Metabolic Syndrome, Its Components and Risk of Cardiometabolic Multimorbidity: Findings From the UK Biobank Cohort

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Abstract

Background: Metabolic syndrome (MetS) and its components have been acknowledged as risk factors for a single cardiometabolic disease, but their relationship with the risk of cardiometabolic multimorbidity is unclear. The present study aimed to prospectively investigate the association of MetS and its components with the risk of cardiometabolic multimorbidity.

Methods: In this prospective cohort study, we analyzed data of 353,427 participants from the UK Biobank. Participants with a previous diagnosis of cardiometabolic disease or those with missing data on the items of MetS were not eligible. Cardiometabolic multimorbidity was defined as the co-existence of two and more conditions of type 2 diabetes, coronary heart disease (CHD), and stroke. Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the relationship between MetS, components of MetS and cardiometabolic multimorbidity.

Results: During a median of 8.9 years of follow-up, 3389 participants developed the cardiometabolic multimorbidity. Compared with individuals without MetS, individuals with MetS had a three times higher risk of developing cardiometabolic multimorbidity (adjusted HR: 3.02, 95% CI: 2.82-3.24). The accumulation of MetS components was associated, in a dose-response manner, with the risk of cardiometabolic multimorbidity (*P* for trend <0.0001). For the temporal sequences in the development of cardiometabolic diseases, the corresponding HRs (95% CIs) for individuals with ≥4 metabolic abnormalities were 1.57 (1.47-1.68) for cardiovascular disease only, 10.27 (7.62-13.84) for cardiovascular disease with subsequent diabetes, 25.34 (21.95-29.24) for diabetes only, and 42.97 (21.19-87.13) for diabetes with subsequent cardiovascular disease.

Conclusions: MetS was independently associated with the risk of cardiometabolic multimorbidity, and the risk substantially increased with a greater number of MetS components. Our findings highlight the importance of screening and treatment of MetS in the prevention of cardiometabolic multimorbidity.

Introduction

Over the last decades, the prevalence of multimorbidity increased rapidly and up to 55%-98% in the middle-aged and older population [1, 2]. Multimorbidity caused enormous socioeconomic and medical burdens, including a higher risk of mortality, functional decline, lower health-related quality of life, and higher healthcare cost [1, 3, 4]. Previous studies of multimorbidity found that the simultaneous occurrence of several chronic conditions in a patient was not random, but due to potential shared risk factors and biological changes [5]. Among multimorbidity patterns, cardiometabolic multimorbidity, which was typically defined as the co-existence of at least two conditions of diabetes, coronary heart disease (CHD) and stroke, was the most common pattern in the general population [5, 6]. Thomas et al. reported that more than 32% of diabetes patients had cardiometabolic multimorbidity, and cardiovascular disease was the leading cause of mortality for diabetes patients [7]. A pooled study of 689,300 participants from 91 cohorts found that participants with one cardiometabolic disease had almost twice

the risk of all-cause mortality than those with no such diseases, whereas the risk was almost 4 to 7 times in participants with cardiometabolic multimorbidity. [8]. Moreover, compared with patients with no or a single cardiometabolic condition, patients hospitalized for Covid-19 with cardiometabolic multimorbidity had a higher risk of adverse outcomes including mechanical ventilation, admission to an intensive care unit (ICU), or death [9]. In order to reduce the severe burden caused by cardiometabolic multimorbidity, it is not only urgently needed to design effective treatments but also to develop the comprehensive preventive strategies for cardiometabolic multimorbidity. However, previous studies mostly focus on the single cardiometabolic disease, and studies on the risk factors of cardiometabolic multimorbidity are sparse.

Metabolic syndrome (MetS) refers to a clustering of interrelated cardiometabolic risk factors including central obesity, hypertension, hyperglycemia, reduced high-density lipoprotein (HDL) cholesterol level, and high triglyceride level [10, 11]. From the National Health and Nutrition Examination Survey data, more than a fifth of U.S. adults met the criterion of MetS [12] and its prevalence is projected to still increase following the increasing proportion of central obesity and aging population [13, 14]. Moreover, large amounts of evidence showed that MetS and its components significantly increased the risk of single cardiometabolic diseases and mortality from cardiovascular diseases [15–18]. These findings may suggest that MetS could influence the development of cardiometabolic multimorbidity, but to date, no studies have examined whether and the extent to which MetS and its components are associated with cardiometabolic multimorbidity.

