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Exercise and chronic disease

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Exercise and chronic disease

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Editorial: Exercise and chronic disease

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Editorial on the Research Topic
Exercise and chronic disease

With the development of medical science and technology, human longevity has been extended and advanced medical treatments come to be true. Human beings are happy to welcome the prolonged lifespan, while the bad news is the extended duration of bedtime, which requires special care in daily life and in sick time because of illness or chronic disease. The fast pace of life and the vast pressure of work not only harm the health status of young, middle-aged and older adults but also deteriorate the life quality of adolescents and children. Of all the health-related risk factors, a deficiency in daily physical activity is always the crucial element of degraded life capacity (1). In other words, there are significant, solid and positive associations between regular exercise behaviors and the health level of human beings. It has been well-evidenced that exercise can prevent various diseases and improve physical and mental health (2). As a long-lasting condition that can be controlled but not cured, chronic disease is no longer taken as a single problematic dimension but the result of multiple body systems acting together and complicated mechanisms interacting with each other. Besides, the coverage of chronic concepts has extended from heart disease, diabetes and cancer to mental problems such as depression and anxiety. Traditional treatments may not fit the preventative purpose and regular exercise behavior as the endogenous medicine cabinet can provide sufficient self-protection to maintain sound health in daily life (3).

Under the topic of exercise and chronic disease, the included papers cover diverse aspects of exercise to chronic-related research. Topics range from the acute effects of various exercise forms on executive function and cerebral hemodynamics in hospitalized Type 2 Diabetes Mellitus (T2DM) patients (Wang H. et al.) to investigating the associations between grip strength, comorbidities, and all-cause mortality in older hypertensive adults (Wang Y. et al.). Cohort studies explore the relationships between cardiorespiratory fitness, body mass index, cardiovascular disease, and mortality in young men (Gorny et al.). Additionally, a systematic review and meta-analyses focused on the effects of aquatic exercises on postmenopausal women's physical fitness and quality of life (Zhou et al.). With the background of COVID-19, the impact of pre-pandemic physical activity on COVID-19 infection and mortality is explored, drawing evidence from the National Health Insurance Service (Park et al.). Other studies investigate ideal cardiovascular health in rural northeast China (Shao et al.), the joint association of physical activity and sedentary behavior with metabolic syndrome in urban men aged 60+ (Lou et al.), and trends in the rate of regular exercise among adults in Jiangsu, China, from 2010 to 2018 (Su et al.). The importance of careful consideration of overall movement behaviors for preventing, treating, and following up on cancer risks and patients is also emphasized (Ennequin et al.). In summary, the focused topic provides new evidence on exercise improving health and contributes to deepening the understanding of exercise benefits to human beings.

By dialectical thinking, exercise can prevent chronic diseases of human beings, and people with chronic diseases would enhance or give up exercise behaviors depending on the symptoms of chronic disease. Scientific researchers have plunged into exploring the dosage of exercise prescription for various chronic diseases, while a huge gap still exists between research and practice. It is necessary to re-think the essentials of exercise itself. Fundamentally speaking, exercise is a kind of human behavior. Since ancient times, physical activity has been one of the essential behaviors for sustaining human existence in the world. In modern society, exercise serves as the cornerstone for maintaining the physiological functions of the human body. With the advanced industrial and technological developments, people are increasingly inclined toward a sedentary lifestyle, which contradicts the basic needs of human life. Along with further elucidation of physiological mechanisms underlying exercise promoting health, there is a pressing need to focus on the strategies to sustain and enhance daily physical activity and exercise-the basic behaviors of human beings.

The following suggestions are therefore provided for future research and clinical practice. At the individual level, it is crucial to raise awareness among the general public about the benefits of exercise and scientific training methods and provide opportunities for individuals to engage in exercise and diversify their choices. From the perspectives of family, school, and community, future research should consider the unique characteristics of different regions or countries, creating a sport-friendly environment with facilities and equipment suitable for diverse populations to exercise. Additionally, it should be highly recommended to integrate exercise as a necessary part of lifestyle with small-scale events weekly and large-scale competitions monthly. At the national level, it is imperative to incorporate exercise into social and cultural development by promoting, encouraging, and supporting individuals' engagement in exercise.

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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.

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The joint association of physical activity and sedentary behavior with metabolic syndrome among urban men aged 60+ years in regional China

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Objectives: Metabolic syndrome (MetS) is a major public health issue worldwide, which is preventable through physical activity (PA) promotion and sedentary behavior (SB) reduction. However, the joint association of PA and SB with MetS was not well-investigated, particularly in elderly people. This study aimed to examine separate and joint associations of PA and SB with MetS among elderly urban men in China.

Methods: In this cross-sectional study conducted in mid-2018, participants were urban men aged 60+ years randomly selected from in Nanjing of China. Exposure variables were PA and SB. The outcome variable was MetS. A participant was categorized as "having MetS" or "not having MetS" in the analysis. Independent variables were PA and SB, which were categorized as "sufficient PA or insufficient PA" and "shortened SB or prolonged SB", respectively. Mixed-effects logistics regression models were applied to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to assess the association of PA and SB with MetS.

Results: Totally, 5,520 from 5,792 eligible participants were randomly recruited and their mean age was 68.9 (standard deviation: 16.9) years. The prevalence of MetS was 30.8% (95%CI = 29.6%, 32.0%) among urban men aged 60+ years in the study. After adjustment for potential confounders, subjects with sufficient PA were less likely (OR = 0.77, 95%CI = 0.67, 0.88) to experience MetS, independently of SB, relative to their counterparts with insufficient PA, while a lower odds (OR = 0.74; 95%CI = 0.61, 0.89) of experiencing MetS was examined for participants with shortened SB, also independently of PA, compared to those with prolonged SB in the study. Furthermore, compared to participants with insufficient PA and prolonged SB, those either within categories of insufficient PA and shortened SB (OR = 0.81; 95%CI = 0.65, 0.99), sufficient PA and prolonged SB (OR = 0.80; 95%CI = 0.70, 0.92), or sufficient PA and shortened SB (OR = 0.41; 95%CI = 0.26, 0.63) were at significantly lower risk to experience MetS, respectively.

Conclusions: PA was negatively associated with MetS, and SB was positively linked to MetS, which were independent of each other. Moreover, sufficient PA and shortened SB might exert additively joint influence on MetS. This study has important implications that concurrent PA promotion and SB reduction shall be encouraged for people to optimize the effectiveness of MetS prevention.

KEYWORDS

metabolic syndrome, elderly men, physical activity, sedentary behavior, exercise

Introduction

Metabolic syndrome (MetS) is a complex metabolic concept, which is characterized typically by the concurrence of at least three of the following cardio-metabolic conditions: abdominal obesity (AO), increased fasting blood glucose (increased-FBG), raised blood pressure (raised-BP), elevated triglycerides (elevated-TG), and/or lowered high-density lipoprotein cholesterol (lowered-HDL-C) (1). It has been examined that individuals with MetS are at high risk of diabetes, cardiovascular and cerebral diseases, some cancers and neurodegenerative diseases (2–4). As different identification criteria of these five MetS components were suggested for ethnic-specific population, there is no globally uniform diagnostic criterion of MetS, (5). Currently, three widely-used MetS definitions for population-based surveys were recommended by World Health organization (6), National Cholesterol Education Program (7) and International Diabetes Federation (1, 8). However, regardless of different diagnostic criteria of MetS, it has been estimated that the prevalence of MetS was ∼25% for adult population worldwide (9), and one-third and 24.5% among adults, respectively, in USA (10) and China (11). Therefore, from the perspective of population health, MetS is a major issue worldwide and a priority of public health concern.

Fortunately, MetS and its components are preventable through lifestyle and behavior intervention, particularly physical activity (PA) promotion or/and sedentary behavior (SB) reduction campaigns (12). In both developed and developing societies, PA has been examined to be negatively associated with MetS (10, 13–15), while SB was in positive relation to MetS (10, 16–18). Among those studies on the relationship between PA, SB and MetS, the majority reported the separate association of PA, SB with MetS, and very few documented the combined relationship between PA, SB and MetS (13–17). To maximize the output-input ratio, PA promotion and SB reduction were encouraged to be integrated into a single intervention campaign for prevention of chronic diseases including MetS and its components. Thus, it is of particular interest to well understand the joint association of PA and SB with MetS in addition to the separate relationship between them.

MetS was examined to be highly age-dependent, as its prevalence was observed consistently higher among the older than the younger across different ethnic sub-populations worldwide (19). Meanwhile, elderly people have more discretionary time in daily life relative to their younger counterparts, as they, particularly urban residents, typically get retired and no longer have to do jobs. So, elderly people bear a heavy burden of MetS and its components, and, on the other hand, they have sufficient leisure time. Consequently, elderly people are the priority population for MetS prevention through leisure-time PA promotion and/or sedentary behavior reduction. In China, the prevalence of MetS increased from 13.7% in 2000 to 24.5% in 2015 among adult population (12, 20), while the proportion of elderly people aged 60+ years (the mandatory age for retirement) increased from 10.4% in 2000 to 18.7% (about 260 million) in 2020 and the urbanization rate increased from 36.0% in 2000 to 63.9% (∼902 million) in 2020 (21). Clearly, China has been witnessing an alarming increase in a multi-burden caused by MetS, rapid aging of population and urbanization over the past two decades. Thus, it is of public health significance to well investigate the joint association of PA and SB with MetS among elderly people, particularly those urban retirees, in China, as it is important for community-based MetS prevention through precision intervention of leisure—time PA and SB among older residents.

To date, there was a lack of studies that documented the combined relationship between PA, SB and MetS among elderly people in urban areas of China. To fill this gap, a population-based study was conducted among urban men aged 60+ years in Nanjing municipality of China, with aims to examine whether: (1) PA and SB were associated with MetS independent of each other, and (2) an additive effect of sufficient PA and shortened SB on MetS existed.

Methods

Study design and participants

A cross-sectional survey was conducted initially for estimating the prevalence of diabetes and hypertension comorbidity among urban elderly men during mid-2018 in Nanjing, a typical mega-city in eastern region of China (DiaHyCom study). The eligible participants referred to those locally registered urban residents who: (1) were men aged 60+ years, (2) were without physical disability or/and psychiatric disorders, and (3) had no cognitive/literal problems. Participants were randomly chosen using a multi-stage sampling approach. The sample size was determined with consideration of the sampling method, estimated prevalence (7.5%) of diabetes and hypertension comorbidity among elderly people in China (22), and the expected statistical power (90%). Thus, ∼4,500 participants would be sufficient for DiaHyCom study.

Currently, China has a five-stratum administrative system, including central government, province/municipality, urban district/rural country, administrative street/town and administrative urban community/rural village. Each administrative community or village is usually composed of different numbers of neighborhoods. In Nanjing, there were totally five urban and six suburban districts in 2018. For recruitment of participants in the study, all the five urban districts were included and the sampling unit was neighborhood. Prior to selection of participants, two figures were estimated: (1) a specific number of participants was calculated for each district based on the proportion of elderly population of the district to the overall of all five urban districts; and (2) with the assumption that, on average, one household had one elderly man aged 60+ years, the number of participating household was computed for each district. Then, a multi-stage sampling approach was used to randomly select participants from each district. Firstly, three administrative streets were randomly chosen from each of the five urban districts. Secondly, two administrative communities were randomly selected from each chosen street. Thirdly, neighborhoods were randomly determined from each involved administrative community according to the number of participating households, resulting in a total of 54 neighborhoods selected. Finally, all eligible men aged 60+ years within each involved neighborhood were invited to take part in the study. Participant's selection flowchart was shown in Figure 1.

Written informed consents were obtained from all participants before the survey. The data analyzed to examine the relationship between PA, SB and MetS in the present study were derived from DiaHyCom survey and de-identified before analysis. Thus, second-hand data were analyzed in this study, which was also reviewed by The Ethics Committee of Geriatric Hospital of Nanjing Medical University. The methods performed in the present study were in accordance with relevant recommendations by the Declaration of Helsinki.

Data collection

Information on participant's socio-demographic characteristics (including age, educational attainment, marital status, etc), history of major chronic diseases, family history of diabetes and hypertension, physical activity and sedentary behavior, cigarette smoking, drinking, consumption of meat were gathered *via* a standardized questionnaire (23). All the information was self-reported by participants *via* a face-to-face interview which was administered by our research team members.

Data on each participant's blood pressure and anthropometry were objectively measured. Blood pressure was assessed with calibrated sphygmomanometers based on the Chinese guidelines for blood pressure measurement (24). In the guidelines, Korotkoff sounds were used to determine participant's blood pressure with a standardized procedure (24). Moreover, at least two readings were recorded and the mean value was used for analysis (24). With regard to anthropometric measurement, all participants were asked to stay in a quiet room for a minimal 5-min rest prior to measurement. Waist circumference (WC) was measured to the nearest 0.1 cm at the midpoint between costal inferior and iliac crest for each participant who was with light indoor clothing (25). WC was also recorded twice and the mean value was used for each participant in the analysis.

For assessing the levels of blood glucose, triglyceride and high density lipoprotein cholesterol, a 5-ml fasting venous blood sample was collected from each participant. All the blood samples were sent to the laboratory of a designated hospital for analysis by well-trained staff. The automatic biomedical analysis instrument was HITACHI7180 analyzer (Hitachi Co., Japan) and detection kits were from Shanghai Fosun Long March Medical Science Co., China.

Study variables

Outcome variable

The outcome variable was MetS, which was defined based on the diagnostic criteria recommended specially for Chinese adults by Chinese Diabetes Society (CDS) in 2017 (26). A participant was categorized as "having MetS", if he concurrently experienced at least three of the following abnormal health conditions: abdominal obesity (WC $\geq$ 90 cm) for a man, increased fasting blood glucose (FBG $\geq$6.1 mmol/L, and/or diagnosed with diabetes), raised blood pressure (BP $\geq$130/85 mmHg, and/or diagnosed with hypertension), elevated triglycerides (TG $\geq$1.70 mmol/L), and/or lowered high-density lipoprotein cholesterol (HDL-C $<$ 1.04 mmol/L). Otherwise, a participant was classified as "not having MetS".

Independent variables

There were two explanatory variables, PA and SB, in this study. Both of them referred to leisure-time activities and were assessed using the validated Chinese version of International Physical Activity Questionnaire (IPAQ-CHN) (27, 28). This IPAQ-CHN was professionally translated from the original IPAQ and has been validated for Chinese adults (28, 29). For each participant, PA and SB time in the last seven days was

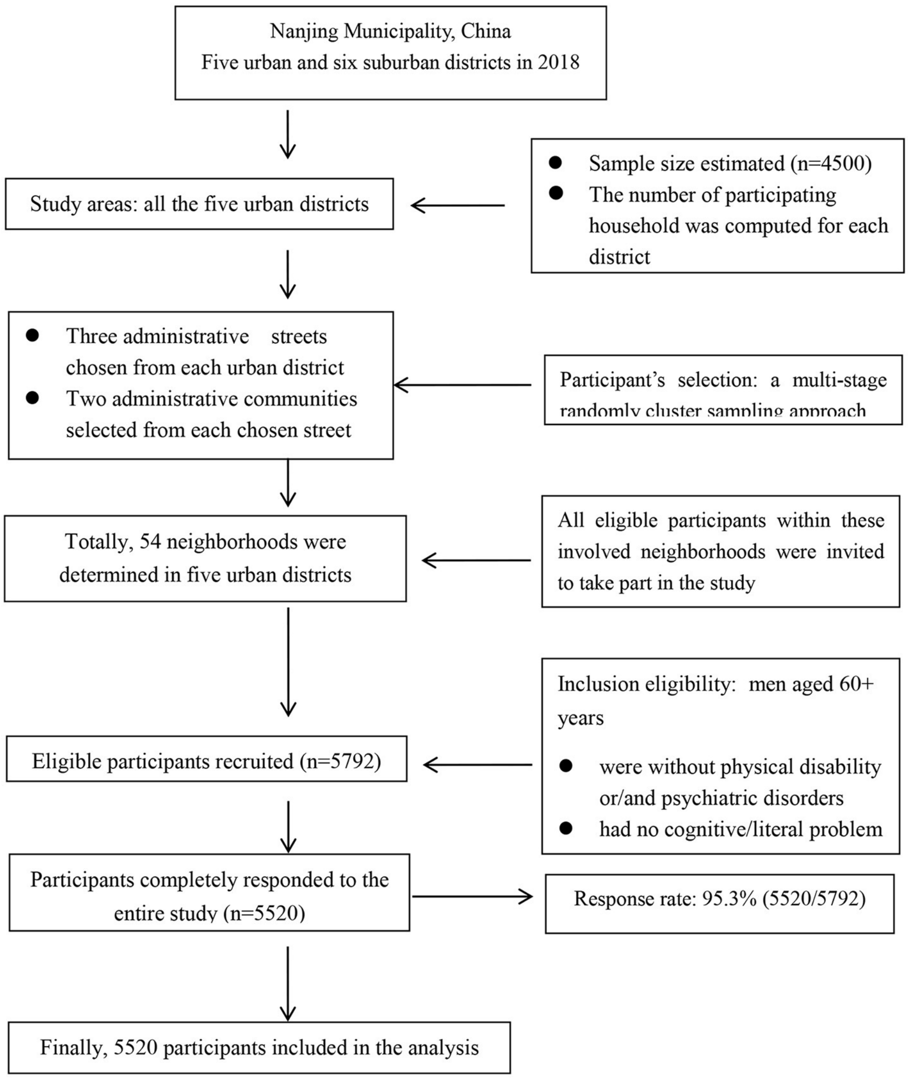

FIGURE 1
Flow chart of participant's selection in the study.

self-reported using IPAQ-CHN. The weekly time of moderate and vigorous PA was recorded separately. Then, based on the sum of weekly moderate PA time plus doubled vigorous PA time (moderate and vigorous physical activity, MVPA), a participant was classified into the sub-group of "sufficient PA (≥150 min/week)" or "insufficient PA (<150 min/week)" in the analysis (29, 30). On the other hand, daily sedentary behavior time was defined as screen viewing time, which was assessed with a question asking each participant about the time he spend sitting each day for screen viewing in the last 7days. Then, SB time was also computed and used to categorize participants into: "shortened SB (<2 h/day)" or "prolonged SB (≥2 h/day)" according to SB time recommendations for Chinese people (29).

In addition to separate relationship between PA, SB and MetS examined in the present study, the combined association of PA and SB with MetS was also investigated. Thus, participants were further classified into one of the following sub-groups: insufficient PA and prolonged SB (the reference with the highest risk), insufficient PA and shortened SB, sufficient PA and prolonged SB, or sufficient PA and shortened SB (the lowest risk group).

Covariates

Some classical covariates were controlled for in the analysis. They were age (younger: 60–69, middle: 70–79 or older: 80+ years), educational attainment (≤9, 10–12 or 13+ schooling years), cigarette smoking, alcohol drinking, consumption of meat, family histories of diabetes and hypertension.

A participant was defined as a current smoker, if he smoked one or more cigarettes every day for at least 1 year or smoked 18+ packs per year in total (25). If a person had quit smoking for at least 1 year, he was categorized as an ex-smoker (25). Otherwise, he would be classified as a non-smoker (25). In this study, smokers referred to both current smokers and ex-smokers. Drinkers were defined as persons who drank alcohol, on average, at least two times a week for more than 1 year, while non-drinkers were those people who did not meet drinker's criterion in this study (25).

Dietary consumption was measured with a validated Chinese version of food frequency questionnaire (FFQ) (31). The weekly frequency of meat intake was used for analysis in the study. The frequency of meat consumption, at least seven times per week on average, was recommended for Chinese old people by Chinese Nutrition Society (32). Thus, participants were categorized into two sub-groups based on whether or not they reached this meat intake recommendation: reached recommendation ("Yes") or not reach recommendation ("No").

A participant was defined as having a positive family history ("Yes") of diabetes or hypertension, if at least one of his parents had been identified as diabetic or hypertensive patient, respectively. Otherwise, a participant was classified as not having a positive family history ("No").

Data analysis

Descriptive analysis was implemented to present participant's characteristics (%). Differences in personal characteristics between age, PA, SB and MetS were, separately, compared with chi-square test. And, the differences in mean values (standard deviation, SD) of age, WC, FBG, BP, TG and HDL-C were examined using ANOVA approach. Then, two mixed-effects logistic regression models were employed to compute odds ratios (ORs) and 95% confidence intervals (CIs) for investigating the separate and joint associations of PA and SB with MetS. Model 1 was a univariate logistic regression analysis with PA, SB or their joint category as the single independent variable. Model 2 was a multivariate logistic regression analysis with PA, SB or their joint category as the independent variable and with adjustment for age, educational attainment, smoking, drinking, meat consumption, PA (where applicable), SB (where applicable), family history of diabetes and hypertension. In both mixed-effects logistic regression models, neighborhood-level potential clustering effects were considered as the random effect. Two-sided statistical significance level was set at $p < 0.05$. Data were entered with EpiData 3.1 (The EpiData Association 2008, Odense, Denmark) and analyzed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Selected participants' characteristics

Although the estimated sample size was 4,500, the actually chosen participants were 5,792 elderly men from 54 neighborhoods due to the cluster sampling approach applied in this study. Among those 5,792 participants, 5,520 (95.3%) completely responded to the entire study, including questionnaire survey, anthropometric assessment and blood sample collection. There was no difference in age and education level between those completed and did not complete the study. Table 1 displayed the selected characteristics of participants by age in this study. The majority (63.9%) of participants obtained educational attainment of 10–12 schooling years. And, the proportion of participants with 10–12 schooling years was 69.2, 57.3 and 44.3 for subjects aged 60–69, 70–79, and 80+ years, respectively ($p < 0.001$). The mean value of MVPA time was 89.8 (SD = 147.1) minutes in last week, while the mean sedentary behavior time was 4.1 (SD = 2.5) hours per day among the overall participants.

Prevalence of PA, SB and MetS among participants

Table 2 presented the prevalence of PA, SB and MetS by selected characteristics of participants in the study. The proportion of participants with sufficient PA and prolonged SB was, separately, 26.9% (95%CI = 25.7, 28.1%) and 87.5% (95%CI = 86.6, 88.4%) in the study. The overall prevalence of MetS was 30.8% (95%CI = 29.6, 32.0%) among urban men aged 60+ years in the present study, while the stratified prevalence of MetS significantly differed among participants aged 60–69 years (29.7%; 95%CI = 28.2, 31.3%), 70–79 years (33.2%; 95%CI = 30.5, 36.0%) and 80+ years (30.7%; 95%CI = 26.2, 35.6%) in the study. Moreover, the difference in MetS prevalence was examined also significant between education, drinking, family histories of diabetes and hypertension.

Distribution of age, WC, FBG, BP, TG and HDL-C by PA and SB among participants

Table 3 demonstrated the distribution of age, WC, FBG, BP, TG and HDL-C among overall and stratified participants by PA and SB. For overall participants, their mean age (SD) was 68.9 (16.9) years, while the mean value (SD) of WC, FBG, systolic and diastolic BP, TG and HDL-C was, respectively, 87.2 (9.1) cm, 6.0 (1.7) mmol/L, 134.2 (16.3) mmHg, 80.7 (9.6) mmHg, 1.6 (1.2) mmol/L and 1.37 (0.50) mmol/L. Moreover, the mean value of age, WC and systolic BP each differed in participants with insufficient and sufficient PA, and mean values of WC, systolic

TABLE 1 Selected characteristics of participants by age in this study.

	All participants		60-69 years		70-79 years		80+ years		*p*-value*
	N	%/Mean (±SD)	*N*	%/Mean (±SD)	*N*	%/Mean (±SD)	*N*	%/Mean (±SD)	
Overall	5,520	100.0	3,518	63.7	1,611	29.2	391	7.1	
Educational attainment (schooling years)									
0-9	994	18.0	560	15.9	331	20.5	103	26.3	<0.001
10-,12	3,530	63.9	2,435	69.2	922	57.3	173	44.3	
13+	996	18.1	523	14.9	258	22.2	115	29.4	
Moderate and doubled vigorous PA time (minutes in last week)									
Mean (±SD)	5,520	89.8 (147.1)	3,518	92.2 (147.4)	1,611	90.4 (150.3)	391	65.2 (127.6)	<0.01
Sedentary behavior time (hours per day)									
Mean (±SD)	5,520	4.1 (2.5)	3,518	4.2 (2.5)	1,611	4.0(2.4)	391	3.9 (2.3)	<0.01
Smoking[a]									
No	3,187	57.7	1,801	51.2	1,080	67.0	306	78.3	<0.001
Yes	2,333	42.3	1,717	48.8	531	33.0	85	21.7	
Drinking[b]									
No	3,257	59.0	1,864	53.0	1,085	67.3	308	78.8	<0.001
Yes	2,263	41.0	1,654	47.0	526	32.7	83	21.2	
Meat consumption (reached recommendation)[c]									
No	4,331	78.5	2,660	75.6	1,340	83.2	331	84.7	<0.001
Yes	1,189	21.5	858	24.4	271	16.8	60	15.3	
Family history of hypertension[d]									
No	3,751	68.0	2,274	64.6	1,159	71.9	318	81.3	<0.001
Yes	1,769	32.0	1,244	35.4	452	28.1	73	18.7	
Family history of diabetes[e]									
No	4,948	89.6	3,079	87.5	1,490	92.5	379	96.9	<0.001
Yes	572	10.4	439	12.5	121	7.5	12	3.1	

*Chi-square test.

[a]Smoking status was defined as smokers (current- and ex-smokers) and non-smokers (who never smoked cigarettes).

[b]Drinkers were defined as persons who drank alcohol, on average, at least two times a week for more than one year, while non-drinkers were those people who did not meet drinker's definition.

[c]Meat consumption was classified as "reached recommendation" and "not reach recommendation" based on the frequency of meat consumption recommended for Chinese old people by Chinese Nutrition Society.

[d]Family history of hypertension was categorized as having a positive family history ("Yes") of hypertension, if at least one of parents had been identified as hypertensive patient.

[e]Family history of diabetes was classified as having a positive family history ("Yes") of diabetes, if at least one of parents had been identified as diabetic patient.

and diastolic BP, and TG were different between subjects with shortened and prolonged SB, separately.

Separate and joint associations of PA and SB with MetS

Table 4 showed associations of PA and SB with MetS among participants of the study. There were 32.1% (95%CI = 30.7, 33.6%) and 27.2% (95%CI = 25.5, 30.1%) of participants with insufficient and sufficient PA, separately, experienced MetS. And, 31.7% (95%CI = 30.4, 33.0%) and 21.6% (95%CI = 21.5, 28.0%) of subjects with prolonged and shortened SB had MetS, respectively. After adjustment for potential confounding factors, subjects with sufficient PA were less likely (OR = 0.77, 95%CI = 0.67, 0.88) to experience MetS, independently of SB, relative to their counterparts with insufficient PA, while a lower odds (OR = 0.74; 95%CI = 0.61, 0.89) of experiencing MetS was examined for participants with shortened SB, also independently of PA, compared to those with prolonged SB in the study.

Among participants with shortened SB, these with sufficient PA were less likely to experience MetS relative to the counterparts with insufficient PA (OR = 0.48; 95%CI = 0.29, 0.77). On the other hand, for subjects with sufficient PA, those with shortened SB than their counterparts with prolonged SB were also less likely to have MetS (OR = 0.47; 95%CI = 0.30, 0.75). Furthermore, compared to participants in the sub-group of insufficient PA and prolonged SB, those either within

TABLE 2 The proportion of participants by physical activity, sedentary time and metabolic syndrome among urban men aged 60+ years in regional China.

	N of participants	Participants with sufficient PA[a]		*p*-value*	Participants with prolonged SB[b]		*p*-value*	Participants with MetS[c]		*p*-value*
		%	*n*		%	*n*		%	*n*	
Overall	5,520	26.9	1,485		87.5	4,830		30.8	1,699	
Age (years)										
60–69	3,518	28.3	996		87.4	3,074		29.7	1,044	
70–79	1,611	26.0	419	<0.001	87.8	1,414	0.93	33.2	535	0.04
80+	391	17.9	70		87.5	342		30.7	120	
Educational attainment (schooling years)										
0-9	994	23.2	231		74.2	738		25.7	255	
10-12	3,530	27.2	959	<0.01	89.0	3143	<0.001	32.3	1,141	<0.001
13+	996	29.6	295		95.3	949		30.4	303	
Smoking[d]										
No	3,187	25.6	816	0.01	88.0	2,806	0.15	29.9	953	0.10
Yes	2,133	28.7	669		868	1,824		32.0	746	
Drinking [e]										
No	3,257	25.4	828	<0.01	87.0	2,932	0.14	29.7	968	0.04
Yes	2,263	29.0	657		88.3	1,998		32.3	731	
Meat consumption (reached recommendation)[f]										
No	4,331	27.8	1,204	<0.01	86.9	3,765	0.02	30.6	1326	0.62
Yes	1,189	23.6	281		89.6	1065		31.4	373	
Family history of hypertension[g]										
No	3,751	26.3	987	0.15	86.7	3,253	0.01	27.6	1,035	<0.001
Yes	1,769	28.2	498		89.1	1,577		37.5	664	
Family history of diabetes[h]										
No	4,948	26.6	1,316	0.13	87.2	4,313	0.03	29.5	1,458	<0.001
Yes	572	29.5	169		90.4	517		42.1	241	

*Chi-square test.
[a]Physical activity was categorized into "insufficient PA (<150 min/week)"and "sufficient PA (≥150 min/week)" based on weekly moderate physical activity time.
[b]Sedentary behavior was classified as "shortened SB time (<2 h/day)" or "prolonged SB time (≥2 h/day)" according to SB recommendations for Chinese people.
[c]MetS was identified according to diagnostic criteria recommended by Chinese Diabetes Society.
[d]Smoking status was defined as smokers (current- and ex-smokers) and non-smokers (who never smoked cigarettes).
[e]Drinkers were defined as persons who drank alcohol, on average, at least two times a week for more than one year, while non-drinkers were those people who did not meet drinker's definition.
[f]Meat consumption was classified as "reached recommendation" and "not reach recommendation" based on the frequency of meat consumption recommended for Chinese old people by Chinese Nutrition Society.
[g]Family history of hypertension was categorized as having a positive family history ("Yes") of hypertension, if at least one of parents had been identified as hypertensive patient.
[h]Family history of diabetes was classified as having a positive family history ("Yes") of diabetes, if at least one of parents had been identified as diabetic patient.

categories of insufficient PA and shortened SB (OR = 0.81; 95%CI = 0.65, 0.99), sufficient PA and prolonged SB (OR = 0.80; 95%CI = 0.70, 0.92), or sufficient PA and shortened SB (OR = 0.41; 95%CI = 0.26, 0.63) were at significantly lower risk to experience MetS, respectively.

Discussion

The main purposes of this population-based study were to investigate the separate and combined relationship between PA, SB and MetS among urban men aged 60+ years in regional China. It was found that PA was in a positive and SB in a negative relation to MetS. Moreover, a joint association was observed that sufficient PA and shortened SB might exert an additive influence on MetS. Further, the association of PA with MetS and the link between SB and MetS were independent of each other.

Our findings regarding the individual associations of PA and SB with Mets were in line with previous studies conducted among people aged either 60+ or 18+ years in both developed countries and developing societies including China (10, 13–18, 33). This suggests that the separate relationships between

TABLE 3 Distribution of age, WC, FBG, BP, TG and HDL-C by PA and SB among urban men aged 60+ years in regional China.

		Overall participants (N = 5,520)	Mean value (SD)*					*p*-value[#]
			PA[†]		*p*-value[#]	SB[‡]		
			Insufficient	Sufficient		Shortened	Prolonged	
Age (years)		68.9 (16.9)	69.2 (16.9)	68.2 (6.1)	0.02	68.8 (6.7)	69.0 (15.6)	0.73
WC (cm)[a]		87.2 (9.1)	87.4 (9.2)	86.5 (8.6)	<0.01	86.3 (9.4)	87.3 (9.0)	<0.01
FBG (mmol/L)[b]		6.0 (1.7)	6.0 (1.7)	6.0 (1.7)	0.74	5.9 (1.7)	6.0 (1.7)	0.16
BP (mmHg)[c]								
	Systolic BP	134.2 (16.3)	134.5 (16.8)	133.3 (14.8)	0.02	137.0 (17.7)	133.0 (16.8)	<0.01
	Diastolic BP	80.7 (9.6)	80.9 (9.7)	80.4 (9.2)	0.15	82.2 (10.4)	80.5 (9.5)	<0.01
TG (mmol/L)[d]		1.6 (1.2)	1.6 (1.2)	1.6 (1.1)	0.19	1.5 (1.0)	1.6 (1.2)	<0.01
HDL-C (mmol/L)[e]		1.37 (0.50)	1.37 (0.51)	1.36 (0.48)	0.70	1.36 (0.40)	1.37 (0.51)	0.76

*SD: standard deviation.
[#]Differences in age, WC, FBG, BP, TG and HDL-C were examined with ANOVA approach.
[†]PA, Physical activity was categorized into "insufficient PA (<150 min/week)"and "sufficient PA (≥150 min/week)" based on weekly moderate physical activity time.
[‡]SB: Sedentary behavior was classified as "shortened SB time (<2 h/day)" or "prolonged SB time (≥2 h/day)" according to SB recommendations for Chinese people.
[a]WC, Waist circumference.
[b]FBG, Fasting blood glucose.
[c]BP, Blood pressure.
[d]TG, Triglycerides.
[e]HDL-C, High-density lipoprotein cholesterol.

PA, SB and MetS are strongly consistent among adults with different ages and from societies with different cultural and social contexts worldwide. Meanwhile, in our study, it was also observed that sufficient PA might predict lower odds of MetS even for participants with shortened SB, and, shortened SB could reduce the likelihood of MetS for those with sufficient PA. This implies that sufficient PA and shortened SB can not substitute for one another regarding their individual association with MetS. A recent study conducted among adults aged 65 years in Canada reported that, even for those extremely active people, increased SB was also significantly associated with an elevated risk of MetS (34). This adds further evidence that PA promotion and/or SB reduction are in significantly favorable relation to Mets for people irrespective of their present status of SB and/or PA. Thus, it is of public health importance that campaigns on PA promotion and/or SB reduction are beneficial for general population without necessary consideration of residents' status of SB and PA.

Another major finding of our study was that sufficient PA and shortened SB might exert additive influence on MetS among urban elderly men in regional China. Compared to the reference people who were with insufficient PA and prolonged SB, participants with either insufficient PA and shortened SB or sufficient PA and prolonged SB were at significantly lower risk of MetS, while those subjects with concurrent sufficient PA and shortened SB were at just a half-fold likelihood of MetS. One study using the data from 2009 and 2015 China Health and Nutrition Surveys (CHNS) also identified a joint association of PA and SB with MetS among adults aged 18+ years in China (33). However, in this CHNS study, participant's PA level was calculated based on the sum of occupational, domestic and leisure-time physical activities (33), which was different from that only leisure-time PA was used in our study. Similar findings on joint associations of PA and SB with MetS were also reported from studies conducted among adults in Brazil and Denmark (35, 36). MetS was diagnosed using the NCEP-ATP III criteria, and PA was assessed with a semi-quantitative scale, the Baecke questionnaire, among adults aged 50+years in the Brazilian study (35). For the study conducted among Danish subjects with a mean age of 52 years, MetS was measured with IDF criteria using non-fasting venous blood samples, and PA referred to self-reported average level of leisure-time PA over the past year (36). Consistent evidence from different studies suggests that such an additive relationship between PA, SB and MetS may hold widely among adults with different age and from different societies.

There are some epidemiological and physiological explanations on the relationship between PA, SB and MetS. Based on population-level epidemiological evidence, it has been well-proved worldwide that PA was negatively and SB was positively associated with all the five components of MetS (37, 38). Thus, it is plausible that PA and SB exert influence on MetS through its components, which reasonably results in a consistent direction of associations of PA and SB with MetS and its components. This may, at least partly, explain the negative relationship between PA and MetS as well as the positive association of SB with MetS.

Moreover, there may be several potential physiological mechanisms behind the relationship between PA, SB and MetS. PA is a major pathway of energy expenditure, and it benefits energy balance through not only short-term caloric

TABLE 4 The separate and joint association of PA, SB and MetS in urban men aged 60+ years in regional China.

	Explanatory variable		Prevalence of MetS [a]	OR (95%CI) for experiencing MetS [b]					
	PA [c]	SB [d]	% (n/N)	Model 1 [†]			Model 2 [‡]		
Overall									
Separate	Insufficient		32.1 (1,295/4035)	1			1		
	Sufficient		27.2 (404/1,485)	0.79 (0.69, 0.90)			0.77 (0.67, 0.88)		
		Prolonged	31.7 (1,529/4,830)	1			1		
		Shortened	24.6 (170/690)	0.71 (0.59, 0.85)			0.74 (0.61, 0.89)		
Joint	Insufficient	Prolonged	32.9 (1,150/3,500)	1			1		
	Insufficient	Shortened	27.1 (145/535)	0.76 (0.62, 0.93)	1		0.81 (0.65, 0.99)	1	
	Sufficient	Prolonged	28.5 (379/1330)	0.81 (0.71, 0.94)		1	0.80 (0.70, 0.92)		1
	Sufficient	Shortened	16.1 (25/155)	0.39 (0.26, 0.61)	0.52 (0.32, 0.83)	0.48 (0.31, 0.75)	0.41 (0.26, 0.63)	0.48 (0.29, 0.77)	0.47 (0.30, 0.75)

MetS: metabolic syndrome.
[a] MetS was identified according to diagnostic criteria recommended by Chinese Diabetes Society.
[b] OR: odds ratio; CI: confidence interval.
[c] Physical activity was categorized into "insufficient PA (<150 min/week)"and "sufficient PA (≥150 min/week)" based on weekly moderate physical activity time.
[d] Sedentary behavior was classified as "shortened SB time (<2 h/day)" or "prolonged SB time (≥2 h/day)" according to SB recommendations for Chinese people.
[†] Model 1 was an unadjusted mixed-effect logistic regression model with PA as the single predictor and adjustment for neighborhood-level clustering effects.
[‡] Model 2 was a multivariate mixed-effect logistics regression model with adjustment for age, educational attainment, meat consumption, smoking, drinking, physical activity (where applicable), sedentary time (where applicable), history of hypertension and diabetes and neighborhood-level clustering effects.

expenditure (39) but also long-term energy expenditure such as changes in muscle structure, an increase in mitochondria in fiber and secretion of metabolically beneficial hormone, and a decrease in postprandialhepatic lipogenesis (40). On the other hand, prolonged SB may cause a reduction in levels of glucose transporter 4 (GLUT 4) in skeletal muscles (41) and a decrease in insulin sensitivity (42). Muscle lipoprotein lipase, an enzyme that hydrolyzes circulating triglyceride-rich lipoproteins, is highly sensitive to SB (43). Thus, prolonged SB may reduce the activity of muscle lipoprotein lipase and consequently increases plasma triglyceride levels through reducing triglyceride hydrolysis (43). Therefore, this may partially explained the associations of PA and SB with MetS from the perspective of physiology.

This study has important public health implications for future campaigns of population-based MetS prevention among elderly people in China. For those residents aged 60+, they get retired and thus have no job to do. Consequently, they have so much discretionary leisure time. Therefore, the problem is that retirees not only have sufficient discretionary time to do PA but also to engage in SB. The challenge for elderly people to prevent MetS is to spend sufficient time in moderate/vigorous PA and, in the meantime, to spend the shorter time in SB the better. Major findings from our study demonstrated that PA and SB individually exerted opposite effect on MetS independently of each other, and moreover sufficient PA and shortened SB together exerted additive favorable influence on MetS. These strongly suggest that regularly concurrent PA promotion and SB reduction shall be encouraged for elderly people to prevent MetS from the perspective of public health.

Several strengths of this study are worthy of being mentioned. First, study participants were representative of general urban elderly men in a typical mega-city in China. Moreover, a high response rate (95.3%) implies generalizability of study findings. Second, an ethnicity-specific definition of MetS was used to identify MetS, which warranted a tailored diagnosis of MetS for Chinese participants in the study. Third, stratified and cross-over analysis approaches were applied to examine individual and joint associations of PA and SB with MetS. The last, interesting findings, not only an independently separate relationship between PA, SB and MetS but also an additively joint association of sufficient PA and shortened SB with MetS were observed.

