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Population medicine and health economics

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Population medicine and health economics

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Air Pollution, Foreign Direct Investment, and Mental Health: Evidence From China

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Recently, there has been interest in the relationship between mental health and air pollution; however, the results are inconsistent and the contribution of foreign direct investment (FDI) has received little attention. This article studies the effects of air pollution on mental health and the moderating role of FDI based on the China Health and Retirement Longitudinal Study (CHARLS) data in 2015 and 2018 applying the fixed effects panel regression approach and the threshold model. The results show that mental health is adversely affected by air pollution, especially $PM_{2.5}$, PM_{10}, sulfur dioxide (SO_2), carbon monoxide (CO), and nitrogen dioxide (NO_2). Second, FDI has an alleviating influence on the negative relationship. Third, the effects of air pollution and FDI are heterogeneous based on regional characteristics, including location, medical resource and investment in science and technology, and individual characteristics covering education level, age, income, and physical health. Finally, the threshold effects show that FDI has a moderating effect when it is >1,745.59 million renminbi (RMB). There are only 11.19% of cities exceeding the threshold value in China. When the value of air quality index (AQI) exceeds 92.79, air pollution is more harmful to mental health. Government should actively introduce high-quality FDI at the effective level and control air pollution to improve mental health.

Keywords: mental health, FDI, air pollution, threshold, CHARLS

INTRODUCTION

Mental health, as an important public health challenge, has received increased attention, especially during coronavirus disease 2019 (COVID-19) outbreak. Mental health refers not only to cognitive ability and the absence of mental diseases, but also to a good mental state (1). Air pollution is concerned as one of leading ten risk factors for human (2), mainly including particulate matter ($PM_{2.5}$ and PM_{10}), carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3). Air pollution can increase the mortality, subjective illness, and medical and psychological problems (3–6). There were 6.67 million deaths worldwide due to air pollution according to the Global Burden of Disease Report 2019. Numerous studies have examined the impacts of air pollution on physical health (7). In recent years, there has been a surge of interest

in the effects of air pollution on mental health (8, 9). The incidences of mental illness will increase 6.67%, if the concentration of $PM_{2.5}$ increases a one SD (10).

China, the focus of this study, is one of countries with serious air pollution in the world. A large number of air pollutants are brought by rapid economic growth. In China, 135 cities have exceeded environmental air quality standard, accounting for 40.1% of the total 337 cities according to 2020 China Ecological and Environmental Quality Bulletin. The World Health Statistics 2021 reports that air pollution has caused 112.7 deaths per 100,000 population in China in 2016. The elderly and children, who are more vulnerable to air pollution (11, 12), have attracted considerable scholarly attention (13). Therefore, we study the effects of air pollution on mental health, including memory, cognitive ability, and emotions of middle-aged and elderly residents. A better understanding of different influences of air pollution would help to put forward the corresponding countermeasures and reduce adverse effects on health. The results also have implications for other developing countries.

Although previous studies have shown the relationship between mental health and air pollution, there are some inconsistent findings (14). The answers to the above questions and the moderating role of foreign direct investment (FDI) need to be further studied and judged in the light of China's current situation. In addition, it is challenging to accurately identifying the relationship between mental health and air pollution because of endogenous problems. The first is reverse causality. Mental illness may lower labor supply (15) and make workers less productive (16), which, in turn, also affects air pollution caused by economic activities. The second is measurement error of air pollution, which will bias the estimated results (17). We instrument air pollution using the ventilation coefficient to avoid the endogenous biases (18).

In addition, there has been little discussion about the moderating effect of FDI on this nexus. China has witnessed a rapidly growing economy since the reform and opening-up. A large number of FDI play an important role during the period. China has become the largest country in foreign capital inflows owing to a series of preferential policies. Global FDI plunged by 42% to $859 billion in 2020, while FDI in China bucked the decreasing trend and rose to $163 billion. China has ranked as the largest counties of foreign capital inflow, surpassing the United States for the first time according to the Organization for Economic Cooperation and Development. Economic growth in China owes too much large inflows of FDI and its impacts on environment have gradually become a topic. On one hand, FDI could increase the investment of residents and government in mental health through promoting economic growth and arousing the awareness against pollution. Income level is associated with affordability for health investment, thus influencing mental health. On the other hand, China's government has encouraged more FDI to flow into the high-tech industry in recent years. These FDI supports the "pollution halo" hypothesis, which will also help to alleviate the effect of air pollution. Therefore, we study the influence of FDI to have a better understanding of the influencing mechanism of air pollution on mental health.

This article makes several contributions. First, we use entropy weight method to construct the mental health index, which consists of episodic memory, cognitive ability, and depressive symptoms (Center for Epidemiologic Studies-Depression). According to the definition of the WHO, mental health includes not only the absence of mental diseases, but also a good cognitive ability and welfare state (1). Most studies on mental health refer to only one aspect such as happiness, depression, and life satisfaction (19, 20). Besides mental state, this study also investigates the impact of air pollution on the episodic memory and cognitive ability of residents. Although Shen et al. study the same three indicators as in this article, they used a simple arithmetic average method (7). The entropy method is based on the variation degree to avoid the deviation caused by human factors, which could evaluate mental health more accurately.

Second, prior studies neglected the moderating effect of FDI on the relationship between air pollution and mental health. Whether and how the effects of air pollution on mental health when FDI levels are considered become an empirical question. The role of FDI in the light of China's current situation is uncertain. This article attempts to fill the gaps in the literature.

Third, the effects of air pollution and FDI on mental health can be very diverse in regional and individual characteristics. Moreover, air quality index (AQI), as the measurement indicator of air pollution, is calculated as a composite indicator of $PM_{2.5}$, PM_{10}, CO, NO_2, SO_2, and O_3. Different types of air pollution may differ in their characteristics. We study heterogeneity in the effects of air pollution and FDI on mental health not only including the difference of regional and individual characteristics, but also the different types of air pollutants. A deeper understanding of the effects of various types and characteristics can help guide policymakers in crafting appropriate strategies.

Finally, most studies only focus on the causal relationship between air pollution and mental health, but few attentions have been to explore the level at which AQI and FDI matter. To fill this gap in the literature, we adopt the threshold model. We study that the impact of air pollution on mental health partly depends on the levels of air pollution and the scale of FDI. It is important for local government to set air pollution standards and control the quantity of foreign investment.

This article has been organized in the following ways: Section Literature Review is the literature review. The data and the methodology are introduced in Section Data and Methodology. Section Empirical Results presents the results. Section Discussion discusses the significant findings and the final section concludes.

LITERATURE REVIEW

The first strand of the literature investigated the relationship between health and air pollution. A large number of studies have examined the effects of air pollution on physical health (7). They found that air pollution could lead to various diseases such as malignant tumor, asthma, lung cancer, and respiratory diseases (21, 22). Among these, the elderly and children are more vulnerable to air pollution (11, 12). In recent years, there

has been a surge of interest in the effects of air pollution on mental health (8, 9). Air pollution affects mental health mainly in three ways: First, air pollutants cause depression and neurodegeneration by increasing oxidative stress and cardiac medical conditions in the body (23, 24). Second, air pollution damages physical health and reduces outdoor activities, thus increasing people's loneliness and anxiety. Third, air pollution leads to the loss of human capital, which results in lower income and, ultimately, lower life satisfaction. On empirical side, however, there are some inconsistent findings on the relationship between air pollution and mental health (25). Some found that air pollution has negative effects on mental health through causing depression, restlessness, and stress (21, 26–28). There are possible associations between particulates and suicide, schizophrenia, and psychosis (29–31). The results of Zijlema et al. showed positive relationship between air pollution and mental health (14). The answers to the above questions need to be further studied and judged.

The influence of FDI on the nexus between air pollution and mental health is still uncertain. FDI plays a role mainly through the three channels as follows. (1) Income channel. On one hand, the production process of FDI is increasing returns to scale and FDI will promote economic growth and raise the income level (32). Higher income level leads to higher affordability for health investments, thus improving mental health (33). On the other hand, FDI has a positive effect on wages of skilled workers in the host country, which aggravates the income gap between skilled and unskilled workers (34, 35). This will increase frustration and stress among unskilled workers and make them more easily affected by air pollution; (2) Medical resource channel. FDI can improve the supply of medical services in host countries by directly flowing into the health sector (36). In addition, the increase in FDI helps the local government to increase the revenue intake and invest more medical and health services, which will reduce adverse effects of air pollution on health (37); and (3) Environment channel. Some studies supported the "pollution heaven" theory (38, 39). This implies that low-quality FDI tends to flow to the host country with lower environmental standards, thus leading to deteriorating air quality (40, 41). Others proved the "pollution halo" effects. They argued that FDI could improve air quality through new technologies and green production, which could moderate the negative impact on mental health (42, 43).

DATA AND METHODOLOGY

Methodology

Main Effects Model

We adopted a panel dataset to consider individual heterogeneity. Therefore, this article uses the fixed effects regression model to study the effects of air pollution on mental health.

$$mental\ health_{ijt} = a_0 + a_1 AQI_{ijt} + a_2 X_{ijt} + \gamma_i + \delta_t + \varepsilon_{ijt} \quad (1)$$

where i represents the individual, j is the city, $mental\ health_{ijt}$ is the mental health state of i who lives in city j on year t, AQI_{ijt} is air quality index representing air pollution, X_{ijt} is control variables influencing mental health at the individual, household, and regional levels, γ_i is the individual fixed effect, and δ_t is the time fixed effects.

However, due to the endogeneity caused by reverse causation and measurement error, the effects of air pollution on mental health will be biased. Therefore, we adopt the two-stage least squares (2SLS) for IV estimation. The ventilation coefficient (*VC*) is chosen referring to Broner et al. (18), which is the product of wind speed (*ws*) determining horizontal diffusion rate and atmospheric boundary layer height (*blh*) determining the height which air pollution disperses. On one hand, the *VC* satisfies the correlation requirement. The larger the ventilation coefficient is, the stronger transport and diffusion capacity of air pollutants is, leading to the lower concentration of air pollution. On the other hand, the *VC* is determined by exogenous geographical characteristics. Therefore, the *VC* satisfies requirements of instrumental variables. The IV estimation can be written as follows:

$$AQI_{ijt} = a_0 + a_1 VC_{ijt} + a_2 X_{ijt} + \gamma_i + \delta_t + \varepsilon_{1ijt} \quad (2)$$

$$mental\ health_{ijt} = a_0 + a_1 \widehat{AQI}_{ijt} + a_2 X_{ijt} + \gamma_i + \delta_t + \varepsilon_{2ijt} \quad (3)$$

Moderation Effect Model

Furthermore, we add the interaction term between FDI and air pollution to study whether FDI has a moderating effect on the nexus between mental health and air pollution as follows:

$$mental\ health_{ijt} = \beta_0 + \beta_1 AQI_{ijt} + \beta_2 FDI_{ijt} + \beta_3 AQI_{ijt} \times FDI_{ijt} + \beta_4 X_{ijt} + \gamma_i + \delta_t + \varepsilon_{ijt} \quad (4)$$

where β_3 represents the extent of moderating effects of FDI_{ijt}.

Threshold Effect Model

Some studies have proved the non-linear relationship between FDI and air pollution (44). We further conjecture that the effects of air pollution on mental health could be different when FDI and air pollution are at various levels. We apply the threshold model proposed by Hansen to test the threshold effects of FDI and AQI (45). The threshold estimation model taking FDI as an example is presented as follows:

$$mental\ health_{ijt} = \begin{cases} \beta_0 + \beta_1 AQI_{ijt} + \beta_2 FDI_{ijt} + \beta_3 AQI_{ijt} \times FDI_{ijt} + \beta_4 X_{ijt} + \varepsilon_{ijt} & if\ FDI_{ijt} \le \tau \\ \beta_0 + \gamma_1 AQI_{ijt} + \beta_2 FDI_{ijt} + \gamma_3 AQI_{ijt} \times FDI_{ijt} + \beta_4 X_{ijt} + \varepsilon_{ijt} & if\ FDI_{ijt} > \tau \end{cases} \quad (5)$$

where $I(\bullet)$ is the indicator function.

We determine the number of thresholds based on the minimization of the squared residuals. The details of this article are given in **Figure 1**.

Data

The data is from the China Health and Retirement Longitudinal Study (CHARLS) organized by the National School of Development of Peking University. The survey covers ∼19,000 residents from 150 county-level units of 28 provinces-level units, reflecting the health, lifestyle, family, and economy of residents.

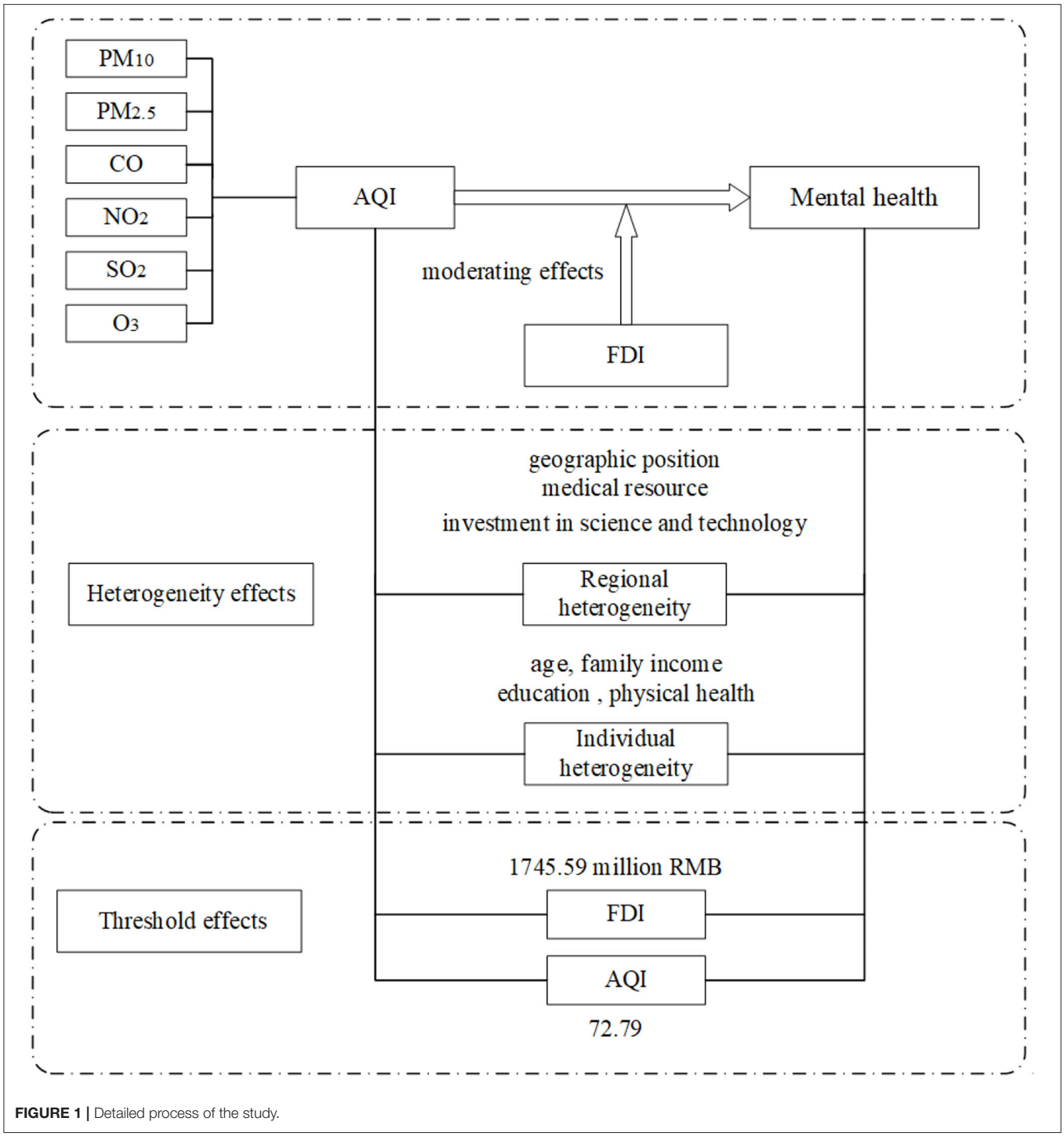

FIGURE 1 | Detailed process of the study.

The AQI index is fully available since 2014 and comes from Ministry of Ecology and Environment of the People's Republic of China (https://www.mee.gov.cn/). Therefore, we adopt the 2015 and 2018 CHARLS data. After deleting the missing and abnormal values, 8,992 effective samples aged 45 years or older are finally used. Variables of regional characters are collected from China City Statistical Yearbook.

The explained variable is mental health, including episodic memory, cognitive ability, and depressive symptoms [Center for Epidemiologic Studies-Depression (CES-D)]. We use the entropy weight method to construct the index, which has commonly been used (46). The method could avoid the deviation caused by human factors. We construct the mental health indicator and weights are shown in **Table 1**.

The bigger the variable of mental health, the healthier the people are.

The explanatory variable is air pollution measured by 1-year lagged air quality index (AQI) and six major air pollutants ($PM_{2.5}$, PM_{10}, CO, NO_2, SO_2, and O_3). The value of AQI ranges from 0 to 500 and the higher the value, the more serious the air pollution. The moderator is FDI measured by the amount of foreign investment actually used in each city. The value of FDI is converted into renminbi (RMB) using the annual average exchange rate and is adjusted to eliminate the price effect with 2,000 as the base period. The logarithm of FDI, fiscal expenditure, and gross domestic product (GDP) are adopted. GDP and fiscal expenditure are adjusted to eliminate the price effect with 2,000 as the base period. The CHARLS data is matched the air quality and regional variables with the country code. The descriptive statistics and the definition are shown in **Table 2**. The mean of AQI is 90.78 and the mean FDI is 7,600.06 million RMB. The proportions of males and females are 51 and 49%, respectively. Married people account for mostly 89%. The mean years of education were 8.01. The secondary industry, which is usually energy consuming and pollution intensive, is still the main pillar and accounts for 46.64%.

Figure 2 presents the distribution of FDI in 2014 and 2017. The FDI is relatively higher in eastern and central regions. It can be seen in **Figure 3** that the concentration of $PM_{2.5}$ is relatively higher in central regions, while it is relatively lower in southeast coastal regions.

EMPIRICAL RESULTS

Main Effect and Moderating Effect

The effects of air pollution on mental health and the moderating effects of FDI are shown in **Table 3**. The results of the fixed effects estimation [models (1) and (3)] represent the negative effect of air pollution on mental health and the moderating effects of FDI. The result of Hausman specification test rejects the null hypothesis that all the variables are exogenous[1]. We further resort to using the ventilation coefficient (VC) for an IV estimation, which is supported by the first-stage results. There exists a positive relationship between the VC and AQI and the F statistics are considerable. As shown in model (4), when FDI is at the mean level, the impact of air pollution on mental health is 0.371. The coefficient of the interaction term of FDI and air pollution is significantly positive and equal to 5.559. That implies

[1]The result of Hausman specification test is 92.71 and rejects the null hypothesis that all the variables are exogenous at the 1% level of significance.

TABLE 1 | Construction of mental health index.

Index		Definition	Range	Weight
Episodic memory	Short-Term	10 questions: one point for each correct answer	[0, 10]	0.1963
	LONG-TERM	10 questions: one point for each correct answer	[0, 10]	0.2000
Cognitive ability		The number of correct answers questions including calculations, dates, seasons, etc	[0, 10]	0.1986
CES-D	Negative	Questions about respondents' feelings and behavior in the last week	[−32, 0]	0.1976
	Positive		[0, 8]	0.2074

TABLE 2 | Descriptive statistics.

Variables	Definition	Mean	Std.Dev	Min	Max
Mental health	Episodic memory, cognitive ability and depressive symptoms	55.60	15.05	7.81	95.84
AQI	Air quality index	90.78	27.32	46.12	173.11
FDI	Foreign direct investment in a city (million)	7,600.06	13,608.3	30.82	89,354.98
Gender	Male = 1; Female = 0	0.51	0.50	0	1
Age	Age (years)	61.40	8.17	47	84
Rural types	Agriculture hukou = 1; Others = 0	0.62	0.49	0	1
Married	Married = 1; Others = 0	0.89	0.31	0	1
health	Very healthy = 1; health = 2; relatively healthy = 3; general = 4; unhealthy = 5	3.17	0.99	1	5
Education	Years of schooling (years)	8.01	5.22	0	25
Activity	Done voluntary or charity work yes = 1; no = 0	0.02	0.15	0	1
Per income	Personal income (yuan)	11,105.19	20,697.6	0	500,000
All income	Family income (yuan)	26,017.82	88,721.3	−150,000	5,400,000
GDP	GDP of the city (million yuan)	241,000	84,351	2,507.65	661,844
Fiscal exp	Fiscal expenditure (million yuan)	42,589.16	52,359.3	5,586.02	569,785.2
Industry	The proportion of secondary industry (%)	46.64	7.75	19.01	66.26
Medical resource	Doctors per 10,000 people	26.12	10.01	13.11	83.59
Hospital	The number of hospitals	216.68	135.01	31	988

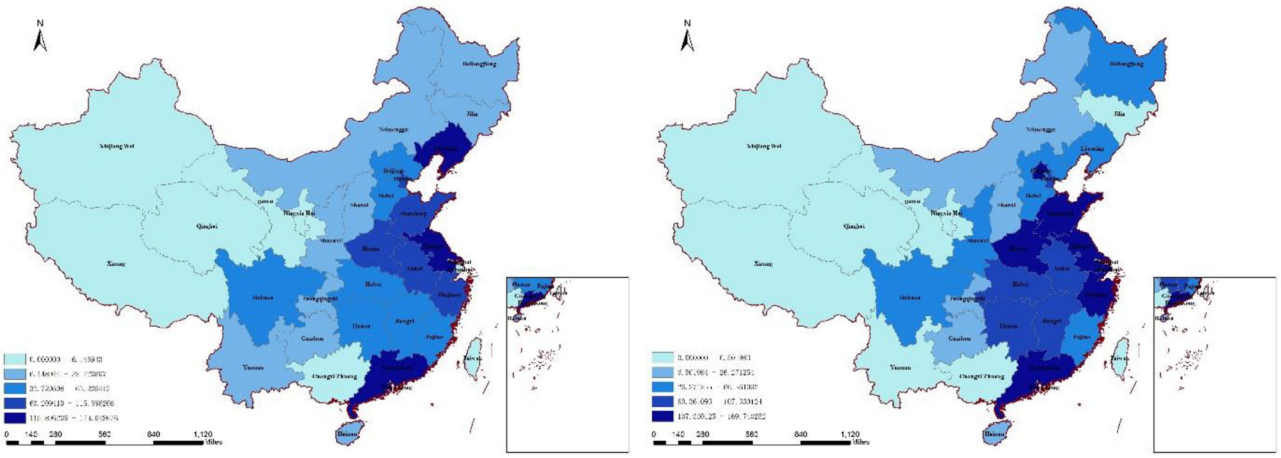

FIGURE 2 | Foreign direct investment (FDI) in 2014 and 2017.

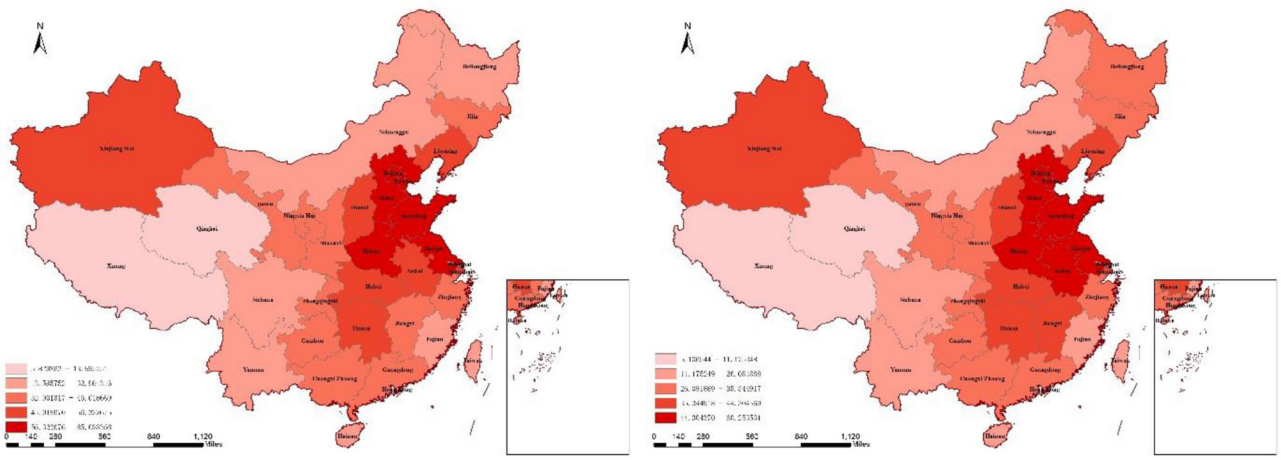

FIGURE 3 | The concentration of $PM_{2.5}$ in 2014 and 2017.

that FDI has an alleviating effect on the negative impacts of air pollution.

Table 3 also reports the impacts of control variables on mental health. It can be observed that people with higher personal income have better mental health. Older people are associated with lower mental health index (column 2 in model 4). People with better health are associated with a decrease of 1.032 in mental health. Moreover, cities with higher GDP and investment in science and technology will be beneficial for people's mental health.

Furthermore, we replace AQI with the concentration of $PM_{2.5}$, PM_{10}, CO, NO_2, SO_2, and O_3 to study the different impacts of the six air pollutants on mental health. It can be observed in **Table 4** that the effects vary by the type of air pollution. $PM_{2.5}$, PM_{10}, SO_2, CO, and NO_2 have negative impacts on mental health at the 5% level of significance, while the effects of O_3 are not significant. In addition, the estimated coefficients of the interaction term of FDI and $PM_{2.5}$ and PM_{10} are 1.789 and 2.224, all of which are significant. The moderating effects of FDI are more obvious on particulate matter.

Robustness Test

In this section, we test the robustness of our main results by three methods. First, we use the variable whether participating in social activities such as dancing and sports to represent mental health. The reason is that people with better mental health are likely to go to sport, social, or other clubs. Air pollution is harmful to physical health and reduces outdoor activities, which could damage mental health in the long term. Second, we replace the mental health index with negative emotions[2]. Third, we delete a part of independent variables. Local governments may falsify the AQI index because environmental indicators such as AQI are included in performance assessment. The qualified AQI indicates

[2]In the CHARLS questionnaire, there are eight questions in CES-D referring to how people have felt and behaved negatively during the last week.

TABLE 3 | Regression results for the main effect and moderating effect.

Variable	Main effect			Moderating effect		
	(1) FE	(2) IV estimation		(3) FE	(4) IV estimation	
		First stage	Second stage		First stage	Second stage
AQI	−0.057***		−0.684*	−0.072***		−0.371**
	(0.022)		(0.365)	(0.022)		(0.166)
AQI*FDI				1.420***		5.559*
				(0.495)		(3.274)
VC		16.885***			14.012**	
		(5.601)			(5.546)	
VC*FDI					4.451***	
					(0.497)	
FDI				−0.275	−4.958**	−0.818
				(0.424)	(0.4255)	(0.742)
Age	−3.287***	−3.501***	−5.899***	−3.411***	−4.974***	−4.975***
	(0.384)	(0.007)	(1.444)	(0.464)	(0.512)	(0.935)
Education	0.002	−0.317	−0.296	−0.024	−0.227	−0.356
	(0.383)	(0.500)	(0.787)	(0.377)	(0.476)	(0.698)
Married	1.339	−0.550	1.050	1.682	−0.070	2.368
	(2.083)	(1.723)	(2.971)	(2.081)	(1.796)	(2.811)
Per income	0.778***	0.262	0.984***	0.814***	0.307	1.103***
	(0.171)	(0.204)	(0.307)	(0.172)	(0.197)	(0.302)
Health	1.071***	0.296	1.149**	1.071***	0.348	1.032**
	(0.322)	(0.399)	(0.520)	(0.321)	(0.390)	(0.451)
Activity	2.123	−0.068	1.580	2.009	−0.641	0.991
	(1.407)	(1.696)	(2.310)	(1.391)	(1.567)	(1.983)
Chronic	−0.858**	0.840	−0.204	−0.871**	0.529	−0.584
	(0.401)	(0.577)	(0.707)	(0.401)	(0.569)	(0.599)
Per GDP	0.191	5.688***	4.103*	1.398	5.154***	6.274**
	(0.831)	(0.920)	(2.470)	(0.897)	(0.921)	(3.143)
Industry	−0.183***	−0.972***	−0.842**	−0.265***	−1.113***	−0.752***
	(0.054)	(0.001)	(0.376)	(0.060)	(0.055)	(0.255)
Fiscal exp	4.958	−53.717***	−24.069	5.023	−39.260***	−4.852
	(3.621)	(4.239)	(19.570)	(3.946)	(4.364)	(9.621)
Medical resource	−0.093	−0.553***	−0.600**	−0.136	−0.912***	−0.533**
	(0.094)	(0.135)	(0.279)	(0.096)	(0.155)	(0.213)
Hospital	−0.002	−0.023***	−0.023**	−0.003	−0.019***	−0.015**
	(0.003)	(0.003)	(0.010)	(0.003)	(0.003)	(0.006)
Technology	−0.874	7.495***	3.695	0.116	8.969***	4.913*
	(0.883)	(0.773)	(2.805)	(0.944)	(0.784)	(2.856)
Fixed effects						
Individual	Yes	Yes	Yes	Yes	Yes	Yes
Year	Yes	Yes	Yes	Yes	Yes	Yes
F statistics	57.19	374.92		65.59	314.45	
	0.1439	0.7501		0.1478	0.7607	
N	6,729	4,836	4,836	6,729	4,836	4,836

****, **, and *, respectively, indicate significance at the 1, 5, and 10 levels.*

TABLE 4 | Regression results of six major air pollutants as the independent variables.

	Main effect	Moderating effect		Main effect	Moderating effect
	$PM_{2.5}$			**NO_2**	
$PM_{2.5}$	−0.546**	−0.385*	NO_2	−2.296*	−2.353
	(0.002)	(0.197)		(1.299)	(1.518)
FDI		−1.237*	FDI		−1.263
		(0.656)			(1.004)
$PM^*_{2.5}$FDI		1.789**	NO^*_2FDI		−0.670
		(0.779)			(1.783)
Control variable	Yes	Yes	Yes	Yes	Yes
Fixed effects	Yes	Yes	Yes	Yes	Yes
N	4,836	4,836		4,836	4,836
	PM_{10}			**CO**	
PM_{10}	−0.376*	−0.384**	**CO**	−23.305**	−25.106**
	(0.192)	(0.189)		(10.854)	(11.337)
FDI		−0.0004	FDI		1.171
		(0.0004)			(1.170)
PM^*_{10}FDI		2.224*	NO^*_2FDI		−0.440
		(1.148)			(0.580)
Control variable	Yes	Yes	Yes	Yes	Yes
Fixed effects	Yes	Yes	Yes	Yes	Yes
N	4,836	4,836		4,836	4,836
	SO_2			**O_3**	
SO_2	−0.307**	−0.313**	O_3	1.147	1.254
	(0.142)	(0.144)		(1.024)	(1.136)
FDI		−0.0003	FDI		−4.504
		(0.0004)			(3.897)
SO^*_2FDI		0.547	O^*_3FDI		2.115
		(0.565)			(1.765)
Control variable	Yes	Yes	Yes	Yes	Yes
Fixed effects	Yes	Yes	Yes	Yes	Yes
N	4,836	4,836		4,836	4,836

*** and *, respectively, indicate significance at the 1, 5, and 10 levels.*

its value <100 and AQI forgery usually does not deviate too far from the truth. Therefore, we delete the values of AQI index between 99 and 100, which are likely to be tampered. It can be seen in **Table 5** that air pollution negatively affects mental health and FDI has an alleviating influence on the relationship between air pollution and mental health. Our results are robust.

Heterogeneity Test

This section discerns the effects of air pollution and FDI among the groups with different individual and regional characteristics. **Tables 6**, **7** show regional heterogeneity based on the difference of location, medical resource, and investment in science and technology. **Table 8** reports individual heterogeneity based on education, age, family income, and physical health difference.

Regional Heterogeneity

We first examine the influence across three regions: eastern, western, and central regions. It can be observed in **Table 6** that the negative effect of air pollution is significant for people in eastern region, as one rise in AQI index causes an 0.086 (column 1 in **Table 6**) decrease in mental health. Besides, FDI reduces the harmful impact of air pollution and the coefficient of the interaction term is equal to 1.605. In contrast, air pollution and FDI have no significant effects on mental health in central and western regions.

We divide the sample into the two groups according to medical resources: "relative abundance" and "relative lack." "Relative abundance" is defined as the cities' hospitals per 10,000 population that are higher than the average for all the cities. **Table 7** shows that the effect of air pollution on people living in cities with less medical resources is significantly negative and equal to −0.269. FDI plays a moderating role in cities with abundant medical resources. We further define "more investment" as the region's investment in science and technology above the average, while the cities below the average are "less investment." It can be observed that people in the "less

TABLE 5 | Robustness test.

	Robustness test 1 entertainment		Robustness test 2 Negative emotions		Robustness test 3 deleting AQI 99–101	
AQI	−0.022*	−0.014**	0.224*	0.097	−0.523*	−0.494*
	(0.013)	(0.006)	(0.135)	(0.062)	(0.309)	(0.277)
FDI		−0.002		−0.137		−2.485**
		(0.019)		(0.308)		(0.980)
AQI*FDI		0.151*		−2.349*		2.140*
		(0.088)		(1.265)		(1.202)
Control variable	Yes	Yes	Yes	Yes	Yes	Yes
Fixed effects	Yes	Yes	Yes	Yes	Yes	Yes
N	4,836	4,836	4,836	4,836	4,523	4,523

*** and *, respectively, indicate significance at the 1, 5, and 10 levels.*

TABLE 6 | Heterogeneity in the eastern, western, and central regions.

	Region					
	Eastern		Central		Western	
AQI	−0.086***	−0.098***	0.033	−0.023	−0.015	0.055
	(0.019)	(0.019)	(0.161)	(0.170)	(0.080)	(0.143)
FDI		−0.494		−2.765		−0.630
		(0.421)		(3.185)		(1.178)
AQI*FDI		1.605***		−0.760		2.264
		(0.434)		(1.933)		(3.596)
Control variable	Yes	Yes	Yes	Yes	Yes	Yes
Fixed effects	Yes	Yes	Yes	Yes	Yes	Yes
N	5,495	5,495	1,914	1,914	1,546	1,546

*** , respectively, indicate significance at the 1, 5, and 10 levels.*

investment" group suffer from air pollution. FDI moderates the adverse impact of air pollution on people living in cities with more investment in science and technology.

Individual Heterogeneity

In this section, we divide the samples according to the education level, age, income, and changes of physical health. **Table 8** summarizes the estimated results. First, low-educated people are defined who did not enter university (<16 years); otherwise, people are categorized as the high educated. It can be observed that air pollution has a negative impact on mental health of low-educated people and high-educated people are less affected by air pollution. Moreover, the moderating effect of FDI is more related to low-educated people. Second, we further study the age difference in response to air pollution and set 60 years old as the classification standard. Older people are more vulnerable to air pollution and FDI only moderates the adverse impact of air pollution on older people's mental health. Third, the samples' family income level below the average is defined as "low income," while higher than the average income level is defined as "high income." Compared with the low-income groups, air pollution has a significant impact on mental health of high-income people. The coefficient of the interaction term of FDI and air pollution is significant and equal to 3.009, implying that FDI could alleviate harmful effects of air pollution for low-income people. Finally, we divide samples into the two groups according to the changes of self-rated health level. Mental health of people whose physical health gets worse is more susceptible to air pollution. FDI could alleviate the adverse impact of air pollution on people whose physical health becomes better.

Threshold Effects

Table 9 summarizes the threshold effects of FDI and AQI, showing the effects of different levels of AQI and FDI. The F statistics of threshold effect test on AQI and FDI is 22.11 and 21.41, which verify the threshold effects. The threshold value of FDI is 1,745.591 million RMB. This result shows that FDI more than the threshold value will insignificantly affect the negative effect of air pollution on mental health. FDI has an alleviating effect on the harmful effects of air pollution when the FDI is >1,745.591 million RMB. There are 11.19% of cities in our sample exceed the threshold value and mainly belong to the eastern region. Second, the threshold value of AQI is 92.79, which is lower than the qualified AQI (100) in China. When the value of AQI exceeds this threshold, the coefficient of the effects of air pollution decreases from −0.045 to −0.06. Only if AQI is <92.79, the moderating effect of FDI is significantly positive and equal to 2.172.

TABLE 7 | Heterogeneity based on medical resource and investment in science and technology.

	Medical resources			
Variables	**Relative abundance**		**Relative lack**	
AQI	−6.552	−0.372	−0.269*	−0.268*
	(9.927)	(0.230)	(0.163)	(0.160)
FDI		−1.696		−0.589
		(1.543)		(0.874)
AQI*FDI		4.640**		1.320
		(2.363)		(1.123)
N	1,763	1,763	3,073	3,073
	Government investment in science and technology			
Variables	**More investment**		**Less investment**	
AQI	2.543**	−0.600	−0.761*	0.035
	(0.754)	(0.778)	(0.394)	(0.250)
FDI		−19.863***		5.761
		(7.227)		(4.868)
AQI*FDI		27.450***		19.985
		(8.602)		(12.997)
N	758	758	4,078	4,078
Fixed effects	Yes	Yes	Yes	Yes
Control variable	Yes	Yes	Yes	Yes

****, **, and *, respectively, indicate significance at the 1, 5, and 10 levels.*

DISCUSSION

Based on the above results, air pollution has a negative effect on mental health, which confirms the finding of Shen et al. (7). Air pollutants cause anxiety and depression symptoms (47, 48) by increasing oxidative stress and cardiac medical conditions in the body (23, 24, 49). Air pollution also reduces outdoor activities, therefore increasing people's loneliness (50). In addition, air pollution causes the loss of human capital, which leads to lower income and ultimately reduces our happiness. The results also support that FDI dilutes the adverse impacts of air pollution on mental health (51). On one hand, FDI may increase people and government's investment in mental health through promoting economic growth and arousing the awareness against pollution (52). Higher income level leads to higher affordability for health investments for residents and government, thus improving mental health. On the other hand, China's government has given priority to protect environment and encouraged more FDI enterprises to the high-tech industry in recent years. The role of FDI in China supports the "pollution halo" hypothesis, which will also help to alleviate the effect of air pollution.

There are differences in the influence of different types of pollutants on mental health. Among the six kinds of air pollutants, $PM_{2.5}$, PM_{10}, CO, NO_2, and SO_2 have a significantly negative impact on the mental health. This result may be due to the different nature and concentration of these pollutants in China. Particulate matter is the one among the most ubiquitous pollutant deteriorating the air quality (29, 53, 54). $PM_{2.5}$ and PM_{10} are not only harmful to human health such as chronic problems, but also play a vital role in haze and climate change. CO and NO_2 could damage physical health, in particular, respiratory diseases (55) and cardiovascular diseases (56, 57). High concentrations of CO and NO_2 are linked to cancer and death (58). Long-term exposure to CO and NO_2 will reduce ability to work and decrease human capital. Lower income and depression are caused by air pollution that could harm to mental health. Results reflect those of Chen et al. (59) and O'Neill et al. (60) who also found that higher concentration of $PM_{2.5}$ lead to mental illnesses. O_3 has no significant effect on mental health, which is contrary to some previous studies (61). This inconsistency may be due to the difference of the amount and time of exposure, the accumulation of O_3, study designs, and definition of mental health (25). In addition, FDI has moderating effects on the relationship between mental health and $PM_{2.5}$ and PM_{10}. Anthropogenic activities, which are regarded as the main source of particulate matter, include combustion of fossil fuels and industrial emissions. FDI with the advanced antipollution technology can benefit the environment and reduce the harmful impact of mental health.

Regarding region differences, it is found that only in eastern region, air pollution has a negative effect on mental health, which is also confirmed in **Figure 2**. People in eastern region are exposed to higher levels of particulate matter. The moderating effect of FDI is also obvious. A possible explanation may be that cities in eastern region have higher levels of economic development and better infrastructure. Therefore, the government is more likely to invest in healthcare (52). Opening health sector to international

TABLE 8 | Heterogeneity based on education, age, income, and changes of physical health.

Education level				
Variables	**High-Educated**		**Low-Educated**	
AQI	0.047	0.061	−0.824*	−0.422**
	(0.329)	(0.384)	(0.003)	(0.182)
FDI		2.215		−0.929
		(5.160)		(0.752)
AQI*FDI		7.473		5.851*
		(15.966)		(3.315)
N	239	239	4,597	4,597
Age				
Variables	**<60 years**		**> or =60 years**	
AQI	−1.044	−0.303	−1.074*	−0.654**
	(1.001)	(0.254)	(0.637)	(0.319)
FDI		5.582		−0.475
		(4.614)		(1.605)
AQI*FDI		−0.662		15.567**
		(1.106)		(7.290)
N	2,393	2,393	2,220	2,220
Family income				
Variables	**High-Income**		**Low-Income**	
AQI	−0.037*	−0.047**	0.004	−0.040
	(0.021)	(0.021)	(0.068)	(0.067)
FDI		−0.151		−0.525
		(0.362)		(1.227)
AQI*FDI		0.864**		3.009**
		(0.432)		(1.400)
N	6,871	6,871	2,084	2,084
Physical health				
Variables	**Better**		**Worse**	
AQI	−0.039**	−0.053***	−0.262***	−0.300***
	(0.019)	(0.019)	(0.059)	(0.061)
FDI		−0.589*		−3.331**
		(0.327)		(1.444)
AQI*FDI		0.988***		1.665
		(0.360)		(1.609)
N	7,062	7,062	1,353	1,353
Fixed effects	Yes	Yes	Yes	Yes
Control variable	Yes	Yes	Yes	Yes

****, **, and *, respectively, indicate significance at the 1, 5, and 10 levels.*

participation would also enable to reduce adverse effects of air pollution (36).

The moderating effects of FDI are significant in cities with abundant medical resource. The result validates the way that FDI plays a moderating role, i.e., FDI can improve the supply of medical services and help the local government to invest more medical resources (36). Regarding the difference of the investment in science and technology, the above results imply that cities with more attention to science and technology tend to attract FDI with more advanced technology and lower pollutant

emissions. The green investment and production will improve air quality and mental health. However, cities with less investment in technology still rely on heavy industry. Foreign-funded projects in these cities are mainly pollution intensive and less involved in health sectors.

The mental health of people who are elder, low educated, high income, or getting worse physical health are more susceptible to air pollution. FDI also has a moderating effect on mental health of older, low-educated, or more unhealthy people. There are several possible explanations. Compared with low-educated people, high-educated people learn more environmental knowledge and air pollution and they have more strategies to self-protect against pollution. Second, the effects of air pollution and FDI are more significant to the low-income group (4). The high-income people generally have a better understanding of air pollutants and take some preventive actions for self-preservation. Therefore, FDI has higher marginal benefits to low-income people. Finally, people whose health gets worse are more vulnerable to air pollution. They have stronger concern about the harm for their health when facing up to pollution, thus may lead to depression, helplessness, and stress. FDI can dilute the adverse effects of air pollution on people with better physical fitness because they are more energetic to make use of resources from FDI.

The threshold effect adds further insight of the effects of different levels of FDI and AQI. FDI causes a reduction in the negative relationship between air pollution and mental health, when the FDI is >1,745.591 million RMB. When FDI scale is low, local governments have a strong incentive to introduce foreign investment to promote economic development with lower environmental standards. These will ignore health guidance and investment and lead to the increase of air pollutants (62, 63). As increase in FDI and income level, the attention shifts to protect environment, take actions to reduce harmful effects of air pollution, and improve mental health. There are still 88.81% of cities' FDI lower than the threshold. It is worth noting that the air pollution has exceed the threshold value in about half of the cities where the role of FDI is not significant.

Our conclusions have some limitations. First, although AQI includes six major air pollutants, it cannot sufficiently study the impact of air pollution, especially the effects of total number of pollutants. Second, due to the limitation of data, this study cannot cover the impact of COVID-19 outbreak. COVID-19 outbreak may alter the supply and demand of FDI and directly affect mental health and the attitude to air pollution. Third, the CHARLS opens its data on the location only in the city level. Therefore, we use city-wide average air pollution concentrations rather than personal exposure measures, which may not precisely reflect the effects of air pollution on mental health.

TABLE 9 | Regression results of the threshold model.

		AQI	AQI*FDI
	Percentage	**The threshold effect of FDI**	
FDI ≤ 1,745.59	88.81%	−0.076*** (0.016)	0.449 (0.447)
FDI > 1,745.59	11.19%	−0.056*** (0.018)	1.110** (0.497)
Control variables		Yes	Yes
Fixed effects		Yes	Yes
	Percentage	**The threshold effect of AQI**	
AQI ≤ 92.79	54.41%	−0.045** (0.019)	2.172*** (0.469)
AQI > 92.79	45.59%	−0.060*** (0.016)	0.461 (0.522)
Control variables		Yes	Yes
Fixed effects		Yes	Yes

*** and ** respectively, indicate significance at the 1, 5, and 10 levels.

CONCLUSION AND POLICY IMPLICATIONS

This article examines the relationship between air pollution and mental health and the moderating role of FDI based on the CHARLS data in 2015 and 2018 using the IV fixed effects model and threshold model. First, air pollution has negative effects on mental health. Among the six types of air pollution, $PM_{2.5}$, PM_{10}, SO_2, CO, and NO_2 have significantly negative impacts on mental health. Second, FDI has an alleviating influence on the negative relationship between air pollution and mental health. Third, the regional heterogeneity shows that the negative effect of air pollution and the moderating effect of FDI are significant for people in eastern region. FDI positively affects people living in cities with more investment in science and technology and abundant medical resources. In addition, the individual heterogeneity results show that air pollution has more heavily negative impacts on people who are elder, low educated, high income, or unhealthy. Finally, FDI moderates the adverse impact between air pollution and mental health when it is >1,745.591 million RMB. Air pollution has larger negative effects on mental health when the value of AQI is >92.79. There are only 11.19% of cities in our sample that exceed the threshold value in China. Therefore, how to attract and use FDI effectively to moderate the relationship between air pollution and mental health for governments and enterprises could also be a far-reaching direction for future studies.

The above findings have a number of practical implications for policymakers. First, it is important to pay particular attention to the effects of air pollution not only on the physical health, but also on mental health. Policymakers need to explicitly consider the effects on mental health when formulating environmental protection policy, as well as policy evaluation. Second, the "polluted heaven" hypothesis for air pollution is not valid in China. An important policy priority should, therefore, be to provide subsidies or finance support to encourage businesses to receive high-quality foreign investment. In addition, the government should control and guide the scale of FDI and the level of air pollution according to the threshold value. Fourth, the effects of different types of air pollutants should be fully recognized. There should be a greater focus placed on $PM_{2.5}$, PM_{10}, SO_2, CO, and NO_2 when government crafts appropriate strategies to reduce air pollution. Finally, the findings of regional heterogeneity suggest that government

should actively guide FDI to the central and western region. Cities with less investment in technology should focus on improving their own absorption capacity of FDI and make full use of new technology and experience brought by FDI. Moreover, air pollution and FDI disproportionally affect those who are low education, low income, or older stresses. Therefore, related policies cannot only bring mental health benefits as a whole, but also result in an equitable distribution. There should be improving education level and providing targeted protection and advice to people who are susceptible to air pollution.

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

WJ: conceptualization, methodology, writing—reviewing and editing, and supervision. YC: software, data curation, writing—original draft, and visualization. Both authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.858672/full#supplementary-material

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Patient- and Community-Oriented Primary Care Approaches for Health in Rural, Remote and Resource-Dependent Places: Insights for Eco-Social Praxis

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Accelerating ecological and societal changes require re-imagining the role of primary care and public health to address eco-social concerns in rural and remote places. In this narrative review, we searched literatures on: community-oriented primary care, patient-oriented research engagement, public health and primary care synergies, and primary care addressing social determinants of health. Our analysis was guided by questions oriented to utility for addressing concerns of social-ecological systems in rural, remote contexts characterized by a high degree of reliance on resource extraction and development (e.g., forestry, mining, oil and gas, fisheries, agriculture, ranching and/or renewables). We describe a range of useful frameworks, processes and tools that are oriented toward bolstering the resilience and engagement of both primary care and public health, though few explicitly incorporated considerations of eco-social approaches to health or broader eco-social context(s). In synthesizing the existing evidence base for integration between primary care and public health, the results signal that for community-oriented primary care and related frameworks to be useful in rural and remote community settings, practitioners are required to grapple with complexity, durable relationships, sustainable resources, holistic approaches to clinician training, Indigenous perspectives, and governance.

Keywords: patient engagement, community engagement, public health, primary care, rural health, resource development

HIGHLIGHTS

- Multiple frameworks within the patient-oriented care movement align with principles of eco-social approaches to health.
- Attention to processes of patient and community engagement are crucial for incorporating eco-social approaches to health in primary and public health collaboration.
- Multi-disciplinary teams and other sector organizations can support use of tools identified in this review.

- Frameworks, processes and tools relevant to treating both patients and 'communities of patients' need adaptation for application in rural areas.

INTRODUCTION

Rural and remote places are often defined by their physical isolation from urban centers, strong community connectedness, a high degree of reliance on natural resource extraction (e.g., forestry, mining, oil and gas, agriculture, fisheries, ranching, renewables) to support local livelihoods, and lower levels of access to key services, especially those in the healthcare sector (1). When overlaid with the complex array of impacts from climate change, the foundational contextual components of rural and remote places create unique impacts on the health of rural populations (2), with consequent implications for the health sector (3) and worker training (4). This has necessitated the need for new framing for the role of "environments of health and care" (5) and creative responses in partnership approaches to integrated health care reform that focus attention on upstream causes (6, 7).

However, unpacking "environments of health and care" in rural, remote and resource dependent places requires consideration of not only the broader ecological and social contexts in which health systems operate, but also the complex pathways by which community members become patients due to injury or illness. In this contribution, we review multiple approaches to primary care practice that may enable more engagement with the determinants of health, and merge this literature with eco-social considerations that can enable researchers and practitioners to be more attentive to the community and geographic contexts which influence human health. In other words, this paper seeks to shed light on approaches that can incorporate understanding of health in rural communities where these places have characteristics of social-ecological systems [i.e., reflecting interdependent relationships between the social actors and institutions embedded within a biophysical system; (8)]. We set out to review relevant patient-oriented and community-oriented approaches, and revisit primary care and public health collaboration literatures, and viewing them through an eco-social lens. Specifically, we posed the following question:

> What existing evidence can help health teams better ally with communities in understanding and addressing eco-social pressures relevant for health in rural and remote communities?

Informed by the literature reviewed in this introduction, we begin by characterizing the challenges posed to human health in rural and remote settings and introduce the concept of "eco-social" research and practice. We then provide an overview of our review methods, and go on to present the resources identified in terms of relevant frameworks, processes and. tools identified in the literature reviewed. This leads to an exploration of the implications, challenges, opportunities and questions that warrant ongoing attention in order to support health teams, practices and policies to better reflect the eco-social context for health in the rural and remote communities they serve. Our analysis underscores six areas of innovation emerging in Canada and beyond, including Indigenous leadership and other integrative approaches to health that reflect the nuances of rural and remote contexts.

The Challenges of Health in Rural, Remote and Resource-Dependent Contexts: Introducing the Eco-Social Approach

The challenges of reflecting the complex health context for rural and remote communities are a topic of long-standing interest among health researchers and policy makers. For example, some literatures focus on the broader political economic drivers of rural and remote resource development as a key health determinant, highlighting the role of extractivism inexorably shaping conditions for health, via multiple intrusive pathways ranging from toxicological exposures to changes in the determinants of health (9–11). In grappling with the complexity of rurality, others have focused on the importance of social relationships in isolated places—often framed as "context"—particularly for rural mental health (12). Moreover, Bourke et al. (1) developed a framework highlighting the dynamic interplay between societal structures and individual agency to conceptualize the multi-layered, diverse components involved in rural health. Less common have been explorations of rurality and physical environments in determining the health of populations in rural places (13, 14). The disproportionate impact of wildfires on rural communities (15) and cumulative adversity impacts on mental health in rural settings (16) serve as exemplars of the interlinkages between social and ecological systems in rural and remote places, and how they shape health outcomes.

Accelerating ecological, physical, environmental, and societal changes have prompted an urgent need to better reflect the combined ecological and social context for health in rural and remote places. A narrative review of research priorities for rural and remote primary health care included responding to climate change as an important priority (17). Similarly public health actors have focused on the important role of ecological determinants of health (18) to complement the social determinants of health, as part of an expanding array of approaches linking ecosystems, environments and health (19, 20). In other words, ecological health can be thought of as the overall health of the biome, which includes humans and all other species, and "eco-social" as a framing of the dynamic interactions between ecological and social contexts and their role in shaping health status (21). Eco-social focuses "attention on the reciprocity among the ecological and the social as essential features of a proactive orientation to future health and collective well-being, especially in the face of rapid planetary-scale ecological changes that threaten human well-being and societal stability" [(22), p 61]. The framing of "eco-social" here is therefore strongly related to early conceptualizations of "ecosocial" by Krieger (23) who used the term intentionally to reflect the social production of health and illness across multiple scales. However, our use of "eco-social" is intended to reclaim the "eco" to be more overtly ecological, which has been markedly absent from the "ecosocial" literature (24), despite Krieger (25)

later expanding this orientation to better reflect ecological and biological contributions to health.

As a result of this thinking, health impact assessments of resource extraction and development proposals in rural and remote communities—as one tool to understand the health impacts of major projects which have historically been focused primarily on physical environment determinants, such as contamination of air, water or soil—have been broadened to incorporate social determinants (26) and health equity analyses (27). Broadening the time horizon, the cumulative environmental, community and health impacts of multiple resource development projects have been examined by integrated natural, social and health science teams working collaboratively (14) across all the associated challenges (20).

Eco-social approaches to health acknowledge that within many rural and remote community catchments (in the ecological watershed sense as well as "service-provided" sense) a combination of agriculture, forestry, mining and fracking (among others) all occur on a single land base. These activities generate complex interrelated sets of benefits and costs for the livelihoods, lifestyles and life-choices of the individuals and the communities in which they occur. Both public health and primary care providers may recognize the combined ecological and social influences on the lives of their populations and patients. Yet little guidance is available, beyond generic health promotion approaches, on how to work with both individual patients and communities (as "collectives" of patients) to promote health, in ways that match the complexity of the eco-social concerns which rural and remote communities face. In light of this, what frameworks exist to support health systems engage with the complexity of social-ecological systems, and how can eco-social thinking help?

RESEARCH METHODS

We reviewed approaches deemed relevant by the authors based upon professional, academic and personal experience. We explored opportunities and interactions among the following four broad literatures, focused primarily on the role of primary care providers:

a. an organizational focus on *community-oriented primary care,* one of the earliest approaches to engaging with patient contexts and communities (28);
b. the more recent *patient-oriented research and practice* approaches, fostered in Canada by national health research funders (see Strategy for Patient-Oriented Research or SPOR https://ossu.ca/about-us/what-is-spor/). Patient-oriented research and practice is about engaging patients to improve the delivery of high-quality, appropriate and cost-effective care in ways that can situate patients in the context of their communities and broader life trajectories;
c. approaches explicitly addressing *collaboration among primary care, public health and health systems,* in the integration of engaged communities to create healthy environments [(29), see **Table 1**]; and
d. engagement of *primary care with social determinants of health* (41) as an approach which potential to be expanded to strengthen appreciation of eco-social approaches to health (22).

The timing of our research created some thematic constraints within our review. One example is that the planetary health literature, with a focus on patients and/or communities in rural places, was not extensive within the timeframe of our searches. Likewise, ongoing expansion of Indigenous-led literatures profiling contextually relevant approaches to Indigenous health has far-reaching relevance to an array of rural and remote contexts. Although these literatures were not a main focus of our review, we do introduce literature known through authors' engagement and familiarity in these areas in the final section of discussion and implications.

Searches, Yield and Relevance

Search terms and methods of the English language scholarly literature searches included four targeted areas of literature:

1. Community-oriented primary care (COPC) and its analogs in Medline and EMBASE were searched through the dates 1980–2018. Additional searches were performed of select websites, and using Google Scholar with follow-up of key references. Among the 1,189 articles, 206 named COPC in the abstract. Abstract review of 100 full articles found 50 sufficiently relevant to the integration of public health and primary care. The majority of the latter (64% $n = 32$) were narrative pieces, with some encouraging evaluative work spanning decades.
2. Patient-oriented research and engagement in PubMed, Ovid MEDLINE, CINAHL Complete and Biomed Central from 2009 to 18. Among 376 articles identified, 244 were duplicates, and 44 articles were deemed sufficiently relevant for full-text review. An additional 40 were identified through review of reference lists of these articles (total 84). Perhaps understandably, articles tended to focus on discrete communities of patients dealing with specific health outcomes. The majority (69%, $n = 58$) were in secondary or tertiary care settings, less potentially applicable to primary care.
3. Environment and ecological in public and community health and primary care through Google Scholar without date limits. We primarily relied on scoping reviews (42, 43) and analyses conducted over the last decade (40).
4. Social determinants and primary care through Google Scholar without date limits where we again relied primarily on identified review papers (44).

Article titles and abstracts were screened primarily for relevance to our research question and rural and remote places within the context of resource development activities. For relevance judgements, we drew on the research, policy, practice, training, organizational and lived experience of the authors and research assistants (see acknowledgments). We are all settlers, but live/work or have lived/worked in and with rural and remote communities in Canada and internationally for decades, as primary care providers and clinician consultants, and as

TABLE 1 | Assessment of potentially most relevant frameworks in relation to reflective questions.

First Author(s) [date(s)]*–article type	Framework	Includes diverse patient life trajectories, mobility, vulnerabilities and assets?	Indicators tapping eco-social contexts for health?	State of application?†	Aspects applicable to practices-communities in diverse rural, resource development regions?	Challenges uncovered/addressed for operationalizing?
Gofin and Gofin (30)—review, Gofin and Foz (31)—Catalonia	Community-Oriented Primary Care (COPC)	Mostly, yes	In some applications, particularly in lower and middle income countries, and rural areas	Decades of institutionalization	Some rural applications demonstrated overall framework with multiple steps.	Most successful COPC undertakings have been externally funded and associated with academic institutions (28)
Blumenthal (32)—review and institutional case study	Clinical Community Health	Mostly, yes	No	Promising approach to institutionalization	Varies across particular applications referenced.	Resources to maintain fidelity with the model—Teams, staff, skills, commitment, dedication, time, patience
Bourke et al. (1)—conceptual with two applications	Comprehensive conceptual framework for the analysis of rural and remote health situations	Unclear	Yes	Application in several Australian (33) and other places	Yes, rural in both the primary care reorganization and Aboriginal health promotion applications.	Multiple levels of power and need for negotiation discussed in each of two examples
Bodenheimer and Sinsky (34)—conceptual	Triple and Quadruple Aim	In patient-centeredness	Some applications e.g., Miranda et al. (35)	Promising approach	Elaborated in some applications.	Not addressed
Tipireni et al. (36)—review with case studies	Accountable Communities for Health	Unclear	Yes, in one case study	Empirical evaluation	Unclear extent to which applicable in resource development regions.	Not addressed
Pelletier et al. (37)—case study	Patient partnership in knowledge translation	Yes for those with serious mental illness	No	Promising approach	Urban example, but involvement of patients and families in multiple ways exemplary.	Additional supports needed for active involvement of patients with serious mental illness
Woollard et al. (38)—conceptual	Social accountability	Yes	Not explicitly	Promising approach	Yes, though not explicitly articulated.	Generic
Holroyd-Leduc et al. (39)—case study with review elements	Patient engagement (1rly in research)	Certainly vulnerabilities (focused on frail elderly) and assets	Broadly considered	Promising approach and ethical imperative	Approach used with combination of evidence, face to face and virtual discussions.	Numerous discussed, particularly power differentials, accessibility with multiple suggestions for addressing them
Orkin (40)—review (with descriptive appendix of studies)	Clinical Population Medicine	Varies by application, [see Appendix]	No	Varied, but argue that lots of examples of application	Some potential tools identified (see below).	Generic in this review

*Chronological.

†State of Application categories: interesting idea, promising approach, empirical evaluation, decades of institutionalization.

public health staff and leaders. We are also researcher-mentor-academics engaged with partners at multiple jurisdictional levels (38).

Analysis

Given the broad array of potentially relevant literature, and the plethora of frameworks, processes and tools encountered, the authors used a series of reflective questions to help focus our analysis. These included:

1. Do frameworks, processes and tools identified pick up on diverse patient life trajectories, mobility, vulnerabilities, and assets?
2. Do they explicitly include indicators tapping eco-social concerns for health?
3. What is the state of application of each (ranging from interesting idea, through promising approach, empirical evaluation, to decades of institutionalization)?
4. What aspects of the frameworks, processes and tools could be useful in diverse rural and remote places where resource development is past, occurring or planned?
5. What are the challenges uncovered/addressed for operationalizing the frameworks, processes and tools?
6. What might be gained by more effective collaborations between primary care and public health at the community level?

We used qualitative analysis methods (45) to respond to the questions, organizing our findings on the different resources (frameworks, processes and tools) in tabular form with illustrative examples (See **Tables 1**–**3**). We built on the findings of this narrative review (see Resources Uncovered below) through iterative discussion among the authors, resulting in a synthesis of key implications, challenges, opportunities and questions (see action 4).

RESULTS

Our review of literature identified a range of resources potentially relevant to understanding the complex context for health in rural and remote communities. The frameworks, processes, tools presented here reflect terminology and priorities presented by the authors and, in the following section their implications are discussed in relation to contemporary eco-social context for health.

Frameworks

Our review surfaced a number of frameworks that theorize and describe relationships between primary care and public health in different contexts. Among the 19 named frameworks broadly related to the engagement of patients and communities, a subset of nine seemed most relevant to our overall research question (see **Table 1**).

Historically, Community-Oriented Primary Care (COPC), and its permutations e.g., Clinical Community Health (32), have been the most prominent. Defined by Mullan (66) as "the continuous process by which primary care is provided to a defined community on the basis of assessed health needs through the planned integration of public health practice with the delivery of primary health care services" applications have occurred globally, including in rural areas (30). In this definition, public health practice was primarily understood as clinical prevention services, particularly in assessment of outcomes. A systematic review (67) observed some evidence of effectiveness in increasing coverage of clinical preventive services and the usefulness of COPC as an educational orientation for primary healthcare providers (32). Mixed evidence was available of use of the COPC framework to understand eco-social concerns.

Improving patient access and outcomes, containing costs and improving population health has been the goal of so-called "Triple Aim" approaches, now expanded to the "Quadruple Aim" in order to include the goal of improving the work life of health care providers, both clinicians and staff (34). Related are Accountable Communities for Health (36) as an implementation of social accountability at the community level [e.g., (38)] with the emphasis on both responsiveness to community needs and appropriate governance structures involving community members. Some examples addressed included environmental determinants of healthy behaviors, although this was not the norm in the literature.

Relatively more emphasis was given to researcher-, provider- and patient-initiated partnership approaches (37) and patient-caretaker engagement strategies (39) which could be applied to address eco-social concerns. Indeed, some consideration, particularly in more rural-specific literatures considers "integrated primary care" to include person- and family-centered primary care which can build trust, while establishing accessible and continuous relationships (68). Categorization of clinical population medicine approaches in primary care (40) has been complemented by conceptualization of bridges across or areas for synergy between clinical care and public health (43). These could support integration of eco-social concerns, though this remains a goal yet to be realized. Among the areas for synergy, two were particularly promising: "identifying and addressing community health problems" and "strengthening health promotion and health protection" (43)—see sections Processes and Tools below for further elaboration.

Processes

While frameworks can be helpful to situate relationships between public and primary health systems, they can also be opaque as to the processes which underlie moving from an over-arching goal (e.g., more/better collaboration) through to tangible actions that improve patient and population health (69–71). Structured relationships between health care and community organizations have historically been an important part of COPC (e.g., including community members on boards). Although not the focus of this paper, attention to the nature of engagement-collaboration and governance when engaging patients/communities around eco-social issues remains crucial.

For example, Leonhardt et al. (46) reported on a community-based patient advisory council extending their role from patient medication safety to broader safety initiatives in participating communities. Tisnado et al. (47) described community-partnered research with an ethno-cultural community,

TABLE 2 | Assessment of potentially most relevant processes in relation to reflective questions.

First Author(s) [date(s)]*–article type	Process	Includes diverse patient life trajectories, mobility, vulnerabilities and assets?	Indicators tapping eco-social contexts for health?	State of application?†	Aspects applicable to practices-communities in diverse rural, resource development regions?	Challenges uncovered/addressed for operationalizing?
Leonhardt et al. (46)—case study	Community-based patient advisory council	Focus was medication use safety, not patient distinguished	Not included	Promising approach	Rural county with multiple health centers, so likely applicable.	Health provider involvement, creating trust and respect, time-intensive for personnel involved.
Tisnado et al. (47)—case study	Community-partnered research—CBPR	Of participating community researchers	Not focus	Demonstration project process documentation	Cultural group rather than geographically defined. Working through different values, establishing mechanisms for interaction between community members and providers-researchers all instructive.	Time availability, preferred communication modes, data sharing issues, limited funding for community partners.
Joosten et al. (48, 49)—multiple case study	Community engagement studios	Yes	Not focus	Demonstration project evaluation	Potential for adapting already developed research ideas. Could be done virtually in rural areas, depending on connectivity.	Core funding support and adequate information to stakeholders needed. Reasonable cost.
Etchegary et al. (50)—case study	Town halls on health research	Not directly, though some shared	Not clear	Promising approach	Rural communities included, could tap health research interests.	Time for planning and use of appropriate language.
Marcus et al. (51) [and Moosa et al. (52)]—multiple case study	(ward-based) Primary care outreach	Vulnerabilities and assets yes	Yes, rurally including water and sanitation	Demonstration project evaluation	Yes, complementary responsibilities in communities with travel to households.	Organizational independence as part of regional health services, with separate staffing and resources.
Kaufman et al. (53)—multiple case study	Health Extension broadly, though distinct models in five different states	In some practices, in some states	Not explicit	Demonstration project evaluations	Several explicitly rural efforts. Experience of building sustained relationships with practices and community coalitions; documenting success in broad terms as well as diverse outcomes of meaning to different stakeholders; understanding that health extension can be carried out by an individual or group depending on resources.	Challenge in USA of market-based health care corporations buying up primary care practices. Need for long-term, sustained fundraising beyond grants.
Shahzad et al. (43)—systematic review	Use clinical opportunities to address underlying causes of health problems	Yes	Built environment—housing in the city (54)	Some empirical evaluation around other kinds of information	Issues addressed in encounter EHR could be eco-social relevant ones e.g., exacerbation of asthma or COPD by wildfires (55).	Generic
	Use clinical encounters and share data (e.g., Electronic Health Records) to build community databases (54, 56)	Potential	Not generally	Some demonstra- tion project evaluation around other kinds of information	Sharing of anonymous, aggregate patient utilization and population information example Bruckner and Barr (57) specifically noted collaborative work in rural county.	Generic
Johnston et al. (58)—case study	Community-engaged health services planning	Subsumed	Only indirectly in effects on transportation	Demonstration project evaluation	All, with a focus on health providers, authorities, systems.	Potential power differential between health providers and other engaged partners.

*Chronological.

†State of Application categories: interesting idea, promising approach, empirical evaluation, decades of institutionalization.

TABLE 3 | Assessment of potentially most relevant tools in relation to reflective questions.

First Author(s) [date(s)]*–article type	Tool	Includes diverse patient life trajectories, mobility, vulnerabilities and assets?	Indicators tapping eco-social contexts for health?	State of application?†	Aspects applicable to practices-communities in diverse rural, resource development regions?	Challenges uncovered/ addressed for operationalizing?
Mullan et al. (59)—concept and specific application	Geographic retrofitting	Likely	Not yet	Promising approach	Good potential to map patient sources for primary care, emergency utilization, including unincorporated rural areas	Sparseness of census and other data in rural, remote areas
Dulin et al. (60)—case study of application	Geographic information system (GIS) integration and analysis	Yes through Multi Attribute Primary Care Targeting Strategy (MAPCATS)	Not yet	Promising approach	Good potential to map patient sources for primary care, insurance coverage, emergency and hospitalization use, for regions with rural and urban centers	Smaller populations translate into data limitations from nationally representative surveys where small communities may have few people representing an area
Lebrun et al. (61)—multiple case study [also part of COPC literature]	Community health assessment	Likely	In some health centers engaged with environmental justice organizations	Substantial examples, with some empirical evaluation	Included health centers in rural areas. Complemented community health assessment with community needs assessments, ongoing data collection and analysis, use of surveillance data, and program evaluation	Limited integration and interoperability of data sources, within health centers as well as between health centers and partner organizations
Andermann (44)—review	Screening tools as part of patient encounters	Yes, on vulnerabilities	Housing perhaps	Promising approach	Expanding to eco-social contexts for eco-social concerns and impacts as optional template on electronic health records.	Lewis et al. (62) documented the challenges community health center clinicians faced in identifying, treating and accounting/billing for social determinants of health. Included clinician skills and tools, organizational response capacity, and economics of reimbursement. Similarly Gold et al. (63) re: electronic health record integration challenges.
	Analogous to Social Prescribing referrals	Yes, particularly vulnerabilities	Some, as per Young et al. (64)	Interesting idea	Potential for navigator and champion roles in eco-social prescribing e.g., to community member who shares snow shoes with youth and takes them out for walks in woodlands.	Potential challenges due to smaller tax bases, less health and social service capacity in rural areas. Yet also more green space for land-based healing.
Furst et al. (65)—review	Eight mental healthcare ecosystems description/assessment tools	Mostly diagnosis or demographic descriptors	Ecosystem term applied to health care system at different scales but not explicitly eco-social factors	Empirical evaluations	Relevant to mental health services in broad regions, but lack rural specifics	Several challenges in application for health services research

*Chronological.

†State of Application categories: interesting idea, promising approach, empirical evaluation, decades of institutionalization.

emphasizing the building of relationships around shared values. Joosten et al. (48) developed a structured approach to systematically engage stakeholders through community engagement studios. This intriguing method for more research-oriented university health sciences groups to obtain feedback on research proposals incurred modest additional costs for the helpful feedback received (49). Etchegary et al.' (50) reached out to rural communities with town halls for both research and healthcare improvement discussions and prioritization. Some consultation with communities could probably be done virtually, as per community hub high risk intervention initiatives (72). A project involving multiple partners in consultations for sustainable rural health care systems found relationships and change over time as core emergent themes in their qualitative research (58).

In the literatures examined, collaborative work involving professionals and community stakeholders to identify and better respond to complex determinants of health appeared to be a necessary condition for incorporating community context, including the recognition of the socioeconomic contexts which create conditions for patients to become "super-utilizers" of healthcare systems (73). For example, most patient oriented literature ($N = 84$) spoke to the need for inter-professional teams including: multi-care team + public health + community members (22%, $N = 18$) and public health + primary care teams (14%, $N = 11$). Although some active clinician participation is needed, many commentators note the importance of resources for non-clinical staff to be included in patient population tracking and linkage to other resources, called "enabling service providers" by Lebrun et al. (61) and others [see, for example, (74, 75)]. Tipirneni et al.' (36) noted the importance of organizational mechanisms at multiple levels for addressing determinants of health. Marcus et al. (51) assessed the strengths and weaknesses of (ward-based) primary care outreach to households and communities not currently accessing primary health care [with (52) similar for an urban- setting]. The functions were filled by both existing health center staff (e.g., nurses, and new staff such as community health workers). Their recommendation was for greater independence, both organizational and budgetary, for such outreach initiatives. Kaufman et al. (53) assessed five state initiatives in different kinds of health extension out of academic health science centers, some in rural areas. Widely different kinds of extension activities occurred involving multiple players in public, private and allied social service and health sectors, some of which explicitly engaged in addressing determinants of health in rural communities.

Turning from outreach to more clinically focused primary care activities, Shahzad et al. (43), recommend "use [of] clinical opportunities to identify and address underlying causes of health problems." They cite one example which dealt with a more classic environmental cause: housing quality in a city (54). Nevertheless, one can imagine individual electronic health record data generated through templates including a variety of potential eco-social concerns such as:

- Ecological grief (76);
- Repeated adversity (16), including heat events, wildfires and flooding, such as those experienced by rural populations in British Columbia in 2021, with associated mental health-well being impacts;
- Exposure to wildfire smoke exacerbating respiratory conditions (55), particularly where primary care providers also provide emergency services in many rural settings; and
- Connection to the land as an asset to promote health (77), support more robust recovery from disasters (15) or engage in land-based healing (78).

Such examples of opportunities respond to Shahzad et al. (43) recommendation to develop public health and primary care interfaces to "use clinical encounters and share data to build community-wide databases." Gosling et al. (54) described sharing of anonymous, aggregate primary care patient population information with public health, resource development proponents, social services, and others for program planning and monitoring changes in population health over time. They echoed Calman et al. (56) examples of EHR joint use. Bruckner and Barr (57) provide a strong example of sharing health status and utilization information in a US rural county to address diabetes (though environmental components are underexamined). In contexts characterized by a high degree of reliance on resource extraction and development, one could also imagine using electronic health record data to help identify increased rates of Intimate Partner Violence among populations linked to resource development or the proportion of new pregnancies potentially affected by mutagenic exposures from resource extraction work or waste exposures. Further, crossing sectors, health authorities have linked with wildlife-environmental colleagues reporting networks to address linkages between wildlife and human health (79).

Tools

Given the presence of frameworks and processes to better link public health and primary care in working with communities, what tools might assist integration of eco-social approaches to health? **Table 3** sets out some potential tools for application or extension.

Community health assessment has been a key component of COPC since its inception and was included in Shahzad et al.' (43) review. A good example is the conduct of annual community health needs assessments among US federally-funded health centers in Lebrun et al.' (61) examination of primary care and public health activities. Mullan et al. (59) use of GIS to reflect on patient population dispersion across a county and Dulin et al. (60) work on prioritizing data components and then joint mapping of them could also be useful tools. Unfortunately, population sparseness and geographically large units for analysis in many rural areas pose challenges in achieving precise information. This is in part driven by small populations, but also in part by privacy and reporting concerns to protect patient anonymity. Less substantive, but relevant to appraisal are more recent tools focusing on "local" evidence, such as Quality Assessment of Community Evidence (QACE) Tools which explicitly incorporate qualitative and more anecdotal sources (80). Furst et al. (65) reviewed tools for assessing context relevant to mental healthcare "ecosystems" (another use of the term from our use here), Their inclusion of patient and regional

characteristics would need to be adapted to incorporate eco-social concerns. Moreover, the Social Interventions Research and Evaluation Network (SIREN) produces relevant updates and reviews on tools, which includes for example, the social needs screening tool comparison table to identify the role of housing and workplaces as potential environments. While not explicitly eco-social in nature, these types of tools offer potential to highlight eco-social concerns (81).

