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Running title: Obesity severity, MHO and CVD

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Relationship between obesity severity, metabolic status and cardiovascular disease in obese adults

Abstract

Background: Evidence about the associations between obesity severity, metabolic status and risk of incident cardiovascular disease (CVD) in adults with obesity remains limited.

Methods: The study included 109,301 adults with obesity free of prior CVD based on the UK Biobank cohort. Metabolic status was categorized into metabolically healthy obesity (MHO; free of hypertension, hypercholesterolemia, and diabetes) and metabolically unhealthy obesity (MUO). Obesity severity was classified into three levels: class I (body mass index of 30.0 - 34.9 kg/m^2), II (35.0 - 39.9) and III (≥ 40.0). Cox proportional hazards models were used for analyses.

Results: There were 8,059 incident CVD events during a median follow up of 8.1 years. MUO was significantly associated with a 74% increased CVD risk compared with MHO (HR = 1.74, 95% CI: 1.62 - 1.83). There was a significant interaction between obesity severity and metabolic status on an additive scale regarding CVD risk. When taking class I obesity as reference, class II was non-significantly associated with an increased risk of CVD in the MHO group (HR = 1.07, 95% CI: 0.90 - 1.27), while class III was significantly related to increased risks of CVD (HR = 1.48, 95% CI: 1.12 - 1.96). In the MUO group both classes II and III were significantly related with increased risks of CVD. Significant subgroup effects of age (P = 0.009) and sex (P = 0.047) were observed among participants with MUO, but not in the MHO group.

Conclusions: Both elevated obesity severity and MUO were significantly associated with increased risks of CVD in adults with obesity, while metabolic status could modify the relationship between obesity severity and CVD risk. More research is needed to further clarify the relationship.

Keywords: Cardiovascular disease; Obesity; Obesity severity; Metabolic status; Metabolically healthy obesity

Introduction

Cardiovascular disease (CVD) remains a major public health issue worldwide, posing a substantial healthcare and economic burden. Obesity had been well regarded as a risk factor for CVD [1], whereas some studies suggested that the relationship between obesity and CVD was more complex than we thought [2]. J-shaped or U-shaped associations were generally found between body mass index (BMI) and CVD risk or mortality in the general population in the literature [3]. Nevertheless, evidence about the relationship in the population with obesity remains limited [4].

Recently, the metabolic status in adults with obesity has attracted some attention. Based on various metabolic features including blood pressure, glucose tolerance, and lipid profile, obesity can be categorized as metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO) [5]. Previous studies investigated the metabolic status in relation to risk of CVD with inconsistent conclusions reported, requiring more evidence for clarification [6-12]. Moreover, most prior studies have explored the relationship in the mixed populations that included adults with normal weight, overweight and obesity [11,12]. Given both the heterogeneity between adults with or without obesity and the increasing prevalence of obesity worldwide, evaluating the relationship between metabolic status and CVD risk in participants with obesity could provide evidence for enhanced risk stratification and effective CVD prevention in this specific population, from the perspective of public health.

In this study we aimed to investigate the associations between obesity severity, metabolic status and risk of CVD in participants with obesity, based on population-based cohort data from the UK Biobank study.

Methods

Study population

Details on the UK Biobank study had been described on the website (www.ukbiobank.ac.uk) and in the previous publication [13]. Briefly, the UK Biobank is a large population-based cohort study with over 0.5 million participants aged 37 to 73 years enrolled from 2006 to 2010. Baseline information was collected from participants' self-reports, physical examinations and interviews with trained nurses. The study was approved by the North West Multi-Centre Research Ethics Committee. All participants provided written informed consent before enrollment.

There were 122,244 participants with obesity at baseline (BMI $\geq$ 30 kg/m^2); among them, a total of 12,943 individuals with a baseline diagnosis of CVD were excluded. Therefore, we included 109,301 participants for the present analysis. The flow diagram for the participant selection is shown in **SFigure 1**. Reporting of the study conforms to broad EQUATOR guidelines [14].

Outcome measure

Our primary outcome was event free survival time to the first CVD event, where the CVD event was defined as a composite of incident events including coronary heart disease (CHD), stroke and CVD death. The secondary outcomes were the individual CVD components (CHD, stroke and CVD death).