There are also some limitations in this study. Firstly, data on PA and SB were self-reported by participants, although the instrument, IPAQ, has been validated for Chinese people. Secondly, no causality of the relationships between PA, SB and MetS could be inferred due to the cross-sectional nature of our study. Thirdly, the CDS definition of MetS included an option of 2-h plasma glucose level ≥7.8 mmol/L as elevated blood glucose. However, 2-h plasma glucose was not assessed for participants, which might result in an under-estimation of

MetS prevalence in this study. Finally, due to only one subject with sufficient PA and shortened SB among sub-group of older-old participants aged 80+ years, stratified analysis by age was not appropriate in this study. Therefore, findings reported in the present study need to be interpreted with prudence. In future, longitudinal observational studies and population-based intervention trials are welcome to examine the potential causal associations of PA and SB with MetS, and to assess the impact of PA promotion and SB reduction on MetS among not only urban elderly men but also other subgroups of population in China.

Conclusions

PA was negatively associated with MetS, and SB was positively linked to MetS among urban men aged 60+ years in regional China. The PA-MetS and SB-MetS relationships were independent of each other. Moreover, sufficient PA and shortened SB might exert additively joint influence on MetS. This study has important public health implications that concurrent regular PA promotion and SB reduction need to be recommended for people with the purpose to optimize the effectiveness of MetS prevention.

Data availability statement

The data included in the manuscript are available from the corresponding author FX, upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Geriatric Hospital of Nanjing Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SG and FX conceived and designed the present study. QL, HW, GL, and FX are responsible for data acquisition. FX analyzed the data presented in this manuscript. SG obtained financial support for the present work. QL, HW, GL, YH, QY, SG, and FX wrote and critically reviewed the manuscript. All author approved the final version for submission and was also responsible for all aspects of the work presented in this 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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There is a need for a complete consideration of overall movement behaviors for the prevention, treatment, and follow-up of cancer risks and patients

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Introduction

In 2018, ∼382,000 new cases of cancer (204,600 in men and 177,400 in women) and 157,400 related deaths (89,600 in men and 67,800 in women) were registered in France (1). Significantly, evidence suggests that more than 40% of cases are related to preventable risk factors (2). Environmental and lifestyle factors, including physical inactivity and sedentary behaviors (SBs), are considered to be the fourth leading risk factor for all-cause mortality worldwide (3). They have also been shown to play a major role in the incidence and recurrence of cancer as well as cancer-related mortality rates (4). Thus, faced with this immense public health issue, it is necessary to utilize preventative strategies, such as behavioral interventions, to reduce the global burden of disease associated with cancer.

From physical activity to overall movement behavior profiles

There is no need today to further debate the beneficial role of physical activity (PA) on overall health. It is an essential and key parameter for the prevention and treatment of chronic diseases, such as cancer. PA is defined as any body movement generated by the contraction of skeletal muscle that raises energy expenditure above the resting metabolic rate and is characterized by its modality, frequency, intensity, duration, or context of practice (5). It is currently part of health recommendations for adults that encourage a minimum of 150 to 300 min per week of moderate-intensity (3.0 to <6.0 Metabolic Equivalent of Task, METs), or 75 min to 150 min per week of vigorous-intensity aerobic physical activity (≥6.0 METs), or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity (MVPA) (6). In terms of primary prevention, being physically active is associated with a lower risk of many cancers. In their systematic analysis, Mctiernan et al. effectively reported a clear inverse association between PA level (PAL) and prospective risk for developing several cancers in a dose–response manner (4). According to their results, the higher the level of PA, the lower the incidence of bladder, breast, colon, endometrial, esophageal adenocarcinoma, renal, and gastric cancers for instance. Moreover, they also demonstrated a lower cancer-related mortality rate in patients respecting the health recommendations in terms of PA relative to those that did not. Among the biological mechanisms by which PA is considered to influence cancer risk are body weight management, inflammation reduction, modulation of sex and metabolic hormones, and improvement of immune function (7). Finally, PA is increasingly recognized as an effective non-pharmacological approach to counteract the adverse effects of chemotherapy and other anti-cancer treatments. To illustrate the strength of the association between PA and cancer risk, meta-analyses have clearly indicated that PA can reduce the mortality rate of breast cancer by 34%, disease recurrence by 24%, and even all-cause mortality by as much as 41% after cancer diagnosis (8). Similar results have also been described for colorectal (9) and prostate cancers (10). However, it is worth noting that patients observed less frequent PA after rather than before diagnosis (11), highlighting the physical barriers to PA for patients with cancer. The benefits of PA in tertiary prevention also extend beyond survival by increasing quality of life and reducing fatigue and secondary effects of chemotherapy, among many other benefits.

While PAL has long been studied for its role in non-communicable diseases (12), the implications of SB are increasingly being recognized. For example, the World Health Organization recommends that people must limit the amount of time spent being sedentary (13). SBs, defined as any waking behaviors characterized by an energy expenditure of ≤1.5 METs while in a sitting, reclining, or lying posture, are robustly implicated in negative health outcomes over the lifespan (14). There is also a growing body of evidence highlighting their impact on patients with chronic diseases (15). Regarding cancer, results obtained from a cohort of 8,002 adults indicated a significant association, in a dose–response manner, between the risk of cancer mortality and objectively measured sedentary time, as measured using a hip-mounted accelerometer worn for 7 consecutive days, independently of MVPA levels (16). Gathering results from 34 studies with a total of 1,331,468 participants evaluated at a high scientific standard, Patterson et al. also found strong linear associations between SB and cancer mortality (17). In their review, Jochem and collaborators highlighted a more moderate association between sedentary time and risk of colon, endometrial, and lung cancers, with limited evidence for a dose–response relation and the link with other cancer sites also limited or inconclusive (18). However, because of heterogeneity across studies in terms of sample size, type of sitting time (occupational vs. leisure-time vs. total), and potential confounders, such as body weight and methods of measures (accelerometer, questionnaires, etc.), results need to be taken with caution and further studies are needed. Blecher et al. have more recently reached similar conclusions based on a systematic approach to the available literature, suggesting that there may be some promise for intervention strategies to reduce SB in cancer patients and survivors and highlighting a need for more high-quality randomized controlled trials to understand how best to reduce SB in this population (19). Specifically, education, environmental adaptations, motivational counseling, and technologies (i.e., wearable devices or smartphones) are among the most prominent strategies that should be assessed to determine how cancer patients and survivors may experience clinical benefits through reductions in SB (19).

Movement behavior profile and cancer

As mentioned above, the current literature to date has thoroughly investigated the relationship between PA or SB and cancer, but recent reports suggest that it is necessary to overcome oversimplified terminology such as "PA" *vs.* "SB" or "high" *vs.* "low" PA to describe the complexity of human movement behaviors. Indeed, we and other researchers encourage a move toward a multidimensional approach to PA characterization, and a detailed analysis of body motion and fine movement behaviors (decomposition, structuration, and sequencing of humans' daily movements) to identify more precisely individuals at risk for future chronic disease (20, 21). In other diseases, such as obesity, our team compared the profiles of SB time, MVPA time, and combinations of movement behavior profiles in the investigations of metabolic health. Lower sedentary time was associated with better metabolic health independently of MVPA, which might present a first step in the management of obesity when increasing MVPA is not possible (22). Thus, a better characterization of movement behavior patterns may provide a more comprehensive understanding of the interactions between the preventative potential of PA and the deleterious effects of SB on cancer risk.

TABLE 1 Research gaps and recommendations.

Research gaps and recommendations
To collect data with validated devices targeting movement behavior patterns.
To develop more complex and sophisticated algorithms to better identify and refine movement behavior patterns.
To use a multidimensional approach to PA and to decipher the relationship between PA and SB, and cancer occurrence, recurrence, and related mortality.
Insufficient available evidence to fully describe the dose–response relationship (as threshold values) between PA and cancer occurrence, recurrence, and mortality.
Insufficient available evidence on all the components of movement behavior pattern such as minimal movements (i.e., sit-to-stand transition) and their association with cancer occurrence, recurrence, and mortality.
To investigate the modifications of PA and SB and their associations with cancer severity (primary prevention), types of cancer treatment and to determine whether PA and SB impairments can be considered as long-term consequences/after-effects in cancer survivors (secondary prevention) and risk factor for recurrence (tertiary prevention).
Educate and identify solutions to overcome physical activity barriers through a multidisciplinary approach and increase adhesion to PA improvements and SB limitations.
Assess PA, SB, and overall movement behavior profile during cancer follow-up up to 5 years and beyond.

Indeed, Wolvers et al. investigated the patterns of movement behaviors of 172 participants who suffered from chronic cancer-related fatigue and reported that three profiles of physical behaviors can be distinguished based on the analysis of overall PAL, MVPA, and SB, suggesting that different non-medical therapeutic strategies should be considered depending on the identified profile (23). Similarly, in a prospective cohort of 396 colorectal cancer survivors followed from 6 weeks up to 24 months after the end of the cancer treatment, Kenkhuis and collaborators assessed the longitudinal associations of SB and MVPA independently as well as their joint associations with quality of life and fatigue (24). The authors reported that decreases in SB and increases in MVPA were independently associated with improved quality of life and fatigue. However, low prolonged SB and high MVPA together demonstrated the strongest positive association with increasing quality of life and decreasing fatigue. Finally, a recent prospective study including 1,535 cancer survivors investigated the joint association of SB and PA assessed by the questionnaire (25). The results revealed that the combination of prolonged sitting with a lack of PA was highly prevalent and associated with increased all-cause and cancer-related mortality risks. Overall, these results reinforce the necessity of more precise assessments of movement behavior profiles, which could facilitate a shift toward personalized medicine in cancer patients and survivors.

Research gaps and perspectives

To address these substantial research gaps, we have formulated recommendations for future research (Table 1). First, we encourage large cohort studies to be conducted with device-based measures of SB/PA profiles that assess their associations with incidence, recurrence, and mortality related to cancer at all sites in primary prevention. This would also help to reliably characterize the dose–response relationship between SB/PA and the risk of cancer at different sites. Similarly, post-treatment assessment of SB and PA and defining appropriate movement behavior profiles should be encouraged during the follow-up of cancer survivors. Indeed, a significant decrease in PA levels can be observed following cancer diagnosis and can last for more than 2 years (24). Additionally, it has been observed that a greater decrease in PA is observed among patients with heavier treatments (i.e., radiation and chemotherapy *vs.* surgery only) (26). Thus, physical inactivity and SB could be considered as a potential long-term consequence of cancer, especially in cancer survivors who underwent heavy treatments. Moreover, as studies exhibit methodological discrepancies (e.g., questionnaires, accelerometers, etc.), more consistent and standardized methods are needed when investigating SB and PA. A focused analysis of motion to detect minimal movements (i.e., sit-to-stand transition, leg/body displacement, and very low-intensity exercises) may provide additional information about the functional decline and identify individuals at risk following a cancer diagnosis. As such, it has been reported that breaking sitting time improves the metabolic risk factors in the general population even after adjusting for total SB and MVPA time (27), and recent findings further suggest that interrupting sedentary time may represent an opportunity to mitigate the risk of cancer mortality (16). Commercialized movement trackers have shown satisfactory acceptability in capturing the daily routine of individuals. We suggest building on this platform by developing more complex and sophisticated algorithms to better identify and refine movement behavior profiles. This could help to assess the implications of PA/SB for the evolution of the disease and long-term clinical outcomes.

Furthermore, exercise prescriptions adapted to the functional state of the patient and interventions focusing on SB reduction through education and identification of barriers to PA could be improved and refined (ideally on a daily basis). In the time of precision medicine, characterizing people in terms of movement behavior profile over the lifespan could help to determine individuals at risk for cancer occurrence, recurrence, and death.

Author contributions

GE, DT, and MD conceived the idea, drafted, revised, and edited the manuscript. LD, AR, QJ, and FM revised the manuscript. All authors read and approved the final version of the article.

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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Pre-pandemic physical activity as a predictor of infection and mortality associated with COVID-19: Evidence from the National Health Insurance Service

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Introduction: During the coronavirus disease 2019 (COVID-19) pandemic, many populations have experienced reduced physical activity (PA) levels, weight gain, and increased anxiety and depression. However, according to a previous study, engaging in PA has a positive effect on damages caused by COVID-19. Therefore, this study aimed to investigate the association between PA and COVID-19 using the National Health Insurance Sharing Service Database in South Korea.

Methods: Logistic regression analysis was used to analyze the association of PA with COVID-19 and mortality. The analysis was adjusted for body mass index, sex, age, insurance type, comorbidity, and region of residence at baseline. Disability and lifestyle (weight, smoking, and drinking status) were adjusted consecutively.

Results: The results indicated that engaging in insufficient PA as per the WHO guidelines predicts a higher risk of COVID-19 when controlling for personal characteristics, comorbidity, lifestyle, disability, and mortality.

Discussion: This study revealed the need to engage in PA and manage weight to reduce the risk of infection and mortality associated with COVID-19. Because engaging in PA is an important component of weight management and can help restore physical and mental health after the COVID-19 pandemic, it should be emphasized as a pillar of recovery after COVID-19.

KEYWORDS

physical activity, COVID-19, quarantine, lifestyle, COVID-19-associated mortality

1. Introduction

The novel coronavirus disease 2019 (COVID-19) has been a prominent global issue since its emergence in 2019. It is an infectious respiratory disease with mild-to-severe symptoms, which may include fever, cough, loss of taste or smell, and diarrhea (1, 2). However, in severe cases, chest pain, loss of speech, loss of mobility, and confusion may occur. COVID-19 is rapidly spread by respiratory droplets released during coughing, sneezing, speaking, singing, or breathing by the infected individual (3). Thus, the rapid spread of COVID-19 has caused an unprecedented number of cases and deaths. As of August 2022, there were over 593,236,266 confirmed cases and about 6,448,504 deaths worldwide (4). In South Korea, particularly, the fatality rate of older adults over 80 years old was 2.35% (5).

Recent studies show that COVID-19 has impacted mental health. There is evidence of increased severity of depression compared to those before pandemic (6, 7). It seems that quarantine throughout the COVID-19 pandemic negatively impacted the mental health of previously unaffected individuals; for example, the anxiety and depression of people whose family, colleagues, classmates, or neighbors were affected by quarantine were increased (8). In addition, the risks of anxiety, depression, stress, and sleep disorders in COVID-19 patients were increased (9). Post-traumatic stress symptoms were occasionally experienced after infection, but results concerning physical health were limited (10). However, it is unclear how factors relating to lifestyles are linked to the prognosis of COVID-19.

Engaging in physical activity (PA) has played an important role in improving psychological and physical health. It was found that engaging in regular moderate-to-vigorous PA (MVPA) is associated with reducing anxiety and negative self-perceptions, as well as improving physical health (11). In addition, engaging in MVPA is associated with losing and managing body weight that may predispose individuals to several types of chronic diseases, such as obesity and high blood pressure (12). However, a recent study shows that people spend more time engaging in sedentary behavior and less time engaging in PA than before the pandemic (13). Individuals engaging in PA is found to be more associated with lower risk of COVID-19 and mortality than those who do not meet the recommended PA level (150 min of MVPA at least once a week) (14, 15), although these results did not consider other factors of health such as personal characteristics, comorbidity, and disability level.

Thus, we aimed to examine the associations of MVPA with COVID-19 and mortality. To produce more robust study results, we tried to include controlling variables beyond MVPA, using nationally representative data.

2. Methods

2.1. Database

The National Health Insurance Service (NHIS) of South Korea is a social insurance system for the entire nation, and registration is compulsory; approximately 97% of the Korean population is currently registered (16). The NHIS assists people with scheduling medical checkups every 2 years and records their results automatically. These data include various information such as demographic information, payment specification, consultation statement, diagnosis statements, and prescriptions. With these records they developed the National Health Insurance Sharing Service for researcher to support various studies providing sample cohort DB, customized cohort DB, health screening cohort, etc.

This study used NHIS-COVID19 DB that included 4,363 adult COVID-19 patients in South Korea between January 1, 2020, and July 14, 2020, who had medical records between 2015 and 2018, the most recent data before the pandemic. We selected 67,125 adults for the control group in NHIS DB who also had medical checkup data. We used the most recent records in our study; the final data included COVID-19 status, demographic information, comorbidity, disability status, and lifestyle, including PA and body mass index (BMI). This study conformed to the Guidelines on De-identification of Personal Data of Korea and was approved by the Kyung Hee University's Institutional Review Board (IRB No. KHSIRB20-301[EA]) as a review exemption study. Thus, the requirement for informed consent was waived.

2.2. Variables

2.2.1. PA

PA was measured using a self-report questionnaire from NHIS. Moderate PA (MPA) was measured with the following question: "During the last week, how many times a week and for how many hours a day did you engage in physical activity at a moderate level for more than 10 min (e.g., fast walking, doubles tennis, riding bicycle, cleaning)?" Vigorous PA (VPA) was assessed with the following question: "During the last week, how many days a week and for how many hours a day did you engage in physical activity at a vigorous level for more than 10 min (e.g., running, aerobic, fast riding a bicycle)?" PA was categorized into two groups according to PA guidelines: 150 min of MVPA at least once a week (1 min of VPA = 2 min of MPA). The items have been widely used in the literature (17).

2.2.2. BMI

BMI is a simple obesity indicator calculated as weight/square of height (kg/m^2). In this study, BMI was categorized into four groups according to the World Health Organization (WHO) BMI classification (underweight = BMI $<$18.5, normal range = 18.5 $\leq$ BMI $<$25, overweight = 25 $\leq$ BMI $<$30, obese = 30 $\leq$ BMI).

2.2.3. Covariates

We adjusted for sex, age, region of residence, economic status, the number of comorbidities, disability, smoking status, drinking status, and weight, which are reportedly associated with COVID-19 (18, 19). Residence was categorized into the five regions (Seoul, Daegu, Gyeonggi, Gyeong-buk, and other) of South Korea (from January 1, 2020 to August 14, 2020) with the most confirmed COVID-19 cases.

Economic status was measured using health insurance premiums. Health insurance premiums are categorized into five quintiles. In South Korea, every person must pay part of their income as an insurance premium. Thus, a higher quintile indicates a higher economic status. Basic livelihood security recipients were included in the medical aid.

Comorbidity refers to an underlying condition (e.g., diabetes, hypertension) that may cause and affect other diseases. In this study, the number of comorbidities was investigated with the question: "Among the following diseases, which diseases have you been diagnosed with, or have you been treated for?" with the examples of comorbidity, stroke, heart disease (e.g., myocardial infarction, angina pectoris), hypertension, diabetes, dyslipidemia, pulmonary tuberculosis, and other diseases including cancer.

Disability status included the presence, severity, and type of disability, including non-disabled, physical disability, encephalopathy, visual impairment, hearing impairment, and others. Disabled persons were registered with the Ministry of Health and Welfare of South Korea; hence, the NHIS data included their disability status. Severity and type of disability were measured according to the Act on Welfare of Persons with Disability.

Smoking was measured with the question: "In your life, have you ever smoked over five packs of cigarettes (100 pieces)?" Drinking was measured using the question, "How many times do you drink a week?"

2.3. Statistical analysis

The effects of PA and BMI on infection and mortality associated with COVID-19 were analyzed using logistic regression analysis, which was adjusted for sex, age, insurance type, comorbidities, and region of residence at baseline. Disability and lifestyle (e.g., need for weight management, smoking, and drinking status) were adjusted conjointly. Cases with missing data were excluded from the analysis. The 95% confidence interval (CI) was estimated using the SAS PROC PHREG. Statistical significance was set at $p < 0.05$. Statistical analyses were conducted using the SAS software (SAS Institute Inc., Cary, NC, USA).

3. Results

The analysis included 71,488 participants (62% women) over 20 years of age who had received medical checkups from 2015 to 2018. There were 4,363 COVID-19 confirmed cases (6.1%), including 141 deaths (3.3%; 48 women) (Table 1). Among the participants, 418 people with medical aid were developed COVID-19 (12%), with the highest ratio compared to the other quintiles. According to disability status, severe disability was associated with a higher infection rate (13.6%) than mild disability (6.3%) and non-disability (5.9%). People with comorbidities had a higher infection rate (number of comorbidities: 1 = 8%, 2 = 7%, 3 = 10.4%) than those without comorbidities (5.5%).

Of the confirmed cases, 73.75% of the deaths were of participants aged more than 70 years, while 1.41% were of those under 50 years old. Most deaths occurred in people who lived in Daegu (80 people, fatality rate of 2.8%) and Gyeong-Buk (39 people, fatality rate of 6.8%), whereas only 22 people died in other regions. Regarding comorbidities, 44 patients (1.5%) who had no underlying diseases died, while 97 patients (fatality rate, 1 = 4.2%, 2 = 6.2%, over 3 = 13%) died of COVID-19.

3.1. Associations between PA and COVID-19

According to logistic regression Model 1 of COVID-19 (Table 2), which was adjusted for characteristics and comorbidity, not engaging in sufficient MVPA (95% CI: 0.989–1.119, $p = 0.108$) did not affect the risk COVID-19. According to logistic regression Model 2 of COVID-19, which was additionally adjusted for the need for weight management, smoking, and drinking status, not engaging in sufficient MVPA (OR: 1.116, 95% CI: 1.046–1.191, $p < 0.01$) predicted a higher risk of COVID-19 than engaging in sufficient MVPA. According to logistic regression Model 3 of COVID-19, which was additionally adjusted for disability status, not engaging in sufficient MVPA (OR: 1.078, 95% CI: 1.014–1.147, $p < 0.05$) still predicted a higher risk of COVID-19 than sufficient MVPA.

3.2. Associations between PA and COVID-19-associated mortality

According to logistic regression Model 1 of COVID-19-associated mortality (Table 3), which was adjusted for characteristics and comorbidity, not engaging in sufficient PA (OR: 1.548, 95% CI: 1.051–2.279, $p < 0.05$) predicted a higher risk of COVID-19-associated mortality than engaging in sufficient PA. According to logistic regression Model 2 of COVID-19-associated mortality, which was additionally adjusted for the need for weight management, smoking, and drinking status, not engaging in sufficient MVPA (OR: 1.623, 95% CI: 1.078–2.445, $p < 0.05$) still predicted a higher risk of COVID-19-associated mortality than engaging in sufficient MVPA. According to logistic regression Model 3 of COVID-19-associated mortality, which was additionally adjusted for disability status, engaging in sufficient MVPA (95% CI: 0.96–1.882, $p = 0.085$) did not predict COVID-19-associated mortality. However, the presence of disability and the levels of severity of disability predicted COVID-19-associated mortality.

4. Discussion

This study aimed to determine the effect of MVPA on COVID-19 and the association between BMI and COVID-19, considering disability status. Investigating NHIS data on COVID-19 revealed several associations. Engaging in insufficient MVPA was associated with higher risk of infection and mortality associated with COVID-19, depending on confounding variables.

The importance of engaging in an active lifestyle was found to be influential on the risk of COVID-19 over the pandemic period. The result of this study aligns with those of a recent study, which reported the decrement of PA engagement over the period of COVID-19 (20) and the lower likelihood of developing COVID-19 (14). However, the current study has taken a step forward by utilizing the most recent data available before the pandemic. It is widely known that engaging in adequate MVPA is associated with positive health outcomes. However, the current study adds another piece of information on the role of engaging in MVPA. For example, a special focus should be paid to individuals with disabilities regardless of the type of disabilities. During the pandemic, disadvantaged populations may experience issues with accessing health information and PA programs in local communities. For example, statistics show a 4% decrement in PA participation by individuals with disabilities in 2021, compared to the participation rate in 2020 (21). Thus, it might be important to dedicate effort toward improving their participation. A recent review emphasized the role of supportive environments to stimulate one's autonomy, competence, and relatedness (i.e., social supports from close people) in PA settings (22). Given that older individuals are more susceptible to infection, these efforts must be focused on them. For example, local communities may provide newly developed programs to educate PA leaders, who may motivate older adults in their communities.

Engaging in insufficient MVPA could play an important role in reducing mortality associated with COVID-19. Previously, insufficient MVPA was reported as a negative predictor of all-cause mortality (23). However, the relation has not been confirmed in the patients with COVID-19. Interestingly, the estimates from the mortality results are higher than from the infection results, which suggests the importance of regular MVPA participation. Since the infection is an on-going phenomenon, engaging in MVPA should be recommended in South Korea. Particular attention should be paid to people, who are aged or physically disabled. It is noted that individuals with disability show much higher risks of mortality than those without disability. Thus, barriers to PA should be eliminated,

TABLE 1 Descriptive statistics of COVID-19 infection.

			All		COVID-19 infection				*p*-value	All		COVID-19 mortality				*p*-value
					Infected		Non-infected					Deaths		Survivors		
			n	%	*n*	%	*n*	%		*n*	%	*n*	%	*n*	%	
Domain			71,488	100	4,363	6.1	67,125	93.9	<0.0001	4,363	100	141	3.2	4,222	96.8	<0.0001
Characteristic	Sex	Male	27,044	100	1,615	6.0	25,429	94.0	0.2524	1,615	100	93	5.8	1,522	94.2	<0.0001
		Female	44,444	100	2,748	6.2	41,696	93.8		2,748	100	48	1.7	2,700	98.3	
	Age	20–29	6,550	100	281	4.3	6,269	95.7	<0.0001	281	100	0	0.0	281	100.0	<0.0001
		30–39	6,973	100	400	5.7	6,573	94.3		400	100	0	0.0	400	100.0	
		40–49	11,559	100	757	6.5	10,802	93.5		757	100	2	0.3	755	99.7	
		50–59	19,305	100	1,257	6.5	18,048	93.5		1,257	100	10	0.8	1,247	99.2	
		60–69	15,676	100	991	6.3	14,685	93.7		991	100	25	2.5	966	97.5	
		70–79	7,786	100	465	6.0	7,321	94.0		465	100	44	9.5	421	90.5	
		80-	3,639	100	212	5.8	3,427	94.2		212	100	60	28.3	152	71.7	
	Region of residence	Seoul	4,174	100	267	6.4	3,907	93.6	0.9053	267	100	3	1.1	264	98.9	<0.0001
		Daegu	47,057	100	2,871	6.1	44,186	93.9		2,871	100	80	2.8	2,791	97.2	
		Gyeonggi	3,811	100	224	5.9	3,587	94.1		224	100	10	4.5	214	95.5	
		Gyeong-buk	9,339	100	572	6.1	8,767	93.9		572	100	39	6.8	533	93.2	
		others	7,107	100	429	6.0	6,678	94.0		429	100	9	2.1	420	97.9	
	Health insurance premium	Medical aid	3,497	100	418	12.0	3,079	88.0	<0.0001	418	100	18	4.3	400	95.7	0.0253
		1st quintile	12,336	100	846	6.9	11,490	93.1		846	100	19	2.2	827	97.8	
		2nd quintile	10,485	100	588	5.6	9,897	94.4		588	100	11	1.9	577	98.1	
		3rd quintile	12,612	100	741	5.9	11,871	94.1		741	100	23	3.1	718	96.9	
		4th quintile	14,583	100	769	5.3	13,814	94.7		769	100	25	3.3	744	96.7	
		5th quintile	17,975	100	1,001	5.6	16,974	94.4		1,001	100	45	4.5	956	95.5	
Comorbidity	Number of comorbidities	0	53,053	100	2,893	5.5	50,160	94.5	<0.0001	2,893	100	44	1.5	2,849	98.5	<0.0001
		1	8,524	100	684	8.0	7,840	92.0		684	100	29	4.2	655	95.8	
		2	7,169	100	502	7.0	6,667	93.0		502	100	31	6.2	471	93.8	
		3+	2,742	100	284	10.4	2,458	89.6		284	100	37	13.0	247	87.0	

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TABLE 1 (Continued)

			All		COVID-19 infection				*p*-value	All		COVID-19 mortality				*p*-value
					Infected		Non-infected					Deaths		Survivors		
			n	%	*n*	%	*n*	%		*n*	%	*n*	%	*n*	%	
Disability	Presence	Non-disabled	66,859	100	3,974	5.9	62,885	94.1	<0.0001	3,974	100	107	2.7	3,867	97.3	<0.0001
		Disabled	4,629	100	389	8.4	4,240	91.6		389	100	34	8.7	355	91.3	
	Severity	Non-disabled	66,859	100	3,974	5.9	62,885	94.1	<0.0001	3,974	100	107	2.7	3,867	97.3	<0.0001
		Mild	3,317	100	210	6.3	3,107	93.7		179	100	18	10.1	161	89.9	
		Severe	1,312	100	197	13.6	1,133	86.4		210	100	16	7.6	194	92.4	
	Type	Non-disabled	66,859	100	3,974	5.9	62,885	94.1	<0.0001	3,974	100	107	2.7	3,867	97.3	<0.0001
		Physical disability	2,215	100	139	6.3	2,076	93.7		139	100	11	7.9	128	92.1	
		Encephalopathy	372	100	34	9.1	338	90.9		34	100	4	11.8	30	88.2	
		Visual impairment	483	100	26	5.4	457	94.6		26	100	0	0.0	26	100.0	
		Hearing impairment	875	100	69	7.9	806	92.1		69	100	6	8.7	63	91.3	
		Others	684	100	121	17.7	563	82.3		121	100	13	10.7	108	89.3	
Lifestyle	Smoking	No	53,058	100	3,523	6.6	49,535	93.4	<0.0001	4,061	100	130	3.2	3,931	96.8	0.6757
		Yes	18,430	100	840	4.6	17,590	95.4		302	100	11	3.6	291	96.4	
	Drinking	No	60,961	100	4,061	6.7	56,900	93.3	<0.0001	3,523	100	130	3.7	3,393	96.3	0.0005
		yes	10,527	100	302	2.9	10,225	97.1		840	100	11	1.3	829	98.7	
	Weight management	Unnecessary	36,016	100	2,219	6.2	33,797	93.8	0.5137	2,219	100	70	3.2	2,149	96.8	0.7694
		Necessary	35,472	100	2,144	6.0	33,328	94.0		2,144	100	71	3.3	2,073	96.7	
	BMI	Underweight	2,684	100	148	5.5	2,536	94.5	<0.0001	148	100	4	2.7	144	97.3	0.0928
		Normal	27,927	100	1,576	5.6	26,351	94.4		1,576	100	45	2.9	1,531	97.1	
		Overweight	16,784	100	1,061	6.3	15,723	93.7		1,061	100	27	2.5	1,034	97.5	
		Obese	24,093	100	1,578	6.5	22,515	93.5		1,578	100	65	4.1	1,513	95.9	

PA, physical activity; MVPA, moderate-to-vigorous PA; BMI, body mass index.

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TABLE 2 Results of logistic regression analysis according to COVID-19 infection.

Domain			Model 1				Model 2				Model 3			
			Estimate	95% CI		p-value	Estimate	95% CI		p-value	Estimate	95% CI		p-value
				LR	UR			LR	UR			LR	UR	
PA		Sufficient MVPA	1	1	1	1	1	1	1	1	1	1	1	1
		Insufficient MVPA	1.052	0.989	1.119	0.1078	1.116	1.046	1.191	0.0009	1.078	1.014	1.147	0.016
BMI		Normal	1	1	1	1	1	1	1	1	1	1	1	1
		Underweight	0.985	0.827	1.173	0.8614	1.009	0.847	1.203	0.9194	0.976	0.82	1.161	0.7817
		Overweight	1.127	1.039	1.223	0.0041	1.128	1.039	1.224	0.004	1.128	1.041	1.223	0.0032
		Obese	1.144	1.062	1.232	0.0004	1.182	1.095	1.277	<0.0001	1.172	1.09	1.259	<0.0001
Characteristics	Sex	Male	1	1	1	1	1	1	1	1	1	1	1	1
		Female	1.024	0.958	1.094	0.4873	0.754	0.701	0.81	<0.0001	1.038	0.974	1.105	0.2543
	Age	20–29	1	1	1	1	1	1	1	1	1	1	1	1
		30–39	1.334	1.139	1.562	0.0004	1.304	1.113	1.528	0.001	1.358	1.161	1.588	0.0001
		40–49	1.514	1.312	1.746	<0.0001	1.473	1.276	1.7	<0.0001	1.563	1.359	1.799	<0.0001
		50–59	1.426	1.245	1.633	<0.0001	1.332	1.161	1.528	<0.0001	1.554	1.361	1.774	<0.0001
		60–69	1.301	1.131	1.497	0.0002	1.164	1.01	1.342	0.036	1.506	1.314	1.724	<0.0001
		70–79	1.19	1.015	1.395	0.0318	1.008	0.858	1.185	0.9212	1.417	1.217	1.649	<0.0001
		80-	1.11	0.917	1.345	0.2839	0.907	0.747	1.101	0.3225	1.38	1.149	1.657	0.0006
	Region of residence	Seoul	1	1	1	1	1	1	1	1	1	1	1	1
		Daegu	0.905	0.794	1.032	0.1367	0.898	0.788	1.025	0.1113	0.951	0.835	1.082	0.4453
		Gyeonggi	0.906	0.754	1.089	0.2949	0.916	0.761	1.101	0.3489	0.914	0.761	1.098	0.335
		Gyeong-Buk	0.905	0.777	1.054	0.1985	0.894	0.767	1.042	0.1511	0.955	0.822	1.109	0.5451
		others	0.901	0.768	1.055	0.1953	0.898	0.766	1.053	0.1863	0.94	0.803	1.101	0.4424
	Health insurance premium	Medical aid	1	1	1	1	1	1	1	1	1	1	1	1
		1st quintile	0.568	0.502	0.644	<0.0001	0.564	0.498	0.639	<0.0001	0.542	0.479	0.614	<0.0001
		2nd quintile	0.471	0.412	0.538	<0.0001	0.468	0.409	0.535	<0.0001	0.438	0.384	0.499	<0.0001
		3rd quintile	0.494	0.435	0.562	<0.0001	0.491	0.432	0.558	<0.0001	0.46	0.405	0.522	<0.0001

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TABLE 2 (Continued)

Domain			Model 1				Model 2				Model 3			
			Estimate	95% CI		*p*-value	Estimate	95% CI		*p*-value	Estimate	95% CI		*p*-value
				LR	UR			LR	UR			LR	UR	
		4th quintile	0.429	0.378	0.486	<0.0001	0.419	0.369	0.475	<0.0001	0.41	0.362	0.465	<0.0001
		5th quintile	0.447	0.396	0.505	<0.0001	0.427	0.378	0.482	<0.0001	0.434	0.385	0.49	<0.0001
Comorbidity	Number of comorbidities	0	1	1	1	1	1	1	1	1	1	1	1	1
		1	1.491	1.365	1.629	<0.0001	1.486	1.36	1.624	<0.0001	1.513	1.387	1.65	<0.0001
		2	1.292	1.169	1.429	<0.0001	1.269	1.148	1.404	<0.0001	1.306	1.183	1.44	<0.0001
		3+	1.971	1.725	2.251	<0.0001	1.941	1.698	2.218	<0.0001	2.003	1.762	2.278	<0.0001
Lifestyle	Smoking	No					1	1	1	1	1	1	1	1
		Yes					0.746	0.686	0.812	<0.0001	0.671	0.622	0.725	<0.0001
	Drinking	No					1	1	1	1	1	1	1	1
		yes					0.38	0.334	0.431	<0.0001	0.414	0.368	0.466	<0.0001
	Weight management	Unnecessary					1	1	1	1	1	1	1	1
		Necessary					0.928	0.867	0.992	0.0289	0.98	0.922	1.042	0.5137
Disability	Presence	Non-disabled									1	1	1	1
		Disabled									1.452	1.302	1.618	<0.0001
	Severity	Non-disabled									1	1	1	1
		Mild									1.07	0.927	1.234	0.3581
		Severe									2.5	2.129	2.936	<0.0001
	Type	Non-disabled									1	1	1	1
		Physical disability									1.06	0.89	1.262	0.5166
		Encephalopathy									1.592	1.117	2.268	0.0101
		Visual impairment									0.9	0.606	1.338	0.6035
		Hearing impairment									1.355	1.057	1.736	0.0164
		Others									3.401	2.787	4.15	<0.0001

PA, physical activity; MVPA, moderate-to-vigorous PA; BMI, body mass index.

TABLE 3 Results of logistic regression analysis according to COVID-19 mortality.

Domain			Model 1				Model 2				Model 3			
			Estimate	95% CI		p-value	Estimate	95% CI		p-value	Estimate	95% CI		p-value
				LR	UR			LR	UR			LR	UR	
PA		Sufficient MVPA	1	1	1	1	1	1	1	1	1	1	1	1
		Insufficient MVPA	1.548	1.051	2.279	0.0269	1.623	1.078	2.445	0.0204	1.344	0.96	1.882	0.0846
BMI		Normal	1	1	1	1	1	1	1	1	1	1	1	1
		Underweight	0.737	0.224	2.424	0.6159	0.824	0.246	2.752	0.7524	0.945	0.335	2.665	0.9149
		Overweight	0.829	0.487	1.411	0.4894	0.862	0.504	1.473	0.5859	0.888	0.548	1.441	0.6315
		Obese	1.189	0.769	1.839	0.4368	1.336	0.836	2.134	0.2258	1.462	0.993	2.152	0.0544
Characteristic	Sex	Male	1	1	1	1	1	1	1	1	1	1	1	1
		Female	0.272	0.182	0.405	<0.0001	0.231	0.153	0.35	<0.0001	0.291	0.204	0.414	<0.0001
	Age	20-59	1	1	1	1	1	1	1	1	1	1	1	1
		60-69	4.48	2.213	9.067	<0.0001	4.059	2.001	8.231	0.0001	5.786	2.896	11.562	<0.0001
		70-79	19.832	10.125	38.846	<0.0001	18.229	9.24	35.965	<0.0001	23.367	12.241	44.605	<0.0001
		80-	63.703	31.81	127.573	<0.0001	57.833	28.652	116.731	<0.0001	88.256	46.492	167.54	<0.0001
	Region of residence	Seoul	1	1	1	1	1	1	1	1	1	1	1	1
		Daegu	2.165	0.598	7.835	0.2391	2.079	0.564	7.668	0.2715	2.522	0.791	8.042	0.1178
		Gyeonggi	4.091	0.954	17.531	0.0578	3.761	0.858	16.493	0.0791	4.112	1.118	15.13	0.0334
		Gyeong-buk	3.629	0.967	13.623	0.0561	3.301	0.863	12.622	0.0809	6.439	1.972	21.029	0.002
		others	1.749	0.411	7.437	0.4492	1.556	0.359	6.751	0.555	1.886	0.506	7.029	0.3447
	Health insurance premium	Medical aid	1	1	1	1	1	1	1	1	1	1	1	1
		1st quintile	0.425	0.203	0.888	0.0229	0.443	0.212	0.926	0.0304	0.511	0.265	0.983	0.0445
		2nd quintile	0.552	0.239	1.273	0.1633	0.572	0.248	1.321	0.1909	0.424	0.198	0.907	0.0269

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TABLE 3 (Continued)

Domain			Model 1				Model 2				Model 3			
			Estimate	95% CI		*p*-value	Estimate	95% CI		*p*-value	Estimate	95% CI		*p*-value
				LR	UR			LR	UR			LR	UR	
		3rd quintile	0.824	0.41	1.66	0.5888	0.829	0.41	1.675	0.6012	0.712	0.38	1.335	0.2894
		4th quintile	0.579	0.289	1.16	0.1233	0.593	0.295	1.192	0.1424	0.747	0.403	1.385	0.3542
		5th quintile	0.554	0.292	1.054	0.072	0.563	0.294	1.079	0.0836	1.046	0.598	1.829	0.8746
Comorbidity	Number of comorbidities	0	1	1	1	1	1	1	1	1	1	1	1	1
		1	1.88	1.117	3.164	0.0174	1.815	1.075	3.064	0.0258	2.867	1.78	4.616	<0.0001
		2	1.893	1.119	3.202	0.0173	1.853	1.093	3.141	0.022	4.262	2.664	6.817	<0.0001
		3+	2.303	1.345	3.946	0.0024	2.347	1.362	4.045	0.0021	9.703	6.15	15.31	<0.0001
Lifestyle	Smoking	No					1	1	1	1	1	1	1	1
		Yes					0.305	0.151	0.614	0.0009	0.346	0.186	0.644	0.0008
	Drinking	No					1	1	1	1	1	1	1	1
		yes					1.5	0.733	3.068	0.267	1.143	0.611	2.139	0.6759
	Weight management	Unnecessary					1	1	1	1	1	1	1	1
		Necessary					0.864	0.564	1.325	0.5035	1.051	0.752	1.471	0.7694
Disability	Presence	Non-disabled									1	1	1	1
		Disabled									3.461	2.318	5.168	<0.0001
	Severity	Non-disabled									1	1	1	1
		Mild									2.981	1.729	5.139	<0.0001
		Severe									4.041	2.394	6.822	<0.0001
	Type	Non-disabled									1	1	1	1
		Physical disability									3.106	1.629	5.92	0.0006
		Encephalopathy									4.819	1.668	13.92	0.0037
		Visual impairment									<0.001	<0.001	>999.999	0.9787
		Hearing impairment									3.442	1.458	8.127	0.0048
		Others									4.35	2.372	7.979	<0.0001

PA, physical activity; MVPA, moderate-to-vigorous PA; BMI, body mass index.