Andermann (44) reviewed ways clinical providers could better address specific social determinants of health, including a set of tools for screening individual patients and intervening (e.g., poverty screening tool developed by Center for Effective Practice, undated). Such screening could be built upon with electronic health record templates for some of the exposures and conditions relevant to eco-social concerns (see section Processes above). Analogous to social prescribing approaches (82–84), one can imagine greater use of interventions such as nature prescriptions (85). As well, Andermann (44) urged clinicians to work with other stakeholders and implement tools to assess environments [e.g., Thrive, a US piloted Tool for Health and Resilience in Vulnerable Environments (86)], which includes place determinants such as parks and open spaces, and the state of air, water and soil. Further, the BUILD Healthy Places Network—a large, multi-year funded collaborative explores ways to include diverse and marginalized communities in ways that are generally inclusive of primary care and have a rural primer to guide cross-sector collaborations in ways that are attentive to rural spaces (87). Such assessment can inform group activities addressing eco-social concerns and facilitating opportunities for groups of patients and the broader community (64).

IMPLICATIONS, CHALLENGES, OPPORTUNITIES AND QUESTIONS

By exploring four broad literatures, we uncovered substantial prior work on relevant frameworks, processes and tools, drawing upon different traditions of inquiry and activity. Much will be useful, but others will need to be extended and adapted to incorporate eco-social approaches to health in rural and remote areas. Importantly, our review has several limitations. First, by focusing primarily on the peer-reviewed literature, this review may miss important gray literature contributions, especially pertaining to eco-social approaches to primary care delivery in Indigenous contexts. Second, and relatedly, many of the resources identified were drawn from English-language publications on experiences based in the North American, Oceania, and European contexts, which seems to primarily relate to the nature of health system funding and available published literature. This may present opportunities for future research to learn more specifically about patient- and community-oriented approaches to primary care in other eco-social settings (e.g., Africa, Asia, South America). Third, we did not explicitly review papers for ethical issues arising in the deployment of these frameworks, and future work could examine this to unpack ethical guidance and good conduct practices in deploying the tools and processes uncovered herein. Fourth, our focus was primarily on primary-care approaches, viewed through an eco-social lens. Accordingly, there are massive literatures on more community-oriented approaches leveraging the unique strengths of community development and public health that could add additional nuance and understanding to these issues, but which were ultimately beyond the scope of this review [see for example, (88, 89)].

Nonetheless, our review surfaces a number of challenges that require attention adequately integrate eco-social praxis into primary care practice to promote health in rural and remote areas: complexity, limited durations, additional resources, clinician training, Indigenous perspectives, and governance. Each of these is articulated below in greater detail as an opportunity to promote further research.

First, the *complexity* of grappling with both health systems aiming toward greater integration (90) and linkages with other sectors relevant to eco-social concerns, creates challenges for most practitioners and organizations involved (22). The wildly fluctuating drought and flooding cycles, with their huge human health impacts are an example of the complexity of increasing coupling between climate change and human health demanding mitigation measures (91). One unfortunate response is to simplify the complexity, as in environmental assessments of resource development projects which ignore much available social and health data (92). The asynchronous, non-linear process of complex system change can be disorienting, as Strelnick (93) remarked about COPC development. Complex adaptive systems perspectives may be useful to not only guide practitioners through the uncertainties of change, but also to provide some comfort around the incompleteness of any particular transformative effort (94). Expanding to other sectors relevant to ecosystem approaches to health, Waltner-Toews and Kay (95) elegantly laid out various approaches with diverse stakeholders through initial observations-assessment, collaborative learning about both ecological systems-landscapes and societal systems-organizations, and feedback loops during iterative change to improve both landscapes and health. Central to success in this realm is a focus on the *relationships* within the system(s) rather than just the entities within the feedback loops. The non-linear causal loops that characterize complex adaptive systems, although challenging to measure, when seen through an eco-social lens can provide insights and for mutual understanding and more effective joint efforts. This emphasis on complexity and relationships are recognized characteristics of many ecosystem-oriented approaches to health (19, 20).

Second, many reports were of demonstration projects or special initiatives which had *limited durations*, of the order of months to years, with only a few reaching decades. In our experience, personal and organizational continuity is a challenge in many rural and remote places, among health care providers, public health practitioners, academics and partner organizations. In particular, better paying jobs in the private resource development industry are often more attractive for those with skill sets that can apply across sectors, just the kind of boundary crossers needed for addressing eco-social concerns (96). Personnel turnover affects organizational memory and relationships, both important for ongoing transformative

efforts, and a known challenge in work crossed boundaries among sectors, jurisdictions and mandates (19, 97). In this context primary and public health care could be enhanced by creating organizational information systems that are able to track involvements with communities (similar to individual patient electronic health record systems), relationship-informed handover protocols, and options for continued engagement, even if personnel shift to different organizations, are all required to improve continuity of involvements with communities.

Third, *additional resource requirements* by way of grants or research funding were almost universal across the initiatives in the literature reviewed. These mesh poorly with fee-for-service or even capitation reimbursement models, dominant in primary care financing in many jurisdictions, or with itemized activity-based planning in lean public health organizations. For individual care components, efforts toward patient complexity-based funding could be extended to eco-social concerns, as has been advocated for dealing more effectively with SDH vulnerable patients/community members (36). For community-based components, streams of funding, or collaboration with organizations who have such funding, seems essential (53). However, the role of financing in driving desired service change is probably limited and, in rural attempts specifically, ineffective. Gathering the range of perspectives needed in a collaborative, community-based approach, though often challenging, is often more fruitful. For example, the literature reviewed underscored that academic colleagues' can assist in working with frameworks and data tools, research centers can assist with organizational processes, and universities can facilitate student involvement for documenting processes and contributing to analysis and write-up. A formal commitment to collaborative "tables" bringing together different perspectives at scales from the local to provincial/state levels shows promise (14), especially for avoiding mutual excuse/blame cycles that dissipate both energy and good will when approaching complex issues. "Harm reduction" approaches are informative here, working to "actively engage a diversity of players in finding solutions" in ways that "looks throughout the socio-ecological system at drivers of harm to find strengths, possibilities, and opportunities for solutions in the face of prevailing challenges and uncertainties" [(98). p. 5]. Another example is exemplified by the recent symposium generating ideas on roles health providers can play in "Planning Resilient Communities and Adapting Rural Health Services in British Columbia" (99) and the BC Rural and First Nations Health and Wellness Summit Summary Report (100).

Fourth, several reports addressed the need for *clinician training* and programs for acculturation into patient-engaged and community-oriented approaches (32). Public health and preventive medicine colleagues have skills in community assessment and population health (101) but these need to be complemented by those among primary care providers. An international movement is emerging focused on transforming health providers' education to build skills relevant to planetary health and sustainable health care (102). An example is the Rural Health Services Research Network of British Columbia's (99) initiative to build on COVID-19 responses and involve primary care providers in promoting community resilience in the face of climate change. We might imagine extending professional competencies to include addressing eco-social concerns, such as modifying the College of Family Physicians of Canada's physician roles and responsibilities to include: (1) ASSESSING health and its broader eco-social determinants (e.g., comprehensive clinical assessment) [Medical Expert role]; (2) LEARNING from patients in practices both individually and as population panels [Professional, Scholar roles]; and (3) SUPPORTING AND ENGAGING with the community-geographical places with other organizations in settings beyond the clinic [Collaborator, Advocate roles] (see **Figure 1**).

FIGURE 1 | Extending clinical competencies to support the treatment of "communities as patients" in rural and remote places.

More recent efforts to describe the *Primary Care Home* and *Primary Care Neighborhood* (103) can be seen as pursuing a better understanding of the upstream causes of ill health (i.e., "Why is this patient here in the clinic today" in a more complete sense than previous simple reactivity). At the same time, greater attention to Indigenous ways of seeing, knowing and being has pulled health systems to address *wellness* (100) and a vision of holistic health (100, 104). These developments call primary care toward a greater involvement in population health–and hence on a *bridge* to the realm of community/public health that has been sadly lacking for over a century as clinical care became progressively specialized, technological and disease focused. Some of the more effective examples of such bridging may be found in rural and remote Indigenous communities (100).

Fifth, a minority of the literature in colonial contexts e.g., Bourke et al. (1, 33) recognized the growing imperative for primary care and public health systems to be better informed by *Indigenous knowledges and perspectives* in decolonizing research and practice (105). In addition to moving beyond a deficit framing of Indigenous communities in rural and remote regions (9, 106), recognizing the strengths of Indigenous perspectives can overcome false dichotomies between ecological (nature) and social (people) systems. This recognition has perfused recent international calls such as the Association for Medical Education in Europe's consensus statement on Planetary health and education for sustainable healthcare (102, 107, 108). The fact that Indigenous voices and leadership are now being recognized for

their importance to informing integrative, eco-social approaches to health (109), has far-reaching implications across primary and public health (78, 106, 110–112), but particularly for eco-social issues such as climate change (113). Those interested in practice that reflects the complex context of health will face increasing imperatives to learn from and with Indigenous-led work as generative pathways to address eco-social concerns in practice in rural and remote contexts (114).

Sixth, given the important role of multi-disciplinary teams in our findings, no one practitioner should feel overwhelmed with the learning involved. Professional bodies have set out guidelines on how to develop collaborative care arrangements with social and community supports in a patients' medical neighborhood that could be extended to other sectors (103). The competence to address eco-social concerns will need to be collective (115), distributed across organizations (53) as in social accountability frameworks in primary care (38) and other integrative approaches to working together for health (97). Collective competence involving health and non-health sectors could focus on building *healthy, just* and *sustainable* health systems and societies that are resilient in the face of ecological and social change (22). Yet such multi-sectoral, multi-level involvement demands more explicit attention to *governance*, as noted by practitioner scholars whose work spans health, ecosystems and equity (95, 97, 98) and health geographers focusing on health and health care in rural places (116). Intersectoral partnerships focused on health policy and services in rural areas are evolving in British Columbia through a "Pentagram Partnership Plus" approach involving quarterly meetings and interval consultations with senior public servants responsible for the health care system (100). The question remains: how might governance evolve to support creativity in collaborative work with patients, communities and other sectoral partners to better address eco-social concerns in rural and remote, and resource-dependent contexts?

CONCLUSION

Our narrative review of frameworks, processes and tools that can re-imagine and enhance public health and primary care integration to address eco-social health concerns in rural and remote contexts is revealing. While much has been written about the why (e.g., enhancing patient and population health outcomes) and the how (e.g., better intra/inter-organizational collaboration), there was relative little explicit consideration of eco-social approaches to health within these literatures and a potentially problematic tendency to universalize across rural and urban places. Rural, remote and many Indigenous communities face significant pressures when considering the interactions between social and ecological systems. As such, ecological damage is increasingly recognized to exacerbate existing health inequities.

This review identifies the need for more concerted engagement with the combination of ecological decline and ongoing patterns of inequity that need be at the center of increased public health and primary care integration. Mutual goals should include addressing primordial causes of ill-health in rural and remote places, treating patients with humility and in conversation with the places in which they live, work and play, and collectively fostering a sustainable future where health systems are not simply treating the symptoms of ecological decline, but taking an active role in promoting environmental stewardship. This paper outlines hopeful steps in the determined multi-sectoral efforts to change our current "self"-destructive path by broadening the definition of *self* to include the ecosystems on which we depend for our survival.

AUTHOR CONTRIBUTIONS

Authorship order reflects contribution to the research, including overall design, analysis, and writing (co-led by CB, SA, and DC), followed by contributions to design, writing, and oversight in alphabetical order (RF, MP, and RW). All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Individuals' Awareness of and Willingness to Accept Hospital-at-Home Services and Related Factors: A Cross-Sectional Study

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Introduction: Hospital-at-home (HaH) services have become increasingly popular. However, the experience of HaH implementation in Asia is inadequate. Therefore, the purpose of this study was to investigate individuals' willingness to accept HaH services and the potential related factors.

Methods: The researchers visited households to select appropriate participants. An online questionnaire survey was conducted among the inhabitants of selected communities. An individual's awareness, willingness to accept HaH services, and demands such as ideal service providers and more detailed information to accept HaH care were investigated. The outcome measure was the willingness to accept HaH services. Chi-square tests and logistic regression models were used to analyze the factors.

Results: A total of 622 subjects participated in this study. The findings indicate that 55.9% of the participants were not aware of HaH services, while most of the subjects (88.4%) were willing to accept them. Regression models indicated that having health insurance (OR = 2.170, 95% CI: 1.003–4.697), an awareness of the necessity of HaH services (OR = 4.721, 95% CI: 2.471–9.019), very much hoping staff from central hospitals would be service providers (OR = 20.299, 95% CI: 5.718–72.068), and somewhat hoping that staff from central hospitals would be service providers (OR = 9.139, 95% CI: 2.714–30.775) were the factors associated with a greater willingness to accept HaH services.

Conclusion: The study indicates that compared to the awareness of HaH care, residents had a greater willingness to accept such care. The willingness to utilize HaH services among individuals was associated with enabling factors, predisposing factors, and HaH-related demand factors.

Keywords: home care, hospital-based, home care service, willingness, attitude, awareness

INTRODUCTION

With increasing health care demand and shortage of hospital beds around the world, the health care system is currently facing the challenge of decreased quality of care (1). The high incidence rate of chronic diseases such as diabetes, cancer, and hypertension (2) has caused many hospitals to be unable to provide sufficient care to satisfy their clients' needs. Moreover, the increasing number of elderly individuals as the population ages contributes to the challenges facing current health systems to satisfy consumers' demands (3, 4). As the proportion of chronic diseases has increased with population aging, the availability of hospital beds has decreased. Even more noteworthy, since the outbreak of the COVID-19 epidemic, according to the World Health Statistics 2021 launch by the World Health Organization (WHO), the number of confirmed cases of COVID-19 has topped 0.153 billion, which has exacerbated the conflict between the supply and demand for medical resources and made it more difficult for people to obtain medical services[1].

To overcome these complex challenges, an innovative solution that can offer an alternative model of care is needed. With hospital-at-home (HaH) services, originated in 1958, health care professionals provide hospital-level care in patients' homes (1). Gogan suggested that receiving health care at home could help patients recover more rapidly (5). In recent years, HaH care has become increasingly popular as a substitute for inpatient care, and many diseases have been treated through HaH services, including chronic obstructive pulmonary disease and chronic kidney disease (5–10). Compared to inpatient care, HaH services represent substantial cost savings, alleviate the increasing pressures on the inpatient bed supply, and reduce the risks associated with prolonged inpatient care, such as delirium and hospital-acquired infections (11). Mortality and readmission rates do not differ significantly between HaH and inpatient care (6, 7).

The Chinese government has also paid close attention to the implementation of HaH services. The Interim Regulations on HaH Management in Sichuan Province were launched in 2019 and defined the mission, target diseases, leadership, methods, and regulations for HaH services (12). However, compared to several Western countries, such as the United States, United Kingdom, Australia, and Canada, HaH services in China are developing slowly (13). For example, in 2012 a total of 12,200 home health agencies provided home hospital beds in the United States. Insurance coverage for this service was available to 3.43 million patients. A total of 98.6% of these facilities were authorized by Medicare (federal health insurance) and 77.5% were authorized by Medicaid (medical assistance). Home care services were subsidized by Medicare for almost $1.79 billion in 2015 (14, 15). In Canada, health care is mainly provided by a family physician primary care system. Family physicians accompanied by their teams handle more than 80% of disease treatments, and refer patients to appropriate specialists through a referral mechanism when necessary. The Canadian model significantly improves the utilization of medical resources for hospital specialties (16). Due to different cultures, financial development, and compensatory policies, attitudes toward accepting HaH care vary among countries. Despite the prevalence of HaH services in Western countries, studies that explore individuals' willingness to accept HaH services in Asia are limited, and the public perception of HaH services has yet to be well established (13). A deeper comprehension of individuals' attitudes toward HaH care is essential before implementing it in any new setting (17). Moreover, more detailed issues, such as ideal service providers, the proportion of compensation, and the frequency of ward rounds are yet to be determined, and taking individual demands into consideration is crucial in the promotion of HaH development (18).

Therefore, this study adopted the Andersen–Newman behavioral model to explore the willingness of residents to accept HaH services and the potential factors of agreement to HaH services in Asian countries such as China (18), which will be helpful for obtaining a deeper understanding of residents' opinions concerning HaH services and in providing reliable evidence for HaH promotion and service improvement to ensure that targeted services can be offered.

METHODS

Study Design

This was a cross-sectional study carried out with 622 residents of Chengdu City by using a personal characteristics questionnaire and a questionnaire that assessed respondents' awareness of and willingness to accept HaH services.

Participants

The initial sample size ($n = 600$) was calculated by the formula $N = Z^2 \times \{P \times (1 - P)\} \div E^2$(Z = 1.96, $E = 4\%$, and $P = 0.5$). Participants were selected through convenience sampling. Because of the possibility of survey dropout, 700 participants were invited to finish the survey. Volunteers who met the following criteria were enrolled in this study: (1) >18 years old; (2) no cognitive impairment or psychiatric disorder; and (3) permanent residents of Chengdu City. Of the 700 residents invited to participate, 650 answered the questionnaire, and of these, 622 (88.9%) provided complete and usable data to be included in the data analysis. Only complete data were analyzed.

Sample Collection

To ensure that the process of data collection would go smoothly, the researchers discussed with several community leaders in Chengdu. With the consent of the people in charge, the surveys were administered to subjects from five communities in Chengdu City. Through lectures, the researchers explained the HaH concept and function, as well as the proposal and precautions of the survey. After the lectures were completed, three researchers visited households in the community to select subjects who met the inclusion criteria. After the link to the online questionnaire was sent to the subjects by a WeChat QR code, the subjects completed the questionnaires by themselves. During this process, the researchers always answered the subjects' questions to ensure that the subjects fully understood each item of the questionnaire to improve the accuracy of each answer. Through an online questionnaire, the processes of data collection and entry were

[1]https://www.who.int/emergencies/diseases/novel-coronavirus-2019#

integrated. The software package WJX (www.wjx.com) was used to collect data. WJX is a professional online platform widely used in several fields that includes data collection, custom reports, and survey result analysis. More than 0.1 billion individuals in China have registered with WJX software. To ensure rigor in the sample collection process and reduce bias, strict quality control measures were adopted. Misfillinging or omission of filling the questions was avoided by preset single-choice, multiple-choice, and fill-in-the-blank questions. The questionnaires could not be submitted unless they were completed. One person could only fill in the questionnaire once after all the topics were completed. Each questionnaire was screened by automatic screening rules and manually checked by the researchers after submission. Any answer that did not meet the requirements, such as only one option was selected or the questionnaire was finished within 60 s, was marked as invalid and removed.

Instruments

Personal Characteristics Questionnaire

A personal characteristics questionnaire was designed to collect data on the participants' general characteristics, including their gender, age, educational background, occupation, income, family income, and health status, such as whether they currently or previously had any chronic disease, type of chronic disease, family's health status, medication usage, family's medication usage, and family's visual acuity status.

Questionnaire on Residents' Awareness of, Willingness to Accept, and Demands Regarding HaH Services

The researchers designed a questionnaire consisting of 12 multiple-choice items to investigate Chengdu residents' willingness to accept HaH services and potential related factors. This questionnaire was constructed after reading related literature and was revised by many experts; Cronbach's α coefficient (0.821) and Kaiser–Meyer–Olkin measure (0.948) were calculated as reliability and validity indicators. The variables were as follows: whether the subject had heard about HaH services; whether the subject had accepted any HaH services; the necessity of launching HaH services; the reasons why the subject believed that HaH services were important; an awareness of the extent of HaH service reimbursement; the ideal service provider; the frequency of ward rounds by doctors; the frequency of nursing ward rounds; the ideal expense account for family income; the attitude toward doctors and nurses from the central hospitals that provide the services; and willingness to accept HaH services. The primary dependent variable was the willingness of residents to accept HaH services.

Independent and Dependent Variables

The Andersen–Newman behavioral model was constructed by Professor Ronald in 1968 and is one of the classic models for studying the utilization of health services. The model involves three types of determining factors that affect an individual's utilization, namely, predisposing, enabling, and need factors. Predisposing factors refer to personal sociocultural position prior to health service utilization, which consist of demographic characteristics, social structure, and health beliefs. Demographic characteristics indicate one's basic condition, such as age and gender. Social structure includes one's educational background, occupation, social network, and perception of the health service system (18). Therefore, we inquired about individuals' age, gender, educational background, occupation, whether they had heard about HaH care, whether they had accepted HaH services, the necessity of launching HaH services, and their awareness of the extent of HaH service reimbursement as predisposing factors. Enabling factors include the capacity to obtain health services and the availability of health services, such as income and health insurance (18). Therefore, an individual's monthly income, family monthly income, and health insurance status were defined as enabling factors. Need factors indicate the cognitive requirements of individuals for health services, including their health status and disease conditions (18). As for service demands, service provider requirements were also taken into consideration and were defined as the HaH-related demand factor. The dependent variable of the study was willingness to accept HaH services.

Statistical Analysis

The data were analyzed with the SPSS 21.0 software package. Frequency and percentage statistics were used to analyze the participants' predisposing, enabling, need, and HaH-related factors. The results of the questionnaire on the participants' awareness of, willingness to accept, and demands regarding HaH are also presented as frequencies and percentages. The associations among the independent variables and dependent variable were evaluated by using the chi-square test, with $P < 0.05$ considered to be statistically significant. Before a logistic regression was performed, the correlations among the independent variables were also analyzed. To bypass the impact of collinearity between the independent variables on the final findings, stepwise (forward) logistic regression models were run to minimize the effect of the correlation between variables, including only the independent variables associated with the dependent variable.

Ethics

The study was approved by the Ethics Committee of West China Hospital, Sichuan University (No. 848). All participants were informed of the details of this study and agreed to participate in the survey. Written informed consents were provided by each participants.

RESULTS

Participant Characteristics

A total of 622 residents of Chengdu City participated in this study (including 166 males and 456 females). Most were between 30 and 50 years old (mean ± SD: 40.22 ± 12.95). Of the respondents, 36.35% had a bachelor's degree or above, 47.9% were managers, public servants, or professional personnel, and 90.0% had health insurance. A total of 17.4% currently or previously had a chronic disease, while 46.5% of participants' relatives currently or previously had a chronic disease.

TABLE 1 | Participant characteristics, awareness of, willingness to accept, and demands regarding HaH services.

Variables	Total ($n = 622$)
Gender	
Female	166 (26.7%)
Male	456 (73.3%)
Age	
18–30	153 (24.6%)
31–50	362 (58.2%)
51–60	83 (13.3%)
>60	24 (3.9)
Educational background	
Primary school and below	53 (8.5%)
Junior high school	104 (16.7%)
High school	49 (7.9%)
College degree	190 (30.5%)
Bachelor degree and above	226 (36.3%)
Occupation	
Mangers, public institutions, or professional personnel	298 (47.9%)
Workers (production or transportation equipment operators and related personnel)	31 (5.0%)
Farmers	58 (9.3%)
Retirees	116 (18.6%)
Others	21 (3.4%)
Unemployed	98 (15.8%)
Health insurance	
Yes	560 (90.0%)
No	62 (10.0%)
Marital status	
Spinsterhood	141 (22.7%)
Married	468 (75.2%)
Others	13 (2.1%)
Number of offspring	
None	155 (24.9%)
1	304 (48.9%)
2	145 (23.3%)
3 and more	18 (2.9%)
Family monthly income	
6,000 below	188 (30.2%)
6,000–8,000	101 (16.2%)
8,001−−10,000	82 (13.2%)
10,001–15,000	93 (15.0%)
15,001–20,000	80 (12.9%)
20,000 and more	78 (12.5%)
Whether currently or previously had any chronic disease	
Yes	108 (17.4%)
No	514 (82.6)
Disease condition	
High blood pressure	40 (6.4%)
Coronary heart disease	6 (1.0%)
Diabetes	19 (3.1%)
Cancer	23 (3.7%)
Other	18 (2.9%)
Family suffering from chronic disease	
Yes	289,46.5%
No	333,53.5%
Family disease condition	
High blood pressure	211 (33.9%)
Coronary heart disease	58 (9.3%)
Diabetes	127 (20.4%)
Cancer	30 (4.8%)
Other	11 (1.8%)
Awareness	
Yes	274 (44.1%)
No	348 (55.9%)
Accepted before	
Yes	15 (2.4%)
No	607 (97.6%)
Necessity	
Yes	418 (67.2%)
No	204 (32.8%)
Awareness of expense of HaH services reimbursement	
Available to reimburse	153 (24.6%)
Not available to reimburse	78 (12.5%)
Unclear	391 (62.9%)
Ideal service provider	
Doctors and nurses of community hospitals	141 (22.7%)
Doctors and nurses of central hospitals	373 (60.0%)
Do not mind	97 (15.6%)
Other	11 (1.8%)
Frequency of ward rounds by doctors	
Once a week	95 (15.3%)
Twice or three times a week	173 (27.8%)
4–5 times a week	31 (5.0%)
Once a day	67 (10.8%)
Twice a day	74 (11.9%)
According to my demands	182 (29.3%)
Ideal proportion of HaH expenses that account for family income	
20% below	424 (68.2%)
20−30%	145 (23.3%)
30−40%	31 (5.0%)
40% and more	22 (3.5%)
The attitude toward staff from central hospitals providing service	
Very much hoping	338 (54.3%)
Somewhat hoping	226 (36.3%)
Do not mind	40 (6.4%)
Do not hope	18 (2.9%)
Willingness	
Yes	550 (88.4%)
No	72 (11.6%)

Residents' Awareness of, Willingness to Accept, and Demands Regarding HaH Services

The data from this study indicate that 55.9% of participants were not aware of HaH services, while most of the subjects (88.4%) were willing to accept them. Only 2.4% of residents had accepted HaH care before this survey. In this study, 418 (67.2%) of individuals thought that HaH services were necessary. A total of 360 (57.9%) residents were willing to accept better companionship, and 253 (40.7%) were willing to accept this for convenience. Details are shown in **Table 1**.

TABLE 2 | Chi-test of the willingness to accept HaH services.

	Resident's personal characteristics	Categories	Willingness to accept HaH services		*P*-Value
			Yes *n* (%)	No *n* (%)	
Predisposing factors	Educational background	Primary school and below	45 (8.2)	8 (11.1)	<0.001
		Junior high school	81 (14.7)	23 (31.9)	
		High school	39 (7.1)	10 (13.9)	
		College degree	172 (31.3)	18 (25.0)	
		Bachelor degree and above	213 (38.7)	13 (18.1)	
	Occupation	Mangers, public institutions, or professional personnel	280 (50.9)	18 (25.0)	<0.001
		Workers (production or transportation equipment operators and related personnel)	23 (4.2)	8 (11.1)	
		Farmers	50 (9.1)	8 (11.1)	
		Retirees	101 (18.4)	15 (20.8)	
		Others	15 (2.7)	6 (8.3)	
		Unemployed	81 (14.7)	17 (23.6)	
	Awareness	Yes	259 (47.1)	15 (20.8)	<0.001
		No	291 (52.9)	57 (79.2)	
	Necessity	Yes	402 (73.1)	16 (22.2)	<0.001
		No	148 (26.9)	56 (77.8)	
Enabling factors	Health insurance	Yes	507 (92.2)	53 (73.6)	<0.001
		No	43 (7.8)	19 (26.6)	
	Family monthly income	6,000 below	152 (27.6)	36 (50.0)	0.001
		6,000–8,000	87 (15.8)	14 (19.4)	
		8,001–10,000	75 (13.6)	7 (9.7)	
		10,001–15,000	86 (15.6)	7 (9.7)	
		15,001–20,000	78 (14.2)	2 (2.8)	
		20,000 and more	72 (13.1)	6 (8.3)	
HaH-related demand factors[a,b]	Ideal service provider	Doctors and nurses of community hospitals	128 (23.3)	13 (18.1)	<0.001
		Doctors and nurses of central hospitals	344 (62.5)	29 (40.3)	
		Do not mind	68 (12.4)	29 (40.3)	
		Other	10 (1.8)	1 (1.4)	
	Ideal frequency of ward rounds by doctors	Once a week	87 (15.8)	8 (11.1)	0.002
		Twice or three times a week	161 (29.3)	12 (16.7)	
		4–5 times a week	30 (5.5)	1 (1.4)	
		Once a day	57 (10.4)	10 (13.9)	
		Twice a day	56 (10.2)	18 (25.0)	
		According to my demands	159 (28.9)	23 (31.9)	
	Attitude toward staffs from central hospitals provide service	Very much hoping	324 (58.9)	14 (19.4)	<0.001
		Somewhat hoping	200 (36.4)	26 (36.1)	
		Do not mind	21 (3.8)	19 (26.4)	
		Do not hope	5 (0.9)	13 (18.1)	

[a] *HaH, Hospital-at-Home services.*
[b] *Missing data are not included in the values.*

Chi-Test of the Willingness to Accept HaH Services by Predisposing Variables, Enabling Variables, Need Factors, and HaH-Related Demands

The chi-square test detected the potential factors that affected the likelihood of agreeing to HaH services. The participants' educational background, occupation, health insurance status, source of revenue, monthly income, family monthly income, awareness of HaH services, ideal frequency of ward rounds, ideal service providers, and attitudes toward doctors and nurses from the central hospitals that provided services may affect their willingness to accept HaH care (**Table 2**).

Correlation Analysis Among the Independent Variables

The results of the correlation analysis tested the collinearity between the independent variables. The results indicated that there are significant correlations between the variables, especially between demographic variables such as educational background, occupation, and health insurance, which may affect the research results. Therefore, rigorous statistical methods were required. Stepwise (forward) logistic regression models were run to minimize the effect of the correlation between variables (**Table 3**).

Comparison of the Willingness to Accept HaH Services by Predisposing Variables, Enabling Variables, Need Factors, and HaH-Related Demands

A stepwise logistic regression model was used to identify the variables associated with the willingness to accept HaH services, and the final regression model indicated that being enrolled in health insurance (OR = 2.170, 95% CI: 1.003–4.697), an awareness of the necessity of HaH services (OR = 4.721, 95% CI: 2.471–9.019), very much hoping that staff from central hospitals would be the service providers (OR = 20.299, 95% CI: 5.718–72.068), and somewhat hoping that staff from central hospitals would be the service providers (OR = 9.139, 95% CI: 2.714–30.775) were the factors associated with a greater willingness to accept HaH services (**Table 4**).

DISCUSSION

To our knowledge, this study is the first to explore individuals' awareness of and willingness to accept HaH services that focuses on the demands related to HaH services based on the Andersen–Newman behavior model. The findings might serve as guidelines for future HaH promotion and implementation. Our findings emphasize the impact of HaH-related variables such as the awareness of HaH services, service demands, and reimbursement demands on the acceptance of HaH services among individuals in Chengdu City. In contrast to a similar study conducted in Singapore, the vast number of subjects in this study would accept HaH services (13). This phenomenon can be explained by the differing health care service models and resource allocation between China and Singapore. Singapore not only has a dual system of health care services, with a public system provided by the government and a private system provided by the private sector but also has 24.60 medical doctors and 62.43 nursing personnel per 10,000 people (19). In China, medical and health institutions are divided into public and socially run categories. Public medical institutions are the main medical service providers, and they are supplemented by socially run medical institutions, with 22.27 medical doctors and 30.83 nursing personnel per 10,000 people, which are both lower than in Singapore (19). Therefore, we infer that Chinese residents may have to spend more time waiting for effective treatment, as China's health care human resources are more limited. HaH services have been proven to be effective in saving time and alleviating the shortage of medical resources; therefore, Chinese residents are more willing to accept them. Individuals' willingness to accept HaH services is connected to their health insurance status, awareness of their necessity, and attitudes toward staff from the central hospitals that offer HaH services.

The findings of this study indicate that compared to the awareness of HaH services, there was a greater willingness to accept HaH care among the subjects. Because of the shortage of medical resources in recent years, healthcare professionals cannot provide adequate medical services to every patient, which results in patients' needs not being fully met and leads to poor healthcare experiences (20, 21). In addition, the unfamiliarity of the hospital environment can harm patients' mental health, which is not conducive to their recovery (22). Prolonged hospitalization can lead to additional risks, such as delirium and infections (23–28). These problems are mitigated by HaH services, which might be why most of the subjects were willing to accept them. However, there is inadequate advertising and utilization of HaH services. Therefore, the awareness of HaH care is not high. Accordingly, concrete measures are needed to raise awareness of the concept, strengths, and functions of HaH services, such as information disseminated through television, newspapers, and applications, to increase residents' understanding of these services. Individuals' awareness of the necessity of HaH services is related to their willingness to accept HaH services. According to the Andersen–Newman behavioral model, an individual's perception of a medical service before receiving it can influence his or her willingness to accept this service (18). After hearing an explanation of the concept and function of HaH services, subjects might be more aware of the necessity of developing HaH care to ameliorate the shortage of medical resources. Therefore, those who are more aware of the necessity of HaH services might perceive more benefits and exhibit a higher willingness to accept HaH services.

As an enabling factor, health insurance coverage is associated with the willingness to accept HaH services. This result is similar to a study that argued that individuals enrolled in health insurance are more willing to maintain contact with family doctors (29). A previous study confirmed that health insurance status varies by socioeconomic status. Individuals not enrolled in health insurance may have a lower socioeconomic status; therefore, they cannot afford the full cost of HaH care (30, 31).

TABLE 3 | Correlation between the independent variables.

	Educational background	Occupation	Health insurance	Family monthly income	Awareness	Necessity	Ideal service providers	Ideal frequency of ward rounds	The attitude toward staff from central hospitals providing service
Educational background	1.000								
Occupation	−0.604**	1.000							
Health insurance	0.378**	−0.276**	1.000						
Family monthly income	0.600**	−0.512**	0.237**	1.000					
Awareness	−0.292**	0.307**	−0.187**	−0.296**	1.000				
Necessity	−0.349**	0.338**	−0.225**	−0.316**	0.351**	1.000			
Ideal service providers	−0.174**	0.137**	−0.073	−0.117**	0.127**	0.136**	1.000		
Ideal frequency of ward rounds	−0.236**	0.152**	−0.042	−0.112**	0.160**	0.124**	0.227**	1.000	
The attitude toward staff from central hospitals providing service	−0.173**	0.174**	−0.126**	−0.239**	0.135**	0.300**	0.114**	0.114**	1.000

***P < 0.001.*

TABLE 4 | Comparison of the willingness to accept HaH services by predisposing variables, enabling variables, need factors, and HaH-related demands.

Independent variables	*B*	SE	Wals	df	*P*-Value	OR	95% confidence interval	
							Lower	Upper
Health insurance (REF: no)	0.775	0.394	3.867	1	0.049	2.170	1.003	4.697
Necessity (REF: no)	1.552	0.330	22.083	1	0.000	4.721	2.471	9.019
Ideal service provider (REF: doctors and nurses of community hospitals)			10.703	3	0.013			
Doctors and nurses of central hospitals	0.163	0.402	0.164	1	0.686	1.177	0.535	2.587
Do not mind	−0.962	0.433	4.938	1	0.026	0.382	0.163	0.893
Other	−0.048	1.177	0.002	1	0.967	0.953	0.095	9.562
Attitude toward staff from central hospitals providing service (REF: do not hope)			36.766	3	0.000			
Very much hoping	3.011	0.646	21.688	1	0.000	20.299	5.718	72.068
Somewhat hoping	2.213	0.619	12.756	1	0.000	9.139	2.714	30.775
Do not mind	0.755	0.684	1.218	1	0.270	2.127	0.557	8.126
Constant	−2.189	0.880	6.182	1	0.013	0.112		

Being covered by health insurance can reduce the cost of medical services and alleviate patients' stress, which enables them to be available to accept health services (29). Accordingly, individuals not enrolled in health insurance cannot afford the fees for HaH services. Therefore, wider enrollment in health insurance is key to the promotion of HaH services. More mature compensatory policies are needed, and the experience of developed countries is enlightening. For instance, in Norway, home care is free for patients, and in Canada, it is funded by the government (32). Moreover, the results of this study showed that 391 participants were not clear about the cost of HaH services, and most hoped that it would be <20% of their monthly family income. Many countries where HaH services have been widely implemented, such as Australia and the UK, have single-payer systems and strong imperatives to keep medical costs low; related systems need to control the overall cost of HaH care and set proper charging standards (33).

The vast number of the subjects in this study (54.3%) hoped that staff from central hospitals would offer HaH services. This study also found that the participants who very much or somewhat hoped that staff from central hospitals would be service providers were inclined to be more accepting of HaH services. However, in China, HaH care is mostly performed by community staff with only a college degree or below and limited medical skills to meet client requirements (34, 35). Moreover, highly qualified health staff in China always work in central hospitals and do not have time to provide HaH services (35). This phenomenon can be explained by the siphon effect of high-grade hospitals in China; these hospitals attract both large numbers of patients, which gives them a strong "resource siphon" ability, and qualified doctors to actively practice there for more opportunities and career resources (36). However, the workload in central hospitals in China is too heavy for these staff to provide extra HaH services (35). In Spain, each HaH unit consists of at least an internal medicine specialist and a general physician who incorporate specialists such as pulmonologists, geriatricians, and general surgeons. Nurses who provide HaH services must also be trained in hospital specialties and obtain a qualification certificate

(37). In Sweden, nurses who provide home care services are required to have at least a bachelor's degree, and a master's degree is preferable (38). Therefore, related departments should make efforts to encourage health systems to develop HaH services and provide adequate resources for this development to inspire well-trained professionals to participate (13). The experiences of other countries can be studied to understand how to launch HaH services. For instance, it would be useful to develop a curriculum on medical care at home, promote practical home care skills, and train students on the use of portable medical devices to cultivate talent with at least a bachelor's degree in home care (35).

Interestingly, one of the findings of this research contradicts previous literature: socioeconomic factors were not associated with an individual's willingness to accept HaH care (30, 31). As there is a linkage between enrollment in health insurance and an individual's educational background, occupation, and income, it appears that enrollment in health insurance might act as a mediating variable between socioeconomic factors and willingness to accept HaH services. People who have high earnings with higher educational backgrounds care a great deal about their health; therefore, they pay health insurance enrollment fees (39). However, further analysis is needed to better explain this phenomenon. Individuals' health status was also not associated with their willingness to accept HaH services, which might be explained by the fact that there were only 622 participants in this study, and most did not have a chronic disease. Further investigation is also needed on this issue.

China has a total of 1.4 billion people, which accounts for nearly one-third of the total population of Asia, and there are similarities between the health care delivery systems in mainland China and both Japan and South Korea. Therefore, because of the similar health care systems and population ratios in China, we believe that the results of this study may have some generalizable implications. However, due to the differences in the per capita medical human resources and economic development levels, whether the results of this study are representative of Asia requires further discussion.

This study has certain limitations. First, it used a convenience sampling method, not random sampling, which may have resulted in bias. Second, the sample size was only 622, which may lead to the sample being unrepresentative. For example, the gender ratio in Chengdu is nearly 1:1 (50.54%:49.46%) (40); however, male respondents accounted for only 26.7% of the sample in this study. A smaller sample size might fail to reflect the real willingness of the male population. In addition to the male population, the other groups that accounted for a minor proportion, such as workers' estimated willingness (e.g., production or transportation equipment operators and related personnel), may be affected. Third, this study was a cross-sectional study that was unable to explore how individuals' willingness to accept HaH care is shaped. Therefore, longitudinal studies are needed. Fourth, the survey utilized an online method to collect data, and those who were not familiar with the internet may be under-represented. Thus, this study's participants might not represent elderly individuals with more healthcare needs, whose views are also important. However, this study investigated the willingness of residents to accept HaH services and demonstrated the gap between residents' actual demands and willingness to accept HaH services. The results of this study are significant for both the medical system and residents. In terms of the medical systems' viewpoints, a better understanding of residents' perceptions and demands can help develop more targeted services and effective advertising policies to lead to a higher willingness to accept HaH services. Therefore, HaH services can be widely accepted to alleviate medical resource insufficiency. In terms of residents' viewpoints, a better understanding of their opinions and demands can result in better service, more reasonable charging standards, and regular work procedures of HaH care to ensure that people can truly benefit from HaH services.

CONCLUSION

This study shows that there was a lower awareness of but higher willingness to accept HaH services among the participants, which indicates that the awareness of HaH services among the residents of Chengdu City has room for growth. The willingness to accept HaH services among individuals was associated with enabling factors such as health insurance enrollment, predisposing factors such as an awareness of the necessity of HaH services, and HaH-related demand factors such as attitudes toward staff from central hospitals as service providers. Therefore, effective policies and practical measures must be created to motivate the development of HaH services.

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 West China Hospital, Sichuan University. The patients/participants provided their written informed consent to participate in this study. 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

JW and YW were involved in the design of the study, acquisition of data, and development of the statistical framework, and they reviewed the manuscript. MW and XH were involved in the study design and development of the analysis framework. SX and HH developed the statistical framework for data analysis, conducted the statistical analysis, interpreted the data, and drafted the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.823384/full#supplementary-material

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Age-Related Sex Disparities in Esophageal Cancer Survival: A Population-Based Study in the United States

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Background: The association between sex and the survival of patients with esophageal cancer (EC) remains controversial. We sought to systematically investigate sex-based disparities in EC survival using the Surveillance, Epidemiology, and End Results (SEER) registry data from the United States.

Methods: Patients with EC diagnosed from 2004 to 2015 registered in the SEER database were selected. The association between sex and cancer-specific survival (CSS) was evaluated using survival analysis. The Inverse Probability Weighting (IPW) approach was applied to reduce the observed bias between males and females. Subgroup analyses were used to investigate the robustness of the sex-based disparity and to explore potential interaction effects with other variables.

Results: Overall, 29,312 eligible EC patients were analyzed, of whom 5,781 were females, and 23,531 were males. Females had higher crude CSS compared to males (10-year CSS: 24.5 vs. 21.3%; $P < 0.001$). Similar results were obtained after adjusting for selection bias using the IPW approach and multivariate regression. Subgroup analyses confirmed the relative robustness of sex as a prognostic factor. However, significant interactions were observed between sex and other variables, such as age, race, tumor grade, histology, and treatment modality. In particular, there was no survival advantage for premenopausal females compared to their male counterparts, but the association between sex and EC survival was prominent in 46–55-year-old patients.

Conclusions: Female EC patients had better long-term survival than males. The association between sex and EC survival vary according to age, race, tumor grade, histology, and treatment modality. Sex-based disparity in EC-specific survival was age-related in the United States population.

Keywords: esophageal cancer, survival, SEER database, age-related, sex disparities

INTRODUCTION

Esophageal cancer (EC) is one of the most lethal gastrointestinal tumors, ranking sixth in cancer-related deaths. On a global scale, EC was responsible for one in every 18 cancer deaths in 2020 (1). EC is characterized by a unique geographical distribution, with the highest incidences recorded in East Asia and Southeast Africa and the lowest incidences in West Africa (2). The predominant histological types of EC are adenocarcinoma and squamous cell carcinoma. Historically, esophageal squamous cell carcinoma (ESCC) is the most prevalent pathological type. However, the incidence of esophageal adenocarcinoma (EAC) has increased in the last five decades. Esophageal adenocarcinoma has become the most common esophageal malignancy in western countries (3).

Male predominance is a significant epidemiological feature of EC. Globally, males have a 2.58-fold higher risk of EC incidence and a 2.59-fold higher risk of EC mortality than their female counterparts (1). The association between sex and EC survival has previously been examined in a series of studies under different circumstances (4–10). Previous studies have suggested a survival advantage for females compared with males, especially among younger women (4–6). Furthermore, Rowse et al. reported that women were correlated with improved complete pathologic response rates after neoadjuvant chemotherapy and higher recurrence-free survival rates after surgical intervention (7). However, some other studies failed to detect survival differences between males and females (8–10). Taken together, the association between sex and EC survival remains controversial.

Evidence from previous studies showed that sex-based disparities in EC survival could be partly attributed to sex-specific risk exposures, such as age at diagnosis, race, socioeconomic status, smoking, drinking, and histological types (2, 11, 12). However, sex-based disparities in cancer survival are sustained after adjusting for these known risk factors in many cases. In many studies, 55 years of age was generally used as a cut-off age to enter menopause because age is linked to changes in estrogen levels in the life cycle of females (5, 6). Mathieu et al. found that the annual percentage change in esophageal adenocarcinoma incidence rates for female patients during the same period was negatively correlated with ages 50–54 years and 60–64 years (13). Although the incidence of esophageal adenocarcinoma increased in male and female patients, the sex ratio across age peaked in ages 50–54 years and decreased thereafter. Insights from epidemiological studies and experimental research suggested that sex hormone may be an underlying mechanism that drives the survival advantage of females compared to males in patients with EC (4, 14, 15). Given the rationale mentioned above, the present study systematically examined the sex-based disparity in EC survival using the large-scale population obtained from the Surveillance, Epidemiology, and End Results (SEER) registry data in the United States.

PATIENTS AND METHODS

Study Population

Research data were obtained from the SEER registry database after receiving approval for the use of data. We analyzed the database: the Incidence—SEER 18 Regs Custom Data (with additional treatment fields). We included data for EC cases diagnosed between 2004 and 2015, when the sixth edition of the American Joint Committee on Cancer (AJCC) staging system was accessible in the SEER program. Essential inclusion criteria were pathologically confirmed EC with available age, sex, race record, tumor grade, stage, and follow-up data. Any user can obtain the related data using SEER*Stat 8.3.8 software, given that they have been granted permission to access the SEER Program. Ethical approval was not necessary for this study with the publicly available database, as we had adhered to the terms for data usage.

Study Variables and Primary Endpoint

We extracted demographic and clinicopathological characteristics from the SEER database directly using the SEER*Stat 8.3.8 software. The variables investigated were age at diagnosis, sex, tumor grade, histological classifications, disease stage, surgery recode, radiation recode, chemotherapy recodes, year of diagnosis, survival status, and survival time. Cancer-specific survival (CSS) was established as the primary endpoint in the current study. CSS was measured from the date of diagnosis of the disease to the date of death from EC. CSS was established as the primary end point, with the aim of reducing underlying bias caused by sex-based-specific differences other than the EC.

Statistical Analysis

The Chi-square test was performed to examine the distributional differences in patient characteristics between male and female patients. CSS was estimated using the Kaplan-Meier approach. Survival differences were compared using the log-rank test. The association between sex and EC survival was evaluated using univariate and Inverse Probability Weighting (IPW)-adjusted Cox proportional hazards models. The IPW approach was applied to control observed differences in patient characteristics between males and females and then examined the exact association between sex and survival (16). In particular, IPWs were calculated based on propensity scores estimated from a logistic regression model using selected baseline variables. The calculation formula was as follows: $W = \frac{Z}{e} + \frac{1-Z}{1-e}$, where Z indicates sex (Z = 0 for male vs. Z = 1 for female), and e is the propensity score. We estimated the average association between sex and survival using IPWs, yielding a synthetic population where the observed baseline variables could not be confounded. Covariate balances before and after IPW were evaluated using absolute standardized differences (ASD). A difference of 0.05 or less represented an excellent balance. Further subgroup analyses were performed to investigate the robustness of the sex-based association and to examine potential interaction effects between sex and other variables, especially with age. Given that

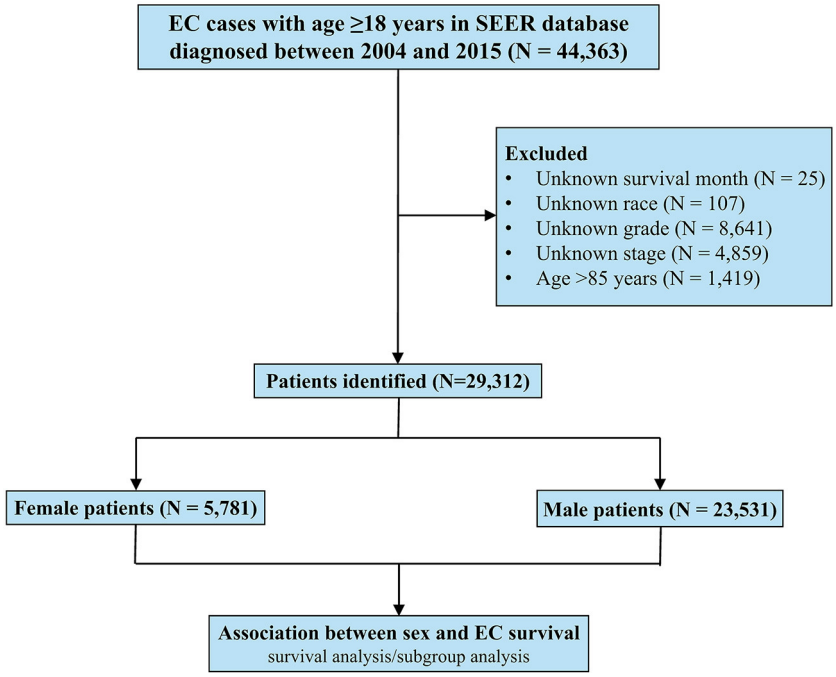

FIGURE 1 | Patient selection flowchart.

estrogen levels might play an essential role in mediating the impact of sex on EC survival. The associations between sex and EC survival were examined in different age subgroups, 18–45, 46–55, and >56 years, corresponding to premenopausal, perimenopausal, and postmenopausal periods, respectively, over the female lifecycle (17, 18). Finally, EAC and ESCC can actually be regarded as two very distinct diseases with different pathogenesis, epidemiology, and tumor biology. The robustness of age-related sex-based disparities on EC survival was also examined in EAC and ESCC, respectively.

All statistical analyses were performed using the R software (version 4.1.0). All tests were two-sided. A *P*-value of 0.05 or less was set as statistically significant.

RESULTS

Patient Characteristics

This study included 29,312 EC patients diagnosed from 2004 to 2015 registered in the SEER database, of whom 5,781 were females and 23,531 were males (**Figure 1**). The patient characteristics stratified by sex are listed in **Table 1**. Female patients were significantly associated with older age (median age, 68 vs. 65 years, $P < 0.001$), black race (14.9 vs. 9.3%, $P < 0.001$), and squamous carcinoma (55.5 vs. 26.4%, $P < 0.001$). Male patients had higher proportions of worse differentiated tumors (54.5 vs. 49.0%, $P < 0.001$) and more advanced diseases (metastatic EC, 38.4 vs. 30.9%, $P < 0.001$), and were more likely to receive both surgery (31.3 vs. 26.3%, $P < 0.001$) and chemotherapy (66.6 vs. 61.9%, $P < 0.001$).

Association Between Sex and EC Survival

After a median follow-up of 75 [95% confidence interval (CI), 74–77] months, 3,594 deaths attributed to EC (62.2%) were recorded in females and 15,143 (64.4%) in males. In the unadjusted Kaplan-Meier analysis, female patients showed a higher CSS rate [10-year CSS: 24.5% (95% CI, 23.0–26.1) vs. 21.3% (95% CI, 20.5–22.0); HR: 1.06 (95% CI 1.02–1.10), $P = 0.001$; **Figure 2A**] and overall survival (OS) rate [10-year OS: 11.9% (95% CI, 10.8–13.1) vs. 10.2% (95% CI, 9.7–10.8); HR: 1.06 (95% CI 1.03–1.10), $P < 0.001$; **Figure 2B**] compared with male patients. Following IPW procedures, excellent balances were achieved between the two groups of sexes regarding all the patient characteristics examined (**Supplementary Figure 1**). IPW-adjusted Kaplan-Meier analyses also demonstrated a significantly better CSS rate [10-year CSS: 24.4% (95% CI, 22.8–26.2) vs. 21.1% (95% CI, 20.4–21.9); IPW-adjusted HR: 1.07 (95% CI 1.03–1.12), $P < 0.001$; **Figure 2C**] and OS rate [10-year OS: 24.4% (95% CI, 22.8–26.2) vs. 21.1% (95% CI, 20.4–21.9); and IPW-adjusted HR: 1.08 (95% CI 1.04–1.12), $P < 0.001$; **Figure 2D**] for female patients than for male patients. Further multivariate analyses revealed that sex was identified as an independent prognostic factor for CSS [HR: 1.14 (95% CI 1.09–1.18), $P < 0.001$] and OS [HR: 1.16 (95% CI 1.12–1.20), $P < 0.001$] in multivariate Cox regression analysis after adjustment for demographic, clinicopathological, and therapeutic factors.

Subgroup Analyses and Interaction Effects

The association between sex and EC survival was further explored in subgroups defined by age, race, tumor grade, histology, disease stage, treatment modalities, and year of diagnosis. The results

TABLE 1 | Patient characteristics stratified by sex.

Characteristics	Female (*N* = 5,781)	Male (*N* = 23,531)	*P*-value
Age (years)	68.0 (59.0–76.0)	65.0 (58.0–73.0)	<0.001
Race			<0.001
Black	862 (14.9)	2,192 (9.3)	
White	4,592 (79.4)	20,205 (85.9)	
Others	327 (5.7)	1,134 (4.8)	
Tumor grade			<0.001
Grade I	339 (5.9)	1,380 (5.9)	
Grade II	2,612 (45.2)	9,346 (39.7)	
Grade III	2,721 (47.1)	12,367 (52.6)	
Grade IV	109 (1.9)	438 (1.86)	
Histology			<0.001
Adenocarcinoma	2,314 (40.0)	16,263 (69.1)	
Squamous carcinoma	3,207 (55.5)	6,204 (26.4)	
Others	260 (4.5)	1,064 (4.5)	
Disease stage			<0.001
Localized EC	3,994 (69.1)	14,500 (61.6)	
Metastatic EC	1,787 (30.9)	9,031 (38.4)	
Surgery			<0.001
No or unknown	4,275 (73.9)	16,168 (68.7)	
Yes	1,506 (26.1)	7,363 (31.3)	
Radiation			0.149
No or unknown	2,356 (40.8)	9,838 (41.8)	
Yes	3,425 (59.2)	13,693 (58.2)	
Chemotherapy			<0.001
No or unknown	2,204 (38.1)	7,858 (33.4)	
Yes	3,577 (61.9)	15,673 (66.6)	
Year of diagnosis			0.044
2004–2007	1,896 (32.8)	7,317 (31.1)	
2008–2011	1,898 (32.8)	7,906 (33.6)	
2012–2015	1,987 (34.4)	8,308 (35.3)	

EC, esophageal cancer.

of the CSS subgroup analyses are displayed in a Forest plot (**Figure 3**). The forest plot confirmed the relative robustness of sex as a prognostic factor in many subgroups. However, some significant interactions were observed between sex and other variables on EC survival, such as age, race, tumor grade, histology, radiotherapy, and chemotherapy. The association between sex and EC survival was more marked in patients aged 46–55 years, black and white race, advanced differentiated or squamous carcinoma, and patients who received radiotherapy and chemotherapy.

Age-Dependent Association Between Sex and EC Survival

We further examined the association between sex and EC survival in different age subgroups. The patient characteristics stratified by sex across different age groups are summarized in **Supplementary Tables 1–3**. We observed a significant interaction between age and sex (P for interaction < 0.05). Kaplan-Meier analyses without adjustment did not show a survival advantage for premenopausal females compared to their male counterparts [10-year CSS: 24.1% (95% CI, 17.2–33.8) vs. 21.7% (95% CI, 18.5–25.6); HR 1.01, 95% CI 0.82–1.24; $P = 0.944$; **Figure 4A**]. Notably, the survival advantage associated with females was most evident in perimenopausal patients [10-year CSS: 30.2% (95% CI, 26.2–34.8) vs. 21.8% (95% CI, 20.1–23.6); HR 1.21, 95% CI 1.09–1.34; $P < 0.001$; **Figure 4B**]. However, such sex benefits declined in postmenopausal patients [10-year CSS: 23.6% (95% CI, 22.0–25.3) vs. 23.1% (95% CI, 20.2–22.0); HR 1.04, 95% CI 1.00–1.08; $P = 0.04$; **Figure 4C**]. Similarly, the IPW approach was applied to control for the observed bias, resulting in well-balanced samples (**Supplementary Figures 2–4**). The IPW-adjusted Kaplan-Meier analyses yielded comparable results as mentioned above (**Figures 4D–F**).

Histology-Based Age-Related Sex-Based Disparities in EC Survival

Given that EAC and ESCC are two very distinct diseases with different pathogenesis, epidemiology and tumor biology. The robustness of age-related sex-based disparities on EC survival was also examined for EAC and ESCC, respectively. The same statistical strategies were used to control the observed bias (**Supplementary Figures 5, 6**). We found that women were associated with worse CSS and OS compared to men, regardless of histology (**Supplementary Figures 7, 8**). In the subgroup analysis that evaluated age-related sex-based disparities in different histology subtypes, similar age-dependent sex-based disparities in the total population were observed. That is, the survival advantage associated with females was not significant in the premenopausal period (**Supplementary Figures 9A,B**, **10A,B**), but was marked in the perimenopausal period (**Supplementary Figures 9C,D**, **10C,D**) and declined in the postmenopausal period (**Supplementary Figures 9E,F, 10E,F**).

DISCUSSION

Mass data from the SEER 18 Registry database allowed us to investigate the sex-based disparity in EC survival in multiple dimensions. To our knowledge, this is one of the most extensive cohort studies to examine the sex-based disparity in EC. We demonstrated a significant survival advantage of females over males in patients with EC. Sex was identified as an independent prognostic factor. Sex-based disparities in EC survival were significantly correlated with age, race, tumor grade, histology, and therapeutic pattern. In particular, sex-based disparities in EC-specific survival appeared to be age dependent.

Over the past few decades, the association between sex and EC survival have been studied. Most of the previous studies focused on studying trends and prognosis (3, 9, 19, 20). The potential interaction with underlying confounding factors has not been fully considered when describing differences in survival based on sex. It has been frequently assumed that sex-based differences are constant throughout the life

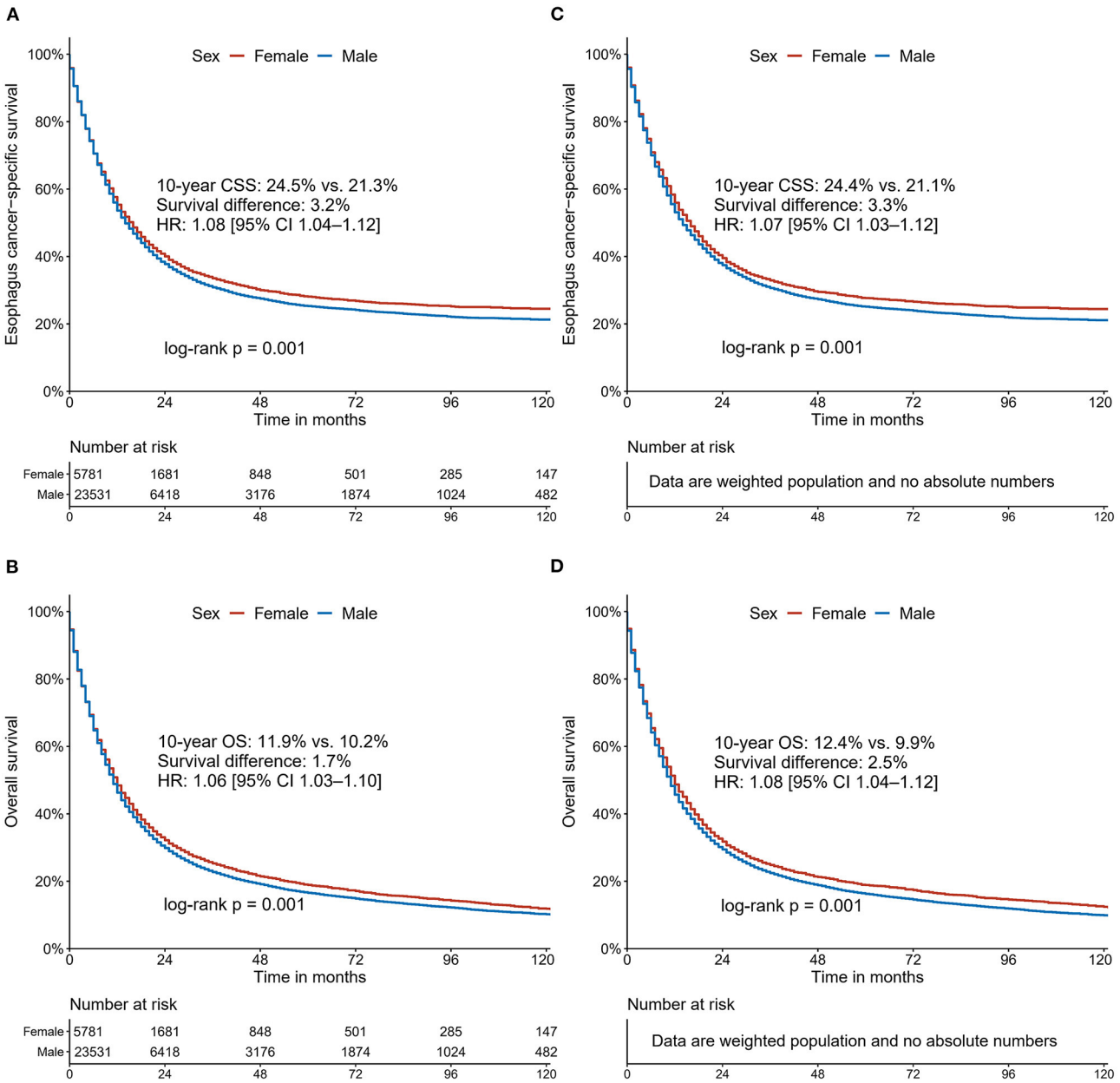

FIGURE 2 | Cancer-specific survival and overall survival curves stratified by sex for patients with esophageal cancer: unadjusted **(A,B)**; Inverse Probability Weighting-adjusted **(C,D)**.

cycle. Other shortcomings include inadequate follow-up, potential selection bias, small sample size, and insufficient bias adjustment. Due to different research settings, these problems will increase the complexity and uncertainty when investigating the association between sex and EC survival. Given the lack of convincing evidence, we examined the association between sex and EC survival using an extensive patient sample with sufficient follow-up duration. The IPW method was used to minimize the underlying confusion and selection bias. At the same time, the interaction of other factors on sex-based survival differences has been studied, and the age-related associations of sex on mortality attributed to EC has been further evaluated.

In previous studies, there has been controversy about the association between sex and the survival of patients with EC. Our findings are in line with the results of several previous studies. Some retrospective series have shown that sex is significantly associated with the prognosis of EC (3, 9, 19, 20). Wang et al. reported that females diagnosed with EC had a significantly prolonged 5-year survival rate than males (female vs. male: 48.2

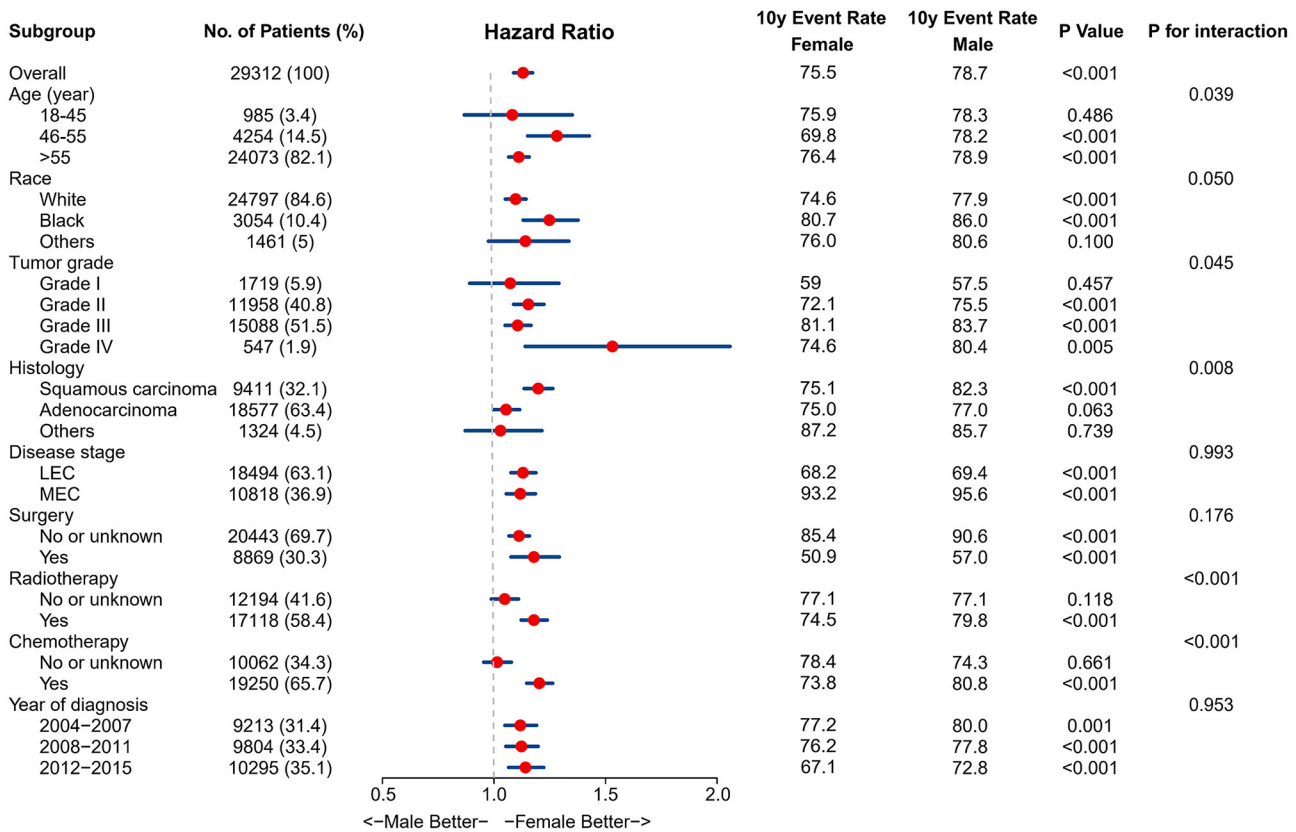

FIGURE 3 | Results for the subgroup analyses and interaction tests of sex-based effects on cancer-specific survival are summarized in a Forest plot.

vs. 28.7%, $P = 0.003$) (21). Similarly, Bohanes et al. demonstrated that women had a more prolonged EC-specific survival than men, regardless of metastatic EC and localized EC cohorts (5). However, another study that included 1,718 Chinese and 1,624 white ESCC patients came to the opposite conclusion (8). Sex was no longer an independent prognostic factor in Chinese and white patients living in the United States (8). In this study, we found that sex was an independent prognostic factor in patients with EC. Females showed higher CSS rates than males, even after adequately adjusting for confounding factors. Furthermore, subgroup analysis confirmed the relative robustness of sex as a prognostic factor.

Interestingly, we found that sex-based differences in survival interacted with age, race, tumor grade, histology, and treatment pattern. The association of sex-based differences and survival was even more profound in patients aged 46–55 years, black and white people, advanced differentiated or squamous carcinoma, and patients who received radiation therapy and chemotherapy. This finding may partially explain the discrepancy in the results of previous studies. Differences in the study population, age structure, and ethnic composition may lead to heterogeneous research results. In this study, we applied the IPW method to reduce the influence of these confounders when examining the association between sex and EC survival, increasing the credibility of our findings.

Our subgroup analysis detected a significant interaction effect between age and sex ($P < 0.05$). In addition, we explored the age-dependent relationship between sex and EC survival. Several previous studies have suggested that intrinsic biological sex hormones could be an underlying mechanism that explains the female advantage in cancer incidence and morbidity (6, 8, 9, 14, 22). Age 46–55 years is generally used as a surrogate for the perimenopausal period. Many studies divide patients into different age groups as a substitute for changes in sex hormone levels (5). Su et al. reported that females younger than 55 years had a reduced risk of dying of ESCC than males of similar age and women and men 55 years or older. Their results suggested that sex hormones may have a protective effect in female patients with EC (6). However, Bohanes et al. failed to explain the sex-based difference in EC survival attributed to hormone protection (5). They reported that females under 55 years of age and those 55 years or older with squamous cell LEC had better ECSS than men. However, only females under 55 years of age had longer ECSS than men in the metastatic squamous cell EC population. The results of the metastatic EC cohort are consistent with the phenomenon of sex hormone protection. Moreover, using the results of a localized EC cohort it is difficult to provide convincing evidence of sex hormone protection because sex-based differences of individuals aged over 55 years old seem to be more pronounced.

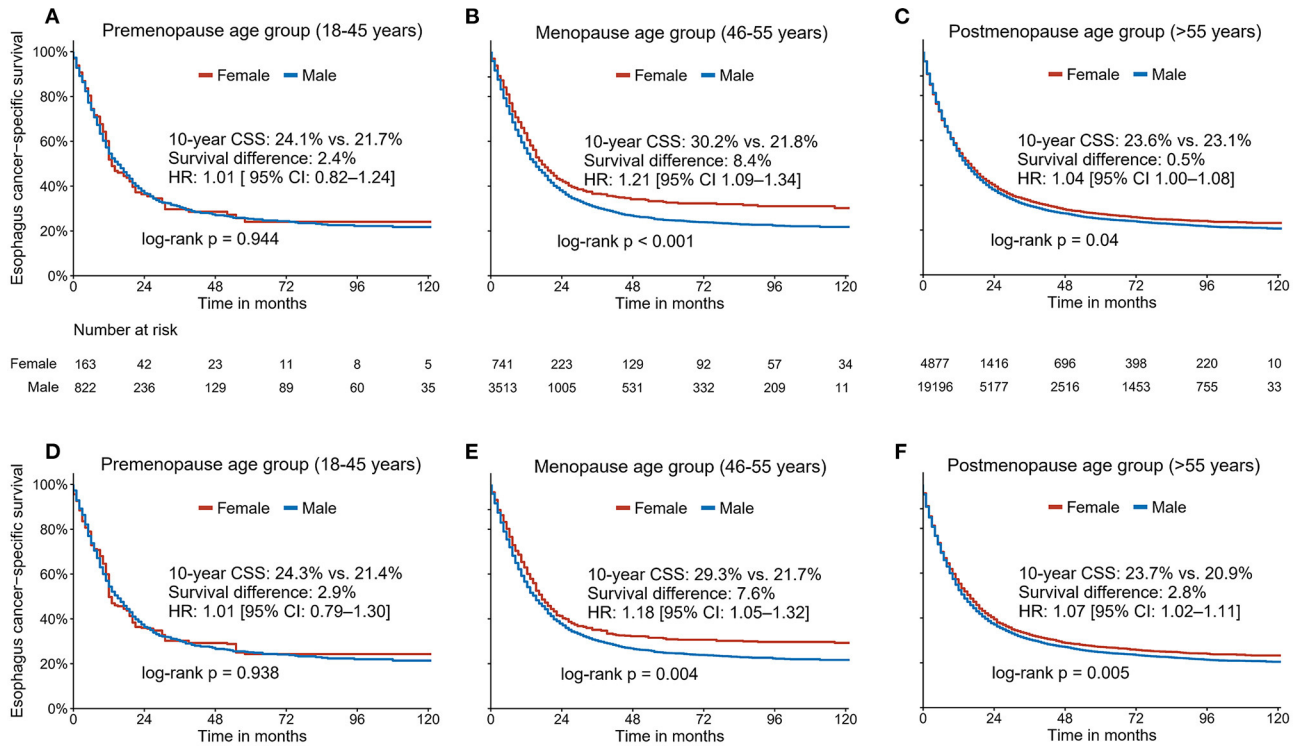

FIGURE 4 | The unadjusted **(A–C)** and Inverse Probability Weighting-adjusted **(D–F)** association between sex and cancer-specific survival in three different age groups (premenopausal age group: age ≤ 45 years; perimenopause age group: ages 46–55; and postmenopausal age group: age ≥ 56 years).

In this study, we divided the patients into three age subgroups: 18–45 years, 46–55 years, and >56 years old, corresponding to the premenopausal, perimenopausal, and postmenopausal periods of women's lifecycle, respectively, and further studied the relationship between sex and EC survival in these periods. Survival analysis showed that premenopausal women (18–45 years) did not have a survival advantage compared to men, and the female-associated survival advantage was evident in menopausal patients (46–55 years). However, this sex-based advantage declined in postmenopausal patients (>55 years). The findings were similar even after adjusting for many clinical parameters. Our results cannot explain the differences based on sex in EC survival possibly due to sex hormone protection. Some studies have reported that the estrogen level of menopausal women is significantly higher than that of premenopausal women, which might explain the apparent phenomenon of a female-related survival advantage in menopausal (46–55 years old) patients (23, 24). It is still challenging to use hormone protection to explain the disappearing survival advantage in premenopausal (18–45 years) and postmenopausal (>55 years) patients. Therefore, we believe that it may be inappropriate to solely explain sex-based differences in EC survival with changes in sex hormone levels. Future studies are needed to reveal the underlying mechanisms for this phenomenon. However, our results correct one misleading conclusion: It may not be appropriate to assume that sex-based differences persist throughout life. Except for sex hormones, the overall survival difference between male and female patients suggests that unexplained mediation factors may explain the age-dependent sex-based disparity in EC survival (25).

This study has some inevitable limitations that must be noted. First, the data were drawn from the SEER registry database. Detailed information on family income, medical insurance, education, smoking, and alcohol consumption is missing and was not considered in our analyses, which could differ between males and females. The above socioeconomic variables could play a role in the survival of EC patients (5, 12, 26–28). Potential interactions between sex and these socioeconomic variables should be considered if possible. Second, due to the nature of the retrospective design and registry database, data on serum sex hormone levels were unavailable. Using age as a surrogate for menopause may raise confounding bias. Third, the study population derived from the United States, and external validation of the results from other countries will enhance our findings. Lastly, though we have detected statistical significances, the absolute survival differences between males and females were not large in the entire cohort. Besides, we did not examine to what degree the sex-based disparities in the survival of EC could be explained by mediating or confounding effects.

In conclusion, female patients with EC had better CSS than their male counterparts. This sex-based disparity interacted with age, race, tumor grade, histology, and

therapeutic pattern. Sex-based disparity in EC-specific survival was age-related in the United States population. Future studies should continue to explore the potential causes of sex-based differences in survival in patients with EC.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

E-DS, Z-CM, and Z-FX designed the study and participated in the acquisition of data. Z-FX developed the methodology of the study, analyzed and interpreted the data, and wrote the manuscript. All authors reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Cost-effectiveness analysis of colonoscopy and fecal immunochemical testing for colorectal cancer screening in China

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Objective: This study aimed to evaluate the cost-effectiveness of the colorectal cancer screening in China, and that when the screening was implemented in a specific region.

Methods: A 13-state Markov model was established to compare four screening protocols, including annual fecal immunochemical testing (FIT1), biennial fecal immunochemical testing (FIT2), electronic colonoscopy every 10 years (e-CSPY10), and electronic colonoscopy every 5 years (e-CSPY5), with no screening from the perspective of Chinese healthcare system. The model simulated the health states of a cohort of 100,000 average-risk individuals aging from 50 to 75. Additionally, scenarios including the implementation in a specific region, starting from 40, and incompletely successful treatment of cancer were also analyzed.

