International Journal of Obesity www.nature.com/ijo

ARTICLE

Epidemiology and Population Health

Relationship between metabolic status, physical activity and cardiovascular disease in participants with obesity

Yingxin Liu[1], Ai Zhao[2], Guiju Sun[3], Ruoting Wang[1], Jingyi Zhang[1], Gregory Y. H. Lip[4,5,7] and Guowei Li[1,6,7]✉

OBJECTIVE: We aimed to investigate the independent and joint associations between metabolic status, PA (physical activity) and risk of CVD (cardiovascular disease) in participants with obesity.
METHODS: We included 109,301 adults with obesity free of baseline CVD enrolled from 2006 to 2010 in the UK Biobank cohort (aged 56 ± 7.9 years). Based on metabolic status, obesity was grouped into metabolically healthy obesity (MHO; free of hypertension, hypercholesterolemia and diabetes; $n = 26{,}989$; BMI 33 ± 3.3 kg/m^2) and metabolically unhealthy obesity (MUO; $n = 82{,}312$; BMI 34 ± 4.0 kg/m^2). PA was categorized into four groups according to moderate-to-vigorous PA (MVPA): none, low, medium, and high. Multivariable Cox regression models were used for the main analyses adjusting for sociodemographic factors, lifestyles and comorbidities.
RESULTS: There were 8,059 CVD events during a median follow-up of 8.1 years. MHO was associated with a 42% reduced risk of CVD compared with MUO (HR = 0.58, 95% CI: 0.53–0.63). A significant interaction effect between PA and metabolic status on CVD risk was found. Among MUO participants, individuals with PA had significantly decreased CVD risk when compared with no MVPA (HR = 0.87, 95% CI: 0.81–0.94 for low PA; HR = 0.85, 95% CI: 0.78–0.93 for medium PA; and HR = 0.86, 95% CI: 0.80–0.92 for high PA). The lowest CVD risk was observed in MHO & medium PA group when compared with MUO & no MVPA (HR = 0.45, 95% CI: 0.37–0.56).
CONCLUSIONS: Both MHO and any MVPA were associated with reduced risk of CVD in adults with obesity, while PA could modify the relationship between metabolic status and CVD risk.

International Journal of Obesity; https://doi.org/10.1038/s41366-024-01469-8

INTRODUCTION

Cardiovascular disease (CVD) remains a major public health issue worldwide, accounting for one-third of all deaths worldwide [1]. Obesity had been generally considered as a risk factor for accelerating the occurrence and progression of CVD [2]. Depending on some metabolic indicators that include blood pressure, lipid profile and glucose tolerance, individuals with obesity can be described as metabolically healthy obesity (MHO) or metabolically unhealthy obesity (MUO) [3]. Recognizing obesity as a complex medical problem with excess body fat, the interplay between metabolic status and obesity may be associated with heterogeneous risk of CVD. However, some studies investigating MHO and MUO in relation to the risk of CVD have reported inconsistent findings, requiring further clarification [4–8].

Physical activity (PA) is known as a major lifestyle modification for CVD [9]. PA has been extensively studied for its well-known effects on CVD risk and mortality, and has been recommended by current guidelines for CVD prevention and management [10, 11]. Nevertheless, only a few studies have explored PA and CVD risk in combination with metabolic status, in which they were conducted in heterogeneous populations containing all levels of body mass index (BMI) [12, 13]. Another study categorized the study population into eight levels according to BMI (obese/non-obese), PA (any/no) and metabolic status (unhealthy/healthy), taking metabolic healthy non-obese with any MVPA as reference [14]. Pathophysiological changes such as excess adiposity in multiple organ due to obesity are related with metabolic disease developments. The excess adiposity, especially when in combination with unhealthy metabolic status, could significantly induce impaired cardiac structure and function, leading to increased risk of CVD [15]. Whether PA was able to modify the association between metabolic status and CVD risk in the population with obesity, remains largely unknown. Given the growing global prevalence of obesity and the substantial differences in

[1]Center for Clinical Epidemiology and Methodology (CCEM), Guangdong Second Provincial General Hospital, Guangzhou, China. [2]Vanke School of Public Health, Tsinghua University, Beijing, China. [3]Key Laboratory of Environmental Medicine and Engineering of Ministry of Education, Department of Nutrition and Food Hygiene, School of Public Health, Southeast University, Nanjing, China. [4]Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, UK. [5]Danish Center for Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark. [6]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada. [7]These authors jointly supervised this work: Gregory Y. H. Lip, Guowei Li.
✉email: liguowei2005@hotmail.com

Received: 3 April 2023 Revised: 13 November 2023 Accepted: 12 January 2024
Published online: 22 January 2024

pathophysiology between the obesity and non-obesity, assessing the relationship between metabolic status, PA and CVD risk among individuals with obesity might generate evidence for PA engagement and CVD prevention in this specific population from the perspective of public health.

Thus in this study, we aimed to explore the independent and joint associations between metabolic status, PA and CVD risk in individuals with obesity using the UK Biobank data. We hypothesized that PA could be more beneficial for MUO participants in relation to their CVD risk among individuals with obesity.

METHODS

Study population

Details of the UK Biobank study had been reported on its official website (www.ukbiobank.ac.uk) and in other publication [16]. Concisely, the UK Biobank cohort covers more than 0.5 million individuals aged 37–73 years from England, Scotland and Wales between 2006 and 2010. Information of participants at baseline was obtained through physical measurements, self-reports and interviews with trained medical personnel. The study received approval from the North West Multi-Centre Research Ethics Committee. Each participant completed the written informed consent before recruitment.

A total of 122,244 participants were observed with baseline obesity (BMI ≥ 30 kg/m^2); among whom, 12,943 individuals were excluded due to a previous diagnosis of CVD. Overall, we included 109,301 individuals for the main analysis (SFig. 1). Reporting of this study conforms to broad CHAMP guidelines [17].