To address these limitations, we aimed to prospectively investigate the association of MetS and its components with the risk of cardiometabolic multimorbidity using data of 353,427 participants from the UK Biobank. In addition, we also estimated the risk of different developmental sequences of cardiometabolic diseases in participants with metabolic abnormalities, compared with those without such abnormalities.

Methods

Study design and population

UK Biobank is a prospectively population-based study with 502,505 participants from the general population [19, 20]. Between March 2006 and July 2010, these participants attended one of 22 assessment centers across England, Wales, and Scotland, where they completed a touch-screen questionnaire and had anthropometric measurements. Biological samples were collected by a trained nurse for subsequent biomarker assays. The detailed information about the UK Biobank cohort has been described previously [19, 20]. The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee, and written consents were signed by all individuals.

In the current study, participants were excluded if they subsequently withdrew from the study, those who had a history of CHD, stroke, or type 2 diabetes before the baseline interview, and those who had missing

data on any MetS components. Finally, a total of 353,427 participants were included in the present analyses.

Assessment of metabolic syndrome

According to a most used and joint definition [10], MetS was regarded as the presence of three or more of the following five components including abdominal obesity (waist circumference ≥ 88 cm for women and ≥ 102 cm for men), elevated blood pressure (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or use of antihypertensive medication), high fasting glucose level (fasting blood glucose ≥ 5.60 mmol/L or use of insulin), reduced high-density lipoprotein cholesterol level (< 1.3 mmol/L for women and < 1.0 mmol/L for men), elevated triglyceride level (≥ 1.7 mmol/L or use of lipid-lowering medication). In the UK Biobank study, anthropometric measurements were completed by a trained nurse at the assessment centers. Waist circumference was measured at the smallest part of the trunk using a 200 cm tape measure. Systolic and diastolic blood pressures (SBP and DBP) were measured twice using the HEM-7015IT sphygmomanometer after participants had a rest for ≥ 5 minutes, and the mean of two measures was used for analyses. The serum biomarkers were measured with the Beckman Coulter AU5800 analyzer. Details about biomarkers measurements and assay procedure can be found in the online UK Biobank Showcase (http://biobank.ndph.ox.ac.uk/showcase).

Ascertainment of outcomes

The primary outcome in our study was the cardiometabolic multimorbidity, which was defined as the co-existence of two or more conditions of CHD (the 10th edition of the International Classification of Diseases, ICD-10: I20-25), stroke (I60-64, I69), and type 2 diabetes (E11) [21]. The dates of the first diagnosis of these conditions were identified using the first occurrence fields (Category ID: 1712) in the UK Biobank, which were generated for following up a series of health outcomes by harmonizing data from hospital inpatient admissions records from England, Scotland, and Wales and the national health registrations. The incidence date of cardiometabolic multimorbidity was the diagnostic date of the second cardiometabolic disease. Participants were followed up from the completion of baseline interview to the diagnostic date of cardiometabolic multimorbidity, date of death, or the last date of follow-up (31 January 2018), whichever came first.

Other covariates

At the baseline interview, participants also provided information on demographic factors, smoking status, alcohol drinking, socioeconomic status, and physical activity. Ethnic background was classified as White, mixed, Asian/Asian British, Black/Black British, and others. Smoking status was categorized into never, former and current smoking. The average frequency of alcohol drinking over the last year was self-reported by participants, including never, special occasions only, one to three times a month, once or twice a week, three or four times a week, and daily. Socioeconomic status was determined using the Townsend deprivation index, and was categorized into four groups based on the quartiles of indices. The Townsend deprivation index was derived from national census data of housing, employment, social class and car availability, with a higher index indicating more deprivation. Physical activity was determined by the total

Metabolic Equivalent Task (MET) minutes for all activities over the previous week. Consistent with the previous study, physical activity was classified as none, low (MET < 600 minutes/week), moderate (600–3000 MET), and high (≥ 3000 MET) [22]. For the above categorical covariates, we created a separate response category for missing value and/or selection of unknown and/or preferring not to answer.