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particularly perceived barriers, such as feeling uncomfortable, a lack of time, and other priorities (24). A technique to overcome these barriers could be providing clear intervention based on the stage of intention of individuals with disability. It is important for researchers and regional practitioners to consider levels of motivation and volition (i.e., psychological willingness to participate in PA) (25) to provide proper PA guidelines.

This study has some limitations. First, this study's sampling period (8 months) was relatively short to determine the tendency of COVID-19, as the situation continues to evolve. At the beginning of this study, in August 2020, there were 4,222 confirmed cases and only 141 people had died of COVID-19 in South Korea. However, there are now more confirmed cases and deaths in South Korea. Second, it is difficult to generalize the results of South Korea and apply them to the rest of the world. Furthermore, the fatality rate in South Korea was deferred from the rate of the world. Thus, the results of this study may not be generalized. Finally, COVID-19 variants continue to evolve and affect individuals differently (26). As a result, the results from this study could not be applied to different variants. Thus, further studies must include various cases and variants to strengthen the associative findings between PA and COVID-19. Lastly, the current study did not examine the roles of light PA and sedentary behavior due to the limited data from the secondary source. Future research may include those variables to clarify the results of the current study.

In conclusion, this study examined the role of sufficient MVPA on both COVID-19 and associated mortality and found that engaging in sufficient MVPA may play a role in reducing the risk of COVID-19 and associated mortality. The main implication of the results is that an active lifestyle should be promoted in the community. In addition, urgent implementation is needed for people who are older or physically disabled.

Data availability statement

Data can be accessed with the permission of NHIS. Datasets of NHIS can be found here: https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do.

Author contributions

Conceptualization and analysis: I-HO and S-YP. Writing: SP and HK. 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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Cardiorespiratory fitness, body mass index, cardiovascular disease, and mortality in young men: A cohort study

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Objective: We examined the association between cardiorespiratory fitness (CRF), body mass index (BMI), incidence of major acute cardiovascular events (MACE), and all-cause mortality (ACM).

Methods: We conducted a retrospective cohort study involving 212,631 healthy young men aged 16 to 25 years who had undergone medical examination and fitness testing (2.4 km run) from 1995 to 2015. Information on the outcomes of major acute cardiovascular events (MACE) and all-cause mortality (ACM) were obtained from the national registry data.

Results: During 2,043,278 person-years of follow-up, 371 first MACE and 243 ACM events were recorded. Compared against the first run-time quintile, adjusted hazard ratios (HR) for MACE in the second to fifth quintiles were 1.26 (95% CI 0.84–1.91), 1.60 (95% CI 1.09–2.35), 1.60 (95% CI 1.10–2.33), and 1.58 (95% CI 1.09–2.30). Compared against the "acceptable risk" BMI category, the adjusted HRs for MACE in the "underweight," "increased risk," and "high-risk" categories were 0.97 (95% CI 0.69–1.37), 1.71 (95% CI 1.33–2.21), and 3.51 (95% CI 2.61–4.72), respectively. The adjusted HRs for ACM were increased in participants from the fifth run-time quintile in the "underweight" and "high-risk" BMI categories. The combined associations of CRF and BMI with MACE showed elevated hazard in the "BMI≥23-fit" category, which was more pronounced in the "BMI≥23-unfit" category. The hazards for ACM were elevated across the "BMI<23-unfit," "BMI≥23-fit," and "BMI≥23-unfit" categories.

Conclusion: Lower CRF and elevated BMI were associated with increased hazards of MACE and ACM. A higher CRF did not fully compensate for elevated BMI in the combined models. CRF and BMI remain important targets for public health intervention in young men.

KEYWORDS

cardiorespiratory fitness, body mass index, Asian, young men, major acute cardiovascular event, all-cause mortality

Introduction

Physical activity (1) (PA), cardiorespiratory fitness (2–4) (CRF), and high body mass index (BMI) are powerful determinants of cardiovascular disease (CVD) and all-cause mortality (ACM) risks (5–7). Globally, less than one-quarter of male adolescents are sufficiently active (8), and this proportion declines further in adulthood (9). Having a high BMI is also an increasing concern in East and Southeast Asia, where the increase in obesity prevalence has been particularly rapid in young men (10).

Prospective studies have shown that BMI measured in adolescence and early adulthood predicted subsequent cardiovascular (CV) morbidity and mortality (11, 12). Our knowledge about CRF measured in adolescence and early adulthood has largely been based on cross-sectional studies examining the associations between low CRF and biomarkers of cardiometabolic risk (13, 14). Two recent systematic reviews of longitudinal studies have suggested that high CRF in adolescence could mitigate the adverse cardiometabolic effects of high BMI (15, 16).

There is consistent evidence to show that, among older adults, high CRF either attenuates or entirely mitigates the harmful effects of BMI in what is described as the "fat-but-fit" paradigm (17, 18). Evidence on whether the paradigm might extend to adolescents and young adults is sparse (19, 20). Therefore, to address this gap in the literature, we sought to study the independent and combined associations of CRF and BMI with CVD and ACM risk in healthy young men.

Methods

Study sample

At the age of 16 years, all male citizens and permanent residents of Singapore are required to enlist in the National Service with the majority entering the military. We accessed the electronic training and medical records of the Singapore Armed Forces to obtain the fitness and BMI data of all-male military service personnel (Figure 1). The participants were included in the study if they had had at least one BMI measurement and fitness test recorded in the years 1998–2015. The participants were subsequently excluded if their age at the time of earliest BMI measurement was below 16 or above 25 years. Subsequently, those whose first fitness test results had been conducted 6 years after their first BMI measurement were also excluded. Finally, any of the participants who were deceased before 01 January 2007 were removed from the analytical dataset.

Of the 627,565 unique male participants identified through the two databases, we excluded 224,252 potential participants due to missing BMI data and another 167,511 participants due to missing fitness test information. We excluded 13,516 participants based on our age criterion for BMI and another 3,200 whose first fitness test result was recorded before the first BMI measure. Another 6,453 participants were excluded as their first fitness test had been conducted more than 6 years after the first BMI measurement. Finally, we removed two participants who were deceased before 01 January 2007.

Baseline measurements

Pre-enlistment medical examinations comprised a review of previous medical records, height taken barefoot on a stadiometer, weight measurements taken in underwear on an electronic scale, physical examination, a resting electrocardiogram, a dipstick urine test, blood tests, and a chest X-ray. As a rule, personnel assessed fit by a medical doctor were required to undergo annual physical fitness testing during National Service. For the purposes of this study, the earliest weight and height recorded were used to calculate BMI at baseline. The annual physical fitness test comprised multiple tests of which one was the 2.4 km timed run, also known as the modified Cooper's test (21). The fitness test was typically conducted during basic military training one to three years after the pre-enlistment medical examination. During the test, the participants were required to run six laps on a 400-m running track at the fastest speed possible. The run-times were recorded by a fitness instructor and entered into an electronic database. For this study, the earliest recorded 2.4 km run-time was used as the baseline measure.

Outcome events

The primary outcome of our study was the time to the first major acute cardiovascular event (MACE) defined as acute myocardial infarction (AMI), stroke, coronary revascularization, or CV mortality, whichever had been recorded earlier. Using the national myocardial infarction (22), stroke (23), and cardiac reperfusion (24) registries, we identified all CV events registered from 01 January 2007, the start date of the AMI and stroke registries, until 31 December 2018. Using the national death registry data, we identified all deaths due to coronary heart disease (ICD-9 codes 410 to 414; ICD-10 codes I20 to I25), stroke (ICD-9 codes 430–434 and 436–438; ICD-10 codes 160–169), and sudden death (ICD-9 code 798; ICD-10 code R96). Deaths due to other heart and vascular diseases were identified manually by a physician on the research team to account for all deaths due to CV causes during the same period. The secondary outcome of our study was the time to death of any cause. An ACM event was defined as any death recorded in the national death registry occurring from 01 January 2007 until 31 December 2018.

Study variables

The common identifier for all data points was Singapore's national registration identity card number. Data were collated from the respective databases and joined by data administrators in the National Registry of Diseases Office (NRDO) to maintain strict confidentiality. As event dates were coded according to month and year by the respective registries, we standardized

Abbreviations: ACM, All-cause mortality; AMI, Acute myocardial infarction; BMI, Body Mass Index; CI, Confidence interval; CRF, Cardiorespiratory fitness; CV, Cardiovascular; CVD, Cardiovascular disease; HR, Hazard ratio; MACE, Major acute cardiovascular event; PA, Physical activity; PCI - Percutaneous coronary intervention.

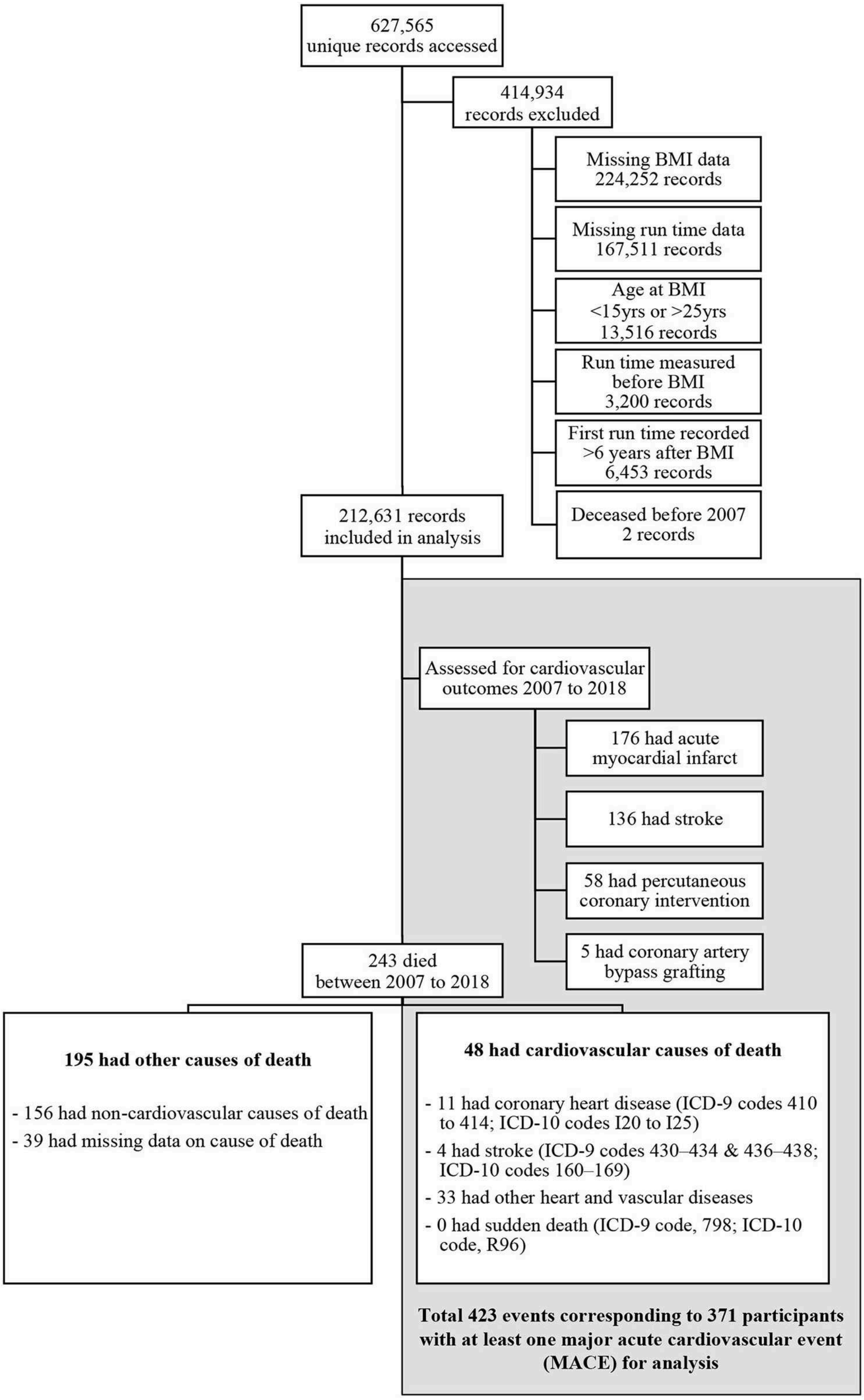

FIGURE 1
Study sample and outcome events.

the event dates to reflect the 15th day of the respective month. All statistical analyses were performed on the final deidentified dataset on a stand-alone terminal at the NRDO's data laboratory.

Statistical analyses

Run-times were converted into seconds before determining the run-time quintile among the participants of the final study sample.

The BMI data were categorized according to the World Health Organization's (WHO) public health action cutoff points for Asian populations (25) that defined the following categories: "underweight" for BMI <18.5 kg/m^2, "acceptable risk" for BMI 18.5 to 22.9 kg/m^2, "increased risk" for BMI 23.0 to 27.4 kg/m^2, and "high risk" for BMI ≥27.5 kg/m^2. Frequencies and percentages were calculated for each run-time quintile and BMI category along with the population mean and standard deviation (SD) of continuous variables. The numbers of the first MACE, the first ACM, the first AMI event, and the first stroke events were compiled for each run-time quintile and BMI category.

Either 01 January 2007 or the date of the first fitness test, whichever was later, was designated as the time of entry into the study period. The onset of the first MACE was specified as the event of interest in primary analyses. Censoring events comprised: Non-CV cause of death, missing causes of death, or being alive at the end of the study period (i.e., 31 December 2018) without the occurrence of MACE during follow-up. The onset of ACM was specified as the event of interest in secondary analyses with the censoring event defined as being alive at the end of the study period regardless of prior MACE. Follow-up time was defined as the time duration from entry to censoring events or the event of interest. Hazard ratios (HR) were estimated using Cox proportional hazard models. The adequacy of the proportional hazard assumptions was assessed using the global goodness-of-fit test proposed by Schoenfeld (26). Run-time quintile and BMI category were the two main exposures of interest. Both the first run-time quintile and the "acceptable risk" BMI category served as references. The basic adjusted models included the year of BMI measurement and the age at the time of entry into the study as confounders. The final models were adjusted for continuous measures of BMI and run-time, where appropriate. To test for linear trends across quintiles (or BMI categories), we assigned numerical values representing the median values of run-time (or BMI) for each run-time quintile (or BMI category). When a test for linear trend returned a non-significant result, we assessed whether the exposure as a categorical variable was a significant factor, meaning at least one of the non-reference HRs was not a significant factor for the model in question. Finally, adapting the approach of Henriksson and coworkers, we created four combined BMI-fitness categories (20) allowing the first to fourth run-time quintile to represent "fit" and the fifth quintile to represent "unfit" participants. A BMI cutoff of 23.0 kg/m^2 that reflected the threshold between the "acceptable risk" and "increased risk" categories in the Asian populations was used to distinguish between "BMI<23" and "BMI≥23" participants. The "BMI<23-fit" category served as the reference in subsequent analyses.

Sensitivity analyses

Where appropriate, we conducted sensitivity analyses to review the robustness of our findings. First, after considering previous evidence of a J-shaped association between BMI and study outcomes (27), we ran additional regression analyses that controlled BMI as a categorical confounding factor. Second, we defined more granular BMI-fitness categories to assess how the selection of cutoff values would affect our estimates. Finally, to address the scenario where the proportional hazards assumption was inadequate, we identified the variable that drove the inadequacy and ran stratified Cox regression models that allowed the strata formed from the identified variable to have different baseline hazards.

MS Excel 2016 (Microsoft Corporation) and STATA Version 13 (StataCorp LLC) were used to conduct all statistical analyses. Findings with a p-value of <0.05 were considered statistically significant. We used the STROBE statement checklist (28) to ensure the completeness of our report.

Conduct and oversight

All authors except the third author conceptualized the study while the sixth author directed the analytical methodology. The first, second, third, and sixth authors planned, executed, and verified the analyses. The original draft was reviewed and edited by all co-authors before submitting for publication. The authors have declared competing interests as listed at the end of this manuscript. No additional funding was required to conduct this study. Any sharing of original data is subject to the approval of the aforementioned data owners. Patients and the public were not involved in the design or conduct of this study. The study protocol was approved by the DSO National Laboratories—Singapore Armed Forces Institutional Review Board, Reference Number 0021/2019.

Results

The final study sample comprised 212,631 healthy male participants who underwent medical examination between 01 January 1998 and 31 December 2015 and had no significant medical history that would have precluded them from participating in maximal intensity physical fitness testing.

At the time of medical examination, the mean age of participants was 19.1 years (standard deviation [SD] 1.4), the mean height was 1.72 m (SD 0.06), and the mean BMI was 21.7 kg/m^2 (SD 3.9). The mean 2.4 km run-time recorded at the first fitness test was 678 s (SD 116). Further participant characteristics within each exposure category are shown in Tables 1, 2 and Supplementary Table 1. There was a positive relationship between BMI and the 2.4-km run-time with a Spearman correlation coefficient of 0.223. With 106,395 (50%) of participants entering the study period on 01 January 2007 and the rest entering between 02 January 2007 and 31 December 2015, the mean age at the year of entry into the study period was 22.4 years (SD 3.3). Primary analyses at the time of the first MACE comprised 2,043,278 person-years of follow-up with each participant contributing on average 9.6 (SD 2.7) years. Secondary analyses of time until ACM comprised 2,044,269 person-years. Of the 371 participants experiencing the first MACE, 176 (47%) participants recorded the first AMI event, 136 (37%) participants recorded the first acute stroke event, 59 (16%) underwent the first PCI procedure, 5 (1%) underwent the first coronary artery bypass grafting procedure, and 48 (13%) died of CV causes. This translated to an incidence rate of 1.82 first MACE per 10,000 person-years. The average age at the time of the first MACE was 33.4 years (SD 4.9). There were 243 deaths due to all causes with 195 (80%) categorized as "non-CV death" or "missing causes of death." This translated to an incidence rate of 1.19 deaths due to all causes per 10,000 person-years. The average age at the time of death was 31.0 years (SD 5.5). Detailed statistics

TABLE 1 Characteristics of the participants by run-time quintile ($n = 212,631$).

	Run time quintile					Total
	Q1	Q2	Q3	Q4	Q5	
n (%)	42,611 (20.0)	42,739 (20.1)	42,244 (19.9)	42,797 (20.1)	42,240 (19.9)	212,631 (100)
Run-time in s						
Range	451 to 585	586 to 643	644 to 676	677 to 725	726 to 1,800	451 to 1,800
Age in years at BMI measurement						
Mean (SD)	18.9 (1.2)	19.0 (1.3)	19.1 (1.3)	19.2 (1.4)	19.4 (1.5)	19.1 (1.4)
Height in m						
Mean (SD)	1.72 (0.06)	1.72 (0.06)	1.72 (0.06)	1.72 (0.06)	1.72 (0.06)	1.72 (0.06)
BMI in kg/m^2						
Mean (SD)	20.6 (2.5)	21.0 (3.0)	21.3 (3.4)	21.8 (3.8)	24.0 (5.3)	21.7 (3.9)
Age at 1st Test in years						
Mean (SD)	20.2 (1.4)	20.4 (1.5)	20.5 (1.5)	20.9 (1.8)	21.5 (2.2)	20.7 (1.8)

BMI, Body mass index.
Q—Quintile.
SD—Standard deviation.

TABLE 2 Frequency counts and column percentages for run-time quintiles and BMI category at baseline ($n = 212,631$).

	Run time quintile					Total
	Q1	Q2	Q3	Q4	Q5	
WHO BMI cutoffs for Asians in kg/m^2	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
"Underweight" $\leq$18.4	7,780 (18)	8,337 (20)	8,011 (19)	7,735 (18)	5,546 (13)	37,409 (18)
"Acceptable risk" 18.5 to 22.9	28,068 (66)	24,989 (58)	22,795 (54)	21,324 (50)	15,653 (37)	112,829 (53)
"Increased risk" 23.0 to 27.4	6,244 (15)	8,056 (19)	9,310 (22)	10,271 (24)	10,725 (25)	44,606 (21)
"High risk" $\geq$27.5	519 (1)	1,357 (3)	2,128 (5)	3,467 (8)	10,316 (24)	17,787 (8)
Total	42,611 (100)	42,739 (100)	42,244 (100)	42,797 (100)	42,240 (100)	212,631 (100)

BMI, Body mass index; WHO, World Health Organization; Q, quintile.

for each run-time quintile and BMI category can be found in the Supplementary Tables 2, 3.

Cardiorespiratory fitness

The association between the 2.4-km run-time and hazard for MACE and ACM are depicted by the hazard ratios (HRs) in Figure 2. Each successive run-time quintile had an incrementally higher unadjusted hazard for MACE. Compared to the first run-time quintile, final adjusted HRs for MACE were 1.26 (95% CI 0.84–1.91), 1.60 (95% CI 1.09–2.35), 1.60 (95% CI 1.10–2.33), and 1.58 (95% CI 1.09–2.30) in the second to fifth quintiles, respectively. The linear trend was nonsignificant ($p = 0.188$) with the HRs plateauing from the third quintile, while the run-time quintile as a categorical variable was a significant factor ($p < 0.001$), suggesting a non-linear trend. The proportional hazard assumption was adequate in the final model for MACE ($p = 0.179$).

Similarly, each successive run-time quintile was associated with an incrementally higher unadjusted hazard for ACM although the associations were generally weaker. Compared to the first run-time quintile, final adjusted HRs for ACM were 1.17 (95% CI 0.74–1.84), 1.38 (95% CI 0.89–2.14), 1.48 (95% CI 0.97–2.27), and 1.68 (95% CI 1.09–2.59) in the second to fifth quintiles, respectively. The linear trend was significant ($p = 0.005$) and the proportional hazard assumption was adequate in the final model for ACM ($p = 0.057$).

Body mass index

The association between BMI and hazard for MACE and ACM are depicted in Figure 3. The "increased risk" and "high risk" BMI categories have higher unadjusted hazards for MACE than the "acceptable risk" BMI category. Compared to the "acceptable risk" BMI category, the final adjusted HRs for MACE were 0.97 (95% CI 0.69–1.37), 1.71 (95% CI 1.33–2.21), and 3.51 (95% CI 2.61–4.72) in

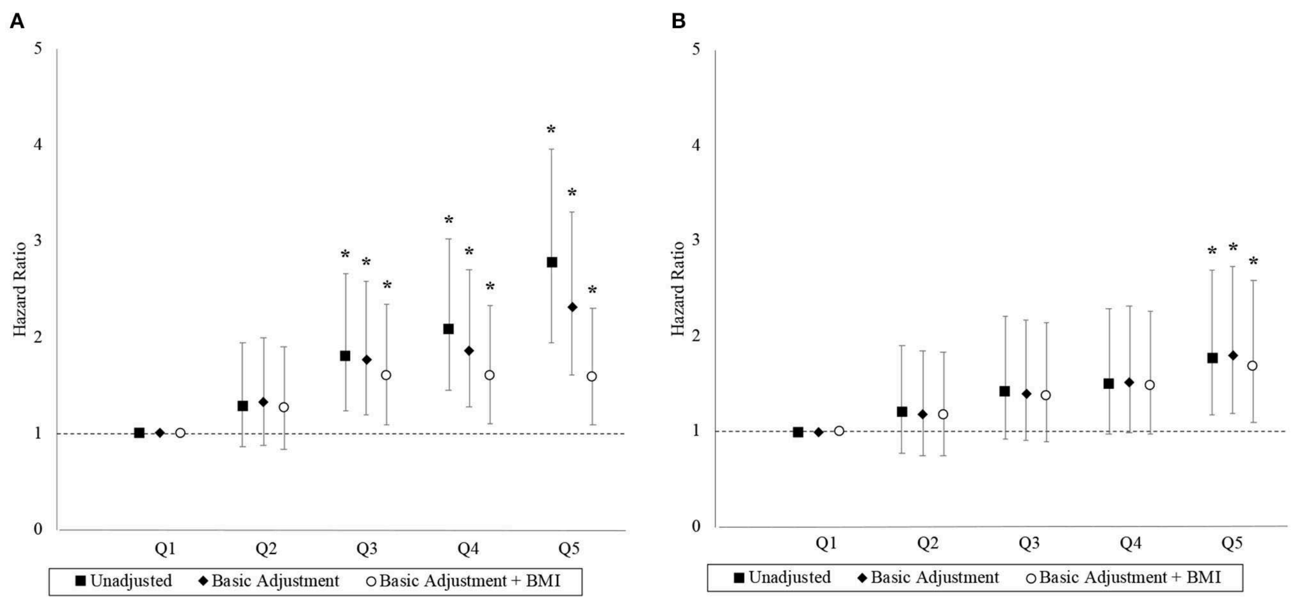

FIGURE 2
Hazard ratios with 95% confidence interval by run-time quintile. Panels **(A, B)** correspond to the MACE and ACM outcomes, respectively. Basic adjustments also included the year of BMI measurement and age at time of entry into the study period as predictors in the models. The models were further adjusted for BMI. An asterisk (*) denotes a hazard ratio that is significantly different from 1 (i.e., $p < 0.05$).

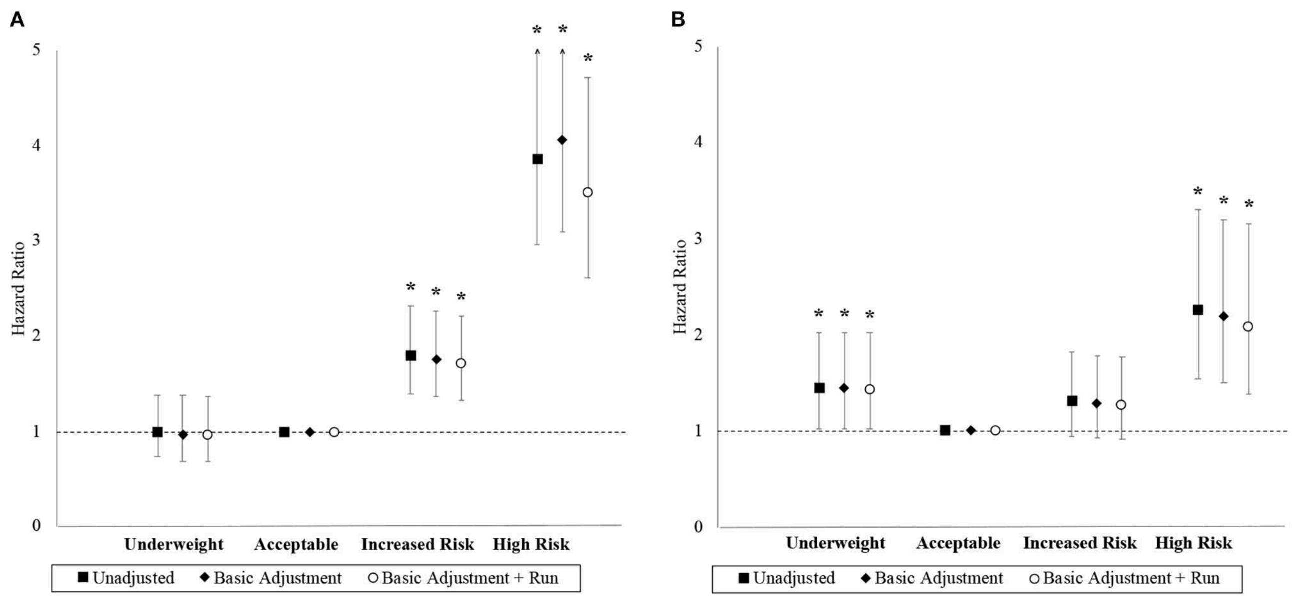

FIGURE 3
Hazard ratios with 95% confidence interval by BMI category. Panels **(A, B)** correspond to the MACE and ACM outcomes, respectively. Basic adjustments also included the year of BMI measurement and age at time of entry into the study period as predictors in the models. Models were further adjusted for the 2.4 km run-time. An asterisk (*) denotes a hazard ratio that is significantly different from 1 (i.e., $p < 0.05$).

the "underweight," "increased risk," and "high risk" BMI categories, respectively. The linear trend was significant ($p = 0.047$), and the proportional hazard assumption was adequate in the final model for MACE ($p = 0.314$).

The "underweight" and "high risk" BMI categories had higher unadjusted hazards for ACM than the "acceptable risk" BMI category, but both the "acceptable risk" and "increased risk" BMI categories had comparable unadjusted hazards. Compared to the "acceptable risk" BMI category, the final adjusted HRs for ACM were 1.43 (95% CI 1.02–2.02), 1.27 (95% CI 0.92–1.77), and 2.08 (95% CI 1.38–3.16) in the "underweight," "increased risk," and "high risk" BMI categories, respectively. Although the linear trend was non-significant ($p = 0.278$), BMI as a categorical variable was a significant factor ($p = 0.024$) with a J-shaped trend observed. The proportional hazards assumption was inadequate in the final model for ACM (p=0.044). Stratified Cox models with the strata corresponding to the "age at

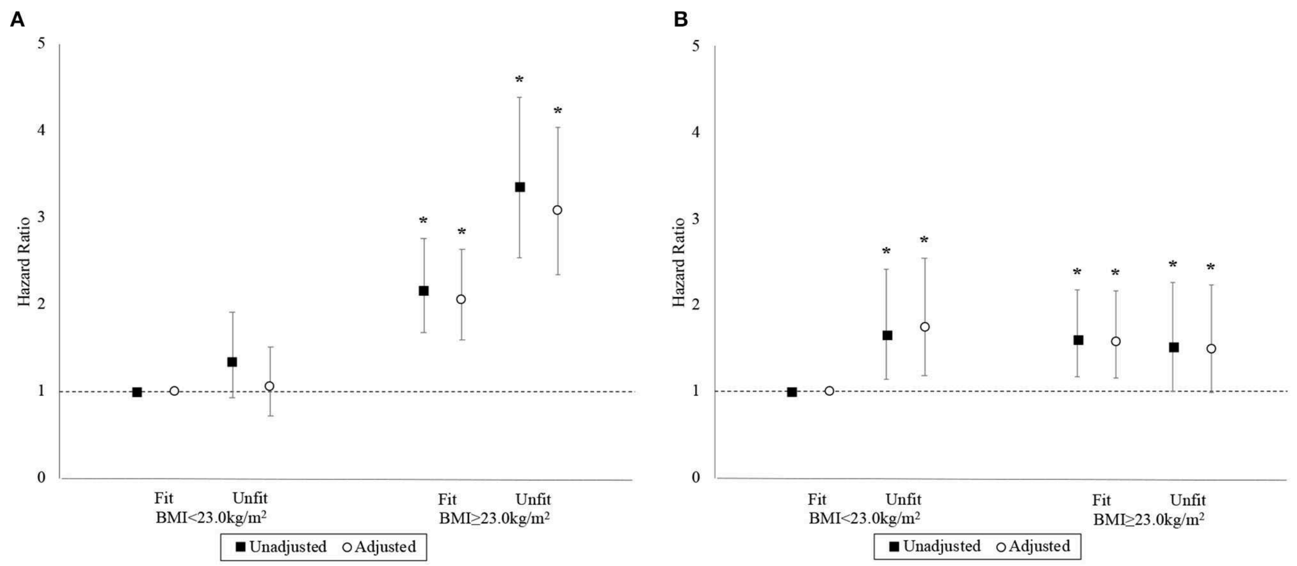

FIGURE 4
Hazard ratios with 95% confidence interval by BMI-fitness category. Panels **(A, B)** correspond to the MACE and ACM outcomes, respectively. Basic adjustments also included the year of BMI measurement and age at time of entry into the study period as predictors in the models. An asterisk (*) denotes a hazard ratio that is significantly different from 1 (i.e., $p < 0.05$).

time of entry into study period" being categorized by its quantiles resolved the non-proportional hazards problem with minimal impact on effect estimates.

Combined associations of cardiorespiratory fitness and body mass index

The associations between the BMI-fitness categories and the hazards for MACE and ACM are depicted in Figure 4. The "BMI<23-unfit" category and the "BMI<23-fit" reference category had similar unadjusted hazards for MACE, while those in the "BMI≥23-fit" and "BMI≥23-unfit" categories experienced markedly greater hazards than the reference category. Compared to the "BMI<23-fit" reference category, final adjusted HRs for MACE were 1.05 (95% CI 0.72–1.51), 2.06 (95% CI 1.60–2.64), and 3.08 (95% CI 2.35–4.04) for the "BMI<23-unfit," "BMI≥23-fit," and "BMI≥23-unfit categories, respectively. The proportional hazard assumption was adequate in the final model for MACE ($p = 0.526$).

Compared to the "BMI<23-fit" reference category, the final adjusted HRs for ACM were 1.74 (95% CI 1.18–2.55), 1.58 (95% CI 1.16–2.16), and 1.49 (95% CI 0.99–2.24) for "BMI<23-unfit," "BMI≥23-fit," and "BMI≥23-unfit," respectively. The proportional hazards assumption was inadequate in the final model for ACM ($p = 0.029$). Yet again, stratified Cox models resolved the non-proportional hazards problem with the same variable identified earlier and minimal impact on effect estimates.

Sensitivity analyses

In the model that controlled for BMI as a categorical variable (Supplementary Figure 1), the effect estimates were largely consistent with the original model for MACE. In the model for ACM, however, the lower bound of the 95% confidence in the fifth run-time quintile dipped to below one, although the test for the trend remained significant ($p = 0.018$).

We created six new BMI-fitness categories comprising three fitness levels along with our original BMI cutoff of 23.0 kg/m^2. "High fitness" comprised the first and second run-time quintiles and "BMI<23-high fitness" served as the new reference category. "Moderate fitness" comprised the third and fourth quintiles, while "low fitness" comprised only the fifth quintile. Crude incidence rates within each category (Supplementary Tables 4, 5) and the Cox model output (Supplementary Figure 2) suggested that the relationships were largely consistent with the output from models that used four BMI-fitness categories.

Among our final adjusted Cox models for ACM, two of the models did not satisfy the proportional hazards assumption. Age at the time of entry into the study period was identified as the variable of concern, and the nonproportional hazards problem was addressed by using models that stratified on this variable (i.e., stratified Cox models). Since differences in HRs were marginal, we reported the results from the Cox model. All final adjusted models for MACE satisfied the proportional hazards assumption.

Discussion

Summary of key findings

This study examined the associations of 2.4-km run-times and BMI with CV morbidity and mortality outcomes in healthy young men. Longer 2.4-km run-times, hence, lower estimated CRF, and higher BMI were associated with an increased hazard of MACE. There was also a significant dose–response effect for the 2.4-km run-time on the hazard of ACM. Combined analyses showed that the membership in the "BMI≥23-fit" category attenuated but did not eliminate the increased risk of MACE associated with increased BMI.

Cardiorespiratory fitness as a predictor of MACE and ACM

Our study has served to further substantiate the findings from studies that described an inverse relationship between CRF and the biomarkers of CVD among adolescents and young adults (13–16). The study was also designed to emulate key studies conducted in older adults (7) that had established CRF as a predictor of MACE and ACM incidence. Primary analyses showed that CVD hazards were elevated 1.60 times from the third run-time quintile, a finding that was consistent with the risk associations observed in a Swedish conscription cohort (20). While the aforementioned cohort produced a linear dose–response curve for the association between CRF and CVD risk, we suspect that differences in study outcomes and follow-up times could explain the absence of the said effect in our sample. Secondary analyses showed that the ACM hazards were elevated 1.68 times in the fifth run-time quintile, an effect estimate that was similar to the previous meta-analysis findings (7).

BMI as a predictor of MACE and ACM

Our analyses reiterate previous findings that elevated BMI in adolescence (11, 12) and early adulthood (29) increase the risks of CVD and ACM. Moreover, the proportion of participants who were classified as having "increased risk" or "high risk" BMI and were shown to experience higher hazards of MACE was 29% in our study. In the Swedish conscription cohort, (20) the proportion of participants who were classified as "overweight" or "obese," i.e., BMI≥25.0 kg/m^2 according to the WHO classification (25) and were shown to experience greater hazards of CVD was 10%. While this difference in proportions was substantial, it is important to note that the Swedish sample was recruited from 1972 to 1994, when global obesity prevalence had only just begun to accelerate (10). Secondary analyses showed elevated hazards of ACM at the upper and lower extremes of the BMI spectrum, a finding that was consistent with the risk associations reported in an Israeli cohort of military conscripts (30). Our study, therefore, strongly reinforces the notion that ACM risks exhibit a J-shaped distribution in relation to BMI even among healthy young adults (27, 31).

Combined associations of cardiorespiratory fitness and BMI

Previous studies in adolescents (15) and older adults (4) have described how high CRF could fully compensate for the negative effects of elevated BMI. Our primary analyses demonstrated an attenuating effect of shorter run-times on MACE risks associated with elevated BMI that has been described in an older cohort (32). Secondary analyses did not show any attenuating effect of shorter run-times on ACM risks associated with elevated BMI. A relatively short duration of follow-up might explain these discrepancies with the literature (33). On the opposite end of the spectrum, however, our finding that run-times, hence estimated CRF, could differentiate ACM risk among participants with a BMI of <23.0 kg/m^2 might offer additional insights into the early health hazards associated with a low BMI (31).

Implications

Under primary care settings, the 10-year CVD risk estimation is a key component of CVD prevention for adults aged 40 to 75 years (34). Our study suggests that measures of BMI and CRF could potentially be used in CVD risk estimation in men under the age of 40 years. Moreover, where monitoring and surveillance data for CRF are available (35, 36), our findings could aid in determining key thresholds for public health action. Finally, our findings on the combined effects of estimated CRF and BMI offer a degree of nuance to the discussion on the "fat-but-fit" paradigm (19) to suggest that superior fitness might not fully eliminate the adverse effects of elevated body weight in young men.

Strengths

To the best of our knowledge, this is the first large-scale longitudinal study examining BMI, estimated CRF, and the longitudinal risk of CVD events and ACM in young Asian men. Our strict eligibility criteria produced a relatively homogeneous sample that had been in good health at baseline, thus assuring the temporality between exposures and outcomes. Our reliance on national registry data, where the reports of death and AMI events are required by law, also increased the quality of outcome measures.

Limitations

A large number of potential participants were excluded on the basis of missing data, thus limiting the representativeness of the sample. Furthermore, most studies cited in our discussion used criterion-measure laboratory protocols involving either a treadmill or cycle ergometer to assess CRF (37). While a meta-analysis of 123 studies based on the criterion-validity of field-based test protocols clearly favors the modified Cooper's test (38), we must consider how misclassification in our exposure data might have attenuated the effect estimates in our population. Our study population also comprised healthy male military conscripts of Asian ethnicity, meaning that comparisons with other populations need to account for putatively greater CRF, lower BMI, and Asian BMI cutoff values in our sample.

Concerning the MACE outcomes, the registry data were consistently available from 01 January 2007, and information on losses to follow-up, for example, through migration, were lacking. The resulting undercount of MACE and inflated follow-up time indicate that we have likely underestimated the MACE incidence for our cohort. Finally, important demographic factors, such as ethnicity, education, socioeconomic status, and smoking, and clinical factors, such as blood pressure, serum lipid concentration, and fasting glucose levels, were not captured in this study limiting our ability to account for important confounders of the relationships between BMI, CRF, MACE, and ACM. This implies that our findings might not be applicable in the context of individual risk management but are potentially more relevant to public health promotion.

Conclusion

While previous research on adolescent males and young men focused on the relationship between CRF, BMI, and cardiometabolic risk factors, our analyses examined the incidence of hard CVD outcomes and ACM within a relatively short duration of follow-up. Our study showed that a greater estimated CRF did not fully mitigate the hazards associated with elevated BMI, thus weakening the argument of a "fat-but-fit" paradigm in young men. Therefore, this study suggests that public health messaging strategies targeting adolescent males and young men ought to address CRF and BMI concurrently.

Evidence before this study

The "fat-but-fit" paradigm, which is now commonplace in health promotion, indicates that high cardiorespiratory fitness (CRF) mitigates the harmful effects of high body mass index (BMI). This phenomenon is largely underpinned by evidence from older populations.

Added value of this study

In our study, young Asian men entering the National Service in Singapore demonstrated that CRF and BMI in adolescence and early adulthood are powerful determinants of cardiovascular disease and all-cause mortality. While a high CRF did not completely mitigate the risks associated with high BMI, a strong attenuating effect was demonstrable within a relatively short duration of follow-up.

Implications of all available evidence

Our findings reiterate the need for population-wide physical activity and CRF promotion that is concurrent with obesity prevention in adolescence and early adulthood.

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.

Ethics statement

The study protocol which involved human participants was reviewed and approved by DSO National Laboratories - Singapore Armed Forces Institutional Review Board, Reference Number 0021/2019. The Ethics Committee waived the requirement of written informed consent for participation.

