ASSOCIATION BETWEEN PHYSICAL ACTIVITY LEVELS AND CARDIOMETABOLIC MULTIMORBIDITY IN CHINESE MIDDLE-AGED AND OLDER ADULTS

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Abstract. Physical activity has been reported to be an effective method to reduce the risk of cardiometabolic multimorbidity (CMM). In this prospective cohort study, we aimed to determine if there is a significant association between physical activity levels and the incidence of CMM among middle-aged and older adults in China in order to inform efforts to reduce CMM in the study population. CMM was defined as the concurrent presence of at least two of the following three diseases: heart disease, stroke, and diabetes, based on self-reported physician diagnoses. This study was based on data from the China Health and Retirement Longitudinal Study (CHARLS) conducted during 2015-2020. Study subjects were randomly selected using multistage stratified probability proportional sampling from 28 provinces across China. Inclusion criteria for study subjects were being aged ≥45 years at baseline (2015), having no history of stroke, diabetes or heart disease at baseline, completing all three waves of follow-up, and having complete data regarding physical activity and other study variables. Exclusion criteria for subjects were having CMM at baseline, incomplete follow-up data and missing key variables. Physical activity level was assessed using a standardized questionnaire asking about vigorous, moderate, and light activities during the previous week, expressed as metabolic equivalents of task in minutes (MET-minutes) per week. Study subjects were then equally divided into 4 groups based on their baseline total weekly MET-minutes as follows: Quartile (Q)1 (reference group) (<1,732.5 MET-min/week), Q2 (1,732.5-5,287.5 MET-min/week), Q3 (5,287.5-11,848.5 MET-min/week) and Q4 (≥11,848.5 MET-min/week). We used time-varying Cox proportional hazards regression analysis and restricted cubic splines to identify significant associations between physical activity levels and CMM incidence. A total of 4,516 subjects were included in the study (1,129 subjects in each quartile): 52.8% (n = 2,384) females. The mean (±standard deviation (SD)) age of study subjects was 57.3 (±8.9) years.

The mean (±SD) body mass index of subjects was 23.8 (±3.7) kg/m². During the follow-up period, 151 subjects (3.3%) developed CMM. The mean (±SD) physical activity levels were 6,190.8 (±7,106.5) MET-min/week for the CMM group and 7,430.9 (±6,779.4) MET-min/week for the non-CMM group (*p*-value = 0.036). After adjusting for age, gender, marital status, residence, education, BMI, smoking, drinking, and retirement status, subjects in Q2, Q3, and Q4 had significantly lower hazard ratios (HR) (Q2: HR = 0.537; 95% confidence interval (CI): 0.351-0.821, p-value = 0.004; Q3: HR = 0.490; 95% CI: 0.313-0.767, *p*-value = 0.002; Q4: HR = 0.479; 95% CI: 0.282-0.814, *p*-value = 0.007) of developing CMM than subjects in Q1. Subgroup analyses revealed that the protective effects of physical activity were particularly pronounced among non-smokers (Q2: HR = 0.382; 95% CI: 0.230-0.634, *p*-value <0.001; Q3: HR = 0.475; 95% CI: 0.293-0.772, *p*-value = 0.003; Q4: HR = 0.522; 95% CI: 0.297-0.918, *p*-value = 0.024) with a significant interaction (*p*-value for interaction = 0.006). The protective effects of activity were also significantly greater among overweight and obese participants (Q2: HR = 0.568; 95% CI: 0.337-0.958, *p*-value = 0.034; Q3: HR = 0.319; 95% CI: 0.168-0.605, *p*-value <0.001; Q4: HR = 0.433; 95% CI: 0.215-0.869, *p*-value = 0.019). Restricted cubic spline analysis revealed a significant overall association between total physical activity and CMM risk (*p*-value for overall = 0.007), although the nonlinear association was not statistically significant (*p*-value for nonlinear = 0.210). In summary, subjects with higher levels of physical activity had significantly lower risk of developing CMM than subjects in the lowest activity quartile, and this protective effect was particularly evident among non-smokers and overweight and obese individuals. We conclude that higher physical activity levels are associated with reduced CMM risk among study subjects. Further studies are needed to determine if interventions to increase physical activity are able to prevent CMM in this population and to elucidate the mechanisms underlying the differential effects across subgroups.