Outcomes

The primary outcome of this study was time to first occurrence of CVD event, in which CVD was regarded as a composite of three disease including stroke, coronary heart disease (CHD) and CVD death. We defined secondary outcomes as the individual CVD elements (stroke, CHD and CVD death).

Information on incident disease and death was obtained through linkages with hospital inpatient records and death registry records in the UK Biobank study. Incident diseases were identified based on the international classification of diseases ninth (ICD-9) and 10th (ICD-10) revisions, whereas the death cause was coded by ICD-10 solely. Stroke was coded as ICD-9 codes 430–434, 436 and ICD-10 codes I60 - I64. CHD was defined using 410–414 for ICD-9 and I20 - I25 for ICD10. CVD death was identified by ICD-10 codes I00 - I99 for both the primary or secondary causes of death.

All individuals were followed up from the date of enrollment until the occurrence of a CVD event, death or censoring date (31 October 2016 for Scotland, 31 March 2017 for England/Wales), whichever came first.

Exposures

In this study, exposures included metabolic status and PA. Baseline *'metabolically healthy'* was defined as being free of the three metabolic disorders (hypertension, diabetes mellitus, and hypercholesterolemia), whereas *'metabolically unhealthy'* had at least one of the aforementioned metabolic disorders [18–21].

Individuals who met at least one of the following conditions were considered to have hypertension: diastolic blood pressure (DBP) ≥ 90 mmHg, systolic blood pressure (SBP) ≥ 140 mmHg, previous hospital inpatient records of hypertension, using anti-hypertensive medications, or a self-reported medical condition of hypertension. Diabetes mellitus was determined if individuals had any of the following conditions: using anti-diabetic medications, hospital inpatient records of diabetes mellitus (ICD-9 code 250 and ICD-10 codes E10 - E14), or a self-reported medical condition of diabetes mellitus. Medical history of high cholesterol or using cholesterol-lowing medications was utilized to define hypercholesterolemia. STable 1 shows the detailed codes of criteria mentioned above.

The International Physical Activity Questionnaire (IPAQ) was conducted to evaluate leisure-time physical activity, and the average weekly energy expenditure was calculated based on metabolic equivalent task (MET) score [22]. According to the guidelines, PA was classified into four groups based on moderate-to-vigorous PA (MVPA), in which the four groups included none (0 MET-mins per week for MVPA), low (<600), medium (600–1199), and high (≥1200) [22, 23].

Covariates

Covariates of consideration covered sociodemographic information, lifestyle data and comorbidities. The sociodemographic information included age, sex (males or females), ethnicity (White or others), residential area (urban or rural), college degree or higher (yes or no) and socioeconomic status (Townsend deprivation index, TDI). Lifestyle data covered body mass index (BMI, in kg/m^2), smoking status and drinking status (current, previous or never), consumption of coffee intake (yes or no), regular vitamin supplements (yes or no) and mineral supplements (yes or no) and sleep pattern. Other comorbidities included depression (yes or no), cancer (yes or no), family history of CVD (yes or no) and family history of diabetes (yes or no).

Sociodemographic information and lifestyle data were collected from individuals' self-reports at recruitment. Comorbidities at baseline were obtained from individuals' self-reports, baseline hospital inpatient records and use of the related medication.

Statistical analyses

Descriptive analyses were performed for baseline continuous (mean and standard deviation [SD]; or median and interquartile range [IQR]) and categorical variables (counts and percentages). Two independent t-tests and Chi-square tests were conducted to compare baseline continuous and categorical variables by metabolic status, respectively.

We first tested the interaction effect between continuous PA and metabolic status, and the result for interaction was significant ($P = 0.02$). Relative excess risk due to interaction (RERI), attributable proportion of interaction (AP) and synergy index (S) were utilized to perform effect modification analysis on additive scales, by evaluating whether the effects of metabolic status on CVD risk differed within the strata of PA [24, 25]. There were significant effect modifications found (RERI = 0.20 (95% CI: −0.02–0.43), AP = 0.10 (95% CI: −0.01–0.22), S = 1.27 (95% CI: 0.94–1.70); all $P < 0.05$) on additive scales as expected (STable 2). Cox proportional hazards regression models were conducted to explore the independent and joint associations between metabolic status and PA as regards the risk of CVD in individuals with obesity, taking MUO & no MVPA as the reference group. Results from the age- and sex-adjusted (basic) model and the fully adjusted models were quantified as hazard ratios (HRs) and 95% confidence intervals (CIs). The fully adjusted model was adjusted for age, sex, ethnicity, college degree, residential area, TDI, BMI, smoking and drinking status, consumption of coffee, vitamin and mineral supplement, depression, cancer, family history of CVD and diabetes mellitus.

To help enhance the straightforward intake of findings, we further displayed results for the associations between PA and risk of CVD stratified by metabolic status. Moreover, PA was modelled using a restricted cubic spline model with four knots (the 5th, 35th, 65th and 95th percentiles) to show the potential nonlinear and dose-response associations with risk of CVD stratified by metabolic status. Subgroup analyses were performed to investigate whether any significant subgroup effect existed on the associations between metabolic status and PA with CVD risk by sex and age (<65 years versus ≥65 years). In an exploratory analysis, we evaluated the relationship between PA and risk of CVD stratified by metabolic severity, where the metabolic severity included MHO and three MUO groups: mild (with only one of the aforementioned metabolic disorders including hypertension, diabetes mellitus and hypercholesterolemia), moderate (with two metabolic disorders) and severe (with three metabolic disorders). We also explored the joint associations between metabolic severity and PA regarding risk of CVD in participants with obesity. In addition, we investigated the relationship between PA and CVD risk in MHO participants who were close to the cut-points for MUO (SBP 130–139 or DBP 80–90).