Results: Annual and biennial FIT could save 8.13USD (US Dollar) and 44.96USD per person, and increase 0.0705QALYs (Quality-Adjusted Life Years) and 0.2341 QALYs compared with no screening, respectively. Annual FIT could decrease costs by 36.81USD per person and increase 0.1637 QALYs in comparison to biennial FIT. The results showed that both annual and biennial FIT for screening were dominant over no screening, and annual FIT was dominant over biennial FIT. The ICER (Incremental Cost-Effectiveness Ratio) for e-CSPY10 were 1183.51USD/QALY and 536.66USD/QALY compared with FIT1 and FIT2. The ICER for e-CSPY5 were 1158.16USD/QALY and 770.85USD/QALY compared with FIT1 and FIT2. And the ICER for e-CSPY5 relative to e-CSPY10 was 358.71USD/QALY. All the ICER values were lower than the economic threshold of 2021 Chinese GDP (Gross Domestic Product) per capita in 2021(12554.42USD).

Conclusions: It is worthwhile to popularize CRC screening in mainland China, as FIT always saving costs and colonoscopy is cost-effective. Regions with high

income can take electronic colonoscopy every 10 years, or even every 5 years into consideration when determining the specific strategies.

KEYWORDS

colorectal cancer, screening, electronic colonoscopy, fecal immunochemical testing, economic evaluation

Introduction

Colorectal cancer (CRC) is currently one of the most common and fatal cancers worldwide. In 2018, there were approximately 1.93 million new cases globally, ranking third in cancer incidence. Simultaneously, the number of deaths caused by CRC worldwide was approximately 940,000, ranking second among all cancers (1). In China, CRC was listed fourth and fifth in incidence and mortality in 2015, with 89,993 new cases and 44,361 deaths. The world standard rates of incidence and mortality were ∼17.12/100,000 and ∼7.85/100,000 (2), respectively. It is estimated that there will be 642,300 cases of CRC in China and 221,100 deaths by 2025 (3). The incidence of CRC increases substantially after the age of 50, peaking around 75 to 80 years old. CRC not only seriously deceases the quality of life but also poses a considerable economic burden. The average costs for the diagnosis and treatment of CRC in China have increased by 6.9 to 9.2% per year, and the personal medical expenses of patients within 1 year of a new diagnosis accounted for approximately 60% of their household income (4).

CRC is associated with various factors, including inflammatory bowel disease, family history of CRC, age over 50 years old, male gender, obesity, type 2 diabetes mellitus, unhealthy living habits, and gut microbiota (5–9). Most CRCs originate from precancerous lesions, which are mainly referred to as polyps. This process begins with abnormal crypts that evolve into polyps and eventually develop into cancer, taking about 10–15 years (10). In addition, the larger the diameter of the polyps, the more villi, and the higher the degree of atypicality, the higher the risk of canceration (11, 12). Moreover, polyps cause hematochezia, gastralgia, and abdominal distension, reducing the quality of life of patients (13). Endoscopic surgeries are usually performed to resect cancerous polyps, whereas adequate surveillance is used to prevent cancer. A systematic analysis showed that the incidence and mortality of CRC after screening were reduced by 40 and 60%, respectively, indicating that early screening combined with timely diagnosis and treatment is an effective method to reduce the disease burden (14).

The screening and diagnostic methods commonly used in China mainly include colonoscopy, fecal immunochemical testing (FIT), sigmoidoscopy, colon computed tomography imaging, and multi-target fecal FIT-DNA detection, with colonoscopy being the gold standard. Moreover, colonoscopy including optical colonoscopy and electronic colonoscopy, with the latter one providing detailed contrast enhancement of the mucosal surface and blood vessel. Additionally, there are no significant differences between the effectiveness of these two technologies in CRC screening. But the unit cost of optical colonoscopy is lower than electronic colonoscopy. In light of this, this study would take electronic colonoscopy as an example to assess the cost-effectiveness of colonoscopy (15, 16). Besides, FIT is commonly used in CRC screening and diagnosis as it is non-invasive and low-cost. There are a lot of researches on the effectiveness of sigmoidoscopy for CRC screening in European and American countries. However, the application of sigmoidoscopy for cancer screening is not common in China, and the guidelines of China not recommending this technology for mass screening in most regions. Additionally, although colon computed tomography imaging is non-invasive and highly sensitive, it is limited for mass screening for its strict requirements for bowel preparation, the lacking of inspection equipment and specialists, and the risk of radiation. Also, multi-target fecal FIT-DNA detection has not been widely used in mass screening because its effectiveness is still need to be confirmed in China, and it is an expensive method which requires central laboratories (17).

The economic evaluations of various strategies in developed countries, such as the United States, the United Kingdom, and France, have demonstrated the cost-effectiveness of screening. However, the results of these studies may not be suitable for developing countries, and relative evaluations are lacking in mainland China. We used index terms containing "colon cancer," "colorectal cancer," "cost effectiveness," "cost utility," "cost benefit,""economic evaluation,""CEA," "CUA," "CBA," "China," and "Chinese" and searched PubMed, Embase, CNKI, and other databases, identifying fewer than 17 studies on screening (18–34). Moreover, the outcome indicators used in these studies were distinct, and the only few economic evaluations did not use incremental cost-effectiveness analysis, resulting in incomparability with international studies.

This study aimed to assess the usefulness and cost-effectiveness of CRC screening in China and analyze the impact of regions, screening frequency, starting age, and therapeutic effect of cancer treatment on the results. We selected Luohu District, Shenzhen, one of the pre-eminent cities in China as

a sample to explore the suitable strategies at the district level. Luohu Hospital Group began implementing the Institution-based Colorectal Cancer Screening Program (I-CRCSP) in 2018, and continued the project annually. The office-working group over 40 years old and retired people younger than 75 years old are screened using electronic colonoscopy (e-CSPY), with females taking account of 52.65% and the average age of the participants being about 53, which was in the range of the starting age recommended by several guidelines. This project is also a pioneer in CRC screening in China, and we predict that the evidence of its effectiveness and cost-effectiveness is of great importance. Moreover, this study would compare the e-CSPY with FIT as it was most common used in CRC screening.

Materials and methods

Study design

Considering that the guidelines of China and USPSTF (United States Preventive Services Taskforce) both recommend the average-risk population who is over 50 to participate CRC screening until 75 (17, 35, 36), this study set the target subjects to enter the model from 50 and exit when he/she is 75.

Screening strategies

The guideline of USPSTF recommends the screening strategies involving all the subsistent methods and corresponding frequencies. However, considering the real situation of China, the screening methods evaluated in this study were FIT and e-CSPY. In addition, it is recommended by the Chinese Journal of Oncology for general population need to be performed every 5 to 10 years and FIT test need to be used each year (37). Therefore, this study analyzed the cost-effectiveness of the colonoscopy at the upper and lower limits of the recommended time range, with e-CSPY was repeated every 10 years(e-CSPY10) and 5 years(e-CSPY5), and FIT being repeated annually (FIT1) and biennially (FIT2).

FIT are immunoassays specific for human hemoglobin, forming an antibody-antigen complex with its globin moiety (38). Usually, one or two stool samples are collected for tests without diet restriction. Those whose results of FIT are positive need to undergo a colonoscopy for diagnosis. FIT has replaced gFOBT (guaiac-based fecal occult blood test) as the Fecal detection technology nowadays. However, the sensitivity of FIT for the detection of precancer is limited, even that for the discovery of cancer is high.

E-CSPY is widely used for full colorectal examinations and treatment. The electron camera probe at the front of the colonoscopy transmits images of the colon mucosa to the processing center, and the pictures are displayed on the monitor screen. Intestinal preparation is required a few h before the examination. Patients are asked to drink laxative until water is excreted. The examination requires general anesthesia. First, the patient is positioned in a left-sided or prone knee-flex position. The colonoscope is passed through the rectum, descending colon, spleen flex, transverse colon, hepatic curvature, and ascending colon in sequence and finally reaches the cecum (39). The physician quickly advances the colonoscope into the intestine and observes the intestinal epithelium while slowly withdrawing. The induction takes approximately 4 min, and the withdrawal takes at least 6 min.

Endoscopic resection should be performed whenever the morphological structure of polyps permits (40). Pedunculated polyps are generally removed (41). For sessile or flattened polyps at risk of pT1 cancer, which represents the earliest form of clinically relevant cancer and is the key stage of tumor sequence, surgery is required to completely remove the lesion (42). Specifically, it is necessary to select the appropriate excision methods according to the diameter of the polyp (17, 43–45). Moreover, intraoperative or postoperative bleeding due to resection may require routine hemostasis or additional endoscopic management (46).

In terms of the screening project in Shenzhen, e-CSPY was encouraged before the annual physical examination of the office-working group and carried out with the exam simultaneously. Cancerous patients were excluded based on the Hospital Information System and face-to-face interviews in advance, and the screening was conducted in tertiary hospitals belongs to Luohu Hospital Group. Since 2020, 5,343 participants have been screened, and the misdiagnosed rate was approximately 19.39% (47). The misdiagnosed rate was the number of missed polyps divided by the total number of polyps found in biannual examination. This figure was derived from the retrospective data collected in 250 patients from July, 2007 to July, 2012 of the gastrology department in Shenzhen Luohu hospital. For the purpose of exploring the impact of implement site which reflecting the distinction of factors such as baseline characteristics of population and economy level, this study also simulated scenario where subjects in Shenzhen were tested using FIT, rather than undergoing e-CSPY only.

Model overview

Natural history and Markov model

CRC may develop from three paths: (1) the adenoma-carcinoma sequence, in which the disease progresses according to the sequence of normal epithelial cells, low-risk adenomas, high-risk adenomas, and cancers (48); (2) serrated lesions, mainly referring to hypertrophic polyps and sessile serrated adenomas, both characterized by the serrated structure of the upper part of the crypt, but only the sessile serrated adenoma is cancerous; and (3) de novo, indicating that the cancer starts from

the normal colon mucosa (49). Among them, CRC developing from the de novo pathway accounts for <5%, whereas the proportion of cancer originating from serrated lesions is unknown, ranging from 5 to 30%. Additionally, including these two paths would complicate the model. Therefore, we considered the adenoma-carcinoma sequence only (50).

In this study, low-risk adenoma is defined as polyps with a diameter <10 mm, and high-risk adenoma refers to polyps with a diameter >10 mm or containing more than 25% of the villous structure. The TNM classification of cancer grades was applied.

A Markov model was designed to simulate the disease history of a cohort of 100,000 subjects. The model was proposed and validated by Wong et al. in 2015. We adjusted the model structure and assumptions to match the population of mainland China (see Key assumptions section for details). The health states contained normal, low-risk adenoma, high-risk adenoma, CRC I, CRC II, CRC III, CRC IV, and death. In addition, false positive state was set to reflect the misdiagnosis of the screening technologies. Of note, carcinomatosis was divided into preclinical cancer and post-diagnosis cancer. Preclinical cancer refers to a state in which a patient is asymptomatic but has cancer. And adenomas were removed once detected, and patients returned to normal. High-risk adenomas have a certain probability of progressing to cancer each year.

The model cycle was 1 year, and subjects in each cycle progressed according to the path or were stable when proceeding to the next cycle. Moreover, subjects in all states may die. The CRC-caused mortality was only applied to individuals with cancer, whereas natural mortality was applied to the entire target population.

CRC patients may be diagnosed through clinic visits when they notice symptoms or through screening. Those who participate in screening but are not diagnosed may also be diagnosed through the first route. The natural history of subjects in the screening scenario is the same as those in the scenario without screening. The main difference is that early screening may prevent disease progression at the adenoma stage, and early treatment might also suppress cancer development. Consequently, the number of subjects in each state is different between the two scenarios, ultimately resulting in the distinction of the cost and health benefits. The model was implemented in Excel, and the schematic of the model is shown in Figure 1.

Key assumptions

1. Assuming that the initial state of screening and non-screening scenarios is the same, and the original number of subjects were calculated according to the distribution of disease. Additionally, the number of diagnosed cancer patients is initially zero.
2. Considering that the risk of progression is closely related to the diameter, degree of villous components, and atypicality of adenomas, it is assumed that the disease progresses step by step. For example, low-risk adenoma first progresses to high-risk adenoma and then progresses to cancer. Similarly, high-risk adenoma only progresses to stage I cancer (the first adjustment of the model).
3. We assumed that preclinical cancer patients receive specific treatments according to cancer stages and stop progressing as soon as they are diagnosed.
4. Although screening using colonoscopy may lead to fatal adverse events, such as perforation and bleeding, the probability is extremely small according to expert opinions and literature [perforation 0.01% (51); bleeding 0.22% (17)]. Therefore, death due to adverse events was not considered in this study (the second adjustment of the model).
5. Patients are expected to undergo colonoscopy examinations when they visit doctors. Moreover, this study assumed that the visit rate of adenoma was 0 and that of CRC IV was 100% on the basis of expert interviews.
6. Subjects in false positive state were assumed to receive treatment only for 1 year, and would be back to the normal state in the next cycle.
7. It was assumed that those whose results of FIT were positive but hadn't undergo colonoscopy would not be treated unless they were symptomatic.

Model parameters

Epidemiological data

The number of initial states was calculated based on the prevalence of adenomas and CRC. The prevalence of adenomas was calculated based on the proportion of low-/high-risk adenomas, excluding hypertrophic polyps in Hong Kong and adenomas in mainland China (13, 52). The prevalence of CRC was based on a study on CRC disease burden in China, which used 2017 global burden of disease data to estimate the incidence, prevalence, and mortality of CRC in China from 1990 to 2017 (53). The proportion of patients in CRC stages I to IV was based on data from Hong Kong in 2019 and estimated after excluding patients who could not be graded (54). The prevalence of adenoma and CRC in Luohu District, Shenzhen was calculated by combining the local detection rate and the data mentioned above.

Transition probability

The transition probability from normal to cancer stemmed from a systematic review of natural history models of CRC in China (55). The transition probabilities between various stages of cancer were used only for preclinical states because the development of cancer stops upon diagnosis. This is mainly because although cancers may progress during treatment in the real world, the probabilities will vary over time, as observed from the Kaplan–Meier curves in randomized controlled trials.

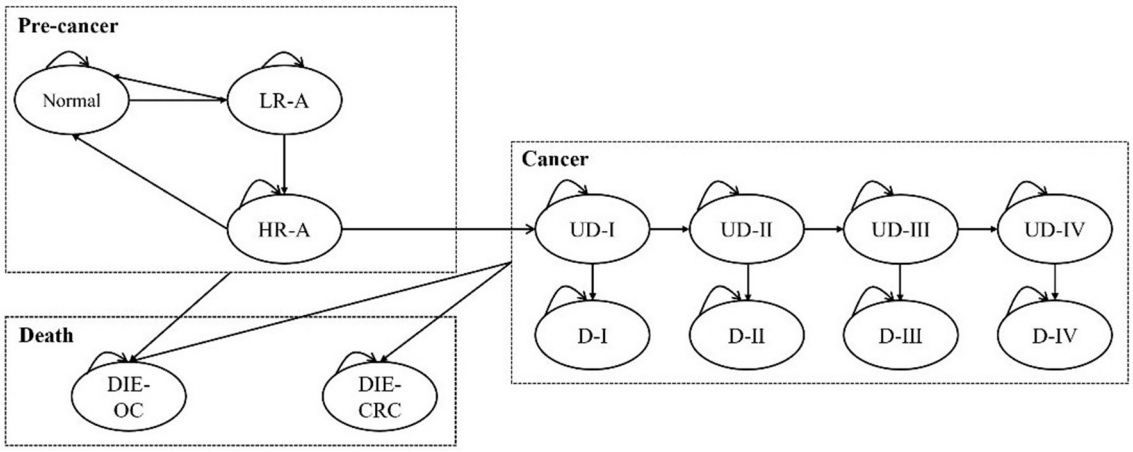

FIGURE 1
The Markov model for the base case analysis. L/HR-A, low/high-risk adenoma; (U)D-I/II/III/IV, (undiagnosed) cancer at stage I/II/III/IV; DIE-CRC, die of colorectal cancer; DIE-OC, die due to other causes.

However, the memoryless property of the Markov model means that it is not possible to distinguish the duration of different individuals being diagnosed in the same state, resulting in the inapplicability of dynamic transition probabilities.

Mortality

Mortality included age-specific natural mortality and cancer-specific mortality. The natural mortality rate was according to the China population and Employment Statistics Yearbook in 2017 (56). The cancer-specific mortality was based on a study in Hong Kong, which conducted an economic evaluation of CRC Screening in Asia.

Utility

The health-related quality of life of patients originated from a study in Hong Kong, which used SF-6D (Short Form health state classification and utility scoring system based on 6 dimensions) to measure the utility score of 151 adenoma patients and 364 CRC patients (57). At the same time, we set the score to 1 for healthy individuals and 0 for those who died.

Screening-related parameters

This section includes participation rate of screening, sensitivity and specificity of FIT and e-CSPY, and excision rate of polyps. The screening participation rate was calculated based on the program in Shenzhen and the performance parameters of screening technologies derived from published literature, with the hypothesis that the specificity of e-CSPY is 100% (50). Furthermore, we assumed that the excision rate was also 100% after interviews with experts. See Supplementary Table A; Table 1 for details.

TABLE 1 Age-specific natural mortality (56).

Age	Mortality
40–44	0.18%
45–49	0.26%
50–54	0.42%
55–59	0.62%
60–64	1.03%
65–69	1.72%
70–74	3.06%

Costs

The health system perspective was applied when evaluating costs; therefore, only the direct medical costs were incorporated in the model. Screening costs included program fees, examination fees of FIT and e-CSPY, polypectomy fees, histopathology examination fees, and follow-up costs. This study hypothesized that all polyps would be removed and examined by pathology, followed by surveillance within 1 year. The costs of adenoma treatment included medical service expenses, diagnosis and examination fees, surgery fees, and surveillance costs. The cost of CRC treatment derived from a study on the economic burden of CRC in Chinese patients in 2017 and was the average expense during the first year after diagnosis (58). The cost of cancer treatment in Shenzhen was based on a study of disease burden in Guangzhou (31), a first-tier city in Guangdong Province. Furthermore, CRC

TABLE 2 Cost parameters.

	Parameters	Value(USD)	Lower value(USD)	Upper value(USD)	Distribution	Resource
Treatment	Low-risk adenoma	593.32	444.99	741.65	Gamma	Calculation
	High-risk adenoma	593.32	444.99	741.65	Gamma	Calculation
	CRC I[a]	11,000.47	8,250.35	13,750.59	Gamma	(58)
	CRC II[a]	12,237.85	9,178.38	15,297.31	Gamma	
	CRC III[a]	13,041.75	9,781.31	16,302.19	Gamma	
	CRC IV[a]	14,225.68	10,669.26	17,782.09	Gamma	
	CRC-follow up	1,907.80	1,430.85	2,384.74	Gamma	Calculation
Treatment in Shenzhen	CRC I[a]	13,273.92	9,955.44	16,592.40	Gamma	(31) (60)
	CRC II[a]	17,796.91	13,347.68	22,246.13	Gamma	
	CRC III[a]	21,667.11	16,250.33	27,083.88	Gamma	
	CRC IV[a]	33,530.59	25,147.94	41,913.23	Gamma	
Screening	Project (total cost)	141,085.27	105,813.95	176,356.59	Gamma	Calculation
	FIT	2.64	1.98	3.29	Gamma	File
	Electronic colonoscope/person	140.72	105.54	175.90	Gamma	File
	Excision/person	283.36	212.52	354.19	Gamma	File
	Pathological examination/person	28.53	21.40	35.66	Gamma	File
	Follow up/person	140.72	105.54	175.90	Gamma	File

[a]CRC I/ II/ III/ IV, colorectal cancer at stage I/ II/ III/ IV.

TABLE 3 Parameters in scenario 3.

	Parameters	Value	Lower value	Upper value	Distribution	Resource
Transition probability	CRC I-II[a]	25%	18.75%	31.25%	Beta	Assumption
	CRC II-III[a]	35%	26.25%	43.75%	Beta	Assumption
	CRC II-III (from I)[b]	40%	30.00%	50.00%	Beta	Assumption
	CRC III-IV[a]	35%	26.25%	43.75%	Beta	Assumption
	CRC III-IV (from II)[b]	40%	30.00%	50.00%	Beta	Assumption
	CRC III-IV (from I)[b]	45%	33.75%	56.25%	Beta	Assumption

[a]CRC I/ II/ III/ IV, colorectal cancer at stage I/ II/ III/ IV. [b]CRC II-III (from I), individuals who transit from stage II cancer to stage III cancer who were diagnosed with stage I cancer initially (the rest states in the similar manner are explained by analogy).

patients are required to receive follow-up surveillance after treatment, according to the "Chinese Protocol of Diagnosis and Treatment of Colorectal Cancer (59)," including routine medical examinations and imaging examinations, and the costs referred to the prices in Shenzhen. It was assumed that the follow-up surveillance stopped 5 years later (59). All prices were converted to 2021 prices at a discount rate of 5% and shown in USD (US Dollar), with 1USD=6.45CNY (Chinese Yuan). See Table 2 for details.

Sensitivity analysis

The sensitivity analysis was conducted to verify the uncertainty of parameters. We explored the impact of each parameter through deterministic sensitivity analysis and presented the results in the form of a tornado figure. We also carried out a probability sensitivity analysis with net monetary benefits as intermediate indicators. A Monte Carlo simulation was conducted to draw from the distributions of parameters randomly for 10,000 iterations. The probability and utility values followed the Beta distribution, and costs followed the gamma distribution. Finally, the results were presented as scatter plots and cost-effective acceptability curves.

Scenario analysis

We considered three scenarios to verify the model uncertainty.

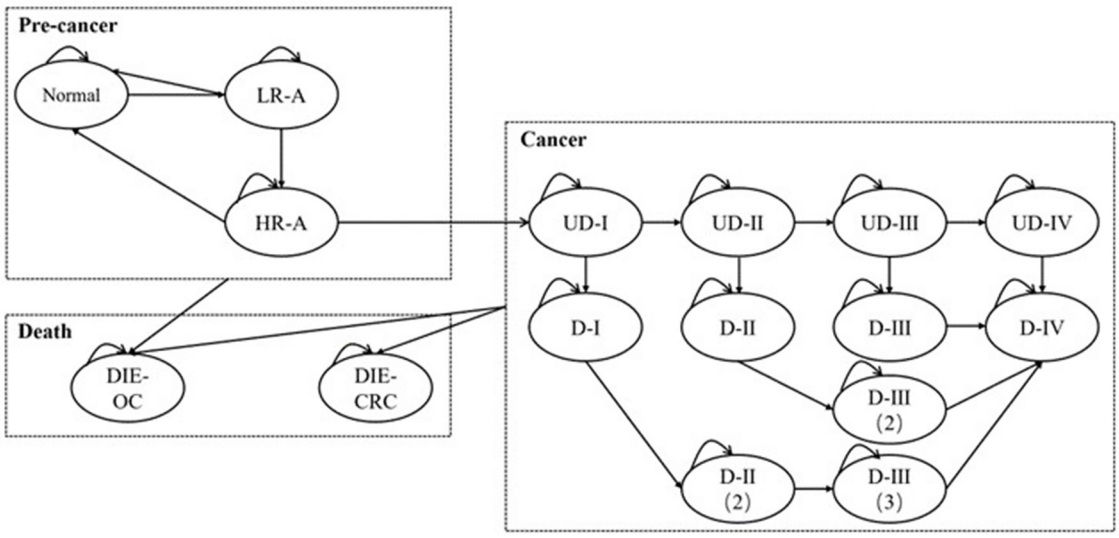

FIGURE 2
The Markov model for analysis in scenario 3. L/HR-A, low/high-risk adenoma; (U)D-I/II/III/IV, (undiagnosed) cancer at stage I/II/III/IV; DIE-CRC: die of colorectal cancer; DIE-OC, die due to other causes.

Scenario 1 Evaluate the cost-effectiveness of CRC screening when the setting is Shenzhen and compare the results with those in China to explore potential factors.

Scenario 2 Set the age of the participants entering the model to 40 and simulate to 75 years old or death in Chinese population to analyze the impact of the starting age on the cost-effectiveness of the screening program.

Scenario 3 Assuming medical treatments cannot completely inhibit the progression of cancers. In real world, cancerous patients may continue to worsen when receiving therapeutic treatment, but the probability of metastasis may lower than that in preclinical stages. However, because of the inapplicability of the time-varying transition probabilities in Markov model, we used stable values for analysis. Additionally, it was assumed that the more times patients receive treatments, the greater the transition probabilities are. The parameters are presented in detail in Table 3, and the structure of the model in scenario 3 is shown in Figure 2.

Additionally, this study evaluated the effectiveness of screening in avoiding advanced cancers and deaths, and the indicators were CRC cases and deaths being prevented. The CRC cases and deaths were the aggregated value of patients suffering from cancer at stage four and those died at the endpoint of the simulation.

Results

Base case analysis

The results of base case analysis showed that both annual and biennial FIT were dominant over non-screening scenario, as well as the comparison with annual FIT and biennial FIT. More precisely, FIT1 and FIT2 saved 8.13USD and 44.96USD per person, and increased 0.0705QALYs (Quality-Adjusted Life Years) and 0.2341QALYs in comparison with no screening. And FIT1 could save 36.81USD per person and increase 0.1637QALYs vs. FIT2.

Strategies of e-CSPY10 and e-CSPY5 increased costs by 39.14USD and 141.84USD per person, and increased 0.3052QALYs and 0.3954QALYs, with the ICER (Incremental Cost-Effectiveness Ratio) being 128.24USD/QALY and 358.73USD/QALY compared with no screening.

The ICER for e-CSPY10 were 1183.51USD/QALY and 536.66USD/QALY compared with FIT1 and FIT2, respectively. And that for e-CSPY5 were 1158.16USD/QALY and 770.85USD/QALY, respectively. In addition, the ICER for e-CSPY5 relative to e-CSPY10 was 358.71USD/QALY.

All of the ICERs were lower than economic threshold of DGP (Gross Domestic Product) per capita of China in 2021(12554.42USD).

See Table 4 for details.

TABLE 4 Results of the base case analysis.

	FIT1	FIT2	e-CSPY10	e-CSPY5
Incremental costs (USD)				
FIT1*	–	–	84.10	178.67
FIT2*	−8.13	–	75.96	178.67
e-CSPY10*	–	–	–	102.71
e-CSPY5*	–	–	–	–
No screening	−44.96	−36.81	39.14	141.84
Incremental QALYs				
FIT1*	–	–	0.0,711	0.1,613
FIT2*	0.0,705	–	0.1,415	0.2,318
e–CSPY10*	–	–	–	0.0,902
e-CSPY5*	–	–	–	–
No screening	0.2,341	0.1,637	0.3,052	0.3,954
ICER (CNY/QALY)				
FIT1*	–	–	1,183.51	1,158.16
FIT2*	−115.41(dominant)	–	536.66	770.85
e-CSPY10*	–	–	–	1,138.19
e-CSPY5*	–	–	–	–
No screening	−192.01(dominant)	−225.00(dominant)	128.24	358.71

* FIT1, Annual FIT; FIT2, Biennial FIT; e-CSPY10, colonoscopy every 10 years; e-CSPY5, colonoscopy every 5 years.

Sensitivity analysis

Deterministic sensitivity analysis showed that the ICER was lower than the threshold value when the parameters varied separately, indicating that the results of base case analysis were robust. When the control group is no screening, the transition probability from high-risk adenoma to undiagnosed CRC was the most sensitive parameter. When compare e-CSPY10 with annual FIT, the sensitivity and specificity of the technologies and attendance rates of screening may influence the results. Additionally, the cost-effectiveness may be impacted by the disease progress, utility of patients, participation rates, and the fees of colonoscopy when comparing e-CSPY at different intervals. See Figure 3 for details.

The results of the probabilistic sensitivity analysis showed that the probability that the screening was cost-effective of FIT1 and e-CSPY5 was the same at the WTP of 1240.31USD. Annual FIT was most likely to be cost-effective when the WTP was less than 1240.31USD, and E-CSPY every 5 years was the optimal choice when the threshold was over 1240.31USD. FIT1 was the most cost-effective strategy mainly due to its low costs, and e-CSPY5 became the most cost-effective tactics may due to its excellent effectiveness in screening. Additionally, the cost-effectiveness of FIT2 wasinferior to FIT1 may on account of the slightly inferior effectiveness for CRC screening, even though it was inexpensive. Likewise, the effect of e-CSPY10 was not up to e-CSPY5 resulting in its disadvantages when the WTP was high despite of the relatively lower costs. See Figures 4, 5 for details.

Scenario analysis

Table 5 showed the results of scenario analysis.

Scenario 1 When the setting of screening was Shenzhen, e-CSPY10 and e-CSPY5 became dominant over no screening. Also, ICERs for e-CSPY10 in comparison to FIT and ICER for e-CSPY5 relative to FIT and e-CSPY were lower than that in base case analysis.

Scenario 2 When the starting age of screening was brought forward to 40, e-CSPY10 became dominant over no screening. ICERs for e-CSPY10 and e-CSPY5 were lower than that in base case analysis, except the value in the comparison between e-CSPY10 and annual FIT.

Scenario 3 Considering that treatment does not completely inhibit the progression of cancer, all the strategies were dominant over no screening. In addition, e-CSPY10 was cost-saving compared with FIT. E-CSPY5 was dominant over biennial FIT. And ICER for e-CSPY5 were much lower than economic threshold compared with annual FIT and e-CSPY10.

Additionally, screening could reduce CRC cases by 1589–4497 and deaths by 1036–2537 in the long run. The number of CRC cases and deaths being avoided mentioned above were the range of the values used in other screening scenarios. Besides, the more frequent the screening and the earlier the starting age, the greater the number of cancers and deaths could be prevented. See Table 6 for details.

Discussion

Colorectal cancer has posed a great threat to human life, and screening has been proved to be a effective solution to decrease the disease burden. Countries around the world developed guidelines of screening for colorectal cancer one by another. For instance, both the guidelines of USPSTF and China listed the existing technologies for screening and diagnosis such as colonoscopy, fecal immunochemical testing (FIT), sigmoidoscopy, colon computed tomography imaging, and multi-target fecal FIT-DNA detection. This study evaluated the effectiveness and cost-effectiveness of the commonly used methods for mass screening in China, namely FIT and electronic colonoscopy in the hope of providing a reference for public health decision-making.

This study found that screening for colorectal cancer in China was cost-effective and conducive to reduce cancer cases and deaths, no matter the method was FIT or electronic

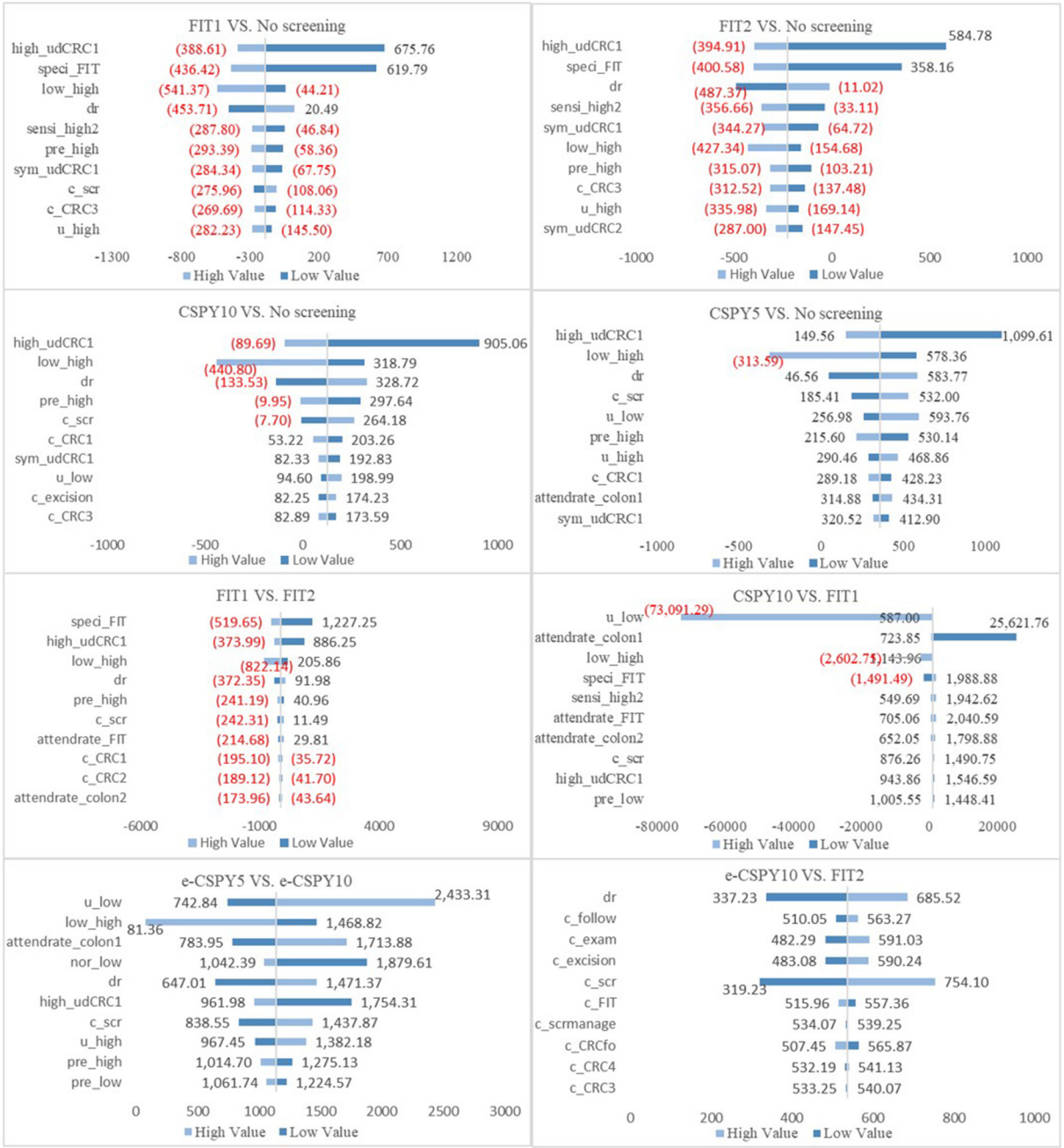

FIGURE 3
The tornado figures of Deterministic Sensitivity Analysis. High, high-risk adenoma; low, low-risk adenoma; nor, normal; udCRC, undiagnosed colorectal cancer; CRC12/3/4, colorectal cancer I/II/III/IV; speci, specificity; sensi, sensitivity; dr, discount rate; c, cost; scr, screening; pre, prevalence rate; colon1, colonoscopy; colon2, colonoscopy following FIT; scrmanage, the management of the screening; E-CSPY10/5, electronic colonoscopy every 10/5 years; FIT1/2, annual/ biennial FIT.

colonoscopy. Moreover, annual FIT and biennial FIT were always cost saving in comparison with no screening, regardless of the starting age, screening frequency or therapeutic effect of cancer. And when the setting of screening was Shenzhen, or the inhibition of cancer treatment was incomplete, both e-CSPY10 and e-CSPY5 became dominant over no screening. Besides, e-CSPY10 could save costs and yield more QALY gains when the starting age was 40. Furthermore, optical colonoscopy would be

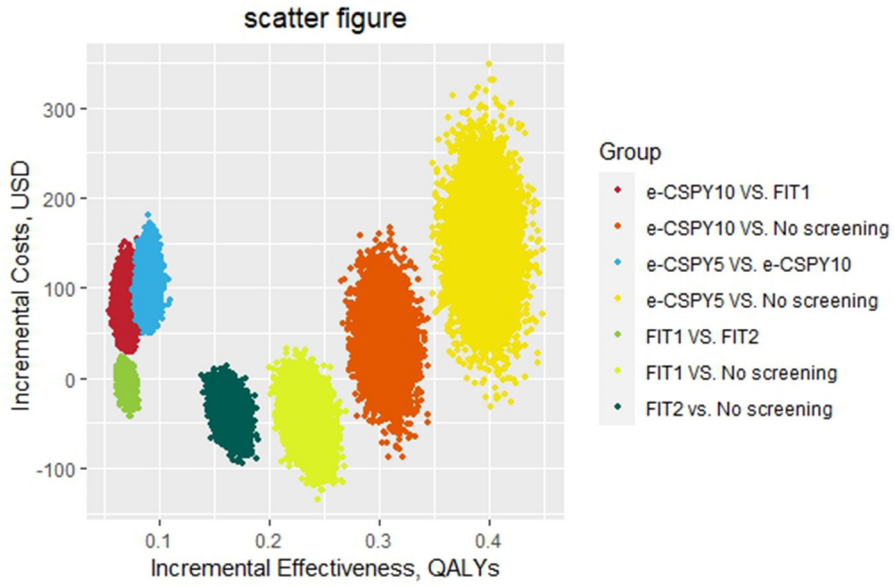

FIGURE 4
The scatter figure of the probabilistic sensitivity analysis. E-CSPY10/5, electronic colonoscopy every 10/5 years; FIT1/2, annual/ biennial FIT.

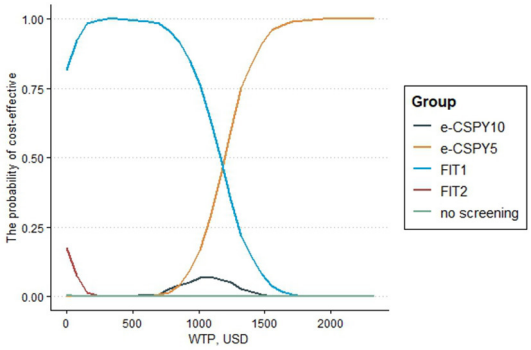

FIGURE 5
The cost-effectiveness acceptability curve. E-CSPY10/5, electronic colonoscopy every 10/5 years; FIT1/2, annual/ biennial FIT; WTP, willingness to pay.

more cost-effective compared with e-CSPY based on the results, due to the similar effectiveness of screening and lower cost.

In addition, e-CSPY was a cost-effective technology for CRC screening, no matter of the screening interval, compared with FIT. The QALY gained from screening with e-CSPY was more than that from screening using FIT, while the implementation of e-CSPY cost more, with the ICER was lower than the economic threshold.

We also found that the results were sensitive to factors such as transition probabilities, characteristics of screening technologies and costs of screening and cancer treatment, indicating the role of the screening in terms of preventing cancers and saving relevant expenses. Specifically, adenomas are usually asymptomatic and neglected, but they are at high risk of progressing to CRC within 5 to 10 years. The higher the transition probabilities and prevalence of diseases, the more CRCs may be prevented by screening. In addition, in case of the relatively low cost of screening and polypectomy, as well as high cost of cancer treatment, the increased expenditure incurred by the screening program would be low while the cost saving of cancer treatment yielding from screening would be high. Furthermore, the more accurate the instruments are, the less expenses would be waste, contributing to more benefits brought from screening. Thus, conducting screening program would be more cost-effective. As expected, a higher compliance of screening would be in favor to the cost-effectiveness of e-CSPY when compared with FIT. This may due to that more cancer cases and death could be prevented, further saving the subsequent high costs of treatment in this circumstance. This suggests the significance of improving the compliance of screening with colonoscopy considering it is invasive and time-consuming.

Moreover, a high frequency of screening and early age of first screening increased health benefits. The ICER increased as the screening frequency improved. In contrast, early screening could decrease the ICER. However, the ICER was less than the threshold value in all cases. In addition, cancer therapy outcomes were demonstrated to affect the cost-effectiveness of screening. Ideally, specific treatments should completely inhibit the progression of cancer, but 30 to 50% of patients relapse

TABLE 5 Results of the cost-effectiveness analysis in different scenarios.

	FIT1	FIT2	e-CSPY10	e-CSPY5
ICER (USD/QALY) in Scenario 1				
FIT1	–	–	1,203.57	958.45
FIT2	−665.71(dominant)	–	273.71	459.82
e-CSPY10	–	–	–	759.86
e–CSPY5	–	–	–	–
No screening	−783.25(dominant)	−833.42(dominant)	−322.14(dominant)	−81.22(dominant)
ICER (USD/QALY) in Scenario 2				
FIT1	–	–	1325.01	1113.34
FIT2	−182.19(dominant)	–	495.85	691.76
e-CSPY10	–	–	–	975.45
e-CSPY5	–	–	–	–
No screening	−319.64(dominant)	−374.48(dominant)	−8.64(dominant)	212.76
ICER (USD/QALY) in Scenario 3				
FIT1	–	–	−345.37(dominant)	132.52
FIT2	−1082.37(dominant)	–	−691.84(dominant)	−235.05(dominant)
e-CSPY10	–	–	–	589.80
e-CSPY5	–	–	–	–
No screening	−766.25(dominant)	−617.08(dominant)	−654.53(dominant)	−384.3(dominant)

TABLE 6 Number of colorectal cancer patients and deaths in all scenarios.

	Number of CRC patients					Number of deaths				
	FIT1	FIT2	e-CSPY10	e-CSPY5	No screening	FIT1	FIT2	e-CSPY10	e-CSPY5	No screening
China	1,681	2,537	1,543	918	4,599	29,478	29,701	29,763	29,555	30,737
50–75	(↓2,918)	(↓2,062)	(↓3,056)	(↓3,681)		(↓1,259)	(↓1,036)	(↓974)	(↓1,182)	
Shenzhen	1,798	2,725	1,636	970	4,981	29,456	29,700	29,768	29,540	30,836
50–75	(↓3183)	(↓2256)	(↓3,345)	(↓4,011)		(↓1380)	(↓1136)	(↓1068)	(↓1296)	
China	2,112	3,315	1,928	1,044	6,425	3,1072	3,1432	3,1507	3,1161	3,3294
40–75	(↓4,313)	(↓3,110)	(↓4,497)	(↓5,381)		(↓2,222)	(↓1,862)	(↓1,787)	(↓2,133s)	
Incompletely	539	1,019	669	282	2,608	30,621	31,219	30,637	30,191	32,728
successful	(↓2,069)	(↓1,589)	(↓1,939)	(↓2,326)		(↓2,107)	(↓1,509)	(↓2,091)	(↓2,537)	
treatment										

The symbol "↓" representing the nuber of cancer cases or deaths which may be avoided by these screening strategies.

after surgeries or systemic chemotherapy (61–64) In this case, screening is more advantageous. This can be explained by the fact that screening prevents more advanced cancers and deaths at this time, thereby saving costs and increasing health benefits. Therefore, the economic evaluations based on the complete cure hypothesis may underestimate the cost-effectiveness of screening (30, 32).

There were numerous studies which proved the cost-effectiveness of FIT and colonoscopy. The results of this study are consistent with the previous evaluations. For instance, M. Aronsson et al. found that in Sweden, both FIT and colonoscopy were cost-effective strategies compared with no screening, and repeated and single screening with colonoscopy were more cost-effective than FIT in the long run (65). Nelya Melnitchouk et al. proved that screening with FIT or colonoscopy could save money and improve health compared with no screening and colonoscopy every 10 years was a superior choice in Ukraine (66). Wong et al. demonstrated in 2015 that screening with annual FIT was the optimal strategy among annual/biennial g-FOBT, annual/biennial FIT, and colonoscopy every 10 years. However, this study found that screening with colonoscopy was more cost-effective than FIT. This was mainly owing to the sensitivity of FIT calculated in the two studies. The sensitivity of FIT for polyps and cancer was 62%, with the specificity was 93%. But the sensitivity of FIT for the detection of polyps in our model was much lower than that in Wong's. The results between two evaluations could be consistent if we used the same value after

verification, suggesting the impact of instrument accuracy on the screening (32).

Recently, most economic evaluations on CRC screening placed emphases on fecal occult blood test and colonoscopy every 10 years in mainland China. But studies evaluating the impact of screening intervals of colonoscopy, starting age of screening and therapeutic effect of cancer treatment are lacking. Furthermore, some economic evaluations of CRC screening in China did not use ICER as an outcome indicator, resulting in incomparability with the international studies. This study analyzed the cost-effectiveness of CRC screening with FIT and colonoscopy following the standardized health economic evaluation procedures, addressing this important research gap. We also estimated the screening not only under the circumstance of the entire China, but also in a specific region. Moreover, we compared the results in different scenarios of various screening frequencies and starting ages, which is helpful for developing detailed strategies.

This study also has limitations. First, excluding the de novo and serrated lesion pathways may lead to overestimation of the cost-effectiveness of the screening. Second, the Markov model was unable to simulate the disease progress of distinct individuals, deviating from the real-world setting. Third, the study did not include direct non-medical costs and indirect costs because of data limitations. Therefore, it is difficult to evaluate screening programs from a societal perspective. Fourth, some parameters such as transition probabilities were derived from authoritative researches in other countries because local data was unavailable. But the deterministic analysis showed that the changes of these parameters would not influence the conclusions, and the results was robust in base-case analysis. At last, due to the lacking of relevant data, the impact of complex instrument and dedicated personnel required by the tests of colonoscopy was not considered which may cause the distinctions between the study and the real world. Despite the above limitations, this study provides evidence that is valuable for public health decision-making in China.

Conclusions

It is cost-effective to implement CRC screening using FIT or electronic colonoscopy in mainland China, with FIT always saving costs. Additionally, colonoscopy is cost-effective compared with FIT, and a five-year interval is cost-effective compared with the 10 year interval, as the ICER was lower than the threshold of the GDP per capita of China in 2021 in all scenarios. Therefore, CRC screening is worth popularizing in China, and the economically developed regions such as Shenzhen could consider the strategy of electronic colonoscopy every 10 years, or even every 5 years.

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

Conceptualization: YR and MZ. Methodology: YR, MZ, and DZ. Validation: MZ, DZ, and WT. Formal analysis, investigation, software, and writing—original draft preparation: YR. Resources: YR and QX. Data curation: YR, MZ, and QX. Writing—review and editing: YR, MZ, and WT. Supervision: FG and WT. Funding acquisition: WT. All authors contributed to the article and approved the submitted version.

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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/fpubh.2022.952378/full#supplementary-material

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Self-reported vaccination-related behavior patterns among healthcare workers and the association with self-directed learning frequency: A nationwide cross-sectional survey

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Background: Healthcare workers play an essential role in improving the public's vaccination uptake, but the full picture of such workers' engagement in vaccination-related behaviors has not been appropriately identified. According to the Integrated Theory of Health Behavior Change, self-directed learning may be a promising intervention for fostering engagement in vaccination-related behaviors, but the association between self-directed learning and such behaviors remains unclear. This study aimed to determine Chinese healthcare workers' level of engagement in behaviors for combatting vaccine-preventable diseases and assess the association between frequency of performing vaccine-focused SDL and engagement in vaccination-related behaviors.

Materials and methods: An online cross-sectional survey was conducted from January 27 to February 21, 2022, using the survey platform "wjx." Respondents were restricted to healthcare workers aged 18–65 years. A Sankey diagram and bar plots were constructed to determine patterns of engagement in a vaccination-related-behavior chain. Unconditional binary logistic regression models were fitted to determine the association between frequency of performing vaccine-focused self-directed learning and engagement in vaccination-related behaviors.

Results: Of the 2,248 survey respondents, data for 2,065 were analyzed. Participants who had received influenza or pneumococcal vaccination, routinely recommended vaccination to patients, tracked patients' vaccination status, and recommended efficiently accounted for 43.2%, 50.8%, 40.3%, and 36.4% of the total participants, respectively. When only considering those who routinely made such recommendations, the proportion of those who

performed tracking and efficient recommendation was 28.8% and 26.2%, respectively. When compared to performing self-directed learning "never to less than once/six months," performing self-directed learning "more than once/week" was positively associated with being vaccinated (OR, 95% CI: 2.30, 1.74–3.03), routinely recommending vaccination (OR, 95% CI: 4.46, 3.30–6.04), and tracking the status of patients so recommended (OR, 95% CI: 6.18, 4.35–8.76).

Conclusions: Chinese healthcare workers' pattern of engagement in vaccination-related behaviors must be improved. Higher frequencies of engagement in self-directed learning are associated with more active engagement in vaccination-related behaviors, meaning raising such frequencies could be a promising intervention for fostering behavior changes in this regard and ultimately increasing vaccination coverage.

KEYWORDS

self-directed learning, healthcare worker, vaccination, recommendation, public health, population medicine

Introduction

In recent years, population medicine has become increasingly popular, which promotes a transition in health systems from treating illness to preventing illness (1, 2). Population medicine encourages healthcare workers (HCWs) to strengthen their awareness of public health and disease-prevention (1, 3) and, thus, causes them to become both beneficiaries (4) and counseling service providers in regard to vaccination uptake (5). Influenza and pneumococcal vaccines are two major contributors for the prevention of lower respiratory tract infection, which is one of the leading causes of deaths and DALYs worldwide (6). Vaccinations have been strongly recommended by the World Health Organization (7) especially for high-risk population, but the vaccination uptake still needs to be improved in some countries (8). HCWs are considered as a priority population for influenza vaccination, not only for protecting themselves but also avoiding spreading the disease to patients (9). They are also encouraged to recommend vaccination to their patients because their recommendations have a strong influence on the vaccination decisions of the general population (10). In addition, studies have indicated that HCWs' behaviors of getting vaccinated are associated with greater willingness to recommend vaccination to their patients (9). Therefore, vaccination-related behaviors among HCWs could influence the vaccination coverage in both HCWs and the public.

Previous studies have investigated receiving and recommending vaccinations among HCWs separately (11–13), but these vaccination-related behaviors could be correlated (9). For the recommendation behavior, it can be an interactive loop that HCWs might follow up the vaccination status of patients after recommending vaccinations to them, then assess the recommendation effect and continue to improve their recommendation skills according to feedback from patients, which is similar to PDCA cycle (Plan-Do-Check-Act), a scientific method to solve problems and improve continuously (14). Though the efficiency of recommendation could be a response from patients, we consider it as HCWs' behavior because it is an indispensable "check" process in the recommendation loop and also an assessment of HCWs' contributions to the vaccination uptake among the general population. Therefore, the vaccination-related-behavior chain involves receiving vaccinations, regularly recommending vaccinations to patients, tracking the vaccination status of patients who have been recommended to obtain a vaccine, and determining the efficiency of one's recommendations. All these behaviors are linked together and could reflect the full picture of the engagement of healthcare workers in vaccination. So far, the full picture of engagement in each element of the vaccination-related-behavior chain has not been appropriately identified among HCWs in China. Considering the low vaccination coverage and the essential role of HCWs in improving this situation, it is necessary to understand the current status of vaccination-related behavior patterns among HCWs and to explore associated factors.

At present, training programs are commonly used interventions to increase awareness and knowledge about vaccination among HCWs (5, 15). However, it may not be a long-term solution because HCWs usually have heavy jobs. Frequent trainings about updated vaccination knowledge would add to their burden and occupy a lot of health resources. More flexible and sustainable interventions are needed to supplement or replace this training method. According to the Integrated Theory of Health Behavior Change, health-behavior change can be enhanced by improving knowledge and beliefs,

increasing self-regulation skills and abilities, and enhancing social facilitation (16). To improve HCWs' vaccine uptake and rate of recommendation of vaccines to patients, it would be insufficient to merely develop a training program that focuses only on enhancing HCWs' knowledge and beliefs about vaccination (although such efforts have previously been reported to increase engagement in vaccination behaviors) (5, 15). Person-centered interventions are needed to achieve all three components of the Integrated Theory of Health Behavior Change (16) and, notably, such interventions have previously been found to be more effective than standardized interventions for enhancing health-behavior change (17, 18). Self-directed learning (SDL) is a typical person-centered intervention, and is defined as a process by which individuals take the initiative, with or without the assistance of others, in diagnosing their learning needs, formulating learning goals, identifying human and material resources to assist their learning, choosing and implementing appropriate learning strategies, and evaluating learning outcomes (19). It is also considered a promising lifelong learning approach in the medicine field (20). Therefore, vaccine-focused SDL could be a more effective and sustainable means of fostering greater engagement in vaccination-related behaviors, but few studies have evaluated the association between SDL and such engagement.

Therefore, to obtain a comprehensive understanding of HCWs' role in combatting vaccine-preventable diseases in China and evaluate the association of vaccine-focused SDL with it, this study aimed to (1) investigate the characteristics of Chinese HCWs' engagement in the vaccination-related-behavior chain, and (2) assess the association between frequency of performing vaccine-focused SDL and engagement in vaccination-related behaviors.

Materials and methods

Study design

For this study, an online cross-sectional survey was jointly designed and conducted by the School of Population Medicine and Public Health, the Chinese Academy of Medical Science & Peking Union Medical College, and the "Breath Circles" platform. The "Breath Circles" platform is a media platform for HCWs with 235,000 subscribers in mainland China. The survey was published using the online survey platform "wjx" (https://www.wjx.cn) on January 27, 2022, with a link to the questionnaire being posted on the "Breath Circles" platform. Data collection finished on February 21, 2022, as no further responses were submitted after this date. This study protocol and questionnaire are approved by the Medical Ethics Committee of the Chinese Academy of Medical Sciences and Pecking Union Medical College, Beijing, China (CAMS&PUMC-IEC-2022-019). All participants had provided informed consent forms to be interviewed before logging in to fill out the questionnaire.

The survey comprised three sections: (1) Sociodemographic information (age, sex, education, years of professional experience, etc.,); (2) Vaccination-related knowledge, beliefs, and recommendation behaviors (frequency of performing vaccine-focused SDL, topics of interest, approaches used to acquire knowledge, frequency of recommending vaccination to others, etc.,); (3) Vaccination against respiratory infectious diseases (whether respondents had received influenza/pneumococcal vaccines, etc.,). We focused on vaccines related to respiratory infectious diseases (influenza and pneumococcal vaccines) when asking HCWs about their behavior of receiving vaccinations because (1) HCWs who work in healthcare settings are more likely to have respiratory infections or transmit infection to their patients; (2) HCWs are considered to be a target group for seasonal influenza vaccination by WHO (7), and those who work in hospitals are provided free influenza vaccinations in China (21). However, we did not limit types of vaccines when involving behaviors related to recommending vaccinations because HCWs from non-respiratory departments or non-hospital institutions may prefer to recommend other vaccines, such as human papillomavirus (HPV) vaccine, haemophilus influenza type b (Hib) vaccine, etc. The inclusion criterion for participants was being a HCW aged 18–65 years.

The surveyed provinces were divided into three geographic regions (eastern, central, and western regions) to reflect the regional economic development, according to the National Bureau of Statistics of China (22). Eastern regions have higher economic level and include Beijing, Tianjin, Hebei, Liaoning, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, and Hainan. Central regions include Shanxi, Jilin, Heilongjiang, Anhui, Jiangxi, Henan, Hubei, and Hunan. Western regions include less developed provinces (autonomous regions, municipalities): Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Shaanxi, Gansu, and Qinghai.

Outcome measures

The vaccination-related-behavior chain was defined as receiving vaccinations, regularly recommending vaccinations to patients, tracking the vaccination status of patients who have been recommended to obtain a vaccine, and determining the efficiency of one's recommendations (i.e., the ratio of patients who received a vaccine after being recommended to do so). The four elements were selected as indicators to evaluate the level of engagement in vaccination-related behaviors, and the latter three behaviors related to recommendation were considered sequential. However, receiving vaccinations and recommending vaccinations were not necessarily in order

because it is reasonable that some HCWs recommend vaccines regularly to others without receiving influenza or pneumococcal vaccines themselves, though studies have suggested that vaccination uptake could be a driving factor in recommending vaccinations (9).

Frequency of performing vaccine-focused SDL was categorized as follows: "at least once a day," "at least once a week," "at least once a month," "at least once every 6 months," "at least once a year," and "never". Considering the relatively small number of people in each group, we combined these frequencies into four groups: "more than once/week," "once/month to less than once/week," "once/six months to once/month," and "never to once/six months" respectively. Participants were classified as having received the influenza vaccine if they had been vaccinated for influenza during any of the latest two flu seasons (this was to allow for the potential influence of the Coronavirus Disease 2019 [COVID-19] Pandemic on respondents' ability to receive vaccinations for other diseases). Frequency of recommending vaccines to others was categorized as follows: "routinely," "occasionally," and "never". The latter two groups were combined into the single group "not routinely" because of the limited sample size for these two groups. The efficiency of recommendations was categorized as follows: "all were vaccinated," "most were vaccinated," "a small number were vaccinated," "none were vaccinated," and "unclear". In the subsequent analysis, respondents who reported that all or most of their patients received vaccinations were classified into the group "efficient recommendation," while the remaining respondents were classified into the group "inefficient recommendation". Those who responded "unclear" were excluded.

Statistical analysis

The participants' basic characteristics were described in terms of their frequencies of performing vaccine-focused SDL. Continuous variables and categorical variables were represented using means ± standard deviations (SDs) [or medians (25^{th}-75^{th} percentile)] and counts (percentage), respectively. Analysis of variance (or nonparametric tests) and chi-squared tests were used to examine the differences across groups. The Nightingale Rose Chart was used to categorize the learning topics and sources of those with different SDL frequencies. A Sankey diagram was created to show the flow of participants with different SDL frequencies along the behavior chain. Additionally, to explicitly compare patterns of engagement in vaccination-related behaviors among participants with different characteristics, bar plots were constructed.

To investigate the association between frequency of performing vaccine-focused SDL and engagement in vaccination-related behaviors, unconditional binary logistic regression models were used. In these models, frequency of performing vaccine-focused SDL was set as the independent variable, and being vaccinated (influenza or pneumococcal), routinely recommending vaccination, tracking the vaccination status of patients recommended to receive a vaccine, and recommendation efficiency were set as dependent variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and the group with the lowest frequency of performing vaccine-focused SDL was set as the reference group. Linear trend tests were also performed by modeling the ordered categories of vaccine-focused SDL frequency as a continuous variable in multivariate models, with the Wald test for hypothesis testing (23, 24). To check the robustness of our results, logistic regression models were also fitted for participants who work in hospitals.

Data analyses were performed using SAS (version 9.4; SAS Institute Inc.), R (version 4.1.3; R Core team 2022), and RStudio (version 2022.2.1.461; RStudio Team, 2022), applying the "ggplot2" and "eulerr" packages. All statistical tests were two-sided, with $p < 0.05$ being considered to represent statistical significance.

Results

Sociodemographic characteristics of the study population

Overall, 2,248 questionnaires were returned. After excluding respondents who were younger or older than the target age (18–65 years) and those who provided illogical answers, there remained 2,065 questionnaires for analysis. This sample covered 162 cities across 28 provinces (autonomous regions, municipalities) of mainland China. Most respondents were from western regions (64.21%), those from eastern regions and central regions accounted for 15.35% and 20.44%, respectively.

The characteristics of the participants, categorized in terms of their frequency of performing vaccine-focused SDL are shown in Table 1. The average age of the sample was 36.88 ± 9.35 years, and the median years of professional experience were 12.00 (5.00–20.00). Overall, 1,701 (82.4%) participants worked in hospitals, of whom 11.4, 22.7, and 66.0% worked in primary, secondary, and tertiary hospitals, respectively. The remaining 364 participants worked in other institutions, including community health centers (7.6%), Centers for Disease Control, and Prevention (3.3%), medical colleges or research institutes (4.7%), and "others" (2.3%). The participants who performed vaccine-focused SDL more frequently tended to be younger, have less professional experience, have lower educational attainment, work in lower-level hospitals, and engage in vaccination-related work.

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TABLE 1 Characteristics of participants by vaccine-focused SDL frequency.

		Vaccine-focused SDL frequency				
	Total ($N = 2,065$)	**≥1 time/week ($N = 596$)**	**1 time/month to <1 time/week ($N = 634$)**	**1 time/6 months to <1 time/month ($N = 340$)**	**Never to <1 time/6 months ($N = 495$)**	***p***
Age (years), Mean ± SD	36.88 ± 9.35	36.32 ± 9.94	37.89 ± 8.82	38.06 ± 8.64	35.47 ± 9.55	<0.001
Age group (years), *n* (%)						<0.001
<30	467 (22.62)	158 (26.51)	109 (17.19)	54 (15.88)	146 (29.49)	
30–39	786 (38.06)	213 (35.74)	255 (40.22)	134 (39.41)	184 (37.17)	
40–49	592 (28.67)	162 (27.18)	201 (31.70)	111 (32.65)	118 (23.84)	
≥50	220 (10.65)	63 (10.57)	69 (10.88)	41 (12.06)	47 (9.49)	
Sex, *n* (%)						0.125
Male	691 (33.46)	195 (32.72)	197 (31.07)	131 (38.53)	168 (33.94)	
Female	1374 (66.54)	401 (67.28)	437 (68.93)	209 (61.47)	327 (66.06)	
Professional experience years, Median (Q1–Q3)	12.00 (5.00–20.00)	10.00 (5.00–20.00)	12.00 (7.00–20.00)	13.00 (7.00–21.00)	10.00 (4.00–17.00)	<0.001
Professional experience years, *n* (%)						<0.001
<5	419 (20.47)	132 (22.34)	93 (14.86)	58 (17.11)	136 (27.70)	
5–9	379 (18.51)	126 (21.32)	104 (16.61)	54 (15.93)	95 (19.35)	
10–14	428 (20.91)	96 (16.24)	159 (25.40)	75 (22.12)	98 (19.96)	
15–19	283 (13.83)	82 (13.87)	89 (14.22)	47 (13.86)	65 (13.24)	
≥20	538 (26.28)	155 (26.23)	181 (28.91)	105 (30.97)	97 (19.76)	
Educational attainment						<0.001
Bachelor's degree and below	1,581 (76.56)	510 (85.57)	481 (75.87)	246 (72.35)	344 (69.49)	
Master's degree and above	484 (23.44)	86 (14.43)	153 (24.13)	94 (27.65)	151 (30.51)	
Institution, *n* (%)						
Hospital	1,701 (82.37)	464 (77.85)	534 (84.23)	295 (86.76)	408 (82.42)	
Community health center	157 (7.60)	61 (10.23)	54 (8.52)	17 (5.00)	25 (5.05)	
CDC	68 (3.29)	30 (5.03)	14 (2.21)	12 (3.53)	12 (2.42)	
Medical schools or research institutes	97 (4.70)	29 (4.87)	22 (3.47)	11 (3.24)	35 (7.07)	
Others	42 (2.03)	12 (2.01)	10 (1.58)	5 (1.47)	15 (3.03)	
Occupation, *n* (%)						<0.001
Doctor	1,111 (54.92)	284 (48.63)	368 (58.97)	197 (58.81)	262 (54.58)	
Nurse	530 (26.20)	191 (32.71)	159 (25.48)	78 (23.28)	102 (21.25)	
Technician	118 (5.83)	30 (5.14)	33 (5.29)	23 (6.87)	32 (6.67)	
Medical school students or researchers	168 (8.30)	48 (8.22)	38 (6.09)	19 (5.67)	63 (13.13)	
Others	96 (4.75)	31 (5.31)	26 (4.17)	18 (5.37)	21 (4.38)	
Hospital level, *n* (%)						<0.001
Primary	193 (11.35)	84 (18.10)	59 (11.05)	32 (10.85)	18 (4.41)	
Secondary	386 (22.69)	128 (27.59)	120 (22.47)	56 (18.98)	82 (20.10)	
Tertiary	1,122 (65.96)	252 (54.31)	355 (66.48)	207 (70.17)	308 (75.49)	
Department, *n* (%)						0.014
Respiratory	864 (50.79)	207 (44.61)	285 (53.37)	150 (50.85)	222 (54.41)	
Others	837 (49.21)	257 (55.39)	249 (46.63)	145 (49.15)	186 (45.59)	
Job title, *n* (%)						<0.001
Junior	524 (25.38)	196 (32.89)	150 (23.66)	69 (20.29)	109 (22.02)	
Middle	714 (34.58)	180 (30.20)	235 (37.07)	126 (37.06)	173 (34.95)	
Senior	595 (28.81)	153 (25.67)	200 (31.55)	119 (35.00)	123 (24.85)	
None	232 (11.23)	67 (11.24)	49 (7.73)	26 (7.65)	90 (18.18)	

(Continued)

TABLE 1 (Continued)

	Total ($N = 2,065$)	Vaccine-focused SDL frequency				p
		≥1 time/week ($N = 596$)	1 time/month to <1 time/week ($N = 634$)	1 time/6 months to <1 time/month ($N = 340$)	Never to <1 time/6 months ($N = 495$)	
Work is related to vaccination, *n* (%)	795 (38.50)	340 (57.05)	281 (44.32)	98 (28.82)	76 (15.35)	<0.001
Geographic regions*, *n* (%)						<0.001
Eastern regions	317 (15.35)	94 (15.77)	78 (12.30)	43 (12.65)	102 (20.61)	
Central regions	422 (20.44)	84 (14.09)	118 (18.61)	71 (20.88)	149 (30.10)	
Western regions	1,326 (64.21)	418 (70.13)	438 (69.09)	226 (66.47)	244 (49.29)	
Vaccination-related behaviors, *n* (%)						
Receiving vaccinations	893 (43.24)	322 (54.03)	272 (42.90)	143 (42.06)	156 (31.52)	<0.001
Recommending routinely	1049 (50.80)	405 (67.95)	350 (55.21)	155 (45.59)	139 (28.08)	<0.001
Tracking the vaccination status of people who were recommended†	833 (44.10)	382 (66.78)	272 (44.81)	113 (34.98)	66 (17.05)	<0.001
Recommending efficiently††	751 (91.36)	355 (93.67)	242 (90.30)	100 (89.29)	54 (85.71)	0.107

*Regions were divided according to the National Bureau of Statistics of China. Eastern regions include Beijing, Tianjin, Hebei, Liaoning, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, and Hainan. Central regions include Shanxi, Jilin, Heilongjiang, Anhui, Jiangxi, Henan, Hubei, and Hunan. Western regions include Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Shaanxi, Gansu, and Qinghai.

† For tracking the vaccination status of people who were recommended, the denominator was the number of participants who have ever recommended patients to receive vaccinations.

†† For recommending efficiently, the denominator was the number of participants who tracked and knew the vaccination status of those who were recommended.

Topics and sources for vaccine-focused self-directed learning

The three main vaccine-related topics that the participants investigated in their SDL were vaccine safety (90.4%), target populations (89.8%), and vaccine efficacy (83.3%). Vaccine types (77.9%), immunization procedures (67.3%), and how vaccines function (66.6%) were also important SDL topics (Figure 1A, Supplementary Table S1). The most common source of knowledge was publicity and education efforts in communities and hospitals (67.3%), followed by books or monographs (56.3%), and WeChat (52.6%; Figure 1B, Supplementary Table S2), respectively. The learning topics and sources for participants with different SDL frequencies are shown in Figures 1A,B.

Pattern of vaccination-related behaviors

A Sankey diagram was constructed to illustrate the flow of engagement in vaccination-related behaviors among participants with different SDL frequencies (Figure 2). This diagram showed the behavior chain for receiving vaccines, routinely recommending vaccination to others, tracking the vaccination status of those recommended to receive vaccines, and efficient recommendation. Overall, 43, 51, 40, and 36% of the total participants performed each of the above behaviors, respectively. When only considering those who performed routine recommendations, those who performed tracking and efficient recommendation accounted for 28.8% and 26.2%, respectively (Figure 3A). Influenza vaccines, COVID-19 vaccines, and pneumococcal vaccines were the leading three vaccines that participants have recommended (Supplementary Table S3). The primary reasons participants did not recommend vaccination were inadequate knowledge about vaccines or target populations and an absence of national or workplace requirements to do so (Supplementary Table S4). The transitions of participants with different SDL frequencies along the behavior chain were also displayed in the diagram (Figure 2). Among the participants with the highest SDL frequency (28.9% of the total participants), 322 (15.6% of the total participants) performed the first behavior, and 355 (17.2% of the total participants) performed the final behavior. As a contrast, the participants with the lowest SDL frequency (24.0% of the total participants) fell from 156 (7.6%) to 54 (2.6%) across these stages, respectively.

Participants who performed vaccination-related work showed much higher rates of engagement in vaccination-related behaviors (51.6% vs. 38.0% for vaccination uptake, 66.3% vs. 41.1% for routine recommendation, 44.0% vs. 19.3% for tracking, and 40.5% vs. 17.3% for efficient recommendation) (Figure 3B). Participants working in community health centers performed better than those working in hospitals for all elements of the behavior chain (49.0% vs. 43.1% for vaccination uptake, 56.1% vs. 52.0% for routine

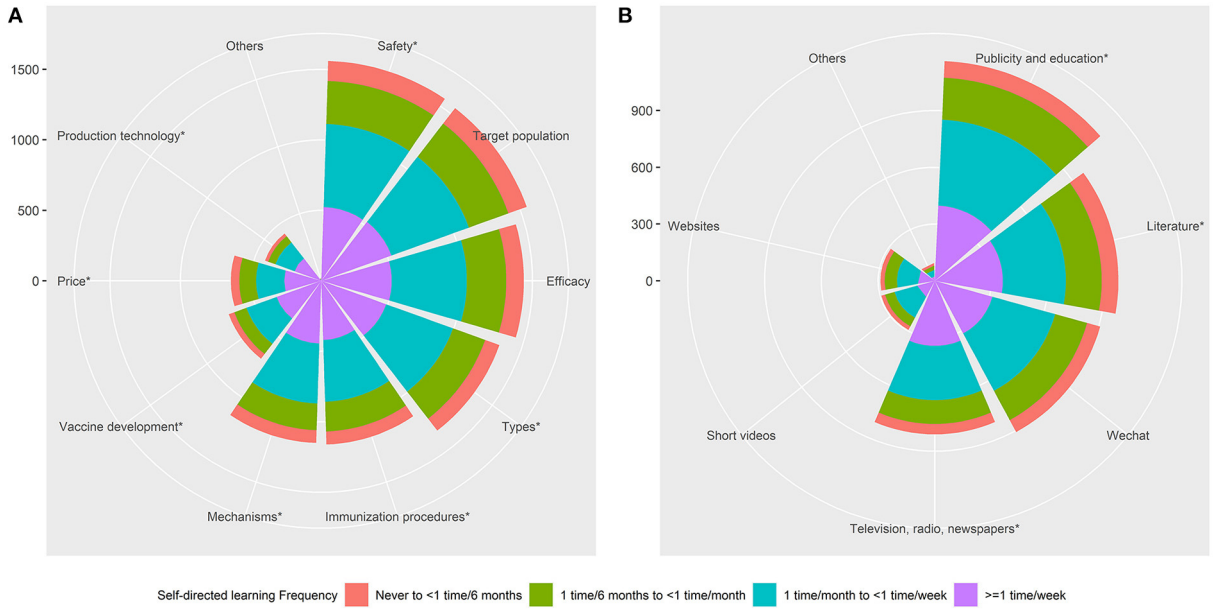

FIGURE 1
Nightingale Rose Chart for learning topics and sources in participants with different SDL frequencies. **(A)** Learning topics. **(B)** Learning sources. Note: The *symbol indicates that there is a significant difference among people with different SDL frequencies on this item.

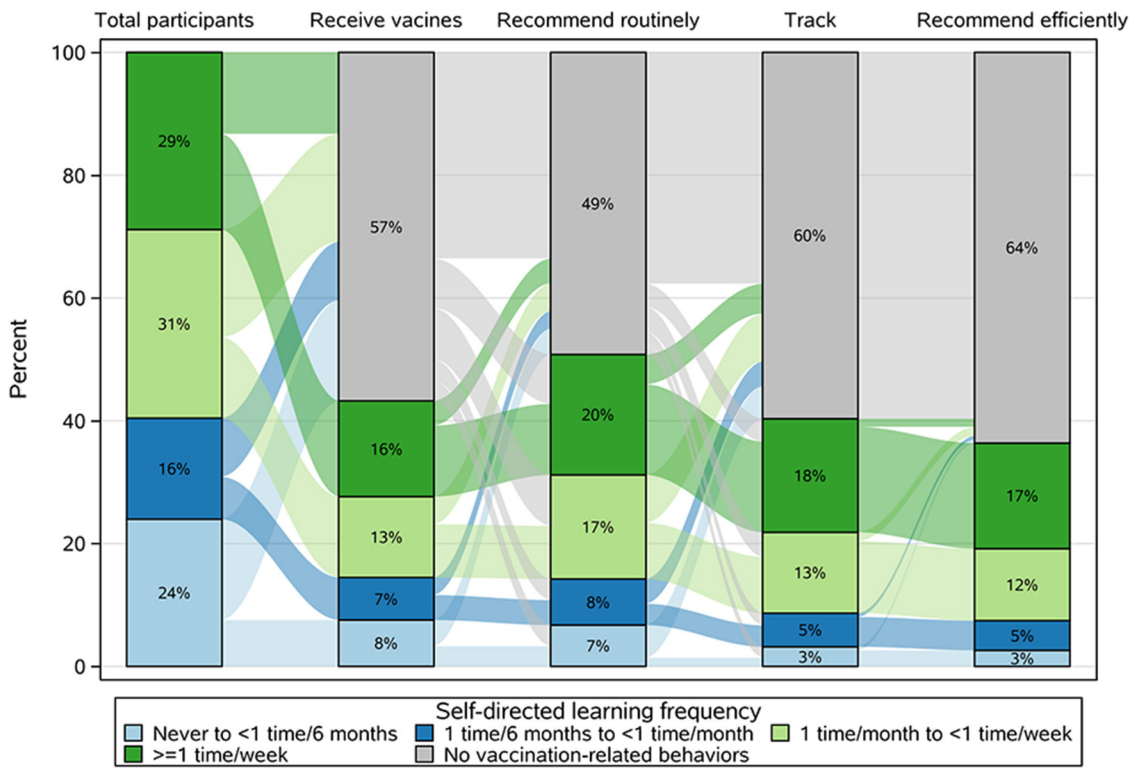

FIGURE 2
Sankey diagram showing the pattern of vaccination-related behaviors among participants with different SDL frequencies.