Statistical analysis

The study population was divided into two groups according to the baseline MetS status. Baseline characteristics of the participants were described as means with standard deviation for continuous variables and frequencies (%) for categorical variables. For comparing the differences between two groups, we performed the student's *t* test and the chi-squared test for continuous and categorical variables, respectively.

In the first set of analyses, cox proportional hazards models were conducted to investigate the association of MetS with cardiometabolic multimorbidity risk. The results were reported as the hazard ratios (HRs) and 95% confidence intervals (95% CIs). Multivariate models were adjusted for age, gender, ethnicity, Townsend deprivation indices, alcohol drinking, smoking, and physical activity. Furthermore, we estimate the effect of different MetS components (binary and continuous variables, respectively) on the development of cardiometabolic multimorbidity.

To explicate the association between MetS and different cardiometabolic disease endpoints, we classified the primary outcome into a multicategory variable with four mutually exclusive combinations of diseases: cardiovascular disease only, including coronary heart disease, stroke or both of two conditions; type 2 diabetes only; cardiovascular disease followed by diabetes; and diabetes followed by cardiovascular disease. Competing risk models were conducted to examine the association of MetS with this multicategory outcome variable.

Additionally, we also performed a series of sensitivity and subgroup analyses to assess the robustness of our findings. Subgroup analyses were performed by age (< 60 *vs* ≥ 60 years) and gender (female *vs* male). As hyperglycemia is the early stage of diabetes mellitus, we performed sensitivity analysis by removing the elevated fasting glucose in the initial definition of MetS. In the sensitivity analysis, the MetS was redefined as three or more of four components, namely central obesity, raised triglyceride level, reduced HDL cholesterol, and elevated blood pressure.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). All statistical tests were two-sided, and $P < 0.05$ was considered as statistical significance.

Results

Of the 353,427 participants who met the inclusion criteria, the mean (SD) age was 56.13 (8.10) years, 55.76% were female and 24.18% had the MetS. The baseline characteristics of the study participants according to the MetS status were summarized in Table 1. Compared with individuals without MetS, individuals with MetS were older, mostly male, more likely to smoke, and had a lower socioeconomic

status (All $P < 0.01$). And the proportions of drinking and physical activity in participants with MetS were lower than those without MetS (All $P < 0.01$).

During a median of 8.9 years of follow-up (interquartile range 8.2 to 9.6 years), 3389 participants developed the cardiometabolic multimorbidity, and the incidence rate was 1.08 per 1000 person-years (0.64 in the non-MetS group and 2.49 in the MetS group). Table 2 showed the multivariate adjusted HRs (95% CIs) of developing cardiometabolic multimorbidity in participants with MetS or a different number of MetS components. After adjustment for potentially confounding factors, the risk of cardiometabolic multimorbidity was three times higher (HR: 3.02, 95% CI: 2.82-3.24) for individuals with MetS as compared with those without MetS. Moreover, the accumulation of MetS components was significantly associated, in a dose-response manner (P for trend <0.0001), with the risk of cardiometabolic multimorbidity. Compared with metabolically healthy subjects, the adjusted HRs of incident cardiometabolic multimorbidity increased from 1.75 (95% CI: 1.43-2.15) in subjects with one metabolic abnormality to 14.19 (95% CI: 11.22-17.94) in subjects with five abnormalities.

Analyses of the association between individual MetS components and cardiometabolic multimorbidity were presented in Table 3. All individual components were independently associated with the development of cardiometabolic multimorbidity. The hazard ratios of experiencing cardiometabolic multimorbidity were 2.29 (95% CI: 2.13-2.47) for individuals with hyperglycemia, 1.97 (95% CI: 1.83-2.12) for individuals with central obesity, 1.50 (95% CI: 1.38-1.62) for individuals with reduced HDL cholesterol, 1.43 (95% CI: 1.30-1.57) for individuals with hypertension, and 1.42 (95% CI: 1.32-1.53) for individuals with raised triglyceride. When individual MetS components were treated as continuous variables, waist circumference was the predominant factor for cardiometabolic multimorbidity risk, followed by SBP. The per standard deviation increase in waist circumference and SBP contributed to 57% and 23% higher risk of cardiometabolic multimorbidity, respectively. But the relationship of per standard deviation increase in DBP with cardiometabolic multimorbidity was not statistically significant (HR: 0.96, 95% CI: 0.92-1.01), after internally adjusting for other MetS components.