Author contributions

AG, JY, WC, KY, and FM-R conceptualized the study while CT directed the analytical methodology. AG, JY, JN, and CT planned, executed, and verified the analyses. The original draft was reviewed and edited by all co-authors before submitting for publication.

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Conflict of interest

JY—treasurer, Singapore Cardiac Society. Has received speaker's honorarium from Biosensors, Boston Scientific, Edwards, Johnson & Johnson, Kaneka, Medtronic, and Terumo in the past 36 months. KY—Vice-Chair and Immediate-past Chair Chapter of Cardiologists, Academy of Medicine Singapore, Council Member Singapore Cardiac Society.

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1076065/full#supplementary-material

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Acute effects of different exercise forms on executive function and the mechanism of cerebral hemodynamics in hospitalized T2DM patients: a within-subject study

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Objective: This study aimed to investigate the acute effects of aerobic exercise (AE), resistance exercise (RE), and integrated concurrent exercise (ICE; i.e., AE plus RE) on executive function among hospitalized type 2 diabetes mellitus (T2DM) inpatients, and the mechanism of cerebral hemodynamics.

Methods: A within-subject design was applied in 30 hospitalized patients with T2DM aged between 45 and 70 years in the Jiangsu Geriatric Hospital, China. The participants were asked to take AE, RE, and ICE for 3 days at 48-h intervals. Three executive function (EF) tests, namely, Stroop, More-odd shifting, and 2-back tests, were applied at baseline and after each exercise. The functional near-infrared spectroscopy brain function imaging system was used to collect cerebral hemodynamic data. The one-way repeated measurement ANOVA was used to explore training effects on each test indicator.

Results: Compared with the baseline data, the EF indicators have been improved after both ICE and RE ($p < 0.05$). Compared with the AE group, the ICE and RE groups have demonstrated significant improvements in inhibition (ICE: MD = − 162.92 ms; RE: MD = −106.86 ms) and conversion functions (ICE: MD = −111.79 ms; RE: MD = −86.95 ms). Based on the cerebral hemodynamic data, the beta values of brain activation in executive function related brain regions increased after three kinds of exercise, the EF improvements after the ICE showed synchronous activation of blood flow in the dorsolateral prefrontal cortex (DLPFC), the frontal polar (FPA) and orbitofrontal cortex (OFC), the improvement of inhibitory function after RE displayed synchronous activation of DLPFC and FPA, and AE mainly activates DLPFC. The HbO_2 concentration in the pars triangularis Broca's area increased significantly after AE, but the EF did not improve significantly.

Conclusion: The ICE is preferred for the improvements of executive function in T2DM patients, while AE is more conducive to the improvements of refresh function. Moreover, a synergistic mechanism exists between cognitive function and blood flow activation in specific brain regions.

KEYWORDS

aerobic exercise, resistance exercise, type 2 diabetes, integrated concurrent exercise, executive function, brain activation

1. Introduction

Diabetes mellitus is the third non-communicable disease threatening human health worldwide (1). According to the global diabetes map published by the International Diabetes Federation, 537 million people were living with diabetes worldwide in 2021, and the number is expected to rise to 643 million by 2030 and 783 million by 2045. The number of diabetics in China accounts for one-quarter of the world (∼140.8 million), ranking first globally, and is expected to increase to 175 million by 2045 (2).

As the highest and most complex cognitive function (3), executive functions (EF) include three sub-functions: inhibition, refresh, and transformation. Clinical evidence showed that the inhibitory, conversion, and refresh function scores in T2DM patients were 12, 21, and 7% lower than those age-matched non-T2DM patients, respectively (4), and the risk of EF injury in middle-aged and older T2DM patients was 19% higher than that in age-matched healthy people (5). Notably, T2DM inpatients had a higher risk of cognitive impairment due to decreased physical activity, depressed mood, and social isolation than patients with T2DM in the community or outpatient setting (6). Studies have found that 13–63% of hospitalized patients have cognitive impairment of varying degrees (7). The incidence of cognitive impairment in hospitalized patients with T2DM was 37.9%, 50.7% of which were EF injuries (8).

As an economical, green, and safe way to prevent diabetes, exercise has been applied to improve EF in hospitalized patients with T2DM (9). To date, aerobic exercise (AE) and resistance exercise (RE) are the two main exercise formats in T2DM patients, and integrated concurrent exercise (ICE; i.e., AE plus RE) has got increased recognition in its efficacy in cognitive function among T2DM patients (10, 11). However, no consensus has been made regarding the preferred exercise format in EF improvement among T2DM inpatients. Some evidence even revealed little effects of 24 weeks of balance combined with resistance training (12) or 10 years of AE (13) on EF in patients with T2DM. Except for the differences in test parameters, the underlying mechanisms of the inconsistent results toward exercise efficacy in EF of T2DM patients remains unknown.

Functional near-infrared spectroscopy (fNIRS) is a non-invasive and real-time way to monitor the cerebral blood oxygen by taking the brain tissue blood volume and oxygen as an information carrier. Cerebral hemodynamics refers to the changes and distribution of blood volume and oxygen in the cerebral cortex. Studies applying fNIRS and EF tasks together have revealed that an acute AE can improve EF and increase cerebral blood flow activation levels among older adults and college students (14–16). In addition, one study has applied the same exercise in both healthy and type 1 diabetic adolescents, and the results showed that people with diabetes would have higher activation in the frontal-parietal network. However, few studies have examined the exercise effects on EF and cerebral blood flow activation together among T2DM inpatients.

Based on the current knowledge and study problems, this study aimed to explore the acute effects of AE, RE, and ICE on each EF indicator in inpatients with T2DM, and the fNIRS was used to explore the underlying cerebral hemodynamic mechanism.

2. Methods

2.1. Study design and participants

A cross-sectional, within-subject design was applied in this study. The sample size was estimated using the G*power 3.1 software. Based upon the results from a related study which examined the acute effects of AE on EF in older adults (16), a moderate effect ($f = 0.27$) was applied with 80% power to calculate the required sample size. Considering 10% drop-out rate, 21 participants were needed. A total of 30 hospitalized T2DM patients aged between 45 and 70 years were recruited from the Endocrinology Department of the Jiangsu Geriatric Hospital. Participant recruitment was done by a chief physician and a researcher. Eligible participants should be (1) with no severe diabetic retinopathy, diabetic nephropathy, or diabetic foot; (2) with normal vision and color discrimination, no color weakness, color blindness, or serious eye disease; and (3) stable and can complete three (non-continuous) sessions of moderate-intensity AE or RE under special supervision for 20 min. The exclusion criteria were (1) glycosylated hemoglobin (HbA1c) ≥ 9%; (2) cognitive dysfunction (Mini-mental State Examination score: education level of primary school < 20 and education level of junior high school and above <24); (3) suffering from depression, mental illness, or a family history of mental illness; (4) drug and alcohol abuse (daily taking more than three drugs); and (5) exercise limitations, such as muscle insufficiency, joint disease, cardiovascular disease, respiratory disorders, or other exercise contraindications to T2DM. Participants were required to sign informed consent before the formal study but were blinded for the primary test outcome of the study.

According to the ACSM's classification of AE intensity (17) and the commonly used exercise intensity for diabetic participants (18, 19), the moderate intensity of AE was set as 60–70% of the maximum heart rate of each individual (220—age). At the same time, based on the ACSM's recommendations on exercise intensity for patients with no regular exercise habits (20) and with the consideration of the commonly applied exercise intensity (21), the moderate intensity of RE was set at 60–70% 1RM. The participants were asked to perform 30 min of AE, RE, and ICE, including 20 min exercise and 10 min warm-up and stretching before and after exercise on separate days with 48 h time intervals. All the participants finished the four times tests in a four-part sequence using a Latin square counterbalancing design to reduce the impact of potential practice effects (22). The assignment of the subjects' exercise order was done by the researcher alone. To avoid the potential time effects on blood glucose fluctuation, tests were conducted at 9:30–10:30 a.m. This study has obtained the approval of the ethics committee of Nanjing Normal University (2022060013).

2.2. Experimental procedure

Before the experiment, basic information about the participants was collected, and cognitive function, cardiopulmonary function, and muscle strength were evaluated to determine the feasible range of moderate-intensity exercise. Four kinds of strength training equipment (chest push/row trainer, KY-701; inner and lateral thigh muscle trainer, KY-702; kick hook trainer, KY-703; and abdominal muscle and back muscle trainer, KY-705) were used to evaluate the 1RM value of individuals by counting the number and resistance level of specific movements completed by corresponding muscle groups within 1 min.

The formal experimental procedure of this study consists of four parts: baseline tests, AE, RE, and ICE. Participants are suggested to be free of vigorous exercise 12 h before tests and arrive at the lab 15 min before formal tests. AE was performed using a Magneto bicycle (Zhiqi, HG-HRUB150T). A heart rate belt (Polar, OH1) was used to monitor heart rate during exercise, and the average intensity was maintained within 60–70% of the maximum heart rate. RE is completed based on the four kinds of strength training equipment, which were adjusted to ensure that the individual exercise intensity was within the 60–70% 1RM. Each movement should be completed 8–12 times/group × 3 groups. The 20 min ICE included AE and RE, and 10 min for each.

After each test session, the self perceived exertion was assessed to ensure the whole exercise was performed at the moderate intensity level, and participants' blood glucose was measured before and immediately after exercise to ensure exercise safety, we paid close attention to the levels of various glucose and lipid metabolism indexes of patients during the exercise experiment.

2.3. Outcomes

Three EF tests were performed using the E-Prime 3.0 system, including the Stroop test, the More-odd shift test, and the 2-back test. The system records the participants' reaction time and accuracy during the test. In addition, we further extracted the Stroop interference (the difference between the mean value of the response time of the inconsistent task and the mean value of the response time of the consistent task), the switch response time of the conversion task (the difference between the mean value of the response time of the converted part and the mean value of the response time of the non-converted part), and the correct response time and the number of the correct response of the refresh task. Referring to existing studies (23, 24) and fNIRS data collection in this experiment and the actual situation of the participants, the specific settings of the three executive function tests are as follows.

In each Stroop trial, the computer screen presented a 500-ms "+", a 500-ms color word stimulus, and a 3,000-ms empty screen rest in the middle. Color word stimulus refers to four kinds of Chinese characters randomly matched with red, blue, green, and yellow font colors (divided into two types of stimulus, consistent and inconsistent, according to whether the meaning and color are consistent). Participants are asked to press the keyboard to judge the color of the stimulus as soon as possible (red according to D, yellow according to F, green according to H, and blue according to J). The tests included 10 trials for practice and 62 trials for formal trials (16 trials for consistent stimulation and 46 trials for inconsistent stimulation) for a total of 4.8 min. In each trial of the More-odd shifting test, a 500 ms fixation point "+" was presented in the center of the computer screen, followed by 1,500 ms of digital stimulation (1–9, excluding 5) and 3,000 ms of empty screen rest. The participants were required to convert and judge according to the color of the numbers. When the numbers were black, the size of the numbers was judged (according to the F for <5 and according to the L for more than 5), while the number is green means the requirements to judge the parity (according to the J for odd numbers and according to the K for even numbers). This task included 18 trials for practice and 88 trials for formal tests. The duration is 8.83 min. In each trial of the 2-Back test, the computer screen presented 1,000 ms of stimulus numbers (including 2, 4, 5, 7, 9) in the center, followed by a 3,000-ms empty screen rest. The participants were asked to judge the consistency of numbers by checking if the number was the same as the number presented separately (according to the Y for same and according to the N for different). The task consisted of practicing 12 trials and formally testing 54 trials with a duration of 4.4 min.

The multi-channel fNIRS system (NirSmart-6000A, Danyang Huichuang Medical Equipment Co., Ltd., China) was used to continuously collect the change data of local cerebral oxygenated hemoglobin concentration (HbO_2) during EF tests. According to the distribution of EF neural-activated brain regions, the fNIRS optical cap mainly covered the prefrontal cortex (PFC) in this experiment. The cap is designed based on the 10/20 international standard lead system. It consists of seven light source transmitting probes and seven light source receiving probes to form 19 effective channels. The light source wavelength is 730 nm, the receiving wavelength is 850 nm, the sampling rate is 11 Hz, and the average distance between the emitter and the detector is 30 mm.

3. Data collection

The E-Data Aid of the E-prime 3.0 system was used to derive the accuracy and overall response time data of EF tests in four experiments per participant, and then we calculated the mean of the data. According to the mark set in the E-prime 3.0 system, the fNIRS optical density data of each trial in the test were intercepted and preprocessed using the Preprocess module in NirSpark1.7.5. The signal standard deviation threshold was set as 6 and the peak threshold as 0.5. The spline interpolation method was used to identify and remove motion artifacts. The noise and interference signals were filtered at 0.01–0.2 Hz. According to the modified Beer–Lambert law, optical density was converted to blood oxygen concentration. The beta value of brain activation after different exercises was calculated in the general linear model (GLM) module of NirSpark1.7.5, and the beta value was used as an indicator to measure the activation degree of corresponding brain regions. The descriptive statistics were reported as mean ± standard deviation.

4. Data analysis

The accuracy and response time of each EF test of 30 participants and the mean value of HbO_2 concentrations in 19 channels were analyzed by using SPSS25.0 statistical software for one-way repeated measures ANOVA for different exercise types (Baseline, AE, RE, and ICE). The Bofferoni was used to correct the significance level of multiple comparisons in the *post-hoc* analysis. An independent sample *t*-test was used to examine gender effects on demographic indicators. The *p*-value of <0.05 was considered a statistical significance.

5. Results

5.1. Basic information of participants

A total of 36 qualified participants were recruited for this study, of which 30 completed the whole experiment, six dropped out during the experiment, three did not complete three times of exercise due to illness limitation, one did not complete three times of refresh function tests due to physical discomfort after exercise, and one was discharged early due to conflict between temporary treatment arrangement and experiment time. Few female participants (1/5 of all participants) were affected by exercise willingness and illness. There were significant differences between male and female participants only in height ($t = 4.58$, $p < 0.001$). There were no significant gender differences in other indicators ($p > 0.05$). In addition, the mean BMI of women was higher than that of men, which was in the overweight range (≥24 kg/m^2). The average WHR of the participants was generally high, indicating abdominal obesity. Participants were in the age range of 45–70 years, and the median age was 65 years. Approximately 93.3% of the participants had a high school education or above and were well educated without cognitive impairment (Table 1). All participants had their conditions under control during hospitalization and obtained the doctor's permission to exercise before carrying out the exercise experiment. There were no aggravations or injuries during the whole experiment.

TABLE 1 Basic information of participants.

Index	N (%)/Mean (±SD)		
	Male	Female	Overall
N^a	24(80%)	6(20%)	30
N^b	22 (92%)	6 (100%)	28 (93%)
Age (years)	64.71 ± 5.47	62.00 ± 8.00	64.17 ± 5.99
Height (cm)	171.83 ± 5.50	160.17 ± 5.95*	169.50 ± 7.25
Weight (kg)	69.55 ± 9.64	65.40 ± 8.75	68.72 ± 9.47
BMI (kg/m^2)	23.48 ± 2.95	25.45 ± 3.15	23.87 ± 3.05
WHR	0.93 ± 0.03	0.94 ± 0.03	0.93 ± 0.03
MMSE Score	27.05 ± 1.62	27.00 ± 2.37	26.77 ± 2.05
FBG (mmol/L)	7.50 ± 2.12	7.26 ± 2.30	7.45 ± 2.11
2hPG (mmol/L)	14.74 ± 4.10	14.42 ± 3.34	14.68 ± 3.92
HbAc1 (%)	8.56 ± 2.31	7.38 ± 1.19	8.32 ± 2.17
TC (mmol/L)	4.10 ± 1.12	4.23 ± 0.96	4.13 ± 1.07
TG (mmol/L)	1.61 ± 1.07	1.31 ± 0.39	1.55 ± 0.97
LDL-C (mmol/L)	2.39 ± 0.96	2.41 ± 0.67	2.39 ± 0.89
HDL-C (mmol/L)	0.96 ± 0.25	1.07 ± 0.10	0.98 ± 0.23

*$p < 0.05$.
N^a, number of all participants; N^b, number of participants with middle school experience and above; BMI, body mass index; WHR, waist-to-hip ratio; MMSE, Mini-mental State Examination; HbA1c, glycosylated hemoglobin type A1c; TC, total cholesterol; TG, triglyceride; FBG, fasting blood glucose; 2hPG, 2 h postprandial blood glucose; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein.

5.2. Executive function data

5.2.1. Inhibition function data

The results of one-way repeated measurement analysis of variance showed that the four tests had a significant effect on the accuracy of inconsistent tasks [$F_{(3,87)} = 5.88$, $p = 0.003$, partial $\eta^2 = 0.169$]. Compared with the baseline level, RE and ICE can effectively improve the accuracy of inconsistent tasks (resistance: mean difference = 6.40%, $p = 0.04$; ICE: mean difference = 8.19%, $p = 0.012$). After RE, the accuracy of consistent tasks improved the most (RE> ICE> AE); and after ICE, the accuracy of inconsistent tasks improved the most (ICE> RE> AE).

All four tests showed significant effects on response time under consistent [$F_{(3,87)} = 14.38$, $p < 0.001$, partial $\eta^2 = 0.331$] and inconsistent [$F_{(3,87)} = 12.47$, $p < 0.001$, partial $\eta^2 = 0.301$] tasks. Both RE and ICE significantly reduced reaction time for consistent (RE: mean difference = −180.09 ms, $p < 0.001$; ICE: mean difference = −219.39 ms, $p < 0.001$) and inconsistent (RE: mean difference = −149.54 ms, $p = 0.01$; ICE: mean difference = −205.59 ms, $p < 0.001$) tasks compared to baseline levels. In addition, compared with AE, both consistent (ICE: mean difference = −129.12 ms, $p = 0.002$; RE: mean difference = −89.83 ms, $p = 0.006$) and inconsistent (CE: mean difference = −162.92 ms, $p<0.001$; RE: mean difference = −106.86 ms, $p = 0.001$) task response times were significantly reduced after ICE and RE.

There was no significant difference in Stroop interference [$F_{(3,87)} = 1.13$, $p = 0.33$, partial $\eta^2 = 0.038$] to the four tests, but the improvement trend of the amount of reaction time conflict after the three types of exercise was from large to small: ICE > RE> AE.

5.2.2. Conversion function data

The results of one-way repeated measurement analysis of variance showed that there were significant differences in the accuracy [$F_{(3,87)} = 3.80$, $p = 0.013$, partial $\eta^2 = 0.116$] and response time [$F_{(3,87)} = 0.51$, $p < 0.001$, partial $\eta^2 = 0.249$] of the four tests. Compared with the baseline level, the task accuracy (mean difference = 7.68%, $p < 0.001$) and response time (mean difference = −100.69 ms, $p < 0.001$) were significantly improved after ICE. After RE, only the task response time improved significantly (mean difference = −75.85 ms, $p = 0.039$). In addition, compared with AE, ICE (mean difference = −111.79 ms, $p < 0.001$) and RE (mean difference = −86.95 ms, $p = 0.021$) showed a significant reduction in task response time, but no significant difference in switch reaction time. However, compared with the baseline level, the conversion response showed a decreasing trend after the three types of exercise, and the decreasing amplitude in descending order was ICE > RE > AE.

TABLE 2 Performance of EF tests after different exercises.

EF	Group		Baseline	AE	RE	ICE
Inhibitory function	Accuracy rate (%)	Consistent	92.91 ± 1.16	92.29 ± 1.36	97.29 ± 0.54	92.65 ± 1.87
		Inconsistency	83.44 ± 1.93	86.34 ± 1.64	89.84 ± 1.38#	91.63 ± 1.14#
	Overall reaction time (ms)	Consistent	1,166.83 ± 304.72	1,076.57 ± 262.52	986.74 ± 252.88#*	947.45 ± 200.08#*
		Inconsistency	1,285.08 ± 291.78	1,242.40 ± 281.87	1,135.54 ± 270.43#*	1,079.49 ± 253.73#*
	Stroop interference (ms)	Inconsistency-Consistent	118.25 ± 123.79	165.83 ± 118.53	148.80 ± 86.91	132.05 ± 142.15
Conversion function	Accuracy rate (%)		85.08 ± 1.39	87.66 ± 1.32	89.77 ± 1.13	92.76 ± 0.83#
	Overall reaction time (ms)		1,124.08 ± 167.07	1,135.17 ± 186.18	1,048.22 ± 165.44#*	1,023.39 ± 185.37#*
	Switch reaction time (ms)		382.42 ± 162.94	365.72 ± 205.07	365.17 ± 148.90	341.98 ± 145.11
Refresh function	Accuracy rate (%)		66.68 ± 2.44	75.13 ± 2.02	77.77 ± 2.12	81.67 ± 1.77#
	Correct responses (n)		29.34 ± 10.75	33.06 ± 8.88	34.22 ± 9.34	35.93 ± 7.80#
	Correct reaction time (ms)		1,120.25 ± 296.26	912.87 ± 190.57#	963.19 ± 209.97#	968.34 ± 225.17#
	Reaction time (ms)		1,107.72 ± 265.55	1,027.23 ± 216.36	964.75 ± 210.00#	966.10 ± 219.57#

AE, aerobic exercise; RE, resistance exercise; ICE, Integrated concurrent exercise.
#$p < 0.05$, indicating a significant difference from the baseline level.
*$p < 0.05$, indicating significant difference with aerobic exercise.

5.2.3. Refreshing function data

The four tests showed significant differences in the number and rate of correct responses [$F_{(3,87)} = 3.54$, $p = 0.018$, partial $\eta^2 = 0.109$], reaction time [$F_{(3,87)} = 6.33$, $p = 0.001$, partial $\eta^2 = 0.179$], and correct response time [$F_{(3,87)} = 6.11$, $p = 0.004$, partial $\eta^2 = 0.174$]. Compared with the baseline level, the number of correct responses (mean difference = 6.60, $p = 0.027$), correct rate (mean difference = 14.99%, $p = 0.027$), and reaction time (mean difference = −141.62 ms, $p = 0.007$) were significantly improved after ICE. Reaction time (mean difference = −142.97 ms, $p = 0.002$) and correct response time (mean difference = −157.06 ms, $p = 0.007$) decreased significantly after RE, while AE only improved in response time to correct answer (mean difference = −207.38 ms, $p = 0.046$). In addition, there was no significant difference between the three different types of exercise in the performance of refresh function tasks, but all the test indicators showed a certain degree of improvement trend; the correct rate and the number of correct responses increased the most after ICE, the response improved the most after RE, and the correct response decreased the most after AE (Table 2).

5.3. Cerebral hemodynamics data

5.3.1. Brain activation during functional inhibition tests

One-way repeated measure analysis of variance showed that under inconsistent tasks, the four tests showed significant differences in dorsolateral prefrontal cortex (DLPFC; Channel S3-D3: $F_{(3,87)} = 3.856$, $p = 0.012$, partial $\eta^2 = 0.117$; S5-D5: $F_{(3,87)} = 4.694$, $p = 0.012$, partial $\eta^2 = 0.139$; S7-D3: $F_{(3,87)} = 3.456$, $p = 0.020$, partial $\eta^2 = 0.106$), orbitofrontal area (OFC; S2-D1: $F_{(3,87)} = 8.350$, $p < 0.001$, partial $\eta^2 = 0.224$) and inferior prefrontal gyrus (IPG; S4-D3; $F_{(3,87)} = 3.033$, $p = 0.033$, partial $\eta^2 = 0.095$). Under the consistent task, there were significant differences in DLPFC (S5-D5: $F_{(3,87)} = 4.314$, $p = 0.007$, partial $\eta^2 = 0.129$) and frontal polar region (FPA; S6-D5: $F_{(3,87)} = 3.262$, $p = 0.025$, partial $\eta^2 = 0.101$) in the four tests.

Cerebral blood perfusion in the DLPFC (S5-D5) was significantly increased after resistance exercise compared to baseline under consistent tasks (mean difference = 0.155, $p = 0.047$). Compared with AE, cerebral blood oxygen level in frontal polar region (S6-D5) after RE was significantly increased (mean difference = 0.171, $p = 0.022$); The level of cerebral blood oxygen in DLPFC (S5-D5) was significantly increased after resistance exercise compared with ICE (mean difference = 0.180, $p = 0.009$). Cerebral blood oxygen level in DLPFC (Channels S3-D3, S5-D5, S7-D3) significantly increased after ICE (S3-D3: mean difference = 0.173, $p = 0.046$; S5-D5: mean difference = 0.149, $p = 0.035$; S7-D3: mean difference = 0.171, $p = 0.025$) (Table 3). The brain activation of inconsistent tasks after four tests is shown in Figure 1, and that of consistent tasks is shown in Figure 2.

5.3.2. Brain activation during functional conversion tests

There was no significant difference in the level of brain activation after the three exercises, but in the DLPFC (Channels S1-D1, S5-D1, S5-D5, S7-D3, S7-D6) and FPA (S3-D3, S3-D6, S6-D2) showed a trend of increased blood perfusion level. Compared with AE and RE, ICE activated more brain regions and triggered a greater increase in cerebral blood perfusion (Figure 3).

TABLE 3 Beta mean changes of major brain activation areas in EF test after different exercise.

EF	Task type	Brain region	Channel	Baseline	AE	RE	ICE
Inhibitory function	Inconsistency	DLPFC	S3-D3	0.011 ± 0.266	0.087 ± 0.196$^{\Delta}$	−0.126 ± 0.283	0.047 ± 0.272$^{\Delta}$
			S5-D5	0.087 ± 0.160	0.099 ± 0.405	−0.127 ± 0.199	0.021 ± 0.238$^{\Delta}$
			S7-D3	−0.050 ± 0.216	0.070 ± 0.363	−0.105 ± 0.210	0.066 ± 0.229$^{\Delta}$
		OFC	S2-D1	0.128 ± 0.167	0.130 ± 0.218$^{\Delta}$	−0.134 ± 0.251	−0.007 ± 0.275
		IPG	S4-D3	0.008 ± 0.315	0.131 ± 0.262	−0.091 ± 0.341	0.037 ± 0.267
		Broca	S7-D7	0.044 ± 0.139	0.128 ± 0.266	0.006 ± 0.174	0.093 ± 0.197
	Consistent	DLFPC	S5-D5	−0.016 ± 0.192	−0.069 ± 0.362	0.139 ± 0.223$^{\#}$	−0.041 ± 0.225$^{\Delta}$
		FPA	S6-D5	0.024 ± 0.241	−0.069 ± 0.192	0.102 ± 0.197*	−0.017 ± 0.198
Conversion function		DLPFC	S1-D1	0.071 ± 0.443	0.037 ± 0.429	0.058 ± 0.248	0.071 ± 0.295
			S5-D1	0.100 ± 0.351	0.046 ± 0.360	0.070 ± 0.255	0.118 ± 0.451
			S5-D5	0.077 ± 0.248	0.101 ± 0.341	0.066 ± 0.230	0.046 ± 0.333
			S7-D3	0.040 ± 0.283	0.015 ± 0.415	0.041 ± 0.280	0.152 ± 0.395
			S7-D6	0.095 ± 0.248	−0.063 ± 0.316	−0.014 ± 0.266	0.047 ± 0.329
		FPA	S3-D3	0.111 ± 0.307	0.093 ± 0.327	0.049 ± 0.319	0.133 ± 0.355
			S3-D6	0.082 ± 0.277	0.087 ± 0.281	0.012 ± 0.259	0.090 ± 0.326
			S6-D2	0.065 ± 0.334	0.078 ± 0.299	−0.035 ± 0.212	0.053 ± 0.303
Refresh function		FPA	S2-D5	0.035 ± 0.363	0.056 ± 0.310	0.050 ± 0.295	0.037 ± 0.490
			S3-D6	0.071 ± 0.283	0.118 ± 0.256	0.035 ± 0.367	0.040 ± 0.292
			S6-D5	−0.050 ± 0.276	0.031 ± 0.210	−0.014 ± 0.228	−0.011 ± 0.266
			S6-D6	0.065 ± 0.313	0.123 ± 0.276	−0.021 ± 0.323	−0.009 ± 0.351
		OFC	S2-D1	0.048 ± 0.376	0.182 ± 0.306	−0.015 ± 0.464	0.109 ± 0.384
			S2-D2	0.050 ± 0.374	0.054 ± 0.299	−0.006 ± 0.342	0.028 ± 0.455
			S3-D2	0.058 ± 0.323	0.110 ± 0.287	−0.039 ± 0.313	0.091 ± 0.417
		DLPFC	S7-D6	−0.030 ± 0.292	0.086 ± 0.239	−0.001 ± 0.227	0.091 ± 0.279
		Broca	S5-D4	−0.038 ± 0.267	0.005 ± 0.318	−0.060 ± 0.349	0.052 ± 0.448

AE, aerobic exercise; RE, resistance exercise; ICE, Integrated concurrent exercise.
$^{\#}p < 0.05$, indicating a significant difference from the baseline level.
$^{*}p < 0.05$, indicating significant difference with AE. $\Delta p < 0.05$, indicating significant difference with RE.

5.3.3. Refresh brain activation during functional test

There was no significant difference in the level of brain activation after different types of exercise ($p > 0.05$), but FPA brain regions (channels S2-D5, S3-D6, S6-D5, S6-D6), OFC regions (S2-D1, S2D2, S3D2), DLPFC regions (S7-D6) and Pars triangularis Broca's area(Broca; S5-D4) showed increased cerebral blood perfusion, and the brain activation degree of ICE and AE was greater than that of resistance exercise (Figure 4).

5.4. Blood glucose data

The results of one-way repeated measure ANOVA showed a significant difference in blood glucose changes (pre-exercise minus post-exercise blood glucose) after different exercise types, $F_{(2,58)} = 7.542$, $p = 0.003$, partial $\eta^2 = 0.206$. Compared with RE, blood glucose decreased significantly after AE (mean difference = −1.25 mmol/L, $p = 0.005$). After exercise, blood glucose decreased from large to small in the order: AE (2.52 mmol/L) > ICE (1.85 mmol/L) > RE (1.28 mmol/L).

6. Discussion

6.1. Main findings

This study aimed to explore the acute effects of different exercise modes on executive function (inhibition, conversion, and refresh function) in T2DM patients and to reveal the hemodynamic mechanism of relevant brain regions after exercise through the simultaneous collection of cerebral blood oxygenation levels in the prefrontal cortex. This study confirmed that 20 min of moderate-intensity AE, RE, or ICE has different effects on participants' EF and cerebral blood flow activation degree. ICE can synchronize and significantly improve the three executive functions and the corresponding HbO_2 concentration in brain regions, and RE has limited effects on EF. However, AE only showed a synchronous

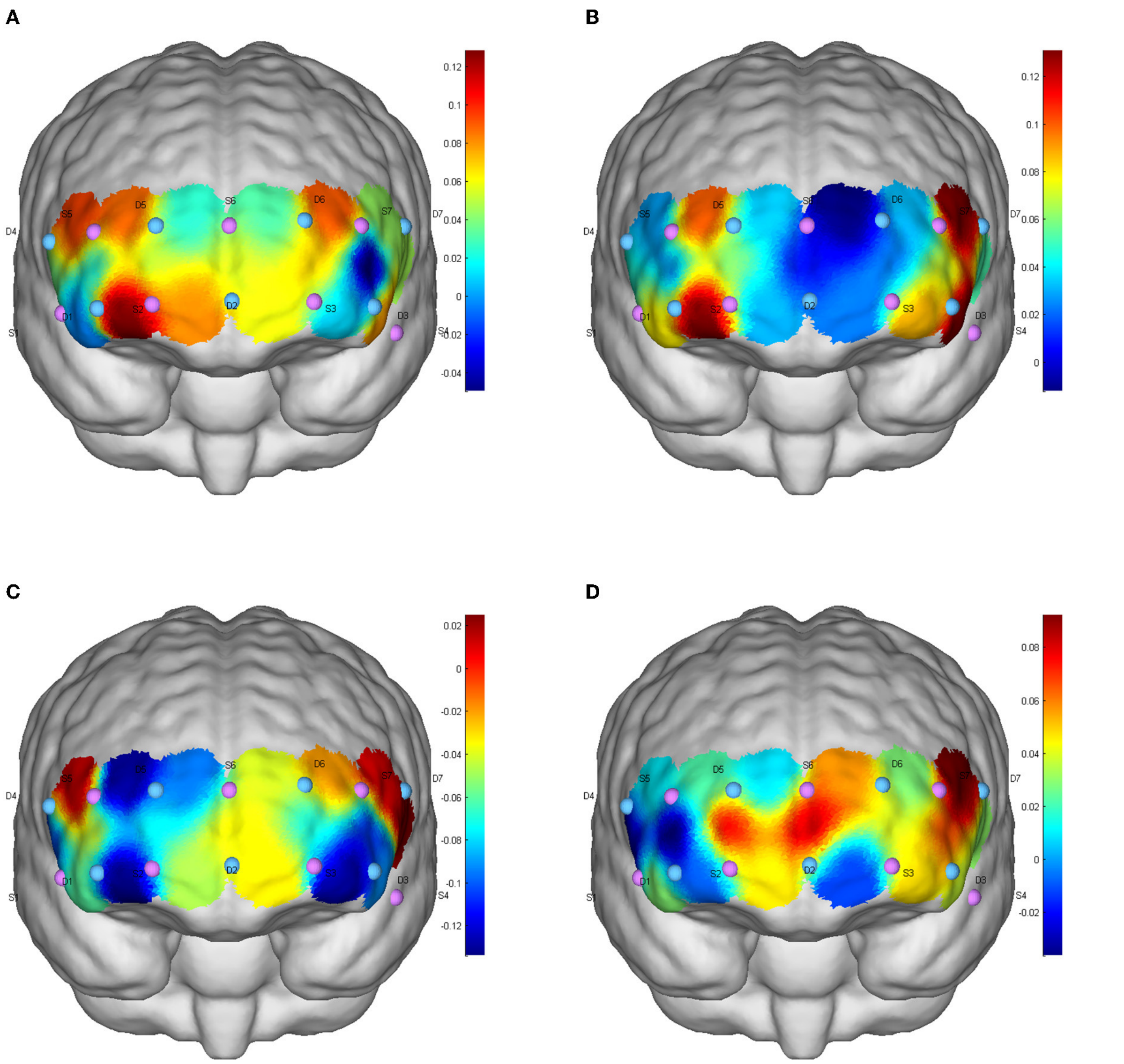

FIGURE 1
Inhibition function of CBF activation after different exercises in inconsistent tasks. **(A)** Baseline level; **(B)** aerobic exercise; **(C)** resistance exercise; **(D)** integrated concurrent exercise.

increase of HbO_2 concentration in the corresponding brain area of refresh function.

6.2. Effect of ICE on executive function

Compared with RE or AE alone, ICE could be more preferred in EF improvements, which is in consistent with previous studies (25). The intermediate effects would exist in metabolism changes. Current studies have found that, compared with exercise focusing on single dimension, multicomponent exercise could significantly improve the overall insulin sensitivity and glucose and lipid metabolism of older adults, and can promote brain blood microcirculation, which would finally improve cognitive function (26, 27). Similar findings were confirmed in older adults (28). This study further revealed that ICE can improve EF and at the same time it can significantly increase blood oxygen level in the DLPFC. In addition, compared with AE, ICE showed more improvements in the conversion function, and synchronously increase the HbO_2 concentration in the corresponding brain regions. Asynergistic mechanism would be existed in the relations between brain activation degree and EF improvements. It is therefore suggested that clinicians should not limit exercise prescription to single exercise form but encourage multicomponent exercise forms.

6.3. Effect of RE on inhibitory function

Results from this study confirmed the safety and efficacy of resistance training in hospitalized T2DM inpatients. Muscle is not only the prominent place of blood glucose metabolism but also one of the essential target tissues of insulin (29). Since numerous studies have confirmed the efficacy of RE in muscle mass and strength, it is reasonably to understand the EF improvements through

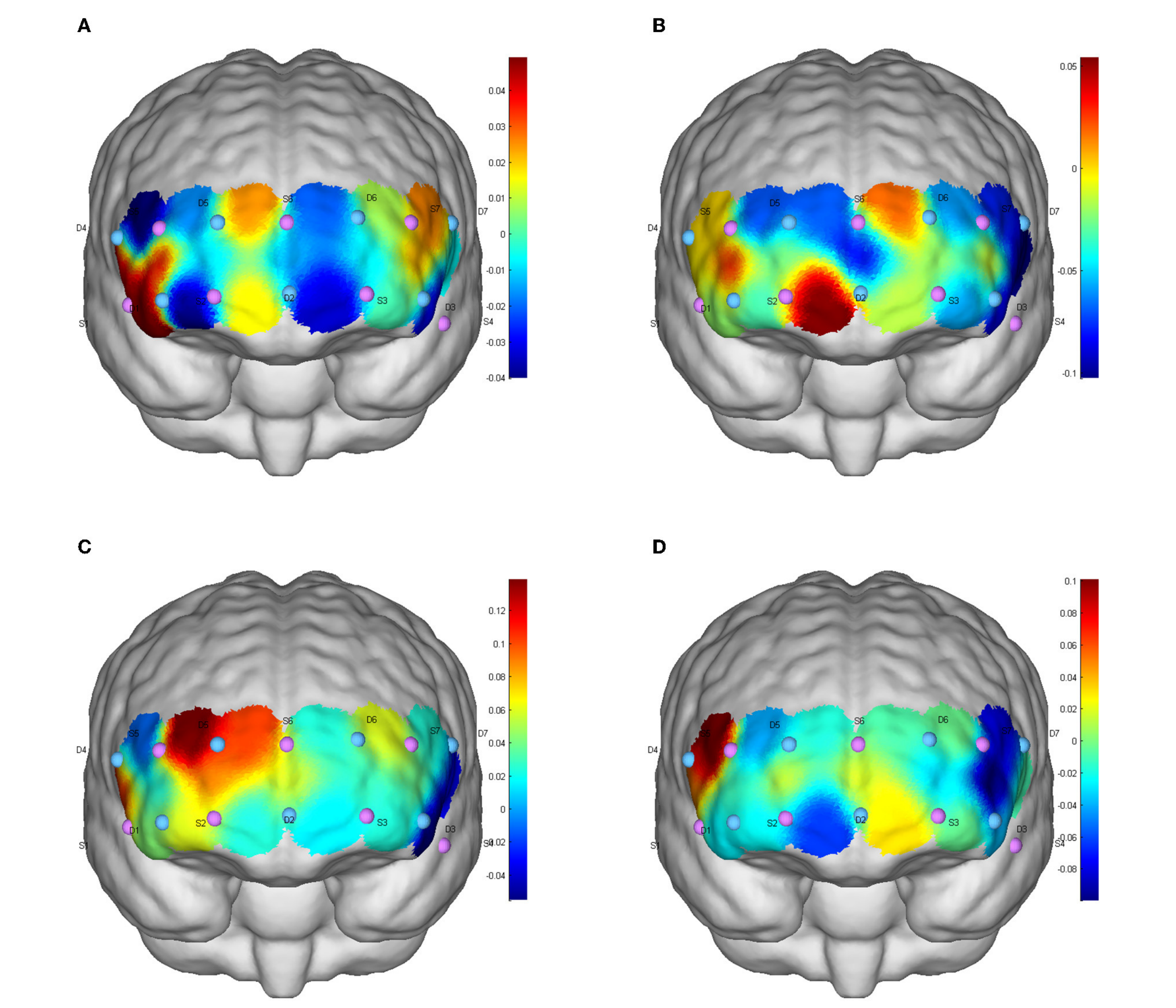

FIGURE 2
Inhibition function of CBF activation after different exercises in consistent tasks. **(A)** Baseline level; **(B)** aerobic exercise; **(C)** resistance exercise; **(D)** integrated concurrent exercise.

the increased insulin sensitivity, improved body metabolism, and reduced neuronal damage (30, 31). To date, studies have found that 6 months of progressive RE can improve EF in patients with mild cognitive impairment (32), older women (33), and healthy people (34). In line with previous studies (35–37), this study found that RE showed more efficacy that AE in the improvements of inhibition function. This can be explained by the increased blood flow velocity and blood oxygen level in the prefrontal brain area as well as the degree of nerve activation during RE; all these would provide the necessary basis for the enhanced inhibition function (38, 39). In addition, the performance on resistance movements may involve more inhibitory function. Taking the kicking and hooking movements as an example, they all require the quadriceps muscles of both legs to exert force against the equipment resistance, and lift the legs and maintain the posture for 2–3 s. In the leg lifting and holding process, participants's instinct is to drop their legs because of gravity and equipment resistance. However, such instinct response should be suppressed due to the task requirements, and the leg lifting state should be maintained for a while. The movement process is full of emotional regulation and mood inhibition, which would help explain why RE is more conducive to improve inhibitory function. It is thus would be more preferred for people with diabetes who are short of awareness of diet control and self-management to take RE as daily exercise.

