)	−0.085 (0.078)	−0.052 (0.295)	−0.092 (0.055)
Age	**0.139** (0.014)	0.098 (0.080)	−0.012 (0.834)	−0.022 (0.683)	0.051 (0.365)	0.025 (0.649)
Education	−0.039 (0.348)	−0.031 (0.443)	−0.036 (0.392)	−0.055 (0.173)	−0.047 (0.260)	−0.059 (0.133)
Working experience	**−0.153** (0.006)	**−0.114** (0.036)	0.013 (0.819)	0.048 (0.365)	−0.057 (0.308)	−0.100 (0.849)
Department general practitioner						
Internist/pediatrician	0.052 (0.234)	0.055 (0.198)	−0.014 (0.742)	−0.006 (0.881)	0.011 (0.808)	0.019 (0.651)
Surgeon	0.031 (0.464)	0.003 (0.950)	0.084 (0.051)	**0.085** (0.040)	0.083 (0.055)	0.071 (0.082)
Gynecologist	−0.041 (0.410)	0.016 (0.739)	0.055 (0.272)	0.092 (0.055)	0.028 (0.571)	0.084 (0.074)
Chinese medical practitioner	0.024 (0.569)	0.008 (0.846)	−0.021 (0.608)	−0.002 (0.953)	−0.008 (0.856)	0.001 (0.973)
Work values						
Intrinsic values		**−0.080** (0.040)		**−0.073** (0.045)		**−0.098** (0.010)
Extrinsic values		−0.073 (0.061)		0.036 (0.348)		0.001 (0.961)
Reward values		**0.230** (<0.001)		**0.112** (0.004)		**0.194** (<0.001)
Social values		0.033 (0.397)		**0.280** (<0.001)		**0.248** (<0.001)
Altruistic values		**0.120** (0.002)		**0.150** (<0.001)		**0.180** (<0.001)
R^2	0.007	0.076	0.003	0.117	0.001	0.135

Boldface indicates statistical significance ($P < 0.05$);
^{a}models M11, M21, M31 with controlled variables;
^{b}models M21, M22, M32 with both controlled variables and work value dimensions.

focused on the influence of work values on behavioral intentions regarding antibiotic use. Our study highlighted the intention of primary physicians to reduce antibiotic use, which was influenced by their work values. In this context, the existing literature provides similar results.

Primary Physicians' Intentions to Reduce Antibiotic Use

Our results found that primary physicians showed intentions to reduce antibiotic use. Scholars have identified some interventions that can reduce prescribing behaviors or intentions among primary physicians (39–42). For example, a study showed that persuasive communication intervention could help to reduce physicians' intentions to inappropriate antibiotic use (β = 0.90, 95%CI: 0.41–1.38). General practitioners who received the persuasive communication intervention had a stronger behavioral intention to manage upper respiratory tract infection (URTI) without prescribing an antibiotic (Mean = 5.25, SD = 1.59) than those who did not receive it (Mean = 4.83, SD = 1.73), and they prescribed 0.47 fewer patients (39). Perz et al. found an 11% decrease in the rate of antibiotic prescribing among children by a multi-faceted educational intervention (95%CI: 8–14%, $P < 0.001$) (41, 42). A national trial in England found that the rate of antibiotic items dispensed per 1,000 population in the social norm feedback intervention group was 4.27 lower than that in the control group (3.3%; 95% CI = 0.957–0.977, $P < 0.001$), representing an estimated 73,406 fewer antibiotic items dispensed (42). Overall, these physicians' intentions to improve antibiotic prescribing behaviors is consistent with our study, indicating that the inappropriate use of antibiotics could be improved by more effective interventions.

Primary Physicians' Work Values Influencing Behavioral Intentions

Primary Physicians Showed Intentions to Prescribe Fewer Antibiotics When Perceiving Higher Intrinsic Values

Our study indicated that primary physicians showed a stronger intention to reduce antibiotic prescriptions when perceiving higher intrinsic values. Previous studies also found the influence of intrinsic values on behavioral intentions (43, 44). A study showed a significant influence of work values on personal intention to leave (β = 0.289, $P < 0.01$), which was mediated by organizational supplies, because the individuals were more satisfied, experienced fewer psychological complaints, and had less intention to leave when organizations provided them with adequate intrinsic rewards (β = −0.790, $P < 0.01$) (43). Regarding to health workers, although scholars demonstrated that nurses in different sectors had various views on intrinsic values, they still considered it necessary to pay attention to intrinsic values (44). Moreover, some scholars indicated workers would have emotional exhaustion and burnout without adequate intrinsic rewards, which might eventually lead workers to behave contrary to desired goals (45), such as unwillingness to reduce antibiotic use. Therefore, improving primary physicians' intrinsic values may contribute to the reduction of antibiotic use.

Primary Physicians Showed Higher Intentions to Prescribe More Antibiotics When Perceiving Higher Reward Values, Social Values, and Altruistic Values

Firstly, primary physicians intended to prescribe more antibiotics if they strongly perceived the influence of social values. It was consistent with the notion put forward by psychologists that pursuit of social values was a basic human motivation (46). A previous study in the lifeguards found that perceived social values was a significant predictor of helping behavior ($\beta = 0.65$, $P < 0.05$), in which workers perceived their work as having a stronger duty and relationship with other people through heightened perceptions of social values, and resulted in investing additional time and energy in work (47). Other researches in medical field have also indicated that the enhancement of social recognition and the increase of social pressure could influence physicians' behavioral intentions, such as perceived higher patient pressure was associated with higher use of antibiotics ($\beta = 0.102$, $P = 0.022$) (11, 32). Thus, the attention to social values may broaden existing knowledge about the antibiotic prescribing behavioral intentions.

Secondly, primary physicians' intentions to prescribe antibiotics might increase if they put more emphasis on reward values (career promotion and self-enhancement). A longitudinal study of MBA graduates demonstrated that for both men and women, receiving rewards (such as promotion) made them intend to work longer per week ($\beta = 0.108$, $P < 0.05$; $\beta = 0.170$, $P < 0.05$) (48). Similarly, the emphases on rewards were also found in nurse group, with a study providing evidence that nurses perceived their skills and experience as extremely or quite unrewarded within the workplace (36% aged care, 42% public and 42% private), which might influence their work satisfaction thus affect their care decisions (44). Moreover, researches in the field of economics showed the influence of self-enhancement (authority and achievement) on entrepreneurial intentions ($\beta = 0.147$, $P < 0.001$), which also coincided with our results (26).

Thirdly, the positive influence of altruistic value on prescribing behavioral intentions indicated that primary physicians' emphasis on altruism made them more likely to prescribe antibiotics. The positive relationship between altruistic values and behaviors was confirmed in psychological researches (47, 49). A meta-analysis demonstrated perceptions that one could act to benefit others signified judgments of expectancy (effort will lead to effective performance, $z = 6.02$, $P < 0.01$) and instrumentality (effective performance will benefit others, $z = 11.70$, $P < 0.01$), motivating workers to invest additional time and energy in their work to achieve these outcomes (49). This view was confirmed by a study on the significance of task, in which the authors found that perceiving more altruistic values was able to enhance lifeguards' work risk spirit ($\beta = 0.42$, $P < 0.05$) (47). It also coincided with our results where primary physicians perceived their prescribing behaviors as altruistic, leading them to intend to prescribe more antibiotics. However, relevant literature pointed out that such altruistic behavioral intentions of physicians was likely to be subjective and might lead to inappropriate antibiotic use as well as impair the patient's health due to insufficient knowledge and complacency (11).

Overall, the primary physicians have shown a behavioral intention to change the inappropriate use of antibiotics. The relationship between behavioral intention and work values of primary physicians is complex. These results present evidences, which may contribute to more effective interventions for improving antibiotic prescribing in primary care facilities.

Strengths and Limitations

This study is the first to link work values with specific antibiotic prescribing behavioral intentions, providing a new perspective for understanding antibiotic use and its management intervention in primary physicians. However, several limitations in this study are acknowledged. First, this study was conducted in primary care facilities in developing regions; but the generalization of the findings to other regions should be cautious. Second, in this study, behavioral intention was used as proxy measures for physicians' actual behavior. While there is evidence to suggest that behavioral intention is a reliable proxy for actual behavior, the deviation between actual behavior and intention still cannot be completely eliminated.

CONCLUSION

The primary physicians have an intention to change the inappropriate antibiotic use. What's more, the influence of work values on the prescribing behavioral intentions regarding antibiotic use is significant. It suggests that training and education of work values may be an entry point for intervention when trying to improve public health and antibiotic stewardship efforts.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data that support the findings of this study are available from surveyed local institutions and governments but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of surveyed local institutions and governments. Requests to access the datasets should be directed to junyu_lu12@hust.edu.cn.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (NO: IORG 0003571). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XZ conceived and designed the study. JL contributed to analysis, interpretation of data, and participated in writing of the manuscript. CL and DW participated in the cleaning and interpretation of data. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by the National Natural Science Foundation of China (grant no. 71373092).

ACKNOWLEDGMENTS

We thank the participating physicians, the managers of the included institutions and local governments, and the investigators for their support in data collection.