Keywords: cardiometabolic multimorbidity, physical activity, middle-aged and older adults

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INTRODUCTION

Cardiometabolic multimorbidity (CMM), defined as the concurrent presence of two or more cardiometabolic diseases, such as heart disease, stroke and diabetes, has become a major public health challenge worldwide (Han *et al*, 2021). In the United States, the prevalence of CMM was 14.4% during 2017-2018, with a significant increasing trend over the past two decades (Cheng *et al*, 2022). The burden appears even greater in China, where approximately 33.1% of women aged ≥45 years have CMM, with prevalence increasing with age (Zhao *et al*, 2023). In addition to its high prevalence, CMM is associated with elevated mortality risk: individuals with two or more cardiometabolic conditions have 3.6-6.0 times greater all-cause mortality than those without these diseases (Di Angelantonio *et al*, 2015). CMM puts a substantial burden on healthcare systems and quality of life, particularly in rapidly aging populations such as China.

Physical activity is a major modifiable factor for preventing CMM. Evidence, primarily from Western populations, shows greater physical activity is associated with lower risk of developing CMM. A UK Biobank study of 359,773 participants found greater intensity physical activity reduced cardiometabolic disease incidence by 13% and mortality risk by 27% (Liu *et al*, 2023). Another prospective analysis from the same cohort showed that engaging in recommended physical activity levels reduced CMM incidence, particularly among individuals initially free of cardiometabolic diseases (Chen *et al*, 2022). A systematic review and meta-analysis further reported that an increase of 11.25 MET-hours per week in physical activity was associated with a 23% lower risk of dying from cardiovascular disease and a 26% lower risk of developing type 2 diabetes (Wahid *et al*, 2016). These findings underscore the importance of promoting physical activity as a CMM primary prevention strategy.

However, most studies have been conducted in Western populations and evidence from Asian populations is relatively limited. A study among middle-aged and older Chinese adults reported a high physical activity level was protective against cardiometabolic disease and association with a 29.9% lower risk of developing diabetes (Zhang and Liu, 2024). The association between physical activity and CMM incidence among middle-aged and older Chinese adults needs further investigation. Given the high prevalence of CMM among middle-aged and older Chinese adults, understanding the association between physical activity and CMM using a nationally representative sample could provide important evidence for developing targeted prevention strategies.

In this study, we aimed to determine the association between physical activity levels and CMM incidence among middle-aged and older Chinese adults using data from the China Health and Retirement Longitudinal Study (CHARLS) in order to inform efforts to prevent CMM in this population.

MATERIALS AND METHODS

Study population

The data for this study was obtained from the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative cohort study (Zhao *et al*, 2014). CHARLS employed a multistage stratified probability proportional sampling method to conduct the national baseline survey during 2011-2012, covering 150 counties and 450 villages/communities across 28 provinces in China. The study adopted a face-to-face follow-up mode every 2-3 years, with continuous tracking until 2020.

The data for this study was obtained from subjects who participate in all 3 waves of the CHARLS study 2015-2020. We started with 23,435 subjects of the CHARLS who participated in these three waves. The subjects included in our study were screened as follows. First, participants aged

≥45 years at baseline (2015) were selected for our study, excluding 3,448 participants who did not meet the age criteria, giving 19,987 participants. Second, participants who had stroke, diabetes or heart disease at baseline (n = 4,535) were excluded, giving 15,452 participants. Third, only participants who completed all three waves of follow-up were included, excluding 3,220 individuals with incomplete follow-up, leaving 12,232 participants. Finally, participants with missing values for key variables were excluded (n = 7,716), of whom 6,508 had missing physical activity data and 1,208 had other missing variable data. This left us with a total study population of 4,516 subjects, who were included in our study.