6.4. Effect of RE on conversion and refresh function

Results of this study showed that RE can significantly improve three executive sub-functions, but only the consistent task of inhibitory function revealed significant activation of the corresponding brain regions, while the activation level of conversion and refresh functions maintained low. This could be

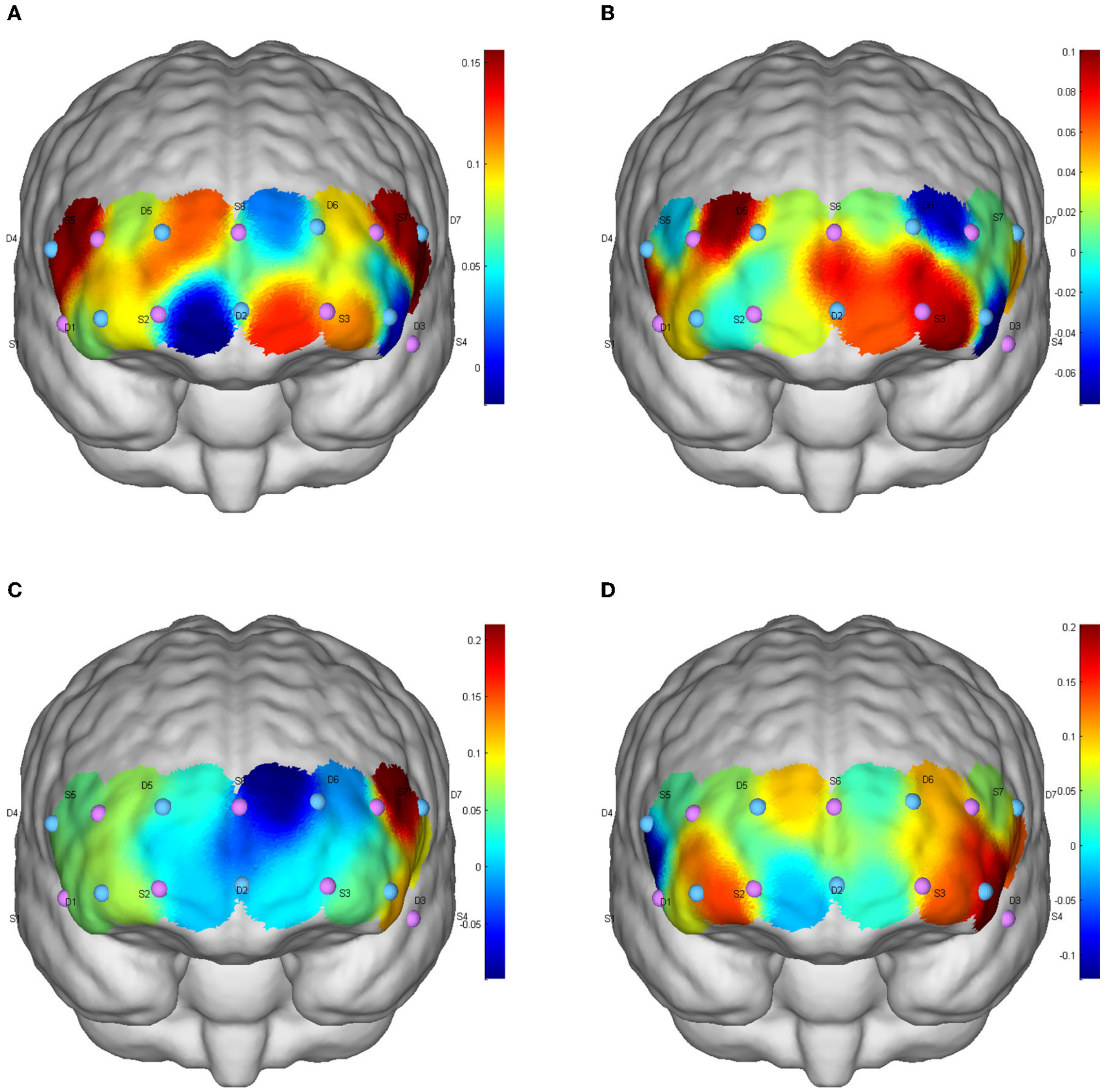

FIGURE 3
CBF activation after different exercises during the conversion function test. **(A)** Baseline level; **(B)** aerobic exercise; **(C)** resistance exercise; **(D)** integrated concurrent exercise.

related with participants' physical and mental condition during hospitalization. Most patients have reported physical weakness and lousy mood during hospitalization (40, 41). Negative emotions (e.g., anxiety and tension) can not only increase the speed of CBF but also increase the concentration of HbO_2 in PFC (42), which may lead to increased cerebral blood perfusion in the baseline test (43), just as showed in Figures 1A). Since hospitalized patients are physically weak, energy cost and HbO_2 would primarily concentrated in visceral and limb muscles, and thus limiting the increases of HbO_2 in the brain regions (44, 45).

6.5. Effect of AE on refresh function

The positive effects of AE only showed in the rate of correct response to the refresh function test, and the cerebral blood perfusion were increased in the FPA, OFC and Broca region during the test. A synergistic mechanism would exist given the activative level of FPA and OFC and the improvement of refresh function after AE. The Broca region, as the main motor-associated brain region involved in motor imagination, motor execution, and motor behavior (46, 47), shows synchronous activation in exercise. To date, there is no consistent opinion towards the acute effects of AE on brain function. A previous study confirmed that 12 weeks of moderate-intensity AE performed five times a week can improve cognitive function in older adults (48). Wen and his colleagues found that acute AE could increase EF and HbO_2 concentration in the corresponding brain region of healthy adults (16). Vincent found that acute AE could not significantly improve EF in people with T2DM (49). The variations in the AE effect to middle-aged and older adults with T2DM may be related to the blood glucose fluctuation in patients with T2DM during

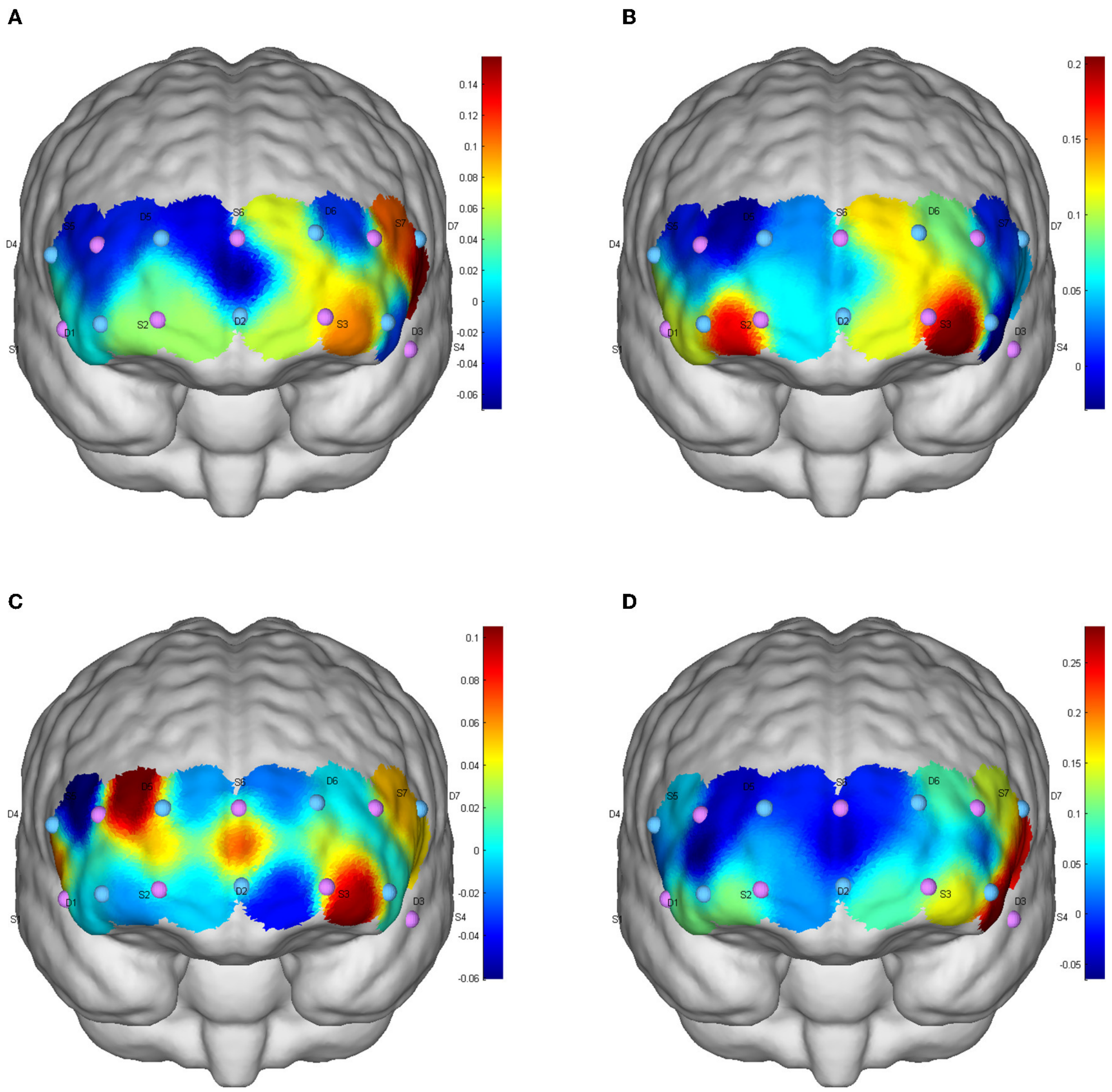

FIGURE 4
CBF activation after different exercises during the refresh function test. **(A)** Baseline level; **(B)** aerobic exercise; **(C)** resistance exercise; **(D)** integrated concurrent exercise.

exercise. The present results revealed decreased blood glucose immediately after AE. The short-term sharp fluctuations in blood glucose may aggravate oxidative stress damage in the hippocampus, which is not conducive to improve cognitive function in patients with T2DM older adults (50, 51). Compared with other exercise forms, AE causes lower arterial CO_2 concentration, promotes cerebral vascular contraction, and reduces cerebral blood perfusion levels (44, 52). It is recommended that patients with T2DM choose multicomponent exercise forms and closely pay attention to changes of blood glucose level during and after exercise to prevent further damage to EF due to a significant drop in blood glucose. In addition, it is recommended that future studies increase time interval between exercise and cerebral hemodynamic test to obtain more stable data.

This study explored the effects of three kinds of acute exercise on executive function and the mechanism of cerebral hemodynamics, providing a theoretical basis for long-term exercise intervention. This study made a preliminary exploration of the optimal exercise mode for the prevention and treatment of executive function decline in patients with T2DM and increased the scientific nature of exercise in patients with diabetes, which is conducive to the guidance and practice of clinical exercise.

6.6. Limitations

Given the limited hospitalization period (5–10 days) and the situation of the COVID-19 pandemic, the time interval within the three exercises (48 h) is relatively shorter than those in the related studies. Future studies are suggested to increase the interval time of exercise intervention to reduce potential effects of exercise fatigue on test outcomes. In addition, the participants in this study were those hospitalized T2DM patients. Although doctors have verified that moderate exercise can be carried out among the participants during such special period, potential interference of other factors could affect outcomes. Future studies are thus suggested to further examine the comprehensive effects of different exercise dosage on EF by reducing participant heterogeneity.

7. Conclusion

ICE is preferred for the improvements of EF in T2DM patients, while AE is more conducive to the improvements of refresh function. A synergistic mechanism exists between cognitive function and blood flow activation in brain regions.

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.

Ethics statement

The studies involving human participants were reviewed and approved by Biomedical Research Ethics Committee, Nanjing Normal University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YZ and HW conceived and designed the present study and wrote and critically reviewed the manuscript. HW and WT are responsible for participant recruitment and data acquisition. HW analyzed the data presented in this manuscript. YZ obtained financial support for the present work. All authors approved the final version for submission and were also responsible for all aspects of the study presented in this 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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Prevalence of ideal cardiovascular health and its relationship with relative handgrip strength in rural northeast China

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Objectives: We aimed to investigate ideal cardiovascular health (CVH), its relationship with handgrip strength, and its components in rural China.
Methods: We conducted a cross-sectional study of 3,203 rural Chinese individuals aged ≥35 years in Liaoning Province, China. Of these, 2,088 participants completed the follow-up survey. Handgrip strength was estimated using a handheld dynamometer and was normalized to body mass. Ideal CVH was assessed using seven health indicators (smoking, body mass index, physical activity, diet, cholesterol, blood pressure, and glucose). Binary logistic regression analyses were performed to assess the correlation between handgrip strength and ideal CVH.
Results: Women had a higher rate of ideal cardiovascular health (CVH) than men (15.7% vs. 6.8%, $P < 0.001$). Higher handgrip strength correlated with a higher proportion of ideal CVH (P for trend <0.001). After adjusting for confounding factors, the odds ratios (95% confidence interval) of ideal CVH across increasing handgrip strength tripartite were 1.00 (reference), 2.368 (1.773, 3.164), and 3.642 (2.605, 5.093) in the cross-sectional study and 1.00 (reference), 2.088 (1.074, 4.060), and 3.804 (1.829, 7.913) in the follow-up study (all $P < 0.05$).
Conclusion: In rural China, the ideal CVH rate was low, and positively correlated with handgrip strength. Grip strength can be a rough predictor of ideal CVH and can be used to provide guidelines for improving CVH in rural China.

KEYWORDS
handgrip strength, ideal cardiovascular health, cross-sectional study, rural China, follow-up study

1. Introduction

In 2019, there were an estimated 523 million cases of cardiovascular disease (CVD) and 18.6 million CVD-related deaths globally; thus, CVD remains an important cause of health problems worldwide (1). It has been the major cause of death in China, and the proportion of deaths caused by CVDs continues to increase, particularly in rural populations (2). Studies on CVD risk in rural China demonstrate an alarmingly high prevalence of hypertension, dyslipidemia, and metabolic syndrome. These are relatively high in rural northeast China (3–5). Overall, previous results have shown that 36.2% of adults in rural northeast China have hypertension, 69.4% have at least one type of dyslipidemia, and 34.7% have metabolic syndrome (3–5). Early prevention and intervention are important, because adults who engage in muscle-strengthening activities at various levels show a greatly reduced risk of all-cause and CVD-related mortality. The American Heart Association (AHA) has developed the concept of an ideal cardiovascular health (CVH) score in response to the growing burden of cardiovascular disease (CVD). The goal of the CVH score is to shift attention from reducing the incidence of CVD to improving the overall CVH status of the population (6). CVH can be evaluated using seven health indicators, i.e., nonsmoking status, body mass index (BMI) < 25 kg/m^2, reaching target levels of physical activity, following a recommended healthy diet, blood pressure <120/<80 mmHg, total cholesterol <200 mg/dl, and fasting blood glucose <100 mg/dl (6). One study showed that the prevalence of individuals with 6–7 ideal CVH metrics in US studies ranged from 0.5% to 12% (7). Studies have shown that the proportion of Chinese adults with ideal CVH (meeting 7 ideal metrics) is very low, and the estimated percentage of ideal CVH is 0.2% (0.1% for males and 0.4% for females) (8). Among the 7 ideal CVH metrics, an ideal diet is the least commonly achieved (8). Another study on an urban Chinese population showed that only 0.5% of participants met the ideal level of all 7 CVH metrics, and 26.9% of participants met 5 to 7 ideal CVH metrics, among which fasting glucose was the most common metric (71.2%) and physical activity was the least common metric (18.1%) (9). Research on industrial cities in northern China shown that 9.1% of the participants achieved 5–7 ideal metrics, while only 0.1% of the participants achieved the 7 ideal CVH metrics (10). A study of Peruvian adults over the age of 35 years showed that none of the 3,058 participants met all 7 ideal CVH metrics, while 10.5% met less than one ideal CVH metric, in which fasting glucose was the most common CVH metric (72%) (11). Poor cardiovascular health (CVH) status can have negative impacts on people's lives. Studies have shown that having an ideal CVH is associated with better prognosis of cardiovascular-related diseases. A study in a Japanese population found that people with ideal CVH had a significantly reduced risk of developing atrial fibrillation (12). Another study found that women who had an increase in relative grip strength had a lower 10-year risk of developing cardiovascular disease (13). Higher relative grip strength is associated with better CVD biomarkers (14), including triglycerides and glucose, in both men and women (14–16) Reduced grip strength correlated with increased all-cause mortality and cardiovascular mortality (17, 18). Therefore, improving CVH status is an urgent public health problem.

Grip strength is associated with ideal CVH metrics. One study showed that adopting a healthy lifestyle (adequate levels of physical activity, regular consumption of fruits and vegetables, drinking less alcohol, and not smoking) can lead to increased muscle strength in adults and older adults (19). Findings from a prospective association study on muscle strength and physical activity, found that grip strength was positively correlated with physical activity at follow-up. The study also found that poor grip strength could independently predict lower activity level at follow-up (20). Studies have shown that grip strength correlated positively with high-density lipoprotein cholesterol (HDL-C) levels (15). Higher relative muscle strength was significantly associated with more favorable CVD biomarkers, including systolic blood pressure, triglyceride, HDL-C, glucose, and plasma insulin levels in both men and women (14). A study assessing muscle strength by grip strength found that absolute muscle strength and highly standardized muscle strength were directly related to diastolic blood pressure (16). Another study on community-dwelling older adults showed that isometric grip strength training resulted in a significant decrease of 9 mmHg in resting systolic blood pressure (21). Studies on older community-dwelling individuals showed that muscle mass and grip strength are significantly negatively correlated with elevated hypertension (22). A different cross-sectional study found that having a higher relative grip strength was associated with lower risks of impaired fasting glucose, elevated triglycerides, abdominal obesity, and general obesity (23).

To the best of our knowledge, only a few studies have analyzed the association between ideal CVH and muscle strength in children, adolescents, and Colombian college students, and the results showed a positive correlation (24, 25). Studies examining the association between handgrip strength and ideal CVH have primarily been conducted in developed countries. However, given the distinct differences in CVH and grip strength levels between China and developed nations, further research is warranted to elucidate the relationship between these factors in the Chinese population. In addition, the prevalence of ideal CVH has not yet been examined among rural Chinese residents. Moreover, previous studies were mostly cross-sectional studies, rather than a follow-up cohort study. The investigation of ideal CVH in rural China can aid local governments in developing relevant prevention strategies. Analyzing the association between relative grip strength and ideal CVH can provide a basis for early intervention to promote strength preservation as part of the original prevention.

Therefore, in this study, we aimed to investigate the prevalence of ideal CVH, as well as the association between handgrip strength and ideal CVH and its components, among rural residents in China in a cross-sectional and follow-up study.

2. Materials and methods

2.1. Study population and design

This study was based on a cross-sectional and follow-up survey performed in rural areas in Fuxin County, Liaoning Province, China. According to geographical regions, four towns and 33 villages were randomly selected for data collection in 2019 from the east, south, and north regions. Of the four towns selected, two towns were located in the east, one in the south, and one in the north. We included local residents who had lived in the area for more than 5 years; were willing to sign a consent form; and were aged ≥35 years. Pregnant women, individuals with malignant tumors, those with severe hepatic and renal insufficiency, and those unwilling to participate in the study were excluded. Finally, data from 4,689 individuals were collected at baseline. Of the participants included at baseline, 1,309 lacked information on grip strength and were excluded. A total of 177 participants were excluded because data on ideal CVH metrics, such as total cholesterol ($n = 17$), blood pressure ($n = 8$), physical activity ($n = 145$), BMI ($n = 2$), smoking ($n = 4$), and diet ($n = 1$), were missing. At baseline, 3,203 study participants were selected. A follow-up survey was conducted in 2021.

However, 1,844 participants did not participate in the follow-up study. Of these, 146 lacked information on grip strength and were excluded. A total of 452 participants were excluded as data on ideal CVH metrics, such as total cholesterol ($n = 50$), blood pressure ($n = 311$), physical activity ($n = 87$), BMI ($n = 3$), and smoking ($n = 1$), were missing for 2021. Ultimately, 761 participants were included in the final analysis (**Supplementary Figure S1**).

The procedures of the study were in accordance with the ethical standards of the Committee for Human Experimentation of China Medical University [2018083], and written informed consent was obtained from all participants.

2.2. Assessment of ideal CVH

Ideal CVH as defined by the AHA includes four behavioral metrics (smoking, physical activity, BMI, diet) and three biological metrics (total cholesterol, blood pressure, and blood glucose). Self-reported questionnaires were used to collect information on smoking, physical activity, and diet. In this study, we adopted the AHA definition and made several adjustments. In terms of smoking, participants were classified as never smokers (never smoked or quit ≥12 months ago), former smokers (quit <12 months ago), and current smokers. Diet was measured using five components: (1) ≥250 g cereals and potatoes; (2) ≥500 g fruits and vegetables; (3) <75 g meat and poultry/aquatic products; (4) <50 g sugar; (5) <6 g salt; and (6) in accordance with the current "Dietary Guidelines for Chinese Residents" (26). The researchers judged whether the diet was ideal according to the ideal status of the five dietary components, in which achieving 0-1 dietary components was poor, 2-3 was intermediate, and 4-5 was ideal. BMI, measured by a trained medical professional, was calculated as weight (kg) divided by height squared $(m)^2$. According to the AHA protocol, after participants had rested for 5 min, a trained and certified observer took blood pressure measurements three times in a sitting position, at measurement intervals of at least 1 min. The average blood pressure value was used in the final analysis. Blood pressure was estimated using a standardized electronic sphygmomanometer (HEM-8102A; Omron, Dalian, China). The researchers obtained fasting blood samples in the morning from participants who had fasted for at least 8 h. Specific criteria are listed in **Supplementary Table S1**.

2.3. Assessment of handgrip strength

The research staff used a handheld dynamometer (Jamar Plus+, Patterson Medical, Warrenville, IL, USA) to measure handgrip strength according to a standardized protocol (27). During the test, participants were asked to sit while the dynamometer was suspended from their necks with their forearms at 90°. The measurement required rapid exertion, and the participants were asked to hold the dynamometer with maximum force and press it for 3 s. Measurements were taken on each hand, three times, at intervals of 30 s. The final results were recorded at the end of the test. The average grip strength from both hands was used for analysis with the handgrip strength normalized to body mass (28, 29).

2.4. Statistical analysis

All analyses were performed using IBM SPSS Statistics v26 (IBM SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant. Data are expressed as mean ± standard deviation (SD), frequency, and percentage. When normality and homogeneity assumptions were satisfied, a two-sample t-test was used to examine the differences in numerical variables between male and female participants. Continuous variables were compared using one-way analysis of variance, and categorical variables were tested using the chi-squared test. In addition, binary logistic regression was performed to determine the correlation between relative grip strength and ideal CVH after adjusting for factors such as age, sex, education, ethnicity, history of stroke, and history of coronary heart disease. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. At baseline, based on relative grip strength, participants were divided into tripartite groups (group 1: ≤ 0.36, group 2: 0.36–0.46, group 3: > 0.46), with the first group as the reference category. In the follow-up study, based on relative grip strength, participants were divided into tripartite groups (group 1: ≤ 0.37, group 2: 0.37–0.46, group 3: > 0.46), with the first group acting as the reference category. Logistic regression analysis was performed using three models: model 1 was unadjusted, model 2 was adjusted for sex and age, and model 3 was adjusted for sex, age, education, ethnicity, history of stroke, and history of coronary heart disease.

2.5. Patient and public involvement

All data were obtained from a cross-sectional and follow-up study conducted in rural areas in Fuxin County, Liaoning Province, China. None of the patients or the public were involved in the design or planning of this study.

3. Results

Of the 3,203 participants in the cross-sectional study, 63.2% were women, and the average age was 57.0 ± 9.9 years. **Table 1** compares the differences in the characteristics of CVH according to sex. Women participants in this study were younger, less educated, and had lower grip strength than men. However, in the

TABLE 1 Characteristics of rural adults in China in the cross-sectional study (mean ± standard deviation or frequency) ($n = 3{,}203$).

	Male	Female	*P* value
Age, years	59.9 ± 9.8	57.0 ± 9.9	<0.001
Education level, *n* (%)			<0.001
≤primary school	360 (30.6)	921 (45.6)	
>primary school	818 (69.4)	1,100 (54.4)	
Ethnicity, *n* (%)			0.354
Han	765 (65.0)	1,275 (63.1)	
Mongolian	370 (31.4)	656 (32.5)	
Others	42 (3.6)	90 (4.5)	
Body mass, kg	68.1 ± 12.2	61.8 ± 10.5	<0.001
Body mass index, kg/m^2	24.4 ± 3.7	25.0 ± 4.8	<0.001
Handgrip strength, kg	34.3 ± 8.2	22.2 ± 5.4	<0.001
Handgrip strength/body mass	0.5 ± 0.9	0.4 ± 0.1	<0.001
Ideal health metrics			
Smoking	528 (44.8)	1,721 (85.0)	<0.001
Physical activity	194 (16.5)	397 (19.6)	0.086
Body mass index	686 (58.2)	1,030 (50.9)	<0.001
Diet	225 (19.1)	366 (18.1)	0.114
Blood pressure	188 (15.9)	628 (31.0)	<0.001
Fasting plasma glucose	665 (56.4)	1,127 (55.7)	0.191
Total cholesterol	661 (56.1)	1,006 (49.7)	<0.001
Global CVH, *n* (%)			<0.001
0–2 Metrics	542 (46.0)	696 (34.4)	
3–4 Metrics	556 (47.2)	1,010 (49.9)	
5–7 Metrics	80 (6.8)	318(15.7)	

Characteristics of Chinese rural adults are expressed as mean ± standard deviation in continuous variables, and frequencies and proportions in categorical variables. CVH, cardiovascular health.

crude analysis, men were more often at the ideal level for all CVH indicators, except smoking and blood pressure. Women were twice as likely as men to have ideal CVH (15.7% vs. 6.8%, $P < 0.001$) (Table 1).

Tables 2, 3 compare the differences in CVH characteristics by grip strength. Compared with participants with low relative grip strength, those with higher relative grip strength had better BMI, fasting plasma glucose, total cholesterol, and ideal CVH in the cross-sectional as well as in the follow-up study (Tables 2, 3).

3.1. Association between grip strength and ideal CVH in the cross-sectional study

Table 4 present the adjusted relationships between grip strength and the Ideal Global CVH Score in the cross-sectional study. As presented in Table 4, the maximum grip strength group had better global CVH [odds ratio (OR), 95% CI: 3.613, 2.580–5.058], behavioral CVH (OR, 95% CI: 2.200, 1.603–3.021), and biological CVH (OR, 95% CI: 2.567, 1.801–3.657) at baseline. In the cross-sectional study, the OR values of BMI, blood pressure, blood glucose, and total cholesterol in the group with the highest grip strength were higher than those in the group with the lowest grip strength (P for trend < 0.05). However, the OR values of smoking in the group with the highest grip strength were lower than those in the group with the lowest grip strength ($P < 0.05$) (Supplementary Table S2).

TABLE 2 Characteristics of Chinese rural adults in the cross-sectional study (mean ± standard deviation or frequency) ($n = 3{,}203$).

		Relative handgrip strength in 2019			*P* value
	Total	0.36 ≥ NGS > 0	0.46 ≥ NGS > 0.36	NGS > 0.46	
Age, years	58.1 ± 10.0	60.7 ± 9.6	57.6 ± 9.9	55.9 ± 9.8	<0.001
Education level, *n* (%)					<0.001
≤primary school	1,281 (40.0)	562 (52.7)	426 (40.0)	293 (27.5)	
>primary school	1,918 (59.9)	505 (47.3)	639 (60.0)	774 (72.5)	
Ethnicity, *n* (%)					0.012
Han	2,040 (63.7)	661 (62.0)	663 (62.3)	716 (67.0)	
Mongolian	1,026 (32.0)	370 (34.7)	346 (32.5)	310 (29.0)	
Others	132 (4.1)	35 (3.3)	55 (5.2)	42 (3.9)	
SBP, mm Hg	134.0 ± 18.5	134.0 ± 18.5	130.9 ± 19.0	131.1 ± 17.9	<0.001
DBP, mm Hg		80.2 ± 10.2	79.6 ± 10.7	80.5 ± 10.7	0.090
Fasting plasma glucose, mg/dl	106.3 ± 33.3	110.7 ± 37.9	105.6 ± 32.0	102.6 ± 28.8	<0.001
Total cholesterol, mg/dl	198.4 ± 37.5	203.4 ± 37.8	198.9 ± 38.0	193.1 ± 35.8	<0.001
Body mass index, kg/m^2	24.8 ± 4.4	26.5 ± 3.7	24.8 ± 3.4	23.2 ± 5.4	<0.001
Ideal health metrics					
Smoking	2,249 (70.2)	891 (83.4)	816 (76.5)	542 (50.7)	<0.001
Physical activity	591 (18.5)	221 (20.7)	191 (17.9)	179 (16.8)	0.056
Body mass index	1,716 (53.6)	375 (35.1)	571 (53.5)	770 (72.1)	<0.001
Diet	591 (18.5)	186 (17.4)	194 (18.2)	211 (19.8)	0.364
Blood pressure	816 (25.5)	233 (21.8)	297 (27.8)	286 (26.8)	0.003
Fasting plasma glucose	1,792 (55.9)	499 (46.7)	627 (58.8)	666 (62.4)	<0.001
Total cholesterol	1,667 (52.0)	475 (44.5)	565 (53.0)	627 (58.7)	<0.001
Global CVH, *n* (%)					<0.001
0–2 Metrics	1,238 (38.7)	486 (45.5)	380 (35.6)	372 (34.9)	
3–4 Metrics	1,566 (48.9)	500 (46.8)	523 (49.0)	543 (50.9)	
5–7 Metrics	398(12.4)	82(7.7)	164(15.4)	152(14.2)	

Characteristics of Chinese rural adults are expressed as mean ± standard deviation in continuous variables, and frequencies and proportions in categorical variables. NGS, normalized handgrip strength; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVH, cardiovascular health.

TABLE 3 Baseline characteristics of Chinese rural adults in the follow-up study (mean ± standard deviation or frequency) (n = 761).

		Relative handgrip strength in 2021			P value
	Total	0.36 ≥ NGS > 0	0.45 ≥ NGS > 0.36	NGS > 0.45	
Age, years	58.9 ± 9.4	60.9 ± 9.2	58.0 ± 8.8	57.8 ± 9.7	<0.001
Education level, n (%)					<0.001
≤primary school	277 (36.4)	122 (48.0)	88 (34.6)	67 (26.5)	
>primary school	484 (63.6)	132 (52.0)	166 (65.4)	186 (73.5)	
Ethnicity, n (%)					0.204
Han	495 (65.1)	159 (62.8)	162 (63.8)	174 (68.8)	
Mongolian	246 (32.4)	91 (36.0)	83 (32.7)	72 (28.5)	
Others	19 (2.5)	3 (1.2)	9 (3.5)	7 (2.8)	
SBP, mm Hg	132.4 ± 18.3	134.3 ± 18.8	130.8 ± 18.4	132.0 ± 17.6	0.093
DBP, mm Hg	79.7 ± 10.6	80.2 ± 10.8	79.3 ± 10.4	79.8 ± 10.6	0.625
Fasting plasma glucose, mg/dl	107.1 ± 31.6	112.8 ± 41.2	106.1 ± 27.7	102.5 ± 22.0	0.001
Total cholesterol, mg/dl	199.9 ± 37.3	204.1 ± 37.3	202.6 ± 39.7	193.1 ± 33.7	0.001
Body mass index, kg/m^2	24.9 ± 3.6	26.7 ± 3.5	24.9 ± 3.1	23.3 ± 3.2	<0.001
Ideal health metrics					
Smoking	556 (73.1)	214 (84.3)	194 (76.4)	148 (58.5)	<0.001
Physical activity	144 (18.9)	55 (21.7)	50 (19.7)	39 (15.4)	0.186
Body mass index	390 (51.2)	81 (31.9)	134 (52.8)	175 (69.2)	<0.001
Diet	138 (18.1)	43 (16.9)	47 (18.5)	48 (19.0)	0.882
Blood pressure	193 (25.4)	58 (22.8)	71 (28.0)	64 (25.3)	0.415
Fasting plasma glucose	392 (51.5)	111 (43.7)	134 (52.8)	147 (58.1)	0.005
Total cholesterol	380 (49.9)	109 (42.9)	123 (48.4)	148 (58.5)	0.002
Global CVH, n (%)					0.006
0–2 Metrics	313 (41.1)	123 (48.4)	101 (39.8)	89 (35.2)	
3–4 Metrics	365 (48.0)	114 (44.9)	117 (46.1)	134 (53.0)	
5–7 Metrics	83(10.9)	17(6.7)	36(14.2)	30(11.9)	

Characteristics of Chinese rural adults are expressed as mean ± standard deviation in continuous variables, and frequencies and proportions in categorical variables.
NGS, normalized handgrip strength; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVH, cardiovascular health.

TABLE 4 Association between relative handgrip strength and global CVH score, behavioral CVH score, biological CVH score in the cross-sectional study (n = 3,203).

		Handgrip strength/body mass			P for trend
		0.36 ≥ NGS > 0	0.46 ≥ NGS > 0.36	NGS > 0.46	
Global CVH Score	Crude Model	1.0 (Reference)	2.184 (1.650,2.890)	1.997 (1.505,2.651)	<0.001
	Model I	1.0 (Reference)	2.340 (1.754,3.122)	3.636 (2.604,5.076)	<0.001
	Model II	1.0 (Reference)	2.358 (1.763,3.153)	3.613 (2.580,5.058)	<0.001
Behavioral CVH Score	Crude Model	1.0 (Reference)	1.246 (0.970,1.601)	1.063 (0.822,1.375)	0.648
	Model I	1.0 (Reference)	1.614 (1.245,2.093)	2.264 (1.652,3.102)	<0.001
	Model II	1.0 (Reference)	1.590 (1.224,2.064)	2.200 (1.603,3.021)	<0.001
Biological CVH Score	Crude Model	1.0 (Reference)	2.082 (1.554,2.791)	2.282 (1.708,3.048)	<0.001
	Model I	1.0 (Reference)	1.849 (1.360,2.514)	2.634 (1.856,3.738)	<0.001
	Model II	1.0 (Reference)	1.841 (1.351,2.509)	2.567 (1.801,3.657)	<0.001

Logistic regression analysis assess the correlation between relative grip strength and Global CVH Score, Behavioral CVH Score, Biological CVH Score.
Global CVH Score consists of the following 7 indicators: smoking, physical activity, body mass index, diet, total cholesterol, blood pressure, and fasting plasma glucose.
Behavioral CVH Score consists of the following 4 indicators: smoking, physical activity, body mass index, diet.
Biological CVH Score consists of the following 3 indicators: total cholesterol, blood pressure, fasting plasma glucose. NGS, normalized handgrip strength; CVH, cardiovascular health.
Crude Model: Adjust for none; **Model I**: Adjust for age, sex**;** **Model II**: Adjust for age, sex, Education, Ethnicity, History of stroke, History of coronary heart disease.

3.2. Association between grip strength and ideal CVH in the follow-up study

Table 5 presents the adjusted relationships between grip strength and Ideal Global CVH Score in follow-up study. As summarized in **Table 5**, the maximum grip strength group had better global CVH (OR, 95% CI: 3.763, 1.805–7.844), behavioral CVH (OR, 95% CI: 2.580, 1.333–4.990), and biological CVH (OR, 95% CI: 2.164, 0.999–4.686) in the follow-up study. In the follow-up study, there was no trend for smoking or blood pressure (**Supplementary Table S3**).

TABLE 5 Association between relative handgrip strength and global CVH score, behavioral CVH score, biological CVH score of Chinese rural adults in follow-up study ($n = 761$).

		Handgrip strength/body mass			*P* for trend
		0.36 ≥ NGS > 0	0.45 ≥ NGS > 0.36	NGS > 0.45	
Global CVH Score	Crude Model	1.0 (Reference)	2.054 (1.073,3.931)	2.643 (1.408,4.962)	0.003
	Model I	1.0 (Reference)	2.100 (1.082,4.076)	3.735 (1.802,7.744)	<0.001
	Model II	1.0 (Reference)	2.058 (1.058,4.005)	3.763 (1.805,7.844)	<0.001
Behavioral CVH Score	Crude Model	1.0 (Reference)	1.787 (1.061,3.011)	1.361 (0.791,2.344)	0.291
	Model I	1.0 (Reference)	2.301 (1.337,3.960)	2.555 (1.331,4.903)	0.003
	Model II	1.0 (Reference)	2.252 (1.303,3.891)	2.580 (1.333,4.990)	0.003
Biological CVH Score	Crude Model	1.0 (Reference)	2.134 (1.118,4.071)	2.143 (1.123,4.090)	0.026
	Model I	1.0 (Reference)	1.907 (0.976,3.726)	2.114 (0.985,4.534)	0.054
	Model II	1.0 (Reference)	1.898 (0.967,3.727)	2.164 (0.999,4.686)	0.049

Logistic regression analysis assess the correlation between relative grip strength and Global CVH Score, Behavioral CVH Score, Biological CVH Score.
Global CVH Score consists of the following 7 indicators: smoking, physical activity, body mass index, diet, total cholesterol, blood pressure, and fasting plasma glucose.
Behavioral CVH Score consists of the following 4 indicators: smoking, physical activity, body mass index, diet.
Biological CVH Score consists of the following 3 indicators: total cholesterol, blood pressure, fasting plasma glucose. NGS, normalized handgrip strength; CVH, cardiovascular health.
Crude Model: Adjust for none; **Model I**: Adjust for age, sex; **Model II**: Adjust for age, sex, Education, Ethnicity, History of stroke, History of coronary heart disease.

4. Discussion

Based on data from the cross-sectional study, our study showed that the ideal CVH rate was 12.4% in the rural area of China. The results suggest that after adjusting for confounding factors, high grip strength led to better ideal CVH, as compared with low grip strength. This association did not change in this cohort study. Among the CVH metrics, BMI, blood glucose, and total cholesterol showed a better trend with increased grip strength. Previous studies have suggested that poor rural family environment and low nutritional status of parents were negatively associated with midlife physical capability (30). Moreover, similar to some studies, we found that grip strength may be an under-recognized and controllable determinant of cardiometabolic risk factors in middle-aged and older adults in rural China (31).

Our study found that the proportion of ideal CVH was 12.4% in rural China, which was lower than that in developed countries, but higher than that in some developing countries (32–34). Some studies have shown that approximately 16% of participants have ideal CVH when 5–7 ideal indicators are identified (35). Other studies have shown that 7.8% of participants had ideal CVH metrics in ELSA-Brasil (33). Ideal CVH in rural China has become a serious public health concern. Consistent with previous reports, women were more often at the ideal level for smoking and blood pressure than were men; however, they had worse outcomes than did men in total cholesterol levels (36). In this study, no difference in diet between men and women was observed, which was related to the similar diet of rural residents. Our study also found that women had a lower ideal BMI than did men, which differed from the results of previous studies (36). Another reason may be the low educational level of local women. Studies in rural China have shown that education level is negatively correlated with general and abdominal obesity in women (37). At baseline, compared with other CVH studies in rural China, the ideal levels of BMI, total cholesterol, and fasting plasma glucose in this area were low and need to be improved.

Currently, little research on this topic exists, and previous studies have shown that relative grip strength is positively correlated with ideal CVH indicators in children and adolescents (24, 38). Another study on college students showed that the level of ideal CVH increases with increased grip strength (25). Ramírez-Vélez et al. provided evidence of an association between the components of ideal CVH and grip strength, which was partly consistent with the results of this study (24). However, few studies have examined the relationship between relative grip strength and the ideal CVH in rural China, where grip strength levels and ideal CVH differed from those in developed countries.

In the cross-sectional study, we found a link between glucose, total cholesterol, and muscular strength. This is consistent with a study showing that low-load resistance training is safe and beneficial in improving blood glucose and total cholesterol levels (19). In this study, we also found that as grip strength increased, the ideal level of blood pressure increased. This was consistent with studies of older adults in the community, which showed that isometric grip strength training resulted in a significant decrease of 9 mmHg in resting systolic blood pressure (21).In addition, in this cross-sectional study, BMI and muscle strength were correlated, which was consistent with the results of a previous study (39). To date, the effect of grip strength on ideal behavioral CVH has not been well established. In the cross-sectional study, neither physical activity nor diet were found to increase the ideal CVH level with the increase in grip strength, which is different from the results of previous studies. Previous cross-sectional and cohort studies have shown a positive relationship between grip strength and physical activity (40).