REFERENCES

1. Goossens H, Ferech M, Stichele R. Vander, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet.* (2005) 365:579–87. doi: 10.1016/S0140-6736(05)17907-0
2. Van De Sande-Bruinsma N, Grundmann H, Verloo D, Tiemersma E, Monen J, Goossens H, et al. Antimicrobial drug use and resistance in Europe. *Emerg Infect Dis.* (2008) 14:1722–30. doi: 10.3201/eid1411.070467
3. Yin X, Song F, Gong Y, Tu X, Wang Y, Cao S, et al. Systematic review of antibiotic utilization in China. *J Antimicrob Chemother.* (2013) 68:2445–52. doi: 10.1093/jac/dkt223
4. Mendelson M, Matsoso MP. The world health organization global action plan for antimicrobial resistance. *South African Med J.* (2015) 105:325. doi: 10.7196/SAMJ.9644
5. Howard DH, Scott II RD. The economic burden of drug resistance. *Clin Infect Dis.* (2005) 41:S283–6. doi: 10.1086/430792
6. Reed SD, Friedman JY, Engemann JJ, Griffiths RI, Anstrom KJ, Kaye KS, et al. Costs and outcomes among hemodialysis-dependent patients with methicillin-resistant or methicillin-susceptible staphylococcus aureus bacteremia. *Infect Control Hosp Epidemiol.* (2005) 26:175–83. doi: 10.1086/502523
7. Kollef MH. The importance of appropriate initial antibiotic therapy for hospital-acquired infections. *Am J Med.* (2003) 115:582–4. doi: 10.1016/j.amjmed.2003.09.002
8. Pichichero ME. Dynamics of antibiotic prescribing for children. *JAMA.* (2002) 287:3133–5. doi: 10.1001/jama.287.23.3133
9. Shapiro DJ, Hicks LA, Pavia AT, Hersh AL. Antibiotic prescribing for adults in ambulatory care in the USA, 2007–09. *J Antimicrob Chemother.* (2014) 69:234–40. doi: 10.1093/jac/dkt301
10. Reynolds L, McKee M. Factors influencing antibiotic prescribing in China: an exploratory analysis. *Health Policy (New York).* (2009) 90:32–6. doi: 10.1016/j.healthpol.2008.09.002
11. Teixeira Rodrigues A, Roque F, Falcão A, Figueiras A, Herdeiro MT. Understanding physician antibiotic prescribing behaviour: a systematic review of qualitative studies. *Int J Antimicrob Agents.* (2013) 41:203–12. doi: 10.1016/j.ijantimicag.2012.09.003
12. Gahan P, Abeysekera L. What shapes an individual's work values? an integrated model of the relationship between work values, national culture and self-construal. *Int J Hum Resour Manag.* (2009) 20:126–47. doi: 10.1080/09585190802528524
13. Louis, A. Busacca, Ronald, S, Beebe, Sarah, M, Toman. Life and work values of counselor trainees: a national survey. *Career Dev Q.* (2010) 59:2–18. doi: 10.1002/j.2161-0045.2010.tb00126.x
14. McCullough AR, Rathbone J, Parekh S, Hoffmann TC, Del Mar CB. Not in my backyard: a systematic review of clinicians' knowledge and beliefs about antibiotic resistance. *J Antimicrob Chemother.* (2015) 70:2465–73. doi: 10.1093/jac/dkv164
15. Lopez-Vazquez P, Vazquez-Lago JM, Figueiras A. Misprescription of antibiotics in primary care: a critical systematic review of its determinants. *J Eval Clin Pr.* (2012) 18:473–84. doi: 10.1111/j.1365-2753.2010.01610.x
16. Currie J, Lin W, Meng J. Addressing antibiotic abuse in China: an experimental audit study. *J Dev Econ.* (2014) 110:39–51. doi: 10.1016/j.jdeveco.2014.05.006
17. Roe RA, Ester P. Values and work: empirical findings and theoretical perspective. *Appl Psychol.* (1999) 48:1–21. doi: 10.1111/j.1464-0597.1999.tb00046.x
18. Lyons ST, Higgins CA, Duxbury L. Work values: development of a new three-dimensional structure based on confirmatory smallest space analysis. *J Organ Behav.* (2010) 31:969–1002. doi: 10.1002/job.658
19. Super DE. *Work Values Inventory*. Boston: Houghton Mifflin (1968).
20. Elizur D, Borg I, Hunt R, Beck IM. The structure of work values: a cross cultural comparison. *J Organ Behav.* (1991) 12:21–38. doi: 10.1002/job.4030120103
21. Ros M, Schwartz SH, Surkiss S. Basic individual values, work values, and the meaning of work. *Appl Psychol.* (1999) 48:49–71. doi: 10.1111/j.1464-0597.1999.tb00048.x
22. Gleichgerrcht E, Decety J. Empathy in clinical practice: how individual dispositions, gender, and experience moderate empathic concern, burnout, and emotional distress in physicians. *PLoS ONE.* (2013) 8:e61526. doi: 10.1371/journal.pone.0061526
23. Dyrbye LN, Massie FS, Eacker A, Harper W, Power D, Durning SJ, et al. Relationship between burnout and professional conduct and attitudes among US medical students. *JAMA.* (2010) 304:1173–80. doi: 10.1001/jama.2010.1318
24. Vuorio Anna M, Puumalainen K, Fellnhofer K. Drivers of entrepreneurial intentions in sustainable entrepreneurship. *Int J Entrep Behav Res.* (2018) 24:359–81. doi: 10.1108/IJEBR-03-2016-0097
25. Wöhrmann AM, Fasbender U, Deller J. Using work values to predict post-retirement work intentions. *Career Dev Q.* (2016) 64:98–113. doi: 10.1002/cdq.12044
26. Espíritu-Olmos R, Sastre-Castillo MA. Personality traits versus work values: comparing psychological theories on entrepreneurial intention. *J Bus Res.* (2015) 68:1595–8. doi: 10.1016/j.jbusres.2015.02.001
27. Bao YJ, Vedina R, Moodie S, Dolan S. The relationship between value incongruence and individual and organizational well-being outcomes: an exploratory study among catalan nurses. *J Adv Nurs.* (2013) 69:631–41. doi: 10.1111/j.1365-2648.2012.06045.x
28. Mills AC, Blaesing SL, A. lesson from the last nursing shortage: the influence of work values on career satisfaction with nursing. *J Nurs Adm.* (2000) 30:309–15. doi: 10.1097/00005110-200006000-00009
29. Takase M, Maude P, Manias E. Explaining nurses' work behaviour from their perception of the environment and work values. *Int J Nurs Stud.* (2005) 42:889–98. doi: 10.1016/j.ijnurstu.2004.12.008
30. *Sample Size Calculator for Estimating a Single Mean*. Available Online at: http://statulator.com/SampleSize/ss1M.html (Accessed July 29, 2018)
31. Liu C, Liu C, Wang D, Deng Z, Tang Y, Zhang X. Determinants of antibiotic prescribing behaviors of primary care physicians in Hubei of China: a structural equation model based on the theory of planned behavior. *Antimicrob Resist Infect Control.* (2019) 8:1. doi: 10.1186/s13756-019-0478-6
32. Liu C, Liu C, Wang D, Zhang X. Intrinsic and external determinants of antibiotic prescribing: a multi-level path analysis of primary care prescriptions in Hubei, China. *Antimicrob Resist Infect Control.* (2019) 8:132. doi: 10.1186/s13756-019-0592-5
33. Weiss DJ, Dawis R V. England GW. Manual for the minnesota satisfaction questionnaire. *J Vocat Behav*. (1967) 22:120. doi: 10.1037/t05540-000

34. Barttlett MS, A. further note on tests of significance in factor analysis. *Br J Stat Psychol.* (1951) 4:1–2. doi: 10.1111/j.2044-8317.1951.tb00299.x
35. Hu LT, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. *Struct Equ Model.* (1999) 6:1–55. doi: 10.1080/10705519909540118
36. Francis J, Eccles MP, Johnston M, Walker A, Grimshaw J, Foy R. *Constructing Questionnaires Based on the Theory of Planned Behaviour: A Manual for Health Services Researchers*. Newcastle upon Tyne: Centre for Health Services Research; University of Newcastle (2004). Available Online at: https://openaccess.city.ac.uk/id/eprint/1735/ (accessed July 29, 2018).
37. WHO. *Using Indicators to Measure Country Pharmaceutical Situations: Fact Book on WHO Level One and Level Two Monitoring Indicators*. Geneva: World Health Organization (2006).
38. Nakagawa S, Schielzeth H, A. general and simple method for obtaining R^2 from generalized linear mixed-effects models. *Methods Ecol Evol.* (2013) 4:133–42. doi: 10.1111/j.2041-210x.2012.00261.x
39. Hrisos S, Eccles M, Johnston M, Francis J, Kaner EFS, Steen N, et al. An intervention modelling experiment to change GPs' intentions to implement evidence-based practice: using theory-based interventions to promote GP management of upper respiratory tract infection without prescribing antibiotics #2. *BMC Health Serv Res.* (2008) 8:10. doi: 10.1186/1472-6963-8-10
40. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database Syst Rev.* (2005) 2005:Cd003539. doi: 10.1002/14651858.CD003539.pub2
41. Perz JF, Craig AS, Coffey CS, Jorgensen DM, Mitchel E, Hall S, et al. Changes in antibiotic prescribing for children after a community-wide campaign. *JAMA.* (2002) 287:3103–9. doi: 10.1001/jama.287.23.3103
42. Hallsworth M, Chadborn T, Sallis A, Sanders M, Berry D, Greaves F, et al. Provision of social norm feedback to high prescribers of antibiotics in general practice: a pragmatic national randomised controlled trial. *Lancet.* (2016) 387:1743–52. doi: 10.1016/S0140-6736(16)00215-4
43. Taris R, Feij JA. Longitudinal examination of the relationship between supplies-values fit and work outcomes. *Appl Psychol An Int Rev.* (2001) 50:52. doi: 10.1111/1464-0597.00048
44. Hegney D, Plank A, Parker V. Extrinsic and intrinsic work values: their impact on job satisfaction in nursing. *J Nurs Manag.* (2006) 14:271–81. doi: 10.1111/j.1365-2934.2006.00618.x
45. Christina M, Schaufeli WB, Leiter MP. Job burnout. *Annu Rev Psychol.* (2001) 52:397–422. doi: 10.1146/annurev.psych.52.1.397
46. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *Am Psychol.* (2000) 55:68–78. doi: 10.1037/0003-066X.55.1.68
47. Grant AM. The significance of task significance: job performance effects, relational mechanisms, and boundary conditions. *J Appl Psychol.* (2008) 93:108–24. doi: 10.1037/0021-9010.93.1.108
48. Frieze IH, Olson JE, Murrell AJ, Selvan MS. Work values and their effect on work behavior and work outcomes in female and male managers. *Sex Roles.* (2006) 54:83–93. doi: 10.1007/s11199-006-8871-z
49. Van Eerde W, Thierry H. Vroom's expectancy models and work-related criteria: a meta-analysis. *J Appl Psychol.* (1996) 81:575–86. doi: 10.1037/0021-9010.81.5.575

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 18 August 2022
DOI 10.3389/fmed.2022.856379

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SPECIALTY SECTION
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Medicine

RECEIVED 17 January 2022
ACCEPTED 25 July 2022
PUBLISHED 18 August 2022

CITATION
Chen Y, You Y, Wang Y, Wang Y and Dai T (2022) Systematic and meta-based evaluation on job satisfaction of village doctors: An urgent need for solution issue. *Front. Med.* 9:856379. doi: 10.3389/fmed.2022.856379

Systematic and meta-based evaluation on job satisfaction of village doctors: An urgent need for solution issue

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Background: Village doctors are the health "gatekeepers" of rural residents in most developing countries. They undertake a series of strenuous but pivotal missions, including prevention, diagnosis, and treatment of complicated diseases, sanitation services and management, and preventive healthcare and education tasks. Hence, it is of great importance to evaluate the village doctors' job satisfaction status, which is one of the most important indicators that can reflect the current working state, to provide guidelines for the healthcare policies.

Methods: Literature search was conducted in 7 authoritative databases, including PubMed, EMBASE, Web of Science, and China National Knowledge Infrastructure (CNKI). Experts in the field of social medicine were consulted to achieve supplement and obtain relevant literature. China was selected as a representative of the village doctor system for the in-depth analysis. Building on the previous literature, we modified and proposed a novel strategy that can transform and integrate the outcome indicators to conduct a meta-based and quantitative assessment on job satisfaction.

Results: A total of 37 publications and 23,595 village doctors were included in this research. The meta-analysis showed that the overall job satisfaction score of village doctors was 3.1858 (total score: 5.00), 95% *CI*: 2.9675–3.404, which represented the level of "neither satisfied nor dissatisfied." However, in the subsequent adjustment of publication bias, this score reduced to 2.7579, 95% *CI*: 2.5254–2.9904, which indicated a direct "dissatisfied" level. To discover the underlying causes, a holistic analysis of each dimension and influencing factors of job satisfaction was conducted, and the results demonstrated that "Financial Rewards" (2.49) was the most important factor causing dissatisfaction among village doctors, followed by "Job Security (2.52)" and "Work Stress (3.05)." Several important themes were also identified and assessed to explore the factors related to this topic.

Conclusion: This study indicated that there is an urgent need to improve the working status of health workers in rural and remote areas, especially in the middle- and low-income countries. Health policy makers should not only improve the current remuneration and subsidies of village doctors but also guide the professional development and give them more job security to enhance the work stability of this group. More specifically, in the context of the COVID-19 pandemic, further surveys on job satisfaction of village doctors should be carried out to take targeted measures.

Systematic review registration: [https://www.crd.york.ac.uk/PROSPERO/], identifier [CRD42021289139].