Assessment of physical activity and metabolic equivalents

Physical activity was obtained from the CHARLS questionnaire, which was adapted from the International Physical Activity Questionnaire (IPAQ), which has been validated in the Chinese population (Macfarlane *et al*, 2007). Subjects were asked to report the frequency (days per week) and duration of physical activity at 3 intensity levels: vigorous (*eg,* weightlifting and digging), moderate (*eg,* cycling and mopping) and light (*eg,* walking). Duration of activity was recorded and categorized (0, 10-29, 30-119, 120-239, and ≥240 minutes per week). We used the time interval midpoint to perform our calculations, as done in previous studies (Tian and Shi, 2022; Zhao *et al*, 2025). Metabolic equivalent of task (MET) value was assigned to each intensity level following standard guidelines: 8.0 METs for vigorous activity, 4.0 METs for moderate activity and 3.0 METs for light activity (Ainsworth *et al*, 2011). Total weekly physical activity was then calculated as the sum of MET-minutes per week for all activity types using the formula: MET value × duration (minutes) × frequency (days per week) (Mou *et al*, 2025). To examine the dose-response relationship between physical activity and CMM risk, participants were categorized into four groups based on quartile distribution: Quartile (Q)1 (<1732.5 MET-min/week, reference group), Q2 (1,732.5–5,287.5 MET-min/week), Q3 (5,287.5–11,848.5 MET-min/week), and Q4 (≥11,848.5 MET-min/week).

Definitions used in our study

All disease diagnoses in this study were based on subject self-reported physician diagnoses. Heart disease was defined as coronary heart disease, angina, congestive heart failure or other heart disease. Stroke was defined as any cerebrovascular accident. Diabetes was defined as impaired glucose tolerance or diabetes. For our study, CMM was defined as having at least 2 of the following 3 diseases: heart disease, stroke, and diabetes (Han *et al*, 2021).

Study covariates

Covariates included in our study were: sociodemographic characteristics, lifestyle factors and health status indicators. Sociodemographic characteristics were age (continuous variable), gender (male/female), education level, marital status (unmarried/married/divorced or widowed), residence (urban/rural) and retirement status (yes/no). Lifestyle factors were smoking status (smoker/non-smoker) and alcohol drinking status (drinker/non-drinker). The health status indicator was body mass index (BMI) in kg/m^2 (continuous variable). BMI was classified following Chinese adult standards (Wu, 2006): underweight (<18.5 kg/m^2), normal weight (18.5-23.9 kg/m^2), and overweight or obese (≥24.0 kg/m^2).

Statistical analysis

For descriptive analyses, continuous variables were presented as means and standard deviations, and categorical variables were presented as frequencies and percentages. Baseline characteristics were compared between groups by CMM incidence status (CMM group *vs* non-CMM group). Group differences in continuous variables were evaluated using independent samples t-tests. Group differences in categorical variables were evaluated using chi-square tests.

We employed time-varying Cox proportional hazards regression models to assess the association between physical activity metabolic equivalents and CMM incidence. Three progressively adjusted models were constructed to evaluate this association. Model 1 was an unadjusted model. Model 2 adjusted for three major confounders: age, gender and BMI. Model 3 was fully adjusted for all studied variables: age, gender, BMI, education level, marital status, residence, retirement status, smoking status and alcohol drinking status. Results are expressed as hazard ratios (HRs) and their 95% confidence intervals (CIs).

Subgroup analyses were performed to explore the heterogeneity of physical activity protective effects across different populations. Stratification variables were age (<65/≥65years), gender (male/female), BMI category (underweight/normal weight/overweight or obese), smoking status (yes/no) and alcohol drinking status (yes/no). Likelihood ratio tests were used to assess the statistical significance of effect modification by adding multiplicative interaction terms between physical activity metabolic equivalents and subgroup variables in the fully adjusted model.

Based on the fully adjusted Cox regression model, we employed restricted cubic spline analysis to explore the dose-response relationship between total metabolic equivalents and CMM incidence risk. Knot positions were set at the 10th, 50th, and 90th percentiles to better capture potential nonlinear features of the exposure-outcome relationship.

All statistical analyses were performed using R software (version 4.5.0) (R Foundation for Statistical Computing, Vienna, Austria; available at URL: https://cran.r-project.org/bin/windows/base/old/4.5.0). All hypothesis tests were two-sided, and *p*-value <0.05 was considered statistically significant.