In our follow-up study, the correlations between grip strength and BMI, total cholesterol, and blood glucose were consistent with the results of the cross-sectional and previous studies. Insulin-stimulated glucose uptake occurs primarily in skeletal muscle, highlighting its importance in glucose control (41). The loss of skeletal muscle mass results in insulin resistance and reduced protein synthesis (42). Relative grip strength is positively correlated with ideal fasting glucose levels but negatively correlated with abdominal obesity and obesity (23, 39). Sarcopenia may be aggravated by obesity with excessive intramuscular fat deposition, probably because muscle loss and fat accumulation act synergistically (43). In addition, higher levels of C-reactive protein, interleukin6, and tumor necrosis factorα are associated with lower handgrip strength (44, 45). A study examining the effects of low-load resistance training on functional health and metabolic biomarkers in older women suggested that low-load resistance training is safe and beneficial in improving metabolic biomarkers, such as blood glucose and total cholesterol levels (19).

However, in our follow-up study, we found that smoking, physical activity, diet, and blood pressure did not improve as grip strength increased, which differed from the results of previous studies (24). The reason may be that in our study, local residents were mostly engaged in agricultural activities, and improvement in grip strength was partly related to occupation. This weakened the association between physical activity and grip strength. As for diet, there is less research on the relationship between grip strength and a healthy diet in China; hence, it is difficult to compare results. A study from outside China showed a correlation between adherence to the Mediterranean- Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay (MIND) diet pattern and better muscle strength (46). However, further research is needed to confirm these findings. Smoking and blood pressure did not rise as grip strength increased in the follow-up study, as compared to the cross-sectional study. In terms of blood pressure, a randomized controlled trial found that isometric handgrip exercise can lead to reductions in resting systolic blood pressure in older adults (21). In individuals with hypertension, isometric handgrip training can also tend to lower central systolic blood pressure (47). Our study did not find a significant association between a more ideal blood pressure status and an increase in grip strength in the cohort, which may be attributed to the limitation of a single grip strength test that may not accurately reflect long-term strength training.

Previous studies have indicated that grip strength is a better predictor of cardiovascular mortality than systolic blood pressure (48). Our study found a positive association between grip strength and ideal CVH from the cross-sectional and cohort study. In cross-sectional and follow-up studies, ideal BMI, total cholesterol, and blood glucose levels rose with increasing grip strength. To ensure the best cardiovascular health for local residents, grip strength levels need to be improved. Among the seven ideal cardiovascular health metrics, the ideal ratio of diet and blood pressure was low. To improve their cardiovascular health, locals should be urged to adopt good eating habits and intensify blood pressure monitoring. More research is needed to refine the mechanisms underlying the association between grip strength and ideal CVH components. In conclusion, our study is particularly important from a public health perspective, given the importance of determining the relationship between grip strength and ideal CVH status and the direction of improvement needed in rural areas for future CVH in these regions. We conducted a cohort study of grip strength and ideal CVH in middle-aged and older adults. We simultaneously also conducted a preliminary analysis and explored the components of ideal CVH and grip strength.

The strength of our study is that it described ideal CVH in rural areas of China, where grip strength levels and ideal CVH differ from those in urban and other developed countries. We further explored the relationship between relative grip strength and ideal cardiovascular score and its components in rural areas in a follow-up study. In the light of our results, some limitations of this study should be considered. First, we only surveyed rural areas in the Liaoning province, where a higher proportion of the Mongolian population is located; these individuals are less educated and have less access to healthcare, limiting the generalizability of our study findings. Further verification is required for other Chinese provinces. Second, owing to the COVID-19 pandemic and the lack of contact information of some participants, the follow-up rate was not very high, which needs to be improved in future studies.

In conclusion, our study found that the ideal CVH status in rural areas of the Liaoning province was low. The ideal CVH of men was 6.8%, whereas that of women was 15.7%, which was more than twice that of men. We report that, compared with high grip strength, low grip strength resulted in lower ideal CVH levels. Grip strength is thus a rough predictor of ideal CVH. More attention should be paid to ideal CVH in rural China, and particularly to the men in these rural areas. To improve ideal CVH in rural areas, it is important to strengthen the control of smoking in rural men, while it is essential to encourage women to control their BMI and blood glucose levels. Strengthening grip strength levels in both men and women in rural areas can improve local ideal CVH.

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 Committee for Human Experimentation of China Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZS, LZ, JS, and BY: contributed to conception and design of the study. JS and JX: collected the data. JS, JW, and ZY: performed the statistical analysis. JS: wrote the first draft of the manuscript. YM, LZ, and ZS: contributed to the critical interpretation of the results and development of the report. 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.

The handling editor [HL] declared a shared parent affiliation with the authors [JX, LZ] at the time of review.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1124757/full#supplementary-material.

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Effects of aquatic exercises on physical fitness and quality of life in postmenopausal women: an updated systematic review and meta-analysis

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Objective: In the present systematic review and meta-analysis, we aimed to evaluate and update the effects of aquatic exercise on physical fitness and quality of life (QoL) in postmenopausal women.

Methods: The databases Cochrane Library, PubMed, Web of Science, and MEDLINE were searched for randomized controlled trials (RCTs) on the topic from inception to July 2022. The GetData software was used to extract data from the published images. RevMan5.4 software was used for statistical analysis. Data are expressed as standardized mean difference (SMD) with 95% confidence intervals (CI). I^2 index was employed for heterogeneity. Egger's test was used to assess publication bias. We evaluated the methodological quality of included studies using the Physiotherapy Evidence Database scale.

Results: We included 594 participants in 16 RCTs (19 comparison groups). The results indicated that aquatic exercise can significantly improve lower limb strength (LLS), upper limb strength (ULS), agility, flexibility, and overall QoL. No significant effects were found on aerobic capacity. Subgroup-analysis results indicated that aquatic exercise only significantly improved LLS, ULS, agility, and flexibility in postmenopausal women < 65 years of age. However, aquatic exercise improves the overall QoL both in postmenopausal women < 65 years and ≥ 65 years. Aquatic resistance exercise significantly improves LLS, ULS, agility and flexibility. In addition, aquatic aerobic exercise can effectively increase LLS, and combined aquatic aerobic and resistance exercise can enhance the overall QoL.

Conclusions: Aquatic exercise can effectively improve physical fitness and overall QoL in postmenopausal women, but has limited effects on aerobic capacity; thus, it is highly recommended in postmenopausal women.

KEYWORDS

hydrotherapy, head-out water exercise, older women, physical performance, muscle strength, agility

Introduction

With a rapidly aging of global population, the societies of many countries are gradually becoming aged (1, 2). A decline in muscle strength, cardiorespiratory fitness, mobility, and flexibility usually accompany the aging process (3–5). The body functional degeneration is more pronounced in older (6) and postmenopausal women (7). Postmenopausal women experience reduced muscle mass, muscle strength, and neuromuscular function due to ovarian degeneration and decreased secretion of estrogen, which in turn further exacerbates the degeneration of the ability to perform daily activities (8–10) and increases the risk of falling (7, 11). About 30% of people over 65 years fall at least once a year (12–14). Daily physical activity and motivation to participate in exercise are limited due to fear of falls and fractures, leading to a sedentary lifestyle and decreased quality of life (QoL) (15–19).

Exercise is a great means to improve physical fitness and emotional and mental health (20, 21). For persons with poor balance, fear of falling, joint pain, and weak muscle strength, aquatic exercise is a better alternative (22–24). Water buoyancy reduces joint load by 50–90%, especially good for people with decreased lower limb strength (LLS), obesity, and joint pain (22, 25). In older adults, aquatic resistance exercise increases muscle mass and strength and reduces the risk of falls (26, 27). Hydrostatic pressure increases blood circulation in the lower limbs (24). However, no consistent opinions have been reached regarding the efficacy of aquatic exercise on physical fitness and QoL in postmenopausal women. According to several authors, aquatic exercise can significantly improve LLS (1, 28–34), while Dong-Hyun et al. (35) found limited improvement in LLS (35). Ha et al. (1), Lopez et al. (32), and Perkins et al. (33) found that those who carried out aquatic exercise significantly achieved improved aerobic capacity compared to the control group (1, 32, 33), while Hafele, Alberton, Hafele et al. (31) had contrasting results (31). Dong-Hyun et al. (35) confirmed that aquatic aerobic exercise cannot significantly improve flexibility and there was no difference between the experimental group and the control group after aquatic exercise (35). Compared with before exercise in the study of Hafele, Alberton, Hafele et al. (31), 16 weeks of aquatic aerobic exercise and combined of aquatic aerobic and resistance exercise did not improve agility, and there was no difference between groups for agility (31). In a systematic review and meta-analysis, Saquetto et al. (36), confirmed that aquatic exercise can significantly improve LLS, flexibility, agility, and aerobic capacity (36). However, studies are lacking for the arrival at a consensus on the issue. In addition, the different types of exercises (aquatic aerobic, resistance, and multicomponent exercise) were not taken into account in most studies, which may result in different benefits from different exercise types. Furthermore, considering the different menopausal ages (37, 38), studies on the different physical fitness benefits were needed to analyze specifically from participating in aquatic exercise between young and older postmenopausal women. In terms of QoL, Hafele et al. (39) found that 16 weeks of aquatic aerobic exercise and combined aquatic aerobic and resistance exercises can significantly improve the overall QoL in postmenopausal women (39). Silva et al. (34) found that aquatic aerobic exercise significantly improved overall QoL compared with pre-exercise, unlike combined aerobic and resistance exercises (34). Therefore, taking into account the influences of exercise types and ages of participants, the present study systematically evaluated and updated the effects of aquatic exercise on physical fitness and overall QoL in postmenopausal women.

Methods

The present study strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (40).

Search strategy

We systematically searched the databases (Cochrane Library, PubMed, Web of Science, and MEDLINE) for randomized controlled trials (RCTs) using the following search terms: (aquatic exercise OR water-based exercise OR water exercise OR head-out water exercise) AND (functional fitness OR physical fitness OR physical capacity OR agility OR flexibility OR cardiorespiratory fitness OR aerobic capacity OR strength endurance OR strength OR quality of life) AND (postmenopausal women OR old women OR older women). All search terms were required to appear in the title or abstract. We also reviewed the reference list of the included literature. The Search was limited to database inception until July 2022. Two researchers (WSZ and SJM) independently completed the databases searching.

Eligibility criteria

(i) RCTs; (ii) with exercise intervention as aquatic exercise or head-out water-based exercise; the control group did not participate in exercise. (iii) with participants being physiological postmenopausal women or women aged > 55 years (41–44); and (iv) with outcomes including physical fitness indicators and the overall QoL.

Study selection and data extraction

Two researchers (W-SZ and S-JM) independently conducted the selection of titles and abstracts from each database. The full text was obtained if the researchers deemed one study eligible. Two researchers (W-SZ and S-JM) independently extracted the study characteristics from eligible articles, including authors, publication year, age, sample size, exercise interventions, and primary outcomes. The corresponding authors of these studies were contacted in case of missing data. We deleted articles whose authors could not be reached or could not provide the data. The GetData software was used for extracting data if the results were presented as figures in the included articles (45, 46). Two researchers (W-SZ and S-JM) independently completed the data extraction and review. A third researcher (S-KZ) was invited and a consensus was reached at in case of discrepancies.

Quality assessment

The Physiotherapy Evidence Database (PEDro) scale was used to assess the methodological quality of the included articles. The PEDro scale is based on 11 items, including eligibility criteria (not contribute to the total score), random allocation, concealed allocation, similarity baseline, subject blinding, therapist blinding, assessor blinding, >85% retention, intention-to-treat, between-group comparisons, and point and variability measures. Each study was assessed as "yes" (1 point) or "no" (0 points), with a maximum total score of 10. A study is considered to be of very good quality if it has a score of 9 or 10, while a score of 6 to 8 indicates good quality, a score of 4 or 5 indicates moderate quality, and a score of 0 to 3 indicates poor quality (47, 48). Two researchers (S-KZ and HX) independently performed the quality assessment, and a third researcher (W-SZ) was invited and a consensus was reached at if there was any discrepancy.

Statistical analysis

Data analysis was performed using the Cochrane Collaboration Review Manager (RevMan, version 5.4, Copenhagen, Denmark) software. Standardized mean difference (SMD) was employed if there were different outcome measures (49). I^2 index was used to test statistic heterogeneity. An I^2 >50% indicated high heterogeneity, and a random-effect model was applied (50). Sensitivity analysis was done by deleting studies one after the other (51). Egger's regression test was used to assess publication bias (52). The statistical significance level was set at $p < 0.05$.

Results

Search results

Using the search strategy, 1,469 studies were retrieved, of which 1,421 studies were deleted because they were duplicates, animal studies, non-RCTs, or included non-postmenopausal women, and so on. Because the participants of 29 studies were on hormonotherapy, nutritional care, or the studies had no control group or failed to extract data, these studies were deleted. Sixteen RCTs (19 comparison groups) were finally included in the present study (Figure 1).

Study characteristics

The 16 RCTs were published between 2006 and 2022 and involved 594 participants (320 received aquatic exercise interventions). The participants were aged from 54 to 74.9 years. Exercise duration was from 8 to 24 weeks, exercise frequency was from 2 to 5 times per week, and exercise time was from 30 to 60 min. Aquatic aerobic exercise (1, 28, 31, 32, 34, 35, 39), aquatic resistance exercise (29, 30, 53–55), and multicomponent exercise (aquatic aerobic and resistance exercises) (27, 31, 33, 34, 39, 56, 57) were the main types of exercises involved. The studies of Hafele, Alberton, Hafele, et al. (2022), Hafele, Alberton, Schaun, et al. (2022), and Silva et al. (2018) included both aquatic aerobic and multicomponent exercise (31, 34, 39). The participants compliance ranges from 73.6 to 100%. Each exercise session was supervised by the researchers. The characteristics of the included studies are summarized in Table 1.

Summary of risk of bias

The ranges of the quality assessment scores of the included studies was from 3–6. Two studies received scores of 6 (good quality) (31, 39), 13 studies received scores of 4–5 (median quality) (1, 27–30, 32–35, 54–57), and 1 study received scores of 3 (poor quality) (53). The mean score was 4.8 (Table 2).

Effects of exercise on physical performance and quality of life

lower limbs strength-30-second chair stand test

Using the 30-second chair stand test, LLS was evaluated by 11 RCTs that involved 334 participants. Due to the difference between the studies' assessments, the meta-analysis was performed with SMD. A random-effect model was applied for instances with a high heterogeneity ($I^2 = 91\%$, $p < 0.00001$). Sensitivity analysis results indicated that excluding any single study resulted in no significant effect on the total effect size. Meta-analysis results demonstrated that aquatic exercise can significantly increase LLS (SMD = 1.37, 95% CI: 0.53, 2.21, $p = 0.001$) (Figure 2).

Subgroup analysis showed that LLS was significantly increased in the age < 65 years (SMD = 3.33, 95% CI: 0.62, 6.03, $p = 0.02$), aquatic aerobic exercise (SMD = 0.81, 95% CI: 0.03, 1.59, $p = 0.04$), and Aquatic resistance exercise subgroups (SMD = 4.51, 95% CI: 3.33, 5.68, $p < 0.00001$). No significant effects were found in the age ≥ 65 years (SMD = 0.55, 95% CI: −0.04, 1.13, $p = 0.07$) and multicomponent exercise subgroups (SMD = 0.32, 95% CI: −0.23, 0.87, $p = 0.26$) when compared with the control group (Table 3).

Upper limbs strength-arm curl test

Using the arm curl test, upper limbs strength (ULS) was evaluated by 3 RCTs that involved 106 participants. A meta-analysis was performed with SMD. A random-effect model was applied in instances with a high heterogeneity ($I^2 = 86\%$, $p = 0.0009$). After removing the study of Lopez et al. (32), sensitivity analysis results indicated that the heterogeneity was lower ($I^2 = 22\%$, $p = 0.26$). However, the total effect size did not change significantly. The meta-analysis results demonstrated that aquatic exercise can significantly increase ULS (SMD = 1.86, 95% CI: 0.55, 3.16, $p = 0.005$) when compared with the control group (Figure 3).

The RCTs of age < 65 years and aquatic resistance exercise subgroups were from the studies of Bocalini et al. (29) and Bocalini et al. (30). Subgroup results showed that ULS had significantly increased in the above two subgroups (SMD = 2.44, 95% CI: 1.74, 3.15, $p < 0.00001$). The RCTs of age ≥ 65 years were from the study of Lopez et al. (32) and no significant effects were found in the age ≥ 65 years subgroup (SMD = 0.58, 95% CI: −0.23, 1.39, $p = 0.16$) (Table 3).

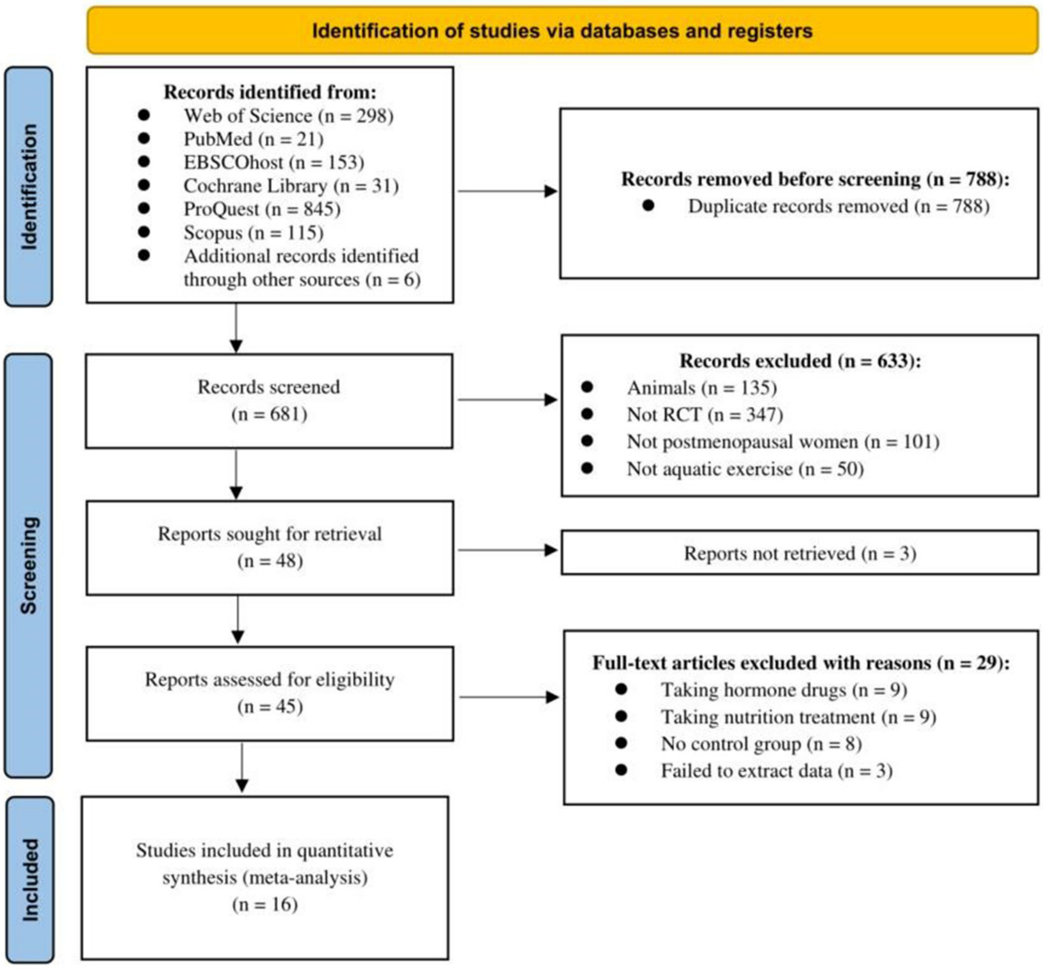

FIGURE 1
Flow diagram of search strategy.

Agility-timed up and go test

Using the timed up and go test, agility was evaluated by 16 RCTs that involved 541 participants. Due to the difference between the studies' assessments, the meta-analysis was performed with SMD. A random-effect model was applied in instances with a high heterogeneity ($I^2 = 80\%$, $p < 0.00001$). Sensitivity analysis results indicated that excluding any single study resulted in no significant effect on the total effect size. The meta-analysis results demonstrated that aquatic exercise can significantly improve agility (SMD = −0.67, 95% CI: −1.09, −0.25, $p = 0.002$) when compared with the control group (Figure 4).

Subgroup analysis results showed that agility was significantly improved in the age < 65 years (SMD = −0.98, 95% CI: −1.51, −0.44, $p = 0.0003$) and aquatic resistance exercise subgroups (SMD = −1.35, 95% CI: −1.87, −0.83, $p < 0.00001$). No significant effects were found in the age ≥ 65 years (SMD = −0.49, 95% CI: −1.07, 0.10, $p = 0.10$), aquatic aerobic exercise (SMD = −0.25, 95% CI: −0.79, 0.30, $p = 0.38$), and multicomponent exercise subgroups (SMD = −0.68, 95% CI: −1.46, 0.10, $p = 0.09$) (Table 3).

Aerobic capacity- 6-min walking test

Using the 6-minute walking test (6MWT), aerobic capacity was evaluated by 7 RCTs that involved 193 participants. Due to the difference between the studies' assessments, the meta-analysis was performed with SMD. A random-effect model was applied for instances with a high heterogeneity ($I^2 = 74\%$, $p = 0.0008$). Sensitivity analysis results indicated that the heterogeneity was lower ($I^2 = 3\%$, $p = 0.39$) after removing the study of Ha et al. (1). However, the total effect size did not change significantly. The meta-analysis results demonstrated that aquatic exercise does not significantly improve aerobic capacity (SMD = 0.47, 95% CI: −0.14, 1.08, $p = 0.13$) when compared with the control group (Figure 5).

Subgroup results showed that aerobic capacity was not significantly improved in the age < 65 years (SMD = 0.25, 95% CI: −0.43, 0.94, $p = 0.47$), age ≥ 65 years (SMD = 0.55, 95% CI: −0.20, 1.29, $p = 0.15$), aquatic aerobic exercise (SMD = 0.68, 95% CI: −0.23, 1.59, $p = 0.14$), and multicomponent exercise subgroups (SMD = 0.15, 95% CI: −0.38, 0.69, $p = 0.57$) (Table 3).

TABLE 1 Characteristics of the included studies ($n = 16$).

Authors, Year	Age	Sample size Compliance (AEG/CG)	AEG	Control	Water level, Temperature	Measured outcomes				
						Overall QoL	Muscle strength	Flexibility	Aerobic capacity	Agility
Aboarrage et al. (28)	65 ± 7	25(15/10) (100%/100%)	20 min main aquatic exercise, 30 min × 3 times/week × 24 weeks	No report	xiphoid, 29°C		30-s CS			8-ft TUG
Araújo et al. (53)	54 ± 4	18(10/8) (88 ± 8%/89 ± 5%)	20 min low limbers resistance exercise, 45 min × 3 times/week × 8 weeks	Daily routine	xiphoid, 26–29°C					3-m TUG
Bento et al. (56)	65.8 ± 4.47	36(20/16) (no report)	20 min aerobic activities and 20 min lower limb strength exercises, 60 min × 3 times/week × 12 weeks	daily routine	xiphoid, 28–30°C					8-ft TUG
Bocalini et al. (29)	63.3 ± 1.09	35(25/10) (92.6%/50%)	45 min endurance-type exercise (arms and legs resistance exercises), 60 min × 3 times/week × 12 weeks	Daily routine	xiphoid, 29°C		30-s AC 30-s CS	SR		8-ft TUG
Bocalini et al. (30)	>62	45(27/18) (90%/90%)	45min endurance training, 60 min × 3 times/week × 12 weeks	Daily activities	no report	WHO-QoL	30-s AC 30-s CS	SR		8-ft TUG
Colado et al. (54)	54 ± 2.12	25(15/10) (>95%)	35–60 min resistance exercise, 35–60 min × 2–3 times/week × 24 weeks	Daily routine	no report			SR		
Dong-Hyun et al. (35)	72.2 ± 4.26	36(18/18) (no report)	40 min aquarobics exercise, 60 min × 3 times/week × 12 weeks	Daily routine	1.1-m, 28–29°C		30-s CS	SR		2.44-m TUG
Ha et al. (1)	74.9 ± 4.76	19(11/8) (no report)	40 min main exercise, 50 min × 3 times/week × 12 weeks	Daily routine	26–28°C		30-s CS	SR	6MWT	8-ft TUG
Hafele et al. (31)	66.15 ± 4.00	52(17/18/17) (100%/100%)	AE: 45 min aerobic exercise; ME: combined of aerobic and resistance training, 60 min × 3 times/week × 16 weeks	Aquatic therapeutic once A week	xiphoid-shoulders 32°C	WHO-QoL				
Hafele et al. (31)	66.15 ± 4.00	52(17/18/17) (100%/100%)	AE: 45 min aerobic exercise; ME: a combination of aerobic and resistance training, 60 min × 3 times/week × 16 weeks	Aquatic therapeutic once A week	xiphoid-shoulders 32°C		30-s CS	SR	6MWT	8-ft TUG
Lopez et al. (32)	74.4 ± 12.69	26(16/10) (73.6%)	30 min aerobic exercise, 50 min × 5 times/week × 12 weeks	Normal activities	no report		30-s AC 30-s CS	SR	6MWT	2.4-m TUG

(Continued)

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TABLE 1 (Continued)

Authors, Year	Age	Sample size Compliance (AEG/CG)	AEG	Control	Water level, Temperature	Measured outcomes				
						Overall QoL	Muscle strength	Flexibility	Aerobic capacity	Agility
Moreira et al. (57)	58.8 ± 6.4	108(64/44) (92.2%/93.2%)	30–40 min strength/power exercises and cardiorespiratory training, 50–60 min × 3 times/week × 24 weeks	No regular exercise	1.1–1.3-m 30–31°C			SR		3-m TUG
Perkins et al. (33)	57 (45–78)	38(26/12) (90%)	40 min aerobic routines, 60 min × 5 times/week × 17 weeks	No regular exercise	29.5°C		30-s CS	SR	6MWT	TUG
Sattar et al. (55)	54.9 ± 4.02	24(14/10) (100%)	30–40 min resistance exercise, 60 min × 3 times/week × 8 weeks	No regular exercise	28–30°C			SR		3-m TUG
Silva et al. (34)	65 ± 4	33(13/11/9) (88 ± 8%/89 ± 5%)	AE: aerobic exercise; ME: a combination of aerobic and resistance training, 2 times/week × 12 weeks	Non-periodized dance/gymnastics	no report	WHO-QoL	30-s CS		6MWT	8-ft TUG
Tsourlou et al. (27)	68.9 ± 4.62	22(12/10) (85.7%/100%)	45 min aerobic and resistance exercise, 60 min × 3 times/week × 24 weeks	Normal activities	0.9-m, 30°C			SR		3-m TUG

AEG, aquatic exercise group; CG, control group; AT, aerobic exercise; ME, multicomponent exercise; overall QoL, overall quality of life; CS, chair stand test; AC, arm curl test; SR, chair sit and reach test; 6MWT, 6 min walking test; TUG, timed up and go. WHO-QoL, The World Health Organization quality of life assessment.

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TABLE 2 Quality assessment of included studies ($n = 16$).

	Included studies	1	2	3	4	5	6	7	8	9	10	11	Total score
1	Aboarrage et al. (28)	1	1	0	1	0	0	0	1	0	1	1	5
2	Araújo et al. (53)	0	1	0	1	0	0	0	0	0	1	0	3
3	Bento et al. (56)	1	1	0	1	0	0	1	0	0	1	1	5
4	Bocalini et al. (29)	1	1	0	1	0	0	0	1	0	1	1	5
5	Bocalini et al. (30)	1	1	0	1	0	0	0	1	0	1	1	5
6	Colado et al. (54)	1	1	0	1	0	0	0	0	0	1	1	4
7	Dong-Hyun et al. (35)	1	1	0	1	0	0	0	1	0	1	1	5
8	Ha et al. (1)	0	1	0	1	0	0	0	1	0	1	1	5
9	Hafele et al. (31)	1	1	0	1	0	0	0	1	1	1	1	6
10	Hafele et al. (31)	1	1	0	1	0	0	0	1	1	1	1	6
11	Lopez et al. (32)	1	1	0	1	0	0	0	1	0	1	1	5
12	Moreira et al. (57)	1	1	0	1	0	0	0	1	0	1	0	4
13	Perkins et al. (33)	1	0	0	0	0	1	1	0	0	1	1	4
14	Sattar et al. (55)	0	1	0	1	0	0	0	1	0	1	1	5
15	Silva et al. (34)	1	1	1	0	0	0	1	0	0	1	1	5
16	Tsourlou et al. (27)	0	1	0	1	0	0	0	1	0	1	1	5

1, eligibility criteria (not contribute to the total score); 2, random allocation; 3, concealed allocation; 4, similarity baseline; 5, subject blinding; 6, therapist blinding; 7, assessor blinding; 8, >85% retention; 9, intention-to-treat; 10, between- group comparisons; 11, point and variability measures.

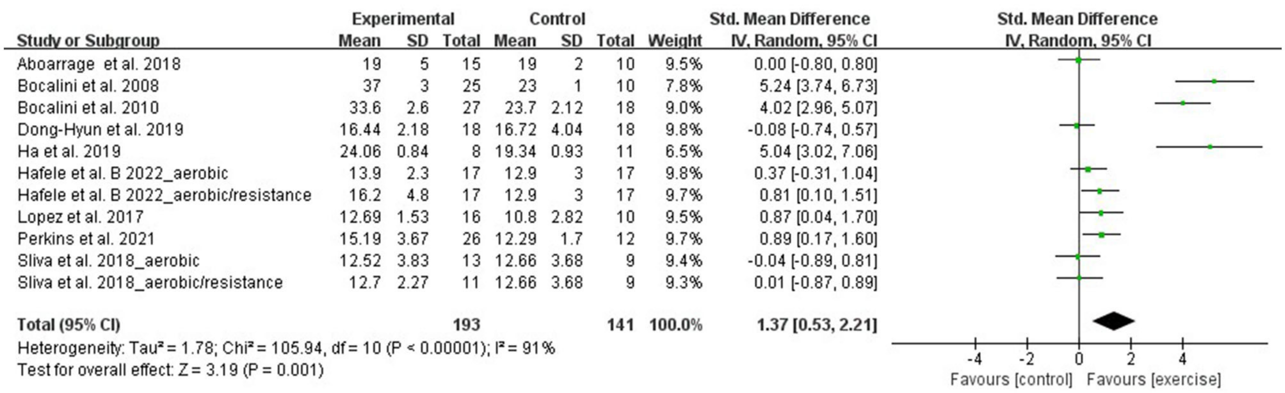

FIGURE 2
Forest plot of the effect of aquatic exercise on lower limbs strength (kg).

Flexibility-chair sit and reach test

Using the chair sit and reach test, flexibility was evaluated by 12 RCTs that involved 446 participants. Due to the difference between the studies' assessments, the meta-analysis was performed with SMD. A random-effect model was applied for instances with a high heterogeneity ($I^2 = 86\%$, $p < 0.00001$). Sensitivity analysis results indicated that excluding any single study resulted in no significant effect on the total effect size. The meta-analysis results demonstrated that aquatic exercise can significantly improve flexibility (SMD = 0.91, 95% CI: 0.35, 1.47, $p = 0.002$) when compared with the control group (Figure 6).

Subgroup results showed that flexibility was significantly improved in the age < 65 years (SMD = 1.38, 95% CI: 0.37, 2.39, $p = 0.008$) and aquatic resistance exercise subgroups (SMD = 2.49, 95% CI: 0.14, 4.84, $p = 0.04$). No significant effects were found in the age ≥ 65 years (SMD = 0.52, 95% CI:−0.07, 1.10, $p = 0.08$), aquatic aerobic exercise (SMD = 0.51, 95% CI: −0.22, 1.24, $p = 0.17$), and multicomponent exercise subgroups (SMD = 0.57, 95% CI: −0.02, 1.17, $p = 0.06$) (Table 3).

Overall quality of life

Five RCTs that involved 128 participants evaluated overall QoL using the World Health Organization quality of life assessment. Due to the difference between the studies' assessments, the meta-analysis was performed with SMD. A random-effect model was

TABLE 3 Subgroup results of aquatic exercise on physical performance and quality of life according to different age groups and exercise types.

Outcomes	Group	Subgroup	N (AEG/CG)	SMD, 95% CI	(SMD) *p* value	I^2 (%)	(I^2) *p* value
LLS	Age	Age < 65 years	78/40	3.33 [0.62, 6.03]	0.02	95.0	< 0.00001
		Age ≥ 65 years	115/101	0.55 [-0.04, 1.13]	0.07	75.0	0.0003
	Exercise type	Aerobic exercise	98/77	0.81 [0.03, 1.59]	0.04	81.0	< 0.00001
		Resistance exercise	52/28	4.51 [3.33, 5.68]	< 0.00001	42.0	0.19
		Multicomponent exercise	43/36	0.32 [-0.23, 0.87]	0.26	31.0	0.23
ULS	Age	Age < 65 years	52/28	2.44 [1.74, 3.15]	< 0.00001	22.0	0.26
		Age ≥ 65 years	16/10	0.58 [-0.23, 1.39]	0.16	Not applicable	Not applicable
	Exercise type	Aerobic exercise	16/10	0.58 [-0.23, 1.39]	0.16	Not applicable	Not applicable
		Resistance exercise	52/28	2.44 [1.74, 3.15]	< 0.00001	22.0	0.26
Agility	Age	Age < 65 years	166/102	−0.98 [-1.51,−0.44]	0.0003	71.0	0.004
		Age ≥ 65 years	148/125	−0.49 [-1.07, 0.10]	0.10	80.0	< 0.00001
	Exercise type	Aerobic exercise	98/75	−0.25 [-0.79, 0.30]	0.38	65.0	0.01
		Resistance exercise	76/46	−1.35 [-1.87,−0.83]	< 0.00001	35.0	0.20
		Multicomponent exercise	140/106	−0.68 [-1.46, 0.10]	0.09	85.0	< 0.00001
Aerobic capacity	Age	Age < 65 years	26/12	0.25 [-0.43, 0.94]	0.47	Not applicable	Not applicable
		Age ≥ 65 years	85/70	0.55 [-0.20, 1.08]	0.15	78.0	0.0003
	Exercise type	Aerobic exercise	83/56	0.68 [-0.23, 1.59]	0.14	82.0	0.0001
		Multicomponent exercise	28/26	0.15 [-0.38, 0.69]	0.57	0	0.93
Flexibility	Age	Age < 65 years	171/104	1.38 [0.37, 2.39]	0.008	91.0	< 0.00001
		Age ≥ 65 years	91/80	0.52 [-0.07, 1.10]	0.08	70.0	0.005
	Exercise type	Aerobic exercise	76/63	0.51 [-0.22, 1.24]	0.17	76.0	0.002
		Resistance exercise	67/38	2.49 [0.14, 4.84]	0.04	95.0	< 0.00001
		Multicomponent exercise	119/83	0.57 [-0.02, 1.17]	0.06	71.0	0.02
Overall QoL	Age	Age < 65 years	27/18	2.98 [2.10, 3.85]	< 0.00001	Not applicable	Not applicable
		Age ≥ 65 years	45/38	0.54 [0.10, 0.99]	0.02	0	0.76
	Exercise type	Aerobic exercise	24/19	0.36 [-0.25, 0.97]	0.25	0	0.53
		Resistance exercise	27/18	2.98 [2.10, 3.85]	< 0.00001	Not applicable	Not applicable
		Multicomponent exercise	21/19	0.75 [0.11, 1.40]	0.02	0	0.92

AEG, aquatic exercise group; CG, control group; LLS, lower limbs strength; ULS, upper limbs strength; Overall QoL, overall quality of life; SMD, standard mean difference; CI, confidence interval.

applied for instances with a high heterogeneity ($I^2 = 84\%$, $p < 0.0001$). Sensitivity analysis results indicated that the heterogeneity was lower ($I^2 = 0$, $p = 0.76$) after removing the study of Bocalini et al. (30). However, the total effect size did not change significantly. The meta-analysis results demonstrated that when compared with the control group, aquatic exercise can significantly improve overall QoL (SMD = 1.04, 95% CI: 0.06, 2.03, $p = 0.04$) (Figure 7).

The RCTs of age < 65 years and aquatic resistance exercise subgroups were from the study of Bocalini et al. (30). Subgroup analysis results showed that overall QoL was significantly improved in the age < 65 years, aquatic resistance exercise (SMD = 2.98, 95% CI: 2.10, 3.85, $p < 0.00001$), age ≥ 65 years (SMD = 0.54, 95% CI: 0.10, 0.99, p =0.02), and multicomponent exercise subgroups (SMD = 0.75, 95% CI: 0.11, 1.40, p =0.02). No significant effects were found in the aquatic aerobic exercise subgroup (SMD = 0.36, 95% CI: −0.25, 0.97, $p = 0.25$) (Table 3).

Publication bias

Egger test revealed that there was a relatively higher level of publication bias in aerobic capacity ($t = -2.67$, $p = 0.045$). There was no obvious publication bias in LLS ($t = -1.38$, $p = 0.201$), ULS ($t = -0.02$, $p = 0.984$), agility ($t = -0.24$, $p = 0.815$), flexibility ($t = 0.21$, $p = 0.838$), and overall QoL ($t = -1.76$, $p = 0.177$) (Supplementary material).

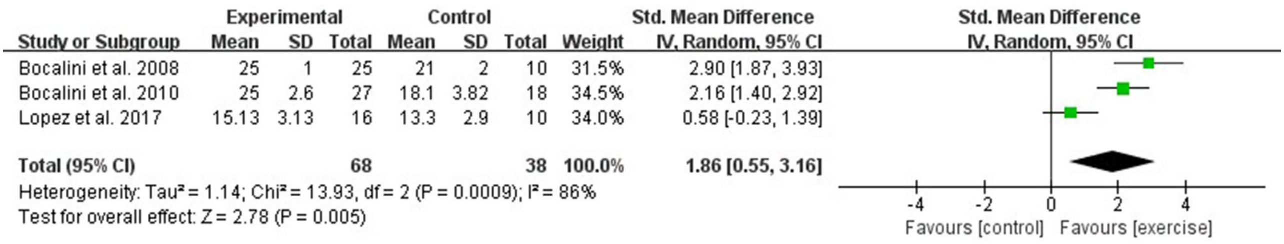

FIGURE 3
Forest plot of the effect of aquatic exercise on upper limbs strength (kg).

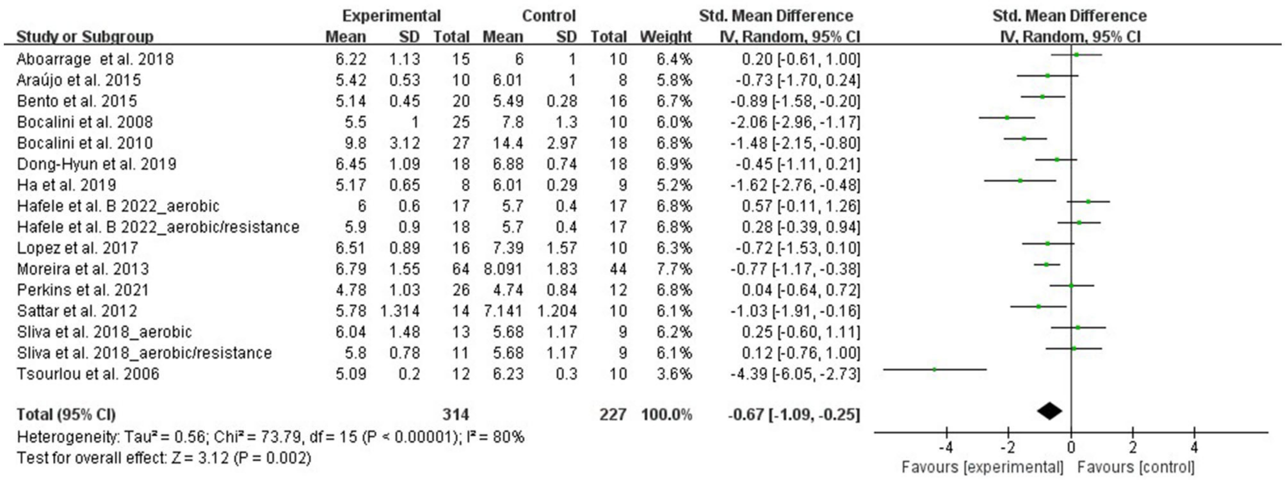

FIGURE 4
Forest plot of the effect of aquatic exercise on agility (sec).