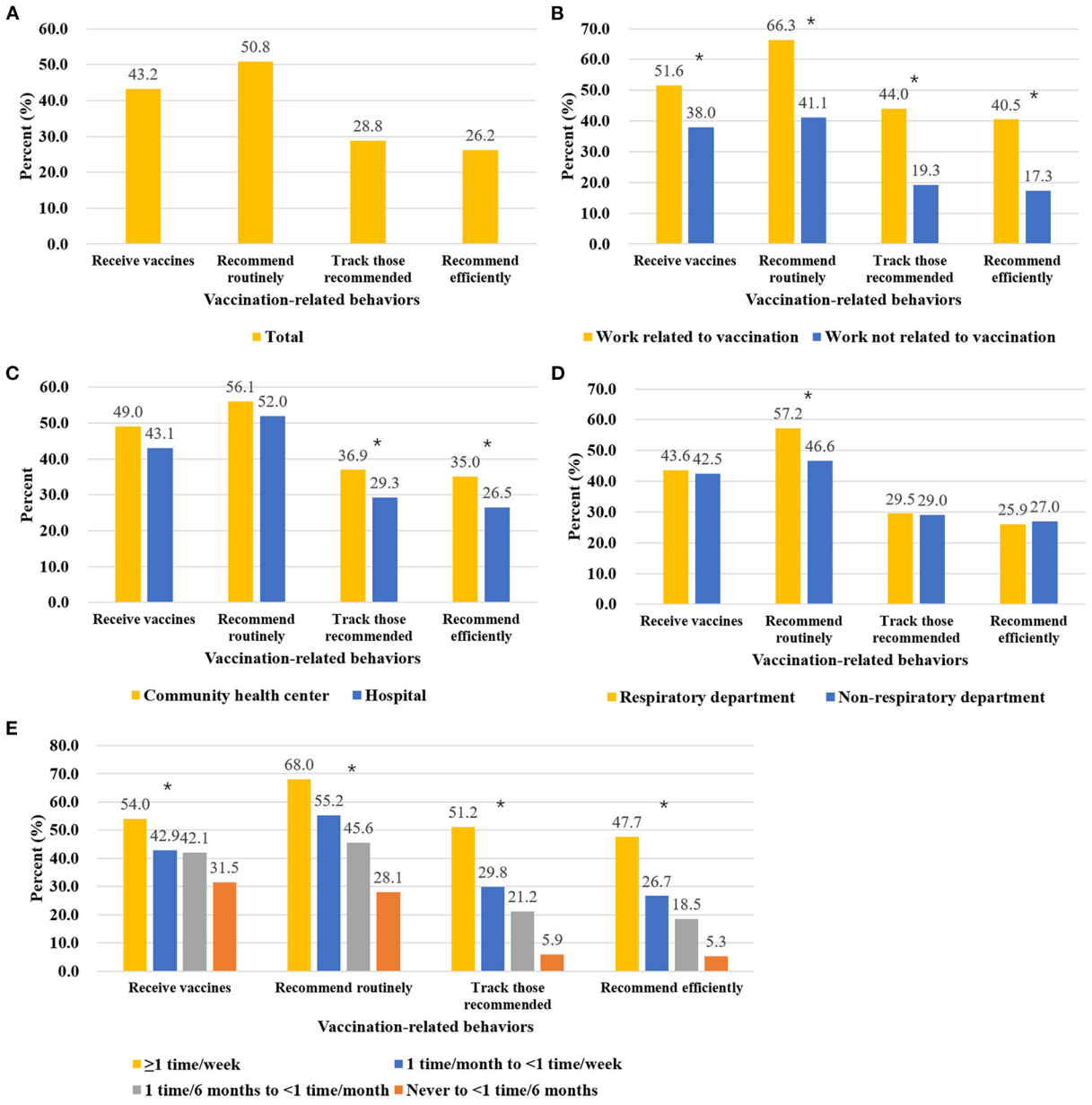

FIGURE 3
Engagement in vaccination-related behaviors among different groups of participants. **(A)** Total participants. **(B)** Participants performing vaccination-related work or not. **(C)** Participants working in hospitals or community health centers. **(D)** Participants working in respiratory or non-respiratory departments. **(E)** Participants with different SDL frequencies. When evaluating the engagement in behaviors of tracking or efficient recommendation, only participants who recommend vaccination routinely were included. Chi-square tests were applied to test the difference among different groups of participants, and the *symbol indicates p-value of <0.05.

recommendation, 36.9% vs. 29.3% for tracking, and 35.0% vs. 26.5 for efficient recommendation, though only the latter two comparisons had significant differences) (Figure 3C). Among participants who worked in hospitals, the rate of engagement in routine recommendation was approximately 10% higher among those who worked in respiratory departments than those who worked in non-respiratory departments (Figure 3D). Statistical tests were provided in Supplementary Table S5.

Higher SDL frequency was associated with higher engagement in all vaccination-related behaviors (Figure 3E). For the participants with the highest SDL frequency, 54.0, 68, and

51.2% were vaccinated, routinely recommended vaccination, and tracked patients' vaccination status, respectively; meanwhile, for the participants with the lowest SDL frequency, these rates were 31.5, 28.1, and 5.9%, respectively. Finally, across the four SDL groups, of those who routinely recommended vaccination and tracking, 93.1, 89.4, 87.5, and 89.7% (from high SDL frequency to low SDL frequency, respectively) did so efficiently.

Association between performing self-directed learning and engagement in vaccination-related behaviors

After controlling for covariates, frequency of performing vaccine-focused SDL was positively associated with engagement in all vaccination-related behaviors except efficient recommendation (Table 2). When compared with the

TABLE 2 Associations between vaccine-focused SDL frequency and vaccination-related behaviors.

	Model 1[a] All participants		Model 2[b] Participants working in hospitals	
Vaccine-focused SDL frequency	**Case/ Control***	**OR (95% CI)**	**Case/ Control**	**OR (95% CI)**
Receiving vaccinations	893 / 1,172		733 / 968	
Never to <1 time/6 months	156 / 339	Ref	132 / 276	Ref
1 time/6 months to <1 time/month	143 / 197	1.46 (1.08–1.98)	126 / 169	1.44 (1.04–1.99)
1 time/month to <1 time/week	272 / 362	1.50 (1.15–1.96)	229 / 305	1.38 (1.03–1.85)
≥1 time/week	322 / 274	2.30 (1.74–3.03)	246 / 218	2.11 (1.55–2.88)
P trend		<0.001		<0.001
Recommend routinely	1,049 / 1,016		884 / 817	
Never to <1 time/6 months	139 / 356	Ref	124 / 284	Ref
1 time/6 months to <1 time/month	155 / 185	1.60 (1.16–2.20)	139 / 156	1.67 (1.19–2.35)
1 time/month to <1 time/week	350 / 284	2.30 (1.74–3.05)	298 / 236	2.19 (1.62–2.97)
≥1 time/week	405 / 191	4.46 (3.30–6.04)	323 / 141	4.80 (3.43–6.72)
P trend		<0.001		<0.001
Track the vaccination status of those recommended to receive a vaccine	833 / 1,056		692 / 889	
Never to <1 time/6 months	66 / 321	Ref	57 / 273	Ref
1 time/6 months to <1 time/month	113 / 210	2.16 (1.48–3.14)	91 / 193	1.80 (1.20–2.69)
1 time/month to <1 time/week	272 / 335	3.08(2.20–4.31)	231 / 283	2.92 (2.04–4.18)
≥1 time/week	382 / 190	6.18 (4.35–8.76)	313 / 140	6.33 (4.33–9.27)
P trend		<0.001		<0.001
Recommend efficiently	751 / 71		623 / 60	
Never to <1 time/6 months	54 / 9	Ref	46 / 8	Ref
1 time/6 months to <1 time/month	100 / 12	1.10 (0.40–3.00)	79 / 11	1.01 (0.34–3.01)
1 time/month to <1 time/week	242 / 26	1.35 (0.55–3.29)	205 / 23	1.27 (0.49–3.30)
≥1 time/week	355 / 24	1.99 (0.79–5.04)	293 / 18	2.28 (0.82–6.35)
P trend	751 / 71	0.080		0.052

[a]Model 1: For the model of receiving vaccinations, covariates included age (<30, 30–39, 40–49, ≥50), sex (Male, Female), years of professional experience (<5, 5–9, 10–14, 15–19, ≥20), educational attainment (Bachelor's degree and below, Master's degree and above), institution (Hospital, Community health center, CDC, Medical schools or research institutes, Others), occupation (Doctor, Nurse, Technician, Medical school students or researchers, Others), job title (Junior, Middle, Senior, None), whether perform vaccination-related work (Yes, No), and geographic regions (Eastern regions, Central regions, Western regions). For models of recommending vaccination routinely, whether getting influenza/ pneumococcal vaccination (Yes, No) was further adjusted. For models of recommending vaccination efficiently, whether getting influenza/ pneumococcal vaccination (Yes, No) and whether recommend routinely (Yes, No) were further adjusted.

[b]Model 2: For the model of receiving vaccinations, covariates included age (<30, 30–39, 40–49, ≥50), sex (Male, Female), years of professional experience (<5, 5–9, 10–14, 15–19, ≥20), educational attainment (Bachelor's degree and below, Master's degree and above), occupation (Doctor, Nurse, Technician, Others), department (Respiratory, non-respiratory), job title (Junior, Middle, Senior, None), whether perform vaccination-related work (Yes, No), whether one works in a hospital that offers on-site vaccination (Yes, No), and geographic regions (Eastern regions, Central regions, Western regions). For models of recommending vaccination routinely, whether getting influenza/ pneumococcal vaccination (Yes, No) was further adjusted. For models of recommending vaccination efficiently, whether getting influenza/ pneumococcal vaccination (Yes, No) and whether recommend routinely (Yes, No) were further adjusted.

*Case represents the number of participants with the indicated behavior, and Control represents the number of participants without the indicated behavior. For tracking vaccination status, the sum of Case and Control was the number of participants who have ever recommended patients to receive vaccinations. For recommending efficiently, the sum of Case and Control was the number of participants who tracked and knew the vaccination status of those who were recommended.

SDL frequency of never to less than once/six months, the SDL frequency of more than once/week was associated with 2.30-times higher odds of being vaccinated, 4.46-times higher odds of routinely recommending vaccination, and 6.18-times higher odds of tracking the status of patients recommended to receive vaccination. A monotonic increase in ORs with increasing SDL frequency was observed for these three behaviors (p-values for trend: <0.001). Similar results were also observed for those working in hospitals (Table 2).

In addition, HCWs with lower levels of education, vaccination-related work, history of influenza or pneumococcus vaccination, doctors, and those in central or western regions of China were more likely to make vaccination recommendations. HCWs with vaccination-related work, nurses, and those in eastern regions of China were more likely to be vaccinated (Supplementary Tables S6, S7).

Discussion

According to the concept of population medicine, to achieve improvements in population health, HCWs should have both individual- and population-based health perspectives, and incorporate disease-prevention into clinical practice (1, 2). Vaccination has been proven to be an efficient approach for disease-prevention and improving public health, and the role of HCWs in promoting vaccination has been highlighted in several previous studies (5). The present study investigated Chinese HCWs' patterns of engagement in a vaccination-related-behavior chain, and the impact that their frequency of vaccine-focused SDL has on these patterns. This chain comprised receiving vaccinations, routinely recommending vaccination to patients, tracking the vaccination status of patients so recommended, and efficiently recommending vaccination. Overall, 43, 51, 40, and 36% of the total participants of this study performed these behaviors, respectively. When only considering participants who routinely recommended vaccination, 28.8% and 26.2% tracked vaccination status and recommended efficiently, respectively. Participants whose work was related to vaccination and those who worked in community health centers or the respiratory departments of hospitals performed better in this regard. Also, higher SDL frequency was associated with greater engagement in vaccination-related behaviors.

Studies have shown that HCWs are twice as likely to be infected with influenza when compared to the general population (4), and that vaccination can reduce illness-related absences among HCWs (25). To increase the vaccination rate among HCWs, the Chinese government has mandated that hospitals provide free influenza vaccinations for such workers (21). However, the rate of influenza and pneumococcal vaccination among HCWs in hospitals remains low, as shown in this study (43.1%). This rate is higher than that reported for seasonal influenza vaccination during the 2018–2019 season (11.6%) (12), but still lower than rates in other countries, such as England (69% in the 2017–2018 season) (26) and the United States (78.4% in the 2017–2018 season) (27). The rate observed in the present study may have been impacted by the COVID-19 Pandemic, which probably disrupted HCWs' routines regarding obtaining vaccinations; however, in this study participants were considered to have received the influenza vaccine if they had gotten vaccinated during any of the previous two flu seasons.

The national influenza-prevention policy of China suggests that recommendations from HCWs are an essential means of promoting influenza vaccination (28). In this study, only half of the total participants routinely recommended vaccination, which is similar to that reported in other studies conducted in China (29, 30). Those who performed vaccination-related work showed an approximately 15%-higher recommendation rate than those who performed other work, and those from respiratory departments showed an approximately 10%-higher rate than those from other departments. Thus, the specific professions of HCWs may be associated with their engagement in vaccination-related behaviors. This accords with the findings of a study that examined professionals who had important roles regarding public human papillomavirus vaccination; the study found that such individuals engaged in relatively higher recommendation behavior (74.8%) (13). Participants who worked in community health centers showed higher recommendation willingness than those who worked in hospitals, which is consistent with previous studies (29, 31). Additionally, an absence of national or workplace requirements to provide vaccination recommendations to patients was reported as being a primary reason participants were unwilling to recommend vaccination. It suggests that it is necessary to organize programs or training to help health professionals understand vaccination policy and enhance their awareness of their roles in public vaccination.

Among participants who routinely recommended vaccination to patients, only 40% tracked the vaccination status of the patients to whom they had made such recommendations. However, the latter group showed a high efficiency of recommendation that over 90% of participants reported that most of their patients received vaccination after being recommended. It is not possible to determine the vaccination status of the untracked patients, but it is reasonable to speculate that patients who were aware that HCWs were tracking their vaccination status had higher motivation to obtain vaccination. Besides, there was no significant difference in the efficiency of recommendation among HCWs with different characteristics (e.g., knowledge, occupation) (32), which suggests that all HCWs' recommendations about vaccination have positive effect on patients' vaccination decisions. Therefore, we consider it a good intervention to encourage HCWs to recommend vaccinations to their patients. Though we did not find any association between the efficiency of recommendation and

HCWs' characteristics, other factors that we did not include in the analysis may influence the recommendation efficiency, such as patients' own perceptions about diseases and vaccines, psychological and social context (e.g., support of family, National Immunization Program vaccines), and practical issues (e.g., affordability, ease of access) (33). Promoting vaccination uptake is a comprehensive issue that it might be insufficient to rely only on HCWs' recommendations. Instead, integrated interventions should be developed, including publicity and education efforts of communities, the positive leading of mass media, government financial support for vaccination.

SDL is an essential life-long learning practice for HCWs, but the current situation regarding HCWs' level of engagement in vaccine-focused SDL must be improved. In this study, almost one-quarter of the participants did not perform vaccine-focused SDL on even a semi-annual basis (although 60% reported that they did so at least once a month). Knowledge limitations have been identified as obstacles to HCWs' vaccination uptake and willingness to recommend vaccination to patients, while greater knowledge has been determined to be a key predictor of HCWs' likelihood of recommending vaccines (because it instills greater confidence regarding counseling patients about vaccines) (13, 34). As expected, in this study SDL was found to be positively associated with active engagement in vaccination behaviors. There was a decreasing trend in engagement in vaccination-related behaviors as SDL frequency decreased. When compared to those with the lowest SDL frequency, the participants with the highest SDL frequency were 2.3-times more likely to uptake vaccination, 4.5-times more likely to recommend vaccination, and 6.2-times more likely to track the vaccination status of patients so recommended. This finding may be explained by the fact that SDL is as effective as traditional teaching methods for improving health professionals' education (35), and is associated with problem-solving ability, which is necessary when offering consultation services for patients (36). Therefore, along with providing training for HCWs, which has been considered by many researchers (37, 38), promoting engagement in vaccine-focused SDL could also play an important role in improving vaccination coverage. Additionally, compared with traditional education and training, SDL, which is a person-centered intervention, involves self-regulation skills and abilities, and allows learners to transfer proximal learner outcomes into distal (long-term) outcomes (16). Hence, it can be suggested that SDL is associated with more sustainable behavior change than standard educational training. However, further investigation is needed to compare these two approaches in practice.

There are some other crucial factors associated with HCWs' engagement with the vaccination-related behavior chain. Although studies have indicated that education can have both a positive and negative effect on vaccine acceptance (39), this study showed that HCWs with higher educational attainment are more likely to receive vaccines; such experience with vaccination could, in turn, increase the likelihood that these workers routinely recommend vaccines and perform tracking of patients so recommended. This is consistent with the view that improving the vaccination uptake among HCWs could have a positive influence on public vaccination (40, 41). We also found that, among our participants, performing vaccine-related work was associated with higher rates of vaccination uptake, routine recommendation, and tracking; this could be explained by the fact that such workers were more knowledgeable about vaccines (and may have had greater recognition of their responsibility for public health in this regard) (40, 41). In China, HCWs' duties regarding vaccination or health education of the public can vary; for example, community health centers are the main institutions that provide vaccination services. Thus, HCWs who work in other facilities may be unaware of the importance of vaccine recommendation and tracking. Therefore, such workers should be provided with training to change their beliefs and attitudes toward public health and disease-prevention. It is also noticeable that on-site vaccination in hospitals increases vaccination coverage among HCWs (because of convenient access to vaccination services), but does not influence the regularity of their recommendations or their recommendation efficiency. This may be because, to get a vaccination, the general population is usually required to make an appointment with a community health center rather than receive a vaccination directly in a hospital. It would be helpful to grant HCWs the authority to provide vaccinations to patients who are willing to get vaccinated in the hospital. Regional economic level was also an associated factor that HCWs from more developed regions tended to receive vaccines while those from less developed regions were more likely to recommend vaccination to patients. The low vaccination uptake in less developed regions is consistent with previous studies (33, 42), which may be due to limited medical resources or insufficient education about vaccination in less developed regions. The reason for the more active recommending behavior in less developed regions could be that HCWs there may have fewer daily visits and have enough time to provide counseling services to their patients.

However, this study nevertheless has several limitations. The sample size was limited and the self-selection bias could exist as many other web surveys because the study let HCWs decide if they would like to participate in the survey, which may result in a sample of individuals that is not representative of the overall population. For instance, it is possible for these participants to have more exposure to self-learning materials than those non-subscribers of the media platform and our study may have overestimated the self-learning behaviors. However, the promotion of SDL is highlighted because the real gap between the current situation of SDL behavior and the expectation is even larger. For the association between SDL behavior and vaccination-related behaviors, the estimation bias could be reduced because we adjusted several sociodemographic characteristics of these participants that might confound our estimation. Besides, the HCWs examined mainly worked in the respiratory departments of hospitals, which could have led to selection bias. However, workers in hospital respiratory

departments are a high-risk population for vaccine-preventable infectious diseases such as influenza and pneumococcal diseases, and their engagement in vaccination-related behaviors would be expected to be better than others. Therefore, this study, by determining their actual level of engagement in vaccination-related behaviors, could clarify the gap between reality and expectation. In addition, vulnerable populations (such as older adults, pregnant women, and children) (7) are more likely to be recommended to get the influenza vaccine, so the vaccination uptake and recommendation rate of HCWs may differ among different hospital departments. However, participants from other departments, such as the department of geriatrics, pediatric department, etc., are fewer, which make it difficult to do a more detailed analysis. Furthermore, some HCWs may have misconceptions about influenza and influenza vaccination or are unaware of latest national guidelines and reimbursement policy for the influenza vaccine (12, 29, 41), but we did not take into account this information (such as their knowledge of influenza and influenza vaccination, perception of vaccine effectiveness and side effects, perceived risk of influenza, the vaccine price, etc.,), so there might be confounding factors that were not investigated, which we will explore further in our future study. Additionally, vaccination-related behaviors were reported by the HCWs themselves and, thus, could be biased. Finally, the recommendation efficiency of HCWs who did not track the vaccination status of patients could not be evaluated. Considering that HCWs who track patients' vaccination status may have more awareness of vaccination importance to their patients and spend more efforts in advocating vaccination for them, our study may have overestimated the efficiency of recommendations.

This is the first nationwide, China-based study to investigate the current status of HCWs' engagement with each phase of a vaccination-related-behavior chain, and it would be helpful to obtain a more comprehensive understanding of HCWs' role in fighting vaccine-preventable diseases in China. This is also the first study to explore the impact performing vaccine-focused SDL has on HCWs' engagement in vaccination-related behaviors; thus, an alternative, potentially more efficient intervention could be suggested. We found that the pattern of engagement in vaccination-related behaviors among Chinese HCWs must be improved. It is necessary to develop interventions to help HCWs understand vaccination policy and enhance their awareness of their roles in public vaccination. Importantly, performing vaccine-focused SDL is positively associated with engaging in vaccination-related behaviors and, thus, could be utilized to foster behavior change and ultimately improve vaccination coverage.

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 studies involving human participants were reviewed and approved by the Medical Ethics Committee of the Chinese Academy of Medical Sciences and Pecking Union Medical College, Beijing, China. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LM, LF, and YM designed the study. DL, YY, and YX were responsible for data collection. YM, XH, and WL performed the statistical analysis and drafted the manuscript. YM, WY, LF, and LM engaged in further writing and review. All authors contributed to the article and approved the submitted version.

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Conflict of interest

DL was employed by Breath Circles Network Platform.

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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.951818/full#supplementary-material

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Optimal information disclosure strategy in the primary healthcare service market: From the perspective of signaling theory

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The promotion of general practitioner (GP) contract service is one of the key components of China's healthcare reform. We consider GPs providing primary health services with private competency information over two periods, where patients decide when to sign. Two types of GPs are considered: those with higher and lower competency. Under asymmetric information, to spur the patients' incentive to sign, the GPs can move to offer competency disclosure schemes to patients, for example, separating or pooling, through which true competency information is revealed, respectively. We investigate three scenarios, which are referred to as "separating-separating," "pooling-separating," and "pooling-pooling." The results of the three scenarios yield intriguing insights into the impact of the GP's competency disclosure decisions. Findings include that GPs prefer the "pooling-separating" strategy, but patients prefer "separating-separating." Besides, an extremely low cure rate may enable GPs to conceal some competency information. Furthermore, low-competency GPs may exaggerate their competency level for profit, but greater efforts in disclosing competency information may result in diminished benefits. Therefore, to promote the services of GPs, the core is always to improve GPs' competency.

KEYWORDS

general practitioner, competency, information disclosure, signaling theory, primary healthcare

Introduction

A general practitioner (GP), also known as the "gatekeeper" of the primary healthcare system, is at the vanguard of comprehensive primary care services and holds a prominent position in expanding access to primary care services (1, 2). For the advantages of enhancing the residents' health along with cost reduction (3), the practice of GP service has gained wider acceptance in the primary health market worldwide (4–6). Therefore, in 2016, China proposed to establish a general practitioner system to provide contract services, ensuring that all citizens can reach comprehensive, preventive public health services and the achievement of Health China 2030 (7, 8).

Competency is the foundation for GPs' effective provision of contracted services and plays a supporting role in the construction of the hierarchical medical system. Building on the prior definitions, competency in healthcare refers to the habitual and judicious use of communication, knowledge, technical skills, clinical reasoning, emotions, values, and reflection in daily practice for the benefit of the individual and the community being served (9–12). The existing literature manifests that GPs' competency can influence demand for signing based on its impact on medical quality (13–16). However, in China, providers working in primary healthcare market with doctoral and master degrees are only 0.3 and 5.5%, along with the information asymmetry between providers and patients (17), resulting in the prejudice of patients and difficulties in promoting GP contract service in China. This problem directly leads to the decline in Chinese residents' willingness to seek medical treatment at the grassroots level. The proportion of residents who visit primary medical institutions has dropped from 57.6% in 2016 to 33.9% in 2021, putting additional strain on medical resource allocation. Since the Chinese government has been raising investment in its primary healthcare system, a better disclosure strategy of the competency, which can encourage the signing willingness of those patients, is crucial for dispersing GPs' services. This justification compels decision-makers to address GPs' competency disclosure.

Information disclosure, as one of the important tools for improving patient–provider alignment, can help patients understand professional medical information and improve the efficiency of the healthcare market (18). The reason for greater transparency is that patients value the quality of their healthcare providers (19, 20). The theory behind such activities is to improve the accountability of service providers through the disclosure of quality-of-care information (21), enabling (i) patients to seek providers with higher quality, and (ii) medical service providers to enhance quality to possess their market share. Eventually, creating a healthcare system in which social welfare is expected to increase (22). For decades, policymakers worldwide have been stepping up efforts to establish mature medical information disclosure systems (23). For example, in 2002, America launched the Hospital Quality Alliance (HQA), a national public–private organization, to announce hospital care information to the public (24). The Hospital Comparison Website was launched by the Centers for Medicare and Medicaid Services (CMS) in 2005. In 2011, British Prime Minister David Cameron pledged that the National Health Service (NHS) would publish performance data to provide citizens with modern, personalized, and long-term public services (25).

Disclosure programs undoubtedly provide the ability to provide patients with timely, relevant, and broader information, while all previous contributions ignore the issue of disclosing competency strategies among different GPs. As GPs are in advantageous positions in possessing their own competency information, some low-level GPs may take opportunistic actions to obtain more contract orders, for example, exaggerating their competency. Such activities exacerbate provider–patient conflicts and lead to the phenomenon of "bad money driving out good money" in the primary healthcare market. Accordingly, this last paper introduces the signaling theory to investigate the optimal disclosure strategy of GPs. As a fundamental tool for solving the problem of information asymmetry between two players (26), signaling theory occupies an outstanding position in various management pieces of literature, such as logistics management, entrepreneurship, human resource management, and quality management (27). A recent study of CSR governance, for example, identifies how decision-makers signal the unobservable good greenwashing of their firms to potential consumers *via* the observable CSR investments (28). Signaling theory is also vital to human resource management, where Ke and Zhu examined the signaling matching problem that happens between recruiters with private preferences information and freelancers on the decentralized freelance platform (29).

In this paper, to spur the patients into signing with the GP, combining the signaling theory, we develop a two-period game model of competency disclosure. To begin with, we assume that there exists asymmetric information between GPs and patients regarding GPs' competency. We specifically study two types of GPs based on their different levels of performance (30): those with high- (low-) competency are referred to as h-type (l-type) GPs. GPs can decide on different intensities of competency disclosure through the public report or other activities. Taking online medical services as an example, physicians can use system-generated information (education background, work experience, and number of papers) to help patients determine the quality of their service and attract more visitors (31). Also, patients are uninformed about their competency in the first stage, while they can access a signal about their competency in the second stage from the patients who have signed with GPs in stage 1 for their habit of relying on the recommendations of others (32, 33). Besides, the GP can choose one of two disclosure equilibrium strategies (separating or pooling) to distribute the competency information. Under the separating disclosing strategy, GPs are allowed to decide different disclosure intensities (e.g., publishing a different number of articles), helping patients infer the true competency. A pooling strategy permits two types of GPs to set the same disclosure intensity (e.g., similar working experience), hindering patients from extrapolating true competency. The mix of two disclosing decisions in two periods leads to

three scenarios. The GP can select one of them to control the competency information. By contrasting the outcomes of the three scenarios, we intend to answer the following research questions:

(i) Which competency disclosure strategies are preferred by the GPs and by the patients?
(ii) Under the three information disclosure decisions, will low-competency GPs take deceptive behavior? Whether can they make more profits by cheating than those with high-competency?
(iii) During the process of the signing service, what factors will affect GPs' disclosure efforts and the respective benefits of GPs and patients?

The following summarizes our main results. First, preferences for the competency disclosure strategies of GPs and patients differ. GPs prefer the pooling-separating strategy while considering the maximization of their social welfare, patients prefer the separating-separating strategy. Second, when the level of primary medical facilities is too low, GPs may not be willing to announce their competency to society and even conceal some information. This finding further corroborates previous research (34). Third, to maximize their profits, low-competency GPs may inflate their competency levels to attract patients to contract with them, while increased disclosure efforts do not always result in increased benefits and can sometimes lead to additional costs. Therefore, for GPs, the core work is still to strengthen training and improve the level of competency.

The rest of this study is organized as follows. Section Methods presents the model configuration. Section Results outlines the equilibrium outcomes in various circumstances and conducts the comparison with some numerical results. Section Discussion is devoted to making some closing remarks and management insights. The proofs are included in the Supplementary material.

Methods

Model setup

In this section, we establish a model relying on classical signal theory, which is composed of a representative GP ("sender") and a representative patient ("receiver"). Table 1 summarizes the notations used along with the paper. To build a model that can assist us in understanding the influence of disclosing the competency of GPs on the choices of patients, we consider a fixed continuum of patients with a total mass normalized to one that seeks treatment from j type GPs over two periods $i = 1, 2$. Here, $j=h,l$ denotes high-competency GP and low-competency GP, respectively, which is determined at the outset by nature, and the GPs learn their unique type. A GP has a prior probability γ of being a high-competency type (e_h).

TABLE 1 Notations for variables and parameters.

Notation	Description
i	index of the signing period, $i = 1, 2$
j	type of the GPs, j = h, l
ρ	discount factor
s_j	signal's type
a	accuracy of the signal
e_j	actual competency of the GP j
c_{ij}	competency information disclosure level of the j-type GP at signing period i
n_{ij}	the volume of patients having the willingness to sign with the j-type GP at period i
N_{ij}	the volume of patients signing with the j-type GP at signing period i
π_{ij}	signing profit of the j-type GP at signing period i
H_{ij}	the cost of the competency disclosure activities
PS	patients' social welfare
p	signing fee
m	initial signing rate of the GPs
γ	the probability that the competency of the GP is high

Equilibrium concept

We adopt the concept of perfect Bayesian equilibrium as a solution (35). In brief, given the prior belief γ about the type of GP, the patient fine-tunes the patient's belief in light of Bayes' rule and optimally reacts to the GPs' observed disclosure actions. The GP optimally determines their competency information disclosure level according to the patient's posterior belief and reactions.

Specifically, patients in the first stage can only obtain a prior probability about the GP's competency, but patients in the second stage have access to a posterior probability. Let e_j ($j=h,l$) denotes the true competency of GP j, while s_j characterizes the signal about the competency obtained by the patients in period 2 from the first-stage patients. Using a to depict the accuracy of the signal from the early patients, that is, $\Pr(s_h|e_h) = \Pr(s_l|e_l) = a$. Such information structure has been widely applied in modeling incomplete information in previous research (36, 37).

Hence, the Bayesian-updated probabilities of competency based on the comments s_h and s_l are as follows:

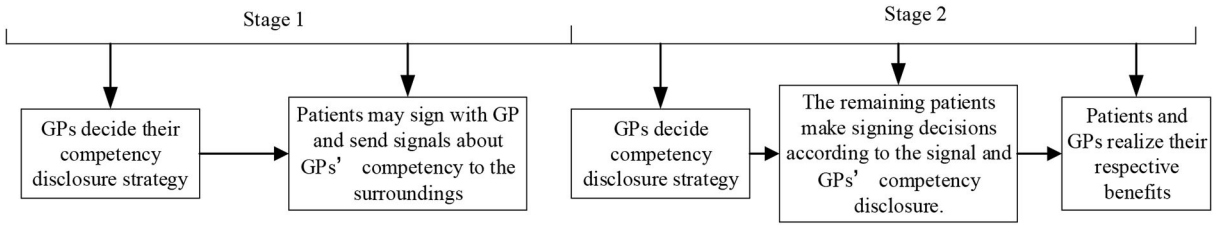

FIGURE 1
Decision sequence.

$$Pr(e_h|s_h) = \frac{a\gamma}{Pr(s_h)},\ \Pr\left(e_l|s_h\right) = \frac{(1-a)(1-\gamma)}{Pr(s_h)}, \Pr\left(e_h|s_l\right) = \frac{(1-a)(\gamma)}{Pr(s_l)}, \Pr\left(e_l|s_l\right) = \frac{a(1-\gamma)}{Pr(s_l)},$$

where $\Pr\left(s_h\right) = a\gamma + (1-a)(1-\gamma)$ and $\Pr\left(s_l\right) = \gamma(1-a) + a(1-\gamma)$.

The equivalent competency e depending on the signals are as follows:

$$E\left[e|s_h\right] = e_l \Pr\left(e_l|s_h\right) + e_h Pr(e_h|s_h), E\left[e|s_l\right] = e_l \Pr\left(e_l|s_l\right) + e_h Pr(e_h|s_l).$$

As in the previous literature (28, 38), our study only concentrates on pure-strategy equilibria in this paper, that is, separating equilibrium and pooling equilibrium. Under the premise of the same signing fee p, in the separating equilibrium, different types of GPs will choose different competency information disclosure efforts, such as the different number of published articles, work, and study experience, to assist patients in accurately determining the type of GPs; in a pooling equilibrium, two types of GPs choose to publish the same information. For example, if two types of GPs publish the same number of papers, the same information makes it impossible for patients to determine the true type of GPs, only the prior probability. Based on the preceding analysis, and given that this paper is an intertemporal decision-making problem, Figure 1 depicts the sequence of each player's decisions. We shall consider three disclosure scenarios:

Separating-separating equilibrium: GPs who own different level of competency optimizes their respective profit by choosing different disclosure strategies over time $\overrightarrow{c_{1j}}$, $\overrightarrow{c_{2j}}$, $j \in \{h,l\}$. By assessing the separating information about GPs' competency in the stage 1, all patients can perfectly infer the true competency of each GP by analyzing the information in both signing stages.

Pooling-separating equilibrium: There could be a pooling equilibrium in period 1, in which the two types of GPs disclose the same information about their competency, that is, $\widetilde{c_1}=c_{1j}$, whereas the information disclosed in period 2 differs, $\widetilde{c_{2j}}$, $j \in \{h,l\}$. Hence, patients cannot distinguish the GP's competency level in the first signing stage, but can exactly deduce the GPs' competency in the second signing stage.

Pooling-pooling equilibrium: Different types of GPs disclose the same information in each signing stage, that is, $\hat{c_1}=c_{1j}$, $\hat{c_2}=c_{2j}$ $j \in \{h,l\}$. Therefore, patients cannot tell the GP's true type in the first period, while in the second signing stage, prospective patients can get a signal regarding competency from the patients in the first stage. Thus, the patients can renew their expectation about GP's competency taking account of this signal.

Patients' utility

As for the patients, they can choose to sign with the GP immediately or postpone the signing until the second stage.

To model a patient's choice, we assume the utility of a patient who chooses GP j depends on the competency and signing fee. Given the signing bonus p and the perceived information c_{1j} that the GPs j diclose, the patients' expected utility from signing the contract with the specific GP in the first stage is as follows:

$$U_1 = v + c_{1j} + E[e_j] - p, \quad (1)$$

where the $E[e_j] = \gamma\ e_h + (1-\gamma)\ e_h = \mu$.

Similar to Bisceglia et al. (39), v is the patient's private valuation of the medical service provided by the specific GP j. It describes the initial signing willingness of patients with those specific GPs. Due to that there exists heterogeneity of signing intention among different individuals, this study supposes it is uniformly distributed over [0, 1]. When their valuations of j GP are higher than $\overrightarrow{v_j}$, a total of $n_1 = 1-\overrightarrow{v_j}$ patients will have the willingness to sign with the j GP in the first phase. The threshold $\overrightarrow{v_j}$ divides patients who seek the GPs into the early and late signing stage. This paper is a classical intertemporal selection problem, which requires patients to trade off costs and benefits at different points in time (40). We introduce the discount factor $\rho > 0$, and the value of threshold $\overrightarrow{v_j}$ can be accessed by solving

$U_1 > \rho U_2$. Because of information asymmetry, the true value of e is the GPs' intimate message about their competency, which is also not originally known by patients who merely have access to the prior distribution $E[e_j]$. Besides, the utility of the patients increases with the competency disclosure level c_{1j} and decreases with the signing fee p.

Those patients with valuations below $\overrightarrow{v_j}$ would delay signing to the second period. At this moment, they get additional competency signals as they receive evaluation information from the patients who have signed with the specific GP in stage 1. Hence, the patients' expected utility in stage 2 is as follows:

$$U_2 = v + c_{2j} + E[e|s_j] - p, \tag{2}$$

Here, $E[e|s_j]$ portrays the patients in the second stage can know the posterior quality probability of GPs' competency level, because they can access a signal about competency by reviewing comments from the patients who have signed with GPs in stage 1. The corresponding information set $I_t = (I^1, I^2)$ depicts the information available to the patient in three scenarios $t = 1, 2, 3$, where I^1 denotes the perceived information of patients in period 1, and I^2 represents that in period 2. Notice that $I_1 = (e_j, e_j)$, $I_2 = (E[e], e_j)$, $I_3 = (E[e], s_j)$. In this phase, the remaining patients with a non-negative utility will consider signing the contract with the j GP, that is, $U_2 > 0$, which formulates the minimum threshold of the valuation and the potential volume of the contracts $n_2 = \overrightarrow{v_j} - \max\{0, vj\}$.

To emulate the perspective of society as a whole, or equivalently that of a decision-maker charged with preserving societal interests, we define patients' social welfare as the sum of the expected surplus in both periods obtained by all patients, as provided by the following:

$$PS_1 = \sum Pr(e_j) \int_{\overrightarrow{v_j}}^{1} \{v + E[e|I^1] + c_{1j} - p\} dv, \tag{3}$$

$$PS_2 = \sum Pr(e_j) \int_{\max\{0,\}}^{\overrightarrow{v_j}} \{v + E[e|I^2] + E[c_{2j}|I^2] - p\} dv, \tag{4}$$

or

$$PS_2 = \sum Pr(s_j) \int_{\max\{0,\}}^{\overrightarrow{v_j}} \{v + E[e|I^2] + E[c_{2j}|I^2] - p\} v,\ j \in \{h, l\}. \tag{5}$$

Patients would consider the sum of welfare in signing stage 1 and the expected welfare in stage 2 when making their respective signing decisions. The total patients' social welfare is $PS = PS_1 + \rho PS_2$.

GPs' objectives

Of note, although a significant number n_{ij} of patients might have the willingness to opt for j GPs, not all of them end up signing with them. Hence, they need to decide their competency information disclosure levels c_{ij} to attract patients to sign with them, maximizing their signing profits. Based on this hypothesis, the actual number of people signing up with j GP is as follows:

$$N_{ij}(c_{ij}) = n_{ij}^{*} m^{*} (1 + c_{ij}).$$

In this setting, $m \in (0, 1)$ represents the initial signing rate of the patients, which is affected by the competency disclosure level c_{ij}. For simplicity, denote by r cure rate of j GP and by m the resulting patients' initial signing rate with j GP, with $m = f(r)$, where $f()$ is an increasing function. Assuming a monotone increasing relationship between cure and initial contract rate, we can express the total signing volume as a function of initial contract rate m and competency disclosure level c_{ij}.

We consider the following function for the cost of competency disclosure activities:

$$H_{ij}(c_{ij}) = \frac{1}{2} {c_{ij}}^2.$$

This functional form assumes that the cost of each GP's disclosure actions is strictly growing and convex.

Citing the functional forms given above, the j GP's optimization problem in the first period is as follows:

$$\pi_{1j} = \max_{c_{1j}} \{(1 - \overrightarrow{v_j})^{*} p^{*} (m^{*}(1 + c_{1j})) - \frac{1}{2} {c_{1j}}^2 + \rho \pi_{2j}\}, \tag{6}$$

which means that GP obtains a benefit from the signing fee p, the total volume of the contracts N_{ij} that depend on the competency disclosure level c_{1j}, and pays the cost of investment in competency disclosure H_{ij} at that period. Besides, in the first signing period, GP has to consider the discounted profit in the stage 2, in which discount factor is labeled as ρ.

Consistent with π_{1j}, we model the profit to the GP of type j in the second stage as follows:

$$\pi_{2j} = \max_{c_{2j}} \{(\overrightarrow{v_j} - \max\{0, \})^{*} p^{*} (m^{*}(1 + c_{2j})) - \frac{1}{2} {c_{2j}}^2\}. \tag{7}$$

Results

This section derives the optimal competency disclosure decisions for three scenarios.

Separating-separating equilibrium

In this case, GPs choose different intensity levels of competency disclosure c_{ij}, which means that all patients can distinguish the true competency level of the medical services e_j by analyzing the information. The GP's optimization is as follows:

$$\vec{\pi}_{1j} = \max_{\vec{c}_{ij}}\{\left(1-\vec{v}_j\right) pm\left(1+\vec{c}_{1j}\right) - \frac{\vec{c}_{1j}^{\,2}}{2} + \rho\left(\left(\vec{v}_j - \left(p - e_j - \vec{c}_{2j}\right)\right) mp\left(1+\vec{c}_{2j}\right) - \frac{\vec{c}_{2j}^{\,2}}{2}\right)\}.$$

The GP's strategies and profits are summarized in the following propositions.

Proposition 1. *In the case of separating-separating equilibrium, the competency information disclosure level of the j GP in the first period is given by*

$$\vec{c}_{1h} = \frac{-b_1 + \sqrt{c_1}}{1 + \frac{2mp(-1+2mp)}{1+mp(-2+\rho)-\rho} + \frac{m^2p^2(-1+2mp)\rho}{(1+mp(-2+\rho)-\rho)^2}}, \tag{8}$$

and

$$\vec{c}_{cc} = \frac{\begin{array}{c} mp(-m^2p^3(-2+\rho)^2 + 2(-1+\rho)^2 \\ +2mp^2(2+m(4-3\rho)-3\rho+\rho^2)+A_{11}) \end{array}}{\begin{array}{c} (-1+\rho)^2 + 2m^3p^3(-4+3\rho) + m^2p^2(12-11\rho+\rho^2) \\ -2mp(3-4\rho+\rho^2) \end{array}}, \tag{9}$$

respectively, where the expression of c_1, b_1, *and* A_{11} *is given in Supplementary material.*

The corresponding second-period information disclosure level is

$$\vec{c}_{2h} = -\frac{mp(-1+\rho+\vec{c}_{1h})}{1+mp(-2+\rho)-\rho}, \tag{10}$$

$$\vec{c}_{2l} = \frac{\begin{array}{c} mp(m^2p^2(8+p(-2+\rho)-6\rho)+(-1+\rho)^2 \\ -mp(-1+\rho)(-6+p+\rho)+A_{12}) \end{array}}{\begin{array}{c} (-1+\rho)^2 + 2m^3p^3(-4+3\rho) + m^2p^2(12-11\rho+\rho^2) \\ -2mp(3-4\rho+\rho^2) \end{array}}, \tag{11}$$

respectively, where the expression of A_{12} *is also shown in Supplementary material.*

Proof. See Supplementary material.

By substituting the above equilibrium outcomes of competency disclosure level into the objective functions, we can calculate the respective revenue of j GP in each stage $\vec{\pi}_{ij}, i \in \{1,2\}, j \in \{h,l\}$, as well as the gross revenues $\vec{\pi}_j$. Here, we can infer that the total profit of different GPs is equal, that is, $\vec{\pi}_h = \vec{\pi}_l$. This outcome illustrates that to distinguish themselves from the low-competency GP, h GPs have to increase their disclosure level to the point where the l GP does not want to emulate without affecting h GP's earnings. However, this decision leads to profit loss of h GPs.

Pooling-separating equilibrium

In this scenario, the GPs determine the same disclosure level in the first period and different disclosure level in period 2. Recall that the profit function is given by the following:

$$\widetilde{\pi}_{1j} = \max_{\widetilde{c}_1, \widetilde{c}_{2j}}\{(1-\widetilde{v})pm(1+\widetilde{c}_1) - \frac{\widetilde{c}_1^{\,2}}{2} + \rho((\widetilde{v} - (p - e_j - c_{2j}))pm(1+c_{2j}) - \frac{{c_{2j}}^2}{2})\}.$$

The following proposition gives, albeit not in an explicit form, the optimal strategies in the two periods.

Proposition 2. *In the case of pooling-separating equilibrium, the competency information disclosure level of the j GP in the first period is given by*

$$\widetilde{c}_{2h} = \frac{-mp(mp-\widetilde{v}-e_h-1) + \sqrt{\begin{array}{c} mp(e_h-e_l)(2-2mp-2mp^2 \\ +2mp\widetilde{v}+mpe_l+mpe_h) \end{array}}}{(1-2mp)}, \tag{12}$$

and

$$\widetilde{c}_{2l} = \frac{-mp\widetilde{v} - mpe_l - mp + mp^2}{(2mp-1)}, \tag{13}$$

respectively, where the expression of $\widetilde{v}$ *is given in Supplementary material. Then, the GP's first-period disclosure intensity is the positive root of the following polynomial:*

$$\widetilde{\pi} = \max_{\widetilde{c}_1}\{(1-\widetilde{v})pm(1+\widetilde{c}_1) - \frac{1}{2}\widetilde{c}_1^{\,2} + \rho(\gamma\widetilde{\pi}_{2h} + (1-\gamma)\widetilde{\pi}_{2l})\}.$$

By substituting $\widetilde{c}_1$ *into the following profit functions can obtain the respective benefits of each*

$$\widetilde{\pi}_h = (1-\widetilde{v})pm(1+\widetilde{c_1}) - \frac{1}{2}\widetilde{c_1}^2 + \rho\widetilde{\pi}_{2h}, \widetilde{\pi}_l$$
$$= (1-\widetilde{v})pm(1+\widetilde{c_1}) - \frac{1}{2}\widetilde{c_1}^2 + \rho\widetilde{\pi}_{2l}$$

Proof. See Supplementary material.

As explained in Supplementary material, the root of $\widetilde{c_1}$ cannot be analyzed without resorting to numerical simulations. For the rest, we will illustrate our results numerically with parameter values.

Pooling-pooling equilibrium

Given that in this scenario, the GPs of different types disclose the same level of competency information in each period, the objective function becomes

$$\hat{\pi} = \max_{\hat{c_1},\hat{c_2}}\{(1-\hat{v})pm(1+\hat{c_1}) - \frac{1}{2}\hat{c_1}^2 + \rho(Pr(s_h)\pi_{2j}(s_h) + Pr(s_l)\pi_{2j}(s_l))\},$$

where $\pi_{2j}(s_h)$ and $\pi_{2j}(s_l)$ represent the benefits obtained by the GP when prospective patients infer the GP's type by assessing the signal about the GP from early sufferers. That is, according to this signal, profits will vary as these patients update their expectations about the GPs' type.

The GP's optimal disclosure strategies in each period when the patients receive different signals are summarized in the following proposition.

Proposition 3. *In the case of pooling-pooling equilibrium, the competency information disclosure level of the j GP in the second period is given by*

$$\hat{c_2}(s_h) = \frac{mp(-1+a+p-ap+\gamma-2a\gamma-p\gamma+2ap\gamma+(-1+a+\gamma-2a\gamma)\hat{v}+(-1+a+\gamma-a\gamma)e_l-a\gamma e_h)}{(-1+2mp)(1-\gamma+a(-1+2\gamma))}, \quad (14)$$

and

$$\hat{c_2}(s_l) = \frac{mp(a-ap+\gamma-2a\gamma-p\gamma+2ap\gamma+(a+\gamma-2a\gamma)\hat{v}+(a-a\gamma)e_l+\gamma e_h-a\gamma e_h)}{(-1+2mp)(-\gamma+a(-1+2\gamma))}, \quad (15)$$

respectively, where the expression of $\hat{v}$ is given in the Supplementary material. Then, the GP's first-period disclosure intensity is the positive root of the following polynomial:

$$\hat{\pi} = \max_{\hat{c_1}}\{(1-\hat{v})pm(1+\hat{c_1}) - \frac{1}{2}\hat{c_1}^2 + \rho(Pr(s_h)\pi_{2j}(s_h) + Pr(s_l)\pi_{2j}(s_l))\}.$$

Proof. See Supplementary material.

Similar to the previous, since the explicit solution of the first stage cannot be solved, we obtain the optimal equilibrium strategy of the first stage through numerical simulation.

Numerical analysis

In the previous sections, we characterize the equilibrium solutions for the high- and low-competency GPs under the three scenarios. In this part, the numerical simulation is conducted to identify the effects of the modeling parameters, including signing fee p, initial signing rate m, and the competency parameters e on the equilibrium intensity of competency disclosure c, profits π, and patients' social welfare PS, among the above strategies. We start by describing the methodology used and, next, show the outcomes.

The first step is to select the standard for determining the most efficient equilibrium result. Then, we consult the previous literature to determine the parameter values for this paper, and we use the Mathematica software to simulate the trajectories of the results obtained in the preceding subsections. Finally, we examine the responses of the equilibrium strategies to the key parameters using the sensitivity test. During this process, we also vary relevant parameters within a range of ±15% to check whether the qualitative outcomes of the equilibrium strategies are robust to the model calibration (41). Here, we only present the partial results of the robustness test for the parameter γ in Figure 2, but we verify that the robust tests of the rest parameters also hold.

We cite the concept of lexicographically maximum sequential equilibrium (LMSE) as the standard for choosing the most efficient equilibrium outcome (42). According to this principle, the revenue of players who have the most incentive to reveal their true type will be viewed as the criteria for judging the optimal outcome, that is, h GP. Specifically, the pooling equilibrium strategy would be selected if the high-competency GP can gain more profits under the pooling equilibrium than under the separating strategy.

We performed various numerical simulations by varying the different parameter values around the following benchmark: $p = 0.8$, $\rho = 0.95$, $a = 0.7$, $e_h = 0.09$, $e_l = 0.01$, $m = 0.5$, $\gamma = 0.4$.

The results are shown in a series of charts. In each diagram, we plot the variation of equilibrium outcomes that change one parameter, while the rest retain at their base case level.

Impact of *m* on equilibrium outcomes

Using the previous baseline values, we illustrate in figures the influence of m on the equilibrium disclosure intensity, profit, and patients' social welfare, respectively. To meet the concavity of the functions and avoid trivial results, that is, $2mp - 1 < 0$, the range of values of m is finite (see the Supplementary material for more details).

Conjecture 1. *Figures 2A,B presents that for three scenarios, the profits of GPs and patients both increase with the signing rate, whereas the preferences for optimal disclosure strategies of each deviate. According to LMSE, the high-competency GP has an incentive to choose the pooling-separating strategy, while the patients prefer the separating-separating strategy. Formally:*

$$\widetilde{\pi_h} > \hat{\pi} > \overrightarrow{\pi}, \overrightarrow{PS} > \hat{PS} > \widetilde{PS}.$$

To interpret this conjecture, the signing rate m is positively correlated with the cure rate of the GPs. Intuitively, the signing rate raises prospective patients' utility, stimulating the total demand, which finally brings about higher profits and higher patients' welfare. As such, the increased cure rate leads to a win–win outcome for the GPs and patients.

Conjecture 2. *Comparing the trajectories in Figures 3A–C:*

1. *The equilibrium disclosure level c increases with the initial signing rate m.*
2. *An extremely low cure rate leads to the phenomenon of concealing competency.*
3. *Implementation of the competency disclosure may lead to more costs, resulting in a certain loss of revenue.*

Figure 3 reveals that first, in all scenarios, the equilibrium disclosure level small fluctuates, but generally increases with the signing rate m. This illustrates the importance of increasing the contracting rate, which requires increased investment in medical equipment, since the initial contracting rate is positively correlated with the cure rate. Second, we find that the value of c is negative when the m is too low. This finding indicates that an extremely low cure rate may enable GP to conceal some competency information, which further confirms the previous findings. Third, combined with Figure 2, in the pooling-separating equilibrium strategy, although the information disclosure level of h GP is less than that of h GP in the separating-separating equilibrium strategy, the income of h GPs is higher than that of the separating-separating equilibrium strategy, which means that the implementation of the separating-separating strategy leads to more disclosure costs, resulting in a certain loss of revenue. Therefore, it is necessary to establish necessary information disclosure mechanisms, such as information sharing platforms, to reduce the cost of disclosure. In the long run, it is possible to realize the supervision of the competency of GPs and encourage them to continuously improve their competency, prevent the occurrence of bad money driving out good money, and promote the growth of the entire GP medical team and the improvement of the comprehensive medical level.

Impact of *p* on equilibrium outcomes

Based on the previous parameter values and $m = 0.5$, the following part portrays the influence of the signing fee p on the equilibrium disclosure level, profit, and patients' social welfare in Figures 4, 5, respectively.

Conjecture 3. *Figures 4A,B presents that for three scenarios, the profits of GPs increase with the signing fee p, whereas the welfare of the patients decreases. Besides, the preferences of both are in line with those in Conjecture 1.*

The statement for Conjecture 3 illustrates how the different signing fee p affect the benefits. The above claim indicates that the signing fee p acts as an incentive for the GPs to increase their effort to attract more residents signing with them and at the same time results in a loss of welfare for these patients. Therefore, given the unattractive benefits of patients in this situation, it is necessary for the government and relevant departments to strengthen the subsidy for contracting fee p, reducing the contracting costs of residents. Only by this way, we can promote more patients to sign with those specific GPs.

Conjecture 4. *Comparing the trajectories in Figures 5A–C:*

1. *The equilibrium disclosure level c increases with the signing fee p.*
2. *Similar to Figure 3A, l GP might exaggerate their true competency to maximize profits, resulting in a lack of trust between patients and GPs.*

For GPs, once a patient signs up with them, it will bring them benefits. For profit-seeking purposes, l GPs may exaggerate their competency and send false signals. However, patients' trust levels decreased when competency signals were concentrated at higher levels. In addition, increasing disclosure practices also incurs additional costs. Such intuitions induce the instantaneous profit of h GP is still higher than that of l GP. Therefore, for GPs, daily normalized information disclosure is necessary, but the investment in their competency level cannot be ignored.

Discussion

In this research, we compare the effects of three competency disclosure strategies that have seldom been considered in previous research. By considering patients' behaviors, this research tries to investigate the GP's disclosing strategy and provide more managerial insights into the interaction between patients and the GP. To the best of our knowledge, this research that draws on signaling theory to explore GPs'

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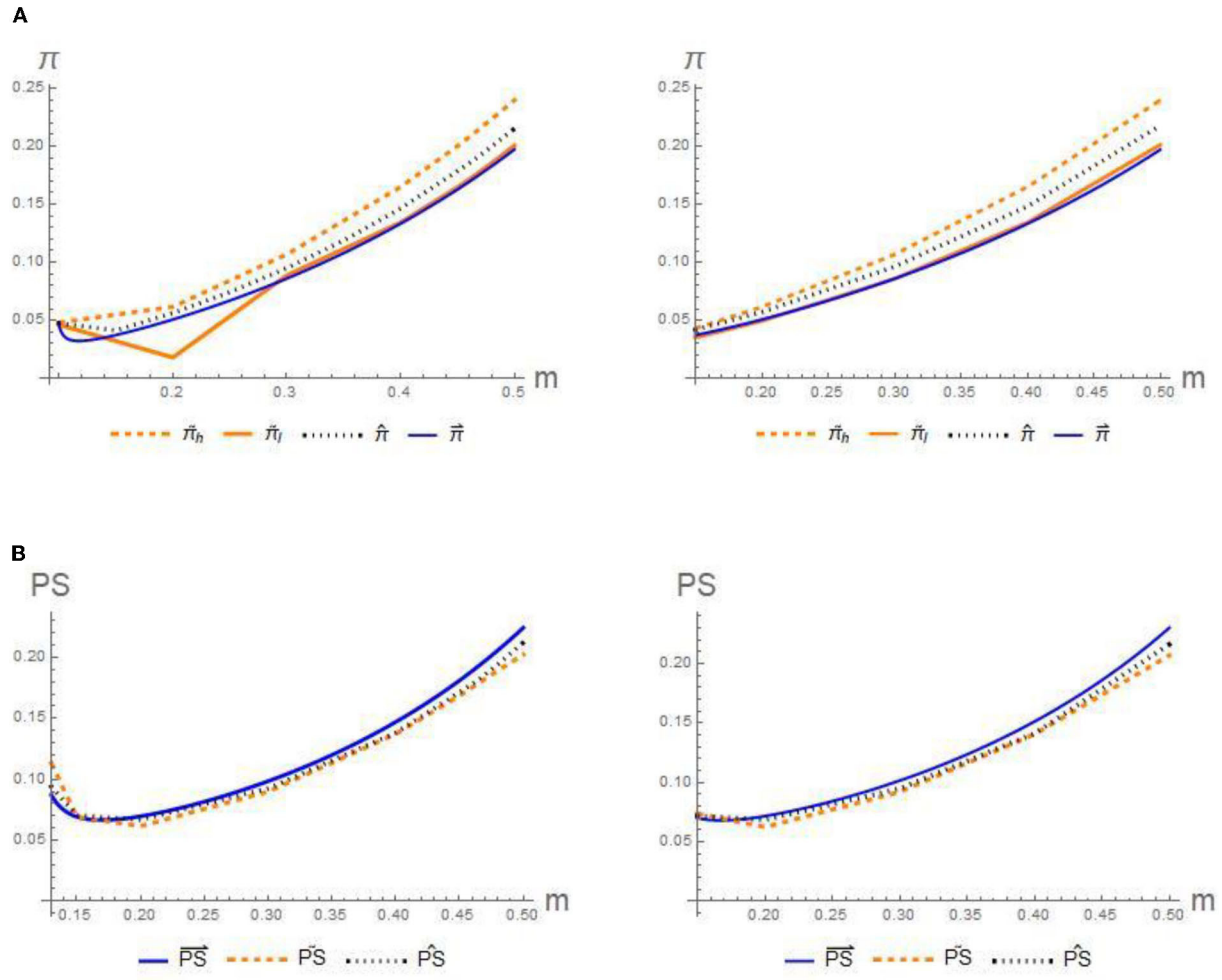

FIGURE 2
Impact of initial signing rate on the **(A)** profits π and **(B)** patients' social welfare *PS*.

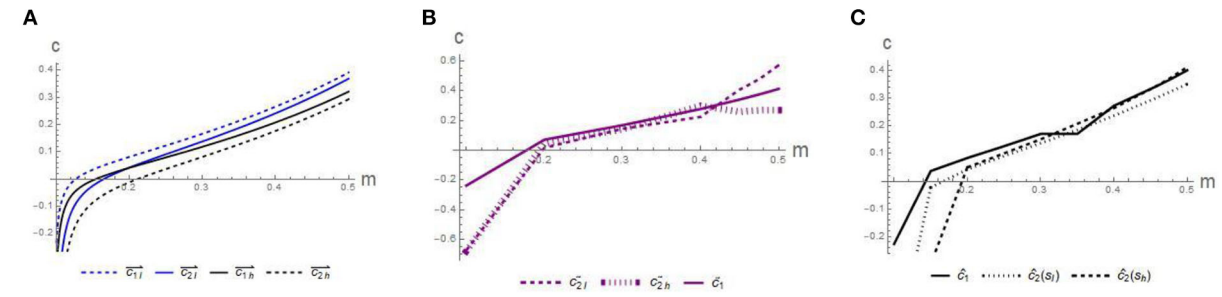

FIGURE 3
Impact of initial signing rate on the disclosure intensity *c* in scenario: **(A)** separating-separating, **(B)** pooling-separating, and **(C)** pooling-pooling.

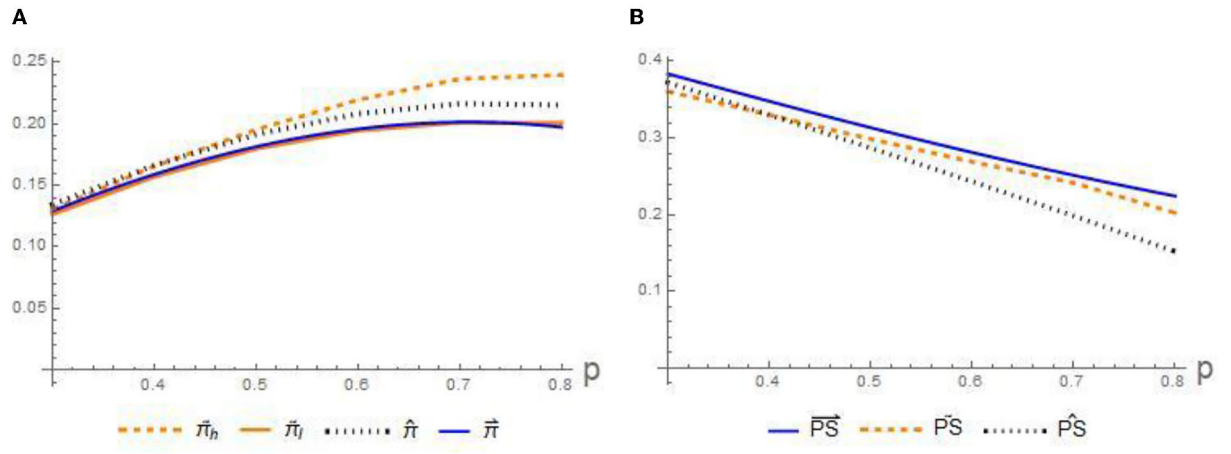

FIGURE 4
Impact of signing fee on the profits on **(A)** profits π and **(B)** patients' social welfare *PS*.

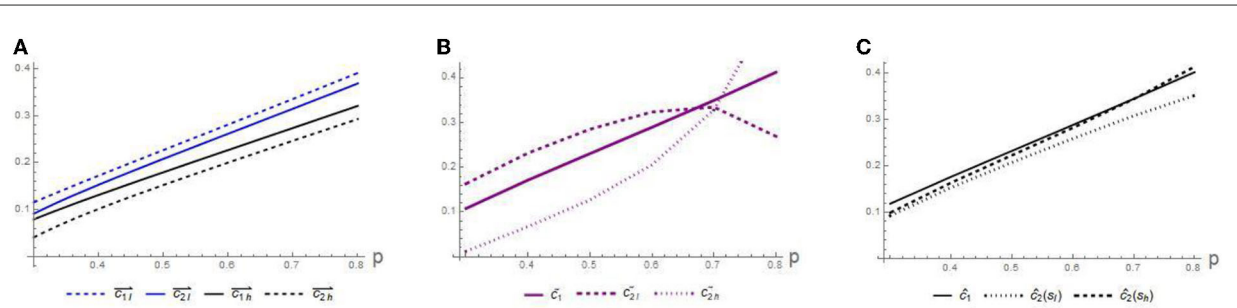

FIGURE 5
Impact of signing fee on the disclosure intensity *c* in scenario: **(A)** separating-separating, **(B)** pooling-separating, and **(C)** pooling-pooling.

competency disclosure decisions has never been brought to light in the literature.

Based on our analysis, we derive the following results and managerial insights. The main is summarized as follows. First, through numerical simulations, we can find that, for the *h* GP, it is always optimal to implement a pooling-separating disclosure strategy for profit in this scenario max. While for the patients, the social welfare of the patients will deviate due to the impact of the contract fee. Therefore, for the health department, relevant institutions need to strengthen the subsidy for signing fees to increase the utility of these patients, and in the long run, such activities would ensure the promotion and application of GP services in society. Second, increased disclosure efforts do not always result in increased overall benefits and may sometimes result in additional costs. Accordingly, for GPs, the core work is still to strengthen training and improve the level of their competency. Third, for pursuing more profits, *l* GPs may exaggerate their level of competency, which will exacerbate distrust between doctors and patient. Hence, the establishment of a standardized medical information sharing platform can not only reduce the cost of disclosure, but also improve the trust level of patients, and promote a win–win situation for patients and GPs. Finally, extremely low cure rate may allow GPs to withhold some competency information. This also requires policymakers to invest more in primary health services, medical equipment, etc., upgrading the hardware of primary medical and health institutions, and changing patients' prejudice that primary medical and health institutions are poor.

There are certain limitations to our study. In this paper, we make some simplifying assumptions that are worth investigating in future investigations. First, how would the results change if the residents' signing willingness affected the evolution of the GP's competency? This question is of interest since signing willingness can affect the GPs' perception of career satisfaction. Second, we can use empirical or data-driven methods to calibrate model parameters and make the theories in this study more applicable.

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.

Author contributions

ZM and JL: conceptualization, literature review, writing, and editing. JL and JS: methodology. JL: calculation. BG: checking. All authors have read and agreed to the published version of the manuscript.

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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/fpubh.2022.959032/full#supplementary-material

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Prevalence of multimorbidity combinations and their association with medical costs and poor health: A population-based study of U.S. adults

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Background: Multimorbidity is common, but the prevalence and burden of the specific combinations of coexisting disease has not been systematically examined in the general U.S. adult population.

Objective: To identify and estimate the burden of highly prevalent combinations of chronic conditions that are treated among one million or more adults in the United States.

Methods: Cross-sectional analysis of U.S. households in the Medical Expenditure Panel Survey (MEPS), 2016–2019, a large nationally-representative sample of the community-dwelling population. Association rule mining was used to identify the most common combinations of 20 chronic conditions that have high relevance, impact, and prevalence in primary care. The main measures and outcomes were annual treated prevalence, total medical expenditures, and perceived poor health. Logistic regression models with poor health as the outcome and each multimorbidity combination as the exposure were used to calculate adjusted odds ratios and 95% confidence intervals.

Results: Frequent pattern mining yielded 223 unique combinations of chronic disease, including 74 two-way (dyad), 115 three-way (triad), and 34 four-way combinations that are treated in one million or more U.S. adults. Hypertension-hyperlipidemia was the most common two-way combination occurring in 30.8 million adults. The combination of diabetes-arthritis-cardiovascular disease was associated with the highest median annual medical expenditures ($23,850, interquartile range: $11,593–$44,616), and the combination of diabetes-arthritis-asthma/COPD had the highest age-race-sex adjusted odds ratio of poor self-rated health (adjusted odd ratio: 6.9, 95%CI: 5.4–8.8).

Conclusion: This study demonstrates that many multimorbidity combinations are highly prevalent among U.S. adults, yet most research and practice-guidelines remain single disease focused. Highly prevalent and burdensome multimorbidity combinations could be prioritized for evidence-based research on optimal prevention and treatment strategies.

KEYWORDS

multimorbidity, comorbidity, multiple chronic conditions, chronic disease, practice guidelines as topic, health status, healthcare economics, epidemiology

Introduction

An estimated 42% percent of American adults 18 and older suffer from multiple chronic conditions (i.e., multimorbidity) (1). Persons with multimorbidity have higher mortality rates, lower health-related quality life, increased healthcare use, and are at higher risk for many poor health outcome events including adverse drug events (2–6).

Despite the high frequency of multimorbidity in the population, most clinical practice guidelines, and the evidence they are based upon are single disease focused. Adhering to multiple, sometimes conflicting, guidelines for multiple individual diseases is burdensome (7) and conveys considerable risk to the patient in terms of drug-drug or drug-disease interactions (8, 9). The overall optimal treatment plan for a given patient with multimorbidity is unlikely to be the linear combination of the best treatment for each individual condition (9, 10). There is a clear need to develop guidelines, care management plans, and patient education programs that meet the needs of patients with multimorbidity. Understanding which conditions most commonly coexist together and their impact on outcomes is a critical first step to establish research priorities for building the evidence-base necessary to achieve this.

Understanding the rate that disease coexist or cluster together at higher-than-expected rates, may also provide clues about the etiology between two or more conditions. For example, inflammation has been shown to be a mechanism for numerous conditions including cancer, cardiovascular disease, chronic kidney disease, and diabetes (11). Damage caused by vascular diseases may be a cause of Alzheimer's Disease and other dementias (12). Understanding these shared risk factors and pathways could lead to the development of medications or behavioral interventions that target more than one condition simultaneously, hence reducing polypharmacy and treatment burden in this population.

While numerous data exist on the prevalence of single chronic conditions (1, 13), much less is known about the prevalence of *specific combinations* of multimorbidity. Most prevalence studies of multimorbidity are based on counts of conditions (14, 15). However, measuring the impact of multimorbidity based on counts of conditions or weighted scores may miss important heterogeneity, because the specific combinations of chronic disease matter in terms of health outcomes (16) including mortality and poor health (5), activity of daily living and instrumental activity of daily living limitations (17, 18), cost and utilization (6), and quality of care (19).

Studies that have examined the prevalence of specific combinations of multimorbidity in the US have been mostly limited to dyad and triad combinations (20–23), a small number of conditions (17, 24) conducted in a specific sub-populations (21) or geographic areas (25), or limited to older adults (24, 26). The prevalence of specific multimorbidity combinations of the general community-dwelling adult population has not been established comprehensively in the United States.

The goal of this study was to fill this knowledge gap and identify and rank the most frequent multiway (two-way, three-way, four-way, etc...) combinations of multimorbidity treated among adults in the United States. An innovative machine learning algorithm –association rule mining – was used to identify all combinations of multimorbidity occurring in one million or more U.S. adults. The association with average and median per capita direct medical expenditures and perceived fair or poor health status was also examined, to identify combinations associated with the most burden.

Methods

Design, setting, and participants

This study was a cross-sectional analysis of the 2016–2019 Medical Expenditure Panel Survey Household Component (MEPS). The MEPS is a large-scale panel survey of a nationally representative sample of households in the United States and is administered by the Agency for Healthcare Research and Quality (AHRQ) (27). The MEPS collects data at the person-level on numerous topics including medical expenditures, utilization, medical conditions, health status, and demographics. Interviews are conducted in-person using computer-assisted personal interview (CAPI) technology. The MEPS is designed in a way that it can be used for both longitudinal analysis over a 2-year period, and cross-sectional analysis to obtain annual estimates in a single year (28) or pooled across multiple years (29). This study uses cross-sectional methods and weights as the main goal was to produce national estimates of prevalence. The 2016–2019 data was chosen as these are the most recent currently available data and earlier years used ICD-9-CM coding for medical conditions. Multiple years of data were pooled together to provide a larger sample size as some combinations will occur in <1% of the total study population (29). This study included all adults age 18 and older with non-zero weights. Subjects with missing data on self-reported health or expenditures were excluded ($n \leq 10$). The final unweighted sample was 89,947 adults (Supplementary Figure 1).

Ethics statement

The MEPS data used in this study is publicly available and de-identified. The Case Western Reserve University Institutional Review Board reviewed the protocol for this study and deemed it to be exempt under U.S. federal law.

Measures

Health conditions were self-reported through open-ended questions about conditions reported to be treated with prescription medications or associated with health care utilization (30). The respondents verbatim text responses were coded according to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). Treatment of these conditions may have been received through inpatient stays, outpatient or office-based visits, emergency department visits, home health care, or prescribed medications. Chronic conditions were then classified into one of 20 chronic conditions, used in recent studies of multimorbidity (31–33). These 20 conditions were chosen based on a tool developed by Fortin et al., in which they used the following criteria to select conditions: (1) their relevance to primary care services; (2) the impact on affected patients; (3) their prevalence among the primary care users; and (4) how often the conditions were present among the lists retrieved from the scoping review (31). A list of each chronic condition categories and corresponding ICD-10-CM codes is included in the Supplementary Table 1.

Perceived health was assessed by asking respondents to rate their health as excellent (1), very good (2), good (3), fair (4), or poor (5). The variable was dichotomized into two values: a response of excellent, very good, or good was categorized as good perceived health, while a response of fair or poor was categorized as poor perceived health.

Medical expenditures were defined as the sum of direct payments for care provided during the year, including out-of-pocket payments and payments by private insurance, Medicaid, Medicare, and other sources. Expenditure data were collected in the MEPS through both self-report and through data collected from the respondents' physicians, hospitals, and pharmacies, when available. The MEPS provides imputed values when data are missing or payments are made under capitated plans (34). Total expenditures were adjusted for annual inflation and are reported in terms of 2019 dollars using the Personal Consumption Expenditure Health Price Index from the Bureau of Economic Analysis (35). Out-of-pocket expenditures were adjusted for inflation using the Consumer Price indices for medical care (CPI–M) (35).

Statistical analysis

The main analytic techniques in this study were association rule mining and frequent pattern mining (36). In brief, association rule mining can be thought of as a two-step process. In the first step (frequent pattern mining) all combinations of items with a minimum support (i.e., prevalence in the study population) are discovered. In the second step, "association rules" of the form $X \rightarrow Y$ are created, where X is one or more items (chronic conditions in this study) and Y is a single-item consequent (poor health or medical expenditures in our study) that X is associated with.

The method was applied here by treating each subject in the study data as the "transaction," and each chronic condition as the "items" to find the most frequently coexisting combinations out of the 1,048,576 (2^{20}) possible combinations of 20 conditions. The minimum support (prevalence) threshold was set at 0.20% for the initial pass, and then after applying survey weights, any combinations with a point estimate of <1 million adults ($\sim$0.40% of the U.S. adult population) was dropped.

The MEPS uses a complex stratified random sampling design. Design-based survey methods (i.e., Taylor series estimation) were used to account for stratification and clustering effects when estimating variances (37). Person-level weights in each year were divided by four (number of total years of data) and applied to get the annualized estimated number and percent of persons with a disease combination and 95% confidence interval (28). Likewise, the median and average annual per capita medical expenditures, per capita out-of-pocket expenses, and percent self-reporting poor health status was calculated for each combination after applying weights.

Combinations of conditions and corresponding prevalence estimates represent "at least," rather than "exactly." For example, people with hypertension-hyperlipidemia-diabetes would be a subset of the people with hypertension-diabetes.

For each combination, we calculated the observed-to-expected prevalence ratio (also known as lift), which is the observed prevalence of the combination divided by the expected prevalence given all single diseases in the combination are independent of each other. Lift significantly greater (or lower) than 1 indicates the coexistence of diseases is unlikely due to chance alone.

To identify specific combinations associated with the highest average cost and perceived poor health burden, we filtered out combinations that were redundant in that they offered little new information on the outcome measure over a more parsimonious (i.e., superset) combination, using a minimum improvement criteria of 10% (38, 39).

Survey-weighted logistic regression was used to estimate the age-race-sex adjusted odds ratios, with poor health status as the outcome, and each disease combination as the exposure, accounting for clustering and stratification. Adjustment variables were age as a continuous variable with splines, race (Hispanic, non-Hispanic white, non-Hispanic black, non-Hispanic Asian, and other), and sex. Subgroup analysis was performed by sex as a secondary analysis.

Data pre-processing was performed using SAS version 9.4 for Windows. The analysis was conducted using R version 4.1.0, RStudio (v. 1.4.1717), and R packages: arules (v. 1.6-8) and survey (v. 4.1-1) (40, 41).

Results

The total weighted study population was 249.2 million adults age 18 and older, with 82.0 million (32.9%) reporting receiving treatment for two or more conditions (Table 1) in a single year. 51.7 million (20.7%) adults have three or more conditions, and 30.6 million (12.3%) have 4 or more conditions. A dose response increase is evident between number of chronic conditions and the percentage reporting poor perceived health and average annual medical expenditures. The prevalence of multimorbidity is highest in those ages 65 and older (73.0% or 38.0 million people), followed by age 40 to 64 (35% or 36.4 million people), and 18–39 (7.9% or 7.5 million).

Frequent pattern mining yielded 223 unique combinations of chronic disease, including 74 two-way, 115 three-way, and 34 four-way combinations that affect one million or more of the weighted study population. There are eight combinations that affect 10 million or more adults, 32 combinations that affect 5 million or more adults, and 129 that affect 2 million or more adults per year. There were not any five-way or higher combinations that met the minimum prevalence threshold. The full table is included in the Supplementary Table 2.

Figure 1 shows the most prevalent combinations along with their associated total medical expenditures (in billions of U.S. Dollars) and percent of the population reporting poor perceived health. An estimated 30.8 million people (12.4%, 95%CI: 12.0–12.8%) of the U.S. adult population are treated for hypertension and hyperlipidemia – the most common combination (Figure 1). An estimated 11.5 million people (4.6%, 95%CI: 4.4–4.9%) have hypertension, hyperlipidemia, and diabetes – the most common 3-way combination, and fifth most common combination overall. Hypertension, hyperlipidemia, musculoskeletal disorder, diabetes and arthritis was the most common 5-way combination (1.1%, 95%CI: 1.0–1.2%). Combinations including hypertension and/or hyperlipidemia plus another condition comprise the majority of the most prevalent combinations. An alternate version of the analysis excluding hypertension and hyperlipidemia is included in the Supplementary Figure 2.