Several sensitivity analyses were conducted to evaluate the robustness of main analyses. First, the Fine-Gray competing risk regression model was performed using all-cause death as a competing event [26]. Taking reverse causation into consideration, we re-conducted the Cox regression models after removing CVD events that occurred within the first year and the first two years of follow-up. In another sensitivity analysis, we utilized the Adult Treatment Panel III criteria (ATP III) to re-define the metabolic status and compared the new results with the main results, where the MUO was identified as two or more of the following conditions: (i) DBP ≥ 85 mmHg or SBP ≥ 130 mmHg or using anti-hypertensive medications; (ii) fasting plasma glucose (FPG) > 7.0 mmol/L or using anti-diabetic medications; (iii)

serum triglycerides (TG) ≥ 1.7 mmol/L or using lipid-lower medications; (iv) blood high-density lipoprotein cholesterol (HDL-C) < 1.04 mmol/L in males or 1.29 mmol/L in females [5, 27]. Moreover, multiple imputation method (seed = 12,345) for the missing data was conducted. We subsequently conducted another post hoc analysis by further adjusting for sleep pattern after multiple imputation, where sleep pattern was defined from a previous study based on the UK Biobank cohort [28]. For females, female-specific factors were considered by further adjusting for the menopausal status and the hormone-replacement therapy. To mitigate the difference in age between MHO and MUO, we conducted another sensitivity analysis by matching the MUO participants to MHO participants at a 1:1 ratio without replacement on their ages, and the joint associations between metabolic severity and PA regarding CVD risk were explored in the matched data.

All statistical tests in this study were two-sided with the significance level of 0.05. All the analyses were performed in R Program software version 4.1.1 and SAS software version 9.4.

RESULTS

There were 109,301 individuals with obesity included for analyses, with a median follow up of 8.1 (IQR: 7.3–8.7) years (Fig. 1). There were 82,312 (75%) and 26,989 (25%) participants with MUO and MHO, respectively. The descriptions of baseline characteristics by metabolic status were demonstrated in Table 1. When compared with MHO individuals, participants with MUO were older, and more likely to be males and smokers. The MUO participants also had higher BMI and lower TDI, and were more likely to have a worse sleep pattern and family history of CVD than MHO individuals.

A total of 8059 incident CVD events were observed during 852,757 person-years of follow up. Results for the independent associations between metabolic status and PA with CVD risk were displayed in Table 2. MHO was significantly associated with a 42% reduced risk of CVD compared with MUO (HR = 0.58, 95% CI: 0.53–0.63 in fully adjusted model). Taking no MVPA as reference, low, medium and high PA were significantly associated with decreased risk of CVD (HR = 0.88, 95% CI: 0.81–0.94 for low PA; HR = 0.85, 95% CI: 0.78–0.92 for medium PA; and HR = 0.87, 95% CI: 0.82–0.94 for high PA).

Results for the joint associations between metabolic status and PA through the eight phenotypes generated from their cross-categorization are displayed in Table 3, with MUO & no MVPA as the reference category. The lowest CVD risk seemed to be in the MHO & medium PA group when compared with MUO & no MVPA (HR = 0.45, 95% CI: 0.37–0.56). Among the MUO participants, low, medium and high PA were significantly related to decreased risk of CVD (HR = 0.87, 95% CI: 0.81–0.94 for low PA; HR = 0.85, 95% CI: 0.78–0.93 for medium PA; and HR = 0.86, 95% CI: 0.80–0.92 for high PA).

STable 3 displays the supplemental analysis results for the association between PA and CVD risk stratified by metabolic status. Any MVPA level (low, medium and high PA) was significantly associated with decreased risk of CVD when compared with no MVPA in both MHO and MUO groups; but no significant trends towards reduced CVD risk among the three PA levels could be found in either MUO or MHO participants (both $P > 0.05$).

SFigure 2 presents the restricted cubic spline curves of adjusted HRs for risk of CVD at different values of PA. The curve for MUO showed a marked reduction of CVD risk within the low range of PA, reaching the lowest risk at approximate 600–700 MET min/week, which was followed by a relatively stable trend as PA values increased. Compared with MUO, the curve for MHO presented a slight reduction of CVD risk within the low range of PA. Similarly, the lowest HR was found at approximate 600–650 MET min/week for MHO participants, with CVD risk steadily increasing as their PA values elevated.

Figure 2 shows the joint associations between metabolic status and PA with CVD risk among different subgroups. No significant