Ethical approval and consent to participate

The CHARLS study was conducted in strict accordance with the ethical principles of the Declaration of Helsinki and was approved by the Biomedical Ethics Committee of Peking University (approval number: IRB00001052-11015). All subjects gave written informed consent prior to participation in the baseline survey and at each of the follow-ups.

RESULTS

Table 1 compares the baseline characteristics between groups by CMM incidence status (CMM group vs non-CMM group). A total of 4,516 participants were included in the study, 52.8% (*n* = 2,384) females. 1,129 subjects were included in each of the 4 study groups. The mean (±standard deviation (SD)) age of study subjects was 57.3 (±8.9) years. 151 subjects (3.3%) had CMM. The mean (±SD) physical activity level among subjects with CMM (6,190.8 (±7,106.5) MET-min/week), was significantly (*p*-value = 0.036) lower than the mean (±SD) physical activity level among subjects without CMM (7,430.9 (±6,779.4) MET-min/week). The physical activity levels varied significantly (*p*-value = 0.009) by quartile group. 36.4% of subjects with CMM were in the lowest quartile (Q1) level of activity while only 18.5% of subjects with CMM were in the highest level of physical activity quartile (Q4).

Forty-five percent of the subjects with CMM were aged ≥65 years versus 28.9% of subjects without CMM (*p*-value <0.001). 79.5% of subjects with CMM were non-smokers and 69.8% of subjects without CMM were smokers (*p*-value = 0.014).

60.9% of subjects with CMM were overweight or obese and 52.4% without CMM were overweight or obese (*p*-value = 0.054). There were also no significant differences in gender, marital status, retirement status, or drinking status between those with and without CMM (*p*-value >0.05).

Cox proportional hazards regression analysis revealed a

Table 1

Baseline characteristics of study subjects by CMM status

Characteristics	Overall	CMM	Non-CMM	p-value
Number of subjects	4,516	151	4,365	
Mean ± SD subject MET-minutes/week	7,389.5 ± 6,793.4)	6,190.8 ± 7,106.5	7,430.9 ± 6,779.4	0.036
Physical activity level (quartiles), n (%)				0.009
Q1	1,252 (27.7)	55 (36.4)	1,197 (27.4)	
Q2	1,008 (22.3)	41 (27.2)	967 (22.2)	
Q3	1,127 (25.0)	27 (17.9)	1,100 (25.2)	
Q4	1,129 (25.0)	28 (18.5)	1,101 (25.2)	
Gender, n (%)				0.616
Male	2,199 (48.7)	70 (46.4)	2,129 (48.8)	
Female	2,317 (51.3)	81 (53.6)	2,236 (51.2)	
Age in years, n (%)			<0.001	
<65 years	3,185 (70.5)	83 (55.0)	3,102 (71.1)	
≥65 years	1,331 (29.5)	68 (45.0)	1,263 (28.9)	
BMI, n (%)				0.054
Underweight	797 (17.6)	17 (11.3)	780 (17.9)	
Normal weight	1,341 (29.7)	42 (27.8)	1,299 (29.8)	
Overweight/obese	2,378 (52.7)	92 (60.9)	2,286 (52.3)	

Table 1 (cont)

Characteristics	Overall	CMM	Non-CMM	p-value
Marital status, n (%)				0.869
Single/divorced/widowed	482 (10.7)	15 (9.9)	467 (10.7)	
Married	4,034 (89.3)	136 (90.1)	3,898 (89.3)	
Retirement status, n (%)				0.304
Not retired	4,100 (90.8)	133 (88.1)	3,967 (90.9)	
Retired	416 (9.2)	18 (11.9)	398 (9.1)	
Smoking status, n (%)				0.014
Non-smoker	3,166 (70.1)	120 (79.5)	3,046 (69.8)	
Smoker	1,350 (29.9)	31 (20.5)	1,319 (30.2)	
Alcohol drinking status, n (%)				0.089
Non-drinker	2,859 (63.3)	106 (70.2)	2,753 (63.1)	
Drinker	1,657 (36.7)	45 (29.8)	1,612 (36.9)	

Physical activity quartiles were: Q1 (<1,732.5 MET-min/week), Q2 (1,732.5-5,287.5 MET-min/week), Q3 (5,287.5-11,848.5 MET-min/week), and Q4 (≥11,848.5 MET-min/week). BMI was classified using Asian standards (Wu, 2006): underweight (<18.5 kg/m^2), normal weight (18.5-23.9 kg/m^2) and overweight or obese (≥24 kg/m^2).