For the temporal sequences in the development of cardiometabolic diseases and cardiometabolic multimorbidity, a total of 9516 subjects experienced diabetes only, 23696 had cardiovascular disease only, 1682 had cardiovascular disease followed by diabetes, 850 had diabetes followed by cardiovascular disease. Competing risk models revealed that the risk of all disease endpoints increased with an increasing number of MetS components (Table 4). And the HR of diabetes with subsequent cardiovascular disease was the highest for participants with the same number of MetS components, followed by diabetes only. For participants with ≥4 components of MetS, the hazard ratios were 1.57 (95% CI: 1.47-1.68) for cardiovascular disease only, 10.27 (95% CI: 7.62-13.84) for cardiovascular disease followed by diabetes, 25.34 (95% CI: 21.95-29.24) for diabetes only, and 42.97 (95% CI: 21.19-87.13) for diabetes followed by cardiovascular disease.

Analyses stratified by age (<60 *vs* ≥60 years old) and gender (female *vs* male) showed that the association between MetS and cardiometabolic multimorbidity was statistically significant in all

subgroups (Figure 1). The HRs were higher in the population with MetS who were younger than 60 years old (HR: 4.26, 95% CI: 3.79-4.80) and female (HR: 3.48 95% CI: 3.10-3.90). Besides, the risk of cardiometabolic multimorbidity also increased for each additional component of MetS in different subgroups. For individuals with 5 MetS components, the HRs (95% CIs) were 16.00 (11.38-22.50) and 24.74 (17.29-35.41) in those who were female and younger than 60 years old, respectively. In the sensitivity analyses in which MetS was redefined using four components, all the results were consistent with those from primary analyses. Compared with participants with metabolic normality, the risk of developing cardiometabolic multimorbidity was seven times higher (HR: 7.06, 95% CI: 5.84-8.54) for participants with four components of MetS (Additional Table 1).

Discussion

In a large-scale prospective cohort study of adults without any cardiometabolic diseases at baseline, we investigated the association of MetS and its components with cardiometabolic multimorbidity. Our results showed that the presence of MetS was significantly associated with the risk of developing cardiometabolic multimorbidity, and the risk increased with an increasing number of MetS components. Moreover, the hazard of developing incident diabetes with subsequent cardiovascular disease was the highest for individuals with MetS, followed by incident diabetes only.

In line with previous studies, the positive association between MetS and a single cardiometabolic disease was demonstrated in the current study. For instance, a study showed a positive dose-response relationship between the severity score of MetS and the risk of diabetes, and the HR for participants in the fourth quartile of MetS scores was 17.4 (95% CI: 12.6–24.1) compared with the lowest quartile [16]. Additionally, one systematic review of 951,083 patients reported that MetS was not only associated with the risk of myocardial infarction and stroke, but also with the mortality from cardiovascular diseases and all causes [23]. Notably, when estimating the risks of diabetes alone and cardiovascular diseases alone in the current study, we considered the competing risk of cardiometabolic multimorbidity. Both hazard ratios of the two conditions remained statistically significant after adjustment of potential confounders. Moreover, MetS components were also found to be associated with cardiovascular diseases and diabetes as well. By contrast, a case-cohort study of 3645 women showed that waist circumference, blood pressure, diabetes mellitus, and HDL cholesterol were risk markers for coronary heart disease and ischemic stroke in the model adjusting for age and ethnicity [24]. However, after additionally adjusting for treatment of systolic blood pressure, total and HDL cholesterol levels, diabetes mellitus, and smoking status, the results of waist circumference and diastolic blood pressure were not statistically significant. In the current study, after internal adjustment of all MetS elements, the aforementioned factors were independently associated with cardiometabolic multimorbidity except the continuous variable of diastolic blood pressure.