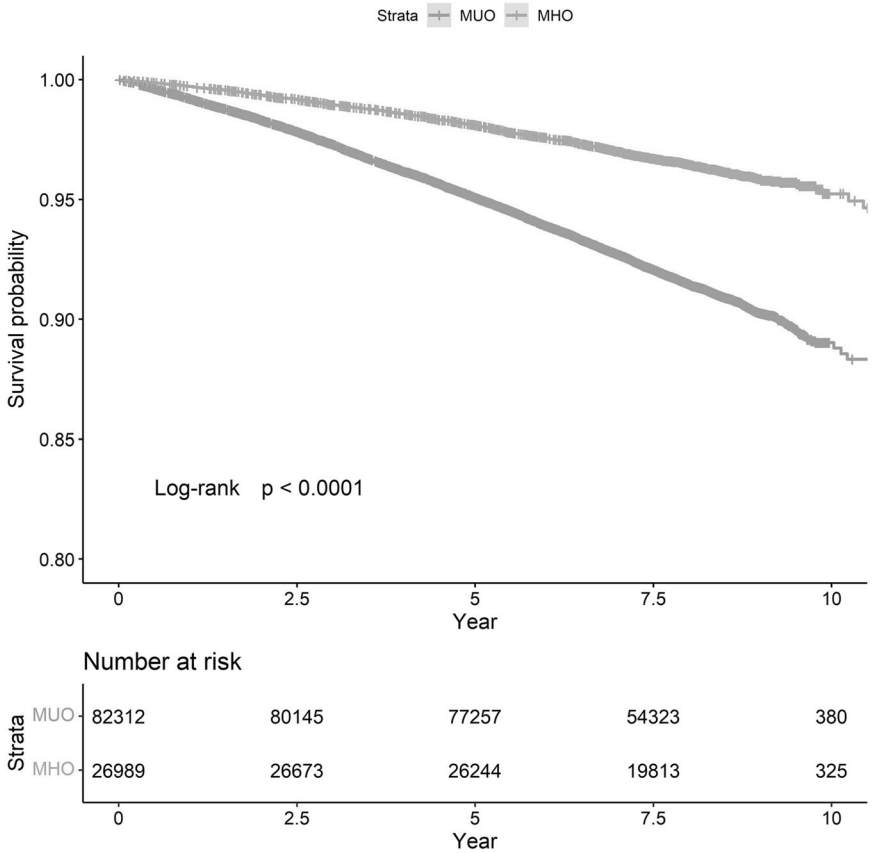

Fig. 1 Kaplan-Meier survival times curves by metabolic status.

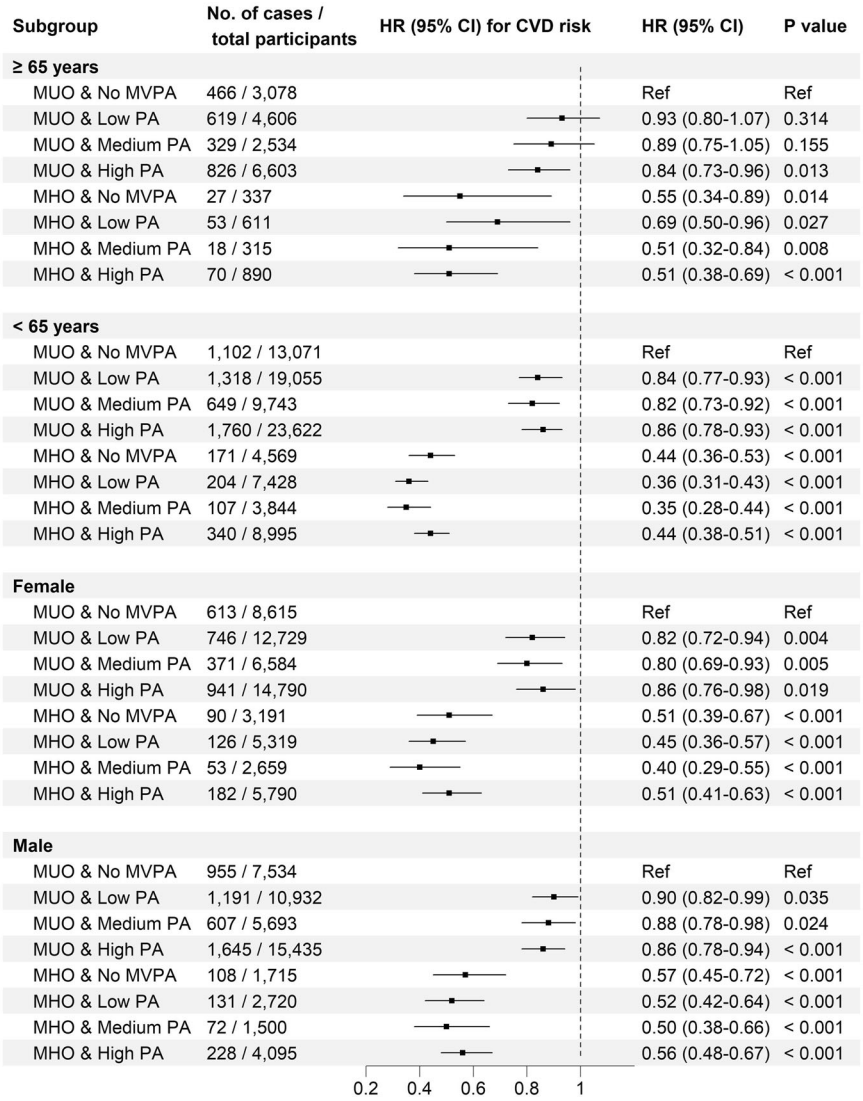

Fig. 2 Joint associations between metabolic status, physical activity and risk of cardiovascular disease by age and sex.

subgroup effects of age ($P = 0.67$) and sex ($P = 0.41$) were observed on the association between PA and CVD risk globally. Likewise, no significant subgroup effects of age and sex were found on PA in relation to risk of CVD within the MHO and MUO groups (STable 4). Among participants aged ≥ 65 years with MUO, only high PA was significantly related to reduced risk of CVD when compared with no MVPA (HR = 0.84, 95% CI: 0.73–0.96).

SFigure 3 and STable 5 display results for secondary outcomes (1,310 stroke, 6,540 CHD, and 1,158 CVD deaths), with similar findings to the primary outcome observed in general. In the exploratory analyses, any PA was significantly related to lower CVD risk in the individuals with moderate MUO (HR = 0.81, 95% CI: 0.72–0.91) and severe MUO (HR = 0.84, 95% CI: 0.72–0.97) when compared with no MVPA (STable 6). Results from the joint associations between metabolic severity and PA indicated that the elevated number of diagnoses was related with increased CVD risk in both the no MVPA and any MVPA categories (STable 7). The sensitivity analyses yielded similar results to findings from the main analyses (STables 8–11, SFigure 4).