In the UK Biobank, incident disease status and death information were identified by linkage with hospital in-patient data and death registry records. The cause of disease was classified according to the international classification of diseases ninth (ICD-9) and 10th (ICD-10) revisions, while the cause of death was defined using ICD-10 codes. The ICD-9 and ICD-10 codes used for CHD were 410 - 414 and I20 - I25, respectively. Stroke was identified by 430 - 434, 436 for ICD-9 and I60 - I64 for ICD-10. CVD death was defined using ICD-10 codes I00 - I99.

All participants were followed up from the date of recruitment (between 2006 and 2010)

until the date of diagnosis of CVD events, death or end of follow-up (31 March 2017 for England/Wales, 31 October 2016 for Scotland), whichever occurred first.

Exposures

Based on the guideline, obesity severity was classified into three levels by BMI measures according to the WHO: class I (BMI of 30.0 - 34.9 kg/m^2), II (35.0 - 39.9) and III (≥ 40.0) [15]. *Metabolically healthy* indicated that none of the three metabolic disorders (hypertension, hypercholesterolemia, and diabetes) existed at baseline [16-18], while *Metabolically unhealthy* had the presence of ≥1 of the above metabolic disorders.

Participants who met at least one of the following criteria were deemed to be hypertensive: systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, taking anti-hypertensive medications, hospital records of hypertension at baseline, or a self-reported history of hypertension. History of high cholesterol or taking cholesterol-lowing medications were used to identify the existence of hypercholesterolemia. Diabetes mellitus was ascertained if participants had one of the following conditions: hospital records of diabetes at baseline (ICD-10 codes E10 - E14 and ICD-9 code 250), taking anti-diabetic medications, or a self-reported history of diabetes (**STable 1**).

Other independent variables

Other baseline independent variables of consideration included sociodemographic factors, lifestyle information and comorbidities. The sociodemographic factors included age (in years), sex (male or female), ethnicity (white or others), college degree or higher (yes or no), residential area (urban or rural) and Townsend Deprivation Index (TDI, a composite index of deprivation integrating non-car and non-home ownership, unemployment, and household overcrowding; a higher index indicating a higher degree of deprivation).

Lifestyle data collected were physical activity (< 600, 600 - 3999 or ≥ 4000 metabolic equivalent task (MET) min per week) [19], smoking status (never, previous or current

smoker), alcohol drinking status (never, previous or current drinker), consumption of regular vitamin supplements (yes or no), mineral supplements (yes or no) and coffee intake (yes or no), and sleep pattern. The sleep pattern was a composite index integrating five sleep factors (chronotype, duration, insomnia, snoring, and excessive daytime sleepiness), where the count of the corresponding healthy characteristics (morning chronotype, adequate sleep duration of 7 - 8 h/night, never or rare insomnia, never or rare snoring, and infrequent daytime sleepiness) was used to define the sleep pattern groups as healthy (with the count of 4 - 5), intermediate (2 - 3) and poor (0 - 1) (**STable 1**) [20]. The comorbidity included depression.

Data on sociodemographic factors and lifestyles were obtained from participant self-reports at baseline from the interview. Data on baseline comorbidities were ascertained from participant self-reports, hospital records at baseline and the corresponding treatment/medication received.

Statistical analyses

We performed descriptive analysis for baseline continuous (mean and standard deviation [SD]) and categorical variables (frequency and percentages). Chi-square test and analysis of variance were conducted to compare categorical and continuous variables grouped by obesity severity, respectively.

We used multiple imputation techniques for the missing data (seed = 12345) before conducting all the analytic analyses. Cox proportional hazards models were used to investigate the associations between obesity severity, metabolic status and CVD risk in participants with obesity. Results from the basic (age- and sex-adjusted) model and the fully adjusted models are shown, with hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) reported. The fully adjusted model was adjusted for sex, age, TDI, ethnicity, physical activity, ethnicity, college degree, residential area, smoking and drinking status, regular intake of coffee, vitamin and mineral supplement, sleep pattern, and comorbidities. We presented main results based on obesity severity (class I, II, and III obesity, taking class I obesity as reference). We also presented results of the

continuous form for BMI measures (per one-unit increase in BMI) as a sensitivity analysis. Moreover, we modeled BMI measures by a restricted cubic spline with four knots located at the 5th, 35th, 65th and 95th percentiles to plot their potential non-linear and dose-response associations with CVD risk.