BMI: body mass index; CMM: cardiometabolic multimorbidity; kg/m^2: kilograms per square meter; MET-min/week: metabolic equivalents in minutes per week; SD: standard deviation.

significant association between higher physical activity levels and reduced CMM risk (Table 2). In the unadjusted Model 1, using the Q1 as reference, the CMM risk was reduced in group Q2 by 48.5% (HR = 0.515; 95% CI: 0.339-0.783, *p*-value = 0.002), group Q3 by 55.7% (HR = 0.443; 95% CI: 0.285-0.688, *p*-value <0.001), and group Q4 by 60.2% (HR = 0.398; 95% CI: 0.238-0.666, *p*-value = 0.001). After adjusting for age, gender and BMI (Model 2), the association between higher activity levels and reduced CMM risk remained significant, with a HR in group Q2 of 0.547 (95% CI: 0.358-0.835, *p*-value = 0.005), Q3 of 0.482 (95% CI: 0.308-0.754, *p*-value = 0.001) and Q4 of 0.449 (95% CI: 0.265-0.759, *p*-value = 0.003). In the fully adjusted Model 3, which controlled for age, gender, BMI, marital status, residence, education, smoking, alcohol drinking and retirement status, the association between higher activity levels and lower risk of CMM persisted, with a HR for the Q2 group of 0.537 (95% CI: 0.351-0.821, *p*-value = 0.004), Q3 of 0.490 (95% CI: 0.313-0.767, *p*-value = 0.002) and Q4 of 0.479 (95% CI: 0.282-0.814, *p*-value = 0.007).

Subgroup analyses were performed stratified by age, gender, BMI, smoking status and alcohol drinking status (Fig 1). On age subgroup analysis, subjects aged <65 years in group Q3 had a 53.7% lower risk of having CMM than subjects in group Q1 (HR = 0.463; 95% CI: 0.231-0.926, *p*-value = 0.030) and in group Q4 had a 58.5% lower risk of CMM than subjects in group Q1 (HR = 0.415; 95% CI: 0.184-0.934, *p*-value = 0.034). Subjects aged ≥65 years in group Q3 had a HR of 0.540 compared to subjects in group Q1 of having CMM (95% CI: 0.303-0.963, *p*-value = 0.037) and in group Q4 had a HR of 0.483 compared to subjects in group Q1 (95% CI: 0.274-0.851, *p*-value = 0.012). No significant difference was seen when comparing subjects by age groups (*p*-value for interaction = 0.750).

Male subjects in group Q3 had a HR of 0.401 compared to male subjects in group Q1 of having CMM (95% CI: 0.197-0.815,

Table 2

Hazard ratios for the association between physical activity levels and cardiometabolic multimorbidity risk

Physical activity	Model 1		Model 2		Model 3	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Q1	1	Ref	1	Ref	1	Ref
Q2	0.515 (0.339-0.783)	0.002	0.547 (0.358-0.835)	0.005	0.537 (0.351-0.821)	0.004
Q3	0.443 (0.285-0.688)	<0.001	0.482 (0.308-0.754)	0.001	0.49 (0.313-0.767)	0.002
Q4	0.398 (0.238-0.666)	0.001	0.449 (0.265-0.759)	0.003	0.479 (0.282-0.814)	0.007

Model 1: unadjusted; Model 2: adjusted for age, gender, and BMI; Model 3: adjusted for age, gender, BMI, marital status, residence, education, smoking status, alcohol drinking status and retirement status. Physical activity quartiles were defined as: Q1 (<1,732.5 MET-min/week), Q2 (1,732.5-5,287.5 MET-min/week), Q3 (5,287.5-11,848.5 MET-min/week), and Q4 (≥11,848.5 MET-min/week). Q1 served as the reference group.