DISCUSSION

Our principal findings were as follows: (i) among individuals with obesity, both MHO and any MVPA (low, medium and high PA) were significantly related to reduced risks of CVD when taking MUO and no MVPA as reference, respectively; (ii) when taking MUO & no MVPA as reference, the MHO & medium PA group seemed to have the lowest CVD risk; MUO individuals with any MVPA were significantly associated with decreased risk of CVD; and non-significant associations was observed among MHO groups; and (iii) no significant subgroup effects of age and sex were observed on the relationship between metabolic status, PA and CVD risk.

It is increasingly recognized that obesity is not a binary diagnosis, whereby 'metabolically healthy' and 'metabolically unhealthy' obesity subgroups can be defined, with implications for CVD risk. The prevalence of MHO is approximately 10–30% among the population with obesity depending on the specific studied population and the definition of MHO, in line with our results of 25% participants with MHO [3]. The relationship between MHO and CVD has been widely studied, while debate over the difference in CVD risk between MHO and MUO continues [29]. Moreover, Mongraw-Chaffin et al. suggested that baseline MHO could not be a stable or reliable indicator of future risk for CVD as it might be a transient state associated with long-term health complications [30]. Unfortunately, no dynamic data on the change from MHO to MUO during follow-up in our study could be available to further explore the relationships between metabolic status, PA and CVD risk.

Table 1. Baseline characteristics by metabolic status.

	Overall ($N = 109,301$)	MHO ($N = 26,989$)	MUO ($N = 82,312$)	*p* value
Age (years), mean (SD)	56.4 (7.9)	52.8 (7.8)	57.5 (7.6)	<0.001
<50	25,125 (23.0)	10,522 (39.0)	14,603 (17.7)	
50–59	38,815 (35.5)	9,936 (36.8)	28,879 (35.1)	
60–64	26,387 (24.1)	4,378 (16.2)	22,009 (26.7)	
≥65	18,974 (17.4)	2,153 (8.0)	16,821 (20.4)	
BMI (kg/m^2), mean (SD)	33.9 (3.9)	33.3 (3.3)	34.1 (4.0)	<0.001
30.0–34.9	78,751 (72.0)	21,169 (78.4)	57,582 (70.0)	
35.0–39.9	22,051 (20.2)	4,542 (16.8)	17,509 (21.3)	
≥40.0	8,499 (7.8)	1,278 (4.7)	7,221 (8.8)	
TDI, mean (SD)	−0.9 (3.2)	−0.9 (3.3)	−0.9 (3.2)	0.007
median (IQR)	−1.7 (4.6)	−1.7 (4.7)	−1.8 (4.6)	
Male Sex, *n* (%)	49,624 (45.4)	10,030 (37.2)	39,594 (48.1)	<0.001
College degree or higher, *n* (%)	27,530 (25.2)	7,827 (29.0)	19,703 (23.9)	<0.001
White Ethnicity, n (%)	102,113 (93.4)	25,023 (92.7)	77,090 (93.7)	<0.001
Area, *n* (%)				
Rural	13,197 (12.1)	3,162 (11.7)	10,035 (12.2)	0.050
Urban	95,022 (86.9)	23,516 (87.1)	71,506 (86.9)	
Physical activity (MET min/week), median (IQR)	640 (1640)	640 (1640)	620 (1640)	
No MVPA	21,055 (19.3)	4,906 (18.2)	16,149 (19.6)	<0.001
Low PA	31,700 (29.0)	8,039 (29.8)	23,661 (28.7)	
Medium PA	16,436 (15.0)	4,159 (15.4)	12,277 (14.9)	
High PA	40,110 (36.7)	9,885 (36.6)	30,225 (36.7)	
Smoking status, *n* (%)				
Never	57,253 (52.4)	14,693 (54.4)	42,560 (51.7)	<0.001
Previous	40,951 (37.5)	8,944 (33.1)	32,007 (38.9)	
Current	10,414 (9.5)	3,192 (11.8)	7,222 (8.8)	
Drinking status, *n* (%)				
Never	5,881 (5.4)	1,435 (5.3)	4,446 (5.4)	0.023
Previous	4,672 (4.3)	1,077 (4.0)	3,595 (4.4)	
Current	98,414 (90.0)	24,396 (90.4)	74,018 (89.9)	
Sleep pattern, *n* (%)				
Poor	3,626 (3.3)	793 (2.9)	2,833 (3.4)	<0.001
Intermediate	41,968 (38.4)	9,964 (36.9)	32,004 (38.9)	
Healthy	43,148 (39.5)	11,141 (41.3)	32,007 (38.9)	
Coffee intake, *n* (%)	83,094 (76.0)	20,187 (74.8)	62,907 (76.4)	<0.001
Vitamin supplement, *n* (%)	31,870 (29.2)	8,039 (29.8)	23,831 (29.0)	0.001
Mineral supplement, *n* (%)	42,918 (39.3)	9,531 (35.3)	33,387 (40.6)	<0.001
Cancer, *n* (%)	12,425 (11.4)	2,746 (10.2)	9,679 (11.8)	<0.001
Depression, *n* (%)	19,205 (17.6)	5,285 (19.6)	13,920 (16.9)	<0.001
Family history of CVD, *n* (%)	59,431 (54.4)	13,055 (48.4)	46,376 (56.3)	<0.001
Family history of diabetes, *n* (%)	23,515 (21.5)	5,748 (21.3)	17,767 (21.6)	0.323
Menopause, *n* (%)	35,155 (32.2)	8,058 (29.9)	27,097 (32.9)	<0.001
Hormone replacement therapy, *n* (%)	22,959 (21.0)	5,128 (19.0)	17,831 (21.7)	<0.001
Hypertension, *n* (%)	78,262 (71.6)	-*	78,262 (95.1)	-*
Diabetes, *n* (%)	13,207 (12.1)	-*	13,207 (16.1)	-*
High Cholesterol, *n* (%)	24,984 (22.9)	-*	24,984 (30.4)	-*

Data are presented as mean and standard variation (SD) or median and interquartile range (IQR) for continuous variables, and as frequency and percentage (%) for categorical variables.