Subgroup analyses were conducted to explore whether there were significant differences in sex (male versus female) and age (< 65 versus ≥ 65 years) groups regarding the association between obesity severity and CVD risk in different metabolic status. Another post hoc subgroup analysis was also conducted by cancer status (with versus without baseline cancer) to assess obesity severity in relation to CVD risk in MHO and MUO group. We further performed an exploratory analysis to explore metabolic severity in relation to CVD risk including MHO and three MUO status (mild, defined as with only one of the metabolic disorders; moderate, defined as with two of the metabolic disorders; and severe, defined as with all of three metabolic disorders). To assess the robustness of main analyses, the Fine-Gray competing risk analysis was conducted as a sensitivity analysis taking all-cause mortality as a competing event for CVD [21]. As another sensitivity analysis, we used the Adult Treatment Panel III (ATP III) definition to define the metabolic status and compare these results with our main findings, where the MUO was defined as two or more of the following components by the ATP III definition [22]: (1) systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg or using antihypertensive drugs; (2) serum triglycerides (TG) of 1.7 mmol/L or more or use of lipid-lower drugs; (3) blood high-density lipoprotein cholesterol (HDL-C) less than 1.04 mmol/L in men and 1.29 mmol/L in women; (4) fasting plasma glucose (FPG) of more than 7.0 mmol/L or use of medications for diabetes.

All tests were two-sided using the α level of 0.05. All the statistical analyses were conducted in SAS software version 9.4 and R software version 4.1.1.

Results

A total of 109,301 participants with obesity were included for analyses, with a median follow up of 8.1 (interquartile range: 7.3 - 8.7) years (**SFigure 2**). There were 78,751 (72%), 22,051 (20%), 8,499 (8%) participants with class I, II, and III obesity respectively. The descriptions and comparisons of baseline characteristics by obesity severity were summarized in **Table 1** (with missing data imputed) and **STable 2** (before missing data imputed). Participants with class III obesity were more likely to be female, have MUO, depression, less physical activities and a poorer sleep pattern when compared with individuals with class I/II obesity.

There were 8,059 incident CVD events among 852,757 person-years documented during follow up. Results for the adjusted associations between obesity severity, metabolic status and CVD risk were demonstrated in **Table 2**. MUO was significantly associated with a 74% increased CVD risk compared with MHO (HR = 1.74, 95% CI: 1.62 - 1.83). Elevated obesity severity and per one-unit increase in BMI were both significantly associated with increased risk of CVD.

Results for joint associations of the six phenotypes generated from the cross-categorization of obesity severity and metabolic status were shown in **STable 3,** with class I obesity & MHO as the reference category. We observed significant interactions on an additive scale ($P < 0.05$) rather than a multiplicative scale ($P = 0.30$) between obesity severity and metabolic status regarding the risk of CVD (**STable 4**). For straightforwardness and simplicity, we studied association between obesity severity and CVD risk stratified by metabolic status in fully adjusted models (**Table 3** and **Figure 1)**. As shown in **Table 3**, when taking class I obesity as reference in the MHO group, class II was non-significantly associated with an increased risk of CVD (HR = 1.07, 95% CI: 0.90 - 1.27), while classes III was significantly related to increased risks of CVD (HR = 1.48, 95% CI: 1.12 - 1.96). In the MUO group both classes II and III were significantly related to increased risks of CVD (HR = 1.15, 95% CI: 1.08 - 1.21 for class II; HR = 1.40, 95% CI: 1.29 - 1.52 for class III). Per one-unit increase in BMI in relation to CVD risk was broadly similar between MHO (HR = 1.04, 95% CI: 1.02 -

1.05) and MUO (HR = 1.03, 95% CI: 1.02 - 1.03) groups.

Figure 1 displays restricted cubic spline curves of adjusted HRs for CVD risk at different values of BMI for MHO and MUO groups separately. Consistent with **Table 3**, steadily increasing HRs were observed for MUO as the BMI elevated. For the MHO group, HRs were similar to those from the MUO participants when their BMI were < 40 kg/m^2; however, a relatively sharp increase in the HRs was found for those with class III obesity.

Table 4 shows results for secondary outcomes (6,540 CHD, 1,310 stroke, and 1,158 CVD death), with similar findings to the primary outcome found in general. **STable 5** presents results for subgroup analyses by sex and age in MHO and MUO groups separately. In the MUO, there were significant subgroup effects of age (P = 0.009) and sex (P = 0.047) on the relationship between obesity severity and CVD risk. By contrast, no significant subgroup effects were found in the MHO. Similar results were observed for the subgroup analysis by cancer status **(STable 5).**

Results from the exploratory analyses showed that the CVD risk was elevated accordingly as the metabolic severity increased (**STable 6)**. Results from competing risk analysis displayed similar findings to those from the main analyses (**STable 7**). Results based on the ATP III definition for metabolic status were also consistent with the findings from the main analyses (**STable 8**, **STable 9**).