What’s more, we found that compared with the reference group, subjects with MetS or its components were at an elevated risk of developing cardiometabolic multimorbidity. Similarly, Kivimäki et al. pooled data of 120,813 adults from 16 cohort studies to estimate the relationship of overweight and obesity with

cardiometabolic multimorbidity [21]. They found that compared with individuals with a normal weight, the odds ratios of cardiometabolic multimorbidity were 4.5 (95% CI 3.5–5.5) and 14.5 (95% CI 10.1–21.0) for individuals with mild obesity (BMI 30.0-34.9 kg/m^2) and severe obesity (BMI ≥ 35.0 kg/m^2), respectively. But in our study, the hazard ratio for abdominal obesity was attenuated to 1.97 (95% CI: 1.83–2.12) after internal adjustment of all components of MetS. It is worth noting that in the above study, the non-case group only included participants who were free of the three cardiometabolic conditions during the follow up, while we regarded participants without or with one condition as the non-cases in our study. Besides, in contrast to their study, we additionally adjusted other cardiovascular risk factors such as hypertension and dyslipidemia in the full-adjusted model, which play an important role in the development of cardiometabolic multimorbidity. Furthermore, Archana et al. and Freisling et al. both found overweight/obesity was also associated with the transition from first cardiometabolic disease to cardiometabolic multimorbidity [25, 26]. However, the association of hypertension and hypercholesteremia with this transition was not statistically significant (HR and 95% CI: 1.02, 0.85–1.24 for hypertension; 1.08, 0.80–1.46 for hypercholesteremia) in the study by Archana et al. We speculated that these non-significant results may result from the insufficient power caused by the small sample size (N = 2,501) for this transition.

For different temporal sequences in the development of cardiometabolic diseases, we found that the risk of diabetes followed by cardiovascular disease was the highest for individuals with MetS, and the risk of diabetes only was higher than that of cardiovascular disease followed by diabetes, which is in agreement with one previous study that assessed the association between overweight/obesity and cardiometabolic multimorbidity [21]. These findings may indicate the role of insulin resistance in the development of cardiometabolic multimorbidity. When defects in insulin action took place, circulating glucose cannot be used appropriately in various tissues, directly resulting in hyperglycemia [27]. The hypothesis that insulin resistance was the central trait of MetS added additional evidence to this association [11]. By contrast, the metabolic abnormality may stimulate the development of atherosclerosis, which indirectly increased the risk of cardiovascular diseases [28]. Additionally, another order of disease onset that cardiovascular disease occurs before diabetes is also biologically plausible, because hypertension and dyslipidemia are more strongly associated with cardiovascular disease than diabetes [29]. In addition, previous studies found that most individuals with MetS also had atherogenic dyslipidemia such as very-low-density lipoprotein and low-density lipoprotein, which was considered to be the primary cause of atherosclerotic cardiovascular disease [30].

The strengths of the current study included the first investigation of this topic, a large sample size, the prospective design, a long follow-up duration, and the complete data on the health outcomes. However, our study has several limitations. First, although we adjusted for demographic characteristics and lifestyle factors such as ethnic background, smoking status, alcohol drinking, and physical activity, there may be other unmeasured and residual confounders that could influence our results. However, all well-known traditional risk factors for cardiovascular diseases and diabetes were adjusted in the multivariate adjusted model. Second, due to most individuals from the UK Biobank were white, our findings may not

be fully generalized to individuals with other ethnic backgrounds. Finally, due to the lack of repeated measurements of MetS components, we were unable to estimate the association between changes in MetS and the risk of cardiometabolic multimorbidity.

Conclusions

In conclusion, we found that the presence of MetS and even its single component significantly increased the risk of incident cardiometabolic multimorbidity, and the risk substantially increased with a greater number of MetS components. For persons with MetS, the hazard of developing diabetes with subsequent cardiovascular disease reached an excessive level. In view of the heavy burden attributable to cardiometabolic multimorbidity, our study has profound implications in public health and clinical practice. The findings indicate that monitoring and treatment of MetS is particularly important for decreasing the incidence of cardiometabolic multimorbidity in the general population. In addition, screening for cardiovascular diseases in diabetes patients with MetS might be an effective strategy for the prevention of cardiometabolic multimorbidity.