BMI: body mass index; CI: confidence interval; HR: hazard ratio; Q: quartile; Ref: Reference; MET-min/week: metabolic equivalents in minutes per week

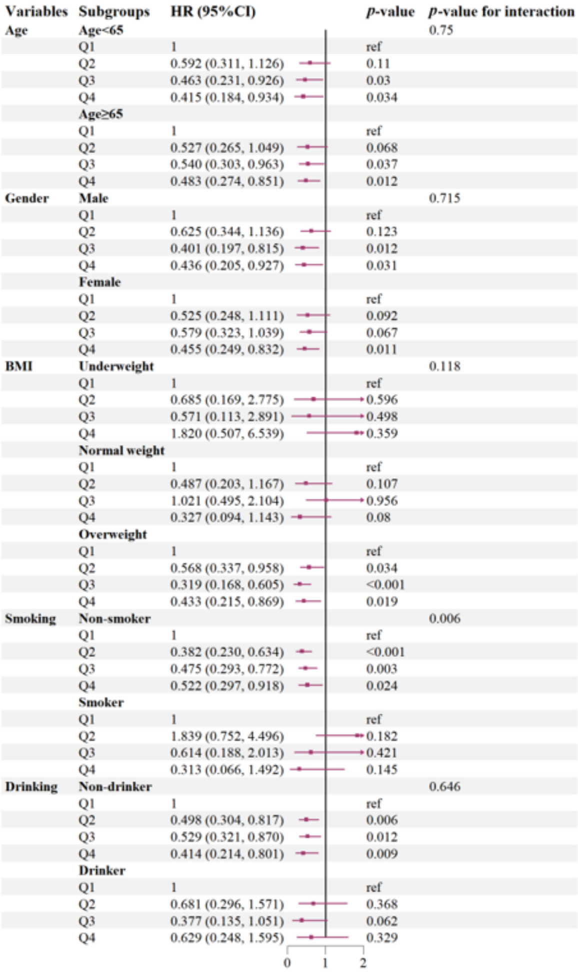

Fig 1 - Subgroup analysis of the association between physical activity and CMM risk stratified by age, gender, BMI, smoking status and alcohol drinking status

Physical activity quartiles: Q1 (<1,732.5 MET-min/week), Q2 (1,732.5-5,287.5 MET-min/week), Q3 (5,287.5-11,848.5 MET-min/week), Q4 (≥11,848.5 MET-min/week). BMI was classified using Asian standards (Wu, 2006): underweight (<18.5 kg/m^2), normal weight (18.5-23.9 kg/m^2), and overweight or obese (≥24 kg/m^2). All analyses were adjusted for age, gender, BMI, marital status, residence, education, smoking status, alcohol drinking status and retirement status.

BMI: body mass index; CI: confidence interval; CMM: cardiometabolic multimorbidity; HR: hazard ratio; kg/m2: kilograms per square meter; MET-min/week: metabolic equivalents in minutes per week; Q: quartile; ref: reference *p*-value = 0.012) and in group Q4 had a HR of 0.436 compared to group Q1 (95% CI: 0.205-0.927, *p*-value = 0.031). Female subjects in group Q4 had a HR of 0.455 compared to female subjects in group Q1 of having CMM (HR = 0.455; 95% CI: 0.249-0.832, *p*-value = 0.011). There were no significant differences between female subjects in groups Q2 and Q3 compared with group Q1. No significant interactions were found between gender and physical activity (*p*-value for interaction = 0.715).

On BMI subgroup analysis, overweight and obese subjects in group Q2, had a significantly lower risk of having CMM than overweight and obese subjects in group Q1 (HR: 0.568; 95% CI: 0.337-0.958, *p*-value = 0.034), as did overweight and obese subjects in group Q3 (HR: 0.319; 95% CI: 0.168-0.605, *p*-value <0.001) and Q4 (HR: 0.433; 95% CI: 0.215-0.869, *p*-value = 0.019). No significant associations were found among underweight and normal weight subjects. The interaction between BMI and physical activity was not statistically significant (*p*-value for interaction = 0.118).