Discussion

In this study, we investigated the associations between obesity severity, metabolic status and CVD risk in participants with obesity. Our principal findings were as follows: (i) among participants with obesity, elevated obesity severity and MUO were significantly associated with increased risks of CVD; (ii) there was a significant interaction between obesity severity and metabolic status on an additive scale; (iii) in the MUO group both II and III classes of obesity were significantly related to increased risks of CVD when taking class I obesity as reference. In the MHO group, class II was non-significantly associated with an increased risk of CVD, while class III was significantly related to increased risks of CVD; and (iv) while the HR for CVD risk increased steadily in MUO, the rate of increase appeared to accelerate in MHO with BMI $\geq$ 40 kg/m^2.

The main analyses showed that both elevated obesity severity and MUO were significantly associated with increased risk of CVD in participants with obesity. Higher BMI has been considered to independently increase CVD risk, while studies suggested that some participants with overweight and obesity might associate with a better CVD outcome when compared to normal weight participants with history of some cardiovascular disorders [23]. To clearly demonstrate obesity in relation to CVD risk, we only included participants with obesity without baseline CVD, and carefully adjusted for metabolic status and lifestyle factors. Besides, debate over CVD risk related to MHO continues [24]. Imbalzano *et al* found the CVD risk in MHO participants was non-significantly higher than in metabolically healthy adults with normal weight, but significantly lower than MUO participants [11]. Hinnouho *et al* found that the CVD risk in MHO participants was higher than in metabolically healthy adults with normal weight, but was similar to the MUO participants [7,25]. Zhou *et al* found those with MHO had a higher CVD risk than metabolically healthy adults with normal weight, where the MHO participants had a significantly lower CVD risk than in MUO [12]. Nonetheless, in our study MUO was significantly associated with a 72% increased CVD risk compared with MHO, which was in line with the study by Ortega *et al* reporting that the MHO group had a 30 - 50% lower risk of CVD compared to MUO [26]. These inconsistent results might be partly due to the heterogeneity between the studies including

differences in study population and characteristics, follow-up durations and data analyses. Moreover, we found that CVD risk elevated as the metabolic severity increased (**STable 6**). Similar to our results, other studies from The Health Improvement Network (THIN) cohort and Programme de Médicalisation des Systèmes d'Information (PMSI) database demonstrated that metabolic severity was associated with increased CVD risk in a dose-dependent manner [9,10]. Furthermore, previous studies only stratified participants into four groups according to BMI measures (obese/non-obese) and metabolic status (healthy/unhealthy) for analyses, failing to take obesity severity into account [10-12]. Unlike their studies, we focused on the obese population with different obesity severity and observed significant interaction between obesity severity and metabolic status on an additive scale regarding their CVD risk. Therefore, our results may provide new evidence for the obese population regarding their weight and metabolic health in relation to CVD risk.

Furthermore, we found HRs for CVD risk increased steadily as the BMI elevated for the MUO, indicating even a slight change in weight could result in elevated CVD risk. For the MHO, a sharp increase in the HRs was found for those with BMI $\geqslant$ 40 kg/m^2, which was consistent with that only class III, but not class II, was significantly related to increased CVD risk (**Table 3**). Several mechanisms have been proposed to explain this phenomenon for the MHO with class II/III obesity [27,28]. For instance, this population might pay intense attention to their health and seek for adequate healthcare proactively [29]. In addition, adipose tissue might also act as a fuel source to provide energy and nutrient supplement at highly catabolic states [27]. Moreover, leptin, interleukin-10 and soluble TNF-alpha receptor produced by fat cells could have immunomodulatory effects that might help improve health for the MHO with class I/II obesity [28]. However, class III obesity has been demonstrated to be highly related to left ventricular remodeling and left ventricular systolic/diastolic dysfunction, which could eventually lead to heart failure and CVD [30,31]. This finding supports the fact that obesity could yield harmful consequences on CVD health, and no healthy pattern of increased weight existed even for the MHO participants. Indeed, excessive visceral adipose tissue (VAT) and ectopic fat are strong contributors to worse cardiovascular health [32].

Managing the weight and controlling body fat, together with improving metabolic health, may be an effective strategy for CVD prevention in adults with obesity. Nevertheless, the observed relationships for BMI and CVD in MHO and MUO group might be essentially the same due to the small sample size resulting in increased uncertainty and fragile findings by chance, even with the interaction between metabolic status and BMI found. Therefore, our results should be interpreted with caution because such analyses were primarily hypothesis-generating with an exploratory nature especially when the data were from an observational study. More research is needed to further explore and clarify the relationship.