KEYWORDS

job satisfaction, village doctors, evidence-based decision making, health policy, meta-analysis

Introduction

Village doctors, who are affectionately known as "gatekeepers" of the rural health service systems, refers to the personnel who have obtained the qualification certificate of village doctors and work in village clinics (1). They are the guardians of people who are living in rural and remote areas (2, 3) and provide basic public health services, mainly including the establishment of rural health archives, education of health knowledge, prevention and control of infectious diseases, healthcare for the elderly, and management of chronic diseases. As the most basic and extensive medical service provider in rural areas, village doctors play an irreplaceable role in ensuring and improving the health level of rural residents.

In most of the developing countries, the medical technology level and service quality of village clinics have been falling behind during the past years due to the lack of official funding. More seriously, the reform of the health system schedule also excluded village doctors from the government project, resulting in not only the low satisfaction of rural residents with medical services but also the poor satisfaction of village doctors themselves (4). Among various developing countries, village doctors in China have a long history. Since the 1950s, there has been a tradition of barefoot doctors (5, 6). One previous research in The Lancet supported that "The barefoot doctor system was considered as a successful example of healthcare provision in developing regions with in-adequate resources by World Health Organization (WHO)" (7). Since entering the twenty-first century, public health has received more attention and it is of great significance to review and evaluate this issue under new situations and circumstances.

Job satisfaction refers to the extent to which people prefer (satisfaction) or refuse (dissatisfaction) their jobs, and can reflect the attitude or emotional response to the workplace (8, 9). It is one of the most important predictors of medical staff burnout, which is a kind of psychological syndrome (10) that refers to a series of psychological and physiological reactions caused by the pressure of interpersonal relationships and work itself. Turnover intention refers to the idea that an individual has to resign from their current job and look for another job (11). In the classical turnover theory, turnover intention is usually regarded as an important cognitive process before turnover behavior. A survey of 1,148 primary care providers (P) in a rural district found that there was a significant direct effect of job satisfaction on burnout and turnover intention, a significant direct effect of burnout on turnover intention, and a significant indirect effect of job satisfaction on turnover intention through burnout as a mediator (12). Another study on job burnout, satisfaction, and turnover intention of primary healthcare staff also confirmed this viewpoint (13).

At present, there are only a few studies on the job satisfaction of village doctors in specific areas or a small range. On one hand, scholars are more interested in the evaluation of the current situation or influencing factors of job satisfaction (9, 14–18), and there are more relevant studies on health workers in urban public hospitals rather than village doctors. On the other hand, different studies may use different methods to evaluate job satisfaction: some scholars directly put forward the concept of overall job satisfaction (19–24), while others (25–28) reported their job satisfaction in multidimensional items (including income satisfaction, work environment satisfaction, and leadership satisfaction). In addition, different surveys reported diverse evaluation scales with several parts in the form of satisfaction distribution (29–33) and others in the form of scores (19–22, 24, 34). Therefore, the realistic dilemma for this research topic is that the evidence on the job satisfaction survey of villager doctors is fragmented and it is not a piece of cake to provide a high-quality reference for the formulation of national policies from an overall and systematic perspective.

Consequently, based on the above situation, we aimed to systematically evaluate the meta-based evidence of job satisfaction in order to provide an important reference basis for stabilizing the structure of rural doctors and improving the development of human resources in the primary medical system as well as the quality of health services. Simultaneously, we also targeted to use the cases in China to present a unique perspective for the systematic review of healthcare workers' job satisfaction in other developing countries or regions worldwide.

Materials and methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols guidelines (35) and is registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42021289139).

Search strategy

A total of 7 databases were searched by computer, including PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), WanFang, China Science and Technology Journal Database (VIP), and Chinese BioMedical Literature Database (CBM). In addition, experts in the field of social medicine were consulted to achieve supplement and obtain relevant literature. Pre-retrieval results showed that there were few publications before 2011. Consequently, the retrieval time limit was set from 01 January 2011 to 01 December 2021 so as to better reflect the latest situation. The search strategy was based on a combination of "rural doctor," "rural physician," "village doctor," "village physician," "work satisfaction," "job satisfaction," "career satisfaction," and so on. The specific literature retrieval strategies of each database can be found in **Supplementary Appendix A**.

Study eligibility

Eligible studies were published literature that reported the prevalence or questionnaire score and related determinants of job satisfaction among village doctors in China. The eligibility criteria included the following: (1) Types of studies: original cross-sectional studies (those presenting non-original data, such as reviews, editorials, opinion papers, or letters to the editor, were excluded); (2) Types of participants: Chinese village doctors; (3) The outcome of job satisfaction measures: the status of job satisfaction (including the distribution of the number of people or score) and its related dimensions were reported. Satisfaction dimensions were diverse in different studies, so they should be grouped by dimensions by conceptual affinity. Closely related dimensions were categorized as one theme (36). All dimensions were formed by reciprocal (supporting or complementing each other) or opposite arguments. (4) The studies that were repeatedly published or whose data information is incomplete and the relevant data cannot be obtained or missing should be excluded.

Data extraction

First, title information for relevant literature was retrieved through the search strategy, and the Endnote *X9* software was used for literature management. After the duplication process of publications included in, two reviewers read the title and abstract for preliminary screening according to the inclusion and exclusion criteria, and then further read the full text to judge the qualification. Disagreements about the inclusion criterion were resolved by a third reviewer. For the qualified literature finally selected, two parallel groups independently extracted the research data and made records, including the first author, survey time, survey area, sampling method, number of satisfied participants, and score of satisfied participants.

Quality assessment

In the study, two reviewers independently evaluated the risk of bias and cross checked the results. When the two reviewers show different opinions, the third reviewer shall decide by discussion. The quality of cross-sectional studies was evaluated by using 11 items of the observational study quality evaluation standard recommended by American healthcare quality and research institutions (37). The total score was 11 points, and all the included studies were grouped according to their scores, which were categorized as good (8–11), moderate (4–7), and poor (0–3). The risk of bias (ROB) of the original study was determined according to the quality of the results.

Data synthesis and statistical analysis

This study applied a meta-based strategy to systematically review the research status of job satisfaction. Unlike other quantitative analysis from documentary ways such as bibliometric (38, 39), meta-analysis can not only provide an evidenced-based insight but also assess the consistency of multiple research results on the same subject, which may help to have a more accurate and objective evaluation of effect indicators and explain the heterogeneity among different research results.

The primary outcome in this review was the difference and status in the score about kinds of dimensions of job satisfaction among groups. The proportion was estimated as the total number of positive cases (i.e., the number of village doctors satisfied with their current job) divided by the total number of participants. The evaluation of job satisfaction is relatively complicated, which is due to the high heterogeneity of the original questionnaire used in each study. To solve this problem, we transformed different calculations of overall and kinds of dimensions of job satisfaction into a common rubric of five-point scores. Original five ratings for satisfaction were as follows: (1) "very dissatisfied" (VD), (2) "dissatisfied"

(DS), (3) "not sure" (NS), (4) "satisfied" (ST), and (5) "very satisfied" (VS). Each of satisfaction levels was converted into five-point scores (VD: 1.00, DS: 2.00, NS: 3.00, ST: 4.00, and VS: 5.00). Furthermore, we defined intervals for satisfaction scores as follows: scores from 0 to 1.99 were defined as VD, 2.00–2.99 as DS, 3.00–3.49 as NS, 3.50–3.99 as ST, and 4.00–5.00 as VS (5). Referring to previous literature, we mainly applied three formulas in the process of conversion (40): (1) Satisfaction = VD% × 1.00 + DS% × 2.00 + NS% × 3.00 + ST% × 4.00 + VS% × 5.00. This formula can convert the number distribution of satisfaction into the corresponding score, which applies to the situation where only the number distribution of overall satisfaction or its dimensions is reported, and the original scale should be a 5-point Likert scale. (2) Satisfaction = reported score/maximum total score × 5.00. This formula can convert the satisfaction dimension of different total scores into a 5-point system in equal proportion. For example, with respect to the questionnaire with a total score of 100, if the reported satisfaction score is 50, the converted score is 50/100 × 5.00 = 2.50. (3) Satisfaction = DS% × 1.50 + NS% × 3.00 + ST% × 4.50. The scope of application of this formula is the same as the first formula, whereas the original scale should be a 3-point Likert scale.

The meta-package in the *R* software (version 4.0.3, Auckland University, United States) was used for data analysis, and a single-arm strategy was applied to assess the results achieved. For the calculation of proportion, first, the normality test was conducted. If the data did not conform to normality, it would be transformed by logarithm, logit, or double anti-sinusoidal transformation. For the evaluation of scores, we used the inverse variance weighting method to combine. Referring to the website StatsToDo (41), when multiple dimensions of a certain theme of job satisfaction are reported simultaneously in the same study, the mean and standard deviation of all dimensions will be combined into a set of values and further combined with other literature using the meta-analysis method.

The Cochrane Q-test and I^2-value were used to test whether there was heterogeneity among all studies (42). According to the Meta-Analysis of Observational Studies in Epidemiology guidelines (43), if $P > 0.10$ and $I^2 \leq 50\%$, there was no statistical heterogeneity among the research results, and the fixed effect model was applied to analyze the results; If $P \leq 0.1$ and $I^2 > 50\%$, the random effect model was used for the meta-analysis. Publication bias was evaluated using *Egger*'s test combined with a funnel plot. To solve potential publication bias, the trim-and-fill method was conducted to adjust for prospective plot asymmetry. Furthermore, sensitivity analysis was performed by grouping or excluding low-quality studies. If it was infeasible to make a quantitative synthesis and conduct a meta-analysis, a narrative approach and descriptive statistics were applied.

Results

Study and sample characteristics

A total of 1,444 studies were obtained from databases. Initially, 689 duplicates were eliminated by using the Endnote *X9* software, and then 327 irrelevant studies was eliminated by reading titles and abstracts, leaving 429 potentially qualified studies. The type of review studies, documents with inconsistent research objects, and incomplete data information were excluded by reading the full text. Finally, 37 studies (2, 3, 5, 8, 19–34, 44–60) were included for all dimensions of job satisfaction analysis. Among them, 25 studies were used to evaluate the overall score of job satisfaction (refer to **Figure 1** for the detailed process).

As presented in **Table 1**, a total of 23,595 village doctors were included. To ensure the accuracy of the inclusion results and to include the research objects as comprehensively as possible in the research of Leiyu Shi, Ping He, and Rui Zhang (19, 22, 23, 59), we only selected the data of rural doctors reported therein for inclusion and analysis (including the number of research objects, corresponding overall job satisfaction scores, and scores of various dimensions). Except for the studies that did not report the survey time (5, 23, 26, 30, 31, 46, 47, 49, 52), the time range of the satisfaction survey basically covered the past decade. In terms of spatial scope, in addition to one study that did not report the specific geographical location (31), it included 28 provincial administrative regions in China, of which 22 studies (2, 3, 5, 8, 19–24, 27, 29, 31, 32, 34, 44, 47, 49, 52, 53, 55, 57–60) reported the satisfaction data of village doctors in eastern China, 7 studies reported the data of western China (2, 20, 26, 27, 32, 34, 53), and 3 studies reported the data of central China (2, 5, 49). Additionally, 4 studies directly used the data obtained from surveys conducted nationwide or in the central, eastern, and western regions (19, 33, 45, 54). After excluding 5 studies that did not report specific sampling methods (22, 23, 31, 49, 57), only 3 studies were conducted based on convenience sampling (8, 59, 60), 18 studies clearly reported that they were conducted based on the principle of random sampling (2, 3, 19, 21, 23, 24, 27, 28, 31, 32, 34, 45, 50–52, 55, 57), and another study was surveyed on the basis of census (54). Of all the studies, only one reported job satisfaction after the COVID-19 pandemic (53). **Supplementary Appendix B** shows the job satisfaction evaluation results and conversion methods of each original study.