On smoking status subgroup analysis, non-smokers had showed a significant interaction (*p*-value for interaction = 0.006). Among non-smokers, subjects in group Q2 had a HR of 0.382 compared to non-smokers in group Q1 of having CMM (95% CI: 0.230-0.634, *p*-value <0.001), for group Q2 the HR was 0.475 (95% CI: 0.293-0.772, *p*-value = 0.003) and group Q4 was 0.522 (95% CI: 0.297-0.918, *p*-value = 0.024). No significant associations were found among smokers by quartile.

On alcohol drinking status subgroup analysis, non-drinkers in group Q2 had HR of 0.498 compared to non-drinkers in Q1 (95% CI: 0.304-0.817, *p*-value = 0.006), and in group Q3 the HR was 0.529 (95% CI: 0.321-0.870, *p*-value = 0.012) and in group Q4 the HR was 0.414 (95% CI: 0.214-0.801, *p*-value = 0.009). No significant associations were observed among drinkers. The interaction between alcohol drinking status and physical activity was not significant (*p*-value for interaction = 0.646).

Restricted cubic spline analysis revealed a significant overall association between total physical activity and CMM risk (p-value for overall = 0.007), although the nonlinear association was not statistically significant (p-value for nonlinear = 0.210) (Fig 2). The curve demonstrated a declining trend in CMM risk with increasing physical activity levels.

DISCUSSION

In our study, we found higher physical activity levels were significantly associated with lower risk of developing CMM, showing a dose-response relationship. These findings are consistent with previous large-scale cohort studies. A UK Biobank study of 359,773 subjects reported high intensity physical activity reduced cardiometabolic disease incidence by 13% and mortality risk by 27% (Liu *et al*, 2023). A prospective study of 73,990 UK Biobank subjects identified a physical activity-related metabolic signature that was associated with a lower risk of developing type 2 diabetes, coronary heart disease and stroke, resulting in 40.56% of the association between physical activity and diabetes (Wang *et al*, 2025a). A Mendelian randomized study reported a significant association between moderate-to-vigorous physical activity and reduced cardiometabolic risk among hypertensive subjects (Wang *et al*, 2025b). Our study was a nation-wide study among middle-aged and older Chinese adults with distinct lifestyle patterns and disease profiles.

The biological mechanisms underlying the protective effects of physical activity on CMM are likely multifaceted. Physical activity improves insulin sensitivity and promotes skeletal muscle glucose uptake, thereby reducing diabetes risk (Elagizi *et al*, 2020). Regular exercise also enhances endothelial function, reduces systemic inflammation and improves lipid metabolism, all of which contribute to reduced cardiovascular disease risk (Magni *et al*, 2025; Pedralli *et al*, 2018). Physical activity also helps regulate blood pressure through modulating the sympathetic