All 223 combinations identified as highly prevalent had lift (and 95% confidence intervals) >1, indicating the coexistence of these two conditions is unlikely due to chance alone. The combination of hypertension, hyperlipidemia, diabetes, and cardiovascular disease had the highest lift of 38.6 (36.4–40.9). Cardiovascular disease and heart failure had the highest lift of 7.4 (95% CI: 6.8–8.2%) for dyad combinations and hypertension, cardiovascular disease, and diabetes had the highest liftof 11.4 (10.8–12.0) for triad conditions.

Figure 2 shows specific combinations of multimorbidity that ranked in either the top 20 in terms of average medical expenditures or perceived poor health. A total of 28 combinations met either criteria, and 12 met both. The combination of heart failure and cardiovascular disease had the highest average annual medical expenditures per capita ($33,451, 95%CI: $29,034–$ 37,868). This was 2.4 times higher than the average for having any two or more chronic conditions ($13,907). Average expenditures were higher than median expenditures across the board, indicating the right-skewed nature of expenditures. The combination of diabetes, asthma/COPD, and arthritis was most associated with perceived poor health status with an adjusted odds ratio of 6.9 (5.4–8.8) (Figure 2). The 62.9% reporting poor health was 2.1 times higher than the average percent reporting poor health among those with any three or more chronic conditions. Supplementary Table 2 provide additional details on the out-of-pocket expenses associated with each combination, and Supplemental Figure 3 shows combinations with the highest average out-of-pocket expenditures.

The top ten combinations among male and female adults in the study population is shown in Figure 3. Hypertension and hyperlipidemia was the top combination for both, but after that the results diverge. Hypertension and diabetes was 2nd for males, but 4th for females. Hypertension and chronic musculoskeletal conditions were 2nd for females, but 4th for males. Combinations with urinary problems appeared twice in the top ten ranking for males, but not for females. Combinations with arthritis, thyroid disorders, stomach problems, and asthma/COPD appeared in the top ten for females but not males.

Discussion

This study combined data mining with survey epidemiology to comprehensively identify and estimate the treatment prevalence of the most frequent combinations of multimorbidity in the United States. This analysis showed that certain multimorbidity combinations of disease are not idiosyncratic, but actually quite common in the US, occurring in one million or more adults.

This paper adds several new contributions to the literature. First, we provide important public health data on the prevalence and associated outcomes of specific multimorbidity combinations. While it was not surprising to find hypertension and hyperlipidemia as the top combination, a fact that is well-established (42), the approximate ranking and estimated prevalence of many other combinations farther down the list was previously unknown. Second, this study provides data on the lift (observed-to-expected prevalence ratio) for each combination. Disease with high lift likely share risk factors or have common pathways for disease, which could spur hypotheses for future research. Finally, we identify combinations with the highest burden in terms of total expenditures and perceived poor health. These combinations could be priority

TABLE 1 Number of chronic conditions treated among U.S. adults by population characteristics.

Variable	No. in unweighted sample	Weighted No. of Adults	0 chronic conditions, row %	1+ chronic conditions, row %	2+ chronic conditions, row %	3+ chronic conditions, row %	4+ chronic conditions, row %
Total	89,947	249,221,000	47.4%	52.6%	32.9%	20.7%	12.3%
Age group							
18–39	17,745	94,573,000	73.9%	26.1%	7.9%	2.7%	0.9%
40–64	19,776	102,614,000	41.1%	58.9%	35.5%	20.0%	10.6%
65 and older	9,311	52,034,000	11.6%	88.4%	73.0%	54.9%	36.1%
Sex							
Male	21,671	120,330,000	52.4%	47.6%	29.9%	18.8%	10.7%
Female	25,161	128,891,000	42.7%	57.3%	35.7%	22.5%	13.7%
Race / Ethnicity							
Hispanic	12,841	40,533,000	63.3%	36.7%	19.5%	11.6%	6.2%
Non-Hispanic White only	21,164	156,551,000	40.7%	59.3%	38.4%	24.5%	14.9%
Non-Hispanic Black only	8,113	29,523,000	53.0%	47.0%	28.9%	18.0%	10.1%
Non-Hispanic Asian only	3,355	15,133,000	62.4%	37.6%	20.0%	11.3%	5.4%
Other or multiple race	1,359	7,481,000	47.8%	52.2%	32.7%	21.0%	12.8%
Self-rated poor health	7,201	31,085,000	19.0%	81.0%	64.6%	48.8%	34.3%
Per capita medical expenditures in 2019 USD (Median, IQR)	—	—	$322 ($0–$1,382)	$4,176 ($1,523–$11,067)	$6,208 ($2,558–$14,858)	$8,177 ($3,610–$18,756)	$10,821 ($5,04–$23,712)
Per capita out-of-pocket medical expenditures in 2019 USD (Median, IQR)			$30 ($0–$287)	$542 ($167–$1,401)	$695 ($243–$1,681)	$808 ($292–$1,865)	$903 ($333–$2,080)

Survey-weighted estimates from pooling the 2016–2019 Medical Expenditure Panel Survey. Weighted estimates have been annualized by taking the average over the 4 year study period. Row percentages are reported under each count of conditions column. Medical expenditures are reported in 2019 US Dollars (USD).

targets for future prevention or treatment interventions targeted toward multimorbidity patients.

Despite the high prevalence of these disease combinations, most evidence-based practice guidelines are single-disease focused (43). This relegates managing people with multimorbidity, who represent the majority of people presenting for primary care (44, 45), to the "art," rather than the science of medicine, and has led to largely untargeted global interventions that show limited or no effect in clinical trials (46). While general approaches for complex patients exist including geriatric care teams (47), the Age-Friendly Health Systems 4M model of care (48), and deprescribing guidelines (e.g., Beers Criteria and STOPP/START) (49, 50), significant evidence gaps remain especially when it comes to specific guidelines for managing patients with specific combinations of conditions. For some conditions, multimorbidity may be the norm. For example, this study showed that 45 million adults are treated for hyperlipidemia, and of those approximately two-thirds are treated for hypertension as well. This means it is more common for a patient to be treated for high cholesterol plus another condition, than just managing cholesterol alone.

The highly prevalent combinations identified in this study could be prioritized for future evidence-based research. Some combinations show the possibility that a single medication could target multiple diseases thus reducing the polypharmacy. For example, a low-dose antidepressant for anxiety, can also treat pain from arthritis or diabetic neuropathy. Other common combinations show the potential of physical activity, diet, and tobacco cessation interventions to positively affect multiple conditions and reduce medication burden.

This was, to the author's knowledge, the most comprehensive, population-based study in the U.S. on the prevalence and associated impact of multimorbidity combinations in terms of the number of conditions, the examination of higher-order combinations (e.g., 4-way or deeper), and the broadness of the study population. Ward and Schiller examined common dyad and triad combinations of ten conditions using the National Health Interview Survey (23). The most common dyad condition was hypertension-arthritis and 26% of adults had multimorbidity. A similar more recent study using 2018 NHIS data estimated that 27.2% of U.S. adults had two or more (51). Weiss et al. (24) used survey weights and

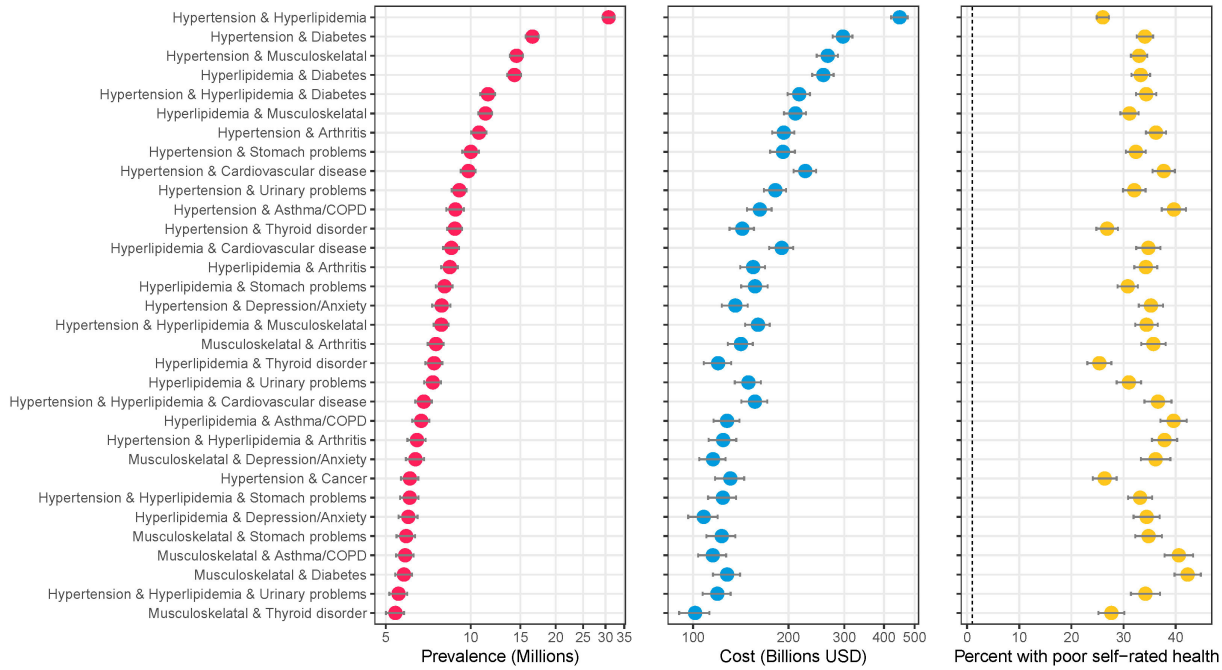

FIGURE 1
Highly prevalent specific combinations of multimorbidity and associated cost and perceived poor health. The figure shows combinations of conditions with an estimated prevalence of 5 million or more adults in the United States. Data source: the 2016–2019 Medical Expenditure Panel Survey (MEPS). Weighted estimates and 95% confidence intervals were calculated by applying population weights using Taylor-series methods (i.e., complex survey methods) to account for the complex sampling design of the MEPS. Weighted estimates have been annualized by taking the average over the 4-year study period. X-axes for prevalence and cost are on the logarithmic scale. Results are sorted by prevalence. Cost is measured as total annual medical expenditures in 2019 US Dollars, and perceived health is an answer of "fair" or "poor" on a 5-point question asking respondents to rank their overall health.

examined deeper combinations of chronic disease, but only in five conditions using 1999–2004 National Health and Nutrition Examination Survey (NHANES) data.

Several studies have been conducted in specific subpopulations of the U.S. using ARM or similar methods to examine combinations of multimorbidity. Koroukian et al. used ARM to identify combinations of multimorbidity associated with high expenditures among Medicare enrollees (26). Ho et al. used ARM to identify high-risk comorbidity combinations for patients undergoing emergency general surgery using the Nationwide Inpatient Sample (26). Quinones et al. (17) and Quinones et al. (52) examined diabetes comorbidities and racial disparities in multimorbidity, respectively using the Health & Retirement Study (17, 52). Quinones et al. examined combinations associated of multimorbidity among patients seeking care at community health centers (53). Steinman et al. examined combinations of multimorbidity impacting older veterans using data form the Veterans Affairs health system (21).

Comparable studies have been conducted internationally outside the U.S., including a study using the Korea Health Panel which found an overall multimorbidity rate of 34.8% in South Korea (54), and a study using Beijing medical claims data in China, which found a higher rate of multimorbidity than our study (51.6% in mid-life adults and 81.3% in older adults). This is probably due to including more conditions. Zemekidun et al. (55) applied cluster analysis and ARM to the UK biobank to identify combinations of multimorbidity Britt et al. (56) examined prevalence and patterns of multimorbidity in patient-reported surveys in Australia across nine morbidity domains. The most common combination was arthritis/chronic back pain + vascular disease (15% of population). Nicholson et al. developed a cluster analysis tool to identify common combinations and sequences in Canada using an approach that seems similar to association rule mining (32).

Strengths

The data mining allowed a more comprehensive identification of high frequency multimorbidity combinations than previous efforts (23, 24). This study uses a national sample, representative of the U.S. population. The MEPS database is also unique among national surveys in that its open-ended condition enumeration approach (rather than a fixed set of questions) allows for a more

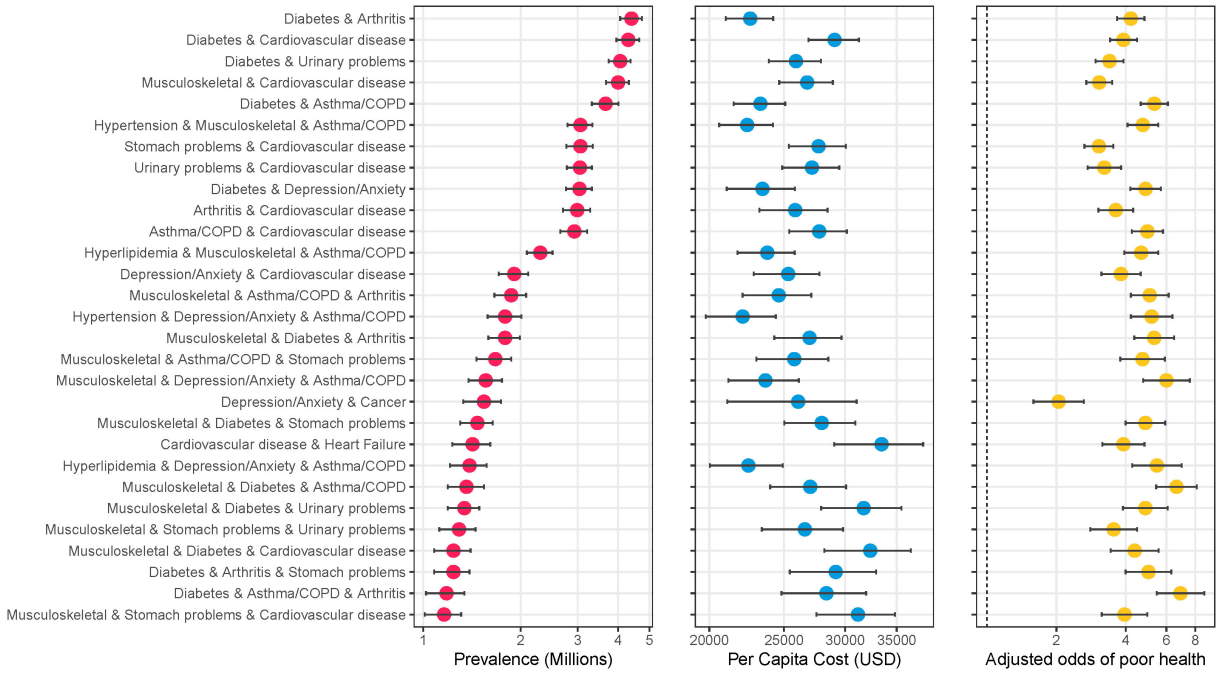

FIGURE 2
Specific combinations of multimorbidity ranked highest in terms of average cost or perceived poor health. The figure shows the specific combinations of multimorbidity that ranked in the top 20 in terms of highest average cost per person or top 20 highest percentage with self-reported poor health. A total of 28 conditions met either criterion, with 12 meeting both. Data source: 2016–2019 Medical Expenditure Panel Survey (MEPS). Weighted estimates and 95% confidence intervals were calculated by applying population weights using Taylor-series methods (i.e., complex survey methods) to account for the complex sampling design of the MEPS. Weighted estimates have been annualized by taking the average over the 4-year study period. Adjusted odds ratios were calculated using log-binomial models adjusting for age, race, and sex, and Taylor-series methods for standard errors. X-axes are on the logarithmic scale, and results are sorted by prevalence.

comprehensive capture of different chronic conditions, compared to other national surveys (17, 23, 24). MEPS covers all payers (even uninsured) and has data on services from all providers, which is an advantage over big data sources like claims data and electronic health records, respectively.

Association rule mining allows for the identification of highly prevalent combinations in a quick and computationally efficient manner, while filtering out combinations that have no observations or are sparse. While our study only focused on combinations occurring in over 1 million adults, the method could also be used to identify higher order combinations by setting a lower prevalence thresholds. Association rule mining is still relatively uncommon in clinical and epidemiological studies. The method could be applied to other areas of research, for example identifying high-risk combinations of risk factors associated with mortality (38), social determinant of health indicators associated with disparities (57), or prescription drug combinations associated with adverse drug events (58). To our knowledge, this is the first study to combine complex survey analysis with association rule mining to yield national estimates of combinations of variables.

Limitations

MEPS provides accurate estimates of treated prevalence for chronic disease, but this is likely lower than the underlying population prevalence for some conditions, especially those that are less salient (30). On the other hand, the focus on treated conditions represent those for which care decisions between multiple conditions may conflict. The MEPS includes community-dwelling subjects only, meaning institutionalized persons such as nursing home and assisted living residents are excluded. Estimates of total expenditures are typically lower than what is estimated from the National Health Expenditure Accounts (NHEA), because the MEPS does not include these institutionalized populations (59). ICD-10 codes were classified into 20 primary-care relevant conditions using an established algorithm, but other classification systems may result in different combinations and prevalence estimates (31). This algorithm was chosen over others because it was originally designed for use on self-reported conditions, and that it could be applied with the 3-digit ICD-10 codes available in MEPS. Many other algorithms require the use of fully-specified ICD-10 codes and/or were designed for use in administrative data, including Elixhauser comorbidities (60), Deyo-Charlson Comorbidity Index (61,

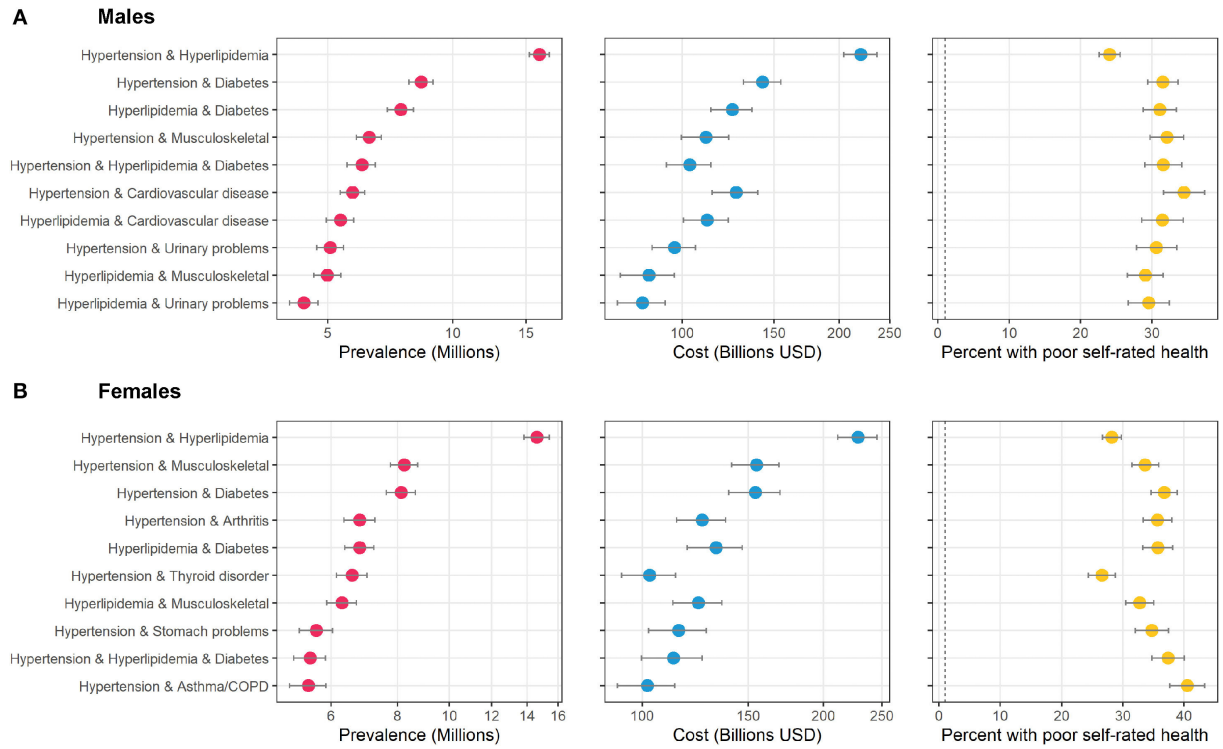

FIGURE 3
Top ten most prevalent specific combinations of multimorbidity by sex and associated cost and perceived poor health. The figure shows the top ten combinations of conditions as ranked by prevalence by sex among adults in the United States. **(A)** shows data on males, and **(B)** shows data on females. Data source: the 2016–2019 Medical Expenditure Panel Survey (MEPS). Weighted estimates and 95% confidence intervals were calculated by applying population weights using Taylor-series methods (i.e., complex survey methods) to account for the complex sampling design of the MEPS. Weighted estimates have been annualized by taking the average over the 4-year study period. X-axes for prevalence and cost are on the logarithmic scale. Results are sorted by prevalence. Cost is measured as total annual medical expenditures in 2019 US Dollars, and perceived health is an answer of "fair" or "poor" on a 5-point question asking respondents to rank their overall health.

62), Clinical Classification Software (63), and Phecodes (64). Consensus on which conditions to include in measures of multimorbidity has not been established, and is a problem that continues to plague the field (65).

This study used the most recent data (2016–2019) available at the time; therefore, the impact of the COVID-19 pandemic was not captured in these results. As comorbidities were among the greatest risk factors of COVID-related death, excess mortality in people with multimorbidity could have lowered population prevalence rates (66–68). However, there is growing evidence of increases in prevalence of certain post-Covid conditions (i.e., long COVID) including respiratory problems, diabetes, heart conditions, neurological conditions, migraines, and mental health conditions (69–73). Understanding the scale and impact of post-COVID conditions is an on-going area of investigation in the scientific community.

Conclusion

This cross-sectional analysis of a nationally-representative survey showed that certain multimorbidity combinations of disease are quite common in the US, occurring in one million or more adults. The combinations reported here could be prioritized for evidence-based research and integration into practice guidelines, especially those most associated with poor health and high medical costs.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: Medical Expenditure Panel Survey. Available at: https://www.meps.ahrq.gov/mepsweb/data_stats/download_data_files.jsp.

Ethics statement

The studies involving human participants were reviewed and approved by Case Western Reserve University Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

NS is the sole author, had full access to the data, and takes responsibility for the integrity of the data and the accuracy of the data analysis, and the entirety of the manuscript, his contributions include conceptualization, design of the study, statistical analysis, interpreting the data, and writing and revising the manuscript.

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Conflict of interest

The author declares 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/fpubh.2022.953886/full#supplementary-material

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Intergenerational transmission of parental risky health behaviors in Chinese children: Are there socioeconomic status differences?

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Background: Risky health behaviors in childhood, including smoking, alcohol consumption, and having a poor diet, are the major sources of non-communicable diseases in adulthood. This study aimed to examine how parents affect children's risky health behaviors and whether intergenerational transmission differs based on socioeconomic status (SES).

Methods: Data were extracted from the 1991–2015 China Health and Nutrition Survey (CHNS). Smoking (n = 5,946), alcohol consumption (n = 7,821), and sugar-sweetened beverages (SSBs) consumption (n = 3,537) were used as proxies for risky health behaviors in children. A binary choice model for panel data with a random-effect specification was employed to examine whether risky health behaviors can be transmitted from parents to their children. Subsequently, we conducted a seemingly unrelated estimation test (SUEST) to explore the differences in parental transmission between the different SES groups.

Results: We found strong intergenerational persistence of smoking, alcohol drinking, and SSBs drinking behaviors, except for the mothers' smoking behavior. Mothers had a greater influence on children's alcohol drinking and SSBs drinking behaviors than fathers both in urban and rural areas and in different SES groups. The intergenerational transmission of SSBs drinking behavior exhibited a decreasing trend with increasing SES for both urban and rural families. In urban areas, mothers' alcohol drinking behavior has a decreasing trend with increasing education level, occupation, and income; however, in rural areas, the influence of mothers' alcohol drinking behavior occurred in the same direction with increasing education level and occupation type. In rural areas, the influence of fathers' drinking and smoking behaviors on children appears to mostly increase with increasing SES. Meanwhile, the influence of such behaviors among urban fathers would decrease with increasing SES.

Conclusion: Parents' behaviors and SES can influence the initiation of risky health behaviors in their offspring. Thus, to promote healthy behaviors, policymakers can introduce health education programs for parents, particularly for those living in rural areas and with a low SES.

KEYWORDS

intergenerational transmission, risky health behaviors, socioeconomic status, socioeconomic differences, CHNS

1. Introduction

Risky health behaviors, such as smoking, drinking alcohol, and having a poor diet, are major potential causes of death (1–6) and are often initiated in childhood and tend to persist into adulthood (5, 7–11). Thus, it is of great significance to prevent them earlier in life as the disease progresses (5, 12). However, the prevalence of smoking, alcohol drinking, and having unhealthy diets, such as sugar-sweetened beverages (SSBs), is substantial among children and adolescents. In 2018, ∼43 million children aged 13–15 years used tobacco (13), and ∼155 million adolescents were current drinkers globally (14). Investigations from the United States and China have found that over 60% of children and adolescents consume SSBs daily (15–18). Although the dangers of tobacco and alcohol are well-known (1, 10, 11, 13, 14), SSBs are dangerous because they often contain caffeine and sugar, which can be addictive. Caffeine addiction is a well-known problem (19, 20), but it has received more attention in recent years. Some animal-based studies have not only revealed similarities between added sugars and substance abuse in binge eating, craving, tolerance, and withdrawal (21) but also some have confirmed similar addictive characteristics in adolescents (22). In addition, some human neuroimaging studies have shown that high sugar intake activates neural circuits and reward systems like those of substance abuse (23, 24). Long-term sugar consumption can lead to obesity and diabetes, among other serious consequences (15–17).

Family is a key environment that influences children's behavior. As children's first teachers and socializing agents, parents' negative health behaviors can act as a bad model for their children (25–28). In addition, parental socioeconomic status (SES) variables, including educational attainment, income, and occupational status, together with parenting styles, constitute the home environment in which children's behaviors are embedded (25, 29–39).

There have already been many studies on the relationship between SES and children's risky health behaviors; however, whether SES differences affect the intergenerational transmission of unhealthy behaviors has not been sufficiently clarified. Previous studies have focused on parents' own behavior and the relationship between SES and parenting styles, which provide a reference for our own research proposition (26, 27, 29–31, 40–44). According to Cockerham's Health Lifestyle Theory (45), high-SES parents not only avoid the transmission of their own negative health behaviors but also their gentle parenting style helps to develop self-control in their children (45). In contrast, low-SES families tend to adopt strict, punitive, and authoritarian parenting styles, leading to children's poor self-control and making them more likely to emulate their parents' risky health behavior (28–31, 33, 34, 39, 46–52). In other words, the intergenerational transmission of risky health behaviors is likely to be in reverse to the SES gradient. However, other research studies showed that with increasing SES, the intergenerational transmission of risky parental health behaviors becomes increasingly apparent (35, 37, 53–55). Yu and Abler (54) proposed that higher education in rural China is often associated with more social activities, and with cigarettes and wine being more accessible. Wu (56) confirmed Yu's conclusion regarding the association between education and alcohol drinking. Furthermore, a Belgian study found that higher-educated mothers tended to have higher workloads and thus spent less time with their children, making them more vulnerable to risky health behaviors (53). Therefore, the contribution of this study is not only to measure the intergenerational transmission effect of these risky health behaviors with panel data including nine waves spanning 15 years but also to further measure whether there are SES differences in the intergenerational transmission effect based on Cockerham's health lifestyle theory with seemingly unrelated estimation test (SUEST). Urban and rural differences are also considered.

In the hope of adding up-to-date evidence to previous cross-sectional studies and using the longitudinal database from the China Health and Nutrition Survey (CHNS), this study aimed to examine how parents affect children's risky health behaviors. China, a developing country with rapid economic growth, is quite different from developed countries that have been studied earlier in this field (28, 31, 33, 39). Thus, the characteristics of this research proposal may be different, and the research conclusions can provide a reference for other

Abbreviations: CHNS, China Health and Nutrition Survey; SSB, sugar-sweetened beverage; SES, socioeconomic status; SUEST, Seemingly Unrelated Estimation Test; OR, odds ratio.

developing countries. As a developing country, and unlike developed countries like the United States, China's laws do not make it clear that children's smoking and drinking behaviors are illegal. Without such legal restrictions, children's behaviors depend more on family constraints, and hence identifying the effects of intergenerational transmission of these risky health behaviors is more critical (25, 57–61). Moreover, considering that adults often have difficulty making behavioral changes to addictive behaviors, it may be more effective to prevent and reduce risky health behaviors in children from the perspective of reducing intergenerational transmission. Therefore, we further explored whether intergenerational transmission differed by parental SES.

2. Methods

2.1. Data

The primary database used in this study was the CHNS. The CHNS is an ongoing nationwide cohort project in China with 10 available waves from 1989 to 2015. These areas are representative and diverse in terms of a wide range of socioeconomic factors (including income, education, and employment) and other related demographic, health, and nutritional factors. As only individuals aged between 20 and 45 years were surveyed in 1989, we excluded the baseline data, and only used data from 1991 to 2015 in the analysis, singling out smoking, alcohol drinking, and SSB drinking as proxies for risky health behaviors in children aged <18 years. We excluded samples with outliers and missing data, leaving 5,946 observations in the smoking group, 7,821 observations in the alcohol drinking group, and 3,537 observations in the SSBs drinking group. After matching the parent's ID with the child's ID, we obtained 24,573 observations in total: 4,609 observations in 1991, 4,140 in 1993, 3,577 in 1997, 3,312 in 2000, 1,972 in 2004, 1,583 in 2006, 1,424 in 2009, 1,782 in 2011, and 2,174 in 2015. Due to the existence of missing values in the dependent and control variables, we had to drop records containing missing values. Finally, we obtained 5,946 observations in the sample of children's smoking behavior, 7,821 observations in the sample of children's alcohol drinking behavior, and 3,537 observations in the sample of children's SSBs drinking behavior.

2.2. Measures

The main dependent variables in this study were children's smoking, alcohol drinking, and SSB drinking behaviors. Smoking was assessed using the question, "Have you ever smoked?," and was coded as 1 if the respondent answered "Yes." Alcohol consumption was assessed based on the question, "Did you drink beer or any other alcoholic beverage?" and was coded as 1 if the respondent answered "Yes." SSBs consumption was assessed based on the question, "Did you drink soft drinks or sugared fruit?" and coded as 1 if the respondent answered "Yes." All risky health behaviors were answered by the respondents. We then linked answers from the parent questionnaires to those of their children.

The independent variables were the risky parental health behaviors of these children, which were also assessed based on the three questions above. To analyze how risky health behaviors are transmitted from parents to their children, we also included parental SES variables, including educational attainment (completed years of formal education in regular schools), household per capita income (RMB in 2015), and career type (manual labor/non-manual labor). Demographic variables, such as age (years) and sex (male/female), were also included. In addition, we controlled the area (categorized as Western: Guangxi, Guizhou, and Chongqing; Northeastern: Liaoning and Heilongjiang; Central: Henan, Hubei, and Hunan; Eastern: Jiangsu, Shandong, Beijing, and Shanghai) and wave (1991, 1993, 1997, 2000, 2004, 2006, 2009, 2011, and 2015) effects. The variable of education was transformed into a dichotomous variable, with >6 years of education being classified as a high level of education, and ≤6 years of education being classified as a low level of education.

2.3. Statistical analysis

Data analyses were conducted using STATA/SE 14.0. Descriptive statistics for both parental and children's risky health behaviors, including smoking, alcohol use, and drinking SSBs, were reported as proportions, with corresponding chi-square tests to examine whether these behaviors were statistically significant for transmission from parents to their children. Parental SES and demographic variables were also estimated as proportions for categorical variables and means for continuous variables; chi-square tests for dichotomous variables and *t*-tests for continuous variables were conducted, and *p*-values were reported.

To investigate whether parental risky health behaviors could be transmitted and how these behaviors were transmitted, we adopted a binary choice model for panel data with random-effect specification after conducting the Hausman test ($p_{smoking}$= 1.000, $p_{alcohol}$= 0.9043, p_{SSBs}= 0.7745). Odds ratios (ORs) with their *p*-values are reported. The model is specified as follows:

$$\begin{aligned} ln\frac{P_{i,t}}{1-P_{i,t}} &= \beta_0 + \beta_1 FatherBehavior_{i,t} + \beta_2 MotherBehavior_{i,t} \\ &+ \sum_{j=1}^{4} \beta_{3j} FatherSES_{ij,t} + \sum_{j=1}^{4} \beta_{4j} MotherSES_{ij,t} \\ &+ \beta_5 Area_{i,t} + \beta_6 Wave_{i,t} + \beta_7 Gender_{i,t} + \beta_8 Age_{i,t} \\ &+ u_{i,t} \end{aligned} \quad (1)$$

where $P_{i,t}$ represents the probability of children's smoking, alcohol drinking, and SSBs drinking behaviors; $FatherBehavior_{i,t}/MotherBehavior_i$ indicates whether the *child* $_i$'s father/mother had this kind of risky health behavior, including smoking, alcohol drinking, and SSBs drinking; $FatherSES_{ij,t}/MotherSES_{ij,t}$ represents the *child* $_i$'s father/mother's SES; $Wave_{i,t}$ indicates the time dummies to explore the dynamic evolution from 1993 to 2015; $Area_{i,t}$ indicates the region dummies to explore the region's effects on children's risky health behaviors; $Gender_{i,t}$ and $Age_{i,t}$ represent the *child* $_i$'s gender and age individually. $u_{i,t}$ represent the individual effects on the child. We used the model above to analyze the total sample, the urban sample, and the rural sample.

To understand the influence of different SES variables on the intergenerational transmission of risky health behaviors, we grouped urban and rural parents according to their education level, income, and occupation type, used model (1) for regression in different subgroups, and drew a bar chart with confidence intervals. Regarding parental education level, we divided parents into low-level (≤6 years) and high-level (>6 years) education subgroups. Regarding income, those with an income equal to or lower than the average were included in the low-income subgroup, whereas those with an income higher than the average were included in the high-income subgroup. Finally, we divided occupations into manual labor and non-manual labor subgroups and then conducted a subgroup analysis. To test the differences in the coefficients $FatherBehavior_{i,t}$ and $MotherBehavior_i$ among different subgroups, a SUEST was used.

3. Results

3.1. Descriptive analysis

The variables used in this study are displayed in Table 1 and include the entire sample, as well as the risky health behavior and non-risky health behavior samples.

The prevalence of smoking, alcohol consumption, and SSBs consumption in children was 4.37, 6.43, and 82.16%, respectively. Boys had significantly higher proportions of these three risky health behaviors than girls. Children who smoked and drank alcohol were significantly older than those who did not smoke and drink alcohol, while those drinking SSBs were significantly younger than those who did not drink SSBs.

Both fathers and mothers of smoking children had higher smoking rates, while the difference in mothers' smoking rates between smoking and non-smoking children was not significant. Both fathers and mothers of children who drank alcohol had a significantly higher rate of alcohol consumption than those who did not drink alcohol. Similarly, among children who drank SSBs, both fathers and mothers had a significantly higher ratio of drinking SSBs than the fathers and mothers of children who did not drink SSBs.

3.2. Logistic regression results

The results of the logistic regression for intergenerational transmission of risky parental health behaviors in Chinese children are presented in Table 2. In the total sample, after controlling for confounding variables, children who had a smoking father were ∼240.9% more likely to smoke ($p < 0.01$) than children who had a non-smoking father. While the intergenerational transmission of fathers' smoking behavior was observed among rural children, the intergenerational transmission effect was even more pronounced among urban children; smoking fathers increased the probability of children smoking by 2,506% ($p = 0.034$). Considering the unreliability of the small sample size on mothers' smoking, maternal smoking transmission is not reported here.

Similarly, to smoking fathers, fathers who drank alcohol increased the possibility of alcohol drinking in their children by 71.5% ($p < 0.01$) in the total sample, 119.4% ($p = 0.01$) in the urban sample, and 52.6% ($p = 0.012$) in the rural sample. Mother's alcohol consumption increased the possibility of alcohol consumption by 257.4% ($p < 0.01$) in the total sample, 214.7% ($p < 0.01$) in the urban sample, and 239.5% ($p < 0.01$) in the rural sample.

Likewise, in the total sample, children whose fathers drank SSBs were ∼161.2% more likely to drink SSBs ($p < 0.01$) than children whose fathers did not drink SSBs. Indeed, SSBs drinking could increase the likelihood of children consuming SSBs by 259.2% ($p < 0.01$). A similar intergenerational transmission of this behavior was observed in both urban and rural children. Gender plays an important role in the intergenerational transmission of risky health behaviors. Boys were ∼8,316, 353.3, and 25.1% more likely to smoke, drink alcohol, and drink SSBs, respectively, than girls. Furthermore, age also plays an important role in the intergenerational transmission of smoking and alcohol consumption. Similar effects were observed in both urban and rural children.

Various parental SES variables were also shown to significantly affect children's behavior. A higher parental per capita income was shown to make both urban and rural children more likely to drink alcohol and SSBs. However, the effects of educational attainment and occupational status were not consistent or even opposite between urban and rural areas and between parents.

3.3. Subgroup analysis

To further clarify the intergenerational transmission of urban and rural parental risky health behaviors between SES groups, the results of the subgroup analysis and SUEST are shown in Table 3, Figures 1, 2. Considering the unreliability of the subgroup analysis due to the small sample size of mothers'

TABLE 1 Descriptive statistics.

Variables	Smoking				Alcohol drinking				SSBs drinking			
	Total ($n = 5,946$)	No ($n = 5,686$)	Yes ($n = 260$)	p^a	Total ($n = 7,821$)	No ($n = 7,318$)	Yes ($n = 503$)	p^a	Total ($n = 3,537$)	No ($n = 631$)	Yes ($n = 2,906$)	p^a
Father's behavior, *n* (%)				0·000				0·000				0·000
No	1,749 (29·41)	1,712 (30·11)	37 (14·23)		2,311 (29·55)	2,212 (30·23)	99 (19·68)		2,418 (68·36)	571 (90·49)	1,847 (63·56)	
Yes	4,197 (70·59)	3,974 (69·89)	223 (85·77)		5,510 (70·45)	5,106 (69·77)	404 (80·32)		1,119 (31·64)	60 (9·51)	1,059 (36·44)	
Mother's behavior, *n* (%)				0·089				0·000				0·000
No	5,792 (97·41)	5,543 (97·49)	249 (95·77)		6,852 (87·61)	6,490 (88·69)	362 (71·97)		1,984 (56·09)	538 (85·26)	1,446 (49·76)	
Yes	154 (2·59)	143 (2·51)	11 (4·23)		969 (12·39)	828 (11·31)	141 (28·03)		1,553 (43·91)	93 (14·74)	1,460 (50·24)	
Father's education				0·000				0 063				0 004
Less or equal to 6 years	2,334 (0.39)	2,203 (0.39)	131 (0.50)		3,007 (0.38)	2,794 (0.38)	213 (0.42)		743 (0.21)	159 (0.25)	584 (0.20)	
More than 6 years	3,612 (0.61)	3,483 (0.61)	129 (0.50)		4,814 (0.62)	4,524 (0.62)	290 (0.58)		2,794 (0.79)	472 (0.75)	2,322 (0.80)	
Mother's education				0·000				0.058				0·000
	3,393 (0.57)	3,205 (0.56)	188 (0.72)		4,394 (0.56)	4,091 (0.56)	303 (0.60)		1,161 (0.33)	267 (0.42)	894 (0.31)	
	2,553 (0.43)	2,481 (0.44)	72 (0.28)		3,427 (0.44)	3,227 (0.44)	200 (0.40)		2,376 (0.67)	364 (0.58)	2,012 (0.69)	
Income (Inflated to 2015, LN), mean (SD)	8·26 (1·17)	8·27 (1·17)	8·26 (1·21)	0·0185	8·08 (1·11)	8·06 (1·11)	8·31 (1·03)	0·0000	8·73 (1·29)	8·32 (1·36)	8·82 (1·25)	0.0000
Father's job, *n* (%)				0·666				0·788				0·000
Manual labor	3,507 (58·98)	3,357 (59·04)	150 (57·69)		4,678 (59·81)	4,380 (59·85)	298 (59·24)		1,936 (54·74)	434 (68·78)	1,502 (51·69)	

(Continued)

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TABLE 1 (Continued)

Variables	Smoking				Alcohol drinking				SSBs drinking			
	Total ($n = 5,946$)	No ($n = 5,686$)	Yes ($n = 260$)	p^a	Total ($n = 7,821$)	No ($n = 7,318$)	Yes ($n = 503$)	p^a	Total ($n = 3,537$)	No ($n = 631$)	Yes ($n = 2,906$)	p^a
Non-manual labor	2,439 (41·02)	2,329 (40·96)	110 (42·31)		3,143 (40·19)	2,938 (40·15)	205 (40·76)		1,601 (45·26)	197 (31·22)	1,404 (48·31)	
Mother's job, *n* (%)				0·516				0·453				0·000
Manual labor	3,775 (63·49)	3,605 (63·40)	170 (65·38)		5,050 (64·57)	4,733 (64·68)	317 (63·02)		2,027 (57·31)	442 (70·05)	1,585 (54·54)	
Non-manual labor	2,171 (36·51)	2,081 (36·60)	90 (34·62)		2,771 (35·43)	2,585 (35·32)	186 (36·98)		1,510 (42·69)	189 (29·95)	1,321 (45·46)	
Age, mean (SD)	14·98 (1·96)	14·89 (1·94)	16·93 (1·31)	0·0000	12·71 (4·50)	12·50 (4·53)	15·72 (2·61)	0·0000	11·87 (3·58)	12·19 (3·76)	11·80 (3·54)	0·0133
Gender, *n* (%)				0·000				0·000				0·099
Male	3,115 (52·39)	2,862 (50·33)	253 (97·31)		4,120 (52·68)	3,723 (50·87)	397 (78·93)		1,949 (55·10)	329 (52·14)	16,20 (55·75)	
Female	2,831 (47·61)	2,824 (49·67)	7 (2·69)		3,701 (47·32)	3,595 (49·13)	106 (21·07)		1,588 (44·90)	302 (47·86)	1,286 (44·25)	
Area, *n* (%)				0·000				0·000				0·001
Western (Ref·)	1,921 (32·31)	1,845 (32·45)	76 (29·23)		2,704 (34·57)	2,523 (34·48)	181 (35·98)		956 (27·03)	197 (31·22)	759 (26·12)	
Northeastern	868 (14·60)	831 (14·61)	37 (14·23)		1,014 (12·97)	964 (13·17)	50 (9·94)		709 (20·05)	143 (22·66)	566 (19·48)	
Central	1,829 (30·76)	1,695 (29·81)	134 (51·54)		2,368 (30·28)	2,177 (29·75)	191 (37·97)		1,100 (31·10)	185 (29·32)	915 (31·49)	
Eastern	1,328 (22·33)	1,315 (23·13)	13 (5·00)		1,735 (22·18)	1,654 (22·60)	81 (16·10)		772 (21·83)	106 (16·80)	666 (22·92)	
Wave, *n* (%)				0·025				0·000				0·000
1991 (Ref·)	1,177 (19·79)	1,104 (19·42)	73 (28·08)		3,009 (38·47)	2,862 (39·11)	147 (29·22)					
1993	1,015 (17·07)	973 (17·11)	42 (16·15)		1,243 (15·89)	1,163 (15·89)	80 (15·90)					
1997	1,008 (16·95)	973 (17·11)	35 (13·46)		982 (12·56)	915 (12·50)	67 (13·32)					
2000	576 (9·69)	545 (9·58)	31 (11·92)		563 (7·20)	517 (7·06)	46 (9·15)					

(Continued)

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TABLE 1 (Continued)

Variables		Smoking				Alcohol drinking				SSBs drinking			
	Total ($n = 5,946$)	No ($n = 5,686$)	Yes ($n = 260$)	p^a	Total ($n = 7,821$)	No ($n = 7,318$)	Yes ($n = 503$)	p^a	Total ($n = 3,537$)	No ($n = 631$)	Yes ($n = 2,906$)	p^a
2004	669 (11·25)	647 (11·38)	22 (8·46)		669 (8·55)	629 (8·60)	40 (7·95)		1,112 (31·44)	286 (45·32)	826 (28·42)	
2006	441 (7·42)	421 (7·40)	20 (7·69)		439 (5·61)	402 (5·49)	37 (7·36)		845 (23·89)	200 (31·70)	645 (22·20)	
2009	358 (6·02)	343 (6·03)	15 (5·77)		358 (4·58)	322 (4·40)	36 (7·16)		706 (19·96)	80 (12·68)	626 (21·54)	
2011	424 (7·13)	410 (7·21)	14 (5·38)		426 (5·45)	386 (5·27)	40 (7·95)		874 (24·71)	65 (10·30)	809 (27·84)	
2015	278 (4·68)	270 (4·75)	8 (3·08)		132 (1·69)	122 (1·67)	10 (1·99)					

N.B. $^a\chi^2$ tests for dichotomous variables and *t*-tests for continuous variables.

smoking, maternal smoking transmission between different SES groups is not reported here.

3.3.1. Subgroup analysis for urban families

The higher the father's education level, the more significant the intergenerational transmission of smoking ($OR_{LowEdu} = 16.89$, $OR_{HighEdu} = 29.52$) and alcohol drinking ($OR_{LowEdu} = 1.997$, $OR_{HighEdu} = 2.314$); however, the OR of SSBs drinking dropped from 5.302 to 2.393, in the low education vs. the high education group, respectively. From low education level to high education level, the OR of the mother's alcohol drinking behavior decreased from 3.545 to 3.509, and the OR of maternal SSBs drinking decreased from 5.090 to 2.972, with insignificant differences in coefficients between the maternal low education and high education groups.

Fathers in the manual labor group had a more significant intergenerational transmission of smoking ($OR_{Manuallabor} = 156.9$, $OR_{Non-manuallabor} = 29.67$), alcohol drinking ($OR_{Manuallabor} = 4.065$, $OR_{Non-manuallabor} = 1.644$), and SSBs drinking ($OR_{Manuallabor} = 5.164$, $OR_{Non-manuallabor} = 2.754$) than fathers in the non-manual labor group. Non-manual labor mothers showed significantly fewer intergenerational transmission effects of alcohol drinking ($OR_{Manuallabor} = 3.660$, $OR_{Non-manuallabor} = 3.050$) and SSBs drinking ($OR_{Manuallabor} = 3.401$, $OR_{Non-manuallabor} = 3.361$).

With an increase in income, fathers' intergenerational transmission effect of smoking and SSBs consumption became weaker and insignificant ($OR_{LowInc} = 174.2$, $OR_{HighInc} = 3.007$; $OR_{LowInc} = 5.071$, $OR_{HighInc} = 2.219$). In contrast, the transmission effect of fathers' wine drinking behavior became stronger ($OR_{LowInc} = 2.061$, $OR_{HighInc} = 2.699$) as income increased. Both mother's alcohol drinking behavior ($OR_{LowInc} = 4.009$, $OR_{HighInc} = 1.874$) and SSBs drinking behavior ($OR_{LowInc} = 2.966$, $OR_{HighInc} = 2.807$) decreased from the low-income to the high-income group.

3.3.2. Subgroup analysis for rural families

With the rise in paternal education level, intergenerational transmission of fathers' smoking ($OR_{LowEdu} = 2.962$, $OR_{HighEdu} = 4.038$) and alcohol drinking ($OR_{LowEdu} = 1.333$, $OR_{HighEdu} = 1.743$) increased, but the OR of fathers' SSBs drinking behavior dropped from 3.294 to 2.339. The OR of highly educated mothers' alcohol drinking behavior increased from 2.542 to 5.354, and that of maternal SSBs drinking reduced from 5.408 to 3.403, with significant coefficient differences ($p_{alcoholofSUEST} = 0.0888$; $p_{ssbsofSUEST} = 0.0203$) than mothers in the low-education group.

Smoking in fathers in non-manual labor jobs had a stronger effect on children's formation of this behavior ($OR_{Manuallabor} = 2.995$, $OR_{Non-manuallabor} = 19.03$) than in fathers in manual labor jobs. Meanwhile, –labored fathers were less connected

TABLE 2 Results of random-effect logistic regression.

Variables	Smoking			Alcohol Drinking			SSBs Drinking		
	All OR(SD)	Urban OR (SD)	Rural OR (SD)	All OR (SD)	Urban OR (SD)	Rural OR(SD)	All OR (SD)	Urban OR (SD)	Rural OR (SD)
Father's behavior: Yes	3·409***	26·06**	2·835***	1·715***	2·194***	1·526**	2·573***	2·748***	2·508***
	(0·882)	(40·05)	(0·737)	(0·234)	(0·526)	(0·257)	(0·421)	(0·876)	(0·492)
Mother's behavior: Yes	1·784	76·22**	1·142	3·574***	3·147***	3·395***	3·592***	3·394***	3·917***
	(0·894)	(164·1)	(0·633)	(0·530)	(0·649)	(0·705)	(0·504)	(0·952)	(0·656)
Father's education	0·961	1·229	0·954	1·007	1·026	0·999	1·005	0·912*	1·030
	(0·0314)	(0·251)	(0·0317)	(0·0197)	(0·0338)	(0·0257)	(0·0201)	(0·0451)	(0·0244)
Mother's education	0·938**	0·706*	0·985	0·992	0·959	1·001	1·037**	1·105**	1·016
	(0·0295)	(0·135)	(0·0328)	(0·0180)	(0·0304)	(0·0249)	(0·0182)	(0·0495)	(0·0212)
Income	0·962	2·281	0·919	1·160**	1·235	1·071	1·165***	1·126	1·162***
	(0·0846)	(1·278)	(0·0801)	(0·0768)	(0·158)	(0·0823)	(0·0468)	(0·0973)	(0·0552)
Father's job: Non-manual labor	1·329	9·559	1·399	0·913	0·998	1·130	1·384**	0·811	1·556**
	(0·338)	(13·53)	(0·374)	(0·136)	(0·226)	(0·234)	(0·207)	(0·251)	(0·294)
Mother's job: Non-manual labor	0·788	5·384	0·454**	0·976	0·897	0·547**	1·244	1·210	1·008
	(0·210)	(8·854)	(0·162)	(0·149)	(0·226)	(0·140)	(0·189)	(0·415)	(0·204)
Age	2·531***	10·13***	2·299***	1·429***	1·454***	1·408***	1·001	1·077**	0·975
	(0·233)	(4·846)	(0·209)	(0·0376)	(0·0608)	(0·0480)	(0·0144)	(0·0354)	(0·0160)
Gender: Male	84·16***	135,565***	53·80***	4·533***	3·982***	5·002***	1·251**	1·193	1·268**
	(42·32)	(405,173)	(27·75)	(0·635)	(0·817)	(0·944)	(0·129)	(0·280)	(0·148)
Area	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wave	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Constant	1·93e-10***	0***	3·50e-09***	2·52e-05***	1·97e-05***	4·69e-05***	0·287***	0·579	0·343**
	(4·05e-10)	(0)	(6·96e-09)	(1·85e-05)	(2·81e-05)	(4·37e-05)	(0·115)	(0·643)	(0·167)
Observations	5,946	1,682	4,264	7,821	2,124	5,697	3,537	1,063	2,474

***$p < 0.01$, **$p < 0.05$, *$p < 0.1$.

with children's alcohol drinking ($OR_{Manuallabor} = 1.847$, $OR_{Non-manuallabor} = 1.171$) and SSBs drinking ($OR_{Manuallabor} = 2.842$, $OR_{Non-manuallabor} = 2.228$). Furthermore, mothers in non-manual labor jobs showed significantly lower effects on children's alcohol drinking ($OR_{Manuallabor} = 3.289$, $OR_{Non-manuallabor} = 5.290$) and SSBs drinking ($OR_{Manuallabor} = 4.045$, $OR_{Non-manuallabor} = 3.916$) than mothers in manual labor jobs.

With an increase in income, the father's intergenerational transmission effect of smoking became stronger ($OR_{LowInc} = 2.683$, $OR_{HighInc} = 29.74$), with a similar effect being observed for fathers' wine drinking behavior ($OR_{LowInc} = 1.577$, $OR_{HighInc} = 1.762$). On the contrary, the influence of fathers' SSBs drinking behavior on their children's behavior went through a process of weakening as income increased ($OR_{LowInc} = 3.310$, $OR_{HighInc} = 1.225$), and the coefficient difference was significant ($p\text{-values}_{ofSUEST} = 0.0003$). Both mother's alcohol drinking behavior ($OR_{LowInc} = 4.054$, $OR_{HighInc} = 1.948$) and SSBs drinking behavior ($OR_{LowInc} = 4.591$, $OR_{HighInc} = 3.035$) decreased from the low-income to the high-income group ($p_{ssbsofSUEST} = 0.0007$), whereas other subgroups did not.

4. Discussion

This study has three central findings: (1) risky health behaviors had significant intergenerational transmission effects; (2) the intergenerational transmission of mothers' alcohol

TABLE 3 Subgroup analysis of intergenerational transmission with different SES.

Variables	Urban			Rural		
	OR (SD)	Suest test	Observations	OR (SD)	Suest test	Observations
Smoking						
Low father education	16·89 (48·27)	$\chi^2 = 0·04$, $p = 0·8468$	187	2·962*** (1·065)	$\chi^2 = 0·76$, $p = 0·3818$	1,858
High father education	29·52** (48·64)		1,206	4·038*** (2·033)		2,406
Low mother education	0·232 (0·795)		336	1·202 (0·641)		2,724
High mother education	9,533** (37,501)		912	–		825
Father's job: Manual labor	156·9 (512·1)	$\chi^2 = 1·42$, $p = 0·2340$	631	2·995*** (0·874)	$\chi^2 = 1·95$, $p = 0·1625$	2,782
Father's job: Non-manual labor	29·67* (58·76)		957	19·03** (25·52)		1,482
Mother's job: Manual labor	9,089 (57,695)		418	0·961 (0·532)		3,229
Mother's job: Non-manual labor	7·763 (15·59)		585	–		1,023
Low income: Father's effect	174·2** (376·2)	$\chi^2 = 0·27$, $p = 0·6013$	478	2·683*** (0·738)	$\chi^2 = 0·01$, $p = 0·9279$	3,271
High income: Father's effect	3·007 (2·479)		411	29·74 (64·33)		744
Low income: Mother's effect	0·00132 (0·00538)		478	1·501 (0·807)		3,271
High income: Mother's effect	8·549** (8·145)		411	–		744
Alcohol drinking						
Low father education	1·997* (0·836)	$\chi^2 = 0·00$, $p = 0·9499$	587	1·333 (0·346)	$\chi^2 = 0·84$, $p = 0·3584$	2,420
High father education	2·314*** (0·699)		1,537	1·743** (0·389)		3,277
Low mother education	3·545*** (0·966)	$\chi^2 = 0·99$, $p = 0·3189$	829	2·542*** (0·658)	$\chi^2 = 2·90$, $p = 0·0888$	3,565
High mother education	3·059*** (0·902)		1,295	5·354*** (1·939)		2,132
Father's job: Manual labor	4·065*** (1·896)	$\chi^2 = 4·81$, $p = 0·0283$	849	1·847*** (0·410)	$\chi^2 = 1·54$, $p = 0·2142$	3,792
Father's job: Non-manual labor	1·644* (0·456)		1,238	1·171 (0·328)		1,905
Mother's job: Manual labor	3·660*** (1·201)	$\chi^2 = 0·45$, $p = 0·5016$	651	3·289*** (0·820)	$\chi^2 = 0·69$, $p = 0·4048$	4,399
Mother's job: Non-manual labor	3·050*** (0·780)		1,473	5·290*** (1·947)		1,298
Low income: Father's effect	2·061** (0·648)	$\chi^2 = 1·25$, $p = 0·2639$	1,348	1·577** (0·306)	$\chi^2 = 1·00$, $p = 0·3710$	4,707
High income: Father's effect	2·699** (1·314)		523	1·762 (0·650)		792
Low income: Mother's effect	4·009*** (1·135)	$\chi^2 = 0·51$, $p = 0·4742$	1,348	4·054*** (0·967)	$\chi^2 = 0·41$, $p = 0·5235$	4,707
High income: Mother's effect	1·874 (0·875)		523	1·948 (0·956)		792
SSBs drinking						
Low father education	5·032 (8·027)	$\chi^2 = 0·35$, $p = 0·5524$	125	3·294*** (1·397)	$\chi^2 = 1·91$, $p = 0·1669$	604
High father education	2·393*** (0·789)		924	2·339*** (0·536)		1,870
Low mother education	5·090*** (3·170)	$\chi^2 = 1·45$, $p = 0·2290$	205	5·408*** (1·650)	$\chi^2 = 5·39$, $p = 0·0203$	933
High mother education	2·972*** (0·943)		835	3·403*** (0·706)		1,541
Father's job: Manual labor	5·164* (4·799)	$\chi^2 = 0·46$, $p = 0·4966$	429	2·842*** (0·701)	$\chi^2 = 3·93$, $p = 0·0473$	1,507
Father's job: Non-manual labor	2·754*** (1·067)		634	2·228** (0·738)		967
Mother's job: Manual labor	3·401* (2·372)	$\chi^2 = 0·35$, $p = 0·5533$	350	4·045*** (0·798)	$\chi^2 = 3·19$, $p = 0·0739$	1,677
Mother's job: Non-manual labor	3·361*** (1·050)		713	3·916*** (1·236)		797
Low income: Father's effect	5·071*** (2·621)	$\chi^2 = 4·43$, $p = 0·0354$	341	3·310*** (0·868)	$\chi^2 = 13·33$, $p = 0·0003$	1,312
High income: Father's effect	2·219 (1·286)		410	1·225 (0·407)		885
Low income: Mother's effect	2·966** (1·253)	$\chi^2 = 0·54$, $p = 0·4610$	341	4·591*** (1·043)	$\chi^2 = 11·51$, $p = 0·0007$	1,312
High income: Mother's effect	2·807* (1·498)		410	3·035*** (0·875)		885

***$p < 0.01$, **$p < 0.05$, *$p < 0.1$.

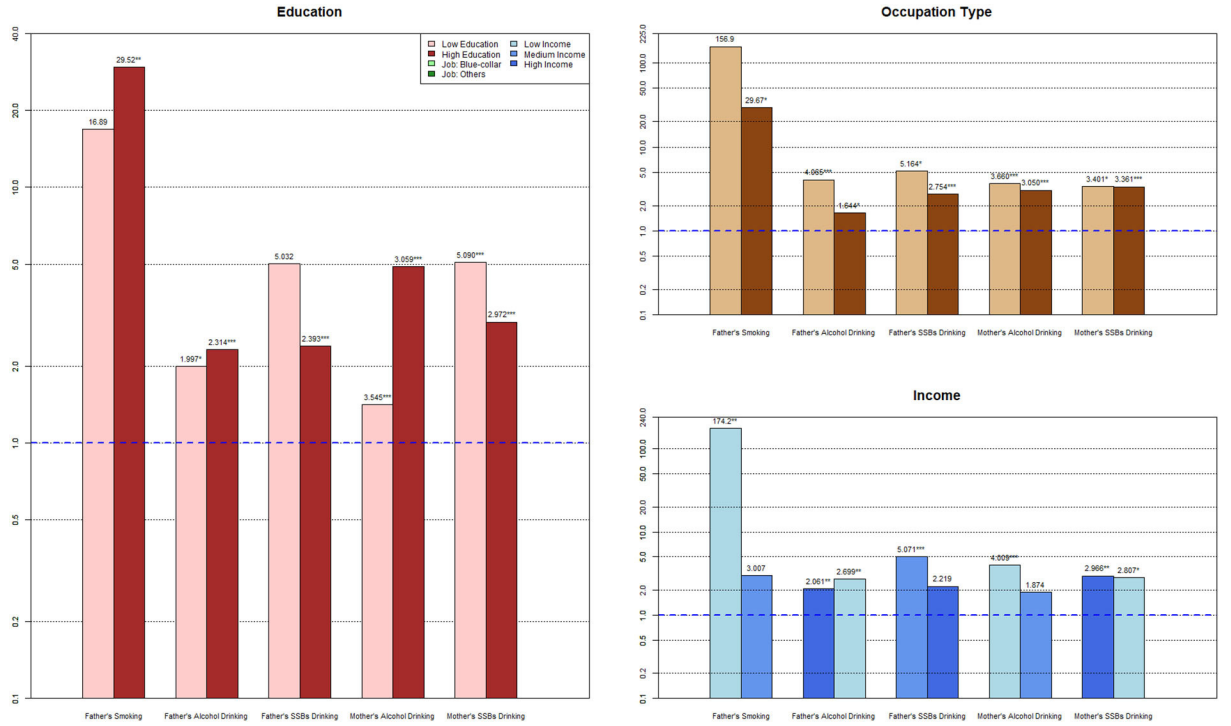

FIGURE 1
Subgroup analysis for urban families.

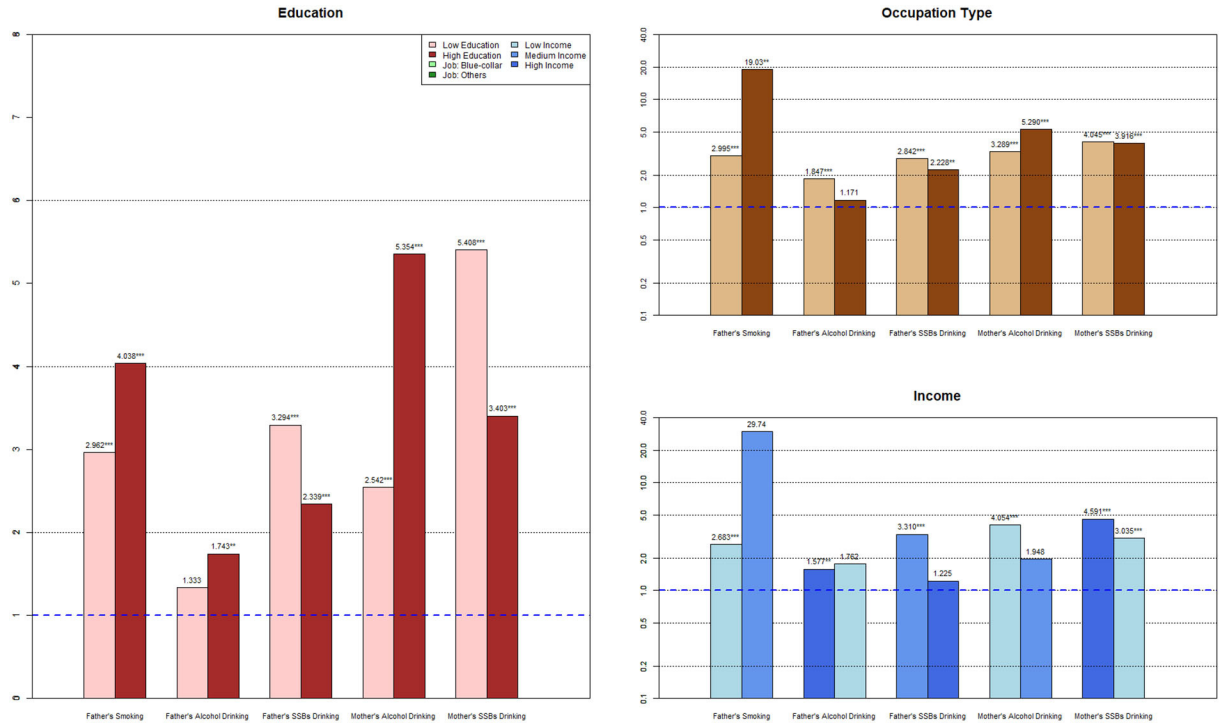

FIGURE 2
Subgroup analysis for rural families.

consumption and SSBs drinking behavior was greater than that of fathers; and (3) the influence of SES on intergenerational transmission in urban areas was different from that of rural children. For addictive behaviors, such as alcohol drinking and smoking, intergenerational transmission mostly exhibited a decreasing trend with increasing SES in urban families but increased with increasing SES for rural families. However, the influence of parental SSBs drinking behaviors showed a consistent decreasing trend with increasing SES for both urban and rural families.

This study showed that, consistent with many previous findings (25, 29–39, 46, 48–50, 62), risky parental health behaviors have a significant risk of being transmitted to their children. It is usually easy for children to imitate their parents' behaviors even if they are negative or unhealthy (25–28, 63, 64), and, therefore, parents' words and deeds are very important in preventing risky health behaviors in children.

Importantly, differences between paternal and maternal influences were also observed. Contrary to many previous studies (25, 29, 32, 33, 65, 66), we found that fathers' smoking behavior had a more significant effect on leading children's smoking behavior than mothers. This may be because the sample size of maternal smokers in this study was too small to make good statistical inferences than previous studies. However, when it came to alcohol drinking and SSBs drinking, the impact of both these behaviors on children was significantly higher from mothers than from fathers, which was consistent with some previous research (29, 49, 61). This may be because mothers generally spend more time with their children than fathers. Therefore, children could be more affected by their mother's behavior than their father's (29, 49, 61).

The role of parental SES in the intergenerational transmission of risky health behaviors in urban and rural children was not exactly the same. In general, there was a significant decrease in the intergenerational transmission of SSBs drinking behavior with increasing SES: the risky health behavior transmission effect of high-SES parents was weaker than that of low-SES parents, and SUEST showed that only the education level of fathers in rural areas had no significant differences between groups, while only fathers' income level had significant differences between groups in urban areas. We also noted that the intergenerational transmission effect of urban mothers' drinking behavior tended to decrease when all three SES variables increased, but rural mothers' alcohol drinking behavior had a similar changing trend with the rise in education level and occupational class. However, SUEST showed that only the education levels of mothers in rural areas differed significantly between the subgroups. A similar situation occurred among fathers: rural fathers' risky health behaviors mainly appeared to show a similar changing trend with SES, while urban fathers' smoking had a reverse changing trend with the rise in occupational type and income. However, SUEST showed that there were significant inter-subgroup differences in the occupation types of fathers in urban areas, but there were no significant differences between the other subgroups.

This reflected that SES had a dual influence on the intergenerational transmission of risky parental health behavior. On the one hand, higher SES means better family capital and better parenting style, which will prevent the formation of children's unhealthy behaviors and reduce the transmission of these behaviors from their parents (26, 27, 30, 41, 42, 49, 67–71). High-SES parents were usually well aware of the dangers of risky health behavior and were therefore inclined to discourage their children from these behaviors, while low-SES parents often did not care whether their children engaged in these behaviors or even engaged in these behaviors in front of their children, setting a bad example for their children and leading them to engage in these behaviors (27, 41, 42, 67, 70–72). Some facts support the standpoint that higher SES can promote people's health and healthy behaviors. In the health model presented by Grossman, more affluent families tend to spend more money on healthcare, such as better-quality medical care and healthy food (40, 68, 71). Well-educated parents are more inclined to adopt healthy behaviors, both for themselves and their children, so the incidence of risky health behaviors among children is lower (68, 69, 71). In addition to the fact that education can lead to a better knowledge of the importance of promoting healthy behaviors, there were also potential indirect effects, such as smoother ways to get a job, better affordability of health-improving goods, less stress, and better work environments due to high-SES parents also being exposed to healthier colleagues (35, 43, 71). However, lower-SES people may care less about their health and that of their family members, be less responsive to health promotion, receive less information about how to get healthy, and have limited access to health promotion services (34, 67, 70). Similar effects of low-SES have been observed in risky health behaviors, such as SSBs consumption, which mainly exists in children and adolescents.

On the contrary, however, higher SES can mean that parents will devote more time to their own careers to cope with higher workloads (53), more often ignoring messages they received, hiring nannies or, in Chinese traditional culture, asking for support from their own retired parents, who are often less educated, leading to the absence of family education. Children with high-SES parents tend to have more disposable pocket money, which makes it easier for them to access substances that pose health risks, such as SSBs and wine (73). All of these factors may increase the risk of unhealthy behaviors in children. If the degree of intergenerational transmission is more severe than that of rural and low SES parents, the effect of parents' actions is greater than the effect of their words, which may promote

intergenerational transmission of risky health behaviors in children. This may be because high-SES parents tend to have a higher status in their children's minds, and children are more likely to imitate risky parental health behaviors (25, 74). In our sample, for traditional rational addictive behaviors such as smoking and alcohol drinking, higher parental occupation and education level could enhance intergenerational transmission, which is an example of the effect of their actions being greater than that of their words. This shows the necessity and importance of behavioral changes starting with the parents.

5. Conclusion

We observed that parents played an important role in the development of risky health behaviors in children. Risky parental health behaviors set a bad example for their children and tempt children to imitate their parents' behaviors. It is worth noting that urban areas, especially urban mothers, mostly reflected the positive effects of SES, whereas fathers, especially those in rural areas, reflected adverse effects. This suggests that we should pay more attention to fathers' behaviors and awareness of health education in rural areas and invest in the rearing of their children. In addition to persuading children to drop these behaviors, more attention should be paid to reducing intergenerational transmission.

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 authors.

Ethics statement

Data for this study was from the China Health and Nutrition Survey (CHNS). CHNS was approved by the Institutional Review Committees of the University of North Carolina at Chapel Hill and the National Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention.

Author contributions

ZY and JL conceptualized and designed the study, participated in explaining the data, and writing and revising the manuscript. ZY analyzed the data. WQ helped to revise the manuscript. All authors approved the final version of the paper and have directly accessed and verified the underlying data reported in the manuscript.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.842817/full#supplementary-material

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Should more attention be paid to polio sequela cases in China?

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Since "Global Polio Eradication Initiative" was launched by World Health Assembly in 1988, the incidence rate of polio has been reduced by more than 99%, and the whole world has entered a post polio era nowadays. China has been a polio free status recognized by World Health Organization for 22 years and most people believe that no more public health concerns need to be given. How is the population of polio survivors in China? What strategies of health economics and actions of public health for those with polio are ethically appropriate? This article, first of all, deeply summarizes and analyzes the history, current situation and unmet needs of population with polio sequelae and post-polio syndrome in China, and then, puts forward important issues faced by polio survivors who natural infected and who due to vaccine associated paralytic polio and vaccine derived poliovirus. The management of polio survivor is not only a medical and rehabilitation problem involving accessibility, accommodations, but also a public health issue, and most importantly, an ethical concern. Furthermore, from the perspective of ethics such as Justice and Cooperation, the author demonstrates the rationality and necessity of continuing to pay more attention to polio sequela cases at this stage in China. Finally, many valuable suggestions and practical recommendations are given.

KEYWORDS

polio, disability, rehabilitation, public health, ethics, population medicine

Introduction

Polio is an acute infectious disease caused by the poliovirus (1). Many people infected with polio have flaccid paralysis of their limbs resulting in lifelong disability. This resulted in a lot of affected sequela cases in the last century particularly in the 1950–1970's. Currently, polio has been nearly eradicated globally with extensive vaccination efforts utilizing the Salk and Sabin vaccines and the joint efforts of people all over the world. At present time, most polio sequela cases are 60–70 years old, and those in China are much younger. Although survivors may have disabilities, it is no longer a significant issue in some countries because they are able to function well with good accessibility to treatment over the years. The status of polio sequela cases in China may be some different.

In China, polio has been reported since the 1950's. The number of polio cases was as high as 10,000–30,000 every year during the 1960's according to an incomplete statistical account (2). In view of this severe situation, the Ministry of Health had Gu, who worked in the Chinese Academy of Medical Sciences, lead a team to the Soviet Union to learn about preparation of polio vaccine in 1959. Professor Gu compared the mechanisms of preparing inactivated and live attenuated vaccines. Given the large population in China at that time, it was imperative to reduce the incidence of polio quickly, and the country's economy could not afford the production costs of an inactivated vaccine. Therefore, the relevant departments approved an immunization strategy using a live attenuated vaccine (2). In March 1960, a live attenuated vaccine was successfully

developed, and it was officially put into production in 1961. Unfortunately, several small-scale outbreaks occurred in the late 1970's and 1980's, because the preservation, transportation, and distribution of vaccines was a complex social procedure, especially in rural areas. A trivalent vaccine was successfully developed in 1985 and popularized nationwide in 1986, which provided a powerful weapon for the complete eradication of polio in China. With this vaccine-preventable disease controlled (3), and through the efforts of the Chinese government and institutions at all levels, there have been no new polio cases caused by indigenous wild poliovirus (WPV) since October 1994. In October 2000, China was declared polio-free of the WPV by the Regional Commission for the Certification of polio Eradication in the World Health Organization (WHO) Western Pacific Region[1]. With the launch of a domestic inactivated polio vaccine, China have began to gradually promote a sequential vaccination program to prevent polio. On May 1, 2016, a 1+3 program was implemented [one dose of inactivated polio vaccine (IPV) and three doses of oral polio vaccine (OPV)], and on January 1, 2020, a 2+2 program was implemented (two doses of IPV and two doses of OPV) (2). Ultimately, IPV will be used for all four doses.

In the current post-polio era, most people believe that there will no longer be polio in China in another 20 years, and polio sequela cases will no longer be a problem as they will need no further care. Should more attention be paid to polio sequela cases in China? Have medical rehabilitation resources met their healthcare needs? How is the care, health, and wellbeing of individuals with polio provided? What strategies of health economics and actions of public health for those with polio are ethically appropriate?

The population of polio sequela cases in China

Polio sequela case, sometimes called "polio survivor" because they survived from the epidemic fortunately. According to the official data of the China Disabled Persons' Federation in 1994 (4), Xinming Song's literature published in 2013 (5), and polio sequala chapter of "Lower Limb Deformities" published in 2020 (6), the size of population of polio survivors in China is about 2.0 million from the last century, accounting for about 1/10 of the total number of the people with limb disabled. Most of these people have varying degrees of lower limb disability, joint dysfunction, and loss of muscle strength and mobility of multiple muscle groups (6). Some have implemented rehabilitation regimes and undergone surgeries (7), some have given up treatment, but most have been searching for rehabilitation and other solutions. They are gradually entering middle-age or have become elderly (8). They often manifest complex symptoms as limb weakness, fatigue, cold intolerance, joint and muscle pain, aggravation of original deformities as well as some new deformities, such as dysphagia, oral motor weakness, and paralysis. These are referred to as post-polio syndrome (PPS). It is estimated that 50% −80% of polio sequela cases suffer from PPS which generally occurs 30 years after the acute onset of polio (9). The demand for surgery and rehabilitation in this population is not disappearing but increasing with disability prevention and social progress, because these syndromes will aggravate their existing movement disorders, reduce their mobility, and affect their life, marriage, family, and work. Polio sequela cases has the distinctive characteristics, which is constantly changing, as well as the demand for medical treatment and rehabilitation during the whole life span.