Table 2 demonstrates the quality evaluation of research methods, including 22 high-quality studies, 15 medium-quality studies, and no low-quality studies (**Table 2**). The average score of the quality of overall studies was 7.76, and the standard deviation was 1.32. Summary plots of the risk bias assessment are shown in **Figure 2**. Additionally, the concrete traffic light plot can be achieved in **Supplementary Appendix C**. After

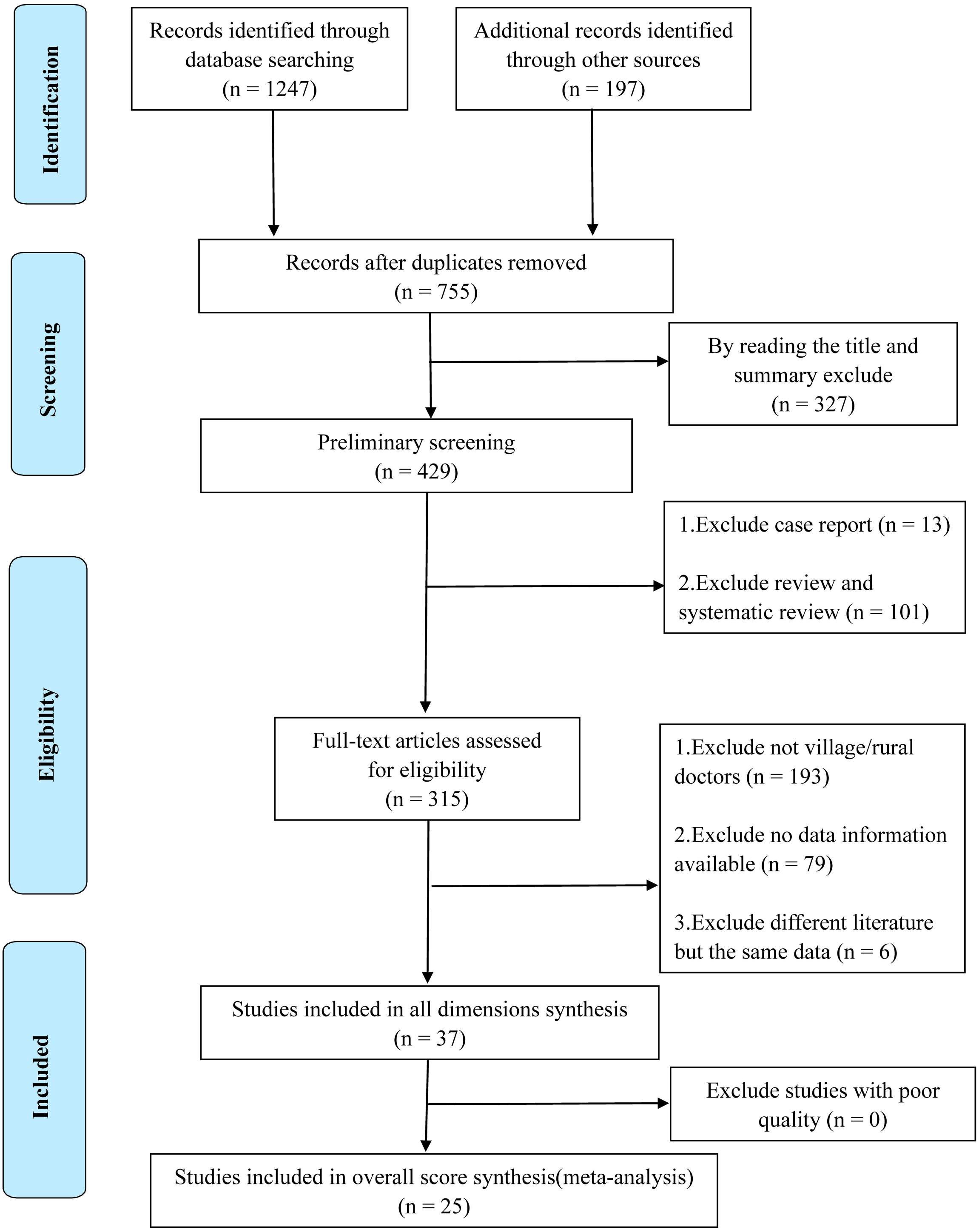

FIGURE 1
PRISMA flowchart of included studies.

quality evaluation, it can be seen that there was no literature that needed to be excluded due to low quality. Therefore, the 37 studies included in the final study can be further analyzed qualitatively and quantitatively.

Overall job satisfaction

Of the 37 studies included, 25 proposed or reported items of overall job satisfaction. After pooling the results

TABLE 1 Characteristic of 37 included studies of the status of Chinese village doctors' job satisfaction.

Study ID	References	Publication year	Survey area	Investigation period	Sampling method
1	Zhang et al. (3)	2021	Shandong Province	2019.05～2019.06	Stratified cluster random sampling
2	Zhang and Fang (5)	2016	Jiangxi Province	*NA*	Multi stage stratified cluster sampling
3	Li et al. (29)	2015	Liaoning Province	2013.04～2013.07	Randomized cluster sampling
4	Zhang et al. (2)	2019	Gansu Province and Sichuan Province	2012～2013	Multi stage stratified sampling method
5	Gu et al. (44)	2019	Shandong Province	2016.06～2016.08	Stratified random sampling
6	Li et al. (45)	2017	Shandong, Guangxi and Shaanxi Provinces	2014.04	Multi stage random sampling
7	Shi et al. (19)	2014	Five provinces representing Eastern, Central, and Western China	2011	Multistage stratified purposive sampling
8	Miao et al. (20)	2017	Ten administrative areas in western China	2009～2011	Multistage stratified random sampling
9	Chen et al. (21)	2021	Shandong Province	2012,2015,2018	Multistage sampling method
10	He et al. (22)	2014	Anhui Province	2012.04	*NA*
11	Fu et al. (30)	2012	Anhui Province	*NA*	Stratified sampling
12	Li et al. (46)	2013	Beijing	*NA*	Stratified sampling
13	Zhang and Zhu (47)	2014	Jiangsu Province	*NA*	Stratified random sampling
14	Zhang et al. (23)	2014	Shaanxi Province	*NA*	*NA*
15	Zhang et al. (48)	2019	Hebei Province	2017.10～2017.12	Stratified sampling
16	Zhang (49)	2014	Hunan Province	*NA*	*NA*
17	Sun et al. (25)	2018	Henan Province	2015.12～2016.06	Stratified random cluster sampling
18	Sun et al. (50)	2017	Shandong Province	2015.10～2015.11	Stratified cluster random sampling
19	Jing et al. (51)	2020	Shandong Province	2018.05	Multi stage stratified random sampling
20	Chen et al. (24)	2016	Shandong Province	2012.08～2012.12	Multi stage stratified sampling
21	Wang (26)	2015	Ningxia Hui Autonomous Region	*NA*	Stratified random sampling
22	Bai et al. (52)	2020	Shandong Province	*NA*	Multi stage stratified random sampling
23	Zhang and Zhu (31)	2013	57 village clinics in a poor county in a mountainous area	*NA*	*NA*
24	Zhao and Zhao (53)	2021	Shaanxi Province	2020.05～2020.06	Stratified random sampling
25	Hu et al. (34)	2011	Guizhou Province	2010.01	Census
26	He et al. (54)	2011	8 provinces in China	2010.03	Stratified random sampling
27	Dai et al. (55)	2017	Anhui Province	2016.06～2016.07	Random sampling
28	Qu et al. (32)	2013	Ningxia Hui Autonomous Region, Sichuan and Yunnan Province	2011.05～2011.11	Cluster sampling
29	Peng (33)	2012	8 provinces in China	Up to 2009.12	Multi stage stratified cluster sampling
30	Ma et al. (56)	2017	Shandong Province	2015.10～2015.11	Multi stage stratified random sampling
31	Ding and Yang (57)	2020	Jiangsu Province	2019.05	*NA*
32	Shen et al. (58)	2019	Shandong Province	2018.07～2018.08	Multi stage stratified random sampling
33	Han et al. (27)	2014	Gansu Province	2012.07	Convenience sampling
34	Wang (59)	2020	Jiangsu Province	2019.07	Stratified sampling and convenience sampling
35	Sun (8)	2017	Anhui Province	2015.09～2017.03	Convenience sampling
36	Zhang and Zhu (60)	2014	Jiangsu Province	2013.05	Simple random sampling
37	Lu et al. (28)	2017	Shandong Province	2016.10～2016.11	Stratified cluster random sampling

NA, not reported.

of 25 studies that reported overall job satisfaction by meta-analysis, the random effect size of the Chinese village doctors' job satisfaction score was 3.1858, 95% *CI*: 2.9675–3.4041, I^2 = 99.8%, and Q = 12,750.88 (**Figure 3C**), indicating that the satisfaction level was "not sure." However, the *Egger*'s test showed that there was significant publication bias in the study of overall job satisfaction ($P = 0.0215 < 0.05$, $t = 2.47$, SE bias = 8.0591, intercept = 2.5795, and SE intercept = 0.1820). At the same time, obvious asymmetry was also observed in the funnel diagram (**Figure 3A**). Therefore, publication bias was corrected by the trim-and-fill method. Corrected results displayed that the total score of job satisfaction became 2.7579,

TABLE 2 Quality evaluation results of systematic review of Chinese village doctors' job satisfaction.