Elevated obesity severity and BMI values were associated with higher risk in men when compared to women in MUO, which was consistent with previous studies [33,34]. The fact that men typically have more VAT than women even with the same BMI values, might contribute to the sex difference [32]. In our study, the association significantly differed in MUO participants aged < 65 years and ≥ 65 years. Unlike our results, one Japanese study reported no difference in the association between BMI and mortality risk in metabolically unhealthy participants aged < 65 years and ≥ 65 years [35]. Racial heterogeneity might contribute to this difference as Asian adults were found to have lower insulin resistance and secretion than Western participants even with the same VAT [36]. Nevertheless, evidence about the impact of age on the association between obesity severity, metabolic status and CVD remain limited.

Although obesity and metabolic health are both regarded as well-established risk factors for CVD and mortality, metabolic dysfunction has been proposed as the downstream on the causal pathway from obesity to CVD [37]. Nonetheless, as both data on the obesity severity and metabolic status were collected at baseline, we did not conduct causal inference analysis in the main analyses given the lack of the time information on both variables. As post hoc explorations, we conducted a mediation analysis using generalized linear model with bootstrapping technique. We found the total effect of obesity on CVD risk was 0.607 (95% CI: 0.307 - 0.839) and the average direct effect was 0.509 (95% CI: 0.229 - 0.725), while the average causal mediation effect through

metabolic health was 0.098 (95% CI: 0.068 - 0.124). Therefore, the mediation proportion of metabolic health was 16.1%, indicating a partial mediation effect. Subsequently, this partial mediation effect might underestimate our results regarding obesity in relation to CVD risk, requiring further studies for clarification and exploration.

To the best of our knowledge, this study is the first to examine the relationship between obesity severity and CVD risk by metabolic status in participants with obesity. One recent study evaluated the association between BMI and CVD mortality by metabolic status[34]. They conducted analyses among adults with general BMI levels stratified by metabolic status (healthy/unhealthy), taking participants with obesity as a group without considering obesity severity. Furthermore, the BMI range of their study did not cover class III obesity (BMI ≥ 40.0 kg/m^2) and hence their results could not be extended to the corresponding population. Individuals with class III obesity have more complex cardiovascular conditions and encounter additional treatment difficulties, provoking healthcare challenges and social burdens [38]. Collectively, our findings confirmed that elevated obesity severity and metabolic severity were both associated with higher CVD risk, which highlighted the importance of controlling weight and metabolic conditions in obese population, even if normal or overweight BMI categories cannot be achieved [1,39]. Our study confirms the importance of metabolic status in participants with obesity, and shows that metabolic status could modify the relationship between obesity severity and risk of CVD. Therefore, our findings may help provide new insights into health management in the obese population.

Strengths and limitations

The study has some strengths. First, we used high-quality data from the large-scale UK Biobank cohort for model building and analyses, which provided us with long follow-up, large sample size and modest statistical power. Second, sensitivity analyses including competing risk analysis and using the ATP III definition, in combination to exploratory analysis based on metabolic severity, could help support the robustness and validity of our findings. Our study might provide some evidence on risk stratification

and optimize CVD health strategies in the obese population from the perspective of public health.

Several limitations need to be noted. First, the UK Biobank cohort was mainly consisted of white European ethnicity, thus the generalizability of our study to other ethnic groups might be limited. Second, taking into account the low response rate to baseline survey of the data (5.5% baseline response rate), whether the participants from the UK Biobank study are representative of general population has been debated. Third, possible bias or residual confounding effects could not be fully precluded in an observational study design. Besides, only BMI was used in this study without considering alternative measures of obesity. Furthermore, lack of direct blood measures in our definition of metabolic status might induce undiagnosed diabetes and hypercholesterolemia. No analyses were performed to explore the changes in metabolic status and BMI during follow-up in estimating risk of CVD, due to the limited data available from the study. Therefore, our results should be interpreted with caution, requiring more evidence to further clarify the relationship between obesity severity, metabolic status and CVD risk in participants with obesity.

Conclusions

Both elevated obesity severity and MUO were significantly associated with increased risks of CVD in participants with obesity, while metabolic status modified the relationship between obesity severity and CVD risk. More research is needed to further clarify the relationship between obesity severity, metabolic status and CVD risk in adults with obesity, and to elucidate the mechanisms by which metabolic health, even in the presence of obesity, protects the cardiovascular system from excess cardiovascular risk.