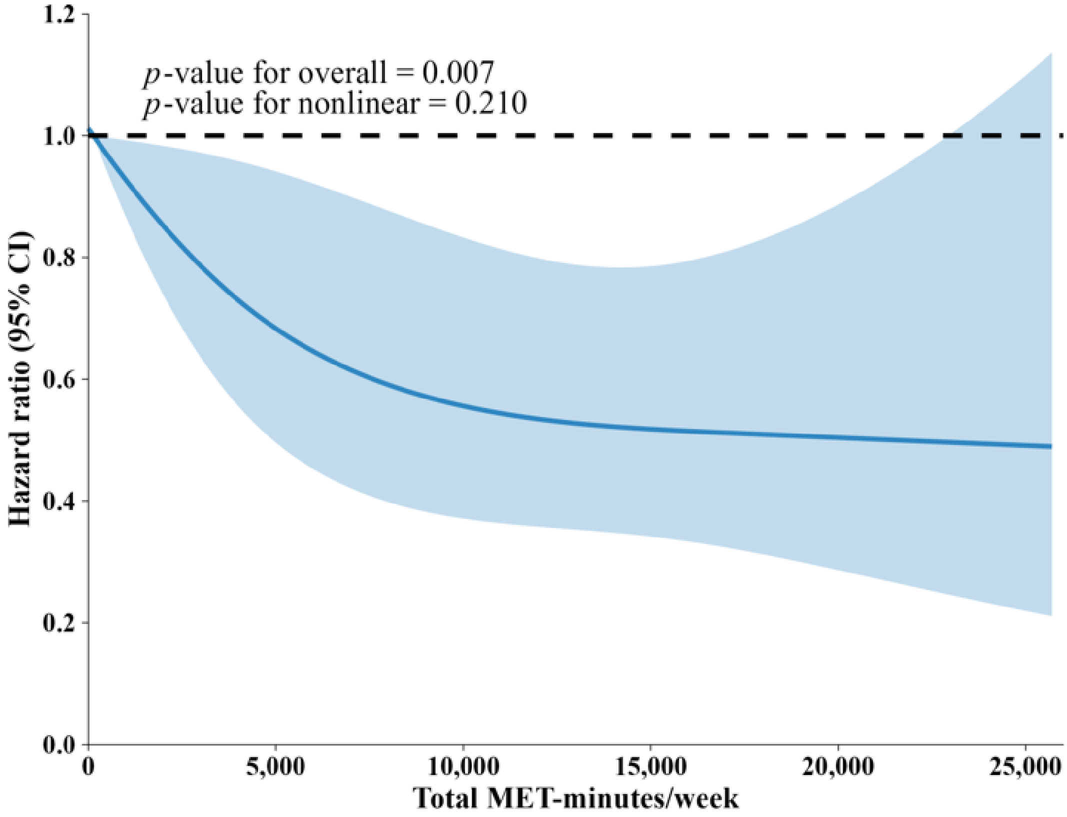

Fig 2 - Dose-response relationship between total physical activity and CMM risk

CI: confidence interval; CMM: cardiometabolic multimorbidity; MET-min/week: metabolic equivalents in minutes per week

nervous and renin-angiotensin systems (Baffour-Awuah *et al*, 2024; Miller and Arnold, 2019). These mechanisms may act synergistically to prevent the development of multiple cardiometabolic conditions simultaneously, which could explain the dose-response relationship observed in our study.

Subgroup analyses revealed stronger protective effects of physical activity among non-smokers, likely because smoking-induced oxidative stress attenuates exercise benefits (Nobari *et al*, 2021). Benefits were also more pronounced in overweight/obese subjects in our study, consistent with a Rotterdam Study that reported the cardiovascular benefits of physical activity may outweigh the impact of BMI among middle-aged and elderly adults (Koolhaas *et al*, 2017). These findings suggest that certain population subgroups, particularly non-smokers and those with excess body weight, may derive greater benefits from physical activity interventions for CMM prevention.

This study had several strengths: a large sample size and study subjects that were selected nation-wide. However, our study also had some limitations: physical activity levels were assessed using a self-reported questionnaire, which may be subject to recall bias and social desirability bias, potentially leading to overestimation of physical activity levels. Disease diagnoses were based on self-reported physician diagnoses, which may result in misclassification. Due to the observational nature of this study, reverse causation cannot be completely ruled out, as disease status may influence physical activity participation. Although we adjusted for multiple covariates, unmeasured confounding from factors, such as dietary patterns, genetic predisposition or medication use, cannot be fully excluded. Finally, as our study population consisted primarily of Chinese middle-aged and older adults, the generalizability of our findings may be limited by racial, cultural, and socioeconomic factors.

In summary, in our study subjects with higher physical activity levels had a significantly lower risk of CMM in a clear dose-response relationship. This was especially seen among non-smokers and overweight and obese subjects. We conclude, in our study population, promotion of physical activity may be a reasonable strategy to prevent CMM. This shows tailored interventions may be the best method to prevent CMM in the study population. Further studies are needed to determine if a program based on these risk groups can indeed prevent CMM in these risk groups.

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CONFLICT OF INTEREST DISCLOSURE

The authors declare they have no conflicts of interest in the conduction of this study or interpretation of the results.

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