Abbreviations

CHD, coronary heart disease; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; HDL, high-density lipoprotein; MetS, metabolic syndrome; MET, metabolic equivalent task; ICU intensive care unit; SBP, systolic blood pressure.

Declarations

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Ethics approval and consent to participate

The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee, and written consents were signed by all individuals.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Competing interests

The authors declare that they have no competing interests

Authors' contributions

Chaofu Ke and Yi Ding conceived and designed the research; Yanan Qiao, Siyuan Liu, and Yanqiang Lu performed the data analysis; Yanan Qiao Siyuan Liu, and Guochen Li wrote the manuscript; and Chaofu Ke, Yi Ding, and Ying Wu revised it critically for important intellectual content. All authors contributed to the interpretations of the findings. All authors reviewed the manuscript.

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Tables

Table 1 Baseline characteristics of participants according to the status of metabolic syndrome

	Metabolic syndrome		
Characteristics	**Yes**	**No**	***P***
N (%)	85,448 (24.18%)	267,979 (75.82%)	-
Age at baseline (years; mean, SD)	57.48 (7.77)	55.70 (8.15)	<0.0001
Gender			<0.0001
Female	45,113 (52.80)	151,962 (56.71)	
Male	40,335 (47.20)	116,017 (43.29)	
Ethnic			<0.0001
White	80,913 (94.69)	252,976 (94.40)	
Mixed	412 (0.48)	1,740 (0.65)	
Asian or Asian British	1,772 (2.07)	4,289 (1.60)	
Black or Black British	1,018 (1.19)	4,473 (1.67)	
Other	889 (1.04)	3,337 (1.25)	
Townsend score quartile			<0.0001
1 (least deprived)	19,769 (23.14)	68,510 (25.58)	
2	20,643 (24.17)	67,429 (25.17)	
3	21,512 (25.18)	66,674 (24.89)	
4 (most deprived)	23,381 (27.37)	64,940 (24.24)	
Smoking			<0.0001
Never smoked	44,199 (51.73)	153,080 (57.12)	
Previous smoker	31,311 (36.64)	87,058 (32.49)	
Current smoker	9,401 (11.00)	26,758 (9.99)	
Drinking			<0.0001
Daily or almost daily	14,792 (17.31)	58,955 (22.00)	
Three or four times a week	17,120 (20.04)	66,579 (24.84)	
Once or twice a week	22,295 (26.09)	69,238 (25.84)	
One to three times a month	10,835 (12.68)	28,288 (10.56)	
Special occasions only	12,157 (14.23)	26,645 (9.94)	
Never	8,003 (9.37)	17,805 (6.64)	

Physical activity			<0.0001
None	1,994 (2.33)	3,231 (1.21)	
Low	14,067 (16.46)	32,469 (12.12)	
Moderate	33,104 (38.74)	112,545 (42.00)	
High	17,732 (20.75)	71,678 (26.75)	
SBP (mmHg; mean, SD)	145.46 (16.49)	135.13 (18.58)	<0.0001
DBP (mmHg; mean, SD)	86.93 (9.28)	81.01 (9.94)	<0.0001
HDL (mmol/L; mean, SD)	1.22 (0.29)	1.55 (0.37)	<0.0001
Triglycerides (mmol/L; mean, SD)	2.59 (1.16)	1.44 (0.77)	<0.0001
Blood glucose (mmol/L; mean, SD)	5.32 (1.17)	4.88 (0.59)	<0.0001
Waist circumference (cm; mean, SD)	100.33 (11.55)	85.91 (11.37)	<0.0001

Data were presented as numbers (percentages) unless stated otherwise.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein.