Data sharing

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

Ethical approval

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

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Figure legend

Figure 1. Associations between BMI and risk of cardiovascular disease by metabolic status

Table 1. Participants' baseline characteristics by obesity severity

Characteristics	Overall (N=109,301)	Class I obesity (N=78,751)	Class II obesity (N=22,051)	Class III obesity (N=8,499)	*P*-value
MUO, n (%)	82,312 (75.31)	57,582 (73.12)	17,509 (79.40)	7,221 (84.96)	< 0.001
Age (years), mean (SD)	56.35 (7.90)	56.58 (7.92)	56.06 (7.83)	54.93 (7.73)	< 0.001
TDI, mean (SD)	-0.90 (3.23)	-1.08 (3.17)	-0.62 (3.29)	-0.03 (3.43)	0.007
Male Sex, n (%)	49,624 (45.40)	38,769 (49.23)	8,381 (38.01)	2,474 (29.11)	< 0.001
College degree or higher, n (%)	27,530 (25.19)	20,954 (26.61)	5,391 (24.45)	1,949 (22.93)	< 0.001
White Ethnicity, n (%)	102,113 (93.42)	73,951 (93.90)	20,623 (93.52)	7,879 (92.71)	0.058
Area, n (%)					
Rural	13,321 (12.19)	10,012 (12.71)	2,505 (11.36)	804 (9.46)	< 0.001
Urban	95,980 (87.81)	68,739 (87.29)	19,546 (88.64)	7,695 (90.54)	
MET activity (min/week), n (%)					
< 600	21,978 (20.11)	14,544 (18.47)	5,009 (22.72)	2,425 (28.53)	0.001
600 - 3,999	63,930 (58.49)	46,362 (58.87)	12,828 (58.17)	4,740 (55.77)	
≥ 4,000	23,393 (21.40)	17,845 (22.66)	4,214 (19.11)	1,334 (15.70)	
Smoking status, n (%)					
Never	57,512 (52.62)	41,140 (52.24)	11,720 (53.15)	4,652 (54.74)	< 0.001
Previous	41,318 (37.80)	29,930 (38.01)	8,301 (37.64)	3,087 (36.32)	
Current	10,471 (9.58)	7,681 (9.75)	2,030 (9.21)	760 (8.94)	
Drinking status, n (%)					
Never	5,884 (5.38)	3,841 (4.88)	1,351 (6.13)	692 (8.14)	< 0.001
Previous	4,795 (4.39)	3,060 (3.89)	1,104 (5.01)	631 (7.42)	
Current	98,622 (90.23)	71,850 (91.24)	19,596 (88.87)	7,176 (84.43)	
Sleep pattern, n (%)					
Poor	4,691 (4.29)	2,829 (3.59)	1,169 (5.30)	693 (8.15)	< 0.001
Intermediate	52,004 (47.58)	36,434 (46.26)	11,008 (49.92)	4,562 (53.68)	
Healthy	52,606 (48.13)	39,488 (50.14)	9,874 (44.78)	3,244 (38.17)	
Coffee intake, n (%)	83,094 (76.02)	60,400 (76.70)	16,487 (74.77)	6,207 (73.03)	< 0.001
Vitamin supplement, n (%)	32,501 (29.74)	23,589 (29.95)	6,405 (29.05)	2,507 (29.50)	0.030
Mineral supplement, n (%)	43,517 (39.81)	31,918 (40.53)	8,393 (38.06)	3,206 (37.72)	< 0.001
Cancer, n (%)	12,425 (11.37)	8,873 (11.27)	2,539 (11.51)	1,013 (11.92)	0.148
Depression, n (%)	19,205 (17.57)	12,831 (16.29)	4,347 (19.71)	2,027 (23.85)	< 0.001
Hypertension, n (%)	78,262 (71.60)	54,590 (69.32)	16,720 (75.82)	6,952 (81.80)	< 0.001

Diabetes, n (%)	13,207 (12.08)	7,710 (9.79)	3,478 (15.77)	2,019 (23.76)	< 0.001
High Cholesterol, n (%)	24,984 (22.86)	17,001 (21.59)	5,548 (25.16)	2,435 (28.65)	< 0.001

Abbreviations: MUO, metabolically unhealthy obesity; MHO, metabolically healthy obesity; BMI, Body Mass Index; TDI, Townsend Deprivation Index; MET, Metabolic Equivalent of Task;