Study ID	References	*D1*	*D2*	*D3*	*D4*	*D5*	*D6*	*D7*	*D8*	*D9*	*D10*	*D11*	Overall
1	Zhang et al. (3)	1	1	1	1	Unclear	1	1	Unclear	1	1	1	9
2	Zhang and Fang (5)	1	1	0	Unclear	Unclear	1	1	1	Unclear	1	1	7
3	Li et al. (29)	1	0	1	1	1	0	0	1	1	1	1	8
4	Zhang et al. (2)	1	1	1	1	1	1	0	Unclear	1	0	1	8
5	Gu et al. (44)	1	1	1	1	Unclear	0	0	Unclear	0	1	1	6
6	Li et al. (45)	1	1	1	1	1	0	1	1	0	1	1	9
7	Shi et al. (19)	1	1	1	Unclear	1	0	0	1	Unclear	0	1	6
8	Miao et al. (20)	1	1	1	1	1	0	0	1	Unclear	0	1	7
9	Chen et al. (21)	1	1	1	1	1	1	1	Unclear	Unclear	1	1	9
10	He et al. (22)	1	1	1	1	1	1	1	0	0	1	1	9
11	Fu et al. (30)	1	1	0	1	1	0	1	1	1	1	1	9
12	Li et al. (46)	1	1	0	1	Unclear	0	1	1	0	1	1	7
13	Zhang and Zhu (47)	1	0	0	1	Unclear	0	1	0	0	1	1	5
14	Zhang et al. (23)	1	1	0	1	Unclear	0	0	0	1	1	1	6
15	Zhang et al. (48)	1	0	1	1	1	1	0	1	1	1	1	9
16	Zhang (49)	1	1	0	Unclear	Unclear	0	1	1	1	1	1	7
17	Sun et al. (25)	1	1	1	1	1	1	0	1	0	1	1	9
18	Sun et al. (50)	1	1	1	1	Unclear	0	1	1	1	1	1	9
19	Jing et al. (51)	1	1	1	1	1	0	1	1	0	1	1	9
20	Chen et al. (21)	1	1	1	1	Unclear	0	1	1	1	1	1	9
21	Wang (26)	1	1	0	1	Unclear	1	0	0	0	1	1	6
22	Bai et al. (52)	1	1	0	1	1	0	0	1	0	1	1	7
23	Zhang and Zhu (60)	Unclear	0	0	Unclear	1	0	1	0	Unclear	1	1	4
24	Zhao and Zhao (53)	1	1	1	1	Unclear	0	0	1	0	1	1	7
25	Hu et al. (34)	1	1	1	1	Unclear	0	0	1	0	1	1	7
26	He et al. (54)	1	1	1	1	Unclear	1	1	1	1	1	1	10
27	Dai et al. (55)	1	0	1	1	1	1	0	Unclear	0	1	1	7
28	Qu et al. (32)	1	1	1	1	1	1	1	0	0	1	1	9
29	Peng (33)	1	1	1	1	1	0	0	Unclear	0	1	1	7
30	Ma et al. (56)	1	1	1	1	1	1	0	1	0	1	1	9
31	Ding and Yang (57)	1	1	1	1	Unclear	0	1	Unclear	1	1	1	8
32	Shen et al. (58)	1	1	1	1	1	1	0	Unclear	0	1	1	8
33	Han et al. (27)	1	1	1	1	1	0	0	1	0	1	1	8
34	Wang (59)	1	1	1	0	1	1	0	0	1	1	1	8
35	Sun (8)	1	1	1	1	Unclear	1	1	1	Unclear	1	1	9
36	Zhang and Zhu (60)	1	1	1	1	Unclear	0	1	1	0	1	1	8
37	Lu et al. (14)	1	0	1	1	1	1	0	Unclear	1	1	1	8

D1, define the source of information (survey and record review); ***D2,*** list inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications; ***D3,*** indicate time period used for identifying patients; ***D4,*** indicate whether or not subjects were consecutive if not population-based; ***D5,*** indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants; ***D6,*** describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements); ***D7,*** explain any patient exclusion from analysis; ***D8,*** describe how confounding was assessed and/or controlled; ***D9,*** if applicable, explain how missing data were handled in the analysis; ***D10,*** summarize patient response rates and completeness of data collection; ***D11,*** clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained.

95% *CI*: 2.5254–2.9904, I^2 = 99.9%, and Q = 28972.64. In other words, the job satisfaction level dropped to "dissatisfied" in this condition. The corrected funnel plot is shown in **Figure 3B**.

For 4 studies (45, 48, 51, 56) could not be transformed into formula calculation, only the proportion of people satisfied with the current job was reported in the original study (**Table 1**). The meta-analysis of "single arm" showed that only 43.2% of village doctors were satisfied with their current work (95% *CI*:33.1–53.2%, I^2 = 97.3%, and Q = 110.88). After the test of publication bias, the results indicated that there was no publication bias (P = 0.4645 > 0.05, t = 0.9, SE bias = 10.7002, intercept = 0.2483, and SE intercept = 0.1717).

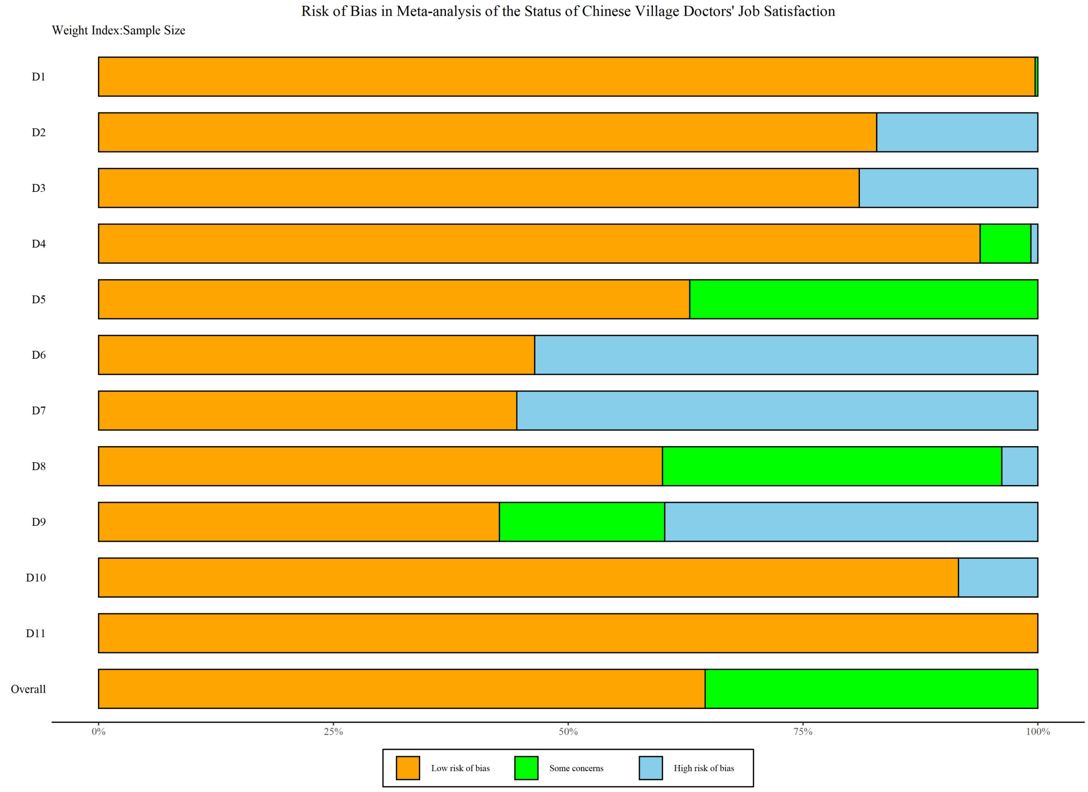

FIGURE 2
Summary plot of risk bias.

Job satisfaction of each theme

All dimensions closely related to job satisfaction were summarized into 9 themes: career development, financial rewards, governance, infrastructure, interpersonal relationships, job security, respect, work value, and work stress. The different dimensions contained under each topic and the scores of which are shown in **Supplementary Appendix D**.

The meta-analysis results of studies under each theme are displayed in **Table 3**, and all results were detected by publication bias. Since no publication bias occurred when the *P*-value reported by the *Egger*'s test was greater than 0.05, our results demonstrated that there was no publication bias in this case (refer to **Figure 4** for the forest plot of each theme, and **Figure 5** for the funnel plot of each theme). Furthermore, the summary results of different themes and the scores of overall job satisfaction are shown in **Figure 6**. Based on the visual comparison between the obtained result value and the picture, we could find that "financial rewards (2.49)" had the lowest satisfaction score, which was at the level of "dissatisfied," and another theme at the same level was "job security (2.52)." Instead, the theme with the highest satisfaction score was "interpersonal relationship (3.80)," which was at the level of "satisfied," and only this theme was at this level. Other themes were consistent with the overall job satisfaction, at the level of "not sure," and were ranked from high to low as follows: "governance (3.32)," "respect (3.18)," "career development (3.12)," "infrastructure (3.09)," "work value (3.08)," and "work stress (3.05)."

Discussion

For the first time, the research on the job satisfaction status and main influencing factors of "village doctors" in global publications was comprehensively summarized and analyzed in this systematic review. For health policy makers, the evaluation results of job satisfaction and its influencing factors are also an essential reference basis, which not only reflects the implementation effect of the current health manpower policy but is also one of the important "wind vanes" for adjusting the policy (12, 24, 61, 62). Considering China as an example, as the "gatekeeper" of the health status of more than 500 million rural residents, village doctors (63) had paid 7.9, 8.0, and 7.6 diagnosis and treatment times per day from 2018 to 2020, which was much higher than the overall status of this index of Chinese medical personnel in corresponding years (64–66). Therefore, under the huge workload, the level of job satisfaction of this group would

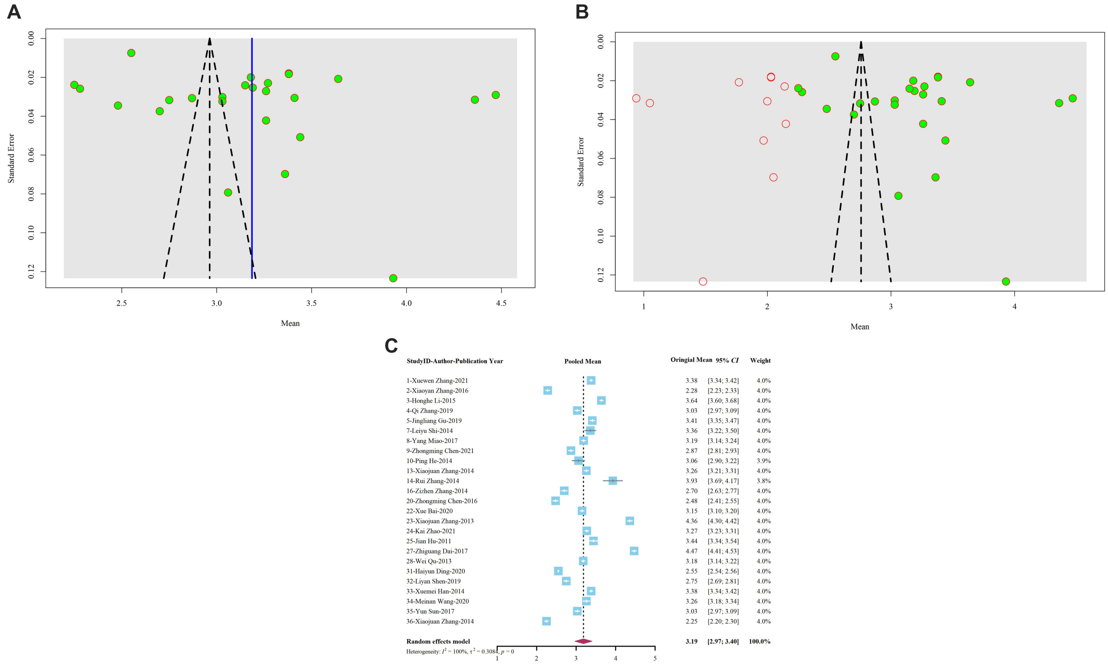

FIGURE 3

(A) Uncorrected funnel plot of overall job satisfaction's meta-analysis. **(B)** Trim-and-fill corrected funnel plot of overall job satisfaction's meta-analysis. **(C)** Forest plot of overall job satisfaction's meta-analysis.

TABLE 3 Meta-analysis summary of score values of different themes.

Theme	*NO.**	I^2 (%)	*Q*	*t**	E.*P**	Mean	95% *CI*
Career development	15	99.9	12021.59	0.4	0.6951	3.1191	2.8447∼3.3935
Financial rewards	20	99.7	6831.21	0.1	0.9218	2.4949	2.3629∼2.6269
Governance	11	99	1009.35	−0.95	0.3686	3.3188	3.1227∼3.5148
Infrastructure	16	99.3	2279.14	1.66	0.1192	3.0945	2.9891∼3.1999
Interpersonal relationship	11	99.3	1432.79	−0.02	0.9873	3.8003	3.5720∼4.0286
Job security	9	99.8	4356.77	−0.45	0.6675	2.5185	2.115∼2.9219
Respect	9	99.9	10089.09	0.13	0.899	3.1844	2.7261∼3.6428
Work value	9	99.7	2451.81	−1.04	0.3319	3.0836	2.8151∼3.3521
Work stress	9	99.6	2028.89	−0.61	0.5585	3.0547	2.6868∼3.4226

NO., number of included samples; E.*P*, P-value of Egger's test; *t*, t-value reported by the Egger's test.

inevitably affect its service quality and then affect the stability of the whole rural healthcare system.