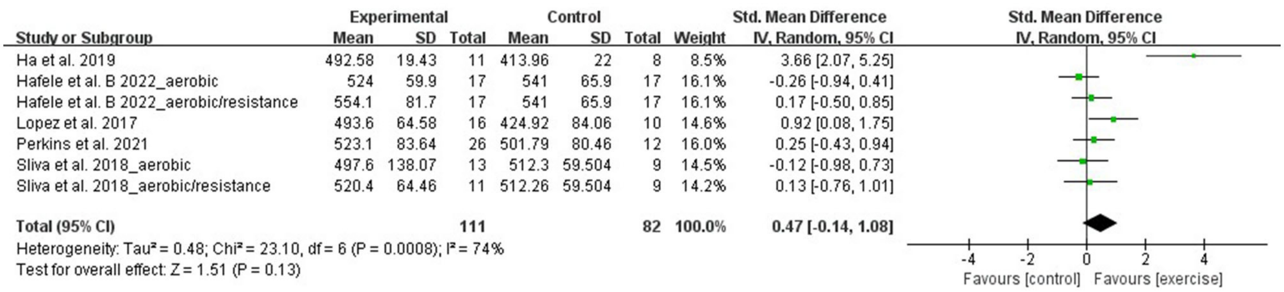

FIGURE 5
Forest plot of the effect of aquatic exercise on aerobic capacity (m).

Discussion

The present systematic review and meta-analysis demonstrated that aquatic exercise can effectively improve LLS, ULS, agility, flexibility, and overall QoL in postmenopausal women, but has limited effects on aerobic capacity. Aquatic exercise can only significantly improve LLS, ULS, agility, and flexibility in postmenopausal women < 65 years old. There was a significant improvement in overall QoL for both < 65 and ≥ 65 years old. As per our findings, aquatic resistance exercise is the best option for postmenopausal women to improve physical fitness and QoL.

Lower- and upper- limbs strength

A decline in muscle mass and balance ability in the older adults commonly accompanies the aging process. This leads to limited mobility and loss of independent living ability, which

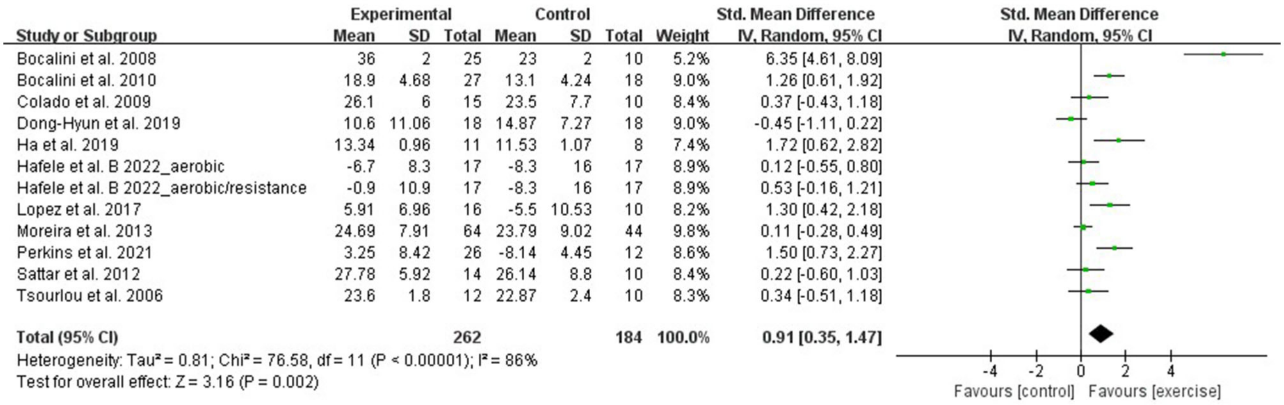

FIGURE 6
Forest plot of the effect of aquatic exercise on flexibility (cm).

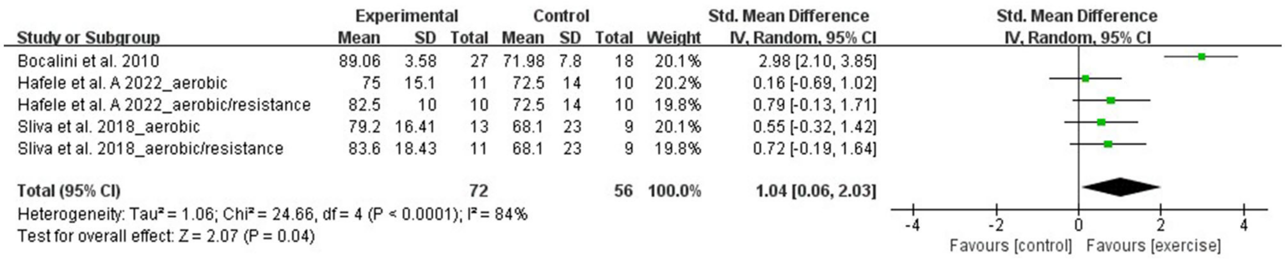

FIGURE 7
Forest plot of the effect of aquatic exercise on overall quality of life.

greatly reduces the quality of life of the older adults (58, 59). It is particularly important to maintain LLS in the older adults. Past studies have indicated that LLS is the basic fitness of balance ability and an important factor in fall prevention in the older adults (60). The present study demonstrated that aquatic exercise significantly increases LLS (SMD = 1.37, $p = 0.001$, $n = 334$) and ULS (SMD = 1.86, $p = 0.005$, $n = 106$). The present findings conform well to those of Saquetto et al. (36), who observed that aquatic exercise significantly increases the muscle strength of knee extension (SMD = 3.34, $p = 0.004$, $n = 216$), knee flexion (SMD = 2.51, $p = 0.007$, $n = 82$), and arm curl (SMD = 6.78, $p = 0.0001$, $n = 80$). In the present review, 11 studies analyzed LLS, and 3 studies analyzed ULS, and the sample size of the included studies was larger. Therefore, our findings further updated the results of the previous study. The results of aquatic exercise efficacy in improving upper and lower extremity muscle strength were confirmed. According to many studies, resistance training can significantly improve muscle strength (61, 62). Resistance exercise in water is a great way for increasing strength, especially for ULS. Most of the studies included showed that the depth of the water reaches the xiphoid, which is beneficial for applying ULS exercise and increasing ULS (63). In addition, walking or jumping in the water is challenged by the drag and resistance of the water, thereby improving lower body muscle strength. The physiological mechanism of aquatic exercise to improve muscle strength mainly due to the improvement of neuromuscular system function (64). The trend of muscle strength decline was reversed (64). Previous studies have suggested that degenerated skeletal muscle recruitment patterns and functions are the main cause of decreased muscle strength (65, 66). Resistance training increases muscle strength by improving neuromuscular recruitment and muscle contraction (66, 67). Moreover, it may also be related to increased muscle mass, which is the main cause of increased muscle strength (68). Previous research confirmed that aquatic exercise significantly increases skeletal muscle mass (69, 70).

It is worth noting that aquatic exercise significantly improves LLS in postmenopausal women < 65 years old (SMD = 3.33, $p = 0.02$), but no efficacy was found in the ≥ 65 years subgroup. One possible explanation was that higher age-related muscle weakness, poor joint mobility, and poor balance limited body movement in a water environment lead to insufficient exercise intensity (71). Regarding the exercise types, both aquatic aerobic exercise (SMD = 0.81, $p = 0.04$) and resistance exercise (SMD = 4.51, $p < 0.00001$) significantly improved LLS. Aquatic resistance exercises induced greater magnitudes of improvement.

Regarding the ULS index, the same two studies were included in the age < 65 years and aquatic resistance exercise subgroups (29, 30). ULS was significantly improved (SMD = 2.44, $p < 0.00001$), but no efficacy was found in the age ≥ 65 years and aerobic exercise subgroups (SMD = 0.58, $p = 0.16$). Data for the age ≥ 65 years and aerobic exercise subgroups are from the same study (32). Therefore, the results of these two subgroups should be interpreted and applied with caution, and more studies are needed to be included for a more comprehensive interpretation in the future.

Agility

As ages increase, it becomes increasingly challenging for the elder to move quickly and change direction (72, 73). Decreased agility is a key factor in predicting risk for recurrent falls (74). Exercise training is an important way to maintain and improve agility (75). In the present study, agility was significantly improved in the aquatic exercise group compared with the no exercise group (SMD $= -0.67$, $p = 0.002$). Our study results were in accordance with the meta-analysis of Saquetto et al. (36), in which 165 participants were included, and agility was significantly increased (SMD $= -2.13$, $p = 0.05$). Compared with the study of Saquetto et al. (36), our study has a superiority in including more studies (16 RCTs) and a larger sample size. The effect of improved neuromuscular function on increased muscle strength of the upper and lower limbs may have been responsible for the positive results (76, 77). Agility is the comprehensive embodiment of strength, speed, balance, and coordination, moreover, strength is the foundation of agility (78), and is directly associated with neuromuscular function status (79). In the present study, the overall results showed a significant increase in LLS of 1.37 kg and ULS of 1.86 kg. The results of subgroup showed that agility was improved only in the subgroup with age < 65 years (SMD $= -0.98$, $p = 0.0003$). Moreover, only postmenopausal women aged < 65 years showed significant improvement in LLS (SMD $= 3.33$, $p = 0.02$) and ULS (SMD $= 2.44$, $p < 0.00001$), further emphasizing the importance of strength in improving agility (79, 80). This may also be related to the improvement of joint range of motion. Previous studies have pointed out that agility and flexibility have a significant positive correlation (81), namely the better the flexibility performance, the shorter the agility test time. The present study also indicated that aquatic exercises can significantly improve the flexibility of lower limbs, and thereunto, only the flexibility of the subgroup aged < 65 years was significantly improved (SMD $= 1.38$, $p = 0.008$). Therefore, it is believed that the improvement of flexibility may be one of the possible reasons for the improvement of agility. Among the subgroups, agility was found to be improved in the age < 65 years subgroup, emphasizing that changes in agility improved by aquatic exercise were associated with age, precisely a relatively young age can contribute to better effects. Furthermore, subgroup analysis indicated that only aquatic resistance exercises can improve agility, reminding us that the importance and particularity of aquatic resistance exercises should be significantly considered when designing aquatic exercise programs in the future.

Aerobic capacity

6MWT, as an important index that assesses the aerobic capacity, was adopted in the included studies. 6MWT was a submaximal exercise ability test for the middle-aged and the old adults (82, 83). The present study demonstrated that aquatic exercises cannot significantly improve aerobic capacity in postmenopausal women. In addition, subgroup analysis showed that the aerobic capacity was not improved in the aged< 65 years ($n = 38$), aged ≥ 65 years ($n = 155$), aerobic exercise ($n = 139$), and multicomponent exercise subgroups ($n = 54$). Our findings are consistent with those of the study of Ha et al. (1), who included participants performing aquatic aerobic exercises 3 times a week for a 12-week duration (1). They found that 6MWT was not improved. No significant improvement of 6MWT was found in the study of Perkins et al. (2021) with 60 min of aerobic exercises 5 times a week for a 17-week duration (33). The controversial findings were possibly associated with the low impact when performing aquatic exercises, which was caused by buoyancy and reduced the muscle loads. Although the resistance to water caused the muscle to produce a contractile load, it may not be sufficient to induce a large cardiopulmonary response and therefore did not produce a better adaptive increase in cardiopulmonary function. Furthermore, it may also be related to the lower heart rate level during aquatic exercises. To our knowledge, the reduction in heart rate was mainly due to hydrostatic pressure. Hydrostatic pressure increases venous return and decreases peripheral blood volume. As a result, end-diastolic volume and stroke volume increase, thereby reducing the heart rate (84, 85), accompanied by increased vagal and parasympathetic activity and decreased sympathetic activity caused by atrial and arterial baroreflex mechanisms (86, 87). This results in a lower cardiopulmonary load without an adaptive increase in cardiopulmonary function. We mainly adopted 6MWT to assess the aerobic capacity, and there were also other studies using the VO_{2max} index. The study of Saquetto et al. (36) using VO_{2max} index included 4 articles and the results demonstrated that aquatic exercises could increase VO_{2max} by 4.12 ml/kg, which was inconsistent with the results of our study. Therefore, there was still some controversy about the results of aquatic exercise on improving the aerobic capacity level, and we should be especially cautious when interpreting and applying these results. Our study indicated that there was a relatively higher level of publication bias in aerobic capacity. It may be mainly related to the small number of the included articles. It is well known that participating in exercise for a period of time is helpful to improve aerobic capacity (88), but in the end, it shows negative results in the present study. It is also may be that the research articles with positive results have not been published or published in non-English journals.

Flexibility

Decreased flexibility is associated with the development of musculoskeletal disorders, progressive disability (89), and an increased risk of falls in middle-aged and old adults (90). Exercise is a favorable way to maintain and improve flexibility (91). The present study demonstrated that aquatic exercises can improve lower limb flexibility in postmenopausal women (SMD $= 0.91$, $p = 0.002$). Our study results were consistent with the study of Saquetto et al. (36), including only 3 RCTs vs. 12 RCTs in our study, thereby confirming the effectiveness of aquatic exercises on improving lower limb flexibility. Previous studies have shown that exercises are efficacious in improving flexibility. Aquatic exercises, as an intervention method in our study, can make people more relaxed and the action more stretched. Moreover, the buoyancy of water can reduce the fear of falling in middle-aged and old postmenopausal women, and higher water temperature had the effect of hot compress and massage, which further reduced the stiffness of tissues and muscles around joints (92), thus bringing better advantages to the improvement of joint mobility. In addition, our study has confirmed the effectiveness of aquatic exercise on improving muscle strength, especially the increased muscle strength of the lower limbs leading to more stable joints. Under the hydrostatic pressure of water, the blood circulation is better, the blood flow around the joint is more, and the metabolic wastes are recovered and disposed of, thus improving the range of motion of the joint. The subgroup analysis results of the study showed that the flexibility of the aged < 65 years (SMD $= 1.38$, $p = 0.008$) and the resistance exercises subgroups (SMD $= 2.49$, $p = 0.04$) was significantly increased, while the aged ≥ 65 years, aerobic exercises, and combination exercises subgroups were not significantly improved. It followed then that aquatic exercise can improve the flexibility of postmenopausal women aged < 65 years, and resistance exercise had a better effect on improving flexibility. Due to the importance of flexibility to the ability of voluntary physical activity and fall prevention, older adults should maintain a certain range of joint motion (93).

Quality of life

The decline of physical function associated with aging influenced the ability of daily independent living of older adults. Meanwhile, they had various chronic diseases and emotional burdens, which affect the overall QoL (16, 94, 95). The present study demonstrated that aquatic exercises can significantly improve the overall QoL in postmenopausal women (SMD $= 1.04$, $p = 0.04$), moreover, subgroup analysis indicated that aquatic exercises were significantly associated with the effectiveness in the subgroup aged < 65 years and ≥ 65 years. Since only one article was included in the subgroup of age < 65 years (30), caution should be used in the interpretation and application of this finding. Most noteworthy, although no significant improvement was observed in ULS, LLS, agility, and flexibility in the subgroup aged $\geq$ 65years, aquatic exercise had positive effects on postmenopausal women of this age. It was concluded that aquatic exercise may be a better exercise method to improve the overall QoL of old postmenopausal women. Our findings are consistent with those of the study of Hafele et al. (39), which used aquatic aerobic exercise or a combination of aquatic aerobic and resistance exercise for 60 min three times a week for 16 weeks and showed significant improvements in overall QoL in both exercise intervention groups. However, there was no improvement in the control group (39). Similar to our study, Silva et al. (34) showed a significant 17% improvement in overall QoL in the aquatic aerobic exercise group adopting 12-week aquatic aerobic exercise or a combined aquatic aerobic and resistance exercise intervention with exercise twice a week. Although no beneficial effect of combined aquatic aerobic and resistance exercise was found (34), there was no denying of the relevance of aquatic exercises via improving postmenopausal women population in the area of the body (relating to the pain or discomfort, energy or fatigue, sleep, rest, mobility, daily activities, drug dependence and performance), psychology (including emotion, learning, memory and attention, self-esteem, appearance, spiritual, social, religious, and positive or negative thinking), social identity (personal relationship, social support and sex) and environment (including physical safety, home environment, financial security, information evaluating opportunities, participate in social or cultural activities and leisure time activities). This can be explained by previous studies, which showed that social and psychological problems such as depression, anxiety, or social isolation were significantly associated with chronic diseases (30, 96). In addition, subgroup analysis results showed that the resistance exercise and combination exercise subgroups had a significant improvement in overall QoL, while the aerobic exercise subgroup had no significant effect. The importance of resistance training for postmenopausal women was further emphasized here.

Limitations

There are some limitations in the present study. First, few high-quality studies were included, and most were of moderate quality, especially in terms of blinding subjects, coaches, and measurements. Second, although more articles were included than the study of Saquetto et al. (36), there may still be the risk of insufficient literatures in the analysis of some indexes, especially in the subgroup analysis, so the results of the present study should be interpreted with caution when practicing.

Implications

In the present systematic review and meta-analysis, we evaluated and updated the effects of aquatic exercise on physical fitness and quality of life (QoL) in postmenopausal women. The present findings indicate that, aquatic exercise significantly improved ULS, LLS, agility, flexibility, and overall QoL in postmenopausal women. Aquatic resistance exercise is recommended as the best option for postmenopausal women to improve physical fitness and QoL.

Conclusions

Aquatic exercise significantly improved ULS, LLS, agility, flexibility, and overall QoL in postmenopausal women compared to those with no exercise. The beneficial efficacy of aquatic exercise on ULS, LLS, agility, and flexibility was only seen in postmenopausal women < 65 years old, but that on the overall QoL was seen both in postmenopausal women < 65 years old and ≥ 65 years old. Resistance exercise was better than aerobic/multicomponent exercise in the spectrum of aquatic exercise.

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

W-SZ conceptualized the study, searched the databases, extracted the data, performed the statistical analyses, and wrote an original draft. S-JM searched the databases, extracted the data, and reviewed, and edited the original draft. S-KZ evaluated the methodological quality and performed the statistical analyses. HX evaluated the methodological quality. W-LL edited the final draft. All the authors have reviewed and approved the final 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.

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Supplementary material

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Trends in the rate of regular exercise among adults: results from chronic disease and risk factor surveillance from 2010 to 2018 in Jiangsu, China

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Objective: The aims of this study were to estimate the rates of regular exercise and its trends among the adult population in Jiangsu, from 2010 to 2018, China, and to assess associations with sociodemographic factors.

Methods: Chronic disease and risk factor surveillance data from adults aged ≥18years were gathered in Jiangsu Province from 2010 to 2018. Rates of regular exercise were calculated after post-stratification weighting, and time trends were compared among participants with different characteristics, including gender, age, urban–rural region, educational level, occupation, annual household income, body mass index (BMI), baseline self-reported chronic diseases, smoking status, alcohol consumption, and region. Multivariable logistic regression analyses were performed to assess the associations of sociodemographic characteristics with regular exercise.

Results: A total of 33,448 participants aged 54.05±14.62years and 55.4% female (8,374 in 2010, 8,302 in 2013, 8,372 in 2015, and 8,400 in 2018) were included in this study. The weighted rate of regular exercise was 12.28% (95% confidence interval [CI]: 9.11–15.45%) in 2010 and 21.47% (95% CI, 17.26–25.69%) in 2018, showing an overall increasing trend (*P* for trend=0.009). Nevertheless, stratification analysis showed that the regular exercise rate decreased from 33.79% in 2010 to 29.78% in 2018 among retired adults. Significant associations were observed between regular exercise and age >45years (45–<60years, odds ratio [OR]: 1.24, 95% CI: 1.14–1.34; ≥60years, OR: 1.20, 95% CI: 1.08–1.34), urban residence (OR: 1.43, 95% CI: 1.32–1.54), higher education (primary, OR: 1.30, 95% CI: 1.16–1.46; secondary, OR: 2.00, 95% CI: 1.79–2.25; college or higher, OR: 3.21, 95% CI: 2.77–3.72), occupation (manual work, OR: 1.52, 95% CI: 1.33–1.73; non-manual work, OR: 1.69, 95% CI: 1.54–1.85; not working, OR: 1.22, 95% CI: 1.03–1.44; retired, OR: 2.94, 95% CI: 2.61–3.30), higher income (¥30,000–<¥60,000, OR: 1.16, 95% CI: 1.06–1.28; ≥¥60,000, OR: 1.20, 95% CI: 1.10–1.32), higher BMI (overweight, OR: 1.12, 95% CI: 1.05–1.20), self-reported chronic disease at baseline (OR: 1.24, 95% CI:1.16–1.33), former smoking (OR: 1.15, 95% CI: 1.01–1.31) and ever (30 days ago) drinking (OR: 1.20, 95% CI: 1.11–1.29).

Conclusion: The rate of regular exercise among adults in Jiangsu Province was low, but this rate increased by 9.17% from 2010 to 2018, showing an upward trend. There were differences in the rate of regular exercise among different sociodemographic factors.

KEYWORDS
exercise, physical activity, surveillance, trends, China

Introduction

Physical inactivity is an established risk factor for non-communicable diseases such as hypertension, diabetes, cardiovascular diseases, cancer, and chronic obstructive pulmonary disease (COPD) (1–4). Eliminating physical inactivity would enhance global population life expectancy by 0.68 years (5). Physical inactivity also leads to higher health care costs (6). Despite such negative effects of physical inactivity, a large proportion of Chinese adults do not engage in leisure-time physical activity. According to the findings of the China Health and Nutrition Survey, the age-standardized leisure-time physical activity rate of Chinese adults increased from 7.13% in 2000 to 11.79% in 2011, but then dropped to 7.33% in 2015 (7).

Other studies have found that leisure-time physical activity is associated with reduced risk of all-cause, cardiovascular, type 2 diabetes, and cancer mortality (8, 9), and regular exercise is essential for both physical and mental well-being (10). The World Health Organization 2020 guidelines on physical activity and sedentary behavior recommended regular aerobic exercise for all age groups (11). The most recent national fitness plan (2021–2025), which was announced in August 2021, highlighted the benefits of regular leisure-time physical activity in promoting population health and quality of life (12).

Existing Chinese studies mostly described regular exercise rates in a single year, rather than analyzing changes in trends in regular exercise rates (13, 14). Previous studies have assessed trends in regular exercise rates in Western countries, but definitions of regular exercise rates are not uniform across countries (15, 16). The population in China differs from that in developed countries in terms of the importance of healthy lifestyles, the availability of infrastructure facilities, and the hosting of sports events, but the trends in the rate of regular exercise in the Chinese population may be useful to other developing countries in implementing physical activity programs. Chinese population is changing from a developing country to a developed country. The shift in physical activity is large. For example, the level of leisure-time physical activity showed an increasing trend and the consumption of physical exercise increased (17). As such, the study of trends in physical activity in Chinese population has implications for other developing countries. In addition, "The Health China 2030 Plan Outline" (18) and "Medium- and long-term planning for the prevention and treatment of chronic diseases in China (2017–2025)" (19) propose to increase the proportion of regular physical activity to reduce the burden of chronic diseases. Regular exercise rate and socioeconomic status interact with each other (20). Individuals with higher socioeconomic status are more likely to be exercise, and individuals with lower socioeconomic status are more often engaged in heavy workloads, longer work hours, and more night work, with less time and energy for physical activity (21). Regular exercise leads to more efficient learning, resulting in higher education level, higher income, and higher socioeconomic status (22). In addition, few previous studies have examined the association between regular exercise rates and socioeconomic factors. Investigating the association between regular exercise and socioeconomic status can help develop physical activity promotion interventions that target specific socioeconomic status groups.

Methods

Survey design and participants

Chronic disease and risk factor surveillance (CDRFS) data were collected in Jiangsu Province. The CDRFS is a series of provincially representative cross-sectional surveys on chronic diseases and behavioral risk factors in the general population. In 2010, 2013, 2015, and 2018, the Department of Non-communicable Chronic Disease Control, Jiangsu Provincial Center for Disease Control and Prevention, carried out four surveillance programs on chronic diseases and their risk factors among permanent residents in Jiangsu Province. The CDRFS selected 14 disease surveillance points in Jiangsu Province, covering 13 prefecture-level cities. The subjects of the CDRFS were the general population from the community who had been living in their current residence for at least 6 months and were at least 18 years old. A multistage stratified cluster sampling method was used for the CDRFS. In the first stage, townships (rural) or subdistricts (urban) were randomly selected with Probability Proportionate to Size (PPS) sampling. In the surveys of 2010 and 2013, four townships or subdistricts were selected. In the 2015 and 2018 surveys, three townships or subdistricts were selected. In the second stage, villages (rural) or residential areas (urban) were randomly selected with PPS sampling. Three villages or residential areas were selected in 2010 and 2013, and two were selected in 2015 and 2018. In the third stage, each selected village or residential area was divided into groups of about 50 households, based on existing villager/resident groups in the village or residential area. One group was selected with simple random sampling. In the fourth stage, within each selected household, in the 2010 and 2013 surveys, the Kish method was used to select one permanent resident aged 18 years or older. In the surveys of 2015 and 2018, all permanent residents aged 18 years or older in the household were invited. The CDRFS system has been proven to be provincially representative and can adequately describe the epidemiological characteristics of population health indicators in Jiangsu Province (23, 24). Details of the design, objectives, and survey methods of the CDRFS have been described previously (25, 26).

Each round of the 2010–2018 China Chronic Diseases and Risk Factors Surveillance Survey used independent sampling, with different participants for each survey. From 2010 to 2018, four surveys were conducted. A total of 34,065 community residents aged 18 years and older were surveyed, including 8,400 in 2010, 8,399 in 2013, 8,689 in 2015, and 8,577 in 2018. All participants provided informed consent.

Data collection

Data were collected through questionnaire interviews, anthropometric measurements, and laboratory tests. In each survey, questionnaire interviews included information on sociodemographic (sex, age, residence, region, education, occupation, annual household income, and baseline self-reported chronic diseases) and lifestyle risk factors (physical activity, smoking status, and alcohol consumption). Anthropometric measurements included standing height and weight. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. All were collected by trained and qualified personnel. The questionnaire was formulated and revised by the Chronic Disease Center of the Chinese Center for Disease Control and Prevention. All questionnaire data were required to be entered twice. The Jiangsu Provincial Center for Disease Control and Prevention conducted on-site supervision of surveillance points, randomly checked and reviewed the questionnaires, and audited the final reported questionnaires and database.

Information on physical activity was self-reported by participants using the Global Physical Activity Questionnaire (GPAQ), which was developed by the World Health Organization for physical activity surveillance in countries and has good reliability and validity (27). GPAQ covered three components (intensity, duration, and frequency) and three domains (work-related, transportation-related, and leisure-time physical activity). For leisure-time physical activity, participants were asked "Do you engage in vigorous-intensity activity that lasts at least 10 min and causes a significant increase in breathing and heart rate?." If they answered yes, they were then asked how many days in a typical week and how many minutes per day they performed the activity. The same questions were asked for moderate-intensity activity. Regular exercise was defined as engaging in vigorous and/or moderate leisure-time physical activity at least 3 times a week for at least 10 min per session (28, 29).

Occupations were classified into agriculture-related work (agriculture, forestry, animal husbandry, and fishery), manual work (production and transportation equipment operators and related personnel), non-manual work (business service personnel, persons in charge of institutions, officials and related personnel, professional and technical personnel, soldiers, other workers, students, and houseworkers), not working, and retired. BMI was classified into underweight (<18.5 kg/m^2), normal (18.5 kg/m^2–23.9 kg/m^2), overweight (24.0 kg/m^2–27.9 kg/m^2), and obese (≥28.0 kg/m^2) (30). Self-reported chronic diseases included hypertension, diabetes, dyslipidemia, myocardial infarction, stroke, COPD, and cancer. Self-reported chronic disease at baseline was defined as having at least one chronic disease.

Statistical analysis

Participants with missing data on physical activity ($n = 301$) and missing data on either body weight or height ($n = 316$) across all four surveys were excluded, leaving 33,448 participants included in this analysis. Post-stratification weighting was used to weight the data according to the 2010 Jiangsu provincial census data, to allow comparison of data across surveys from 2010 to 2018. The rate of regular exercise was analyzed by gender (female vs. male), age (18– < 45, 45– < 60, ≥60 years), residence (rural vs. urban), education (no formal education, primary, secondary, college or higher), occupation (agriculture-related, manual work, non-manual work, not working, retired), annual household income (<¥30,000, ¥30,000– < ¥60,000, ≥¥60,000, refusing to answer/unknown), BMI (underweight, normal, overweight, obesity), and self-reported chronic disease at baseline (no vs. yes). The proc. surveyfreq procedure was used to estimate the rate of regular exercise, with standard error and 95% confidence interval (CI) values.

Trends in the rate of regular exercise over time were estimated using a univariate logistic regression model, which included the year of each survey as a continuous variable. A multivariable logistic regression model was used to examine associations between sociodemographic factors and regular exercise. To reduce the influence of differences in sociodemographic factors across years on the associations between regular exercise and sociodemographic factors, adjustment was made for the year of each survey in the multivariable logistic regression model combining the four surveys. A two-tailed p value <0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4.

Results

A total of 33,448 individuals (mean age, 54.05 years [standard deviation, 14.62 years]; 18,544 [55.4%] female) were included in this analysis. A significant difference was found in population distribution across the four survey rounds. Participants were primarily urban residents (59.0%) and residents without chronic disease at baseline (64.2%). A total of 46.3% of the sample had a secondary school degree and 45.8% undertook non-manual work. The percentages of participants with higher household income (≥￥60,000) and obesity increased between 2010 and 2018 (Table 1).

From 2010 to 2018, the overall weighted rate of regular exercise increased by 9.17% from 12.28% (95% CI: 9.11–15.45%) to 21.47% (95% CI: 17.26–25.69%) (P for trend = 0.009). Trends in the overall group and for each gender, residence, and baseline self-reported chronic disease groups remained similar. Among the different age groups, the rate of regular exercise was highest among adults aged ≥60 years in 2010, while the rate among adults aged ≥60 years in 2018 was the lowest. The rate of regular exercise increased with higher education and household income. Regular exercise rates were highest among overweight adults and lowest among underweight adults. The rate of regular exercise among retirees decreased from 33.79% (95% CI: 28.61–38.97%) in 2010 to 29.78% (95% CI: 24.21–35.36%) in 2018. In each year, however, retirees still had the highest rate of regular exercise among all occupations (Figure 1; Supplementary Table S1).

Various sociodemographic factors were positively associated with the rate of regular exercise. After multivariable adjustment, a significantly higher estimated regular exercise rate was observed among participants aged 45– < 60 years, those residing in urban areas, individuals with a college degree or higher, participants who were retired, individuals with annual household income ≥ ￥60,000, overweight participants, those with self-reported chronic diseases at baseline, ever drinkers, and residents of south Jiangsu Province. Compared with participants in the 18– < 45 years old age group, those who were 45– < 60 years old had a 24% higher regular exercise rate (OR: 1.24, 95% CI: 1.14–1.34). Compared with rural residents, the OR for the regular exercise rate for urban residents was 1.43 (95% CI: 1.32–1.54). The rate of regular exercise was higher in participants who were retired than in participants with agriculture-related jobs (OR: 2.94, 95% CI: 2.61–3.30). Relative to participants with a household income <¥30,000, the OR for those

TABLE 1 Characteristics of participants, CDRFS 2010–2018.[a]

Characteristic	No. (%) of participants					*P* value
	2010–2018 (*n* =33,448)	2010 (*n* =8,374)	2013 (*n* =8,302)	2015 (*n* =8,372)	2018 (*n* =8,400)	
Gender						
Female	18,544 (55.4)	4,586 (54.8)	4,737 (57.1)	4,542 (54.3)	4,679 (55.7)	0.002
Male	14,904 (44.6)	3,788 (45.2)	3,565 (42.9)	3,830 (45.7)	3,721 (44.3)	
Age, years						
18- < 45	8,815 (26.4)	2,751 (32.9)	2,460 (29.6)	2,024 (24.2)	1,580 (18.8)	<0.001
45- < 60	12,178 (36.4)	3,046 (36.4)	3,244 (39.1)	2,856 (34.1)	3,032 (36.1)	
≥60	12,455 (37.2)	2,577 (30.8)	2,598 (31.3)	3,492 (41.7)	3,788 (45.1)	
Residence						
Rural	13,727 (41.0)	3,591 (42.9)	2,939 (35.4)	3,580 (42.8)	3,617 (43.1)	<0.001
Urban	19,721 (59.0)	4,783 (57.1)	5,363 (64.6)	4,792 (57.2)	4,783 (56.9)	
Education						
No formal education	6,435 (19.2)	1,732 (20.7)	1,596 (19.2)	1,541 (18.4)	1,566 (18.6)	<0.001
Primary	8,653 (25.9)	2,278 (27.2)	2,138 (25.8)	2,086 (24.9)	2,151 (25.6)	
Secondary	15,481 (46.3)	3,845 (45.9)	3,966 (47.8)	3,785 (45.2)	3,885 (46.2)	
College or higher	2,879 (8.6)	519 (6.2)	602 (7.3)	960 (11.5)	798 (9.5)	
Occupation						
Agriculture-related	9,047 (27.0)	2,699 (32.2)	2,875 (34.6)	1,863 (22.3)	1,610 (19.2)	<0.001
Manual work	2,978 (8.9)	882 (10.5)	945 (11.4)	610 (7.3)	541 (6.4)	
Non-manual work	15,313 (45.8)	3,725 (44.5)	3,416 (41.1)	3,986 (47.6)	4,186 (49.8)	
Not working	1,783 (5.3)	207 (2.5)	321 (3.9)	541 (6.5)	714 (8.5)	
Retired	4,327 (12.9)	861 (10.3)	745 (9.0)	1,372 (16.4)	1,349 (16.1)	
Annual household income, ¥						
<30,000	8,463 (25.3)	3,735 (44.6)	1,524 (18.4)	1,704 (20.4)	1,500 (17.9)	<0.001
30,000- < 60,000	9,019 (27.0)	2,737 (32.7)	2,624 (31.6)	1,950 (23.3)	1,708 (20.3)	
≥60,000	11,426 (34.2)	1,098 (13.1)	2,780 (33.5)	3,571 (42.7)	3,977 (47.3)	
Refuse to answer/Unknown	4,540 (13.6)	804 (9.60)	1,374 (16.6)	1,147 (13.7)	1,215 (14.5)	
BMI categories[b]						
Underweight	711 (2.1)	208 (2.5)	194 (2.3)	155 (1.9)	154 (1.8)	<0.001
Normal	14,038 (42.0)	3,866 (46.2)	3,592 (43.3)	3,297 (39.4)	3,283 (39.1)	
Overweight	13,264 (39.7)	3,159 (37.7)	3,246 (39.1)	3,445 (41.1)	3,414 (40.6)	
Obesity	5,435 (16.2)	1,141 (13.6)	1,270 (15.3)	1,475 (17.6)	1,549 (18.4)	
Self-reported chronic disease						
No	21,467 (64.2)	6,025 (71.9)	5,702 (68.7)	5,133 (61.3)	4,607 (54.8)	<0.001
Yes	11,981 (35.8)	2,349 (28.1)	2,600 (31.3)	3,239 (38.7)	3,793 (45.2)	
Smoking						
Never	23,007 (68.8)	5,580 (66.6)	5,872 (70.7)	5,702 (68.1)	5,853 (69.7)	<0.001
Former	2,160 (6.46)	523 (6.25)	411 (4.95)	625 (7.47)	601 (7.15)	
Current	8,281 (24.8)	2,271 (27.1)	2,019 (24.3)	2,045 (24.4)	1,946 (23.2)	
Drinking						
Never	21,161 (63.3)	5,484 (65.5)	5,626 (67.8)	4,992 (59.6)	5,059 (60.2)	<0.001
Ever, 30 days ago	9,463 (28.3)	2,293 (27.4)	2,148 (25.9)	2,497 (29.8)	2,525 (30.1)	
Ever, within 30 days	2,819 (8.43)	597 (7.13)	528 (6.36)	881 (10.5)	813 (9.68)	

(Continued)

TABLE 1 (Continued)

Characteristic	No. (%) of participants					*P* value
	2010–2018 (*n* =33,448)	2010 (*n* =8,374)	2013 (*n* =8,302)	2015 (*n* =8,372)	2018 (*n* =8,400)	
Region						
South	14,354 (42.9)	3,592 (42.9)	3,580 (43.1)	3,617 (43.2)	3,565 (42.4)	0.956
Central	7,176 (21.5)	1,798 (21.5)	1,776 (21.4)	1,800 (21.5)	1,802 (21.5)	
North	11,918 (35.6)	2,984 (35.6)	2,946 (35.5)	2,955 (35.3)	3,033 (36.1)	

BMI, body mass index; CDRFS, chronic disease and risk factor surveillance.
[a]Data are expressed as unweighted number of participants and unweighted percentages.
[b]Underweight (<18.5 kg/m2), normal (18.5 kg/m^2–23.9 kg/m^2), overweight (24.0 kg/m^2–27.9 kg/m^2), and obesity (≥28.0 kg/m^2).

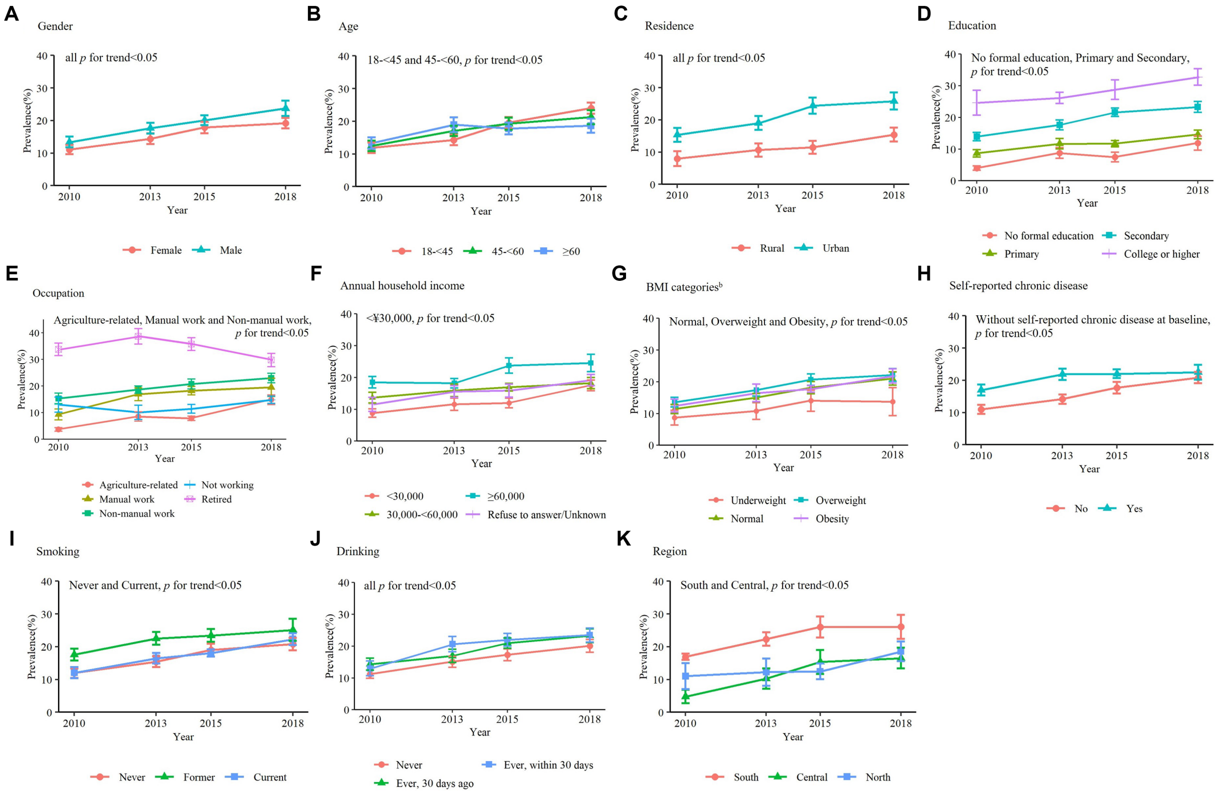

FIGURE 1
Trends in weighted rate of regular exercise, CDRFS 2010-2018[a]. BMI, body mass index; CDRFS, chronic disease and risk factor surveillance. [a]Data were weighted to be provincially representative in each category and error bars indicate 95% CIs. [b]Underweight (<18.5 kg/m^2), normal (18.5 kg/m^2-23.9 kg/m^2), overweight (24.0 kg/m^2-27.9 kg/m^2), and obesity (≥28.0 kg/m^2).

in the ¥30,000– < ¥60,000 was 1.20 (95% CI: 1.10–1.32). Further, participants with higher education and higher BMI tended to exercise more regularly (*P* for trend <0.001). Self-reported chronic disease at baseline was associated with a 24% higher regular exercise rate (OR: 1.24, 95% CI: 1.16–1.33) (Table 2). The rate of regular exercise was 20% higher among those who had consumed alcohol in the previous 30 days relative to those who had never consumed alcohol (OR = 1.20, 95% CI: 1.11–1.29). The association between sociodemographic factors and regular exercise according to each survey was similar to that of the overall survey (Supplementary Table S2). We observed that rural participants with college degrees or higher had higher rates of regular exercise than rural participants without formal education (OR = 4.90, 95% CI: 3.79–6.30; $P_{interaction}$ = 0.001). We did not observe an interaction between smoking and BMI (Supplementary Figures S1, S2).