Table 2. Associations between obesity severity, metabolic status and risk of cardiovascular disease

Exposure	Events/*n*	Basic model[1]	Fully adjusted model[2]
Obesity severity			
Class I obesity	5,591 / 78,751	Ref	Ref
Class II obesity	1,706 / 22,051	1.19 (1.13, 1.26), p < 0.001	1.14 (1.08, 1.20), p < 0.001
Class III obesity	762 / 8,499	1.56 (1.44, 1.68), p < 0.001	1.41 (1.31, 1.53), p < 0.001
MUO*	7,069 / 82,312	1.73 (1.62, 1.86), p < 0.001	1.74 (1.62, 1.83), p < 0.001
Sensitivity analysis by treating BMI as continuous variable			
Per one-unit increase in BMI	8,059 / 109,301	1.04 (1.03, 1.04), p < 0.001	1.03 (1.02, 1.04), p < 0.001
MUO*	7,069 / 82,312	1.72 (1.60, 1.84), p < 0.001	1.72 (1.61, 1.84), p < 0.001

Abbreviations: MUO, metabolically unhealthy obesity; MHO, metabolically healthy obesity; BMI, Body Mass Index.

* taking MHO as reference

[1]Basic models were adjusted for age and sex; data shown as hazard ratios (95% confidence intervals), p -values

[2]Multiple imputed model, adjusted for sex, age, Townsend Deprivation Index, ethnicity, MET activity, college degree, area, smoking and drinking status, regular intake of coffee, vitamin and mineral supplement, sleep pattern, personal medical history of depression; data shown as hazard ratios (95% confidence intervals), p -values

Table 3. Results for the relationship between obesity severity and risk of cardiovascular disease by metabolic status*

Exposure	MHO		MUO	
	Events/*n*	HR (95% CI), p-value	Events/*n*	HR (95% CI), p-value
Obesity severity				
Class I obesity	773 / 21,169	Ref	4,818 / 57,582	Ref
Class II obesity	162 / 4,542	1.07 (0.90, 1.27), p = 0.427	1,544 / 17,509	1.15 (1.08, 1.21), p < 0.001
Class III obesity	55 / 1,278	1.48 (1.12, 1.96), p = 0.006	707 / 7,221	1.40 (1.29, 1.52), p < 0.001
Sensitivity analysis by treating BMI as continuous variable				
Per one-unit increase in BMI	990 / 26,989	1.04 (1.02, 1.05), p < 0.001	7,069 / 82,312	1.03 (1.02, 1.03), p < 0.001

Abbreviations: MUO, metabolically unhealthy obesity; MHO, metabolically healthy obesity; BMI, Body Mass