A comprehensive survey of medical workers' job satisfaction was an important factor in evaluating health policies and predicting the medical staff's turnover rate. However, so far, few job satisfaction scales have been designed for village doctors, and most surveys were mainly applied to medical staffs in large general hospitals or urban medical institutions (16–18, 67–71). The current evidence of job satisfaction measurement for village doctors is scattered, and it is urgent to comprehensively evaluate the overall satisfaction of this group. Therefore, taking the "5-point Likert scale" as the bridge, we evaluated the overall job satisfaction level after formula conversion, which not only directly integrated and evaluated the job satisfaction of Chinese grass-roots health workers but also provided an important reference for the job satisfaction evaluation methods of medical staff in other countries or regions worldwide.

From the evaluations of 23,595 village doctors covering almost all provinces and regions in China, our results showed that the overall satisfaction level of this group was "moderate," and it was directly reduced to the level of "dissatisfied" (2.76) after adjusting for the publication bias. The combined results of the other 4 studies (45, 48, 51, 56) that could not be converted into scores showed that less than half of the village doctors were satisfied with their current work, which further demonstrated the conclusion that the job satisfaction of this group was at the "middle and lower" level. This was in sharp contrast to the job satisfaction of doctors in secondary and tertiary public

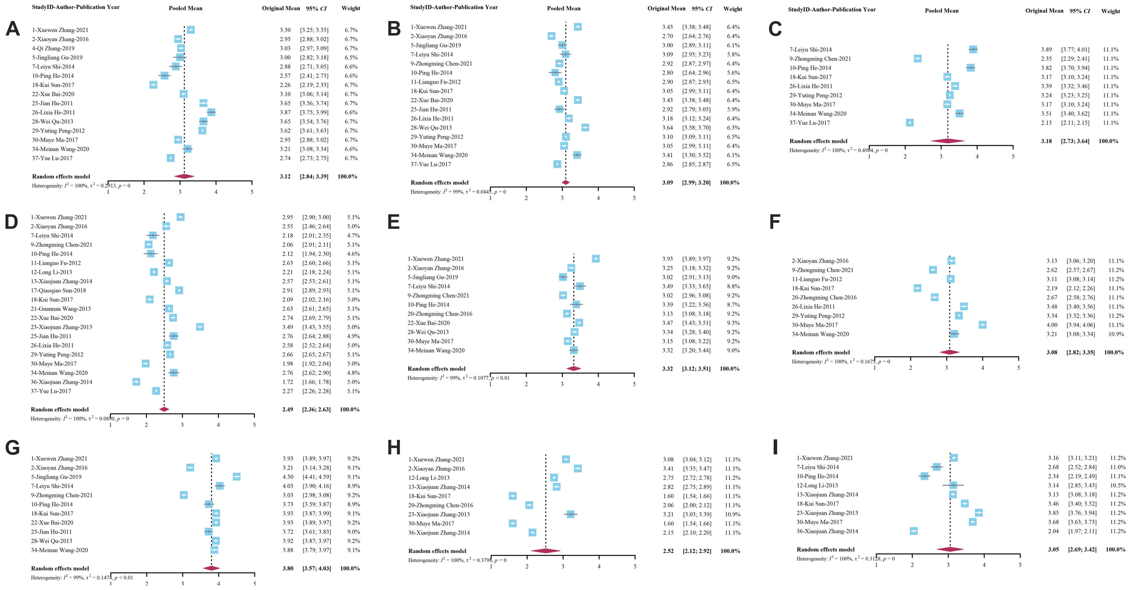

FIGURE 4

Forest plot of meta-analysis for each theme of village doctors' job satisfaction. **(A)** Career development; **(B)** infrastructure; **(C)** respect; **(D)** financial rewards; **(E)** governance; **(F)** work value; **(G)** interpersonal relationship; **(H)** job security; and **(I)** work stress.

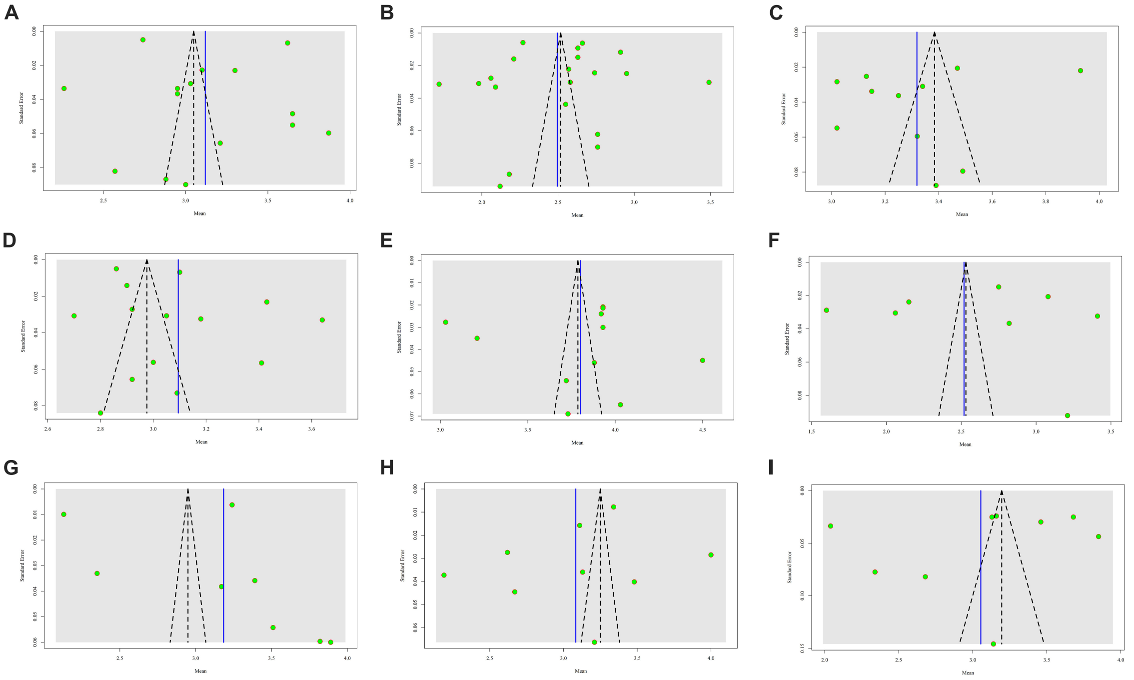

FIGURE 5

Funnel plot of each theme. **(A)** Career development; **(B)** financial rewards; **(C)** governance; **(D)** infrastructure; **(E)** interpersonal relationship; **(F)** job security; **(G)** respect; **(H)** work value; and **(I)** work stress.

hospitals in cities or counties (72–74). A survey on the job satisfaction of 5,677 doctors in public hospitals showed that people who were "satisfied" or above accounted for 78.20% (74) of the total sample, while another study showed that the proportion of dissatisfaction in this group accounts for only 6.60% (73). In addition, a survey on job satisfaction of 638 public

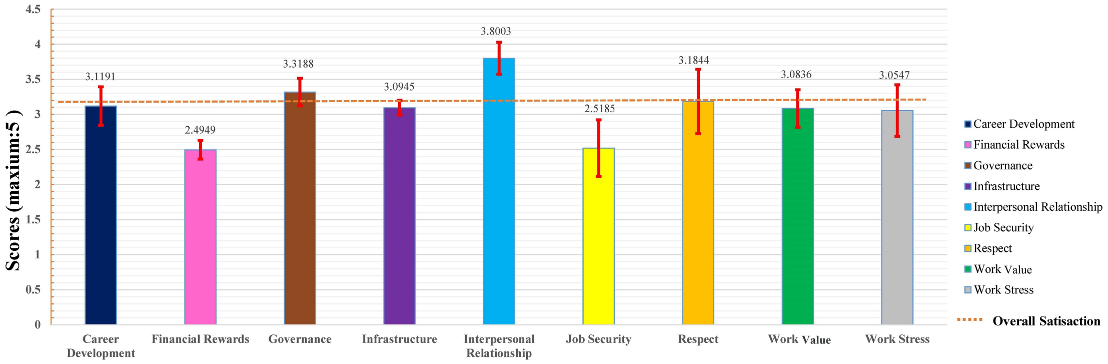

FIGURE 6
Summary results of different themes and the scores of overall job satisfaction.

hospital doctors using the 5-point Likert scale also showed that the total score reached 4.02 ± 0.99, and the average score of each dimension exceeded 3.0 (72). Nonetheless, some studies have shown that the satisfaction of doctors in secondary and tertiary hospitals is relatively low (75), and this phenomenon is also found in 80% of primary healthcare workers in the United States (76).

Subsequently, for the analysis of various dimensions of job satisfaction, it seemed that financial rewards and job security were the most influential factors on job satisfaction, which was consistent with several previous findings (19, 25, 29, 46, 48). As village doctors were an important provider of rural primary medical and health services in China, the imperfection of the income and reward mechanisms of this group was greatly restricting the construction and development of rural primary human resources and forming a vicious circle, which would eventually seriously affect the service capacity of primary health service teams and make the quality of primary medical services unable to be guaranteed (3, 5, 21, 29, 46, 50). Similarly, other countries' research also showed that low wages were the most common cause of job dissatisfaction among primary healthcare workers (PHCWs) in Ghana, for instance, which led to generate the poorly motivated staff and result poor quality services (77). Another study which explored the status of job satisfaction among rural PHCWs in Turkey has indicated that they are generally dissatisfied with their working conditions and that the overall satisfaction was moderate (3.21 ± 0.67 out of 5), while the most important predictor for it was found to be "Liking the workplace" (78). The findings about the determinants of health worker motivation in Ethiopia also supported the premise that financial factors are important ones, such as satisfaction with financial rewards (79). Compared with those with poor job satisfaction status in developing countries, other high-income developed countries showed a reversed trend. A survey of 1,174 primary care doctors aged 50 and under in the United Kingdom by Hann et al. found that most of this group expressed high job satisfaction toward their current jobs and only 11.8% of them had the turnover intention (11). Simultaneously, in a survey of 23,159 nurses in 385 hospitals in 10 European countries, Heinen et al. found that the proportion of them with significant job dissatisfaction was only 9%, and the figure was between 5 and 17% in different countries and specifically, most of them expressed the higher satisfaction toward financial rewards and job security compared to village doctors in developing countries (80). More specifically, a survey showed that during the epidemic peak of COVID-19, 20–30% healthcare staff reached the cutoff levels of disorders in anxiety, depression, and distress (81). This was bound to lead to a decline in job satisfaction. However, there was still hardly any survey on job satisfaction of village doctors during the COVID-19 pandemic.