Unmet needs of polio sequela cases in China

Most healthcare institutions oppose paying attention to this shrinking population

Since the 1980's, the polio epidemic has gradually been effectively controlled globally. The last case of polio in the United States was reported in 1982. The last case of indigenous WPV in China was in 1994, and just 4 cases of WPV importation into the entire country have been reported since 1995 with the last case in 2011. Considering the large number of polio survivors, 10 authorities of the Chinese government, including the Ministry of Civil Affairs, the Ministry of Health, the State Planning Commission, the Ministry of Finance, and the China Disabled Persons' Federation jointly deployed and implemented the national program named "Three Rehabilitation," one of which is polio deformity correction, in September 1988. By the end of 1993, 327,688 patients with polio had received treatment, with an effective rate of 98.7% and a remarkable rate of 81.1% (4). Due to the success of the national immunization program, the number of new polio cases is getting smaller and smaller, Medical treatment and rehabilitation of polio has never been listed in special regulations and national programs again. In order to adapt to changes of the disease spectrum, the original orthopedists, who primarily focused on correcting deformities, were laid off or transferred to other positions when China entered its polio-free status. Hospitals no longer establish polio specialist clinics, and medical colleges or universities have no institutions addressing polio. Concurrently, medical conferences rarely address this issue, and related scientific research is seldom to be found.

Insufficient medical community awareness of polio sequelae and PPS

Once the end of the acute phase of the polio epidemic occurred, people believed that the patient's story was over, and they received their immunizations against it. However, the issue of polio sequela and PPS is occurring right now (10). The clinical manifestations of polio sequela are complex and diverse. It is difficult for inexperienced doctors to distinguish PPS from common diseases of the elderly, and its treatment does not follow a common routine. There is a lack of research on PPS, and patients with PPS are often accused of hypochondriasis. Doctors who are rich knowledge of polio sequela have retired, and there are few institutions engaged in limb disability correction. Most medical staffs and rehabilitation practitioners have little awareness of PPS, and they have a poor understanding of the process for polio care. Furthermore, relatively few doctors and institutions can provide appropriate diagnosis, surgical care, and rehabilitation. As a matter of fact, the existing medical rehabilitation and policy system do not match with the specific needs of polio population, because the development of PPS raises questions of polio as a static disease and it poses a challenge not only to health professionals, but also to policy makers who are responsible for

1 https://www.who.int/china/health-topics/poliomyelitis-(polio)

providing the necessary health care measures and corresponding resources (11).

Medical science popularization and disability education for PPS lags behind

Although previous rehabilitation interventions focused on overcoming disability at all costs, much evidence show that the original deformities from polio are aggravated, or new deformities appear with aging. Good results have been achieved in treating these complications through rehabilitation intervention and orthopedic surgery (12). Even though most people with disability still have difficulty in adapting to the environment and realizing "normalization," the rapid development of new medical technology [exoskeleton, artificial intelligence, and advanced limb reconstruction technology (13)] can greatly improve previously untreatable physical disabilities. However, polio survivors, especially those in rural and remote areas, have a limited awareness of polio itself and PPS due to the relatively low level of medical services and their different culture. There is little space in medical textbooks currently that discuses polio and its sequela. The dearth of education for medical practitioners caring for those with physical disabilities restricts the possibility of quality-of-life improvement for polio survivors among the middle-aged and elderly in China. The lack of access to diagnostic and treatment information for these patients leads to worsening of their own complications, and there is no access to rehabilitation, surgery, and other improvement measures.

Management of cases with vaccine related paralytic polio and vaccine derived poliovirus need more attention

The WHO emphasizes that vaccine related paralytic polio (VAPP) and vaccine derived poliovirus (VDPV) are unavoidable adverse events of vaccination. This is a significant issue with the live attenuated vaccine, and occurs with an incidence of 2–4/1 million newborns (14). They cannot be ignored. In 2019, the Chinese government promulgated *the Vaccine Administration Law of the People's Republic of China*[2]. It formulated relevant policies to help those who experienced these unfortunate complications and established corresponding compensation for those identified with VAPP. However, whether it can meet the requirements of health economics and meet the health and wellbeing of these individuals' entire lifespan, and how to evaluate the relevant departments have effectively investigated and followed-up patients with VAPP and fully implemented the corresponding policies requires further research (15).

Common issues of people disabled faced by polio sequela cases

Polio sequela cases with disabilities in China still face issues including, but not limited to, prejudice, stigmatization, personal dignity, autonomy, privacy, fairness, and active participation in society. In fact, disability of polio survivor and others, such as person with cerebral palsy and motor accident, are similar, but the main difference is that there are various types of physical disabilities, full of complicated changes in different life periods, and lack of corresponding medical treatment and rehabilitation. How to protect equal health rights and promote medical research, how to overcome issues in the provision of public health, and how to ensure the accessibility and affordability of medical treatment, rehabilitation, and assistive devices are still questions. These interests must be balanced against with the need for increased public knowledge and debate concerning disability. It is not just a task for healthcare practitioners and providers, also an important challenge faced by all stakeholders.

Analysis of the reasons

Systematic barriers may have formed

The government of China has promulgated a number of laws and regulations related to people with disabilities such as *the Law of the People's Republic of China on the Protection of the Disabled, Regulations on the Prevention and Rehabilitation of the Disabled, Regulations on the Employment of the Disabled, Regulations on the Construction of an Accessible Environment, Implementation Opinions on Further Promoting the Civilized Practice of Helping the Disabled, and National Action Plan for Disability Prevention (2021–2025)*. The Disabled Persons' Federation and the Ministry of Civil Affairs have set up a special rehabilitation hospital for the disabled. However, there is no specific description of the special needs of the disabled with polio, and they are not accurately identified, perhaps for the reasons of avoiding discrimination.

Thirty years ago, 10 national authorities jointly implemented the program "Three Rehabilitation" one of which has been dedicated to the treatment and rehabilitation of polio cases for five consecutive years and has achieved great success. After the completion, the "Three Rehabilitation Office" was renamed the "National Rehabilitation Office for the Disabled" (4), because the goal is to take care of all the disabled, not only for polio. Unfortunately, the attention paid to the polio population has gradually decreased with the changes. The disadvantages brought about by the fragmentation of information among various authorities have emerged. It's a pity that no national action on polio has been held thereafter. As the time goes on, there are less and less hospitals or departments that can provide treatment and rehabilitation for polio survivors, just only one hospital of the Ministry of Civil Affairs right now. Even for that other disabilities, such as person with sequela of cerebral palsy and trauma event can be treated and recovered in many hospitals.

The healthcare institutions affiliated to the Ministry of Health do not set up a department for polio deformity correction and rehabilitation. The number of doctors familiar with the polio sequela and PPS is limited. The disabled usually go to hospitals first when they need help, while they does not know about disability so much owing to just little space in textbooks. Therefore, polio sequela patients usually cannot receive adequate medical rehabilitation and treatment. For polio cases in rural and remote areas, it is more difficult to meet

2 http://en.npc.gov.cn.cdurl.cn/2019-06/29/c_674711.htm

their medical needs. System barrier directly lead to the rehabilitation of the disabled is separated from Health and Education.

Polio survivors in China need additional helpful experience

The formulation and application of many intervention strategies have played an important role in polio control and prevention worldwide. Among these are the Strategic Plan for the Final Phase of Polio Eradication (2013–2018) (16) the Strategic Plan (2019–2023)[3] and the Polio Eradication Strategy (2022–2026) (17). All of these plans note that polio eradication requires the eradication of cases caused by WPV as well as VAPP and VDPV. As new cases occur in Pakistan (18) Afghanistan (19) and New York (20) there are many reports issued by those who pay attention to and promote the Global Polio Eradication Initiative (21). These reports focus more on the promotion and use of vaccines and virus surveillance (22). Only rarely are policy recommendations for the management of those who have survived polio espoused (23). The elimination of poliovirus is important and well-known, but it does not mean eliminating patients surviving polio. According to the International Classification of Functioning, Disability and Health (ICF), appropriate strategies for the treatment and rehabilitation of those surviving polio are necessary.

Due to the time of prevalence and control of polio epidemic, their population in China is relatively young. Those surviving polio with disabilities in different regions of China have varying needs for deformity correction, education, medical treatment, social environment, and economy. They should still be paid more attention to although the number of polio cases is decreasing. In particular, many countries have polio organization, such as *March of Dimes*[4], *Polio Canada,* and so on, which are accurately guided and organized, making rehabilitation education more accessible. Furthermore, polio clinic, a specialized setting, can clearly organize professionals to take charge of prevention, diagnosis, control, treatment, rehabilitation and health promotion for polio cases. This is what the Chinese group of polio should learn from and vigorously promote and expand. Importantly, Chinese Disabled Persons' Federation should also pay more attention to this relative mature experiences of rehabilitation education, which were the weakness of Chinese polio, and strengthen its guidance and promotion.

The reduction of new polio cases, the formation of barriers between authorities, and the lack of communication between different regions and countries may be the main reasons for the current situation of polio sequelae and their unmet needs. In determining a framework to provide care for polio sequelae cases in China, polio eradication should not be the only goal (24). Early and effective intervention are of great significance for improving their quality of life and social integration. Learning more from international experiences on comprehensive and system governance and considering how to better implement a strategy for the specific populations in China is imperative. It is essential to build an appropriate framework for the entire lifespan of individuals with polio and provide multidimensional care for this whole population.

Ethical consideration

How is it possible to identify the ethical dilemmas faced by polio sequelae cases with physical disabilities? Should we just give up paying more attention to these individuals in China? What strategies of health economics and actions of public health for those with polio are ethically appropriate? It is not only a medical and rehabilitation problem but also a public health concern, and most importantly, it is also an ethical issue.

Justice

This is a misunderstanding for the discussion of needs of polio sequelae cases based on Bentham's philosophy, which may be another important reason why the polio survivors were not given enough attention in reality. It is generally believed that giving priority to the cost-effectiveness of health care resources may lead to the lower priority of treatment for the disabled than other similar non-disabled people. The defenders of cost-effectiveness insist that the cost-effectiveness of treatment for the disabled is low. If we give priority to non-disabled people, we will get greater health benefits. This kind of Utilitarianism is generally held to argue against special attention for the disabled as Dan W and Brock mentioned in their article (25). It implies that disabled persons' lives are of lesser value than those of non-disabled persons. It is disability discrimination. The core value of social public policy should focus on the vulnerable groups firstly. It is injustice if a patient has a lower priority to receive treatment due to his/her illness and disability than others (26). The life value of polio should be respected as well as that of other disabled people. Any disability, no matter how slight or serious, does not mean even worse in political or moral status.

As a vulnerable population, disabled polio survivors need more attention. The option of giving up and waiting for them to naturally disappear cannot be defended ethically. The development and dissemination of helpful medical rehabilitation technologies should be given priority, and more resources and information for polio survivors in different regions should be considered in policy formulation. The relevant diagnosis, treatment, and rehabilitation systems should not be subject to market regulation and excessive influence, otherwise, "the value of medicine" will be devalued, and inequality among people will be aggravated. Nowadays, the government or relevant departments should play a key role in the reasonable allocation of resources, which can be justified by ethics, even if it is different from the calculation results of health economics.

VAPP and VDPV cases are unavoidable adverse events of vaccination. It is not an issue of either getting or not getting polio vaccine, or vaccine effectiveness or ineffectiveness, but an issue of the relationship between individual benefits and public interests. Individuals with VAPP/VDPV face many issues. Their ability to work, provide self-care, mobility, learning ability, and social ability are affected to varying degrees. The progression of their disabilities, in particular with PPS, constitute a heavy social burden. This small group should receive more attention for the implementation of compensation policies by the relevant national authorities following

3 https://polioeradication.org/who-we-are/polio-endgame-strategy-2019-2023/

4 https://socialpresskit.com/march-of-dimes

ethical principles. This will ensure the demonstration of national responsibility and further avoid and reduce vaccine hesitation.

Cooperation

Regarding the consideration for the Barriers, it refers to the information barriers and isolated islands between different authorities, disciplines, groups or countries.

For a long time in China, the diagnosis, treatment and rehabilitation of the disabled are managed by the Ministry of Civil Affairs and the Disabled Persons' Federation, instead of the Ministry of Health. The original intention is to provide better welfare care for the vulnerable population, and a lot of works and achievements have been done. Undoubtedly, such system have achieved better welfare care for disabled persons with disabilities under China's social and economic conditions. With the time changes, such institutional arrangements also exposed some subsequent shortcomings. The prominent problem is that there are "Barriers" and "Splits" between the medical institutions of the Ministry of Civil Affairs and the Ministry of Health, resulting in limitations in medical education, training of medical professional, dissemination of rehabilitation knowledge, etc.

Relevant authorities and disciplines should cooperate and work together to make top-level design, consequently, to break down all the barriers. It is important to learn from helpful experience and not sacrifice or neglect any rights or any opportunities of polio survivors for medical rehabilitation, correction of surgical deformities, and functional reconstruction (6). Looking at international disability prevention action over the past three decades, it is clear that there is increasing awareness that disability is the result of the interaction between people and their environment. Accessibility in every part is an important and universal consideration for society as a whole. Accessibility of polio sequela cases to public facilities and the entire sociocultural environment require the joint participation of everyone, and the formulation of effective intervention plans and methods is necessary.

In addition to the above two important ethical principles, we still need to take into account the basic principles, such as "Beneficence" "Respect", when discussing ethics and governance of the population of polio sequela cases in China.

Policy recommendations

As for ethical governance and policy recommendations, the Chinese government and authorities at all levels have done a significant amount of rewarding work. However, the problems and issues have not been completely solved or integrated into the medical rehabilitation system and the three-level prevention domain of the public health system. We should pay more attention to polio sequela cases in China. There are currently efforts to put forward and supplement defensible ethical governance suggestions for the healthcare provider, medical professionals, scientific researchers, and policy makers.

First of all, with a view to promoting Justice through improving the construction of the disabled medical rehabilitation system, we propose to establish polio clinic (27) to focus on solving the health and wellbeing related problems of polio population especially for whom with PPS. Moreover, a special team should be set up within hospitals' existing operating departments to undertake the diagnosis, treatment, rehabilitation, and orthopedic needs, science popularization and scientific research, the provision of professional knowledge, regular evaluation of the people who could benefit. We should not only focus on polio vaccination for disease prevention, but also pay more attention to the quality of life of those polio survivors. The needs of all of those with polio should be taken into account, and customized intervention measures should be actively developed. In addressing greater accessibility, research, and better awareness, the rational allocation of medical resources will be promoted, and a comprehensive national and regional system for polio clinics will be well-designed and established to avoid resource waste.

Secondly, in the light of principle of Justice, the implementation and revision of VAPP and VDPV compensation strategies based on the effective research of Implementation Science and Economics of Health (28) and highlighting the responsibilities of government and society should be strengthened. To maximize the health and wellbeing of individuals with VAPP, and minimize the negative impact on individuals and this entire population, an appropriate effective governance framework is required. A continuous dialogue between patients, public, professionals, ethicists, and policymakers is essential.

Thirdly, Authorities of Ministry of Civil Affairs, the Disabled Persons' Federation, the Health Commission and the Education Commission can work together to break down the barriers, promote rational allocation of resources, and facilitate the medical treatment of the disabled, the training of doctors, and the compilation of teaching materials. With the concept of Population Medicine (29), system barriers and information islands will be broken among the five groups of "patients" "professionals" "disciplines" "authorities" and "ordinary." All activities should be under girded by the conceptual frame-work of ICF, and must be inclusive of the health and wellbeing of people with disabilities at individual level and population level.

The fourth, with the promotion of the Disabled Persons' Federation and the Ministry of Civil Affairs, we suggest to establish a registration system for polio cases, provide them opportunities for the development of rights such as targeted treatment and rehabilitation interventions as soon as possible, and restart the national polio rehabilitation action when appropriate. Along this way, the network work of polio organizations or alliance in China (24) should be actively promote to improve awareness of polio population, to make health information accessible, like similar group in Canada, United Kingdom, United States, and other countries who always hold regular activities and meetings to popularize relative scientific knowledge.

It is gratifying to note that China has launched a great program "University of Rehabilitation Science" with huge investment. More importantly, it is a joint work organized by the National Disabled Persons' Federation and the National Health Commission. Undoubtedly, it is a good news for Chinese polio sequela cases, and an important measure to promote improvement of their unmet needs. We are full of expectations, especially on the top-level design.

Conclusions

In the 20 years since China became polio free, the population of polio sequela and those with PPS still face many important

issues that have been neglected especially in medical treatment and rehabilitation. It is important to concentrate on the individual and population who with polio at this stage from the ethical perspectives of Justice and Cooperation. Practical actions of public health based on the actual situation in China need to be taken to break down the barriers, to solve these unmet needs, to accumulate valuable experience for polio cases, and to refine Chinese wisdom for polio survivors around the world.

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.

Author contributions

JZ and XZ conceptualized and supervised the paper. XZ provided project administration and resources. JZ wrote the initial draft. JW, XW, KL, and LF revised this draft. All authors contributed, reviewed, and edited the final manuscript draft.

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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.

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Sugemalimab plus chemotherapy vs. chemotherapy for metastatic non-small-cell lung cancer: A cost-effectiveness analysis

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Background: Sugemalimab is a newly developed inhibitor of programmed death ligand 1 (PD-L1). As a first-line treatment for metastatic non-small-cell lung cancer (NSCLC), sugemalimab plus chemotherapy (Sugema-Chemo) has been proven effective. Still, its cost-effectiveness has not yet been determined. The objective of this study was to assess the cost-effectiveness of Sugema-Chemo from a health care perspective in China.

Methods: A partitioned survival model was used. According to the GEMSTONE-302 trial, the clinical characteristics and outcomes of the patients were obtained. The outcomes were costs, quality-adjusted life-years (QALYs), incremental cost-effectiveness ratio (ICER), incremental net health benefits (INHB) and incremental net monetary benefits (INMB). The robustness of the model was further evaluated, as well as subgroup analyses. When the ICER was lower than the willingness to pay (WTP) threshold ($38,017/QALY or $86,376/QALY, defined as three times the per capita gross domestic product value of the general region and Beijing), the cost-effectiveness of Sugema-Chemo was assumed for general regions or Beijing.

Results: Compared with chemotherapy alone, Sugema-Chemo resulted in an incremental gain of 0.82 QALYs, an incremental gain of 1.26 life-years, as well as an average increase cost of $72,472. The ICER was $88,744/QALY. Model outcomes were susceptible to average body weight and cost of sugemalimab. Sugema-Chemo was cost-effective at a WTP threshold of 86,376/QALY if the average body weight was <62.44 kg or if the price of sugemalimab was <$2.996/mg. As well, Sugema-Chemo was also cost-effective when the cost of sugemalimab was <$1.839/mg for a WTP threshold of $38,017/QALY. Sugema-Chemo had a probability of > 50% being considered cost-effective in most subgroups at the $86,376/QALY threshold. However, Sugema-Chemo did not achieve cost-effectiveness (0%) in any of the subgroups when WTP was set at $38,017/QALY.

Conclusion: Sugema-Chemo might not be cost-effective in patients with metastatic NSCLC in China. In deciding between Sugema-Chemo and chemotherapy alone, it is essential to consider both the body weight of patients and the price of sugemalimab. A price reduction of sugemalimab under the National Healthcare Security Administration may be an effective measure to improve the cost-effectiveness of the drug.

KEYWORDS

sugemalimab, partitioned survival model, non-small cell lung cancers, chemotherapy, cost-effectiveness

Introduction

Lung cancer is one of the most common types of cancer, and it is the leading cause of cancer death worldwide (1). Nearly 85% of lung cancers are non-small cell lung cancers (NSCLC) (2). Squamous and non-squamous lung cancers account for 25–30% and 70–75% of all cases of NSCLC, respectively (1, 3). NSCLC is generally diagnosed at an advanced stage and has a poor prognosis for most patients (4). Platinum-based chemotherapy has traditionally been recommended as first-line treatment for patients with advanced NSCLC without targetable genetic alterations (5). However, there was a limited survival benefit associated with these interventions and the median overall survival (OS) was <1 year for these interventions (6). There is an urgent need for novel interventions to improve survival rates in advanced NSCLC, considering its prevalence and poor outcomes (4, 6).

In the past few years, immune checkpoint inhibitors (ICIs) have demonstrated promising benefits and a favorable safety profile, so they are rapidly incorporated into the standard treatment for advanced NSCLC (7). Sugemalimab is a humanized monoclonal antibody that inhibits programmed death ligands (8). As first-line therapy for patients with metastatic NSCLC, sugemalimab plus chemotherapy (Sugema-Chemo) significantly prolonged progression-free survival (PFS) in the GEMSTONE-302 randomized phase 3 trial compared to chemotherapy alone, as well as increasing response rates (8). Accordingly, Sugema-Chemo is a promising first-line treatment option for metastatic NSCLC. Sugemalimab, in combination with pemetrexed and carboplatin, has been approved in China for treating non-squamous NSCLC, and for patients with squamous NSCLC (8, 9).

Despite this, due to the relatively high cost of the combination therapy (Sugema-Chemo), it is urgent to perform a cost-effectiveness analysis of Sugema-Chemo compared to chemotherapy for treating NSCLC. Therefore, the purpose of the present study was to investigate the cost-effectiveness of Sugema-Chemo as first-line therapy for metastatic NSCLC in comparison with chemotherapy alone from a health care perspective in China.

Materials and methods

Patients and intervention

This study was conducted following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (10). Patients with metastatic NSCLC enrolled in the GEMSTONE-302 study were the target population (8). GEMSTONE-302 is designed to enroll patients with metastatic non-squamous or squamous NSCLC who are at least 18 years of age without known EGFR sensitizing mutations, ALK, ROS1, or RET fusions and who have not received any prior systemic therapy for metastatic disease. The study enrolled individuals who received sugemalimab 1,200 mg once every 3 weeks or placebo, in combination with carboplatin and paclitaxel for patients with squamous NSCLC, or combination with carboplatin and pemetrexed for patients with non-squamous NSCLC. The maintenance treatment for squamous NSCLC consisted of sugemalimab or placebo, and the maintenance treatment for non-squamous NSCLC consisted of sugemalimab or placebo.

Model structure

We conducted an economic evaluation and used a partitioned survival model that considers three mutually exclusive health states: progression-free survival (PFS), progressive disease (PD), and death (11). Both treatment arms had a 15-year time horizon, and more than 98% of patients died during this period. The cycle length was 1-week. Based on clinical results from the GEMSTONE-302 trial, the proportions of patients with OS and PFS were established in the model (8). A portion of the OS curve was evaluated for the proportion of patients still alive; the portion of the PFS curve was evaluated for the proportion of patients living with PFS, and the difference between OS and PFS curves was evaluated for the proportion of patients living with PD. This study did not require or obtain an institutional review board review or informed consent because data were obtained from the literature and open databases.

Clinical data inputs

According to Guyot et al.s' algorithm, the OS and PFS of the GEMSTONE-302 trial were extrapolated beyond the follow-up period of the trial using the OS and PFS data obtained from the trial (12). To obtain the individual patient data points, the Kaplan-Meier (K-M) survival curves for OS and PFS were calculated using GetData Graph Digitizer version 2.26 (13). After calculating these data points, we fitted them with parametric survival functions: exponential, Weibull, gamma, lognormal, Gompertz, log-logistic, and generalized gamma. Afterward, the best-fit parametric models for the reconstructed K-M survival curves were selected based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Sugema-Chemo and chemotherapy survival functions and parameterized models are shown in Table 1, while goodness-of-fit results are shown in Supplementary Table 1. Specifically, Log-logistic was selected to fit the PFS K-M curves of Sugema-Chemo or chemotherapy, and the OS K-M curves of Sugema-Chemo. Lognormal was selected to fit the OS K-M curves of chemotherapy alone (Supplementary Figure 1). The key clinical input data are listed in Table 1.

Cost inputs

Several direct medical costs have been evaluated, including those associated with obtaining drugs, the cost of supportive care, the cost of terminal care, and the cost of adverse events (AEs) (Table 1). We obtained the prices in Chinese Yuan and translated them into US dollars using the exchange rate of 2021 (1 US dollar = 6.37 Chinese Yuan) (25). Based on the standard fee database, the drug costs were determined. We assume that the average body surface area (BSA), weight, and creatinine clearance rate (CCR) were 1.80 m^2, 65 kg, and 90 ml/min/1.73 m^2. Those assumption were used to calculate the median dosage of

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TABLE 1 Key model inputs.

Parameter	Value (95% CI)	Distribution	References
Clinical input			
Survival model for sugemalimab plus chemotherapy			
Log-logistic model for OS[a]	$\gamma = 1.3113$ $\lambda = 0.0253$	ND	(8)
Log-logistic model for PFS[a]	$\gamma = 1.6344$ $\lambda = 0.0094$	ND	(8)
Survival model for chemotherapy			
Lognormal model for OS[a]	$\mu = 4.2489$ $\sigma = 1.0432$	ND	(8)
Log-logistic model for PFS[a]	$\gamma = 2.1146$ $\lambda = 0.0446$	ND	(8)
Cost input			
Drug costs per 1 mg			
Sugemalimab	3.05 (2.44–3.66)	Gamma	Local database
Carboplatin	0.12 (0.08–0.16)	Gamma	Local database
Pemetrexed	1.17 (0.22–3.19)	Gamma	Local database
Paclitaxel	0.80 (0.32–1.16)	Gamma	Local database
Nivolumab	15.44 (13.79–17.09)	Gamma	Local database
Docetaxel	1.61 (0.73–2.25)	Gamma	Local database
Second-line treatment in sugemalimab plus chemotherapy arm per cycle	789 (631–947)	Gamma	(8); Local database
Second-line treatment in chemotherapy arm per cycle	1,512 (1,210–1,814)	Gamma	(8); Local database
Cost of terminal care per patient[b]	16,441.83 (12,331.37–20,552.29)	Gamma	(14)
Disease costs per cycle			
Patients with PFS[c]	464.85 (348.64–581.06)	Gamma	(14)
Patients with PD[c]	1,075.49 (806.62–1,344.36)	Gamma	(14)
Cost of managing AEs (grade $\geq$ 3)			
Sugemalimab plus chemotherapy	3,063 (2,450.4–3,675.6)	Gamma	(15–17)
Chemotherapy	2,984 (2,387.2–3,580.8)	Gamma	(15–17)
Supportive care per cycle[d]	72 (58–86)	Gamma	(18)
Cost of drug administration per unit	19.11 (15.288–22.932)	Gamma	(19)
Health utilities			
Disease status utility per year			
Utility of PFS	0.804 (0.64–0.96)	Beta	(20)
Utility of PD	0.321 (0.26–0.39)	Beta	(20)
Death	0	NA	
Disutility due to AEs			
Sugemalimab plus chemotherapy	0.159 (0.119–0.199)	Beta	(20–22)
Chemotherapy	0.147 (0.110–0.184)	Beta	(20–22)
Body surface area, m^2	1.8 (1.44–2.16)	Normal	(23, 24)
Body weight, kg	65 (50–90)	Normal	(23, 24)
Creatinine clearance rate, ml/min/1.73 m^2	90 (80–12)	Normal	(23)

ND, not determined; OS, overall survival; PD, progressed disease; PFS, progression-free survival; AEs, adverse events.
[a]Only expected values are presented for these survival model parameters.
[b]Overall total cost per patient regardless of treatment duration.
[c]It was assumed that these costs would continue until the health state transitioned.
[d]Physician visits, laboratory tests, and examinations were all included in the routine follow-up cost.

TABLE 2 Summary of cost and outcome results in the base-case analysis.

Factor	Sugemalimab plus chemotherapy	Chemotherapy	Incremental change[a]
Cost, $			
Drug	183,444	115,509	67,935
Non-drug[b]	13,435	8,898	4,537
AEs management	637	411	226
Best supportive care	11,759	7,798	3,961
Overall	196,879	124,407	72,472
Life-years			
Progression-free	1.8	0.63	1.17
Overall	3.49	2.23	1.26
QALYs	1.76	0.94	0.82
ICERs, $			
Per life-year	NA	NA	57,706
Per QALY	NA	NA	88,744
INHB, QALY, at threshold 38,017[a]	NA	NA	−1.09
INMB, $, at threshold 38,017[a]	NA	NA	−41,298
INHB, QALY, at WTP threshold 86,376[a]	NA	NA	−0.02
INMB, $, at WTP threshold 86,376[a]	NA	NA	−1,644

AEs, adverse events; ICERs, incremental cost-effectiveness ratios; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NA, not applicable; QALY, quality-adjusted life-year; WTP, willingness-to-pay.
[a]Sugemalimab plus chemotherapy versus chemotherapy.
[b]Non-drug cost includes the costs of AEs management, subsequent best supportive care per patient, follow-up care covering physician monitors, drug administration, and terminal care.

chemotherapy and sugemalimab (23, 24). In addition, the costs for managing Grade ≥ 3 AEs were calculated by multiplying the rates contained in the randomized controlled trial, and the management costs were derived from the literature (Supplementary Table 2) (15–17). Approximately 141 patients (84%) with radiographic progression in the Sugema-Chemo group and 99 patients (86%) with radiographic progression in the chemotherapy group would receive subsequent treatment in the GEMSTONE-302 trial. Based on the lack of detailed information collected in the preliminary trial, we adopted subsequent treatment strategies recommended by the National Comprehensive Cancer Network (NCCN) (26) and the Chinese Society of Clinical Oncology (CSCO) guidelines (27, 28) (Table 1). According to NCCN and CSCO guidelines, nivolumab or docetaxel were used as the subsequent treatment strategies for NSCLC. Based on the published literature, we determined costs related to disease (14), subsequent supportive care (18), terminal care (14), and drug administration (19) during the study.

Utility inputs

There was a range of health utility scores between 0 (death) and 1 (perfect health). Because health utilities for PFS and PD were not included in GEMSTONE-302, we have adopted health utilities from the clinical literature (20). In relation to NSCLC, the utilities of PFS and PD were 0.804 and 0.321, respectively (20). Additionally, disutility values associated with AEs were determined based on the literature (Supplementary Table 2) (20–22).

Base-case analysis

We calculated an incremental cost-effectiveness ratio (ICER), which is the incremental cost per quality-adjusted life year (QALY) gained. We calculated ICERs based on two willingness to pay (WTP) thresholds in consideration of the imbalance in economic development among Chinese socioeconomic regions: three times the per capita gross domestic product (GDP) value of China in 2021 ($38,017/QALY) for general regions, and three times Beijing's per capita GDP value in 2021 ($86,376/QALY) for affluent regions (29). Costs and utility outcomes were discounted at a rate of 5% annually (30). Moreover, we calculated the incremental net health benefit (INHB) as well as the incremental monetary benefit (INMB) (31).

Sensitivity analysis

We conducted a one-way sensitivity analysis in this study in order to identify significantly sensitive variables and evaluate the robustness of the results. Several variables, such as costs and utilities, were subjected to one-way sensitivity analyses, and the uncertainty of each variable was calculated using 95% confidence intervals reported in the literature or estimated by assuming a 20% variation from the fundamental variables (Table 1). Monte Carlo simulations were used to conduct a probabilistic sensitivity analysis with 10,000 iterations. Three distributions were assigned to the parameters in the model: gamma, log-normal, and beta distributions. Gamma distributions were assigned to the cost

parameters, log-normal distributions to the hazard ratios (HRs), and beta distributions to the proportions and probabilities. We then generated a cost-effectiveness acceptability curve to illustrate the possibility that Sugema-Chemo or chemotherapy could be considered a cost-effective option at different WTP levels in terms of per QALYs gained.

Subgroup analysis

We performed a subgroup analysis in order to determine whether different characteristics of patients contribute to the uncertainty of outcomes for each of the subgroups obtained from the GEMSTONE-302 by various HR for PFS (8). In this study, statistical analyses were carried out using R (version 4.0.5, 2021, R Foundation for Statistical Computing) with hesim and heemod packages.

Results

Base-case analysis

The Sugema-Chemo combination resulted in 0.82 QALYs gain and 1.26 overall life-years gain for patients with NSCLC in the base-case analysis, at additional costs of $72,472 compared to chemotherapy alone, which corresponded to an ICER of $88,744/QALY. In addition, at the $38,017/QALY WTP threshold, Sugema-Chemo had an INHB and an INMB of −1.09 QALYs and −$41,298, respectively, compared to chemotherapy alone. Furthermore, Sugema-Chemo had an INHB of −0.02 QALYs and an INMB of -$1,644 when the WTP threshold was set at $86,376/QALY (Table 2).

Sensitivity analysis

According to the one-way sensitivity analysis, the model outcome was largely driven by the average body weight, the utility for PFS, the cost of sugemalimab, and HR for OS (Sugema-Chemo vs. chemotherapy). There was a marginal relationship between the remaining parameters and outcomes (Supplementary Figure 2). We also examined the relationship between these key variables and the ICER between Sugema-Chemo and chemotherapy alone. Sugema-Chemo was cost-effective when the average body weight was lower than 62.44 kg, the utility of PFS exceeded 0.826, Sugemalimab was purchased at <$2.996/mg, or the HR for OS exceeded 0.711 for a WTP threshold of 86,376/QALY. Otherwise, chemotherapy was preferred. The results also demonstrated that Sugema-Chemo may be cost-effective at the WTP threshold of $38,017/QALY when sugemalimab costs <$1.839/mg; otherwise, chemotherapy was preferred (Supplementary Figure 3). Based on the cost-effectiveness acceptability curve, Sugema-Chemo has a 60% probability to be considered cost-effective, at the WTP threshold of $86,376/QALY. Nevertheless, Sugema-Chemo did not have a chance of being considered cost-effective if the WTP threshold was $38,017/QALY (Figure 1).

Subgroup analysis

Variations in the HR for PFS were used for the subgroup analysis. Compared to chemotherapy, the Sugema-Chemo group demonstrated a more significant reduction in death risk. Further, Sugema-Chemo was not significantly superior to chemotherapy in improving PFS in patients with ECOG performance status 0 and with liver metastases. Most subgroups, except for the patients with brain metastases, were likely to consider Sugema-Chemo cost-effective at the WTP threshold of $86,376/QALY. In all subgroups evaluated, Sugema-Chemo was not cost-effective (0%) at a WTP threshold of $38,017/QALY (Figure 2).

Discussion

This study is the first to compare the cost-effectiveness of Sugema-Chemo to chemotherapy alone in patients with metastatic NSCLC in China. In the GEMSTONE-302 trial, Sugema-Chemo statistically extended PFS in patients with metastatic NSCLC compared with chemotherapy alone. Nevertheless, due to the high price of sugemalimab, physicians and patients are uncertain about which is more beneficial. It is urgent to conduct a cost-effectiveness analysis to evaluate the efficacy and cost of Sugema-Chemo.

With a large population and rapid development, China is one of the most populous countries in the world. Therefore, the imbalance between economic development at the provincial level is therefore an objective fact. Taking into consideration regional economic disequilibrium, the WTP threshold for general regions and affluent regions of China was set at $38,017/QALY and $86,376/QALY, respectively. The combined treatment of Sugema-Chemo may not be a cost-effective alternative to chemotherapy alone, as the ICER of $88,744/QALY is higher than the WTP threshold of $38,017/QALY. There was, however, a 60% probability that this ICER would be considered a cost-effective option if it approached the WTP threshold of $86,376/QALY. One-way sensitivity analysis and probabilistic sensitivity analysis indicate that the results of this model are robust. An analysis of the sensitivity of the model indicated that it was susceptible to the average body weight, as well as the utility for PFS, cost of sugemalimab, and HR for OS. With a WTP threshold of 86,376/QALY, Sugema-Chemo was cost-effective if the average body weight was <62.44 kg, or the price was <$2.996/mg. In addition, for a WTP threshold of $38,017/QALY, Sugema-Chemo is cost-effective if the price of sugemalimab is <$1.839/mg; otherwise, chemotherapy is the preferred option.

As far as we know, since the official establishment of the National Healthcare Security Administration (NHSA) in May 2018, there have been several rounds of negotiations with pharmaceutical companies on the price of cancer drugs, aiming to relieve the medical burden of cancer patients through national strategic procurement (32). The NHSA in China has made a great effort to negotiate drug prices with pharmaceutical companies, with the result that the prices of many anticancer drugs have been reduced by 30–70% (32). Considering the circumstances, it is unlikely that a rise in the price of sugemalimab. On the contrary, if negotiations for sugemalimab are conducted, the cost of sugemalimab is highly

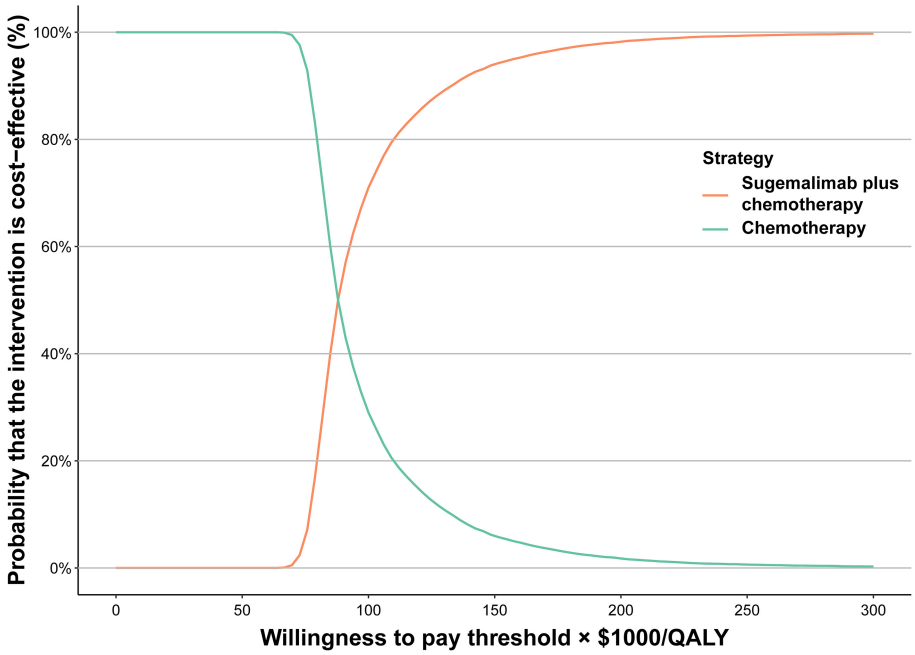

FIGURE 1
Acceptability curves of cost-effectiveness. QALY, quality-adjusted life-year.

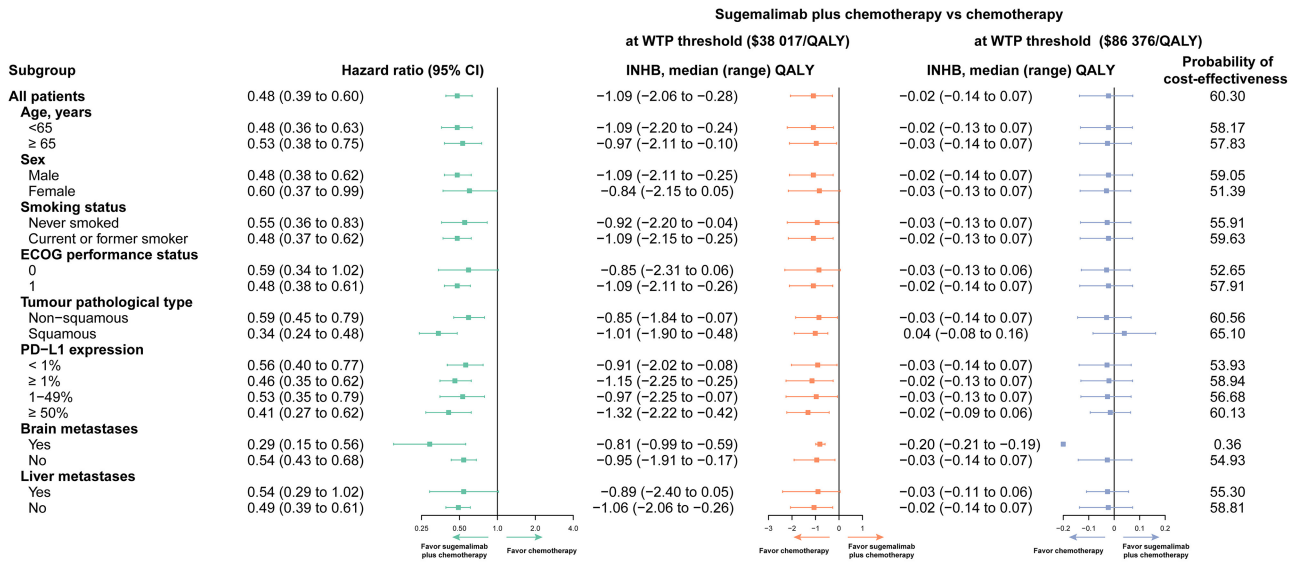

FIGURE 2
Subgroup analyses obtained by varying the hazard ratios (HRs) for progression-free survival (PFS). INHB, incremental net health benefit; WTP, willingness to pay; QALY, quality-adjusted life-year; PD-L1, programmed cell death ligand 1.

likely to decrease. As a result, our findings indicate that Sugema-Chemo can provide adequate first-line treatment for patients with advanced NSCLC within an appropriate price range in a cost-effective manner. The NHSA negotiation will be the most effective approach for optimizing the allocation of medical resources in China for an extended period, providing patients with better health services at low costs (33).

This study has several advantages worth highlighting. First, to our knowledge, this is the first study to examine the cost-effectiveness of Sugema-Chemo combination therapy in treating metastatic NSCLC using a partitioned survival model based on the latest published GEMSTONE-302 trial. Second, at current prices, Sugema-Chemo combination is unlikely to be an attractive cost-effective option over chemotherapy alone. However, clinical trial results indicate that it increases OS and PFS in patients with metastatic NSCLC. Third, the patient population evaluated in the trial was Chinese, which means that race did not influence on the results. Additionally, the partitioned survival

model did not require assumptions for the transition of patients between health states but made it possible to directly partition patients into different health states based on the K-M curves. Last, the present study analyzed the economic outcomes of 18 subgroups evaluated by the GEMSTONE-302 trial. Physicians, patients, and policymakers may benefit from the economic results of the subgroups.

There have some limitations in the analysis. The parameter distributions fitted to the K-M curves were assumed to be effective outcomes that exceeded the follow-up period of the GEMSTONE-302 trial, leading to uncertainty in the model outputs. A sensitivity analysis revealed that this finding is generally robust, indicating that this limitation may not be a significant factor. It is also important to note that there is inherent uncertainty when extrapolating PFS and OS over the longer term. Second, the clinical data included in the model have been derived from the results of GEMSTONE-302 trial. Therefore, any biases within the trial may have affected the results of the trial in terms of cost and effectiveness. Accordingly, the characteristics of patients with NSCLC included in the GEMSTONE-302 study were generally strict. Additionally, clinical trial participants tend to adhere to their treatment regimens more closely than patients in real-world practice. Moreover, with a median follow-up of 8.6 months (IQR 6.1–11.4), the preplanned interim analysis of the GEMSTONE-302 trial and the prediction of cost-effectiveness could potentially be altered if more follow-up data are available. Third, the values of utility and disutility were derived from published literature, some of the data were not obtained from Chinese populations, and bias was not distinguished due to of different treatment strategies (20). Based on the data, NSCLC utility values in China were higher than those in other countries.

Conclusion

Based on the health care perspective in China, this study indicates that Sugema-Chemo may not be cost-effective as the first-line treatment for metastatic NSCLC patients at a WTP threshold of $38,017 or $86,376/QALY and under current drug pricing. Sengemalimab may be economically advantageous if its price is reduced substantially. If individual treatments are tailored based on the factors contributing to the economic outcome, the economicoutcomes may be improved. In treating patients with metastatic NSCLC, the results of this study may assist clinicians in choosing appropriate treatments.

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.

Author contributions

Gathering and analyzing all data: YL. Concept and design: XLia, YL, and XC. Drafting and statistical analysis: YL and XLia. Funding: XC. Technical and material support and supervision: HL and XLiu. Data interpretation and critical revision of the manuscript: all authors. All authors contributed to the article and approved the submitted version.

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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/fpubh.2023.1054405/full#supplementary-material

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Long-term care insurance, mental health of the elderly and its spillovers

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The paper studies the effects of the long-term care insurance (LTCI) program in China on the mental health of older adults and the wellbeing of their families. We employ the staggered difference-in-differences approach based on the LTCI pilots from 2015 to 2017. First, we find the LTCI program improves older adults' happiness and reduces depression symptoms significantly. The effects on the improvement in memory and cognition are associated with the elderly with activities of daily living-related need for care. Second, the effects of LTCI are partially mediated through providing community services, relieving care burdens, and reducing the incidence of diseases. More importantly, LTCI coverage improves caregivers' physical health and social activities, reflecting its welfare spillover effects. Furthermore, the relationship between LTCI and mental health differs due to the difference in LTCI designs and older adults' demographic characteristics. This presents a need to consider mental health in the services and evaluation criteria of LTCI.

KEYWORDS

long-term care insurance, aging population, mental health, spillover effects, China

1. Introduction

Rapid aging has become a worldwide challenge, which has led to marked demands for medical and nursing care, and great financial pressure, especially in the post-COVID-19 era (1). The unmet long-term care has received much attention (2, 3). China, with the largest elderly population over 65, faces greater challenges. China's population aged 65 and over has reached 191 million, accounting for 13.5% of total population.[1] It is expected to reach 366 million by 2050, rapidly advancing toward an aging society.[2] In addition, more than 78% of older people are suffering from chronic disease, mental illness, cognitive and sensory decline or other problems. People living with dementia in China account for nearly 20% of the world (4). The number of older people with needs for activities of daily living–related (ADLs) care is growing rapidly (1). However, traditional care in China provided by older adults' family members is not enough due to smaller families and delayed fertility (5, 6). Also, it is generally of relatively poorer quality (7), which is detrimental to the rehabilitation of older people and has adverse effects on the wellbeing of their caregivers (8, 9).

In response to these challenges, some OECD countries, such as the Netherlands in 1968, the United States in the 1970s, Germany in 1995, and Japan in 2000, have launched the long-term care insurance (LTCI) program (10, 11). The program enables older people to obtain care services and health care, however, universal problems do exist such as insufficient services, unfairness and narrow coverage (12, 13). Considering surging demands for care and inadequate resources, China started the LTCI program in Qingdao in 2012, and officially launched staggered LTCI pilots in 15 cities during 2016 and 2018. By 2021, China's LTCI

1 The seventh national census of China.

2 https://population.un.org/wpp/Download/Standard/Population/

program has covered more than 140 million people in 49 pilot cities. China's aged care market is still underdeveloped. Although older adults covered by LTCI are more easily accessible to health care, the diagnosis and management of mental health are inadequate (14). Therefore, studying the impact of the pilot practices of China's LTCI on older adults' mental health is not trivial, not only because LTCI plays an important role in coping with the mounting and various demands for care, but also empirical evidence on how China responds to rapid aging can provide suggestions for middle-income countries with rapidly aging population to promote, design and reform their LTCI program.

Our paper has several contributions as follows. First, there is little systematic, theoretical or empirical study on the effect of LTCI on comprehensive mental health. This study adds to the emerging evaluation of LTCI programs worldwide. From subjective and objective perspectives, we examine the effects and influencing mechanism of LTCI on the mental health of insured people and those with the need for ADLs care. The mental health of older adults should be paid more attention, because they are more likely to have reduced cognitive abilities and psychological decline with aging, and these changes may further lead to depression. Mental health disorder has become a major problem for older adults (6). Despite the importance of this issue, it remains unclear whether LTCI could improve mental health. Extant studies, merely covering one aspect of mental health, may not be enough to assess the mental health status of older adults. Mental health not only indicates the absence of psychiatric disorders, but also a good cognitive and response function and welfare state according to the definition of the WHO (15). In this regard, we construct four mental indexes, including objective health (memory and cognitive function) and subjective health (depressive symptoms and life satisfaction) to provide a more comprehensive assessment of the effects of LTCI on the elderly's mental health.

Second, we study the staggered LTCI policy implemented in 15 cities from 2015 to 2017 based on the difference-in-differences (DID) approach, and we explore whether and how China's LTCI affects older adults' mental health. On the one hand, China, as the largest developing country, has the largest elderly population in the world. A better understanding of China's LTCI can offer experiences to other developing countries with the same challenge of aging populations and care burdens. On the other hand, the study on China's LTCI is still limited due to its shorter implement time. The recent literature on China's LTCI only studies one pilot city such as Qingdao and Shanghai, or LTCI programs launched in the same year (16–18). Overall, there is still no consensus regarding the impacts of LTCI on mental health, especially in China, and merely considering one pilot or a specific type of health outcome might not capture the relationship between LTCI and mental health. This paper appears to be the first study to investigate China's staggered LTCI policy in the initial 15 pilot cities from 2015 to 2017, and it can provide a more comprehensive overview of the effects of the program. The assessment of the effects and the study on the channels through which China's LTCI influence mental health also have policy implications for promoting the reform and expanding LTCI pilots.

Third, the welfare spillover effects of LTCI on their families especially their caregivers need to be further studied. In fact, some literature documented that caregivers tend to report a lower quality of life and a deterioration of mental health compared to non-caregivers (5, 19, 20). Therefore, this study examines not only the mental health of the covered older adults but also the wellbeing of their spousal caregivers who is the main caregiver in China. Spousal caregivers suffer from higher level of stress than children caregivers (21), and have a common problem of social isolation (22). Accordingly, we examine the effects of LTCI on their self-reported health, life satisfaction and social activities. The findings in our paper offer useful insights to expand beneficiaries.

Finally, we try to figure out the heterogeneity of the relationship between LTCI and mental health. The results of our study confirm LTCI designs (the eligibility for LTCI and financing standards), socioeconomic and demographic differentials (gender, urban or rural, family income, marital status, education, and the family size) in the effects of LTCI on the mental health of older people. Our findings will help policymakers craft appropriate strategies to design and reform China's LTCI system, and eventually improve older adults' mental health and wellbeing.

The rest of the paper is organized as follows. Section 2 presents the background of China's LTCI, and Section 3 is literature review. We show the theoretical influence mechanism, empirical methodology and data in Section 4. Section 6 presents and discusses the empirical results. Section 6 concludes and provides policy implications.

2. Literature review

A large amount of literature has studied the LTCI program in developed countries, including the effects on care recipients' health (23), hospital stay and expenditure (24, 25), the choice of care (26), financial burdens (27), their families (28) and national economic welfare (29). Among these, however, the findings on health outcomes are contradictory. For instance, Lei et al. (4) and Sohn et al. (30) found that LTCI is correlated with better self-reported health and lower mortality risk, while Kim and Lim (27) and Fu et al. (31) argued that LTCI has a limited effect on older adults' health. These inconsistent findings can be partly attributed to the difference in countries' socio-economic characteristics, the LTCI program's key features and its implementation time. In particular, the assessment of the social and economic impacts of developing counties is limited. The implementation of LTCI in China has attracted growing interest from many scholars. For example, Lu et al. (17) and Feng et al. (16) found that China's LTCI significantly reduces medical expenditures and health insurance expenditures. In addition to the reduction in financial burdens, Lei et al. (18) further found that LTCI improves older people's self-reported health and reduces their mortality risks. However, these studies mainly focus on only one pilot city (13, 32). The study on China's LTCI is still not enough, especially the limitation on older adults' mental health and spillover effects. Our study will address this gap.

In addition to its far from conclusive, extant literature on mental health outcomes is not comprehensive not only in the definition of mental health but also in affected members. On the

one hand, previous studies only focused on one aspect of mental health, such as depression symptoms (18), which may not be enough to assess the mental health status of older adults. For instance, Tang et al. (33) found the positive effects of LTCI on mental health measured by older adults' depression symptom. According to the definition of the WHO (15), however, mental health includes the absence of psychiatric disorders and a good cognitive and response function. Yet to date, there is no systematic and empirical evidence on the influence of LTCI on mental health. On the other hand, many researches have sought to give answers to the spillover effects of LTCI. Fu et al. (31) found that LTCI is associated with increased labor supply. Costa-Font and Vilaplana-Prieto (34) documented that caregiving supports could alleviate depressive symptoms of caregivers. However, extant literature has not yet reached a consensus on the effects on caregivers, especially their spouse who are main caregivers and are more likely to suffer from social isolation and depressive symptoms (20, 21). Our focus on caregivers' wellbeing, including life satisfaction, physical health and social participation, complements previous related literature focusing on LTCI's spillover effects (35).

3. Background

Rapid aging, causing lower employment rate and increased demands for medical and nursing care, has become a social problem in China. China has established medical insurance for urban workers (the Urban Employees Basic Medical Insurance, UEBMI), urban residents (Urban Resident Basic Medical Insurance, URBMI), rural population and other people (Urban and Rural Residents Basic Medical Insurance, URRBMI). Although these medical policies share parts of medical costs, older adults' needs for medical or nursing care are unmet. In response to the challenge, Chinese government has decided to establish its independent social insurance to provide socialization of care, relatively separating from previous medical insurance. China officially introduced the LTCI pilots in 15 cities in 2016 and further added 34 pilots in 2020 (36). Qingdao as one of the 15 LTC programs has started the long-term care insurance pilots since 2012 and conducted some reforms in 2015 (37). The LTCI system has covered more than 140 million people in 49 pilot cities by 2021.

We study the initial 15 pilot cities, key features of which are shown in Table 1. China's LTCI system is mainly financed by public medical insurance pooled funds, together with fiscal subsidies, employer contributions and welfare lottery funds (38). It mainly covers people enrolled in UEBMI. Some pilots, such as Qingdao, Changchun and Jingmen, also cover residents enrolled in URRBMI and URBMI. The access to care service is primarily determined by the covered people's disability degree, mostly evaluated by the Barthel scale for ADLs. Some pilot cities also include other factors such as cancer and dementia. As shown in Table 2, care recipients in China are provided with three categories of care services that are home-visit care, community, and institutional care services (designated medical institutions, nursing institutions and aged care institutions). The reimbursement rate mainly depends on the type of services, and the majority covers ∼70–90% of the costs, with a payment ceiling up to 20–60 yuan per person. It is worth noting that the LTCI of Shanghai not only provides care services but also cash benefits.

4. Theoretical and empirical analysis

4.1. Theoretical framework

As shown in Figure 1, the LTCI system influences subjective and objective mental health in four ways. First, the LTCI program in China provide higher-quality care, effective health management and nursing intervention, which could improve older adults' memory and cognitive function (39, 40). To meet the needs for rehabilitation, LTCI also offers better follow-up which is useful to maintain older people's physical and mental health. Second, home-visit care and community services provided by LTCI improve older people's psychosocial contact and support. These services can alleviate their loneliness and depression (18), eventually improving their life satisfaction (41). Third, the promotion of LTCI in China provides much knowledge about health management for an aging population. It not only benefits their physical health through self-rehabilitation but also helps them regulate depression symptoms. Fourth, this long-term care service is a substitute for informal care by family members and expensive institutional care (27, 42). LTCI covers most of care services costs, even in some pilot cities where LTCI provides cash benefits. Therefore, LTCI may improve older adults' mental health by alleviating the psychological burden of expected financial and care costs.

Family members of disabled older people as caregivers are more likely to feel a loss of independence and freedom (43, 44), thus their mental health deteriorates. LTCI plays an important role in the wellbeing of older people's caregivers (45). On the one hand, LTCI has proved a substitute for informal care which releases caregivers' care responsibilities and disposable time (34). The reduction in care burdens gives caregivers opportunities to pursue other activities (46), and increases the sense of personal control over their life (47), thus lowering the prevalence of depression and improving their life satisfaction (48, 49). On the other hand, LTCI is hypothesized to benefit caregivers' physical health by providing health care knowledge and improving their self-care and proactive health management. Based on these considerations, LTCI can also offer significant benefits to caregivers' physical health.

4.2. Model and methods

We construct the staggered difference-in-differences (DID) model which can reduce the endogenous biases and estimate more accurately to study the effects of LTCI on mental health:

$$Y_{ijt} = \beta_0 + \beta_1 LTC_{ijt} + \beta_2 X_{ijt} + \beta_3 Z_{jt} + \lambda_i + \gamma_t + \varepsilon_{ijt} \quad (1)$$

where Y_{ijt} represents mental health outcomes of individual i living in city j in year t, including their memory and cognitive function, depression symptoms and happiness. We choose six pilot cities from the initial 15 pilot cities officially announced in 2016, because they covered persons in the whole city before 2018, which are

TABLE 1 Key features of 15 pilot cities.

City	Date	The covered area	Insured population	Eligibility
Anqing	2017-1	Urban areas	UEBMI	Severe disability
Changchun	2015-3	All	UEBMI; URBMI	Severe disability/advanced cancer
Chengde	2017-1	Urban areas	UEBMI	Severe disability
	2018-12	All		
Chengdu	2017-7	All	UEMBI	Severe disability
Chongqing	2018-1	Dadukou, Banan, Shizhu, Dianjiang	UEBMI	Severe disability
Guangzhou	2017-8	All	UEBMI	Severe disability; dementia plus moderate disability
Jingmen	2016-11	All	UEBMI	Severe disability
	2017-1	All	URRBMI	
Nantong	2016	Urban areas	UEBMI; URBMI	Severe disability; moderate disability
	2019	Haimen, Qidong	URBMI	
Ningbo	2017-12	Urban areas	UEBMI	Severe disability
Qingdao	2012-7	All	UEBMI; URBMI	Disability level 3–5; dementia
	2015-	All	URRBMI	
Qiqihaer	2017-10	Urban areas	UEBMI	Severe disability
Shanghai	2017-7	Xuhui, Putuo, Jinshan	UEBMI; URRBMI	Aged >60 years; disability level 2–6
Shangrao	2017-7	All	UEBMI	Severe disability
	2019	All	UEBMI; URRBMI	
Shihezi	2017	Urban areas	UEBMI; URRBMI	Severe disability
Suzhou	2017-6	All	UEBMI; URRBMI	Severe and moderate disability

TABLE 2 Care services and benefits package of 15 pilot cities.

City	Home-visit/community	Aged care/nursing institutions	Medical institutions
Anqing	Cap 750/m	Co-payment 50%; cap 40/d	Co-payment 60%; cap 50/d
Changchun	–	Co-payment 90% (UEBMI); 80% (URBMI, URRBMI)	
Chengde	70%; cap 40/d	Co-payment 70%; cap 50/d	Co-payment 70%; cap 6/d
Chengdu	Co-payment 75%	Co-payment 70%	Co-payment 70%
Chongqing	Cap 50/d		
Guangzhou	90%; cap 115/d	75%; cap 20/d	75%; cap 1,000/m
Jingmen	80%; cap 100/d (full time); cap 40/d (part time)	75%; 100/d	70%; 150/d
Nantong	Cap 1,200/m	Co-payment 50%	Co-Payment 60%
Ningbo	–	Cap 40/d	Cap 40/d
Qingdao	In 2012: home-care 60/d, 96%; professional care 170 /200/d, 90%; In 2015: home/community/professional care 50/65/170/d; 90% (UEBMI); 80% (children/level 1), 40% (level 2)		
Qiqihaer	50%; cap 20/d	55%; cap 25/d	60%; cap 30/d
Shanghai	Home-visit care 90%; community services 85%;	Co-payment 85%	Co-payment 90%
Shangrao	Family care 450/m; home-visit care 900/m	Cap 1,200/m	–
Shihezi	Cap 25/d; cap 750/m	70%; cap 750/m	70%; cap 750/m
Suzhou	Cap 30/d (severe disability); CAP 25/d (moderate disability)	cap 26/d (severe disability); cap 20/d (moderate disability)	

"Cap" means the daily benefit cap; "/d" means yuan per person per day; "/m" means yuan per person per month.

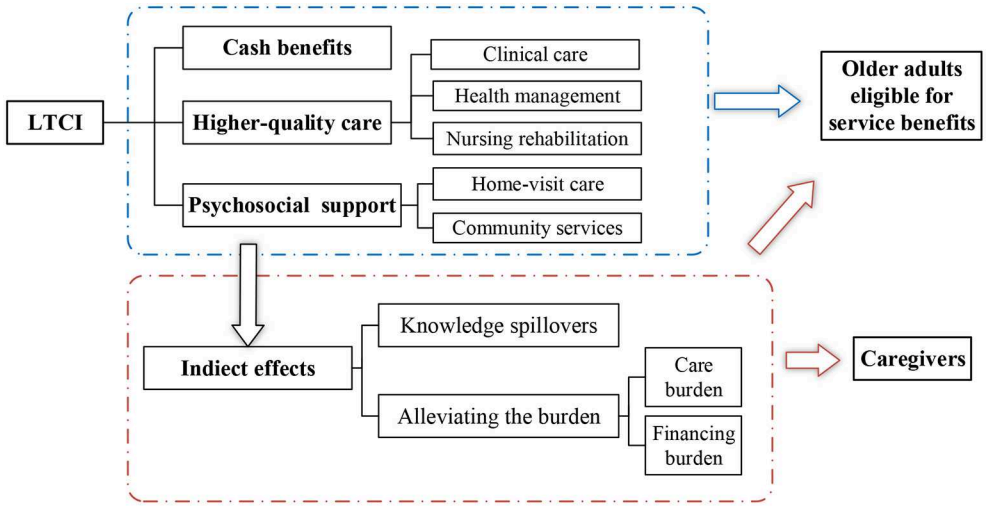

FIGURE 1
Theoretical framework.

TABLE 3 Descriptive statistics.

Variable	Definition	Mean	Std. dev.
Dependent variables			
Memory	20 questions about immediate and delayed recall [0, 20]	7.310	3.360
Cognition	10 questions about calculation and orientation [0, 10]	8.002	1.930
CES-D	Older adults' feeling and behaviors [0, 30]	7.292	5.786
Happiness	Life satisfaction: the higher the value, the better it is [0, 5]	3.267	0.691
Shealth	Caregivers' self-reported health: the higher the value, the healthier it is [0, 5]	2.888	0.963
Shappiness	Caregivers' life satisfaction: the higher the value, the better it is [0, 5]	3.261	0.768
Social	Do social activities (interacted with friends; Play Ma-jong/chess/cards; go to community club) = 1; others = 0	0.382	0.486
Mediating factors			
Care	Receive care by their children = 1	0.084	0.277
Disease	The number of diseases including cancer, stomach/digestive disease, asthma, and dyslipidemia	0.589	0.721
Checkup[a]	Receive regular medical examination=1; others = 0	0.210	0.408
Entertain	Entertainment from community care services=1; others = 0	0.024	0.153
Control variables			
Age	Older adults' age (years)	69.166	5.074
Gender	Male = 1; female = 0	0.623	0.485
Edu	Years of schooling (years)	6.706	3.950
Agri	Agricultural hukou = 1; others = 0	0.642	0.480
Married	Married =1; others = 0	0.836	0.370
Children	The number of older adults' children alive	3.185	1.387
GDP	GDP per capita of the city (million RMB)	449.459	603.280

GDP per capita and fiscal expenditure are adjusted to eliminate the price effect with 2010 as the base period.
[a]The information of community serves (check-up and social) is only available in the 2018 CHARLS.

Qingdao, Chengdu, Guangzhou, Jingmen, Shangrao, and Suzhou. Older adults in other 98 cities that never implement LTCI program and non-covered people in pilot cities during the sample period are defined as control groups. LTC_{ijt} is measured by $treat_{ijt} \times post_{jt}$. $treat_{ijt}$ is a dichotomous variable indicating the treated status. $treat_{ijt} = 1$ means people enrolled in the medical insurance

required by pilot cities. $post_{jt}$ is a dummy variable ($post_{jt} = 0$ for 2011, 2013 and for 2015, 2018 in Qingdao, $post_{jt} = 0$ for 2011, 2013, 2015, and $post_{jt} = 1$ for 2018 in other cities). X_{ijt} is a vector of older adults' time-varying characteristics including their age, marital status, children and physical health status. Z_{jt} is a vector of regional characteristics measured by GDP per capita and fiscal expenditure.λ_i is the individual fixed effects that absorb time-invariant factors such as the respondent's gender, education, treated status ($treat_{ijt}$), and other unobservable variables. γ_t represents year fixed effects.

The access to care service largely depends on covered people's degree of disability, but the CHARLS data has no direct information on current care recipients. Therefore, our estimates are "intention to treat" effects (ITT), indicates overall effects on the targeted population (50). Since ITT is inclined to underestimate the average treatment effect (ATT), our findings are more convincing (51). Moreover, to strength our results, we use the difficulties in ADLs to represent whether the covered older people receive care services. We provide indirect evidence of the different effects of LTCI on the insured people with needs for ADLs care compared to those without needs. We add the interaction term $LTC_{ijt} \times ADL_{ijt}$. $ADL_{ijt} = 1$ indicates the elderly have difficulties in at least one activity among bathing, eating, dressing, moving, and using toilets:

$$\begin{aligned} Y_{ijt} &= \alpha_0 + \alpha_1 LTC_{ijt} + \alpha_2 LTC_{ijt} \times ADL_{ijt} + \alpha_3 ADL_{ijt} + \alpha_4 ADL_{ijt} \\ &\times treat_{ijt} + \alpha_5 ADL_{ijt} \times post_{ijt} + \alpha_6 X_{ijt} + \alpha_7 Z_{jt} \\ &+ \lambda_i + \gamma_t + \nu_{ijt} \end{aligned} \quad (2)$$

According to influencing mechanisms of LTCI on mental health, we further choose four mediating variables to identify the effect path, including community services (health check-ups and entertainment in the community), care burdens of older people's children and the incidence of diseases. Following previous studies (52), we adopt the mediating effects model:

$$M_{ijt} = \rho + \rho_1 LTC_{ijt} + \rho_2 X_{ijt} + \rho_3 Z_{jt} + \lambda_i + \gamma_t + \varsigma_{ijt} \quad (3)$$

$$\begin{aligned} Y_{ijt} &= \omega_0 + \omega_1 LTC_{ijt} + \omega_2 M_{ijt} + \omega_3 X_{ijt} + \omega_4 Z_{jt} + \lambda_i + \gamma_t \\ &+ \xi_{ijt} \end{aligned} \quad (4)$$

Where M_{ijt} is the mediating variable. If both ρ_2 and ω_2 are statistically significant, M_{ijt} can be regarded as a mediator of the effects of LTCI on mental health.

4.3. Data

We use the China Health and Retirement Longitudinal Study (CHARLS) in 2011, 2013, 2015, and 2018 (http://charls.pku.edu.cn/). The data randomly selects 150 counties from 28 provinces in China and collects comprehensive individual and family characteristics of older people aged 45 and above, as representative of China's mid-age and elderly. Considering that age is a primary indicator of care needs, the higher the age, the greater the possibility of disability (16). We choose older adults over 65 years, who are more likely to receive care services, and 4,962 samples are finally used. Table 3 represents the definition and descriptive statistics of variables. Mental health indexes in our paper consist of older people's objective and subjective mental health. Objective mental health index is biomarkers calculated by questions measuring older people's the memory and cognitive function (*Memory* and *Cognition*). Subjective mental health is self-reported measures about biomarkers older adults' subjective feeling ($CES - D$ and *Happiness*). The mean memory index is 7.310, showing the impaired memory function of older adults in China. The elderly's cognition is better according to the mean is over 8. The average age of older people is 69.166 years, 62.3% of whom are men. The education level of them is low with average 6.7 years of schooling. Most older adults in our study sample have a spouse (83.6%) and have three children on average. Table 4 shows older adults' choice of types of care. We observe that their spouse and children (grandchildren) are the main caregivers.

5. Results and discussions

5.1. Main effects on mental health

Table 5 presents the effects of LTCI on the subject and the objective mental health of the elderly. LTCI coverage is recognized as an important role in reducing the insured people's depression and improving their happiness. It is associated with reductions in the score of CES-D by 1.616, and increases in their life satisfaction by 0.109. Attributed to expected reduction in care burden, financial strain and loneliness, the subjective mental health of older people increases. However, a negative impact is found on older adults' memory function and no impact is observed on their cognition function. The reason may be that there exists a moral hazard. Although LTCI could ease older people's fears of care burdens in the future, it also allows them to heavily depend on LTCI, lack the sense of responsibility and reduce health management (13). In addition, Table 5 shows the effects of control variables on older adults' mental health. Older adults who have married experience less memory and

TABLE 4 Types of care.

Types	Spouse	Children (grandchildren)	Other relatives	Institution
Numbers	2,276	2,035	83	53
All[a]	3,991	10,466	3,952	5,758
Proportion	57.03%	19.44%	2.10%	0.92%

[a]The number of older people who answered the question in CHARLS data.

TABLE 5 The effects of LTCI on older people's mental health.

Variables	Memory	Cognition	CES-D	Happiness
LTC	−0.820* (0.460)	−0.151 (0.200)	−1.656** (0.617)	0.112*** (0.023)
Age	−0.209 (0.316)	0.231* (0.116)	0.107 (0.377)	0.009 (0.042)
Agri	0.005 (0.353)	0.084 (0.136)	0.689 (0.499)	0.046 (0.057)
Married	0.827*** (0.258)	0.262* (0.146)	−0.163 (0.500)	0.107** (0.046)
Children	−0.144 (0.128)	−0.112 (0.075)	0.082 (0.183)	−0.004 (0.018)
GDP	−1.008** (0.360)	0.593 (0.389)	1.510 (1.133)	0.014 (0.166)
Year FE	Yes	Yes	Yes	Yes
Individual FE	Yes	Yes	Yes	Yes
Province-by-year FE	Yes	Yes	Yes	Yes
Pseudo R^2	0.391	0.473	0.506	0.328
Observations	4,972	4,972	4,972	4,962

Standard errors are clustered at the city level. ***, **, and * denote significance at the level of 1, 5, and 10%, respectively.

TABLE 6 The effects on the mental health, by difficulties in ADLs.

Variables	Memory	Cognition	CES-D	Happiness
LTC	−1.141** (0.530)	−0.241 (0.224)	−1.425*** (0.472)	0.114 (0.070)
LTC × ADL	2.780** (1.228)	0.830* (0.447)	−7.106*** (1.828)	0.361 (0.827)
ADL	−0.180 (0.140)	−0.276*** (0.078)	1.279*** (0.195)	−0.080*** (0.030)
Controls	Yes	Yes	Yes	Yes
Year FE	Yes	Yes	Yes	Yes
Individual FE	Yes	Yes	Yes	Yes
Province-by-year FE	Yes	Yes	Yes	Yes
PseudoR^2	0.391	0.614	0.477	0.047
Observations	4,962	4,962	4,962	4,962

Standard errors are clustered at the city level. ***, **, and * denote significance at the level of 1, 5, and 10%, respectively.

cognitive decline and have higher levels of life satisfaction. Better physical health of older people could increase their life satisfaction.

The CHARLS data has no direct information on current care recipients. Considering that the insured elderly with a severe disability are more likely to receive care services, we use the interaction term $LTC \times ADL$ denoted in the Methodology section to investigate the impacts of care provided by the LTCI program, and the results are shown in Table 6. As expected, the LTCI significantly improves the memory and cognition function of older people with a need for ADLs care. Care services provided by China's LTCI, including clinical care, health management guidance and rehabilitation training, offer benefits to older adults' objective health. It is also can be observed in Table 6 that LTCI has larger effects on alleviating depression of older people with difficulties in ADLs, relative to those with no LTC need. In addition, the elderly with no need for care experiences a significant increase in happiness. The reasons are as follows. The LTCI has a "peace of mind" effect on the insured people, because it alleviates their fears of expected financial and care costs (18). Another possible explanation is that the insured people with no difficulties in ADLs tend to care for their disabled family numbers and may benefit by freeing from care burdens.

5.2. Robustness test

In this section, we test the robustness of our results by five methods. First, we use the Event study (53) to test the parallel trends assumption on older adults' mental health between the treated and control groups before the implementation of China's LTCI. Figure 2 depicts the results of each year's coefficients. The reference is the year before the program (denoted by −1). It is observed that estimated results are close to 0 in the pre-reform period, implying that there are no confounding pre-existing trends in their mental health. Additionally, the CES-D and happiness experience significant changes in the post-reform period, consistent with our results in Table 4.

Second, we use the Goodman-Bacon decomposition method to examine the bias caused by time-varying treatment effects over time. According to Goodman-Bacon (54), the result of the DID method is calculated by a weighted average of all two-group estimators when the treatment occurs at different times. The incorrect use of already-treated groups as control groups may lead to biases. As shown in Table 7, the weight of the bad control group (T-Later vs. C-Earlier) is only

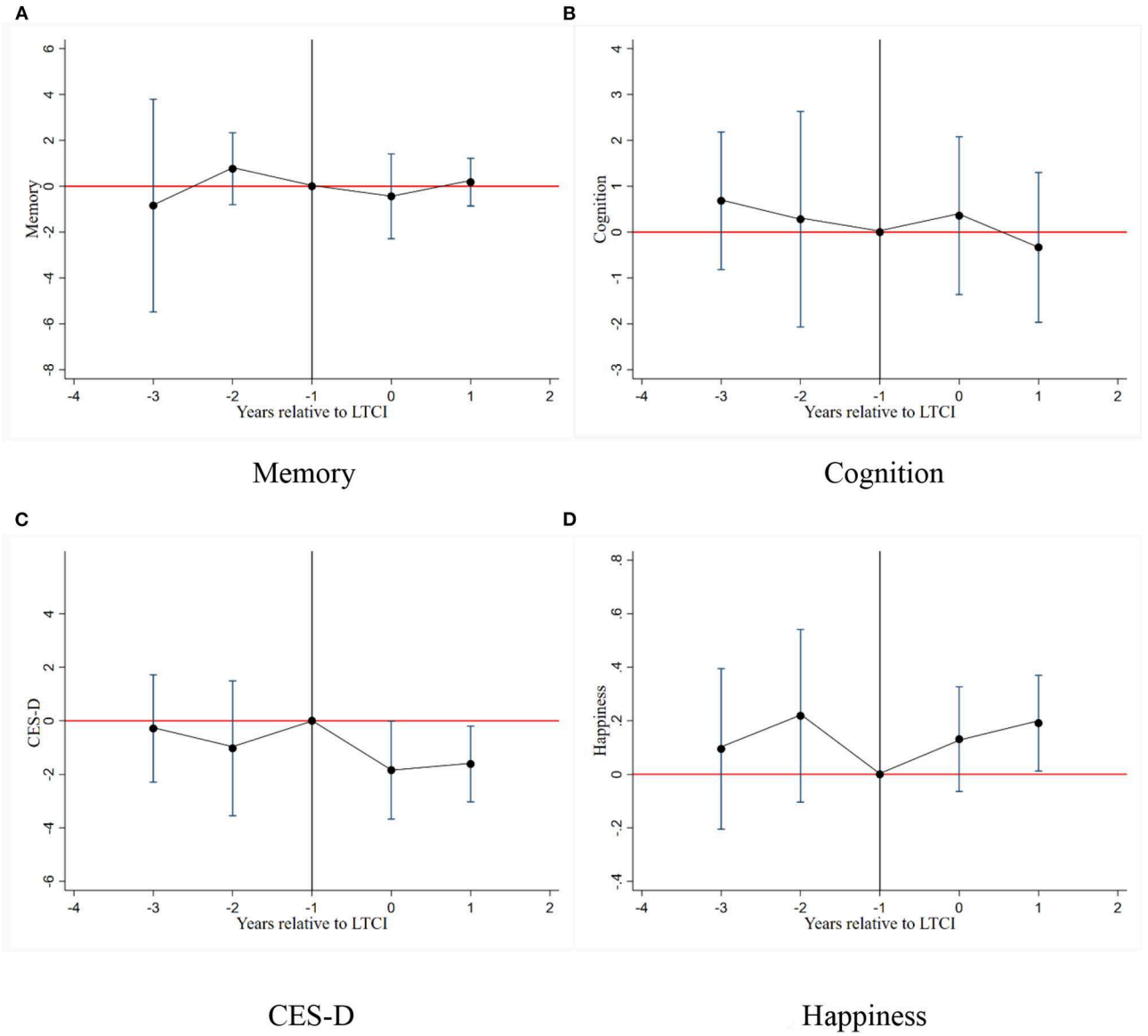

FIGURE 2
Event study for the impact on the mental health. **(A)** Memory. **(B)** Cognition. **(C)** CES-D. **(D)** Happiness.