Discussion

Using provincially representative data from the CDRFS in Jiangsu, China, from 2010 to 2018, we analyzed the weighted rate of regular exercise, estimated its trend over time, and examined associations of regular exercise with demographic factors. Our analysis showed that the regular exercise rate of adults in Jiangsu Province was 16.02% in 2013,

TABLE 2 Association between regular exercise (yes vs. no) and sociodemographic factors using pooled data of CDRFS 2010–2018[a] (OR and 95% CI).

Characteristic	Counts	Rate of regular exercise (%, 95 CI)	OR (95% CI)	*P* value
Gender				
Female	2944/18544	15.46 (12.56–18.37)	ref	
Male	2736/14904	18.46 (15.57–21.36)	0.96 (0.88–1.05)	0.414
Age, years				
18- <45	1428/8815	16.46 (13.45–19.47)	ref	
45- <60	2105/12178	17.45 (14.47–20.44)	1.24 (1.14–1.34)	<0.001
≥60	2147/12455	17.36 (14.52–20.20)	1.20 (1.08–1.34)	<0.001
P for trend[b]			<0.001	
Residence				
Rural	1462/13727	11.24 (7.47–15.02)	ref	
Urban	4218/19721	20.83 (16.97–24.69)	1.43 (1.32–1.54)	<0.001
Education				
No formal education	542/6435	7.82 (5.23–10.40)	ref	
Primary	1077/8653	11.47 (9.31–13.63)	1.30 (1.16–1.46)	<0.001
Secondary	3190/15481	18.78 (16.35–21.20)	2.00 (1.79–2.25)	<0.001
College or higher	871/2879	28.58 (24.54–32.61)	3.21 (2.77–3.72)	<0.001
P for trend[c]			<0.001	
Occupation				
Agriculture-related	730/9047	7.85 (5.85–9.85)	ref	
Manual work	472/2978	15.16 (12.43–17.88)	1.52 (1.33–1.73)	<0.001
Non-manual work	2793/15313	19.44 (16.89–21.99)	1.69 (1.54–1.85)	<0.001
Not working	220/1783	12.54 (9.95–15.14)	1.22 (1.03–1.44)	0.017
Retired	1465/4327	34.04 (30.90–37.19)	2.94 (2.61–3.30)	<0.001
Annual household income, ¥				
<30,000	938/8463	11.25 (8.49–14.01)	ref	
30,000- <60,000	1500/9019	15.68 (12.90–18.47)	1.16 (1.06–1.28)	0.001
≥60,000	2539/11426	21.99 (18.39–25.60)	1.20 (1.10–1.32)	<0.001
Refuse to answer/Unknown	703/4540	15.82 (12.87–18.77)	1.04 (0.93–1.17)	0.449
P for trend[d]			0.170	
BMI categories[e]				
Underweight	83/711	11.52 (8.73–14.30)	0.69 (0.54–0.87)	0.003
Normal	2244/14038	15.91 (13.16–18.65)	ref	
Overweight	2425/13264	18.34 (15.21–21.48)	1.12 (1.05–1.20)	0.001
Obesity	928/5435	17.37 (13.87–20.86)	1.05 (0.96–1.15)	0.250
P for trend[f]			0.010	
Self-reported chronic disease				
No	3224/21467	15.36 (12.61–18.10)	ref	
Yes	2456/11981	21.08 (18.12–24.05)	1.24 (1.16–1.33)	<0.001
Smoking				
Never	3835/23007	16.61 (13.62–19.61)	ref	
Former	463/2160	22.21 (18.98–25.43)	1.15 (1.01–1.31)	0.039
Current	1382/8281	16.81 (14.21–19.41)	0.88 (0.81–0.97)	0.011

(Continued)

TABLE 2 (Continued)

Characteristic	Counts	Rate of regular exercise (%, 95 CI)	OR (95% CI)	*P* value
Drinking				
Never	3367/21161	15.56 (12.67–18.45)	ref	
Ever, 30 days ago	1755/9463	18.80 (15.59–22.02)	1.20 (1.11–1.29)	<0.001
Ever, within 30 days	558/2819	20.04 (17.03–23.04)	1.16 (1.04–1.29)	0.008
Region				
South	3317/14354	22.66 (18.22–27.10)	ref	
Central	791/7176	11.40 (6.64–16.17)	0.62 (0.57–0.68)	<0.001
North	1572/11918	13.39 (6.71–20.07)	0.94 (0.87–1.02)	0.143

BMI, body mass index; CDRFS, chronic disease and risk factor surveillance.
[a]Unweighted estimates and 95%CIs were estimated for the overall survey.
[b]*P* for trend over age was calculated using the median value of each category as a continuous variable.
[c]*P* for trend over education was calculated using education level as a continuous variable.
[d]*P* for trend over annual household income was calculated using the median value of each category as a continuous variable.
[e]Underweight (<18.5 kg/m2), normal (18.5 kg/m^2–23.9 kg/m^2), overweight (24.0 kg/m^2–27.9 kg/m^2), and obesity (≥28.0 kg/m^2).
[f]*P* for trend over BMI categories was calculated using the median value of each category as a continuous variable.

which was higher than the national average level (15.0%) (29). Provinces with similar GDP to Jiangsu Province, e.g., Shandong Province (19.8%) (14), had a higher rate of regular exercise than Jiangsu Province. Provinces with lower GDP than Jiangsu Province, e.g., Gansu Province (13.95%) (13), had a lower rate of regular exercise than Jiangsu Province. Therefore, we speculate that the economy is one of the factors affecting the regular exercise rate. This part needs to be further explored. These findings demonstrate that health policies relevant to Jiangsu Province need to be developed and targeted measures implemented to increase the rate of regular exercise. Additionally, our research demonstrates that the regular exercise rate in Jiangsu Province increased by 9.17% from 2010 to 2018. A study in Beijing found that the regular exercise rate in the city increased by 8.14% from 2008 to 2017 (31, 32). Nevertheless, data reported from Iran and Madrid indicated that the trends in leisure-time physical activity declined, possibly due to increased sedentary time and obesity rates (33, 34).

The rate of regular exercise among retirees generally showed a downward trend over time; however, the rate of regular exercise among retirees was still relatively high compared to that of participants in the other occupation groups, and retirement was positively associated with regular exercise. The decline in the regular exercise rate among retirees could be attributed to the fact that China is transforming into an aging nation and the older adult population is growing rapidly (35). The aging of society makes it more likely that retirees continue working, resulting in a lack of time for leisure-time physical activity (36). Additionally, the increase in older adults taking care of their grandchildren in China has led to a decrease in the time they spend on exercise (37). The average retirement age is 60. Compared with non-retirees under 45 years old, retired people have less stress from study, work, and life and take more exercise (38). We observed a much higher rate of regular exercise in urban than in rural areas, as well as significant increases in regular exercise rates in both areas, consistent with a previous study (39). The disparity between areas may primarily be attributable to the fact that rural areas are less likely to have facilities associated with leisure-time physical activity, such as parks and green spaces (40). Additionally, residents in urban areas have higher incomes and are increasingly concerned about quality of life, and thus exercise more frequently (41).

Positive associations of regular exercise with educational and income levels were observed in our study, consistent with other studies showing that education and income are positive influences on leisure-time physical activity (20, 42). Some previous studies (43, 44) have reported an inverse relationship between BMI and leisure-time physical activity, which contradicts our findings. In our study, overweight adults had the highest regular exercise rate. The possible reasons for these different findings might be that Jiangsu Province implemented "The Outline of the National Fitness Program 2001–2010" to improve fitness publicity for people with overweight and obesity (45). The number of people who consciously participate in exercise increased, with running, square dancing, climbing mountains, and fitness becoming fashionable. Further, individuals with overweight and obesity have greater motivation to take part in physical activity with the aim of weight management and improving their appearance (46, 47). In addition, being overweight may not mean obesity, but may be an increase in muscle mass from exercise (48). Exercise increases muscle mass, and muscle is denser than fat, so people with more muscle mass at the same weight may have a higher BMI (49). Follow-up studies should focus on indicators of both waist circumference and visceral fat.

Multivariable logistic regression analyses suggested that lack of regular exercise was more severe among individuals who were younger, lived in a rural area, had a lower education level, participated in agriculture-related work, and had a lower income. In summary, people in socially/economically disadvantaged positions were more likely to have a low regular exercise rate. In a recent Swedish study, economic stress was associated with low leisure-time physical activity and the strength of the association increased sharply with higher levels of economic stress (50). Therefore, targeted interventions for the abovementioned groups should be created, to encourage them to take more exercise (11).

This study provides data support for the government to develop physical activity policies. The government can launch educational campaigns and awareness programs to promote the benefits of regular exercise and encourage citizens to adopt a more active lifestyle. The government can also improve infrastructure and recreational exercise facilities to encourage citizens to be physically active. Society can support community sports organizations by providing funding, resources, and infrastructure to enable citizens to participate in organized sports activities. Individuals can develop regular exercise habits by raising their awareness of exercise. The strengths of our study include the large sample size, with a representative population and the use of a validated measure of physical activity (51). Our study has some potential limitations. First, the surveys were not conducted annually, which could have allowed for a more detailed and quantitative analysis of the trend. Second, all sociodemographic characteristics and physical activity data were based on self-reported information, which is likely to have introduced bias. Third, the study had a cross-sectional design; hence the causality of relationships between sociodemographic factors and regular exercise could not be determined. However, this study has four different time points, and the time interval can reflect the trend of change.

Conclusion

Our study showed a significant increase in the overall rate of regular exercise in adults in Jiangsu Province over the 8 year period from 2010 to 2018; however, the rate decreased among retired participants. Being older, living in urban areas, having a higher education level, engaging in non-agriculture-related work, having a higher income, having a higher BMI, having a chronic disease at baseline, former smoking, and ever drinking were all positively associated with regular exercise from 2010 to 2018. Interventions targeted at population subgroups with low regular exercise rates, or those showing decreasing trends in regular exercise, are warranted.

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 protocol for the 2015 chronic disease and risk factor surveillance survey was approved by the ethics review committee of the Chinese Center for Disease Control and Prevention (CDC), and all other surveys were approved by the ethical committee of National Center for Chronic and Noncommunicable Disease Control and Prevention (NCNCD), China CDC. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JS and JY designed the research. JY performed the data analyses and drafted the manuscript. JS revised the data analysis. JS, YQ, RT, JY, and SL conducted field investigations and data collection. SL, JZ, and MW revised the manuscript critically for important intellectual content. 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.

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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.2023.1089587/full#supplementary-material

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Association of grip strength and comorbidities with all-cause mortality in the older hypertensive adults

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Background: With growing concerns about global population aging, comorbidity, and disability have emerged as key variables that influence the health of the older adults in terms of disease and function. This study sought to examine the impact of comorbidity and impairment using disease and functional status indicators of all-cause mortality in the older adults. Hypertension, which was chosen as the indicator chosen for disease, has the greatest prevalence in the older population. A total of 15 self-reported chronic conditions were added as indicators of comorbidity, and grip strength was chosen as a measure of functional status. The study also evaluated the association between grip strength and comorbidity, as well as its consequences on all-cause death and survival in a hypertensive senior population.

Methods: We chose a total of 2,990 hypertensive participants aged ≥60years whose data for grip strength were collected in the National Health and Nutrition Examination Survey conducted between 2011 and 2014. The association of all-cause death with grip strength and comorbidity was examined using a Cox proportional hazard regression model. The interaction between comorbidity and all-cause mortality, as well as its association with grip strength, was also examined.

Results: The hazard ratio [95% confidence intervals (CIs)] for all-cause mortality in the highest grip strength tertile was 0.266 (0.168–0.419), compared to the lowest grip strength tertile. The all-cause mortality decreased with an increase in the number of co-morbidities [2.677 (1.557–4.603) in the group with ≥3 chronic diseases]. The weighted generalized model revealed a negative correlation between grip strength and comorbidities in more than three groups after accounting for all possible variables (β=−2.219, −3.178~−1.260, p<0.001). The risk of mortality reduced with increasing grip strength in patients with ≥3 comorbidities (p-value for trend <0.05), but no meaningful difference was found in the interaction between comorbidities and grip strength (p-value for interaction >0.05).

Conclusion: In older hypertension patients, grip strength and comorbidities were correlated with all-cause death, and there was a negative correlation between grip strength and comorbidities. Higher grip strength was associated with fewer fatalities in patients with ≥3 comorbidities, suggesting that functional exercise can improve the prognosis of comorbidities.

KEYWORDS

handgrip strength, comorbidity, hypertension, older adults, mortality

1. Introduction

As global aging accelerates and average life expectancy rises, disability and comorbidities have grown in importance, raising concerns for global health care (1). The US Department of Health and Human Services (DHHS) defines comorbidity as a medical condition involving two or more conditions that have each lasted more than a year. In developed countries, the prevalence of comorbidity in senior people aged 65 and older is >60% (64.75% in the US), and more than half of the older adults have more than three chronic conditions (2, 3). Comorbidities in older adults patients result in more complex diagnoses and treatments.

The number of adults living with cardiovascular disease (CVD) in old age is increasing with the aging population, and so is the number of older adults susceptible to CVD as a normal physiological change of aging. Reportedly, more than 70% of adults have CVD by the age of 70, and more than two-thirds have non-CVD comorbidities (4). Comorbidities are common in the older adults, particularly those having CVD. Further, the functions of human body organs gradually slow down with age, due to a variety of chronic diseases that are prone to geriatric syndrome, which not only reduces independent living ability but can even render people disabled. According to the Centers for Disease Control and Prevention Disability and Health Database, the disability rate among people aged 65 and older in the United States reached 42.3% in 2017. The current clinical care regimen is largely based on clinical practice guidelines for disease diagnosis and treatment, as well as management and decision-making. To evaluate the value of a specific treatment, the majority of randomized controlled trials (RCTs) enroll a reasonably homogeneous sample for a particular disease. Patients with multiple diseases are frequently excluded on purpose. Studies involving cardiovascular RCTs majorly focus on cardiovascular adverse events, which may be less helpful than studies that evaluate the overall benefit of treatment in older patients, such as loss of physical and cognitive function or health-related lifetime treatment (5).

Grip strength is a simple, non-invasive measure of muscle strength and function that has been linked to a variety of age-related health problems, including disability. Reduced grip strength has been shown to predict premature death and disability (6). Therefore, grip strength is a clinically viable tool for screening health status during the process of aging. In several prospective studies, grip strength was found to be inversely related to CVD, etiology-specific mortality, and all-cause mortality outcomes (7–9). In a cross-sectional study of Chinese individuals over the age of 50, reduced grip strength was significantly linked to a higher incidence of 12 and 8 chronic diseases in men and women, respectively (10). The results of the Kara-Age study in Germany showed an independent negative association between grip strength and morbidity in older women (11). In most of these studies, the association of grip strength with comorbidities and all-cause mortality in CVDs remains unclear. Given the high prevalence of hypertension in the global population, the primary goal of our cross-sectional study was to evaluate the association of grip strength with comorbidities and all-cause mortality in a hypertensive population. We also wanted to investigate if the presence of comorbidity in individuals with different grip strength levels affects the survival outcome, by studying the relationship between function and disease in older people with CVDs.

2. Materials and methods

2.1. Study population

The data for this study was provided by the National Health and Nutrition Examination Survey (NHANES), a periodic cross-sectional survey of the U.S. population. The survey used a complex, multi-stage probability sampling method to obtain a nationally representative sample of about 5,000 people per year. The sample design consisted of four stages of multi-year, hierarchical, and clustering samples, with data being released every 2 years. The survey was conducted by the National Centers for Health's Board of Approval Statistics and Institutional Review. Informed consent was obtained from all study participants (12, 13).

A flow chart of the study sample selection process is displayed in Figure 1. Our study included a total of 19,931 participants. Of these, we chose participants with hypertension who were 60 years or older, while excluding those under 60. The final sample group for analysis consisted of 3,525 hypertension patients aged ≥60 years. Those aged ≥60 years and diagnosed with hypertension were eligible for this study if they met any of the following criteria: (1) In response to the interview question, "Have you ever been told by a doctor or other healthcare provider that you have high blood pressure?" The answer was "yes;" (2) In response to the interviewer's question, "Do you use blood pressure medication?" The answer was "yes"; and (3) Patients whose mean blood pressure was >140/90 mm Hg and had their blood pressure measured at least three times on different days.

2.2. Grip strength

Grip strength was measured using a dynamometer (Takei Digital Grip Strength Dynamometer, Model T.K.K.5401; Takei Scientific Instruments Co. Ltd. Niigata, Japan). The participants were instructed to stand and use one hand to exert as much force as they could on the dynamometer. Each hand was tested three times, with a gap of 60 s elapsing between measurements on the same hand. Grip strength (in kg) was calculated as the mean of left and right hands (7). A total of 2,995 participants were finally selected after excluding 98 participants whose values were missing values, 331 participants whose grip strengths could not be measured, and 101 participants who only had one hand grip strength. Grip strength was considered to be a continuous variable, which was divided into three groups (Tertile 1: <23.4 kg, Tertile 2: 23.4–31.9 kg), and Tertile 3: >31.9 kg) based on the grip strength tertile 23.4 kg and 31.9 kg.

2.3. Physical comorbidities

We used data on 15 self-reported chronic diseases, including angina, arthritis, asthma, chronic bronchitis, congestive heart failure, coronary heart disease, diabetes, emphysema, gout, liver disease, myocardial infarction, stroke, thyroid disease, and kidney disease. Participants were classified as having various comorbidities if they answered "yes" to this question. The total comorbidities for each participant were individually calculated and divided into four groups namely, "none," "one," "two," and "three or more."

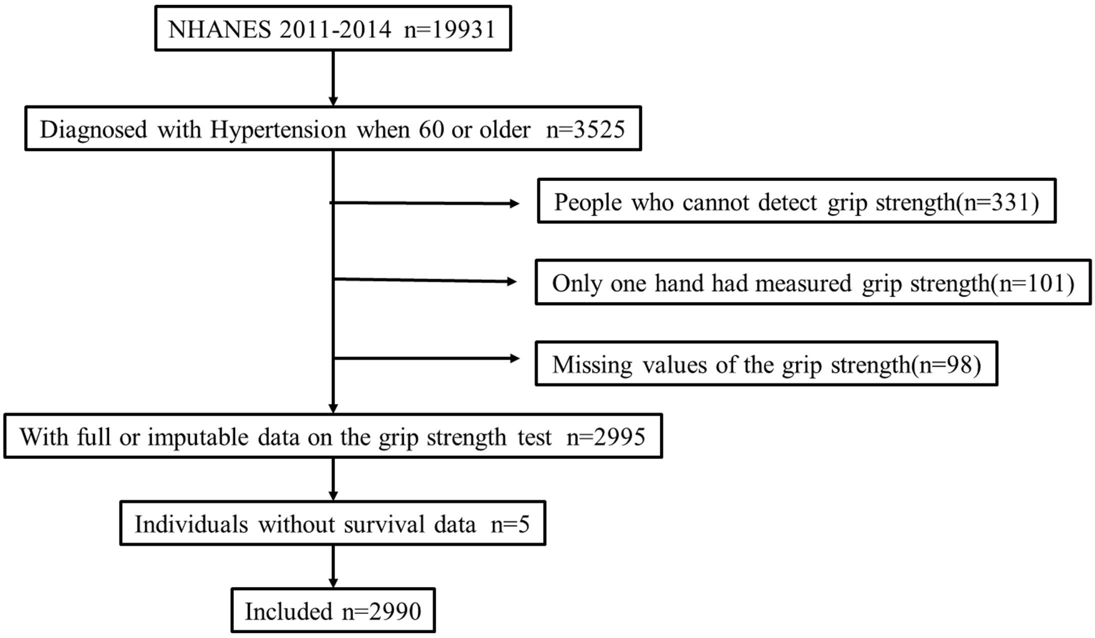

FIGURE 1
Flowchart of the research sample selection process.

2.4. Covariates

The covariates included age, sex, race (white, Mexican American, black, and others), an education level (above high school, high school graduate/General Educational Development (GED), and below high school), citizenship status (married/living with a partner, single, divorced/separated, and widowed), poverty income ratio (PIR), smoking status (never, former, and present), alcohol consumption (<12 drinks per year or ≥ 12 drinks per year), health insurance status (insured and uninsured), body mass index (BMI), and waist circumference (cm).

2.5. Outcome

All-cause mortality, as determined by the National Death Index (NDI), was considered the primary outcome variable. NDI is one of the reliable resources that is widely used in death identification. The cause of death was classified as per the International Classification of Diseases, CD10.

3. Statistical analysis

The statistical analysis was conducted using R Studio (4.2.0, US). We applied proper weights based on the NHANES complex sampling design to ensure that they were representative of the entire U.S. population. Continuous and categorical variables were expressed as the weighted average (standard error) and weighted percentages, respectively. The one-way analysis of variance (ANOVA) test and Kruskal Wallis test were used to analyze the statistical significance of the weighted categorical variables and continuous variables, respectively.

To evaluate all-cause mortality during follow-up, we constructed the cumulative Kaplan–Meier curves based on specific categories of grip strength and commodities. The log-rank test was used to determine whether differences in subgroups were statistically significant. The Cox-proportional risk model was used to analyze the relationship between grip strength, comorbidity, and all-cause mortality. Three different models were constructed using the multivariate Cox regression model: model 1 was adjusted for none; model 2 was adjusted for sex, age, and ethnic; and model 3 was adjusted for all covariates in model 2 along with education level, marital status, insurance status, PIR, BMI, waist circumference, smoking status, and alcohol consumption. The weighted generalized linear regression model was used to investigate the relationship between grip strength and comorbidity, and their linear relationship was discussed while controlling for covariables. A stratification analysis was conducted to examine the relationship between grip strength and all-cause mortality in different comorbidity groups and the interaction between grip strength and comorbidity with all-cause mortality. All statistical analyses had a two-sided *p*-value threshold for significance.

4. Results

Table 1 shows the weighted characteristics of the participants by tertile of grip strength. Overall, significant differences were noted in the age, sex, BMI, waist circumference, ethnic, marital status, education level, PIR, smoking status, alcohol consumption, and total comorbidities of the grip strength tertile groups ($p < 0.05$).

Figure 2 depicts the survival curve of grip strength and comorbidity. Grip strength was inversely correlated with all-cause mortality, with a 5.8% reduction in the probability ($p < 0.0001$) of mortality risk for every 1 SD increase in grip strength. This negative correlation persisted even after multivariate correction (Table 2). When using grip strength was used as a categorical indicator from

TABLE 1 Participants' characteristics by tertile of grip strength.

Variable	Overall	Tertile 1	Tertile 2	Tertile 3	*p*-value
Age	69.46 (0.20)	72.61 (0.30)	68.44 (0.28)	67.57 (0.26)	<0.0001
Sex					<0.0001
Female	1,504 (50.81)	879 (93.82)	579 (69.56)	46 (3.45)	
Male	1,456 (49.19)	105 (6.18)	406 (30.44)	945 (96.55)	
BMI	28.80 (0.20)	28.06 (0.33)	29.20 (0.23)	29.07 (0.31)	0.02
Waist	102.01 (0.54)	97.32 (0.86)	101.51 (0.68)	106.36 (0.73)	<0.0001
Ethnic					<0.0001
Black	716 (24.19)	156 (7.22)	240 (9.46)	320 (9.24)	
Mexican American	254 (8.58)	93 (4.21)	80 (3.24)	81 (2.91)	
White	1,400 (47.3)	506 (76.93)	457 (77.88)	437 (81.44)	
Other	590 (19.93)	229 (11.63)	208 (9.42)	153 (6.42)	
Marital					<0.0001
Divorced/separated	494 (16.71)	167 (13.78)	181 (18.40)	146 (9.55)	
Married/living with Partner	1,676 (56.68)	417 (49.84)	548 (61.35)	711 (80.61)	
Single	171 (5.78)	46 (3.49)	71 (4.53)	54 (4.44)	
Widowed	616 (20.83)	353 (32.89)	184 (15.72)	79 (5.40)	
Education					<0.0001
Above high school	1,444 (48.85)	419 (50.17)	508 (62.50)	517 (66.71)	
HIGH school or GED	686 (23.21)	233 (25.77)	225 (21.70)	228 (18.94)	
Less than high school	826 (27.94)	330 (24.06)	251 (15.80)	245 (14.36)	
PIR	3.08 (0.08)	2.57 (0.11)	3.13 (0.07)	3.47 (0.07)	<0.0001
Insurance status					0.37
No	245 (8.29)	63 (4.27)	96 (5.41)	86 (6.15)	
Yes	2,711 (91.71)	918 (95.73)	888 (94.59)	905 (93.85)	
Smoke					<0.0001
Former	1,108 (37.47)	288 (31.21)	354 (39.36)	466 (47.23)	
Never	1,466 (49.58)	602 (59.67)	499 (49.81)	365 (39.92)	
Now	383 (12.95)	93 (9.12)	131 (10.83)	159 (12.85)	
Alcoholic					<0.0001
No	934 (32.99)	459 (43.93)	312 (27.42)	163 (14.30)	
Yes	1897 (67.01)	468 (56.07)	630 (72.58)	799 (85.70)	
Comorbidities total					<0.0001
None	631 (21.32)	142 (14.22)	207 (20.25)	282 (26.19)	
One	822 (27.77)	250 (25.63)	285 (26.91)	287 (29.85)	
Two	644 (21.76)	217 (20.02)	234 (25.55)	193 (21.18)	
Three or more	863 (29.16)	375 (40.13)	259 (27.30)	229 (22.78)	

Continuous variables are expressed as weighted means (standard error), categorical variables as weighted percentages. BMI: body mass index; PIR: poverty income ratio.

Cox regression estimates, the mortality risks in tertile 2 and tertile 3 groups decreased by 48.1% (95% CI, 0.427–0.632) and 60.2% (95% CI, 0.294–0.539), respectively, as compared to the overall risk of mortality in the tertile 1 group. This trend continued even after the multivariable adjustment analysis (Table 2). The risk of death increased gradually with increasing comorbidities in the model group irrespective of full adjustments (Table 2).

Table 3 shows the correlation between grip strength and comorbidities in the three weighted generalized models. Grip strength and multiple comorbidities had a significant linear negative correlation, but a significantly stronger negative correlation between grip strength and ≥3 comorbidities group ($\beta = -2.219$, -3.178~-1.260, $p < 0.001$) was observed after multivariable adjustment (Model 3; Table 3).

Table 4 shows the correlation between grip strength and mortality, stratified by comorbidities, using the lowest grip strength as the reference group. Grip strength and comorbidities showed no statistically significant associations with mortality. Interestingly, in individuals with ≥3 comorbidities, increasing grip strength decreased the likelihood of death (p for trend = 0.04).

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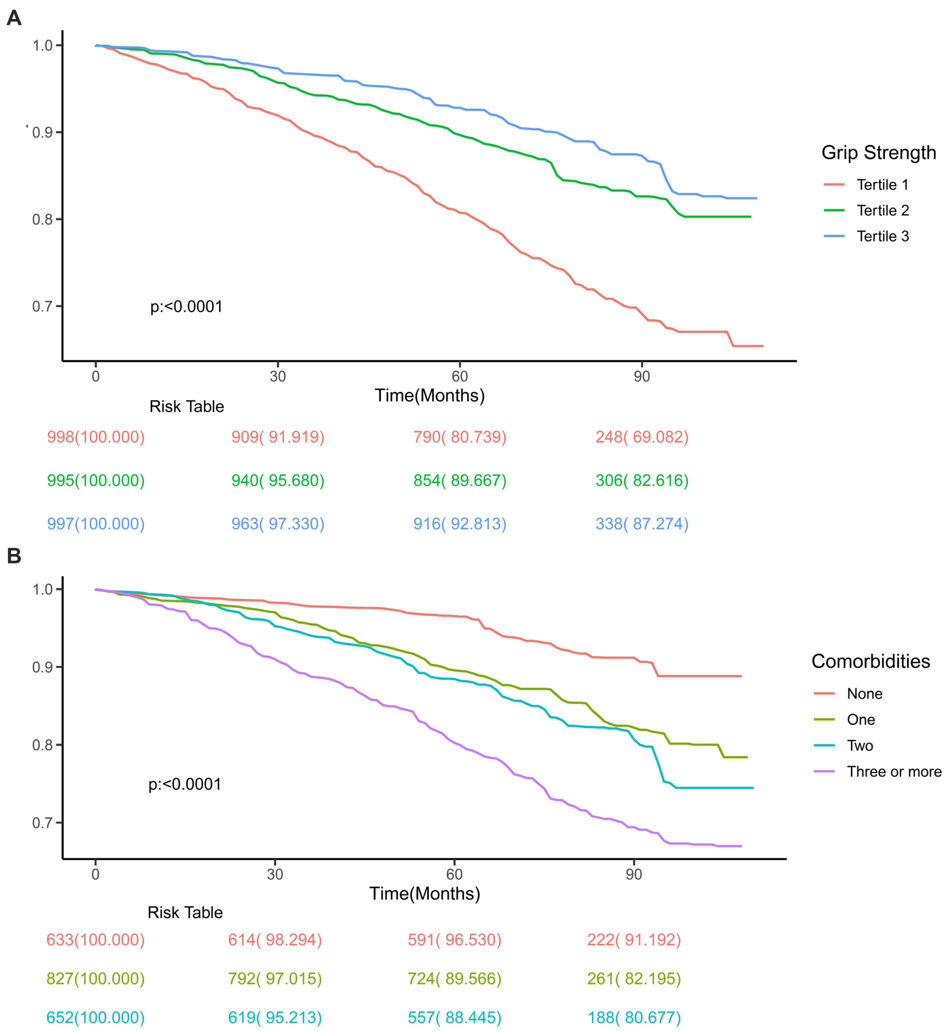

FIGURE 2
Association of grip strength **(A)** and comorbidities **(B)** with all-cause mortality, respectively.

TABLE 2 Associations of the grip strength and Comorbidities with all-cause mortality, respectively.

	Model 1	Model 2	Model 3
Grip strength			
Per 1 SD increase	0.942 (0.930,0.955) <0.0001	0.916 (0.898,0.934) <0.0001	0.929 (0.906,0.952) <0.0001
Grip strength tertile			
Tertile 1	Ref	Ref	Ref
Tertile 2	0.519 (0.427,0.632) <0.0001	0.478 (0.364,0.626) <0.0001	0.528 (0.391,0.713) <0.001
Tertile 3	0.398 (0.294,0.539) <0.0001	0.226 (0.149,0.344) <0.0001	0.266 (0.168,0.419) <0.0001
p for trend	<0.0001	<0.0001	<0.0001
Comorbidities total			
None	Ref	Ref	Ref
One	1.968 (1.190,3.256) 0.008	1.449 (0.941,2.229) 0.092	1.827 (1.048,3.187) 0.034
Two	2.347 (1.475,3.736) <0.001	1.720 (1.112,2.659) 0.015	2.094 (1.217,3.602) 0.008
Three or more	3.806 (2.512,5.765) <0.0001	2.464 (1.644,3.695) <0.0001	2.677 (1.557,4.603) <0.001
p for trend	<0.0001	0.001	0.005

Model 1 was adjusted for none. Model 2 was adjusted for sex, age, and ethnic. Model 3 was adjusted for all covariates in model 2 and education, marital, insurance status, PIR, BMI, waist, smoke, alcoholic.

TABLE 3 Weighted generalized linear regression analysis of the relationship between grip strength and Comorbidities.

	Model 1	Model 2	Model 3
None	Ref	Ref	Ref
One	−2.063 (−3.279,-0.847) 0.002	−0.599 (−1.521, 0.323) 0.193	−0.889 (−1.962, 0.184) 0.096
Two	−2.571 (−3.923,-1.218) <0.001	−0.509 (−1.367, 0.349) 0.233	−0.613 (−1.589, 0.362) 0.196
Three or more	−4.812 (−6.401,-3.223) <0.0001	−1.943 (−2.840,-1.045) <0.001	−2.219 (−3.178,-1.260) <0.001
p for trend	<0.0001	0.002	0.014

Model 1 was adjusted for none. Model 2 was adjusted for sex, age, and ethnic. Model 3 was adjusted for all covariates in model 2 and education, marital, insurance status, PIR, BMI, waist, smoke, alcoholic.

TABLE 4 The association between grip strength and all-cause mortality by Comorbidities.

	Grip strength tertile				
	Tertile 1	Tertile 2	Tertile 3	*p* for trend	*p* for interaction
Comorbidities					
None	Ref	0.99 (0.26, 3.75)	1.55 (0.25, 9.68)	0.56	0.45
One	Ref	0.57 (0.30,1.09)	0.25 (0.12,0.55)	0.09	
Two	Ref	0.62 (0.28,1.38)	0.47 (0.13,1.75)	0.24	
Three or more	Ref	0.54 (0.38,0.78)	0.22 (0.14,0.35)	0.04	

Analyses were adjusted for sex, age, ethnic, Education, marital, insurance status, PIR, BMI, waist, smoke, alcoholic.

5. Discussion

With an increase in the globally aging population, the health of the older adults is the most pressing issue in an aging society. From the standpoint of disease and function, comorbidity and disability are two of the crucial factors that affect the health of older people. The World Health Organization (WHO) released the International Classification of Functioning, Disability and Health (ICF), which is a framework that provides a detailed model for functional health and the relationship between disease symptoms and participation constraints (14). This study attempted to investigate the effects of two disease and functional status indicators, namely comorbidity and disability, on all-cause mortality in the older adults. Hypertension, which has the highest incidence among seniors, was selected as the indicator of the disease, and 15 self-reported chronic diseases were included as indicators of comorbidity; grip strength was chosen as the measurement index for assessing functional status. We, therefore, analyzed the relationship between grip strength and morbidities, and also studied their effects on all-cause mortality in an aged hypertensive population. The findings revealed that grip strength and comorbidities were related to all-cause mortality in an older hypertensive population, but the association of grip strength with mortality was not moderated by the number of comorbidities. The stratified analysis revealed that participants with more than three comorbidities who had higher grip strengths exhibited lower mortality rates.

Grip strength has a dynamic relationship with age. Grip strength is known to increase with age, peaking in adulthood. However, with increasing age, degenerative changes in body functions lead to a decline in grip strength. Our findings are consistent with previous research that found a link between grip strength and all-cause mortality, suggesting that decreased grip strength is associated with a higher risk of mortality (15–17). A meta-analysis of 38 studies involving 1,907,580 participants and 63,087 mortality cases used grip strength as a predictor for muscle strength and found that higher levels of grip strength were associated with a lower risk of all-cause mortality, where the association was slightly stronger in women (18). These results have been backed up by numerous prospective studies. For instance, a prospective cohort study which included data from the Survey of Health, Aging, and Retirement in Europe (2004–2017) revealed a negative correlation between CVD and grip strength in the middle-aged and older population (19). Similarly, a prospective study involving 502,293 participants aged 40–69 years from the UK Biobank discovered that higher all-cause mortality was associated with poor grip strength in both men and women. The majority of the participants in these studies, however, belonged to the general population (8, 16, 18). Our study provided evidence to support the association between grip strength and all-cause mortality in older people with hypertension. In this study, we used data from the NHANES database and found that grip strength was negatively associated with all-cause mortality in 2,990 hypertensive people aged >60. Here, grip strength was included as a continuous variable and the association was found after adjusting for hypertension (age, sex, race, BMI, and waist circumference), lifestyle (smoking and alcohol consumption), and socioeconomic (education, insurance, and PIR) -associated factors. After classifying grip strength into three groups, the older hypertensive patients in the low grip strength group were found to have a significantly lower survival rate than those in the high grip strength group. This suggests that grip strength can be used as a simple and practical predictor of survival in older hypertensive patients, and that increasing grip strength might lower all-cause mortality in older hypertensive patients.

This study proposed that grip strength is associated with mortality in older people with hypertension, where grip strength is a functional indicator that represents the intrinsic capacity of the older population. As the link between grip strength and comorbidity remains unknown, multiple studies have attempted to understand this association. According to Amy M.'s analysis of grip strength and comorbidity involving participants aged >50 years from the United States, grip strength gradually declined in adults with chronic diseases with multiple comorbidities, especially if the person had three or more chronic diseases (20). According to a cross-sectional study involving middle-aged and older community-dwelling adults using nationally representative data from six low- and middle-income countries, poor handgrip strength is associated with multiple chronic physical conditions and comorbidities (21). In a cross-sectional cohort of 1,145 subjects aged 50 and older from Hong Kong, multivariable-adjusted handgrip strength significantly decreased with the number of chronic diseases in men (p trend = 0.001) but had a marginally lesser effect in women (p trend = 0.06) (10). We are not aware of any studies that have been conducted on the relationship between grip strength and disease-specific comorbidity. In this study, the 15 self-reported chronic diseases from the database were chosen as comorbidity measures. In older people with hypertension, grip strength, and comorbidity were found to be linearly correlated. The presence of three or more diseases was significant after accounting for potential biological factors (including age, gender, and ethnicity), lifestyle choices, and socioeconomic factors.

There has been little research into whether functional and disease indicators have an impact on the survival of the older adults. This study did not find any interaction between the two parameters and the survival outcomes. However, stratified analysis revealed that grip strength had a stronger impact on the survival of patients with comorbidities, and enhancing grip strength could reduce mortality in hypertensive patients with more than three comorbidities. Rub'en et al. used marginal structural models (MSM) to provide a causal estimation of the association of hand grip strength with all-cause and cardiovascular mortality in a representative sample of adults aged 50 years or older. They found that these associations warranted promoting muscle-strengthening activities in adults and older adults, particularly those with pre-existing comorbidities (22). We, therefore, propose that older persons, especially those with multiple disorders, be encouraged to strengthen their muscle strength during exercise.

In the Global Report on Aging and Health, the WHO stated that healthy aging is the process of developing and maintaining the functions required for the older adults to live a healthy life. The synthesis of an individual's intrinsic abilities and environmental characteristics, as well as their interaction, is defined as functional play. The five domains, namely locomotion, vitality, cognitive, psychological, and sensory can be used to evaluate these intrinsic abilities. Grip strength testing has proven useful for predicting physical and cognitive decline in older adults, both of which are crucial aspects of intrinsic capacity building (23). Furthermore, Ramirez-Velez R et al. demonstrated that the magnitude of grip strength significantly impacts intrinsic ability in the older adults. Poor grip strength in older people increases the risk of mental illness and contributes to cognitive decline, which reduces their intrinsic ability (24). Our next study will focus on investigating the correlation between grip strength and intrinsic ability in older people with hypertension.

This study has several limitations that are determined by its data source. First, because this was a cross-sectional study, it could not establish a direct causal link between grip strength, comorbidities, and all-cause mortality in older persons with hypertension. Second, because the comorbidity data for older hypertensive patients originated from a questionnaire and self-reported disorders, the accurate decision on the comorbidity status was biased. Thirdly, the inclusion criteria for the older hypertensive population did not allow for classification and risk stratification of the condition.

In conclusion, a significant linear correlation was found between grip strength and the number of comorbidities in the older hypertensive population without adjusting for control variables. Grip strength was negatively correlated with more than three comorbidities, even after adjusting for biological, lifestyle, and other factors, Comorbidity and all-cause mortality showed a positive correlation, while low grip strength was associated with decreased all-cause mortality. Although comorbidities had a greater impact on all-cause mortality, functional exercise appeared to improve the prognosis for patients with more than three diseases. This suggests that chronic disease prevention and appropriate treatment are necessary for older patients with multiple diseases and that functional exercise is assured to maintain good physical function. This lends credence to the concept of healthy aging, which is not always associated with diseases and their corresponding decline in functions.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://www.cdc.gov/nchs/nhanes/index.htm.

Ethics statement

The survey was conducted by the National Centers for Health's Board of Approval Statistics and Institutional Review. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

YW, TM, and YR designed the study. YW and TM wrote the initial draft of the paper. YW and MY analyzed the statistics. XS, XW, and LC helped guide the writing. 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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