Index; HR, hazard ratio; CI, confidence interval

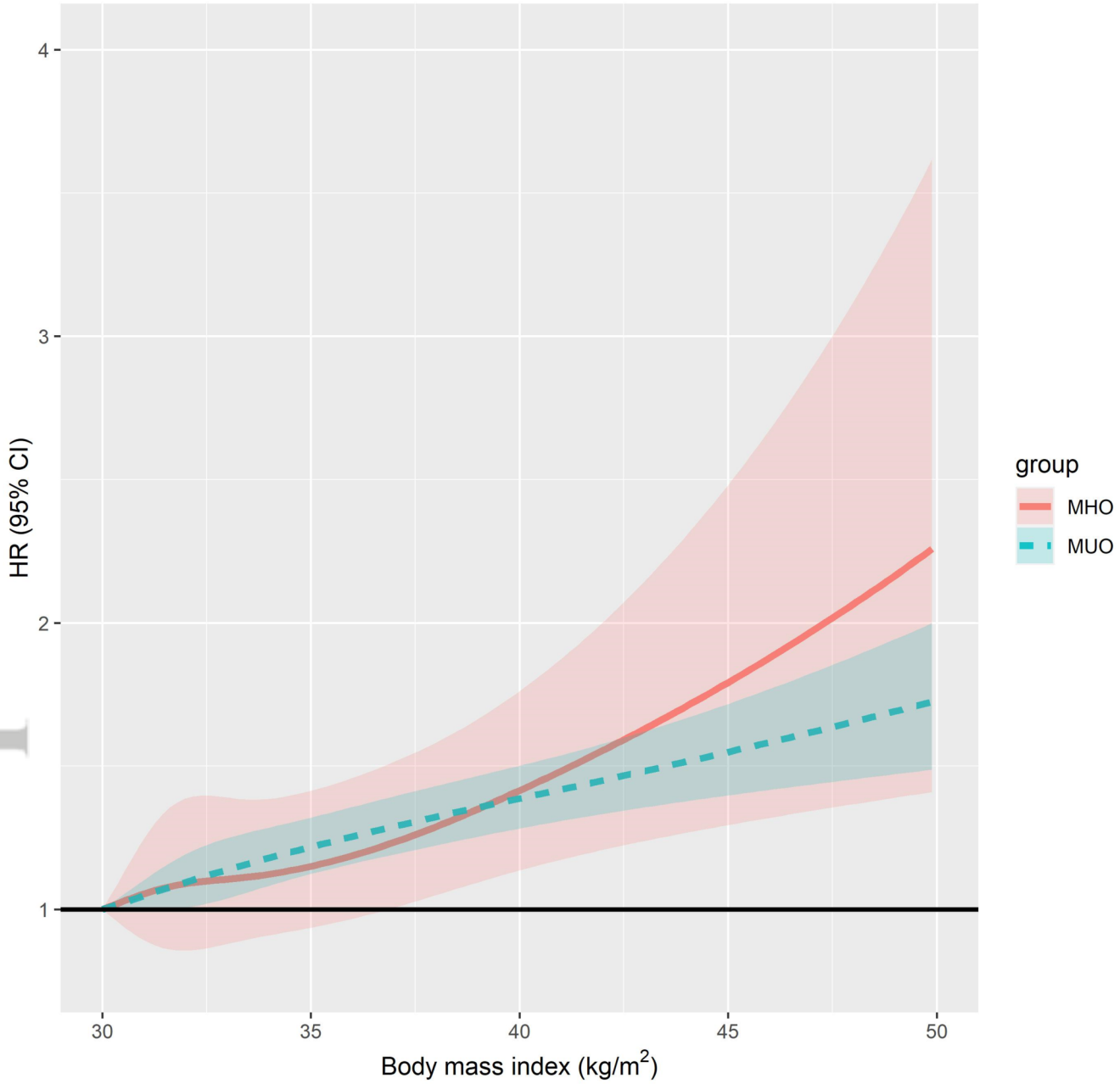
*Adjusted for sex, age, Townsend Deprivation Index, ethnicity, MET physical activity, college degree, area, smoking and drinking status, regular intake of coffee, vitamin and mineral supplement, sleep pattern, personal medical history of depression.

Table 4. Associations between obesity severity and secondary cardiovascular outcomes by metabolic status*

Analysis	CHD (Event number = 6,540)		Stroke (Event number = 1,310)		CVD death (Event number = 1,158)	
	MHO	MUO	MHO	MUO	MHO	MUO
Events/*n*	780 / 26,989	5,760 / 82,312	179 / 26,989	1,131 / 82,312	116 / 26,989	1,042 / 82,312
Obesity severity						
Class I obesity	Ref	Ref	Ref	Ref	Ref	Ref
Class II obesity	1.00 (0.82, 1.22), p = 0.994	1.12 (1.05, 1.19), p < 0.001	1.02 (0.72, 1.80), p = 0.325	1.11 (0.96, 1.29), p = 0.154	1.10 (0.67, 1.81), p = 0.711	1.56 (1.35, 1.81), p < 0.001
Class III obesity	1.34 (0.97, 1.85), p = 0.080	1.26 (1.15, 1.38), p < 0.001	2.04 (1.14, 3.67), p = 0.016	1.60 (1.32, 1.95), p < 0.001	2.03 (0.97, 4.27), p = 0.062	2.78 (2.33, 3.33), p < 0.001
Sensitivity analysis by treating BMI as continuous variable						
Per one-unit increase in BMI	1.02 (1.00, 1.05), p = 0.029	1.02 (1.02, 1.03), p < 0.001	1.07 (1.03, 1.11), p < 0.001	1.03 (1.02, 1.05), p < 0.001	1.06 (1.01, 1.11), p = 0.031	1.09 (1.07, 1.10), p < 0.001

Abbreviations: MUO, metabolically unhealthy obesity; MHO, metabolically healthy obesity; BMI, Body Mass Index; HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular diseases

*Adjusted for sex, age, Townsend Deprivation Index, ethnicity, MET physical activity, college degree, area, smoking and drinking status, regular intake of coffee, vitamin and mineral supplement, sleep pattern, personal medical history of depression; data shown as hazard ratios (95% confidence intervals), p –values.



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