MUO metabolically unhealthy obesity, *MHO* metabolically healthy obesity, *BMI* body mass index, *TDI* Townsend deprivation Index, *MET* metabolic equivalent of task, *MVPA* moderate-to-vigorous physical activity, *PA* physical activity, *CVD* cardiovascular diseases.

*Not available.

Table 2. Adjusted associations between metabolic status, physical activity and risk of cardiovascular disease.

Characteristic	No. of cases /total participants	Basic model	Fully adjusted model
Metabolic status			
MUO	7,069/82,312	Ref	Ref
MHO	990/26,989	0.56 (0.51, 0.60), $p < 0.001$	0.58 (0.53, 0.63), $p < 0.001$
Physical activity			
No MVPA	1,766/21,055	Ref	Ref
Low PA	2,194/31,700	0.81 (0.75, 0.86), $p < 0.001$	0.88 (0.81, 0.94), $p < 0.001$
Medium PA	1,103/16,436	0.77 (0.71, 0.84), $p < 0.001$	0.85 (0.78, 0.92), $p < 0.001$
High PA	2,996/40,110	0.80 (0.75, 0.86), $p < 0.001$	0.87 (0.82, 0.94), $p < 0.001$

MUO metabolically unhealthy obesity, *MHO* metabolically healthy obesity, *MVPA* moderate-to-vigorous physical activity, *HR* hazard ratio, *CI* confidence interval. The models have already adjusted for metabolic status and PA. Basic model was adjusted for age and sex; Fully adjusted model was adjusted for sex, age, body mass index, metabolic status, PA, Townsend Deprivation Index, college degree, ethnicity, area, smoking and drinking status, regular intake of coffee, vitamin and mineral supplement, personal medical history of depression and cancer, family history of CVD and diabetes; data shown as hazard ratios (95% confidence intervals), p-values.

Table 3. Joint associations between metabolic status, physical activity and risk of cardiovascular disease.

Metabolic status & PA	No. of cases /total participants	HR (95% CI), p-value
MUO & No MVPA	1,568/16,149	Ref
MUO & Low PA	1,937/23,661	0.87 (0.81, 0.94), $p < 0.001$
MUO & Medium PA	978/12,277	0.85 (0.78, 0.93), $p < 0.001$
MUO & High PA	2,586/30,225	0.86 (0.80, 0.92), $p < 0.001$
MHO & No MVPA	198/4,906	0.54 (0.45, 0.65), $p < 0.001$
MHO & Low PA	257/8,039	0.49 (0.42, 0.57), $p < 0.001$
MHO & Medium PA	125/4,159	0.45 (0.37, 0.56), $p < 0.001$
MHO & High PA	410/9,885	0.54 (0.48, 0.62), $p < 0.001$

MUO metabolically unhealthy obesity, *MHO* metabolically healthy obesity, *MVPA* moderate-to-vigorous physical activity, *HR* hazard ratio, *CI* confidence interval. Model was adjusted for sex, age, body mass index, Townsend Deprivation Index, college degree, ethnicity, area, smoking and drinking status, regular intake of coffee, vitamin and mineral supplement, personal medical history of depression and cancer, family history of CVD and diabetes

However, previous studies have consistently reported that the MHO group had a significantly lower risk of CVD than the MUO [8, 31]. These inconsistent findings might be partially due to the heterogeneity including participants' characteristics, follow-up durations, outcome definitions and the target study populations. Moreover, prior studies generally explored the association between metabolic status and risk of CVD in heterogeneous populations including participants with normal weight, overweight and obesity [7, 8]. For instance, one recent study investigated the relationship between leisure-time PA, metabolic syndrome and CVD outcomes in a general population sample of 60-year-old men and women, reporting that moderate/high PA was non-significantly related to lower risk of CVD in fully adjusted models in metabolically unhealthy individuals [12]. Given the substantial differences in pathophysiology between participants with and without obesity [15], unlike previous studies, we specifically investigated the population with obesity about the relationship between metabolic status and risk of CVD after taking PA into account. These results about the metabolic status in combination with PA may therefore provide new evidence about the CVD prevention in the participants with obesity.

Previous studies have showed that participating in MVPA could induce a lower risk of CVD across all levels of BMI, including those with obesity [32]. Our study confirms that any MVPA (low, medium and high) were significantly related to lower risk of CVD compared with no MVPA (Table 2). Moreover, the MHO participants consistently displayed lower CVD risk when taking MUO & no MVPA as reference, in which the MHO & medium PA group had the lowest CVD risk (Table 3). Indeed, repeated episodic bouts of exercise could induce chronic functional adaptation and structural arterial remodeling, thereby yielding profound clinical implications on primary and secondary CVD outcomes [33]. Ectopic fat and visceral adipose tissue (VAT) had been shown as significant factors contributing to the deterioration of CVD health [34]. MVPA could reduce VAT even in the absence of caloric restriction, which could mitigate the cardio-metabolic comorbidities in obesity [35].

Some debate remains over whether the inverse relationship between higher PA and lower incidence of CVD exists [36]. We observed no trend towards CVD risk as the PA level increased, while medium PA group, rather than high PA, had the lowest HRs within MHO and MUO participants (STable 3 and SFigure 2). Given the overlapping CIs, it could not support the comparative benefit of reduced CVD risk in the medium PA group when compared with low or high PA group. Furthermore, the results of independent associations showed MHO was associated with a 42% reduced risk of CVD regardless of PA; by contrast, the joint association displayed that MHO & medium PA was related with a 55% reduction in CVD risk when compared with MUO & no MVPA. These findings suggested the importance of carefully accounting for both PA and metabolic status in the obesity when considering their future CVD risk.