Job security, which was closely related to economic returns, was also one of the important factors why village doctors were dissatisfied with their work, mainly including pension issues and whether there was insurance. Compared with doctors in tertiary hospitals, the most fundamental solution to the job security of village doctors was the inclusion of the authorized strength. Over the years, with the promotion of the county medical community and rural integration, village clinics have gradually changed from individual to public welfare. Village doctors had been included in the management of health centers, signed labor contracts with health centers, and changed their identities into temporary employees of village clinics. In China, most of the salaries and activity funds of village doctors with staffing came from the government, so their income was relatively stable, while contract doctors were more likely to face the possibility of non-renewal or termination (2, 5, 82, 83). At the same time, doctors with formal staffing also had a strong sense of belonging, so their turnover intention would be greatly reduced (84). Therefore, we suggest that village doctors should be included in the staffing of local public institutions.

Consequently, at the first step, we suggested that the government should increase financial subsidies for village doctors to ensure that their income level was equal to the average income level of local village cadres, teachers, and other occupations. Second, by standardizing the management of village clinics and the performance evaluation policy of health centers and village clinics, it may help to ensure the work environment of village doctors and then promote their work enthusiasm. Third, it cannot be overemphasized that carrying out vocational education and quality training for rural doctors can help to improve the overall quality level of village doctors. Finally, the government should speed up the improvement of the old-age insurance policy for this group, not only targeting to reflect their contribution to the development of health undertakings but also acknowledging the importance of their missions in the rural health service system.

Several limitations of this study should be mentioned. First, the data collection was only limited to Chinese village doctors, which may lead to region bias to some extent. However, village doctors in China have a cultural background and a robust representativeness of this group in most developing countries, and this targeted group has been widely studied in several previous publications related to this topic. In addition, due to methodological deficiency, the diversity of original survey tools in the included literature can inevitably lead to heterogeneity in this study. In view of this fact, we introduced a novel strategy to integrate all the studies reporting the current situation of job satisfaction for village doctors into consistent outcome indicators, which may help scholars to set up a unified job satisfaction evaluation scale of village doctors in the future. Finally, there was limited research on the interaction between demographics and other factors. Further studies are needed to better express how two or more determinants work together to affect the job satisfaction of village doctors.

Conclusion

Combined with systematic review and meta-analysis, this study integrated the evidence-based health decision-making information to evaluate village doctors' job satisfaction status. Their job satisfaction level was in the "lower middle" level, that is, in the state of "dissatisfied" or "neither satisfied nor dissatisfied." In the issue of building a rural primary healthcare system, we selected China as a typical representative of developing countries, revealing that there is an urgent need to improve the working status of health workers in rural and remote areas, especially in the middle- and low-income countries. It could be concluded that the lack of financial rewards and job security was the most important reason for low job satisfaction. The government should increase financial subsidies for village doctors, take responsibility for their establishment, and introduce various policies to improve work security. Simultaneously, it is worthy of more explorations on the job satisfaction of village doctors under the background of COVID-19 in the future.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

YC and YY: conceptualization, data analysis, writing—original draft preparation, and methodology. YW and YDW: material search. YW, YDW, and YC: data extraction. YC, YY, YW, YDW, and TD: writing—review and editing. TD: supervision, project administration, and funding acquisition. All authors have read and agreed to the published version of the manuscript.

Funding

This work was supported by the Medical and Health Science and Technology Innovation Projects of the Chinese Academy of Medical Sciences: Research on Evaluation of Medical Science and Technology Innovation and Construction of Health Service System (2016-I2M-3-018). The funding bodies did not play any role in the design of the study and collection, analysis, and interpretation of data and in writing this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.856379/full#supplementary-material

References

1. Hu D, Zhu W, Fu Y, Zhang M, Zhao Y, Hanson K, et al. Development of village doctors in China: financial compensation and health system support. *Int J Equity Health.* (2017) 16:9. doi: 10.1186/s12939-016-0505-7

2. Zhang Q, Chen J, Yang M, Pan J, Li X, Yue L, et al. Current status and job satisfaction of village doctors in western China. *Medicine.* (2019) 98:e16693. doi: 10.1097/MD.0000000000016693

3. Zhang X, Bai X, Bian L, Wang M. The influence of personality, alexithymia and work engagement on burnout among village doctors in China: a cross-sectional study. *BMC Public Health.* (2021) 21:1507. doi: 10.1186/s12889-021-11544-8

4. Zhu NS, Ling ZH, Shen J, Lane JM, Hu SL. Factors associated with the decline of the Cooperative Medical System and barefoot doctors in rural China. *Bull World Health Organ.* (1989) 67:431–41.

5. Zhang X, Fang P. Job satisfaction of village doctors during the new healthcare reforms in China. *Aust Health Rev.* (2016) 40:225–33. doi: 10.1071/AH15205

6. Sidel VW. The barefoot doctors of the People's Republic of China. *N Engl J Med.* (1972) 286:1292–300. doi: 10.1056/NEJM197206152862404

7. Zhang D, Unschuld PU. China's barefoot doctor: past, present, and future. *Lancet.* (2008) 372:1865–7. doi: 10.1016/S0140-6736(08)61355-0

8. Sun Y. *Study on the Relationship Between Job Burnout, Job Satisfaction and Turnover Intention of Rural Doctors*. Wuhu: Wannan Medical College (2017).

9. Deng W, Feng Z, Yao X, Yang T, Jiang J, Wang B, et al. Occupational identity, job satisfaction and their effects on turnover intention among Chinese Paediatricians: a cross-sectional study. *BMC Health Serv Res.* (2021) 21:6. doi: 10.1186/s12913-020-05991-z

10. Maslach C. Job burnout: new directions in research and intervention. *Dir Psychol Sci.* (2003) 12:189–92. doi: 10.1111/1467-8721.01258

11. Hann M, Reeves D, Sibbald B. Relationships between job satisfaction, intentions to leave family practice and actually leaving among family physicians in England. *Eur J Public Health.* (2011) 21:499–503. doi: 10.1093/eurpub/ckq005

12. Wang H, Jin Y, Wang D, Zhao S, Sang X, Yuan B. Job satisfaction, burnout, and turnover intention among primary care pro-viders in rural China: results from structural equation modeling. *BMC Fam Pract.* (2020) 21:12. doi: 10.1186/s12875-020-1083-8

13. Ran L, Chen X, Peng S, Zheng F, Tan X, Duan R. Job burnout and turnover intention among Chinese primary healthcare staff: the mediating effect of satisfaction. *BMJ Open.* (2020) 10:e036702. doi: 10.1136/bmjopen-2019-036702

14. Lu Y, Hu X-M, Huang X-L, Zhuang X-D, Guo P, Feng L-F, et al. The relationship between job satisfaction, work stress, work-family conflict, and turnover intention among physicians in Guangdong, China: a cross-sectional study. *BMJ Open.* (2017) 7:e014894. doi: 10.1136/bmjopen-2016-014894

15. Liu W, Zhao S, Shi L, Zhang Z, Liu X, Li L, et al. Workplace violence, job satisfaction, burnout, perceived organisational support and their effects on turnover intention among Chinese nurses in tertiary hospitals: a cross-sectional study. *BMJ Open.* (2018) 8:e019525. doi: 10.1136/bmjopen-2017-019525

16. Zhang Y, Feng X. The relationship between job satisfaction, burnout, and turnover intention among physicians from urban state-owned medical institutions in Hubei, China: a cross-sectional study. *BMC Health Serv Res.* (2011) 11:235. doi: 10.1186/1472-6963-11-235

17. Liu J, Yu W, Ding T, Li M, Zhang L. Cross-sectional survey on job satisfaction and its associated factors among doctors in tertiary public hospitals in Shanghai, China. *BMJ Open.* (2019) 9:e023823. doi: 10.1136/bmjopen-2018-023823

18. Sun J, Ma J, Hu G, Zhao Q, Yuan C, Si W, et al. Welfare, wellness, and job satisfaction of Chinese physicians: a national survey of public tertiary hospitals in China. *Int J Health Plann Manage.* (2017) 32:270–84. doi: 10.1002/hpm.2420

19. Shi L, Song K, Rane S, Sun X, Li H, Meng Q. Factors associated with job satisfaction by Chinese primary care providers. *Prim Health Care Res Dev.* (2014) 15:46–57. doi: 10.1017/S1463423612000692

20. Miao Y, Li L, Bian Y. Gender differences in job quality and job satisfaction among doctors in rural western China. *BMC Health Serv Res.* (2017) 17:848. doi: 10.1186/s12913-017-2786-y

21. Chen Z, Zhou L, Lv H, Sun K, Guo H, Hu J, et al. Effect of healthcare system reforms on job satisfaction among village clinic doctors in China. *Hum Resour Health.* (2021) 19:109. doi: 10.1186/s12960-021-00650-8

22. He P, Zhao X, Liu B, Sun Q, Zun G. Job satisfaction and influencing factors of rural primary health workers in Anhui Province. *Health Resour China.* (2014) 17:60–3.

23. Zhang R, Luan M, Wang Y, Zhu Z, Han Y, Wang M. Study on job satisfaction and its influencing factors of grass-roots health medical staff in Guanzhong Area. *Health Qual Manage China.* (2014) 21:63–7.

24. Chen Z, Yin W, Tang M, Tan H, Ma M, Cao H. Analysis of influencing factors on the stability of village medical work under the new medical reform policy based on structural equation. *China Health Administ.* (2016) 33:691–3.

25. Sun Q, Duan L, Kang Q, Yin L, Liu H, Zhang Y, et al. Analysis on average monthly income satisfaction and its influencing factors of rural doctors in Sanmenxia City, Henan Province. *Guangxi Med.* (2018) 40:69–72.

26. Wang G. *A Comparative Study on the Salary and Welfare of Rural Doctors in Ningxia Before and After the New Medical Reform*. Yinchuan: Ningxia Medical University (2015).

27. Han X, Wang L, Liang Y, Hu Q, Shao Y, Wang Z, et al. Satisfaction analysis of rural doctors in counties and districts of Lanzhou Based on structural equation model. *Chin Gene Med.* (2014) 17:2933–6.

28. Lu Y, Ju L, Zhu Z, Li J, Li H, Zheng W. Analysis on the current situation and job satisfaction of village doctors in Shandong Province under the hierarchical diagnosis and treatment system. *Proceedings of the 20th annual meeting of China Society of health economics*. Beijing: CSHE (2017). p. 455–63.

29. Li H, Wang Z, Jiang N, Liu Y, Wen D. Lifelong learning of Chinese rural physicians: preliminary psychometrics and influencing factors. *BMC Med Educ.* (2015) 15:192. doi: 10.1186/s12909-015-0460-9

30. Fu L, Wu X, Cheng X, Zhou C, Jia X, Liu Y, et al. Investigation and Analysis on the current situation of medical staff in rural health care network in Anhui Province. *J Bengbu Med Coll.* (2012) 37:993–6.

31. Zhang X, Zhu K. A study on the living conditions of village doctors – Based on a survey in a county in Western China. *Primary Health Care China.* (2013) 27:20–3.

32. Qu W, Ma X, Yue L, Liu Y. Investigation and analysis of factors related to job satisfaction of village doctors in western rural areas. *China Health Administr.* (2013) 30:70–2.

33. Peng Y. *Analysis on the Current Situation of the Transition from Village Doctors to Practicing (Assistant) Doctors in China*. Liaoning: Chinese Medical Sciences University (2012).

34. Hu J, Wu B, Li K, Wu Y. Analysis on job satisfaction and influencing factors of village doctors in Pu'an County. *Chin J Public Health.* (2011) 27:1044–6.

35. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ.* (2015) 350:g7647. doi: 10.1136/bmj.g7647

36. Zhang M, Yang R, Wang W, Gillespie J, Clarke S, Yan F. Job satisfaction of urban community health workers after the 2009 healthcare reform in China: a systematic review. *Int J Qual Health Care.* (2016) 28:14–21. doi: 10.1093/intqhc/mzv111

37. Rostom A, Dubé C, Cranney A. *Celiac disease. Evi- dence Report/Technology Assessment No. 104. AHRQ Publication No. 04-E029-2.* Rockville, MD: Agency for Healthcare Research and Quality (2013).

38. You Y, Min L, Tang M, Chen Y, Ma X. Bibliometric Evaluation of Global Tai Chi Research from 1980-2020. *Int J Environ Res Public Health.* (2021) 18:18116150. doi: 10.3390/ijerph18116150

39. You Y, Li W, Liu J, Li X, Fu Y, Ma X. Bibliometric Review to Explore Emerging High-Intensity Interval Training in Health Promotion: a New Century Picture. *Front Public Health.* (2021) 9:697633. doi: 10.3389/fpubh.2021.697633

40. Le VNT, Dang M-H, Kim J-G, Yang Y-M, Lee D-W. Dentist Job Satisfaction: a Systematic Review and Meta-analysis. *Int Dent J.* (2021) 71:369–77. doi: 10.1016/j.identj.2020.12.018

41. StatsToDo. *Combine Means and SDs Into One Group Program. 2020 2021-12-19.* (2020). Available online at: https://www.statstodo.com/CombineMeansSDs.php (accessed July 19, 2022).

42. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557

43. Y-K Tu, Greenwood DC. *Modern methods for epidemiology*. Berlin: Springer (2012). p. 173–89. doi: 10.1007/978-94-007-3024-3_10

44. Gu J, Zhen T, Song Y, Xu L. Job satisfaction of certified primary care physicians in rural Shandong Province, China: a cross-sectional study. *BMC Health Serv Res.* (2019) 19:75. doi: 10.1186/s12913-019-3893-8

45. Li T, Lei T, Sun F, Xie Z. Determinants of village doctors' job satisfaction under China's health sector reform: a cross-sectional mixed methods study. *Int J Equity Health.* (2017) 16:64. doi: 10.1186/s12939-017-0560-8

46. Li L, Wang X, Wang C, Han Y, Huang H. Analysis of income satisfaction and its influencing factors of rural doctors in Beijing. *Med Soc.* (2013) 26:5–7.

47. Zhang X, Zhu K. Study on compensation and pension of rural doctors in eastern China – Based on the field survey of Changshu City. *Primary Health Care China.* (2014) 28:1–4.

48. Zhang J, Zhang M, Zhao H, Zhang Y, Sun Y, Xing X, et al. Investigation on the work status and training needs of village doctors in Hebei Province. *Chin J Gene Practition.* (2019) 2019:42–6.

49. Zhang Z. Investigation on the construction of village clinics and the training of village doctors in Hengyang City. *Primary Health Care China.* (2014) 28:30–1.

50. Sun K, Yin W, Yu Q, Chen Z, Li Y, Zhao Y. Research on Incentive Strategy of rural doctors based on ERG theory. *China Health Administr.* (2017) 34:679–82.

51. Jing Z, Feng Y, Ding L, Tang X, Zhou C. Analysis on job satisfaction and influencing factors of family doctors in rural areas of Shandong Province from the perspective of suppliers. *Rural Health Manage China.* (2020) 40:230–4.

52. Bai X, Bian L, Zhang X, Jiang J, Meng L, Wang J. Study on the relationship between personality characteristics, job satisfaction and job involvement of rural doctors. *Rural Health Manage China.* (2020) 40:731–5.

53. Zhao K, Zhao Z. Investigation on Influencing Factors of rural health talent development. *Modern Chin Doct.* (2021) 59:159–63.

54. He L, Wang J, He J, Liu F. Investigation and Analysis on the basic situation of village doctors. *Chin J Pract Village Doctors.* (2011) 18:18–20.

55. Dai Z, Sun B, Xu L, Gao P, Li J, Wang G. Investigation and Analysis on the current situation and satisfaction of rural doctors' basic public health service projects. *Anhui Med.* (2017) 38:807–10.

56. Ma M, Yin W, Song J, Tang C, Feng Z, Wen Q, et al. Study on Influencing Factors of job satisfaction of village doctors in Shandong Province. *China Health Administr.* (2017) 34:603–6.

57. Ding H, Yang D. Investigation on satisfaction of rural doctors in Nanjing and Countermeasures. *Jiangsu Healthc Admin.* (2020) 31:246–9.

58. Shen L, Rong X, Yao J, Huang X, Cao F, Liu Y, et al. Study on job satisfaction of village doctors based on two factor theory – A case study of Shandong Province. *Primary Health Care China.* (2019) 33:14–7.

59. Wang M. *A Comparative Study on the Current Situation of Rural Grass-Roots Medical Staff Under the Contract Service Mode of Family Doctors*. Nanjing: Nanjing Medical University (2020).

60. Zhang X, Zhu K. Exploration on compensation and pension of rural doctors in Sheyang County, Jiangsu Province. *Chin Gene Med.* (2014) 17: 3359–62.

61. Halcomb E, Smyth E, McInnes S. Job satisfaction and career intentions of registered nurses in primary health care: an integrative review. *BMC Fam Pract.* (2018) 19:136. doi: 10.1186/s12875-018-0819-1

62. Kabbash IA, El-Sallamy RM, Abdo SAE, Atalla AO. Job satisfaction among physicians in secondary and tertiary medical care levels. *Environ Sci Poll Res Int.* (2020) 27:37565–71. doi: 10.1007/s11356-020-08506-9

63. NHC. *Office of the Leading Group for the Seventh National Census of the State Council. Main Data of the Seventh Population Census in 2020*. (2021). Available online at: http://www.stats.gov.cn/tjsj/pcsj/ (accessed July 19, 2022).

64. NHC. *Department of Planning, Development and Information Technology. Statistical Bulletin of China's Health Development in 2018*. (2019). Available online at: http://www.nhc.gov.cn/guihuaxxs/s10748/201905/9b8d52727cf346049de8acce25ffcbd0.shtml (accessed July 19, 2022).

65. NHC. *Department of Planning, Development and Information Technology. Statistical Bulletin of China's Health Development in 2019*. (2020). Available online at: http://www.nhc.gov.cn/guihuaxxs/s10748/202006/ebfe31f24cc145b198dd730603ec4442.shtml (accessed July 19, 2022).

66. NHC. *Department of Planning, Development and Information Technology. Statistical Bulletin of China's Health Development in 2020*. (2021). Available online at: http://www.nhc.gov.cn/guihuaxxs/s10743/202107/af8a9c98453c4d9593e07895ae0493c8.shtml (accessed July 19, 2022).

67. Zhang D, Liao M, Wang P, Chiu H-C. Development and validation of an instrument in job evaluation factors of physicians in public hospitals in Beijing, China. *PLoS One.* (2021) 16:e0244584. doi: 10.1371/journal.pone.0244584

68. Jiang F, Hu L, Rakofsky J, Liu T, Wu S, Zhao P, et al. Sociodemographic Characteristics and Job Satisfaction of Psychiatrists in China: results From the First Nationwide Survey. *Psychiatr Serv.* (2018) 69:1245–51. doi: 10.1176/appi.ps.201800197

69. Li L, Zhang Z, Sun Z, Zhou H, Liu X, Li H, et al. Relationships between actual and desired workplace characteristics and job satisfaction for community health workers in China: a cross-sectional study. *BMC Fam Pract.* (2014) 15:180. doi: 10.1186/s12875-014-0180-y

70. Li L, Gan Y, Jiang H, Yang Y, Zhou X, Zheng Y, et al. Job Satisfaction and Its Associated Factors Among General Practitioners in China. *J Am Board Fam Med.* (2020) 33:456–9. doi: 10.3122/jabfm.2020.03.190126

71. Jiang F, Zhou H, Hu L, Rakofsky J, Liu T, Wu S, et al. Psychiatry Residents in China: socio-Demographic Characteristics, Career Satisfaction, and Related Factors. *Front Psychiatry.* (2019) 10:177. doi: 10.3389/fpsyt.2019.00177

72. Gu D, Xu P, Wang M, Li Z, Zhang L, Dong X, et al. Study on the relationship between job satisfaction and job involvement of doctors in public hospitals. *J Sichuan Univers.* (2021) 52:87–91.

73. Huang D, Yin W, Yu Q, Sun K, Guo H, Zhao Y. Comparison of satisfaction of doctors in public hospitals before and after the new medical reform. *Chin J Hospit Administr.* (2015) 2015:217–20.

74. Zhang Y, Yin W, Sun K, Huang D, Zhao Y, Li Y. An empirical analysis of doctors' job satisfaction in public hospitals. *Chin J Hospitl Manage.* (2008) 24:459–62.

75. Deng S, Yang N, Li S, Wang W, Yan H, Li H. Doctors' job satisfaction and its relationships with doctor-patient relationship and work-family conflict in China: a structural equation modeling. *Inquiry.* (2018) 55:90831. doi: 10.1177/0046958018790831

76. Continelli T, McGinnis S, Holmes T. The effect of local primary care physician supply on the utilization of preventive health services in the United States. *Health Place.* (2010) 16:942–51. doi: 10.1016/j.healthplace.2010.05.010

77. Agyepong IA, Anafi P, Asiamah E, Ansah EK, Ashon DA, Narh-Dometey C. Health worker (internal customer) satisfaction and motivation in the public sector in Ghana. *Int J Health Plann Manage.* (2004) 19:319–36. doi: 10.1002/hpm.770

78. Erten Bucaktepe PG, Bulut Çelik S, Çelik F. Job satisfaction in primary care after the health reform in a province of Turkey. *Eur Rev Med Pharmacol Sci.* (2022) 26:2363–72.

79. Hotchkiss DR, Banteyerga H, Tharaney M. Job satisfaction and motivation among public sector health workers: evidence from Ethiopia. *Hum Resour Health.* (2015) 13:83. doi: 10.1186/s12960-015-0083-6

80. Heinen MM, van Achterberg T, Schwendimann R, Zander B, Matthews A, Kózka M, et al. Nurses' intention to leave their profession: a cross sectional observational study in 10 European countries. *Int J Nurs Stud.* (2013) 50:174–84. doi: 10.1016/j.ijnurstu.2012.09.019

81. Zhang SX, Liu J, Afshar Jahanshahi A, Nawaser K, Yousefi A, Li J, et al. At the height of the storm: healthcare staff's health conditions and job satisfaction and their associated predictors during the epidemic peak of COVID-19. *Brain Behav Immun.* (2020) 87:144–6. doi: 10.1016/j.bbi.2020.05.010

82. Li X, Lu J, Hu S, Cheng KK, De Maeseneer J, Meng Q, et al. The primary health-care system in China. *Lancet.* (2017) 390:2584–94. doi: 10.1016/S0140-6736(17)33109-4

83. Wen T, Zhang Y, Wang X, Tang G. Factors influencing turnover intention among primary care doctors: a cross-sectional study in Chongqing, China. *Hum Resour Health.* (2018) 16:10. doi: 10.1186/s12960-018-0274-z

84. Fang P, Liu X, Huang L, Zhang X, Fang Z. Factors that influence the turnover intention of Chinese village doctors based on the investigation results of Xiangyang City in Hubei Province. *Int J Equity Health.* (2014) 13:84. doi: 10.1186/s12939-014-0084-4

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