0.2%. The estimates of LTCI's effects on mental health mainly come from the third comparison (99%), implying our results are robust.

Third, cities with a higher degree of aging and better social insurance systems are more likely to be selected as pilot cities, thus initial pilots may not be randomly selected. If there is no implementation of the LTCI program, the mental health outcomes of the elderly in pilot cities may be different from that of other cities, thus resulting in biased results. Therefore, we choose the cities located same provinces with pilot cities announced in 2016 and pilot cities added in 2020 as the control group. The reason is that older people living in these cities have more similar characteristics to the treated groups. The similar estimated results in Table 8 suggest that our findings are robust.

Fourth, we make a placebo test by randomly selecting a city without LTCI during 2011–2018 as the pilot city where older adults act as the treated groups. We repeat the selection 500 times and graph the density distribution of the coefficient of *LTC* and *LTC* × *ADL*. As shown in Figures 3, 4, the results of the simulation are concentrated around 0, indicating there are no other factors affecting our results. The vertical solid line and the imaginary line represent empirical results and the mean of simulation results, respectively. We find that both lines do not overlap. China's LTCI reduces depression and improves the insured people's happiness, and has positive effects on the memory and cognition function of the elderly with ADLs needs for care. Therefore, our findings are confirmed.

Fifth, we use instrumental method to solve the problem of endogeneity. The first instrumental variable selected is the

TABLE 7 The Goodman-Bacon decomposition.

Treated vs. control	Memory	Cognition	CES-D	Happiness
T-earlier vs. C-later	0.7%	0.7%	0.7%	0.8%
T-later vs. C-earlier	0.2%	0.2%	0.2%	0.2%
T vs. never treated	99.1%	99.1%	99.1%	99.0%

"T-earlier vs. C-later" means insured people in Qingdao act as the treated group and insured people in other pilot cities act as control groups. "T-later vs. C-earlier" means insured people in other pilot cities act as treated groups and insured people in Qingdao act as the control group. "T vs. never treated" means the comparison of all insured people vs. never-insured people.

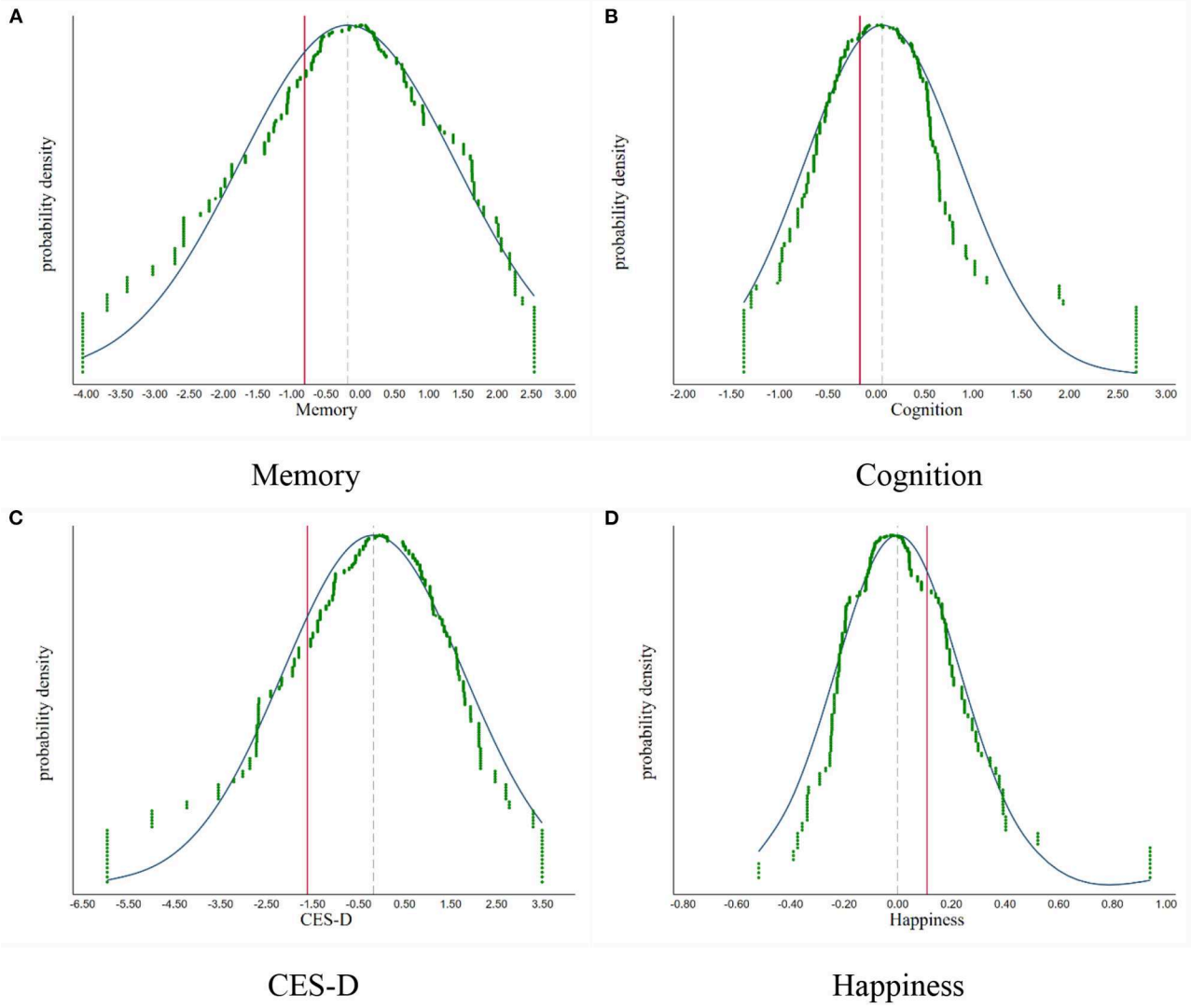

FIGURE 3
The placebo test: simulation results of the *LTC*. **(A)** Memory. **(B)** Cognition. **(C)** CES-D. **(D)** Happiness.

number of family members living together, which are associated with older people's choice to care service types. The supply of community care service is the second instrument, which can affect the availability of LTCI benefits, while not directly related to older people's health. As shown in Table 9, both instrumental variables are valid. We can observe that LTCI reduces older people's depression symptoms and improves their life satisfaction, which confirms our findings.

5.3. Mediating effects

We find that LTCI significantly improves older people's subjective mental health. We further examine three potential channels through which LTCI benefits older people: care burdens (*Care*), the incidence of diseases (*Disease*) and community care services (*Checkup* and *Entertain*). As shown in Table 10, LTCI not only significantly reduces the care services to older adults'

TABLE 8 The effects of LTCI on older people's mental health.

Variables	Memory		Cognition		CES-D		Happiness	
LTC	0.835* (0.436)	−1.141* (0.563)	−0.216 (0.193)	−0.287 (0.241)	−1.740** (0.742)	−1.530** (0.556)	0.105*** (0.009)	0.109 (0.067)
LTC × ADL		2.708* (1.394)		1.015** (0.426)		−7.280*** (2.096)		0.387 (0.875)
ADL		−0.277 (0.226)		−0.051 (0.117)		0.935* (0.434)		−0.051 (0.045)
Controls	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Year FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Individual FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Province-by-year FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Observations	2,028	2,026	2,028	2,026	2,028	2,026	2,024	2,022
PseudoR^2	0.346	0.346	0.531	0.530	0.524	0.528	0.326	0.328

***, **, and * denote significance at the level of 1, 5, and 10%, respectively.

children and the number of diseases (columns 1 and 4), but also promotes them to receive community services (columns 7 and 10). As we all know, care burdens, diseases and community services play significant role on older people's mental health. For instance, community care services provided by LTCI in China provide health checks, rehabilitation exercises and companionship (5), which improve older people's life satisfaction. Therefore, the impacts of LTCI are partially mediated through providing community services, reducing care burdens and the incidence of diseases.

5.4. Heterogeneity

In this section, we compare the effects of LTCI by older adults' socioeconomic and demographic characteristics and the LTCI designs. Figure 5 depicts the respective results of the point estimates and their 95% confidence intervals, which displays unequal effects of China's LTCI. As shown in panels (A) and (B), LTCI coverage has more positive effects on their subjective mental health of men and older adults with no spouse. LTCI has higher marginal benefits to the elderly without a spouse, the loneliness of whom is higher than that of older adults who have a spouse. For the rural population, although LTCI has negative effects on their memory function, it improves their life satisfaction. Panel (D) shows that LTCI benefits both the higher-income and lower-income groups, but the positive effects are larger for lower-income adults. Lower-income and rural people are more likely to be unable to assess private formal care due to their lower affordability (55), and the results imply that China's LTCI reduces inequalities in resources between older adults in urban and rural areas or different income groups. Panel (E) and (F) reflect larger positive effects on life satisfaction of poor-educated people and people with a smaller family.

In addition, we study the difference according to the LTCI designs including its eligibility and financing standards, as shown in panels (G) and (H). The results show that the LTCI system conditional on severe disability significantly improves the cognition function of the elderly. It also confirms the moral hazard, implying that more stringent eligibility makes the elderly increasingly health-conscious, eventually reducing their cognition decline. As shown in panel (H), both financing standards are beneficial for the insured people. A fixed amount of financing more significantly reduces older people's depression symptoms.

5.5. Spillover effects of LTCI

Some studies have confirmed that LTCI benefits the insured people's family members, especially their caregivers (26, 56). The study on China's LTCI is still not enough. We further study the spillover effects on older adults' spouse. They are main caregivers according to the CHARLS data, implying that they are relatively healthy and are less likely to directly enjoy care services provided by LTCI. Therefore, they tend to receive spillover benefits. As shown in Table 11, although LTCI has insignificant effects on the life satisfaction of the insured people's spouses, LTCI significantly improves their physical health and stimulates their social participation. It indicates that LTCI has a positive effect on

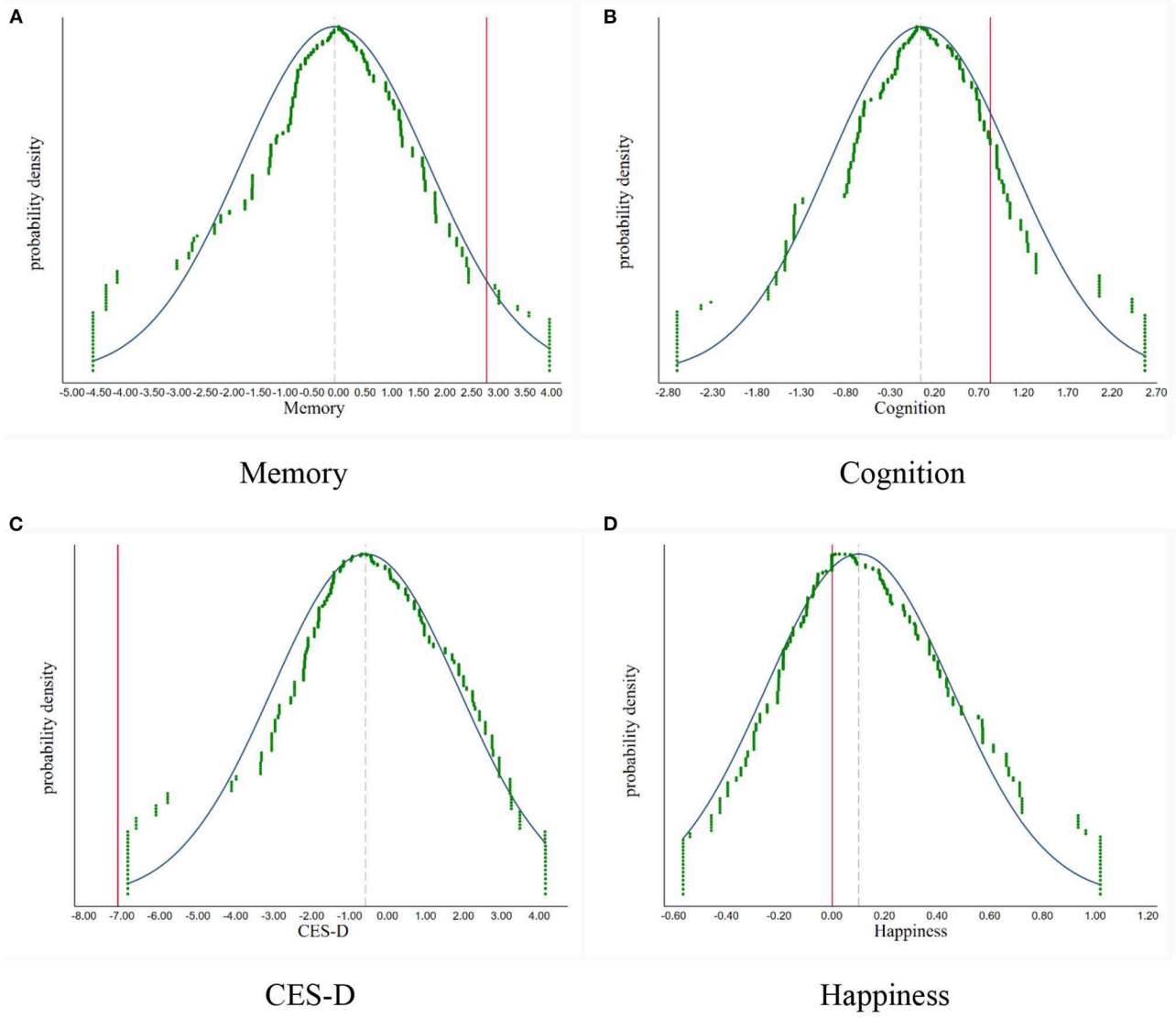

FIGURE 4
The placebo test: simulation results of the *LTC* × *ADL*. **(A)** Memory. **(B)** Cognition. **(C)** CES-D. **(D)** Happiness.

TABLE 9 The effects of LTCI: IV method.

Variables	Memory	Cognition	CES-D	Happiness
LTC	−30.074 (16.411)	7.361 (6.587)	−37.787** (18.931)	5.001** (2.255)
Weak identification test: C-D F statistic	3.432*	2.969*	4.983**	6.130***
Over identification test	0.304	2.053	1.122	1.153
Sargan-Hansen test	(0.582)	(0.152)	(0.289)	(0.283)

***, **, and * denote significance at the level of 1, 5, and 10%, respectively. The value of F statistic in the first-stage model reject the null hypothesis which indicates weak instrument variables. The results of the Sargan-Hansen test (p-values in parentheses) receive the null hypothesis that the instruments are valid.

TABLE 10 The results of mediating effects.

Variables	Care (1)	CES-D (2)	Happiness (3)	Variables	Disease (4)	CES-D (5)	Happiness (6)
LTC	−0.040* (0.018)	−0.770 (0.920)	0.148** (0.069)	LTC	−0.102*** (0.034)	−1.600** (0.219)	0.108*** (0.015)
Care		1.100** (0.449)	−0.054 (0.061)	Disease		0.386* (0.219)	−0.029 (0.023)
Observations	3,439	3,439	3,435	Observations	4,969	4,969	4,959
Year FE	Yes	Yes	Yes	Year FE	Yes	Yes	Yes
Individual FE	Yes	Yes	Yes	Individual FE	Yes	Yes	Yes
Province-by-year FE	Yes	Yes	Yes	Province-by-year FE	Yes	Yes	Yes
Controls	Yes	Yes	Yes	Controls	Yes	Yes	Yes
R^2	0.255	0.499	0.338	R^2	0.764	0.517	0.336
Variables	Checkups (7)	CES-D (8)	Happiness (9)	Variables	Entertain (10)	CES-D (11)	Happiness (12)
LTC	0.835* (0.436)	−0.643 (0.254)	0.073 (0.094)	LTC	0.081** (0.036)	−0.026 (0.847)	0.073 (0.094)
Checkup		−0.643** (0.254)	0.107*** (0.033)	Entertain		−0.999* (0.601)	0.107*** (0.033)
Controls	Yes	Yes	Yes	Controls	Yes	Yes	Yes
Observations	3,154	3,055	3,103	Observations	3,154	3,055	3,103
R^2	0.022	0.187	0.069	R^2	0.016	0.186	0.069

***, **, and * denote significance at the level of 1, 5, and 10%, respectively.

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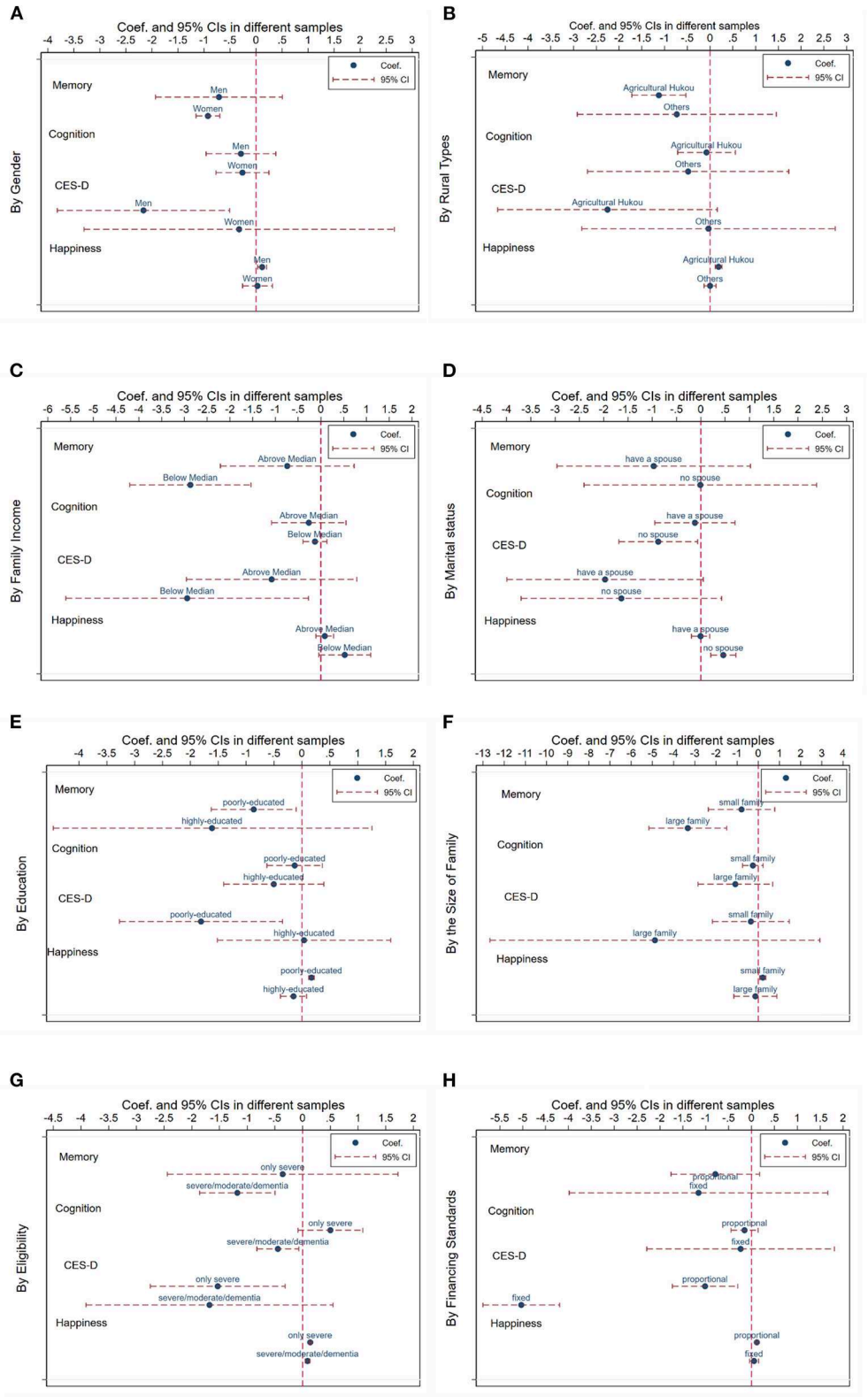

FIGURE 5
Heterogeneous impacts of LTCI. **(A)** Gender. **(B)** Rural types. **(C)** Family income. **(D)** Marital status. **(E)** Education. **(F)** Family size. **(G)** Eligibility. **(H)** Financing standard.

TABLE 11 The spillover effects of LTCI.

Variables	Shealth	Shappiness	Social
LTC	0.407* (0.22149)	−0.004 (0.157)	0.098*** (0.044)
Controls	Yes	Yes	Yes
Year FE	Yes	Yes	Yes
Individual FE	Yes	Yes	Yes
Observations	3,547	3,361	3,686
R^2	0.450	0.275	0.309

*** and * denote significance at the level of 1, 5, and 10%, respectively.

spouse caregivers' health and social isolation. The reason may be that China's LTCI improves spouse caregivers' time flexibility and allows them seek more leisure activities.

6. Conclusion

China has introduced LTCI pilots against the care demands of the growing aging population. This study investigates the effects of China's LTCI program on the mental health of the covered adults, those with needs for ADLs care, and the wellbeing of their families. Based on the CHARLS data in 2011, 2013, 2015, and 2018, we adopt the staggered DID approach to study the initial LTCI pilots from 2015 to 2017. We adopt a rich set of mental health indexes including subjective and objective health status from self-reported measures and biomarkers in CHARLS. We study whether and how China's LTCI affect older people's mental health, and further examine the spillover effects on their spousal caregivers covering their self-reported health, life satisfaction and social activities. Additionally, we compare these effects across different dimensions of older people's characteristics and the LTCI designs.

We find some interesting results. First, LTCI has a significant correlation with insured older adults' depression symptoms and life satisfaction. The care services provided by LTCI also improve the memory and cognition function of insured adults with ADLs needs for care, who is most likely to enjoy LTCI's services. Second, we explore the influence mechanism of older adults' mental health by providing community services, reducing care burdens and the incidence of diseases. Third, LTCI is not only beneficial to the covered people but also their caregivers. LTCI coverage improves caregivers' physical health and entertainment. Additionally, the effects of LTCI on older people's, mental health vary by the LTCI designs and older adults' socioeconomic and demographic characteristics differentials.

This study has some policy implications. First, much attention should be paid to addressing mental health problems and expanding the scope of evaluation criteria, such as mental or psychological state. Second, the ongoing LTCI has positive effects on older adults, especially vulnerable groups such as the lower-income people and rural population. However, China's LTCI currently is not very comprehensive, and only covers a narrow group. Given the important role of government spending, policymakers should expand the coverage and add more LTCI pilots. Third, it is important to promote home care and enrich the types of community services due to its role as the mediator. This is also consistent with China's elderly preference to live with their families in their own homes. Fourth, huge unmet needs still exist. For instance, China's LTCI has limited effects on women. The LTCI system should attach importance to incorporating the different needs and preferences. Additionally, policymakers could apply the big data technology to manage information about the insured people's health status and their needs to achieve efficient resource allocation. Policymakers should also focus on the response of older people to LTCI coverage, which is beneficial to reducing moral hazard, eventually improving older adults' health and happiness.

Due to data limitation, our estimated results are "intention to treat" effects measuring impacts on targeted population, which may underestimate the effects of LTCI. Moreover, this study is limited by the absence of information on what kind of care services qualified older adults received. Therefore, we could not examine differential effects of home-visit, community, and nursing/medical institutional care. We encourage future study to extend knowledge of the impacts of LTCI by collecting on more detailed data on LTC needs and service types.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: http://charls.pku.edu.cn/.

Author contributions

YC: software, data curation, writing—original draft, and visualization. HZ: conceptualization, methodology, writing—review and editing, and supervision. All authors contributed to the article and approved the submitted version.

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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

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A single-patient-use ECG system for cardiothoracic surgery admissions in the UK: A cost-consequence analysis

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Background: Deep sternal wound infections (DSWI) are severe complications in up to 1.36% of coronary artery bypass grafting (CABG) procedures in the United Kingdom. Each event adds between £4,000 and £11,000 in healthcare costs, owing primarily to prolonged hospitalisations. ECG devices have been shown to convey infection throughout perioperative CABG. On the other hand, single-patient ECG devices (spECG) can effectively reduce the incidence of surgical site infections (SSI), including DSWI, but no assessment of spECG impact in NHS cardiac units has been conducted.

Methods: To estimate the impact of spECG on NHS cardiac units, we conducted a cost-consequence analysis modeling the CABG care pathway in the United Kingdom using Simul8 software for a probabilistic, individual-patient simulation. The simulation time was 1 year, with each patient followed from admission through 30 days post-discharge. The base case simulation mirrors the cardiac unit of Bart Health NHS Trust, London. A total of 2,183 patients are generated with demographic and clinical attributes from probabilistic distributions informed by hospital-specific inputs from NHS Digital Data. The Brompton Harefield Infection Score (BHIS) is allocated to gauge the risk of SSI. Results are averaged across 50 independent and randomly seeded iterations.

Results: Simulation results indicate a base-case savings of £388 per patient, determined by the incidence of infections rather than the number of CABG procedures. In the base-case simulation, the mean cost of care with rECG was £13,096, whereas the mean cost with spECG was £12,708, resulting in a cost saving of £388 (2021 GBP). The simulation yielded an overall 8.6% SSI incidence rECG, whereas the incidence of SSIs with spECG was 6.9%. The model was most sensitive to changes in general ward and ICU costs, and infection incidence was a stronger predictor of potential per-patient savings than annual CABG volume.

Conclusion: Single-patient ECG is a sustainable and effective alternative to reusable ECG cables and lead wires in terms of patient safety and resource allocation.

KEYWORDS

CABG, thoracic surgery, single-patient, ECG, cost-consequence analysis, NHS, costs

1. Introduction

Coronary artery bypass grafting (CABG) is the most common cardiac surgery worldwide, generally executed *via* median sternotomy (1, 2). Deep sternal wound infections (DSWIs) are rare yet severe complications in 0.5 to 6.0% of median sternotomy procedures, according to varying estimates (3, 4). DSWIs are challenging to treat and frequently escalate into complications with a poor prognosis, substantially longer hospitalisations, and a 10 to 50% mortality rate (5–7). The United Kingdom's National Institute for Cardiovascular Outcomes Research (NICOR) reported the average countrywide DSWI rate following CABG at 0.3% as of 2019 (8). However, the report elaborates on the heterogeneity of these figures across healthcare structures, with larger hospitals providing more confident rates, as high as 1.36% (8). The conceivable consequences for the healthcare system have been quantified between ∼4,200 and ∼11,000 Great British Pounds (GBP, £) in England, owing primarily to prolonged hospitalisations (or length of stay—LOS), between 9 and 23 days, depending on the primary procedure and complications (9–12).

Initiatives undertaken to improve the DSWI risk assessment and management have deemed certain "minor" aspects within the operating theater essential in preventing DSWI (9, 10), in particular wary perioperative prophylaxis of ECG devices, known vectors of infection (11). The complex surfaces and grooves of equipment, the extra workload on ward staff, and inconsistent protocols make sanitizing reusable ECG (rECG) monitoring wires challenging and often ineffective, leading to an increased risk of cross-contamination (13–15). Single-patient ECG (spECG) components have been shown to reduce the likelihood of surgical site infections (SSIs) in several studies (12, 15–17); The National Institute for Health and Care Excellence (NICE) assessed spECG technology in 2019 (18). Although acknowledging the innovative nature of the technology and its potential beneficial impact, NICE did not envisage the implementation nor resolve the clinical and monetary implications from the National Health Service (NHS) perspective (18).

To assess the potential impact of spECG on NHS cardiac units, we utilized a modeling approach to simulate the CABG care pathway at the individual-patient level. Our model followed patients for one year, from admission to 30 days after discharge, and compared costs and outcomes between spECG and the standard of care rECG, using publicly available NHS Digital Data from the UK's Health and Social Care Information Center.

The modeling approach was chosen due to several factors, including the lack of systematic implementation of spECG in the NHS, the National Institute for Health and Care Excellence's (NICE) call for UK-specific economic analyses (18), and the strain on ICUs caused by the COVID-19 outbreak, which made randomized clinical trials and empirical studies impractical. Our model provides a preliminary assessment of the potential impact of spECG on costs and outcomes in NHS cardiac care to inform future research and decision-making.

2. Methods

A cost-consequence analysis was designed and performed abiding by the good practice guidance from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (19), The National Institute for Health and Care Excellence (NICE) (20), and the European Network for Health Technology Assessment (EUnetHTA) (21). The reporting is aligned with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (22). The model takes the NHS hospital payers' perspective with costs reported in 2021 GBP.

2.1. Data source

Public data from the NHS Digital (23), UK's governmental agency responsible for providing information, data, and IT systems to support health and social care services in England, was used to inform the model of the costs, epidemiology, outcomes of different treatment options for coronary artery bypass grafting (CABG), and hospital-specific statistics on yearly procedures, patient demographics, etc. (Table 1). Specifically, the data used in this study pertains to procedures with codes K401–K404 and K453, which refer to saphenous vein graft replacement of coronary arteries and anastomosis of the mammary artery to the left anterior descending coronary artery, respectively, according to the OPCS-4.9 classification (32). Missing cost data were retrieved from Public Health Scotland, under the assumption that these would not significantly diverge from costs in NHS England. Other parameters were obtained from Barts Health NHS Trust, London, UK, and from a structured search of PubMed and EconLit conducted in August 2021. All key inputs are provided, with their reference sources in Table 1.

2.2. Model design and structure

The CABG care pathway (Figure 1) to estimate the impact on costs and outcomes of spECG monitoring in cardiac units was designed from PS's clinical experience and hospital management perspective. The model is a probabilistic, individual-patient, discrete-event simulation as defined in Brennan et al. (33). The pathway simulation was developed in Simul8 (Simul8 Corporation, Boston, MA, USA) based on our published Markov model (34). The model progresses in one-minute increments, returning 1,440 assessments per patient per simulated day. Each simulation and each patient are seeded entities, such that the "same" patients are used for generating estimates during the same iteration with spECG and rECG. To address the intrinsic stochastic uncertainty (35), the base-case simulation is iterated 50 times on the same seeded population, helping to ensure robustness and precision in estimating the model's outputs by accounting for the probabilistic nature of simulation runs.

Based on user input, the model generates and simulates as many unique patients as necessary to represent varied cardiac units. Each patient is assigned age, sex, Body Mass Index (BMI), diabetes (hemoglobin HbA1c >7.5%), and left ventricular ejection

TABLE 1 Input parameters for the base-case simulation.

Parameter	Value	SD	Distribution	Unit	References
CABG	2,275	N/a	N/a	*n*/year	Barts data, NHS Digital (23)
Age	68.0	3.0	Normal	Year	UKHSA (24)
Sex	81.7	4.0	Binomial	% male	UKHSA (24)
BMI	28.6	4.5	Normal	kg/m^2	UKHSA (24, 25)
Diabetes	23.7	0.0	Binomial	%	(25)
HbA1c >7.5	7.5	0.0	Bernoulli	%	(26)
LVEF <45%	5.0	0.0	Bernoulli	%	Barts data, NHS Digital (23)
Requires MV	40.0	2.0	Normal	%	Barts data, NHS Digital (23)
MV time	8.0	2.0	Normal	Hour	Barts data, NHS Digital (23)
ECG time	24.0	4.0	Normal	Hour	Barts data, NHS Digital (23)
ICU LOS	1.0	0.2	Triangular	Day	Barts data, NHS Digital (23)
GW LOS	9.7	1.2	Triangular	Day	Barts data, NHS Digital (23)
Emergency surgery	2.0	1.0	Binomial	% CABG	UKHSA (24), NHS Digital (23)
spECG	[0.0 | 100.0]	N/a	N/a	% CABG	assumption
rECGs reuses	100.0	N/a	N/a	n	Cardinal Health Inc.
SSI incidence and consequences					
Additional LOS, deep SSI	24.6	2.5	Normal	Day	Barts data, NHS Digital (23)
Additional LOS, SSI	8.0	0.8	Normal	Day	UKHSA (24)
After time period	11.6	1.2	Normal	Day	Barts data, NHS Digital (23)
DSWI incidence	20.0	2.0	Normal	% SSI	UKHSA (24)
Readmission LOS	12.6	1.3	Normal	Day	Barts data, NHS Digital (23)
SSI incidence	3.96	0.0	N/a	%	Barts data, NHS Digital (23)
Resource cost					
Consultant	122.0	3.5	Normal	GBP/hour	PSSRU 2021 (27)
DSWI	12.0	2.0	Normal	GBP/day	PSSRU 2021 (27)
GW	28.0	2.8	Normal	GBP/hour	PHS, D025_2019 (28)
ICU	82.0	4.0	Normal	GBP/hour	PHS, R040X_2019 (29)
Mediastinitis	18.0	2.0	Normal	GBP/day	PSSRU 2021 (27)
MV	40.0	12.0	Normal	GBP/day	Barts data, NHS Digital (23)
Nurse	44.0	4.4	Normal	GBP/hour	PSSRU 2021 (27)
Outpatient SSI treatment	40.0	4.0	Normal	GBP/visit	PSSRU 2021 (27)
PACU	82.0	8.2	Normal	GBP/hour	Assumed as ICU
rECG cable	60.0	4.0	Normal	GBP/unit	Barts data, NHS Digital (23)
rECG decontamination	0.2	0.1	Normal	GBP/unit	Cardinal Health Inc.
rECG lead	80.0	5.0	Normal	GBP/unit	Barts data, NHS Digital (23)
spECG (Kendall DL^{TM})	12.7	1.3	Normal	GBP/unit	Cardinal Health Inc.
SSI treatment	5.0	1.0	Normal	GBP/day	PSSRU 2021 (27)
Surgery	594.0	59.4	Normal	GBP/hour	PHS, R142X_2019 (29)
Staff resources					
Consultant handover time	5.0	1.0	Normal	Minute	Barts data, NHS Digital (23)
Consultant ICU examination time	5.0	1.0	Normal	Minute	Barts data, NHS Digital (23)

(Continued)

TABLE 1 (Continued)

Parameter	Value	SD	Distribution	Unit	References
Nurse check time	1.0	1.0	Normal	Minute	Barts data, NHS Digital (23)
Nurse discharge time	10.0	1.0	Normal	Minute	Barts data, NHS Digital (23)
Nurse handover time	5.0	1.0	Normal	Minute	Barts data, NHS Digital (23)
Nurse ICU examination time	10.0	1.0	Normal	Minute	Barts data, NHS Digital (23)
Surgical preparation	45.0	5.0	Normal	Minute	Barts data, NHS Digital (23)
Mortality					
Surgery related mortality	1.5	0.0	N/a	%	(30)
With DSWI	0.8	0.0	N/a	%	(30)
SSI risk					
BHIS [0, 1]	0.57	0.0	N/a	N/a	(26)
BHIS [2, 3]	1.32	0.0	N/a	N/a	(26)
BHIS ≥4	3.51	0.0	N/a	N/a	(26)
Relative SSI risk with spECG	0.76	0.0	N/a	N/a	(13, 15, 16, 31)
Model timings					
Surgery	2.0	0.2	Normal	Hour	Barts data, NHS Digital (23)
GW check	4.0	0.0	N/a	Hour	Barts data, NHS Digital (23)
ICU check	2.0	0.0	N/a	Hour	Barts data, NHS Digital (23)
Initial ICU time	4.0	0.2	Normal	Hour	Barts data, NHS Digital (23)
PACU time	2.0	0.2	Normal	Hour	Barts data, NHS Digital (23)

Costs are given in 2021 GBP. Barts, Barts Health NHS Trust, London, UK; BHIS, Brompton and Harefield Infection Score; BMI, body mass index; CABG, coronary artery bypass grafting; DSWI, deep sternal wound infection; ECG, electrocardiography; GW, general ward; HbA1c, glycated hemoglobin A1c; ICU, intensive care unit; LOS, length of stay; LVEF, ejection fraction; MV, mechanical ventilation; N/A, not applicable; NHS, National Health Service; PACU, post-anesthesia care unit; PHS, Public Health Scotland; PSSRU, Personal Social Services Research Unit; R025, PHS Scotland data series on board level aggregate of hospital running cost; R040X, PHS Scotland data series speciality costs and activity-inpatients in long stay specialities, by speciality; R142X, PHS Scotland data series on average theater running costs and usage by speciality and by board, from Public Health Scotland; rEGC, reusable ECG; spECG, single-patient ECG; UKHSA, United Kingdom Health Safety Agency.

fraction (LVEF, <45%) at random from normal (age and BMI) or binomial (sex, diabetes, HbA1c, and LVEF) distributions described by mean and standard deviation (Table 1). These parameters are used to assign a Brompton Harefield Infection Score (BHIS) for adjusting the risk of SSI (36). In addition, the need for postoperative mechanical ventilation is assigned from a binomial distribution. The time on mechanical ventilation, the time in the intensive care unit (ICU), and time on the general ward (GW) are instead simulated per patient, drawing on normal distributions with a 10% standard deviation. A comprehensive list of inputs is found in Table 1.

2.3. Care pathway

Patients proceed through "locations" within the care pathway (Figure 1) and remain therein for periods assigned from distributions in Table 1 through non-independent time points. Health state transitions proceed through a Markov model (Figure 2) relevant to SSIs, with each patient assumed to exit CABG surgery with a "clean wound." State-transition probabilities are calculated relative to the iterations per day and the patient's individual risk (BHIS). The model accounts for the surgical suite, the ICU, the GW, and the outpatient settings (Figure 1). Patients scheduled for CABG enter the simulation in "Surgical preparation" and progress to the "Operating room" and the "post-anesthesia care unit" (PACU). Patients are then transferred to the "ICU," either on or off mechanical ventilation (MV), assessed for SSI by a nurse at set intervals, and evaluated for discharge onto the "General ward." In the eventuality of SSI, a consultant evaluates the SSI as superficial, deep sternal, or mediastinal and accordingly assigns appropriate treatment. Upon developing mediastinitis, patients may be treated surgically (reoperation) or non-surgically. Patients are only transferred to the GW if they have no SSI and are not on MV.

As in the ICU, on the GW, patients undergo regular assessments by nursing staff. If an SSI is detected, a consultant assigns appropriate treatment. Patients are redirected to the ICU in the event of DSWI or mediastinitis. Superficial SSIs are treated on the GW. Patients are discharged upon completion of their hospital stay. Post-discharge SSIs (up to 30 days) are assessed in the "Outpatient" setting and treated at home if superficial. DSWI and mediastinitis result in readmission to the ICU.

After surgery, every patient is assumed to have a "Clean wound" (Figure 2). The probability of the "Clean wound" becoming contaminated is dependent on user inputs for the SSI incidence (the percentage of patients experiencing an SSI, Table 1, and the

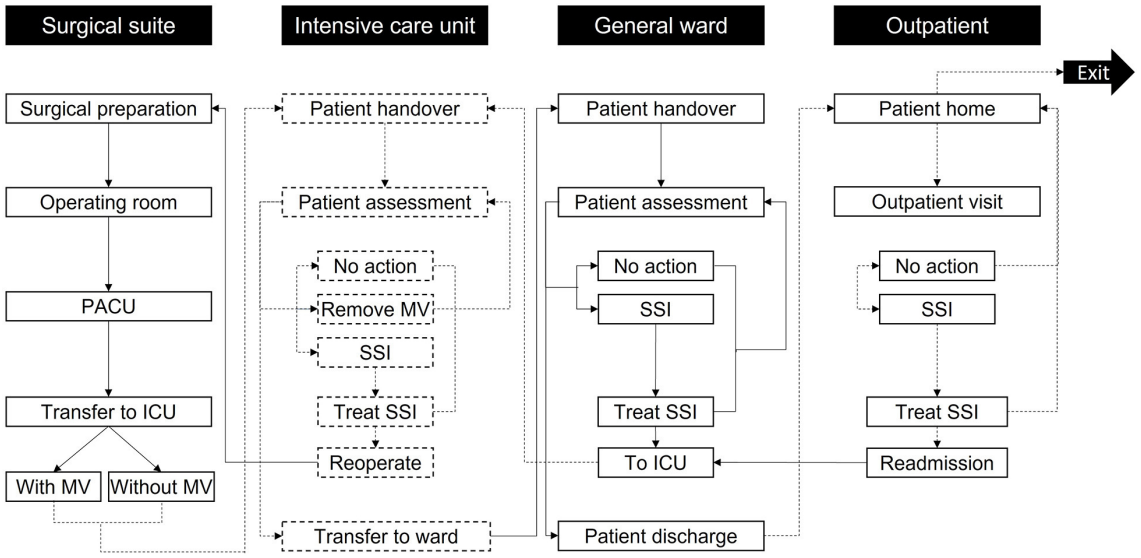

FIGURE 1
Model care settings and activities. Patients enter the simulation at surgical preparation and then progress through the care pathway until exiting the simulation after 30 days in the outpatient setting. Reoperation is only accessed if the patient develops mediastinitis; otherwise, other non-operative treatments are used in the "Treat SSI" activities. The labels in the black boxes indicate the care setting, while the labels in the white boxes show activities in each care setting. To help differentiate the activities per setting, the boxes referring to the surgical suite and GW activities are marked with solid black lines, while the boxes concerning the ICU and outpatient use activities are marked with dashed black lines. Arrows linking activities follow the same principle based on the activity they go to. ICU, Intensive Care Unit; MV, Mechanical ventilation; PACU, Post-Anesthesia Care Unit; SSI, Surgical-site infection.

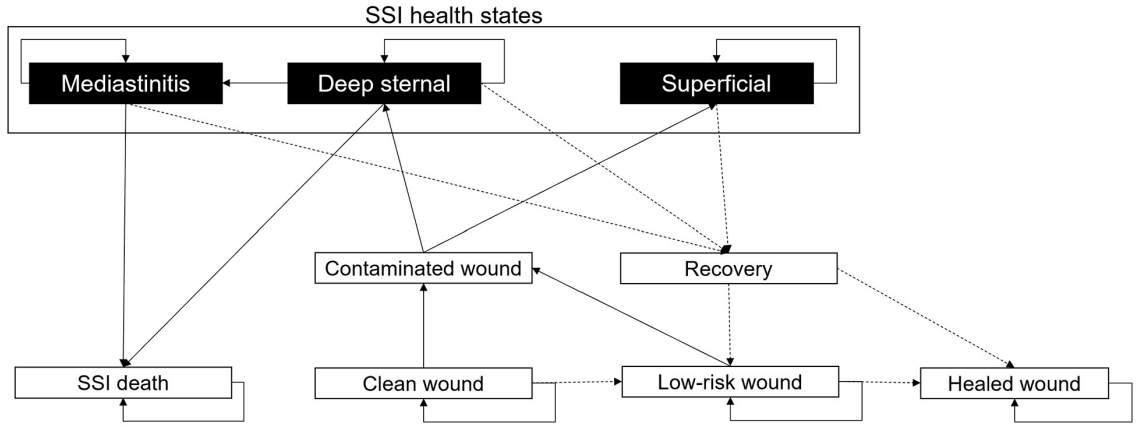

FIGURE 2
Markov model describing the development of SSIs. All patients are assigned a "Clean wound" following CABG surgery. From here, they have the chance to maintain a "Clean wound," develop a "Contaminated wound," or continue healing to a "Low-risk wound." If the patient develops a "Contaminated wound," then there is the chance of this being "Superficial" or "Deep-sternal." A "Deep-sternal" infection can develop into "Mediastinitis." "Deep-sternal" infection and "Mediastinitis" can lead to patient death, an "SSI death." From any SSI health state, a patient's wound infection can recover with treatment; upon "Recovery," the wound may be either considered a "Low-risk wound" or a "Healed wound." From a "Healed wound," no SSI will develop. A "Low-risk wound" may heal to a "Healed wound" or return to "Contaminated wound." All patients discharged from hospital will have a "Low-risk wound." In the diagram, solid black arrows indicate wound stability or infection progression, and dashed black arrows represent healing.

number of days on which this SSI incidence was recorded (SSI^{Days}). The equation for the overall SSI probability per minute is given by $1 - e^{\left(\frac{-\ln[1-SSI_{\%}]}{\ln[1-SSI_{day}\times 1{,}440]}\right)}$, adjusted by 0.76 relative risk for the spECG arm (13, 15, 16, 31). For a "Low-risk wound," the probability of developing a "Contaminated wound" is 0.25 times (one quarter) that of a "Clean wound." A "Low-risk wound" transitions to a "Healed wound" after 30 days. "Superficial" SSIs, "Deep sternal" infections, and "Mediastinitis" that do not result in patient death transition to recovery after a user-inputted number of days.

2.4. Model inputs

The NHS Digital Data (23) for K401-K404 (saphenous vein graft replacement of coronary arteries) and K453 (anastomosis of the mammary artery to the left anterior descending coronary artery) procedures were used to input the model with cardiac unit size, number of CABG per year, patient demographics and clinical characteristics, SSI and DSWI incidence, requirement for MV, timings (on ward and ICU/PACU check intervals and duration), staff resources and costs (Table 1). Other costs were taken from NHS England national reports and the Personal Social Services Research Unit (PSSRU) (27). Cost inputs unavailable for England were sourced from the Information Services Division (ISD) of NHS Scotland (28, 29). The relative risk of SSI with spECG (0.76) was informed by a structured literature search (13, 15, 16, 31).

2.5. Costs and consequences

The outcomes considered in this cost-consequence analysis were care costs, LOS, and SSI events. Costs were collected by care setting (surgical, ICU, GW, and outpatient) and ECG monitoring costs. The overall mean cost per patient was calculated at the end of the simulation. The consequences considered in this model were LOS in ICU, LOS on GW (both reported in total and mean days per patient), and SSI events. The SSI events were detailed as superficial or DSWI (including mediastinitis). The total cost of care and the potential savings ascribable to spECG were also reported.

2.6. Sensitivity analysis

We performed a semi-probabilistic sensitivity analysis to comprehensively assess the impact of changes in the mean input values on the model output (35). Mean input values for all model inputs were changed by an arbitrary ±10% from the base case while retaining specific probability distribution and standard deviation. Each sensitivity simulation is, therefore, a probabilistic simulation of each patient's progression through the model, averaged across 50 independent, seeded iterations to ensure robustness and precision (as with the base case). The same rationale was adopted for the semi-probabilistic three-way sensitivity analysis on the expected savings as a function of CABG/year and SSI incidence. The sensitivity results are reported as the percentage of deviation from base-case savings (Figure 3). A positive delta reflects larger predicted savings.

The model response to SSI incidence and cardiac unit size (CABGs per year) was further investigated in a semi-probabilistic three-way, discrete-point analysis (Figure 4B). The SSI incidence interval was arbitrarily drawn around the base-case value, ranging between 1 and 8%. Incidence rates <1% were excluded due to surging inaccuracy in estimating the cost per patient, while rates >8% were deemed implausible. Similar logic led to the exclusion of structures with <500 CABGs per year. The annual upper limit was arbitrarily fixed at 3,000 CABGs. Data points were calculated in 0.25% SSI incidence increments and 125 CABG per year. The cost per patient at each discrete data point was computed with

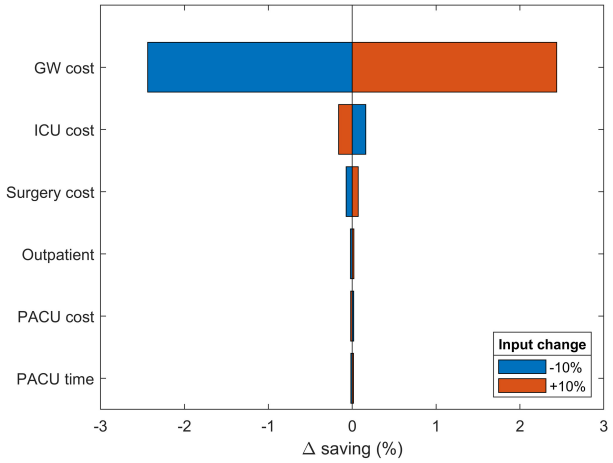

FIGURE 3
One-way sensitivity analysis. Changes in modeled savings upon ±10% variation in most impactful input parameters. The results are provided as the percentage deviation from the base case savings. Positive values favor spECG. Other inputs had irrelevant impact on savings and were therefore omitted.

95.0% confidence over 50 seeded simulation runs with (100%, $spECG_{[100]}$) and without spECG (0% usage, $spECG_{[0]}$). Cost savings per patient were calculated as $spECG_{[100]} - spECG_{[0]}$. The linear regression coefficients were obtained from $Z_{x,y} \sim \beta_0 + \beta_i X_i + \sigma_{res}$, where $Z_{x,y}$ is the delta cost (saving) per patient, β_0 the intercept, β_i the regression coefficient for the X_i independent variable (SSI incidence and number of CABG), and σ_{res} the residual standard deviation.

3. Results

3.1. Base case

The economic and clinical outcomes from the base-case simulation are summarized in Table 2. According to NHS Digital Data (23), patients admitted for CABG at Barts Health NHS Trust hospitals had an average LOS of 11.6 days, reduced to 10.7 days without an SSI. Inpatient SSI occurred in 3.96% of cases and added 24.6 days to the LOS; readmission due to SSI occurred in 3.51% of cases and had an average LOS of 12.6 days. The mean base-case simulation cost of care with rECG was GBP 13,096 [95% CI (13,093, 13,099)]. GW was the largest cost contributor, with ECG being the least at 0.015%. The mean LOS was 9.98 [95% CI (9.97, 9.99)] days, closely aligned with input values. The simulation yielded a total of 214 SSI cases, including 202 [95% CI (201, 203)] superficial SSIs and 12 DSWIs [95% CI (12, 12)], compared to the total of 170 cases reported in NHS Digital. The overall incidence of SSIs with rECG was 8.57% (inpatient SSI + readmission due to SSI). The spECG devices reduced the average cost per patient to GBP 12,708 [95% CI (12,698, 12,718)], i.e., a GBP 388 saving [95% CI (−398, −378)] when compared to rECG. As with rECG, the GW was the largest contributor to costs with spECG, and in this setup, ECG monitoring accounted for 0.10% of care costs

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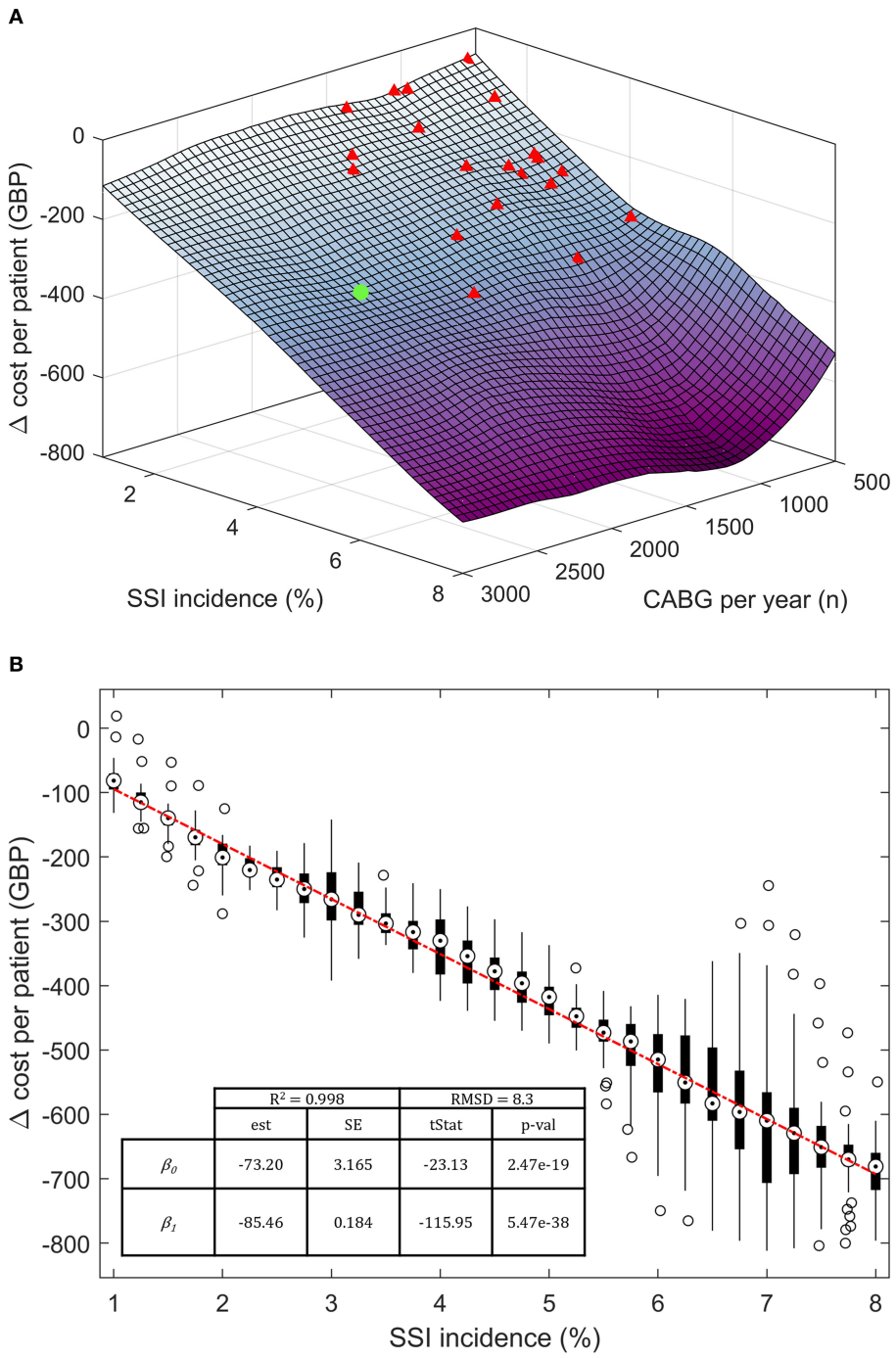

FIGURE 4
Three-way, discrete-point response saving response scenario. **(A)** Three-dimensional saving per patient response surface at varying SSI incidence and number of patients per year. **(B)** Bivariate regression on Δ cost per patient on the SSI incidence. Target markers are the median point of each cost vector. The boxes extend between the 25th and 75th percentiles. Hollow circles represent >2σ outliers. The base case is noted as a green dot; other NHS cardiac units are represented as red triangles. β0, intercept; β1, regression coefficient; est, estimates; SE, standard error, tStat, t-statistics; RMSD, root-mean-square deviation; R^2, coefficient of determination.

due to higher spECG procurement costs. The mean LOS was similar to rECG (9.98 vs. 9.82 days). The simulation resulted in 161 superficial and 10 deep sternal SSIs: −51 superficial [−25.25%, 95% CI (−53, −49)] and −2 DSWI [-16.67%, 95% CI (−2, −2)] compared to rECG. The overall incidence of SSIs with spECG was 6.92%.

3.2. Sensitivity analysis

A semi-probabilistic one-way sensitivity analysis was used to examine the robustness of the model to changes in all input parameters (Figure 3). In accordance with the base-case results, the model is predominantly sensitive to changes in GW cost. Increasing

TABLE 2 Model outcomes from the base-case simulation.

	rECG, point estimate (95% CI)	spECG, point estimate (95% CI)	Difference, point estimate (95% CI)
Economic outcomes			
ECG monitoring, £	4,361 [4,356, 4,366]	28,115 [28,082, 28,148]	23,754 [23,748, 23,760]
Surgery, £	3,037,908 [3,034,336, 3,041,480]	3,043,959 [3,041,573, 3,046,345]	6,051 [2,479, 9,623]
ICU, £	10,818,640 [10,801,678, 10,835,602]	10,172,291 [10,168,304, 10,176,278]	−646,349 [−663,311, −629,387]
GW, £	14,701,963 [14,684,675, 14,719,251]	14,472,018 [14,460,673, 14,483,363]	−229,945 [−247,233, −212,657]
Outpatient, £	26,013 [25,962, 26,064]	25,783 [25,732, 25,834]	−230 [−281, −179]
Cost per patient, £	13,096 [13,093, 13,099]	12,708 [12,698, 12,718]	−388 [−398, −378]
Total cost, £	28,588,895 [28,577,689, 28,600,101]	27,742,175 [27,720,427, 27,763,923]	−846,720 [−857,926, −835,514]
Consequence outcomes			
Superficial SSI, *n*	202.0 [200.6, 203.4]	151.0 [149.6, 152.4]	−51.0 [−52.5, −49.5]
DSWI, *n*	12.0 [11.7, 12.3]	10.0 [9.8, 10.2]	−2.0 [−2.4, −1.6]
SSI incidence, %	9.25 [9.18, 9.32]	6.92 [6.86, 6.98]	−2.0 [−2.5, −2.2]
ICU, days	2,663 [2,660.9, 2,665.1]	2,620 [2,618.0, 2,622.0]	−43.0 [−45.2, −40.8]
GW, days	21,786 [21,768.9, 21,803.1]	21,437 [21,420.2, 21,453.8]	−349.0 [−366.2, −331.8]
ICU, days/patient	1.22 [1.22, 1.22]	1.20 [1.20, 1.20]	−0.02 [−0.04, 0.00]
GW days/patient	9.98 [9.97, 9.9]	9.82 [9.81, 9.83]	−0.16 [−0.21, −0.11]

Costs are given in 2021 GBP, £, at 95% CI (rounded at the nearest integer, where applicable), confidence interval; ICU, intensive care unit; GW, general ward; SSI, surgical site infection; DSWI, deep sternal wound infection; SOC, standard of care.

GW costs provide an extra 2.54% savings advantage to spECG over rECG. Increasing ICU and surgical costs have limited consequences (<0.5%), whereas PACU cost and time, device procurement, MV cost, and operative time have no bearing on the modeled savings.

The modeled spECR-related savings was tested as a function of SSI incidence (between 1 and 8%) and the number of CABG per year (Figure 4A). A strong dominance of incidence emerged as the driving variable for per-patient savings, while the facility size in terms of yearly CABG is marginal. In fact, NHS facilities (red triangle) far smaller than the base case (green dot) are projected to achieve analogous cost savings, assuming they operate within the same SSI incidence range. Three smaller cardiac units encompassing a large interval of annual CABGs may virtually realize even greater savings per patient than the much larger base case. The contribution of SSI incidence can be estimated at an additional 85 GBP per percentage point of SSI (Figure 4B). In contrast, changes in the number of procedures have a minor and non-significative budget impact of ∼8 GBP (*p*-value 0.63) per increment of a thousand CABGs per year (data not shown).

4. Discussion

While a randomized clinical trial or other empirical studies would undoubtedly be more conclusive in informing decision-makers and healthcare professionals, these require extensive, lengthy, and expensive data collection, made unpracticable by the COVID-19 outbreak and the consequent strain on ICUs. In addition, limited or non-existent data regarding spECG in the NHS Digital database at the time of writing drove the choice of modeling, an established and practical alternative for simulating hypothetical scenarios with a reasonable degree of approximation in the optic of a preliminary assessment of the technology's potentiality on costs and outcomes.

Drawing on the NICOR's National Adult Cardiac Survey Audit (NACSA) 2021 report (8) and the current literature on the soundness of spECG technology in perioperative cardiac prophylaxis, this model offers an initial assessment of the potential impact on NHS cardiac units. Beyond relevant clinical arguments for improved patient safety addressed in the literature, our model suggests that disposable spECG devices can yield base-case budgetary benefits of about GBP 388 per patient, 95% CI (−398, −378). Savings are driven by a 25 and 17% reduction in the incidence of superficial and deep sternal-wound infections, respectively, compared to rECG. Cutbacks in ICU (6.0%) and GW (1.5%) costs were the primary determinants in consequence of reduced LOS [−1.6% or −0.02 days/patients in ICU −95% CI (−0.04, 0.00), and −1.6% or 0.16 days/patient on GW, 95% CI (−0.21, −0.11)]. Accordingly, the model proved most susceptible to GW and ICU costs in the sensitivity analysis while only marginally affected by other variables. Notable is the preponderant impact of the incidence rate of SSIs on the expected savings with respect to the number of CABG procedures. Variations in SSI by a percentage point predict tangible budgetary shifts, while leaps in the thousands of patients per year yield only marginal gains. This circumvents

the assumption that a critical mass of CABG procedures would primarily determine the break-even point for a cost-effective adoption of spECR. Provided they operate within the same SSI incidence interval, relatively small cardiac units can expect relative savings comparable to considerably larger settings. In this respect, consistent with the conclusions from NACSA 2021 (8), it is pertinent to note how small and medium-sized hospitals are most prone to imprecise, underestimated SSI rates amid fragmentary and unexhaustive literature concerning the extent of rECG-related infections (11, 18). The significance of spECG is to be contextualized as part of a bundle of synergistic SSI control measures (e.g., perioperative hygiene programs, wound care, antibiotic prophylaxis, etc.), cost-effective across diverse surgical specialities (37–42).

The anatomy of CABG forces ECG leads and cables in close proximity to sternal wounds, inherently exposing patients to avoidable and potentially fatal complications (13–15). Infection prevention is crucial as durable non-antibiotic prophylactic interventions are becoming increasingly valuable amid grim prospects for nosocomial antibiotic resistance (43, 44). On the other hand, single-use devices in OR operations represent a significant source of hospital waste, disposal costs, and environmental impact (45). Therefore, targeting disposable devices at high-risk procedures is a reasonable compromise to safeguard patients' safety and intervention sustainability.

The reader should be wary of direct extrapolation to other geographies or settings and consider these results within the model's limitations. Nevertheless, conceived with a modular structure from its outset, the model is readily transposable to different scenarios and malleable to implement parameters for the minute simulation of any specific healthcare setup. Altogether, spECGs prospect improved prophylaxis in complex cardiothoracic surgery scenarios along with significant monetary benefits within the NHS setting. Although the model reasonably describes CABG's surgical and postoperative course, some limitations persist. The model's tendency to slightly overestimate the cumulative incidence of infection can be ascribed to two possible reasons. On the one hand, the source data from NHS Digital (23) is rounded to the nearest five, introducing a non-trivial approximation to figures from smaller facilities. On the other hand, in terms of the model, the simulated incidence may be distorted by the BHIS infection risk assignment system. In fact, at this stage, no correlation matrix between the characteristics of the patients could be implemented in the model, and some of the patients entering the simulation may have been assigned unrealistic combinations of characteristics. However, this effect should cancel out in purely probabilistic terms due to the equally likely assignment of under and overestimated BHIS. At last, while the model and sensitivity analysis encompass both first and second-order uncertainty, the OWSA may certainly fail in capturing interactions between input variables, the impact of extreme values or outliers in the input distributions, and assumes that the input distributions are independent, which may not always be the case in practice. However, in this specific case, the model is sensitive primarily to cost inputs and no joint interactions between these inputs can be assumed. In addition, since costs are calculated ex-post to population outcomes, cost inputs have no cross-interactions with other input parameters to affect simulated patient outcomes.

5. Conclusions

Based on our analysis, cost savings from reduced SSI incidence are expected to outweigh the additional procurement cost of spECG. As such, spECG has the potential to offer hospitals performing CABG a beneficial alternative to reusable ECG cables and lead wires, both in terms of enhanced patient safety and resource allocation.

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.

Author contributions

RS contributed to the conceptualization of the study, design of the model, implementation of the model, collection of input data, interpretation of results, and manuscript writing. MC contributed to the model's implementation, formal data analysis, data visualization, interpretation of the results, and manuscript writing. PS contributed to the conceptualization of the study, clinical expertise, development of the model, and the editing of the manuscript. All authors contributed substantially to the research and read and approved the manuscript.

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Conflict of interest

This study was supported by funding from Cardinal Health Inc. Cardinal Health Inc. had no role in any planning, executing, and interpreting of the results of this study. Coreva Scientific GmbH & Co KG received consultancy fees from Cardinal Health for work related to this manuscript. MC is an employee at Coreva Scientific GmbH & Co. RS is the founder and owner of Coreva Scientific GmbH & Co. PS did not receive any incentive (monetary or otherwise) from Cardinal Health Inc. for his contributions to this manuscript.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1027977/full#supplementary-material

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Out-of-pocket health expenditure and associated factors among patients with hypertension in Debre-Tabor Comphrensive Specialized Hospital, South Gondar zone, Northwest Ethiopia, 2020

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Introduction: Hypertension is a non-communicable chronic disease that has a wide financial effect at the individual and household levels especially in developing countries due to its complexity and chronicity. Nevertheless, there are limited studies in Ethiopia. Therefore the aim of this study was to assess out-of pocket health expenditure and associated factors among adult patients with hypertension in Debre-Tabor Comphrensive Specialized Hospital.

Methods: A facility-based cross-sectional study was conducted in total of 357 adult hypertensive patients from March to April 2020 using a systematic random sampling technique. Descriptive stastics were used to estimate the magnitude of out-of-pocket health expenditure, while after checking the assumptions linear regression model was fitted for identifying the factors associated with the outcome variable at a significance level of value of p <0.05 and 95% confidence interval.

Result: A total of 346 study participants interviewed with a response rate of 96.92%. Annual mean out of pocket health expenditure of the participant was $113.40±$10.18 with 95% CI=(102.63, 124.16) per patient. The direct medical mean out of pocket health expenditure of the participant was $68.86 per patient per year and the median of non-medical components of the out of pocket health expenditure of the participant was $3.53. Sex, wealth status, distance from hospital, comorbidity, health insurance and number of visit are factors significantly associated to out-of-pocket expenditure.

Conclusion: This study revealed that out of pocket health expenditure among adult patients with hypertension was found high compared to the national *per capita* health expenditure. Sex, wealth index, distance away from hospital, frequency of visit, comorbidities, and health insurance coverage were factors significantly associated with high out-of-pocket health expenditure. Ministry of health together with regional health bureaus and other concerned stakeholders work on strengthening early detection and prevention strategies of chronic comorbidities of hypertensive patients,promote health insurance coverage and better to subsidize medication costs for the poors.

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KEYWORDS

out-of-pocket expenditure, expenditure, hypertension, catastrophic health care expenditure, Ethiopia

Introduction

Hypertension is defined as a rise in systemic blood pressure above 140 mmHg or a rise in diastolic blood pressure above 90 mmHg (1). It is one of the most prevalent chronic noncommunicable diseases in the world, as well as a major risk factor for stroke, myocardial infarction, vascular disease, and chronic kidney disease (2, 3). Globally, an estimated 1.4 billion people had high blood pressure of 140/90 mmHg, accounting for 12.8% of all deaths and 18 million cardiovascular deaths each year, with two-thirds living in low-and middle-income countries (1, 3, 4). Hypertension is the leading cause of heart failure in Africa, where 46% of hypertensive adults develop cardiovascular disease (5). Hypertension prevalence in Ethiopia ranged from 12.5 to 28.37%, with a pooled prevalence of 19.6% (2, 5–8).

Out-of-pocket health expenditure (OOPHE) is defined as household spending incurred when using a service to obtain any type of health care (Promotive, preventive, curative, rehabilitative, palliative, or long-term) (9). According to the World Health Organization, catastrophic out-of-pocket health expenditure occurs when direct OOP payments exceed 40% of household income minus subsistence needs or OOP payments exceed 10% of total household income (10, 11). Household health expenditure is estimated to account for 45% of total global health expenditure and 23% of health expenditure in the developing world (12). An estimated 1.3 billion people worldwide lack access to effective and affordable health care. Approximately 170 million of those who do are forced to spend more than 40% of their household income on medical treatment (13). Every year, out-of-pocket health expenditure pushes 25 million households, or more than 100 million people, into poverty (14).

Between 2000 and 2015, out-of-pocket health spending contributed to global poverty and living below the poverty line (15). Financial risk-pooling mechanisms have been developed over several decades in developed countries' health-care systems. Nonetheless, despite the existence of reasonably well-developed financial risk protection mechanisms, some households in these countries are still confronted with high out-of-pocket health expenditure (11).

In Ethiopia, poor health care financing remains a major challenge for the health system. In which the health system is dominated by low government spending, strong reliance on out-of-pocket health expenditure, inefficient and inequitable utilization of resources, poorly harmonized and unpredictable donor funding, households are vulnerable to impoverishment from out-of-pocket health expenditure (16). According to Ethiopia's seventh national health accounts (2016), out-of-pocket health spending on general health was much higher than the global recommended target of 20% (17). However, much effort has been made to protect households from financial risks by increasing nominal and *per capita* health expenditures, establishing and expanding community-based health insurance (CBHI) schemes, and subsidizing some specific services (fee-waiver and exemption) (18, 19).

Hypertension is one of the 21st century's silent killers and one of the most serious global public health issues, costing households more than other diseases.

In the United States, patients receiving hypertension treatment (13.1%) were significantly higher than other chronically ill (10.5%) and well patients (5.3%). Similarly, pooled data from the United States of America from 2003 to 2014 (20) revealed that the mean annual medical expenditure attributable to patients with hypertension was $9089 compared to patients without hypertension (21).

Direct OOP payments accounted for more than half of total health expenditures in the majority of low-income countries in 2007 (12). India is one of those countries that spends more than one-third of total income on cardiovascular diseases (CVD) and hypertension (22). The average annual cost of hypertension in Malawi was Rs. 5831.5 (23), while the average annual cost of hypertension in Kenya was $475 (24).

According to some studies on the cost of hypertension conducted in Ethiopia, the mean annual cost of hypertension is high (ranging from $91.72 to US $267.6) (25, 26). According to an Addis study on cardiovascular disease, approximately 27% of households (26.7, 95% CI 23.1 to 30.6) had catastrophic health expenditure (10).

According to studies conducted on hypertension out-of-pocket expenditure in Columbia and Malawi, the average annual hypertension-attributable out-of-pocket expenditure was USD $147.75 and Rs. 4042 and Rs. 7621 for government and private facilities, respectively (23, 27). Findings in Pakistan revealed that, in addition to higher OOP medical spending, the incidence of catastrophic health expenditure is higher for BPD (blood pressure and diabetes) medication consuming households, reaching as high as 12.96% among BPD medication consuming households and only 5.84% among households "not" consuming BPD medication (20). Furthermore, a study on the OOP of HTN conducted in Addis Abeba revealed that the total out-of-pocket expenditure was estimated to be 5279.50 (mean 7194.00) birr/month (28).

Out-of-pocket health expenditure is influenced by a variety of factors, which are broadly classified as socioeconomic, clinical, and payment type. In the literature, socio-demographic and economic factors such as occupation (29), education, family size, sex, age, marital status (30), residence, and wealth index (29) were factors influencing out-of-pocket expenditure. Payment type factors include drug cost (29), health insurance membership (21, 29), waived or exempted service users, and distance from the hospital (26). Clinical factors include the presence of complications, the duration of the disease, and the stage of hypertension (30).

Abbreviations: BPD, Blood pressure and diabetes; CBHI, Community Based Health Insurance; CVD, Cardio Vascular Disease; HTN, Hypertension; OOP, Out of Pocket; OOPHE, Out of Pocket Health Expenditure; USD –PPP, Purchasing Power Party; WHO, World Health Organization.

In general, hypertension is a major contributory factor to subsequent morbidity and mortality in Ethiopia, and out-of-pocket health spending for hypertension imposes a significant economic burden on patients and societies. As the health system is dominated by out-of-pocket payment systems, which push individuals and households into poverty and disrupt household welfare. There have been few studies on the magnitude of hypertensive patients' out-of-pocket health expenditure,which didnot include the detailed factors and the study time is some what long. As a result, the purpose of this study is to estimate the burden of out-of-pocket health expenditure and identify the associated factors in hypertensive patients, which helps to provide updated baseline information for health planners on how to intervene.

Methods

Study design, period and setting

This facility-based cross-sectional study was conducted at Debre-Tabor Referral Hospital Chronic Illness Follow-up Outpatient department (OPD) from March to April 2020 to assess the level of out-of-pocket health expenditure among patients with hypertension.

From March to April 2020, the Debre-Tabor Comphrensive Specialized Hospital Chronic Illness Follow-up Outpatient Department (OPD) conducted a facility-based cross-sectional study to assess the level of out-of-pocket health expenditure among hypertensive patients.

Debre-Tabor Comprhensive Specialized Hospital is located in South Gondar Administrative Zone, Amhara National Regional State, 667 kilometers from Addis Ababa (Ethiopia's capital city) and 97 kilometers from Bahir Dar (the regional capital). Currently, the hospital is one of Ethiopia's and the Amhara region's Comprhensive Specialized health care facilities, serving 2,609,823 people in the South Gondar zone and the surrounding zones. It offers an outpatient hypertensive clinic 5 days a week, with a patient flow of approximately 721 hypertensive patients per month.

Sample size determination

The sample size for the first objective is calculated using a single population mean formula from a previous study done in Ethiopia in public hospitals at Addis Abeba (13). The sample size was 357 based on the assumptions Zà/2 1.96, and annual mean ± SDof out-of-pocket health expenditure with of $158.64 ± $29, and a margin of error (d) of 2% of the mean. On average, every month, around 721 patients come to the hypertensive outpatient clinic. Using systematic random sampling with a *K* value of 2 (721/357), every other hypertensive patient was selected and interviewed for the study.

The population consisted of all adult hypertensive patients attending an outpatient chronic illness follow-up clinic in Debre-Tabor Comprhensive and Speciaalized Hospital during the study. All patients who were diagnosed with hypertension for at least 1 year were included, while patients who were unable to communicate were excluded.

Data collection tools and procedure

A Semi-structured interviewer administered questionnaire adopted by reviewing different literature was used. The tool comprises an out-of-pocket health expenditure questionnaire with 16 items, socio-economic and demographic characteristics, clinical, and payment type/modalities to collect information from the patients. From March 15 to April 20, 2020, three diploma nurses with one supervisor were assigned for data collection. The questionnaire was initially prepared in English and translated into Amharic (the local language) for understandability, and after data collection, it was retranslated back to English to keep its consistency.

Direct medical payments are defined as payments directly related to the illness or condition, such as medication, folder fees, consultation, and laboratory test expenses for hypertensive patients, and are measured as values per visit per patient per month in ETB.