Significant risk reductions in CVD risk for any MVPA were observed among those with moderate and severe MUO, implying that individuals with elevated metabolic severity were more likely to receive benefits through PA (STable 5). Interestingly, within the MHO participants, any MVPA was non-significantly related with decreased CVD risk when compared with no MVPA (STable 3, STable 5, SFigure 2). This may partly support our hypothesis that

PA could be more beneficial for MUO participants regarding mitigation of CVD risk. The fact that PA could mitigate the cardio-metabolic comorbidities by reducing VAT might help explain this finding [35], given that MHO participants tended to have healthier lifestyles and less cardio-metabolic comorbidities including hypertension, diabetes and high cholesterol. Nevertheless, the non-significant results for MHO may also be partly due to the relatively small sample size and insufficient statistical power. Therefore, our findings needed to be interpreted with caution, and further studies should explore and clarify the relationships between metabolic status, PA and CVD risk.

Results from our subgroup analysis found that only high PA group was significantly associated with the lowest risk of CVD among MUO participants over 65 years. As the updated 2018 American PA guidelines have highlighted, older patients are one of the populations who could receive the maximum benefit from PA [11]. It had been reported that higher fitness was associated with improved survival in older adults aged over 70 years [37], while even modest increases in activity could lead to remarkable reduction in CVD risk for older population [38]. Our non-statistically significant results for low and medium PA in older MUO participants in relation to CVD risk may reflect lack of power and require further clarification, given the subgroup findings from an observational study with a hypothesis-generating nature.

According to the current guidelines, medium MVPA has been recommended for CVD prevention targeting all adults, while those with overweight and obesity have been advised to participate in long-term weight loss programs including low-calorie diet and adequate PA involvement [39]. Our study suggests that medium PA might seem to have the lowest CVD risk especially in MUO participants, though the differences in CVD risks between three MVPA groups when compared with no MVPA were not significant in either MHO or MUO groups. Although from a non-randomized design study, our findings may provide some evidence of the importance of PA to CVD risk and thus generate some insights into risk management from the perspective of PA in the obesity.

Strengths and limitations

The study has some merits. To the best of our knowledge, our study was the first to investigate the relationship between metabolic status, PA and CVD in the obesity. First, the data were from the nationwide prospective cohort with a large amount of information and long follow-up periods. Rigorous methodology and extensive analyses supported the validity and robustness of our findings. Our study may yield some evidence for PA engagement and CVD prevention in the MHO and MUO populations.

Several limitations need to be noted. First, over 90% of participants in the UK Biobank study were of white European race, which might restrict the generalizability of this study to other racial groups. Likewise, considering the low response rate at baseline (5.5%), the generalizability of our findings might be compromised [40]. Second, potential bias or residual confounding cannot be completely controlled in an observational study design. Third, the data on PA were collected through the self-reported IPAQ, possibly inducing overestimation due to social desirability and recall bias. Moreover, no analyses could be conducted to assess the changes in metabolic status and PA during follow-up, given the lack of these data in this study. Future studies were needed to further explore the relationship between metabolic status, PA and risk of CVD.

CONCLUSIONS

Both MHO and any MVPA were significantly associated with reduced risks of CVD in adults with obesity, while PA could modify the relationship between metabolic status and CVD risk.

DATA AVAILABILITY

The data can be available on application to the UK Biobank (www.ukbiobank.ac.uk/).

REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation. 2020;141:e139–e596.
2. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, et al. Obesity and Cardiovascular Disease: A scientific statement from the American Heart Association. Circulation. 2021;143:e984–e1010.
3. Blüher M. Metabolically healthy obesity. Endocr Rev. 2020;41:bnaa004.
4. Thomsen M, Nordestgaard BG. Myocardial infarction and ischemic heart disease in overweight and obesity with and without metabolic syndrome. JAMA Intern Med. 2014;174:15–22.
5. Hinnouho GM, Czernichow S, Dugravot A, Nabi H, Brunner EJ, Kivimaki M, et al. Metabolically healthy obesity and the risk of cardiovascular disease and type 2 diabetes: the Whitehall II cohort study. Eur Heart J. 2015;36:551–9.
6. Caleyachetty R, Thomas GN, Toulis KA, Mohammed N, Gokhale KM, Balachandran K, et al. Metabolically healthy obese and incident cardiovascular disease events among 3.5 million men and women. J Am Coll Cardiol. 2017;70:1429–37.
7. Zhou Z, Macpherson J, Gray SR, Gill JMR, Welsh P, Celis-Morales C, et al. Are people with metabolically healthy obesity really healthy? A prospective cohort study of 381,363 UK Biobank participants. Diabetologia. 2021;64:1963–72.
8. Imbalzano E, Russo GT, Giandalia A, Sciacqua A, Orlando L, Russo V, et al. Sex-specific impact of different obesity/metabolic phenotypes on long-term cardiovascular outcomes in acute coronary syndrome patients. Biomedicines. 2022;10:424.
9. Price KJ, Gordon BA, Bird SR, Benson AC. A review of guidelines for cardiac rehabilitation exercise programmes: Is there an international consensus? Eur J Prev Cardiol. 2016;23:1715–33.
10. Zhuo C, Zhao J, Chen M, Lu Y. Physical activity and risks of cardiovascular diseases: a mendelian randomization study. Front Cardiovasc Med. 2021;8:722154.
11. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The Physical Activity Guidelines for Americans. JAMA. 2018;320:2020–8.
12. Ekblom-Bak E, Halldin M, Vikström M, Stenling A, Gigante B, de Faire U, et al. Physical activity attenuates cardiovascular risk and mortality in men and women with and without the metabolic syndrome - a 20-year follow-up of a population-based cohort of 60-year-olds. Eur J Prev Cardiol. 2021;28:1376–85.
13. Park S, Han K, Lee S, Kim Y, Lee Y, Kang MW, et al. Association between moderate-to-vigorous physical activity and the risk of major adverse cardiovascular events or mortality in people with various metabolic syndrome status: a nationwide population-based cohort study including 6 million people. J Am Heart Assoc. 2020;9:e016806.
14. Moon S, Oh CM, Choi MK, Park YK, Chun S, Choi M, et al. The influence of physical activity on risk of cardiovascular disease in people who are obese but metabolically healthy. PLoS One. 2017;12:e0185127.
15. Elagizi A, Kachur S, Carbone S, Lavie CJ, Blair SN. A review of obesity, physical activity, and cardiovascular disease. Curr Obes Rep. 2020;9:571–81.
16. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12:e1001779.
17. Mansournia MA, Collins GS, Nielsen RO, Nazemipour M, Jewell NP, Altman DG, et al. A CHecklist for statistical Assessment of Medical Papers (the CHAMP statement): explanation and elaboration. Br J Sports Med. 2021;55:1009–17.
18. Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. Lancet Diabetes Endocrinol. 2018;6:714–24.
19. Wang R, Olier I, Ortega-Martorell S, Liu Y, Ye Z, Lip GY, et al. Association between metabolically healthy obesity and risk of atrial fibrillation: taking physical activity into consideration. Cardiovasc Diabetol. 2022;21:208.
20. Liu Y, Douglas PS, Lip GYH, Thabane L, Li L, Ye Z, et al. Relationship between obesity severity, metabolic status and cardiovascular disease in obese adults. Eur J Clin Invest. 2023;53:e13912.
21. Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: facts and fantasies. J Clin Invest. 2019;129:3978–89.
22. Huang BH, Duncan MJ, Cistulli PA, Nassar N, Hamer M, Stamatakis E. Sleep and physical activity in relation to all-cause, cardiovascular disease and cancer mortality risk. Br J Sports Med. 2022;56:718–24.
23. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35:1381–95.