Direct non-medical payments are defined as payments which are not directly related to the illness or condition but indirectly related to the illness, which includes transport and food for hypertension patients and their caregivers' expenditure measured per visit per month.

Indirect payment was a time devoted by hypertensive patients and their caregivers to seeking treatment for 1 year.

Out-of-pocket health expenditure is referred to as payments (OOPs) directly or indirectly related to the illness or condition, which includes direct medical payments and non-medical payments. Which were measured by out-of-pocket health expenditure per visit per patient per month, after which the expenditure changed to annual mean values per patient. Finally, the result of the study was reported. According to the commercial bank of Ethiopia, the annual exchange rate between the USD and the Ethiopian Birr (ETB) on May 25, 2020 was USD 1.0 = ETB 33.99.

Data quality control measures

To ensure the quality of the data, one-day training on the contents of the questionnaire and the purpose of the study was given to the data collectors and supervisor. A pre-test was done 1 week before the actual data collection among 18 patients in Wogeda Primary Hospital. During the pretest, the questionnaire was checked for its clarity, simplicity, understandability, completeness, consistency, and coherency. Quality of data was also controlled through conducting close supervision and follow-up by supervisors and principal investigators on the filled questionnaire.

Data management and analysis

Before being exported to Stata14 software for further analysis, all data was entered into Epidata version 4.6, coded, cleaned, and checked for completeness. The wealth index was classified into five quintiles using principal component analysis, which was then analyzed using state 14 software. Summary statistics for the outcome and independent variables were computed. After checking linear regression assumptions such as linearity, normality, homoscedasticity, equal variance, and multicollinearity, simple linear regression and multiple linear regression were used to identify factors associated with out-of-pocket

health expenditure. Variables with a *p*-value <0.05 at 95% confidence intervals were considered statistically significant in multiple linear regression analysis.

Result

Socio-economic and demographic factors

A total of 346 hypertensive patients participated in the study, with a response rate of 96.92%. The majority of the participants, 212 (61.27%) were city dwellers. The majority 220 (63.58%) of the participants were aged between 44 and 64 years, and the mean age of the participants was 54.25 ± 11.02. Among the total participants, 70 (20.24%) were the poorest. The majority of participants, 198 (57.23%), travel less than five kilometers to the health facility (Table 1).

Clinical related factors and payment type factors

The median duration of the diseases was 4 years. The majority of participants (340, or 98%) were followed once per month. While 88 (25.43%) of participants had comorbidities, of which 47 (53.41%) had diabetes mellitus. Furthermore, 86 (24.85%) of the participants had health insurance. The majority of the participants' expenses (258, or 74.57%) were covered by cash, with 194 (56.23%) covered by their own savings (Table 2).

Out of pocket health expenditure

The participant's annual mean out-of-pocket health expenditure was $113.40 ± $10.18 with a 95% CI = (102.63, 124.16) per patient. The direct medical components of the participant's mean out-of-pocket health expenditure were $68.86, 95% CI = (61.65, 76.07) per patient per year. The non-medical components of the participant's median out-of-pocket health expenditure were $3.53 [95% CI = (13.04, 18.40)] per patient per year.

Factors associated with out of pocket health expenditure

Multiple linear regression analysis was conducted after checking assumptions in the final model. The following bivariable regression variables were chosen for the final model multiple linear regression analysis with *p*-value <0.2: gender, marital status, religion, wealth index, distance from hospital, frequency of visit, comorbidity, and health insurance coverage.

Being a female participant expended $17.45 unit more [95% CI = (0.81, 34.09)] than male participants. When comparing out of pocket health expenditure the richest to the poorest, the richest expend extra $31.02 [95% CI = (6.54, 55.50)].

Out-of-pocket health expenditure among hypertensive patients who traveled more than 10 kilometers from the hospital is 71.45 dollars more compared to patients who traveled less than 5 kilometers.

A participant with comorbidities had an increased out-of-pocket health expenditure of $53.66 (95% CI = 34.55, 72.77) as compared with patients without comorbidities.

Out-of-pocket health expenditure for those havenot health insurance is $98.89 more; 95% CI = (79.36, 118.42) compared to those who had health insurance coverage. Participants who had 2 or more visits had an increased out-of-pocket health expenditure of $374.09 [95% CI = (315.35, 432.84)] as compared to those participants who had one visit (Table 3).

Discussion

Hypertension is a common chronic public health problem having a profound effect on individual and household wealth, especially for out-of-pocket payers. The aim of this study was to determine the out-of-pocket expenditure of hypertension patients and associated factors.

This study revealed that the mean annual out-of-pocket health expenditure of patients with hypertension was $113.4 ± $10.18; 95% CI = (102.63, 124.16)/patient/year. This finding is higher than the 7th national health account data in 2016/2017, *per capita*l health expenditure report and study conducted at the University of Gondar Comprehensive Specialized Hospital Northwest Ethiopia ($33.2) and ($v91.72) respectively (17, 25). The possible explanation for this variation might be the study period, the status of the diseases in the participant, or distance from the health facility. On the other hand, it was lower than the studies conducted in Addis Ababa (10). The possible explanation for this variation might be that the study setting difference, Addis abeba is the large city and debre-tabor is zone capital city the expenditure for transport and other activities is different, which leads to an increase in their expenditure. The findings of this study were also lower than those of previous studies conducted in Kenya (24). This disparity could be explained by differences in study settings, time periods, expenditure estimation methods, and participant socioeconomic status. This finding is also lower than that of previous studies in Ethiopia's Southwest Shewa Zone, Oromia Regional State (26). This difference may be due to the fact that a study conducted in Southwest Shewa estimates both direct and indirect costs of hypertension, whereas this study does not.

Female hypertensive patients spend $17.45 more per day than male hypertensive patients [95% CI = (0.81, 34.09] This could be explained by the fact that females are more likely to have supporters and use vehicles for transportation than males, causing them to spend more. A study conducted in the United States (31) lends support to this study.

When compared to the poorest, out-of-pocket health expenditure among the richest is $31.02 more [95% CI = (6.54, 55.50)].The possible explanation might be that the richest have a high income and their wants also vary a lot compared to the poorest, who have limited wants and expend less. This study is supported by studies conducted in Ethiopia, Kenya, Namibia, Nigeria, Albania, Bangladesh, and India which found that the richest individuals and households had higher out-of-pocket expenditures on health care than the poorest households (24, 31–36). Those who belong to the highest Socio-economic Status have a better capacity to pay for health care services, expensive drugs, and diagnosis modalities.

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TABLE 1 Socio-demographic and economic characteristics of study participants at Debre-Tabor General Hospital, North West Ethiopia, 2020 (*n* =346).

Variable	Frequency	Percent (%)	Mean±SD
Residence			
Urban	212	61.27	
Rural	134	38.73	
Sex			
Male	225	65.03	
Female	121	34.97	
Age (in years)			54.25 ± 11.02
18–44	58	16.76	
44–64	220	63.58	
≥64	68	19.66	
Marital status			
Single	12	3.47	
Married	266	76.88	
Divorced	19	5.49	
Windowed	48	13.87	
Separated	1	0.29	
Religion			
Orthodox Christian	270	78.03	
Muslim	66	19.08	
Protestant	10	2.89	
Educational status			
Unable to read and write	123	35.55	
Able to read and write only	68	19.65	
Grade 1–8	30	8.67	
Grade 9–12	30	8.67	
College and above	95	27.46	
Occupational status			
Farmer	106	30.64	
House wife	42	12.14	
Employed	97	28.03	
Merchant	55	15.90	
Daily Labor	15	4.34	
Others	31	8.96	
Wealth status			
Poorest	70	20.24	
Poor	69	19.94	
Middle	69	19.94	
Rich	69	19.94	
Richest	69	19.94	
Distance from the health facility			4
Less than 5 km	198	57.23	
5 km-10 km	35	10.12	
≥10 km	113	32.66	
Means of transport			
Foot	190	54.91	
Vehicle	156	45.09	

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TABLE 2 Clinical related factors of study participants at Debre-Tabor General Hospital, North west Ethiopia, 2020 (n =346).

Variables	Frequency	Percent (%)	Median
Duration of the diseases(in years)			
<5 years	255	73.70	
5–10 years	76	21.97	4
≥10 years	15	4.33	
Frequency of visit			
Less than 2 times	340	98.27	
≥2 times	6	1.73	
Comorbidities			
Yes	88	25.43	
No	258	74.57	
Types of comorbidities			
Diabetes mellitus	47	53.41	
Kidney diseases	7	7.95	
Cardiac disease	23	26.14	
Epilepsy	2	2.27	
Asthma	9	10.23	

In this study, hypertensive patients who lived 10 kilometers or more from the hospital spent $71.45 more [95% CI = (51.56, 91.34)] than hypertensive patients who lived less than 5 kilometers from the hospital. It is supported by studies conducted in Ethiopia (37). The possible explanation could be that hypertensive patients who live far from health care facilities spend more money on transportation and food than those who live close to the hospital.

Participants who visited the hospital twice or more spent an additional $374.09 [95% CI = (315.35, 432.84)] than participants who visited the hospital once. This disparity may be explained by the fact that those who visit the hospital frequently spend more money on transportation, food, and drugs than those who visit the hospital less frequently. Which is not supported by previous studies.

Hypertensive patients with comorbidities spent $53.66 more [95% CI = (34.55, 72.77)] than those without comorbidities. This was supported by a study conducted at the University of Gondar Comprehensive Specialized Hospital Northwest Ethiopia and the US (25, 31). This could be explained by the fact that participants with comorbidities may have spent more money on extra drugs and laboratory tests.

This study also revealed that health insurance coverage has a significant association with out-of-pocket health expenditure. Patients with hypertension who lacked health insurance spent $98.89 [95% CI = (79.36, 118.42)] more than those who did have health insurance. This study was supported by studies conducted in Kenya, Korea, and the US (24, 31, 38). The possible explanation might be that those participants who do not have health insurance may delay care due to financial problems, which leads to complications that demand extra money for different aspects, where as having health insurance membership enables the members to get a service at health facilities free of medication and service charge at the time of hypertension follow up.

TABLE 3 Factors associated with out of pocket health expenditure among patients with hypertension in Debre-Tabor General Hospital, Northwest Ethiopia, 2020.

Variables	COR	p-value	AOR	p-value	(95% CI)
Sex					
Male	Ref	–	Ref	–	–
Female	21.47	0.062	17.45	0.04	(0.81,34.09)*
Maritial status					
Single	Ref	–	Ref	–	–
Married	−91.21	0.002	−40.64	0.06	(−82.74, 1.46)
Divorced	−78.23	0.033	−33.99	0.20	(−86.17,18.18)
Widowed	−34.23	0.285	−13.97	0.55	(−59.80,31.85)
Separated	−133.6	0.197	−76.86	0.33	(−231.05,77.32)
Religion					
Orthodox	Ref	–	Ref	–	–
Muslim	−19.9	0.155	−12.89	0.20	(−32.43,6.64)
Protestant	−22.2	0.49	−0.56	0.98	(−48.96,47.84)
Wealth Status					
Poorest	Ref	–	Ref	–	–
Poor	−3.21	0.85	5.59	0.69	(−21.59,32.77) 32.77111
Medium	10.04	0.55	14.80	0.29	(−12.47,42.07)
Rich	7.6	0.65	4.80	0.70	(−19.41,29.10)
Richest	56.8	0.001	31.02	0.01	(6.54, 55.50)*
Distance from Hospial (km)					
<5	Ref	Ref	Ref	–	–
5–10	4.22	0.82	20.85	0.15	(−7.87,49.56)
≥10	29.4	0.014	71.45	0.000	(51.56, 91.34)**
Frequency of visit (wk)					
<2visit	Ref		Ref	–	–
≥2 visit	392.1	0.001	374.09	0.000	(315.35,432.84)**
Comorbidities					
No	Ref	–	Ref	–	–
Yes	83.8	0.001	53.66	0.000	(34.55,72.77)**
Health Insurance					
Yes	Ref	–	Ref	–	–
No	61.55	0.001	98.89	0.000	(79.36,118.42)**

*Significant at p-value ≤0.05. **Significant at p-value ≤0.001. Km = kilometer.

The information required in calculating costs was based on an investigation of patients and their households rather than documenting.

This study tries to identify factors influencing out-of-pocket expenditure beyond determining out-of-pocket expenditure might be taken as a strength of the study. On the contrary, the limitations are that, as the study includes only adult hypertensive patients attaining outpatient department, this finding may not be generalizable for those patients in inpatient department.

Despite using different leading techniques to minimize recall bias, remembering each cost they expend on each activity is difficult, so there might be underestimation or overestimation.

Conclusion

This study revealed that out-of-pocket health expenditure among adult patients with hypertension was found to be high compared to the national per capita health expenditure. Sex, wealth index, distance from hospital, frequency of visit, comorbidities, and health insurance coverage were associated with high out-of-pocket health spending.

The Ministry of health should provide a better subsidy on the service and medication fees for hypertensive patients. And MOH together with regional health bureaus and other concerned stakeholders, working on strengthening early detection and prevention strategies for chronic comorbidities in hypertensive patients. In addition, the Ethiopian health insurance agency needs to strengthen efforts in implementing strategies that accelerate the enrollment of the community into health insurance schemes, expand social health insurance schemes, and expend other coping mechanisms. Furthermore, healthcare providers focus on primordial prevention to minimize the severity of hypertension diseases and comorbidities and provide better care at home for hypertensive patients to reduce transportation, expenditure, and comorbidities in collaboration with health posts and community health workers. Conducting longitudinal and community-based research on out-of-pocket health expenditure among hypertensive patients is better for more generalization.

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 studies involving human participants were reviewed and approved by Ethical review board of University of Gondar. The patients/participants provided their written informed consent to participate in this study. 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

MA and BA conceptualized the study, analyzed the data, and prepared the manuscript. TH analyzed and helped with writing the manuscript. BA developed and provided feedback for all sections of the review protocol and approved the final manuscript. All authors have read and approved the final manuscript.

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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.

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Willingness to pay for hepatitis B virus vaccine and associated factors among households in Bahir Dar City, northwest Ethiopia: using contingent valuation method

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Background: The prevention of disease burden and death through vaccination is one of the most cost-effective methods. Even though the Hepatitis B Virus (HBV) has significant public health problems in Ethiopia, there is no compulsory HBV vaccination program for adults and the vaccine's market value was not yet estimated in the Ethiopia context. Therefore, this study aimed to assess the willingness to pay (WTP) for the HBV vaccine and its associated factors among households in Bahir Dar City, northwest Ethiopia.

Methods: A cross-sectional study was conducted among 620 households from March 1 to 30, 2020. A systematic random sampling technique was employed to select the required number of households. An interviewer-administered questionnaire was used to collect the necessary information. The contingent valuation method was conducted to measure WTP for the HBV vaccine. A Tobit regression model was employed to investigate significantly associated factors, and variables with a p-value of <0.05 were considered statistically significant.

Results: In this study, 62.17% of households were willing to pay for the HBV vaccine with an average cost of ETB174.24 (US$5.25). Male household heads ($P = 0.014$), favorable attitude ($P = 0.017$), and good knowledge ($P < 0.001$) toward the vaccine were positively associated with WTP, whereas age ($P < 0.001$), single marital status ($P = 0.012$) and divorced/widowed ($P = 0.018$) marital status were negatively associated with WTP.

Conclusions: Overall, most households were willing to pay for the HBV vaccine with an average demand of ETB174.24 (US$5.25). Therefore, a national-level HBV vaccine strategy should be designed considering the households' willingness to pay. In addition, working on attitudes and knowledge toward the vaccine could potentially increase the household's willingness to pay for the HBV vaccine.

KEYWORDS

contingent valuation method (CVM), willingness to pay (WTP), hepatitis B vaccine (HBV), Tobit, Ethiopia

Introduction

Even though hepatitis B virus (HBV) infection is 50–100 times more contagious than human immunodeficiency virus (HIV) (1), less attention was paid worldwide. Hepatitis B infection is caused by HBV that attacks liver resulting in hepatocellular necrosis and inflammation (2). Worldwide, more than two billion people were infected by the virus, and there were about 620,000 HBV-related deaths each year, with one in four progressing to liver disease (3, 4). Globally, the virus causes 60–80% of all primary hepatocellular carcinoma, which is one of the top three causes of cancer death in sub-Saharan Africa (5). In Ethiopia, 12% of medical admissions and 31% of medical wards' mortality is attributable to liver disease (6).

The prevention of disease burden and death through vaccines is one of the most cost-effective methods (7, 8). Hepatitis B vaccine is designed by the World Health Organization (WHO) as the foremost strategy for preventing death and chronic infection that leads to liver cirrhosis or hepatocellular carcinoma (9). The government of Ethiopia added HBV and Hemophilus influenza type B vaccines to the standard expanded program on immunization (EPI) in 2007 targeting children under 1 year of age (10). On the other hand, the adult vaccination of HBV is only given to high-risk groups, such as healthcare workers in public health facilities, and there is no compulsory HBV vaccination program for adults in the rest of the population and the affordable market cost of the vaccine was not set in Ethiopian context. However, setting the evidence on the willingness of households to pay for the vaccine and their cost ability to pay is very crucial for designing a sustainable program as the cost of the vaccines in Ethiopia is largely covered by unpredictable and unharmonized donors' funds (10).

Studies conducted in Malaysia (11), China (12), and Vietnam (13) showed that 37.5% of the households, 35.6% of migrant workers, and 80.8% of reproductive-age women were willing to pay for HBV, respectively. Moreover, participants in Malaysia (11) and China (12) were willing to pay an average cost of US$73 and US$ 4.65, respectively. Another study conducted in Gondar City, Ethiopia, showed that 62.4% of health professionals were willing to pay an average price of US$ 14.39 for the HBV vaccine (14).

Evidence also showed that various factors contribute to an individual's willingness to pay (WTP) and the amount of money for HBV. Sex, age, marital status, occupation, history of exposure to risky behavior, monthly income, awareness about HBV infection, level of education, perceived susceptibility, having children, adequate information concerning the vaccine, attitude, and knowledge level were among the determinants of people's willingness to pay for HBV (12, 15–24).

Taking its effect on the prevention of HBV infection, growing interest has been noted in determining its value from the consumers' perspective. As there is no current adult HBV vaccine program, estimation of demand for vaccination and associated factors are expected to be useful for the later initiation of the program. Moreover, the finding of this study will help to generate evidence to estimate the national-level market value of HBV vaccination. Besides, it provides insights to help the stakeholders to make decisions that serve the immense interest of the community. Finally, it will serve as a baseline for researchers for further investigation. Therefore, this study aimed to assess the willingness to pay for the hepatitis B virus vaccine and its associated factors among households in Bahir Dar City, Northwest Ethiopia.

Methods

Study design and setting

A community-based cross-sectional study was conducted on urban dwellers of Bahir Dar City from March 1 to 30, 2020. Bahir Dar is the capital city of Amhara National Regional State, located 565 KM northwest of Addis Ababa, the capital of Ethiopia. According to the Central Statistical Agency (CSA), the projected population size of the city is estimated to be more than 214,691 in 2017 (25). About 54% of males and 25% of females in Bahir Dar city can fully read and understand. Besides the average monthly income of the households in Bahir Dar city is 4,500 ETB (US$136). The city has six sub-cities and four satellite towns and has a total number of 80,252 households (HHs) (26). It has three public and four private hospitals. Moreover, there are ten health centers and more than 30 private clinics.

Population, sample size determination and sampling technique

The source population of this study was all urban household heads who live in Bahir Dar City whereas the study population was all urban household heads who live in the selected sub-cities and satellite towns. A total of 620 household heads who lived in the selected sub-cities and satellite towns for at least 6 months were included in the study.

Using the formula $n = (Z\alpha/2)^2\sigma^2/d^2$ and assuming US$73 as the mean amount cost that households willing to pay for HBV vaccine (11), 95% confidence level, 4% of the mean as a margin of error and $\sigma = 25$. After adding a 10% non-response rate and a design effect of 2, the final sample size became 620.

Multistage sampling followed by a systematic random sampling technique was used to select the required number of HHs after the proportional allocation was applied to select HHs in each kebele. Two sub-cities and one satellite town were chosen randomly among six sub-cities and four satellite towns, respectively. Then four kebeles from the two sub-cities and one satellite town were selected randomly using the lottery method (Figure 1). The final number of HHs was selected by systematic random sampling with a k value of 15. When the selected household is closed, again it will be checked for the second time, and if it is closed again the next household will be selected and the sampling pattern will keep on the second household.

Study variables

The dependent variable of this study was the household's willingness to pay for HBV, which is the household heads' willingness to pay for the HBV vaccine. It is measured in terms of proportion for their acceptance to take the vaccine (yes/no) and

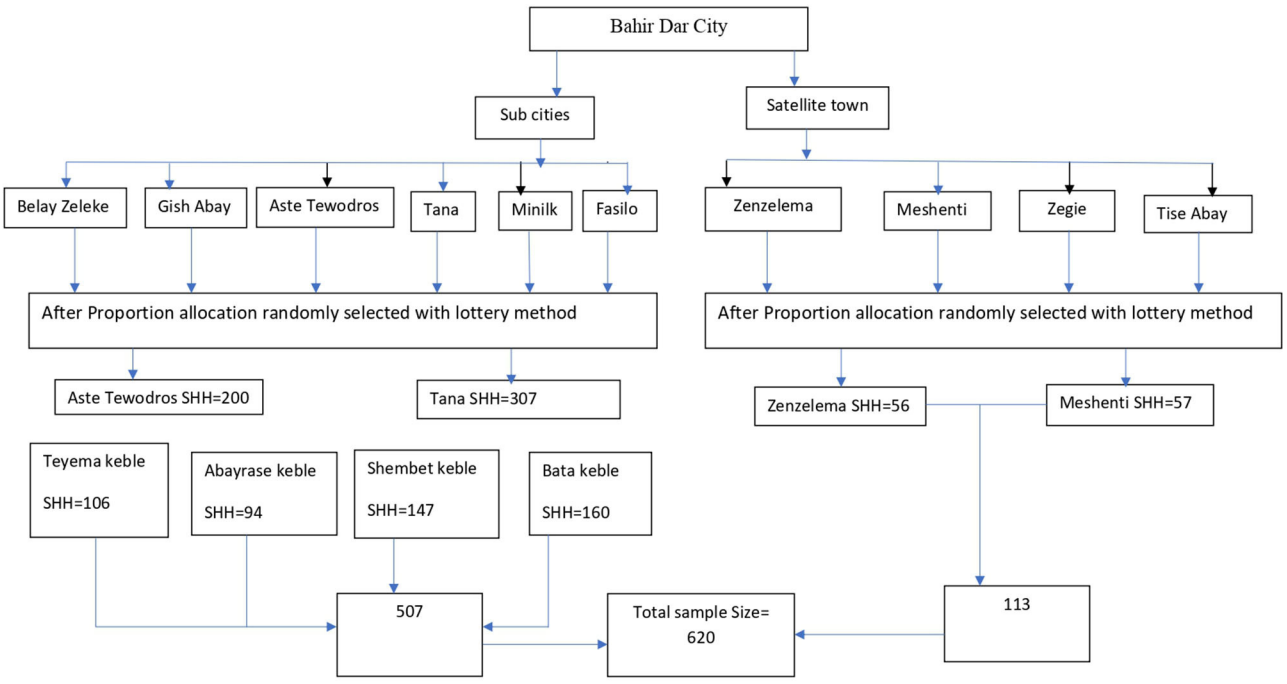

FIGURE 1
Flowchart for multistage sampling procedures of households in Bahir Dar City urban dwellers, northwest Ethiopia, 2020.

if yes, the average number that the HH head is willing to pay for the vaccine will be determined. Whereas, the independent variables were sociodemographic factors (age, sex, marital status, religion, ethnicity, education status, household family size, wealth status, and occupation), knowledge-related factors (knowledge toward HBV, attitude toward HBV, information about HBV infection and vaccine, source of information toward HBV), and HBV risk-related factors (family history of hepatitis B infection, multiple sexual partners, blood transfusion, and tattooing). Knowledge toward the HBV vaccine was measured with nine yes/no questions and those who answered 50% and above were judged as having good knowledge and the remained as poor knowledge. Attitude toward the HBV vaccine was measured by four questions with five Likert scales and those who answered 50% plus were judged as having a favorable attitude.

Eliciting the households toward a willingness to pay for the HBV vaccine

This study employed the contingent valuation method (CVM) to elicit the preference of households toward HBV using a double-bound dichotomous choice and bidding game approach. The CVM refers to a non-market valuation method used to estimate the value of goods placed by individuals by using stated preference information (27). In this study, double-bounded dichotomous choice: a simple yes/no question was used to assess the household's willingness to accept the HBV vaccine. The respondents were told about a hypothetical HBV vaccine with scientifically proven attributes and features in such a way that the respondents suppose that the HBV has 95% effectiveness and no side effects. If respondents accept to take the supposed HBV vaccine, they were asked if they were willing to pay 300 ETB to take the vaccine. If the respondent replied "*yes*" to this question, then they were asked if they were willing to pay a 100 ETB added value. After that, similar questions with the price of 100 ETB addition were asked until they refuse to pay. If the respondent answered "*no*" to the initial question (300 ETB), they were asked to pay the same question with a price of 200 ETB, then 100 ETB. A participant who refused to pay at the lowest bid (i.e., 100 ETB) was considered not willing to pay. Finally, the respondents had to answer an open-ended question about the maximum price they would be willing to pay (28).

Data collection tools and procedure

An interviewer-administered questionnaire was used to collect the data. The tool was developed after the literature review of the related studies (12, 14, 29). It was first prepared in English, then translated to Amharic (the local language), and was translated back to English to check for its consistency with a language expert. A pre-test was conducted among 31 (5% of households) in Gondar town, a city 173 KM far from Bahirdar, and necessary adjustments were made based on the pre-test results regarding questions clarification, adjustment and coherence. A day of training was given for seven data collectors who have a nursing diplomas and two supervisors with a public health degree. Each day after data collection, the principal investigator checked the collected data for its completeness and consistency.

Data processing and analysis

Cleaned data were entered into Epi Info version 7 and exported to Stata version 14 for further analysis. Descriptive statistics such as mean, standard deviation, frequency, and percentage were presented using tables. Tobit model analysis was used to identify factors that had an association with the mean price of HBV vaccine that households were willing to pay. It has been argued that when the nature of the data is continuous with censoring at zero, the most appropriate estimation technique is the limited dependent variable with the Tobit model (30). First, a bi-variable analysis was done to select factors for the final model. Variables at a *p*-value <0.2 were selected for the final Tobit model checking the assumptions of normality and homoscedasticity of error terms. Then *p*-value with a 95% confidence interval (CI) was reported. Independent factors with a *p*-value < 0.05 were considered statistically significant. Finally, the marginal effect that the expected WTP value conditional on being uncensored, E(WTP|WTP>0), was estimated (31). The exchange rate was US$1 = ETB 33.18 (32).

Ethical considerations

This study was conducted following the Declaration of Helsinki. An ethical clearance letter (Ref No/IPH/837/6/2020) was obtained from the Ethical Review Committee of the Institute of Public Health, University of Gondar. A permission letter from the Bahir Dar City Health Office. The purpose and importance of the study were explained in the consent form, including the right to withdraw from the study if they face any inconvenience. After assuring the confidentiality nature of responses, written informed consent was obtained from each participant.

Results

Socio-demographic characteristics of the respondents

A total of 608 participants were interviewed making the response rate 98.06%. The mean (±SD) age of the respondents was 37.67 (±12.88) years. The majority (66.12%) of the participants were female, and more than half (55.92%) were married. Out of the participants, (14.14%) had a family history of hepatitis B infection and the majority (43.26) of the participants had a medium wealth status (Table 1).

WTP for HBV vaccine

The majority (62.17%) of HHs were willing to pay for the HBV vaccine. The mean (SD) amount of money HHs willing to pay was ETB 174.24 (US$5.25) ± 145.44 (US$4.38); of participants who were willing to pay (9%) were agreed to pay more than ETB 300($9.04) (Table 2).

TABLE 1 Socio-demographic characteristics of the households in Bahir Dar City, northwest Ethiopia 2020 ($N = 608$).

Variables	Frequency	Percent
Age in a year: mean (SD)	37.67	12.88
Sex		
Male	206	33.88
Female	402	66.12
Ethnicity		
Amhara	590	97.04
Oromo	10	1.64
Tigray	8	1.32
Marital status		
Married	340	55.92
Divorced/Widowed	145	23.85
Single	123	20.23
Religion		
Orthodox	535	87.99
Muslim	51	8.39
Protestant	22	3.62
Educational status		
Unable to read and write	51	8.38
Primary	158	25.99
Secondary	169	27.80
Diploma	109	17.93
Degree above	121	19.90
Occupation		
Civil servant	162	26.64
Self-employers	155	25.49
Merchant	76	12.50
Unemployed	47	7.73
Housewife	149	24.51
Other	19	3.13
Wealth status		
Poor	152	25.00
Medium	263	43.26
Rich	193	31.74
Knowledge: mean (SD)	3.77	1.85
Poor	12	2.9
Good	401	97.1
Attitude: mean (SD)	15.61 (2.37)	
Unfavorable	60	9.9
Favorable	548	90.1
Household family size: mean (SD)	3.26 (1.49)	

(Continued)

TABLE 1 (Continued)

Variables	Frequency	Percent
Family history of hepatitis B infection		
Yes	86	14.14
No	522	85.86
Information about HBV infection and vaccine		
Yes	467	76.81
No	141	23.19
Source of information ($n = 467$)		
Television/radio	186	39.83
Health professional	104	22.27
Social media	90	19.27
Friend	78	16.70
Others	9	1.93
Multiple sexual partners		
Yes	85	13.98
No	523	86.02
Tattooing on body		
Yes	107	17.60
No	501	82.40
Blood transfused		
Yes	62	10.20
No	546	89.80

HBV, hepatitis B virus; SD, standard deviation.

TABLE 2 Amount of money HHs WTP for HBV vaccine in Bahir Dar City, northwest Ethiopia 2020 ($N = 608$).

Variable	Amount of money in ETB	Frequency (%)
WTP for HBV vaccine $N = 378$	10–150	219 (57.94)
	151–300	125 (33.06)
	301–500	21 (5.56)
	500 above	13 (3.44)

ETB, Ethiopian birr; HBV, hepatitis B virus; WTP, willingness to pay.

Factors associated with WTP for HBV vaccination

In multiple variable analyses sex, age, marital status, attitude, and knowledge were significantly associated with WTP for the HBV vaccine at a p-value of <0.05. Model assumptions of normality and homoscedasticity of error terms were checked and fulfilled. Male respondents were willing to pay higher than females ($P = 0.014$). The amount of money that participants willing to pay were decreased with age ($P < 0.001$); marital status: single participants ($P = 0.012$) and divorced/widowed ($P = 0.018$) were willing to pay a lower amount of money than married individuals, but a good attitude ($P = 0.017$) and knowledge ($P < 0.001$) toward HBV infection and vaccine were associated with higher amount of contribution (Table 3).

Moreover, the marginal effect of the variable, sex, revealed that male participants were willing to pay approximately ETB 34.37 (95% CI = 6.34, 62.40) higher than females. As the age of the household head increased by 1 year, the amount of money willing to pay for the HBV vaccine was reduced by ETB 3.36 (95%CI = −4.51, −2.20). Moreover, single and divorced/widowed were willing to pay ETB 40.13 (95%CI = −69.55, −10.71) and ETB 38.19 (95%CI = −68.29, −8.10) lower than married individuals, correspondingly. Whereas, as the score of attitude and knowledge toward HBV infection and vaccine increased by one the estimated mean of the marginal effects was 6.76 (95%CI = 1.24, 12.27) and 27.11 (95%CI = 18.52, 35.70), respectively (Table 4).

Discussion

The current study aimed to assess the willingness to pay for the HBV vaccine and its associated factors among households in Bahir Dar City. The findings showed that the majority of the participants were willing to pay for the HBV vaccine, and sex, age, marital status, knowledge, and attitude toward the HBV infection were significantly associated with WTP for the vaccine.

In this study, 62.0% of participants were willing to pay for the HBV vaccine. The percentage of participants who were willing to pay is comparable with the study conducted in Gondar, Ethiopia (14). This might be related to the information that the households have toward the infection and vaccine as in the current study 76.81% had information about HBV infection. According to another study (33), a comparable number (60.6%) of households were willing to pay for childhood malaria vaccines among caregivers of under-five children in Northwest Ethiopia (33). On the other hand, the proportion of households that are willing to pay for the HBV vaccine in this study is lower than the 83.4% proportion of households that are willing to pay for cervical cancer screening (34). The number of participants who were willing to pay for the HBV vaccine is higher than in the study conducted in Malaysia (11) where only 37.5% of the households were willing to pay for the HBV vaccine. However, it is lower than the study conducted in Vietnam (13), where 80.8% of the reproductive-age women were willing to pay for the HBV vaccine. The discrepancy might be attributable to the socioeconomic, study participants and sample size differences among the countries.

The study also revealed that the mean amount of money HHs willing to pay was ETB 174.24 (US$5.25) ± 145.44 ($4.38). This average amount of money that individuals were willing to pay was lower than the market price for adult HBV vaccination which ranges from US$65-US$134 (35) and the study conducted in Gondar, Ethiopia (14), where the average cost of HBV vaccine that the participants willing to pay were ETB 325.83 (US$14.39). This might be because participants in the previous study were healthcare professionals who have financial security as government employees than the population of this study that most of them are non-government employees. The amount of money that the households were willing to pay in this study was lower than the US$596 that the population group with the worst health status in Iran was willing to pay for health care (36).

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TABLE 3 Tobit regression analysis on factors influencing WTP for HBV vaccine in Bahir Dar City, northwest Ethiopia, 2020.

Variables	Coef	SE	*P*-value	95% CI
Sex				
Male	61.09	24.77	0.014	12.43, 109.74
Female				
Age	−6.14	1.09	0.000	−8.28, −3.99
Family history of HBV infection				
Yes	45.97	31.28	0.142	−15.45, 107.40
No				
Information about HBV				
Yes	−37.93	32.25	0.240	−101.27, 25.40
No				
Tattoo on the body				
Yes	−45.33	30.42	0.137	−105.06, 14.41
No				
Attitude	12.35	5.14	0.017	2.25, 22.44
Knowledge	49.55	8.04	0.000	33.76, 65.35
Marital status				
Single	−74.54	29.46	0.012	−132.40, −16.68
Divorced/widowed	−70.52	29.72	0.018	−128.88, −12.16
Married				
Education status				
Primary	−29.63	45.94	0.519	−119.86, 60.59
Secondary	−52.87	46.30	0.254	−143.81, 38.07
Diploma	−78.88	50.35	0.118	−177.76, 20.00
Degree and above	13.27	51.18	0.795	−87.24, 113.79
Unable to read and write				
Wealth status				
Poor	32.61	29.70	0.273	−25.72, 90.94
Medium	−47.71	26.60	0.073	−99.95, 4.52
Rich				
Constant	−31.44	102.63	0.759	−233.00, 170.11
Sigma	248.45	9.46		229.87, 267.03

CI, confidence interval; HBV, hepatitis B virus; SE, standard error.

TABLE 4 Marginal effects of factors influencing WTP for HBV vaccine.

Variables	dy/dx	SE	*P*-value	95% CI
Sex				
Male	34.37	14.30	0.016	6.34, 62.40
Female				
Age	−3.36	0.59	0.000	−4.51, −2.20
Family history of HBV infection				
Yes	26.35	18.72	0.159	−10.34, 63.04
No				
Information about HBV				
Yes	−21.36	18.69	0.253	−57.99, 15.27
No				
Tattoo on the body				
Yes	−23.73	15.21	0.119	−53.55, 6.08
No				
Attitude	6.76	2.81	0.016	1.24, 12.27
Knowledge	27.11	4.38	0.000	18.52, 35.70
Marital status				
Single	−40.13	15.01	0.008	−69.55, −10.71
Divorced/widowed	−38.19	15.36	0.013	−68.29, −8.10
Married				
Education status				
Primary	−17.11	27.12	0.528	−70.26, 36.04
Secondary	−29.55	26.99	0.274	−82.46, 23.36
Diploma	−42.45	28.37	0.135	−98.04, 13.15
Degree and above	8.11	31.07	0.794	−52.79, 69.01
Unable to read and write				
Wealth status				
Poor	19.32	17.70	0.275	−15.36, 54.01
Medium	−25.23	14.22	0.076	−53.11, 2.64
Rich				

CI, confidence interval; HBV, hepatitis B virus; SE, standard error.

The current study showed that marital status was statically associated with WTP: single and divorced/widowed were willing to pay ETB 40.13 and ETB 38.19 less than married individuals. The possible explanation for this might be that a widowed HH head might have a high economic burden than a married one as there is no someone to accompany in household expenditure. A study conducted elsewhere (37) also indicated that widowhood is associated with a higher risk of economic deprivation. Besides, consistent with other studies (38–40), male HH heads were willing to pay ETB 34.37 higher for the HBV vaccine than female HH heads. This could be due to males often predominantly dealing with big financial matters as compared to a female who usually deals with recurrent household expenditures in Ethiopian settings. On the other hand, there was also a statistically significant negative relationship between respondents' age and their WTP. As indicated by other scholars (38, 40, 41), as the age of the household head increased by 1 year, the amount of money that the household head was willing to pay for the HBV vaccine was reduced by ETB 3.36. This might be due to the low information toward the presence and benefits of the vaccine among adults as compared to the young population which may affect their willingness. This was also supported by the finding that the respondents' attitudes and knowledge about HBV infection and vaccines were positively associated with WTP. In this study as the knowledge and attitude scores of the respondents increased by one their willingness to

pay for the HBV vaccine will be increased by 6.76 and 27.11, respectively. The findings are consistent with other studies (29, 42–44).

Despite its strengths such as community-based study and employing the contingent valuation method, some limitations need to be considered in interpreting and concluding the results. First, in applying contingent valuation techniques, a possible source of bias might arise from the fact that respondents are not purchasing the vaccine in the practical context but rather hypothetically. Second, the cross-sectional analysis does not allow for the establishment of a causal relationship between the explained and explanatory variables. Finally, even if this finding is promising, it should be explored with another study design such as a discrete choice experiment and needs to cover large settings to conclude for the national level.

Conclusion

Overall, most of the Bahir Dar city households were willing to pay for the HBV vaccine. This showed households demanded the vaccine and the government need to put the HBV vaccine into the national public health strategy. Moreover, attitudes and knowledge were positively associated with willingness to pay. Therefore, strategies should be considered to enhance the household's attitude toward the HPV vaccine, and knowledge level and information about the vaccine should be provided through various modalities such as mass media and campaigns. However, age and female household heads were willing to pay less price for the HBV vaccine compared to their counterparts. As a result, policymakers should consider this difference in the ability to pay for the vaccine while developing a program to cover these population groups.

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 studies involving human participants were reviewed and approved by an ethical clearance letter (Ref No/IPH/837/6/2020) was obtained from the Ethical Review Committee of the Institute of Public Health, University of Gondar. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AA conceived the study, developed data collection tools, performed the analysis and interpretation of data, and obtained research funding. AM, CT, TA, and AYA participated in the development of the study proposal, analysis, and interpretation. AA, CT, and TA drafted the original manuscript. AYA revised the manuscript. All authors have seen and approved the final version of the manuscript for submission.

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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.

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Patients, healthcare providers, and general population preferences for hemodialysis vascular access: a discrete choice experiment

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Background: A patient-centered dialysis treatment option requires an understanding of patient preferences for alternative vascular accesses and nephrologists often face difficulties when recommending vascular access to end-stage kidney disease (ESKD) patients. We aimed to quantify the relative importance of various vascular access characteristics to patients, healthcare providers and general population, and how they affect acceptability for patients and healthcare providers.

Methods: In a discrete choice experiment, patients with maintenance hemodialysis (MHD), healthcare providers, and individuals from the general population were invited to respond to a series of hypothetical vascular access scenarios that differed in five attributes: cumulative patency, infection rate, thrombosis rate, cost, and time to maturation. We estimated the respondents' preference heterogeneity and relative importance of the attributes with a mixed logit model (MXL) and predicted the willingness to pay (WTP) of respondents via a multinomial logit model (MNL).

Results: Healthcare providers (n = 316) and the general population (n = 268) exhibited a favorable inclination toward longer cumulative patency, lower access infection rate and lower access thrombosis rate. In contrast, the patients (n = 253) showed a preference for a 3-year cumulative patency, 8% access infection rate, 35% access thrombosis rate and 1.5 access maturity time, with only the 3-year cumulative patency reaching statistical significance. Among the three respondent groups, the general population found cumulative patency less important than healthcare providers and patients did. Patients demonstrated the highest WTP for cumulative patency, indicating a willingness to pay an extra RMB$24,720(US$3,708) for each additional year of patency time.

Conclusion: Patients and healthcare providers had a strong preference for vascular access with superior patency. While the general population preferred vascular access with lower thrombosis rates. These results indicate that most

patients prefer autogenous arteriovenous fistula (AVF) as an appropriate choice for vascular access due to its superior patency and lower complications than other vascular access types.

KEYWORDS

patients, healthcare providers, general population, hemodialysis, vascular access, discrete choice experiment, preference

Introduction

Chronic kidney disease (CKD) comprises one of the main causes of global morbidity and mortality (1). In recent years, the aging population and the growing incidence of diseases, such as diabetes and hypertension, have led to an increase in CKD incidence by years (2). The global prevalence rate of CKD in the general population has reached 14.3% (3). In China, the prevalence of CKD in patients over 18 years old was 8.2, and 1.8% of patients progress to end-stage kidney disease (ESKD) each year (4). Thus, renal replacement therapy is needed, mainly hemodialysis (HD), peritoneal dialysis (PD), or kidney transplantation (5). Maintenance hemodialysis (MHD) is a treatment to prolong the life of ESKD patients through regular hemodialysis (6). According to the Chinese National Renal Data System (CNRDS), there were approximately 0.63 million HD patients in China in 2019, and the high cost of treatment imposed a huge financial burden on the families of patients and society (2). During the hemodialysis, vascular access is used to transfer blood between the body and the dialysis machine. Morbidity related to vascular access is the leading cause of hospitalization for patients with MHD, the development of complications is the main reason why patients become disillusioned with hemodialysis therapy (7).

Among permanent hemodialysis vascular access, autogenous arteriovenous fistula (AVF), arteriovenous graft (AVG), and tunneled-cuffed catheter (TCC) are widely used, with various discrepancies in dimensions of cumulative patency, infection rate, cost, etc. Previous practice guidelines and initiatives have identified AVF as the best option associated with its better patency and lower complications than other vascular access types (8, 9). However, the strengths of AVF may be overestimated, as a high proportion of AVFs fail to mature successfully before it can be used, and interventions are commonly needed to promote maturation (10–14). Applying temporary catheters during AVF non-maturation time increases the risk of patient exposure to infection, leading to bacteremia and thus endangering the patient's life (15, 16). AVG has been proven to be a suitable alternative of AVF creation for patients due to poor vascular conditions, but this access type's long-term failure and intervention rates are higher than those of AVF (17, 18). Accordingly, nephrologists often face difficulties when making dialysis-related decisions for ESKD patients regarding life expectancy, patients' anatomy, and the associated complications with vascular access types. In clinical practice, doctors and patients have different main considerations when choosing vascular access for hemodialysis. Specifically, clinicians are concerned about the vascular access type and its associated complications. However, patients may have far differing concerns (19, 20), such as the pain and fear of needle and physical disfigurement from an AVF (7), which makes it necessary to understand the rationale behind both options to facilitate transparent shared decision-making, and may further help doctors understand the idiosyncrasies and demands of patients and their families, and choose more appropriate vascular access for patients, which is of vital importance for reducing potential doctor-patient conflicts and general improved patient satisfaction. In this study, the preferences of the general population were used as a reference. In addition, the preferences of the general population can be surveyed as a reference to better understand patient preferences.

Discrete choice experiments (DCEs) have been widely used to assess healthcare priorities, mainly for selecting therapeutic drugs and protocols (21). This approach simulates real-world decisions by simultaneously considering multiple characteristics, thus determining the strength of preferences, including CKD patients regarding organ donation and end-of-life care (22). To our knowledge, no published studies have been conducted on the use of DCE in the selection of vascular access for hemodialysis. Therefore, we aimed to use DCE to simulate clinical conditions to determine the relative influence of various characteristics on nephrologists' recommendations and to explore which factors patients and their families are most sensitive to hemodialysis vascular access, and to quantify the preferences of patients when seeking medical treatments, and to further provide a guideline for doctors to make an appropriate hemodialysis vascular access plan for each patient.

Methods

Attributes and levels design

Discrete choice experiments (DCEs) are experimental designs that typically be used to quantify and weigh the relative importance that patients place on various treatment attributes and outcomes. Discrete choice experiments are based on the multi-attribute utility theory in economics (23), which assumes that commodities consist of a series of attributes and levels, such as treatment methods and expenses. In this experiment, respondents were presented with a sequence of questions and asked to select a preferred option from a set of hypothetical treatment options. These dialysis treatment protocols vary by treatment attributes and levels. The implementation of DCE

Abbreviations: ESKD, end-stage kidney disease; DCE, discrete choice experiment; CKD, chronic kidney disease; HD, hemodialysis; PD, peritoneal dialysis; MHD, maintenance hemodialysis; CNRDS, Chinese National Renal Data System; AVF, autogenous arteriovenous fistula; AVG, arteriovenous graft; TCC, tunneled-cuffed catheter; CLOGIT, conditional logit model; WTP, Willingness to pay.

TABLE 1 Attributes and levels in the DCE.

Attributes	Definition	Levels of Attributes (regression coding)
Cumulative patency	Time from vascular access creation or insertion (central venous catheter) to permanent failure	1 year
		3 years
		5 years
Access infection rate	The occurrence of any infection involving the vascular access	1%
		8%
		15%
Access thrombosis rate	The occurrence of thrombotic occlusion of vascular access	20%
		35%
		50%
Time to maturation	The time from access placement to its successful use for dialysis	0 month
		1.5 months
		3 months
Access creation cost	The total hospitalization cost, including operation fee, physician fee, cost of investigations, cost of supplies and interim dialysis sessions	¥ 10,000
		¥ 25,000
		¥ 40,000

¥, Chinese yuan (1 ¥ ≈ 0.15US dollars).

in this study is in accordance with the ISPOR (International Society for Pharmacoeconomics and Outcomes Research) report (24, 25).

The attributes and the levels were, respectively, determined through a targeted literature review and discussion with experts. We compiled a list of potential attributes from previous studies in the field of hemodialysis over the past decade that included published hemodialysis DCE studies (22, 26, 27), clinical relevant articles (6, 12, 14, 16, 17, 28–32), observational studies (20, 33, 34), systematic review (7). A focus group meeting was then held at Jinan University's Affiliated Hospital to further determine the attribute list, which involved two attending nephrologists with 7 and 8 years of clinical experience, respectively, and three patients with hemodialysis. Based on their preferences, we ranked the attributes from most important to least important. To reduce the cognitive burden on the subjects, we selected the five most relevant attributes from the ranked results (Table 1), because attributes ranked sixth or more were considered less important by experts and patients. Five attributes were finally determined in DCE, specifically: cumulative patency, infection rate, thrombosis rate, time to maturation, and cost. The minimum and maximum levels of the five attributes were determined based on literature review (28, 29, 31, 32) of clinical data resources, characteristics of vascular access, and experts' opinions. The intermediate level was determined by calculating the median value between the minimum and maximum levels. Each attribute has three corresponding levels. Details of the identified attributes and levels are shown in Table 1.

Participants

At the hemodialysis center of Jinan University Affiliated Hospital, Guangzhou, China, patients were recruited by face-to-face contact. All eligible patients should be at least age 18 years, cognitively and verbally intact, and willing to participate. Patients who were on temporary hemodialysis or had mental disorders or hearing or speaking disabilities were excluded. In addition, we recruited nephrology healthcare providers and general population from the national network by snowball sampling (sending emails and WeChat Moments). The eligibility criteria for participation include nephrology healthcare providers who were: (1) at least 18 years of age; (2) engaged in the field of nephrology; (3) capable of independent thinking, listening, speaking, reading and writing; and (4) willing to participate; and included the general population aged 18 years or older, working in non-medical occupations, and not suffering from any kidney disease. Data collection was conducted from December 2020 to May 2021.

Ethical approval and consent to participate

This study has been ethically approved by the Institutional Review Board (IRB) of Jinan University (JNUKY-2020-006). All participants were informed about the study's objective, scope, and research design, and they consented to participate in the study.

Questionnaire and DCE design

The questionnaire consists of two sections. The first section is sociodemographic questions on participants, including age, sex, education background, family monthly income, and medical insurance reimbursement rate. The second part is a set of 12 DCE questions designed by Sawtooth Software (version 9.8.1) using an orthogonal experimental design in a partial factorial design, which is an efficient, fast and economical experimental design method. This study used software for orthogonal experimental design in the experimental design session to achieve the three principles of DCE design: Orthogonality, Level balance, Minimal overlap. In a DCE, participants were provided with a dialysis regimen with a combination of different attribute levels in the form of a questionnaire, also known as choice tasks, and each choice task contained three alternatives of hemodialysis treatment: 'Dialysis A,' 'Dialysis B,' and 'Neither.' For each question, participants were asked to choose one of two alternatives that they thought was better by comparing the attributes and levels. Participants were repeatedly asked which alternative they preferred most. Therefore, the DCEs provided information about the relative importance of each attribute and its level. To better control the quality of data, the DCE included a fixed choice question, which is used to ensure that participants understood the questionnaire and made careful choices, controlling the quality of the questionnaire. An example of a DCE question is shown in Figure 1.

Since many patients were over 55 years old with blurred vision, we conducted a discrete choice experiment in the form of face-to-face interviews for patients. Before the survey started, we informed them in detail about the purpose of the study and the meaning of each attribute and level. For healthcare providers with medical backgrounds, we used an online survey to conduct DCE. The purpose of the study and the explanation of each attribute was presented on the first page of the questionnaire.

	Dialysis A	Dialysis B	Neither
Cumulative patency	3 year	5 year	
Access infection rate	1%	7%	
Access thrombosis rate	35%	20%	
Time to maturation	0 month	3month	
Access creation cost	￥40,000	￥10,000	
I would choose:	○	○	○

FIGURE 1
An example discrete choice experiment question.

Statistical analysis

Participants' demographic information and socioeconomic status information, and participants' DCE choices were analyzed three different types of population separately in STATA BE 18 (Stata Corp LLC, TX, United States) using the mixed logit model (MXL). Specifically, the coefficients were calculated to quantify respondents' relative utility when choosing a specific level within each attribute compared to the reference level. Higher level of the coefficient indicates the specific attribute level was preferred. The core of MXL is the random utility principle (35), and the utility formula that has been applied to estimate our MXL is shown as follows:

$$U_n = V_n + \varepsilon_n = \alpha_1 + \beta_1 X_{1n} + \beta_2 X_{2n} + \ldots + \beta_m X_{mni} + \varepsilon_n$$

where U_n is the total utility of questionnaire respondents, the deterministic component V_n is an observable function concerning m levels, the β_n of X_n represents the random utility or the coefficient of every attribute' levels that bring to the individual relative to the reference level, and ε_n means the fixed utility in our model. The attributes except cost were dummy-coded, and the cost was included as a continuous variable for further analysis. In addition, we calculated the relative importance of attributes by calculating the proportion of one specific attribute to all attributes. We calculated the relative importance using the coefficient difference among a specific attribute, divided by the sum of coefficient differences among each attribute. For instance, in the specific attribute *x*, we use the level with the highest utility (L_H) to minus the level with the lowest utility (L_L), and then we use this difference $L_H - L_L$ to be divided by the sum such differences among all attributes, that is $\sum_{i=1}^{5}(L_H - L_L)_i$ .We also calculated the willingness to pay (WTP) of respondents via the multinomial logit model (MNL) by using the continuous variable cost. As an intuitive tool to quantify respondents' preference for various attribute levels of vascular accesses in the monetary term, WTP is often more intuitive for policymakers and manufacturers.

We have also performed the interaction analysis to investigate whether the demographic information of the participants (especially the general population) interacted with the utility that was brought from the attributes' levels in the DCE choice tasks. Specifically, we conducted the interaction analysis between age and other attributes, sex and other attributes, education and other attributes, income and other attributes, insurance and other attributes. We also conducted a sub-group analysis based on the interaction terms that were statistically significant in the interaction analysis.

After the interaction analysis and sub-group analysis, we constructed some hypothetical hemodialysis vascular access profiles to investigate participants' uptake rate when the attributes' levels were changed compared with the base case profile, which was composed of the reference levels of all attributes.

Results

Respondents' demographic information

After excluding incomplete survey data and data quality controlling by identifying the responses of fixed task choice scenarios, a total of 837 respondents have been included in our study, inclusive of 253 MHD patients, 316 healthcare providers, and the remaining 268 respondents categorized as the general population. Their social-demographic characteristics have been summarized in Table 2. Among those patients, participants had a mean age of 62.5 ± 15.7 years, 110 (44.89%) of them were female, and only 16.40% achieved academic degrees higher than a bachelor's degree. While among those healthcare providers, 199 (62.97%) of them were female, and the majority (99.05%) have achieved academic degrees higher than bachelor's degrees. Among the general population, 166 (61.94%) were female, and 240 (89.55%) of them have achieved academic degrees higher than bachelor's degrees.

Model estimates

The model estimates of the MXL model have been shown in Figure 2A. In the healthcare providers and general population groups, respondents always preferred longer cumulative patency, lower access infection rate and lower access thrombosis rate, and respondents' preference for cumulative patency and access thrombosis rate were sensitive when changing from one level to another level. While in the patients group, 3-year cumulative patency, 8% access infection rate, 35% access thrombosis rate and 1.5 access maturity time were preferred, with only 3-year cumulative patency reaching statistical significance. Respondents in three groups were not sensitive to the attribute access maturity time. Notably, the opt-out option in healthcare providers and the general population group were characterized as a negative sign, indicating negative part-worth utility brought to doctors and the general population (Supplementary Material).

Relative attribute importance

After rescaling and calculation, in healthcare providers and patients group, cumulative patency was the dominant attribute in respondents' preference (58.0 and 57.2% respectively), while access thrombosis rate (41.0%) was cared most in general population. Patients care least about access infection rate (10.9%) while access

TABLE 2 Participants' demographic information.

Variable	MHD patients (n = 253)	Healthcare providers (n = 316)	General population (n = 268)
Age, mean (*SD*)	62.5 ± 15.7	36.5 ± 8.1	32.2 ± 10.8
Gender, %			
Male	139(54.9%)	117(37.0%)	102(38.1%)
Female	114(45.1%)	199(63.0%)	166(61.9%)
Education level, %			
Less than high school	146(57.7%)	0	8(3.0%)
High school	66(26.1%)	3(1.0%)	20(7.5%)
Any college	41(16.2%)	313(99.0%)	240(89.5%)
Monthly family income, %			
CN¥ <5,000	93(36.7%)	21(6.6%)	61(22.8%)
CN¥ 5,000–10,000	86(34.0%)	133(42.1%)	95(35.4%)
CN¥ 10,000–15,000	46(18.2%)	84(26.6%)	53(19.8%)
CN¥ >15,000	28(11.1%)	78(24.7%)	59(22.0%)
Payment, %			
Fully reimbursed	22(8.7%)	4(1.3%)	9(3.3%)
Urban Employee Medical Insurance	117(46.3%)	296(93.7%)	113(42.2%)
Urban Residents Medical Insurance	79(31.2%)	12(3.8%)	98(36.6%)
Off-site Medical Insurance	29(11.4%)	2(0.6%)	18(6.7%)
Paying completely out of pocket	6(2.4%)	2(0.6%)	30(11.2%)

maturity time was cared least in doctors (5.8%) and general population (0.2%). The relative importance of attributes have been shown in Figure 2B.

Willingness to pay

Patients, healthcare providers and the general population had a strong preference for the cumulative patency within 5 years. Patients' WTP for cumulative patency was the highest among the three groups of respondents, which was paying RMB¥ 24,720 (US$ 3,708) for each additional year of patency time. Healthcare providers and the general population were willing to pay RMB¥ 15,000 (US$ 2,250) and RMB¥ 10,600 (US$ 1,590) for a 1-year increase in patency time, respectively. Patients and general population had similar WTP for the infection and the thrombosis rates. Specifically, patients were willing to pay RMB¥ 1,200 (US$ 180) to reduce the 1% extra infection rate and up to RMB¥ 2,420 (US$ 363) to reduce 1% of the thrombosis rate. General population were willing to pay RMB¥ 3,730 (US$ 559.5) to reduce the 1% infection rate and up to RMB¥ 2,350 (US$ 352.5) to reduce 1% of the thrombosis rate. Both patients and general population were less sensitive to the wait time for maturation, patients were not willing to pay for a 1-month decrease in time to maturation, and general population were only willing to pay RMB¥ 143 (US$ 21) for a 1-month reduction in time to maturation. However, compared with infection and thrombosis rates, healthcare providers had higher WTP to shorten the maturation time, which was paying RMB¥ 2,900 (US$ 435) for a 1-month decrease in time to maturation. Healthcare providers were less sensitive to the infection and thrombosis rates, and they were willing to pay RMB¥ 1,050 (US$ 157.5) to reduce the infection rate by 1% and RMB¥ 1,150 (US$ 172.5) to reduce the thrombosis rate by 1% (Table 3).

Interaction analysis and sub-group analysis

In the interaction analysis in the general population, we found that, among the participants' demographic information, only education level and sex were correlated with our attributes, especially the attribute access thrombosis rate attribute and 20% level (Supplementary Table S1). The negative sign of the interaction term of education with access thrombosis rate of 20% indicated that compared with below bachelor's degree participants, those with a bachelor's degree or above have disutility when choosing access with a 20% thrombosis rate.

The sub-group analysis based on the educational level has been presented in Supplementary Table S2. Specifically, we found a statistically significant decrease in utility when choosing access thrombosis rate of 20% for participants with higher educational levels compared with those of lower educational levels. In addition, participants with higher educational levels have similar acceptability for access infection rates of 1 and 8%.

Uptake rate analysis results

We have presented the uptake rate analysis results in Table 4. In terms of the general population, 79.2% (SE: 0.026) would support the improvement of cumulative patency from 1 year to 3 years, decrease

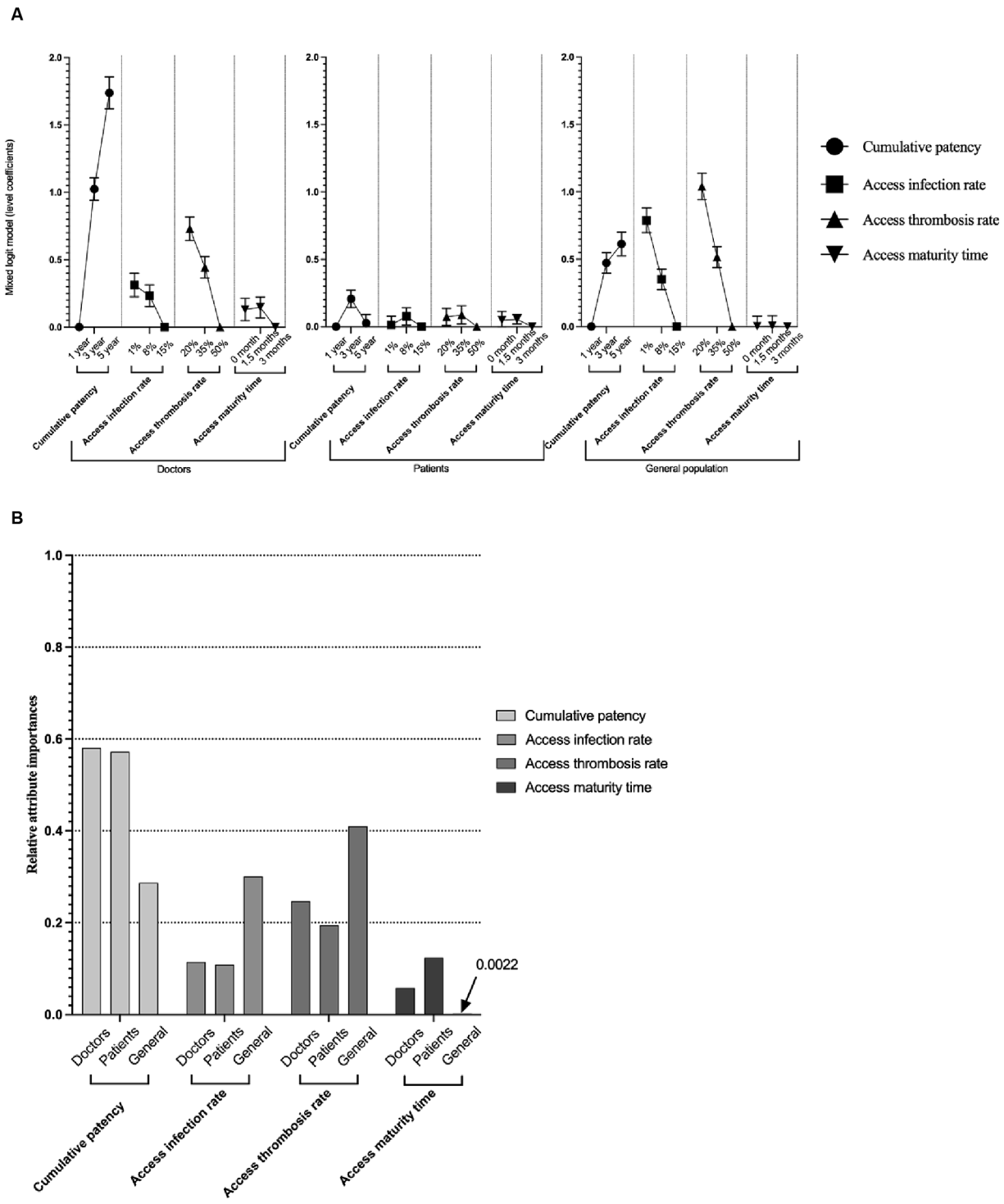

FIGURE 2
Model estimates of mixed logit model and relative importance of attributes. Panel **(A)** shows the model estimation (coefficient and standard error) of the mixed logit model. All the coefficients in the figure are larger or equal to 0. The order of the Panel **(A)** is the preference of doctors, patients, and the general population. Error bars indicate the standard error of the coefficients, and dots with no error bars mean the reference level of that attribute. Panel **(B)** shows the relative importance of attributes among doctors, patients, and the general population. The maximum value was rescaled to 1.

access infection rate from 15 to 8%, decrease time to maturation to 15 months and decrease the access thrombosis rate to 35%. And 92.0% (SE: 0.014) will prefer the improvement of cumulative patency to 5 years, decreasing access infection rate from 15 to 1%. decrease time to maturation to 0 months and decrease the access thrombosis rate to 20%.

In terms of doctors, 92.8% (SE: 0.013) will support the improvement of cumulative patency from 1 year to 5, decrease the

TABLE 3 Willingness to pay of three types of respondents.

Attribute	WTP of patients (*N* = 253)		WTP of Healthcare providers (*N* = 316)		WTP of the general population (*N* = 268)	
	RMB (¥)	USD ($)	RMB (¥)	USD ($)	RMB (¥)	USD ($)
Cumulative patency (per 1-year increase)	24,720	3,708	15,000	2,250	10,600	1,590
Access infection rate (per 1% decrease)	1,200	180	1,050	157.5	3,730	559.5
Access thrombosis rate (per 1% decrease)	2,420	363	1,150	172.5	2,350	352.5
Time to maturation (per 1-month decrease)	−780	−117	2,900	435	140	21
Access creation cost	Ref	Ref	Ref	Ref	Ref	Ref

WTP, willingness to pay. ¥1RMB = $ 0.15USD.

access infection rate from 15 to 8%, decrease the access thrombosis rate to 35% and decrease time to maturation to 15 months. Also, 94.8% (SE: 0.010) will support the improvement of cumulative patency from 1 year to 5, decrease the access infection rate from 15 to 1%, decrease the access thrombosis rate to 20% and decrease time to maturation to 0 months.

In terms of patients, 61.9% (SE: 0.031) will support the improvement of cumulative patency from 1 year to 5, decrease the access infection rate from 15 to 8%, decrease the access thrombosis rate to 35% and decrease time to maturation to 15 months.

Discussion

The National Kidney Foundation Dialysis Outcomes Quality Initiative clinical practice guidelines published in 2019 suggest that patient preference should be one of the main considerations in selecting the type of vascular access for hemodialysis (36). Patient preference for different types of vascular access directly affects patient quality of life and the achievement of life goals. Therefore, it is necessary to consider patient preference for different types of vascular access to optimize decisions on vascular access selection, thereby ultimately improving patient treatment satisfaction and prognosis. Vascular access outcomes are key considerations in selecting the best vascular access for an HD patient, including cumulative access patency, type-specific vascular access outcomes, and associated costs (37). This is the first study assessing the preference of MHD patients and nephrology healthcare providers for various hemodialysis vascular access choices focusing on aspects from various attributes of vascular access outcomes. Our results show that MHD patients and nephrology healthcare providers prefer vascular access with longer cumulative patency, which was a prominent attribute in decision-making. Thrombosis rate and infectious rate are also import factors influencing healthcare providers and general population's decisions. However, respondents were not sensitive to access maturation time. The preference coincides with the characteristics of autologous arteriovenous fistulas (AVF), which have higher long-term patency rates, lower thrombosis rates, and lower costs compared with AVG and TCC. Consequently, it is implied that AVF would be the preferred type of vascular access for MHD patients and health providers based on revealed preference for vascular access attributes.

Cumulative patency is of primary importance for individual patients and healthcare providers, whereas the general population viewed thrombosis events as the most important attribute. This is understandable because, in the long-term clinical treatment process, patients accumulate a lot of knowledge about vascular access since superior patency of vascular access is the pre-conditions and key to ensuring effective hemodialysis treatment. At the same time, the general population has inadequate knowledge about hemodialysis. However, regarding cumulative patency, the general population seems to show a more similar pattern (of the coefficient and *p*-value) to the healthcare providers (of the coefficient and p-value), with preference increasing as the duration of cumulative patency increases. This may make sense because the general population is more well-educated in our sample (Table 2). Most patients are in the "less than high school" category.

In addition, the thrombosis rates also play a significant role in decision-making. Thrombosis often leads to additional surgical interventions to maintain the patency and use of vascular access. These frequent interventions can lead to reductions in patient quality (e.g., discomfort/pain, inconvenience) and increase health care expenditures and, more seriously, most hemodialysis vascular access dysfunction (in both AVF and AVG) is due to stenosis and thrombosis, secondary to venous neointimal hyperplasia (38, 39). For health providers and the general population, infection rates are less important in decision-making than thrombosis rates, possibly because thrombosis is more likely to develop than infections during long-term dialysis (40). In a study focused on investigating patient-reported viewpoints of access-related problems, 97% of patients did not consider infection a major concern (33). Another study suggests that this is because patients believe that the infection is not life-threatening and that even if the catheter is infected, it can be resolved by replacing it with another catheter (34).

The previous literature has reported that income has a significant impact on the choice of initial vascular access in patients with ESKD, which was consistent with our findings. According to a prospective cohort study, total costs of MHD patients are largely determined by treatment requirements rather than by individual characteristics of patients, such as age, sex, social class, diabetes mellitus, hypertension, or time on dialysis (30). It is interesting to note that in our study, the importance of cost consideration for nephrology healthcare providers is also relative high compared with MHD patients. As we learned from the qualitative interviews with nephrologists, the limitations on the total hospitalization cost of each patient in medical insurance policy have resulted in doctors' attempts to control the cost of treatment. Therefore, their medical decisions are often influenced by costs. The results of the general population were presented as reference. The significance of including the general population in our study is to compare whether they differ from patients in their selection

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TABLE 4 Estimated uptake rate of hypothetical profiles compared with based case scenario.

General population	Profiles of access	Base profile	Profile 1	Profile 2	Profile 3	Profile 4	Profile 5	Profile 6
	Cumulative patency	1 year	3 years	3 years	3 years	3 years	5 years	5 years
	Access infection rate	15%	8%	1%	8%	8%	8%	1%
	Access thrombosis rate	50%	35%	35%	20%	35%	35%	20%
	Time to maturation	30 months	15 months	15 months	15 months	0 month	15 months	0 month
	Estimated uptake of hypothetical profile, No. (SE)	NA	0.792 (0.026)	0.855 (0.021)	0.866 (0.020)	0.792 (0.026)	0.815 (0.025)	0.920 (0.14)

Doctors	Profiles of access	Base profile	Profile 1	Profile 2	Profile 3	Profile 4	Profile 5	Profile 6
	Cumulative patency	1 year	3 years	3 years	3 years	3 years	5 years	5 years
	Access infection rate	15%	8%	1%	8%	8%	8%	1%
	Access thrombosis rate	50%	35%	35%	20%	35%	35%	20%
	Time to maturation	30 months	15 months	15 months	15 months	0 month	15 months	0 month
	Estimated uptake of hypothetical profile, No. (SE)	NA	0.864 (0.020)	0.872 (0.019)	0.894 (0.017)	0.862 (0.020)	0.928 (0.013)	0.948 (0.010)

Patients	Profiles of access	Base profile	Profile 1	Profile 2	Profile 3	Profile 4	Profile 5	Profile 6
	Cumulative patency	1 year	3 years	3 years	3 years	3 years	5 years	5 years
	Access infection rate	15%	8%	1%	8%	8%	8%	1%
	Access thrombosis rate	50%	35%	35%	20%	35%	35%	20%
	Time to maturation	30 months	15 months	15 months	15 months	0 month	15 months	0 month
	Estimated uptake of hypothetical profile, No. (SE)	NA	0.604 (0.031)	0.590 (0.032)	0.601 (0.031)	0.603 (0.031)	0.619 (0.031)	0.599 (0.031)

preferences. Compared with doctors and patients, the rate of thrombosis, the rate of infection are more important than the cumulative patency during the decision-making of the general population. This discrepancy may be due to a lack of real-world experience of dialysis. This means that patients newly starting hemodialysis need to be educated about dialysis to increase patient compliance.

Strengths and weaknesses

While previous cross-sectional studies investigated vascular access preferences, focusing on attributes of patient characteristics. The factors underlying patient's decisions varied across the countries and races, but consistently important factors were patients' previous experience with different vascular access, their health status, their desired quality of life, as well as life goals (37). To date, there has been a lack of research comparing preferences for hemodialysis vascular access. This study is the first to use a discrete choice experiment to analyze the importance of vascular access characteristics, which help to provide information for the decision-making process in clinical pathway selection. Our study also provides new insights into how MHD patients and nephrologists make trade-offs between these attributes when making dialysis choices. The US Renal Physicians Association advocates shared decision-making around the initiation of renal replacement therapy (41), which has been described as a process in which physicians and patients agree on a treatment strategy based on a shared understanding of the treatment goals and the risks as well as benefits of the type of treatment chosen (42).

Our results of HD patients were derived from a single health system and not inclusive of the overall picture of HD patients. The study has a limitation in terms of sample representativeness, which could result in selection bias. In terms of the number of attributes, we only included five attributes to describe the characteristics of vascular access to reduce the complexity of the questionnaire and the burden of a questionnaire for respondents. However, other characteristics that will also affect people's choice, such as patients' previous experience with different vascular access, their health status, their desired quality of life, and life goals, were not included. Therefore, the advantage of arteriovenous graft (AVG) over tunneled-cuffed catheter (TCC) is not clear due to the limited attributes included in this study. Moreover, we designed the DCE task choices in this study to be unlabeled DCE, since the study of de Bekker-Grob et al. (43) has discussed that although the label of DCE plays an essential role in an individual's choice, and gives an more realistic feeling, it reduces the attention respondents give to the attributes. While we want respondents to focus more on attributes instead of appearance, etc. However, this DCE does not factor in the influence of the label; therefore, it may result in omitting such

influence. Future research may be required to include such label effect in the consideration.

Implications

These findings emphasize the need for further systematic and longitudinal studies into evaluating vascular access's cumulative patency and thromboembolic events. The results also indicate that both physicians and patients are most concerned about cumulative patency time, but physicians are more concerned about infection and thrombosis rates than patients. Physicians should consider the patient's concerns and take the patient's opinion into account when making decisions. Future research should already investigate other factors that may influence patient decision making and incorporate theory to explore the reasons for differences in treatment preferences between patients and health providers.

Conclusion

Our study showed that when treating MHD patients, nephrology healthcare providers had a strong preference for access with superior patency, lower thrombosis rate, and lower cost. At the same time, the general population preferred access with a lower thrombosis rate, lower infection rate, and longer patency. According to these results, most patients prefer AVF as an appropriate choice for vascular access if vascular conditions and cardiac function allow it. With the demographic characteristics of the hemodialysis population changing in recent years, it is necessary to consider patients' preferences for different vascular access to optimize dialysis decisions to ultimately improve patients' treatment satisfaction and prognosis.

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 authors.

Ethics statement

The studies involving humans were approved by the Institutional Review Board (IRB) review of Jinan University (JNUKY-2020-006). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

T-SW, QC, and BH contributed equally to the study design, data collection and analysis, manuscript drafting, and formatting. TaL, JY, YG, and YH contributed to the data analysis and manuscript drafting. TaL, QZ, ZT, TiL, JL, and LY contributed to study design and data collection. CZ, JH, and W-KM contributed to the manuscript reviewing and supervision of the study. All authors contributed to the article and approved the submitted version.

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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/fpubh.2024.1047769/full#supplementary-material

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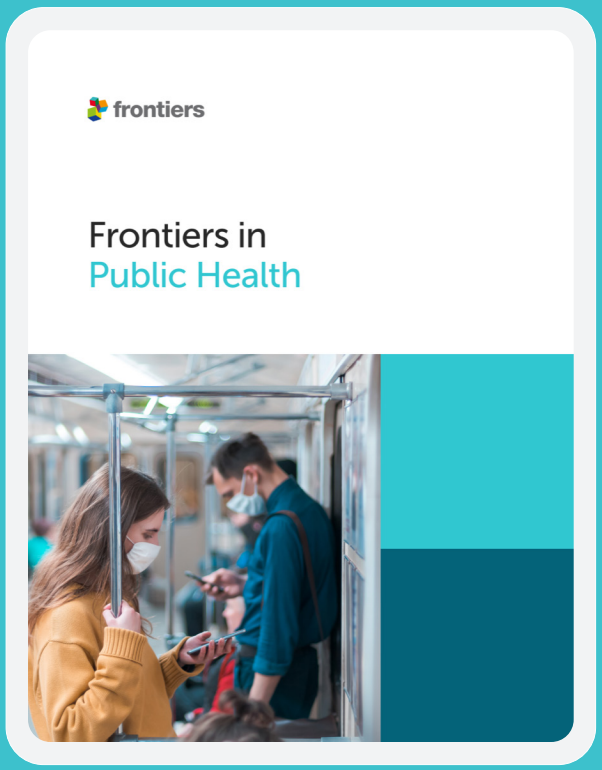

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