24. Alli BY. InteractionR: An R package for full reporting of effect modification and interaction. Software Impacts. 2021;10:100147.
25. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. Int J Epidemiol. 2012;41:514–20.
26. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94:496–509.
27. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285:2486-97.
28. Fan M, Sun D, Zhou T, Heianza Y, Lv J, Li L, et al. Sleep patterns, genetic susceptibility, and incident cardiovascular disease: a prospective study of 385292 UK biobank participants. Eur Heart J. 2020;41:1182–9.
29. Tsatsoulis A, Paschou SA. Metabolically healthy obesity: criteria, epidemiology, controversies, and consequences. Curr Obes Rep. 2020;9:109–20.
30. Mongraw-Chaffin M, Foster MC, Anderson CAM, Burke GL, Haq N, Kalyani RR, et al. Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol. 2018;71:1857–65.
31. Ortega FB, Lee DC, Katzmarzyk PT, Ruiz JR, Sui X, Church TS, et al. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. Eur Heart J. 2013;34:389–97.
32. Carlsson AC, Ärnlöv J, Sundström J, Michaëlsson K, Byberg L, Lind L. Physical activity, obesity and risk of cardiovascular disease in middle-aged men during a median of 30 years of follow-up. Eur J Prev Cardiol. 2016;23:359–65.
33. Green DJ, Smith KJ. Effects of exercise on vascular function, structure, and health in humans. Cold Spring Harb Perspect Med. 2018;8:a029819.
34. Neeland IJ, Ross R, Després JP, Matsuzawa Y, Yamashita S, Shai I, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. Lancet Diabetes Endocrinol. 2019;7:715–25.
35. Niemiro GM, Rewane A, Algotar AM Exercise and Fitness Effect On Obesity. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing.2022; 2022.
36. Ramakrishnan R, Doherty A, Smith-Byrne K, Rahimi K, Bennett D, Woodward M, et al. Accelerometer measured physical activity and the incidence of cardiovascular disease: Evidence from the UK Biobank cohort study. PLoS Med. 2021;18:e1003487.
37. Whelton SP, McAuley PA, Dardari Z, Orimoloye OA, Michos ED, Brawner CA, et al. Fitness and mortality among persons 70 years and older across the spectrum of cardiovascular disease risk factor burden: The FIT Project. Mayo Clin Proc. 2021;96:2376–85.
38. Ferraro RA, Pallazola VA, Michos ED. Physical activity, CVD, and older adults. Aging. 2019;11:2545–6.
39. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140:e596–e646.
40. Li G, Zhang X, Liu Y, Zhang J, Li L, Huang X, et al. Relationship between glucosamine use and the risk of lung cancer: data from a nationwide prospective cohort study. Eur Respir J. 2022;59:2101399.

ACKNOWLEDGEMENTS

This research has been conducted using the UK Biobank Resource under Application Number 63844. This research was supported by Science Foundation of Guangdong Second Provincial General Hospital (number: YY2018-002, recipient: GL).

AUTHOR CONTRIBUTIONS

YL, AZ and GL participated in the design and conception of the study. YL and GL were responsible for data collection. YL performed the data analysis, table designs and all the authors contributed to the interpretation. YL and AZ drafted the manuscript and all the authors revised it critically and gave their approval of the final version. YL and AZ contributed equally to this work. GS, JZ, RW and GYHL provided professional support and made multiple revisions to the manuscript. GYHL and GL shared the joint senior authorship. GL is the study guarantor.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

The UK Biobank study was approved by the North West Multicenter Research Ethics Committee. All participants provided written consent before enrolment.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41366-024-01469-8.

Correspondence and requests for materials should be addressed to Guowei Li.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.