Table 2 Association of metabolic syndrome and the number of its components with the risk of cardiometabolic multimorbidity

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Presence of MetS						
No	Reference		Reference		Reference	
Yes	3.36 (3.14-3.60)	<0.0001	3.27 (3.05-3.50)	<0.0001	3.02 (2.82-3.24)	<0.0001
No. of MetS components						
0	Reference		Reference		Reference	
1	1.78 (1.46-2.19)	<0.0001	1.76 (1.44-2.16)	<0.0001	1.75 (1.43-2.15)	<0.0001
2	2.89 (2.37-3.52)	<0.0001	2.81 (2.31-3.42)	<0.0001	2.71 (2.22-3.30)	<0.0001
3	5.52 (4.54-6.72)	<0.0001	5.32 (4.37-6.47)	<0.0001	4.95 (4.07-6.02)	<0.0001
4	9.57 (7.83-11.69)	<0.0001	9.06 (7.42-11.08)	<0.0001	8.10 (6.62-9.90)	<0.0001
5	17.47 (13.84-22.06)	<0.0001	16.36 (12.96-20.66)	<0.0001	14.19 (11.22-17.94)	<0.0001
	P for trend	<0.0001	*P* for trend	<0.0001	*P* for trend	<0.0001

Model 1 adjusted for age at baseline and gender. Model 2 adjusted for model 1 plus socioeconomic status and ethnicity. Model 3 adjusted for model 2 plus smoking status, alcohol drinking and physical activity. Abbreviations: MetS, metabolic syndrome.

Table 3 Association of individual components of metabolic syndrome with incident cardiometabolic multimorbidity

	Hazard ratio (95% confidence interval)		
	Model 1	**Model 2**	**Model 3**
Binary variables			
Central obesity	2.08 (1.94-2.24)	2.03 (1.89-2.18)	1.97 (1.83-2.12)
Raised triglyceride	1.42 (1.32-1.53)	1.45 (1.35-1.56)	1.42 (1.32-1.53)
Hyperglycemia	2.33 (2.16-2.51)	2.27 (2.11-2.45)	2.29 (2.13-2.47)
Reduced HDL cholesterol	1.75 (1.62-1.89)	1.68 (1.56-1.81)	1.50 (1.38-1.62)
Hypertension	1.37 (1.25-1.50)	1.38 (1.26-1.52)	1.43 (1.30-1.57)
Continue variables[a]			
Waist circumference (cm)	1.62 (1.56-1.68)	1.60 (1.54-1.66)	1.57 (1.52-1.63)
Triglycerides (mmol/L)	1.11 (1.08-1.14)	1.12 (1.09-1.15)	1.11 (1.08-1.14)
Blood glucose (mmol/L)	1.13 (1.12-1.14)	1.13 (1.12-1.14)	1.13 (1.12-1.15)
HDL (mmol/L)	0.72 (0.69-0.76)	0.74 (0.71-0.78)	0.79 (0.75-0.83)
SBP (mmHg)	1.23 (1.17-1.29)	1.23 (1.18-1.29)	1.23 (1.17-1.29)
DBP (mmHg)	0.95 (0.90-0.99)	0.95 (0.90-0.99)	0.96 (0.92-1.01)

[a]Continue variable represent per standard deviation (SD) increase of individual MetS components. Model 1 adjusted for age at baseline and gender. Model 2 adjusted for model 1 plus socioeconomic status and ethnicity. Model 3 adjusted for model 2 plus smoking status, alcohol drinking and physical activity. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein.

Table 4 Association between the number of MetS components and different cardiometabolic diseases endpoints

No. of MetS components	Cardiovascular disease only	Cardiovascular disease followed by diabetes	Diabetes only	Diabetes follow by cardiovascular disease
1	1.49 (1.41-1.57)	1.64 (1.20-2.23)	2.08 (1.79-2.42)	3.12 (1.50-6.51)
2	1.65 (1.56-1.74)	3.08 (2.29-4.15)	4.99 (4.32-5.77)	7.79 (3.82-15.86)
3	1.77 (1.68-1.87)	6.08 (4.53-8.17)	11.16 (9.67-12.87)	18.55 (9.15-37.63)
≥4	1.57 (1.47-1.68)	10.27 (7.62-13.84)	25.34 (21.95-29.24)	42.97 (21.19-87.13)

Data were show as hazard ratios (95% confidence interval).

Models were adjusted for age, gender, ethnicity, alcohol drinking, smoking status, Townsend deprivation indices, ethnicity, and physical activity.

Figures

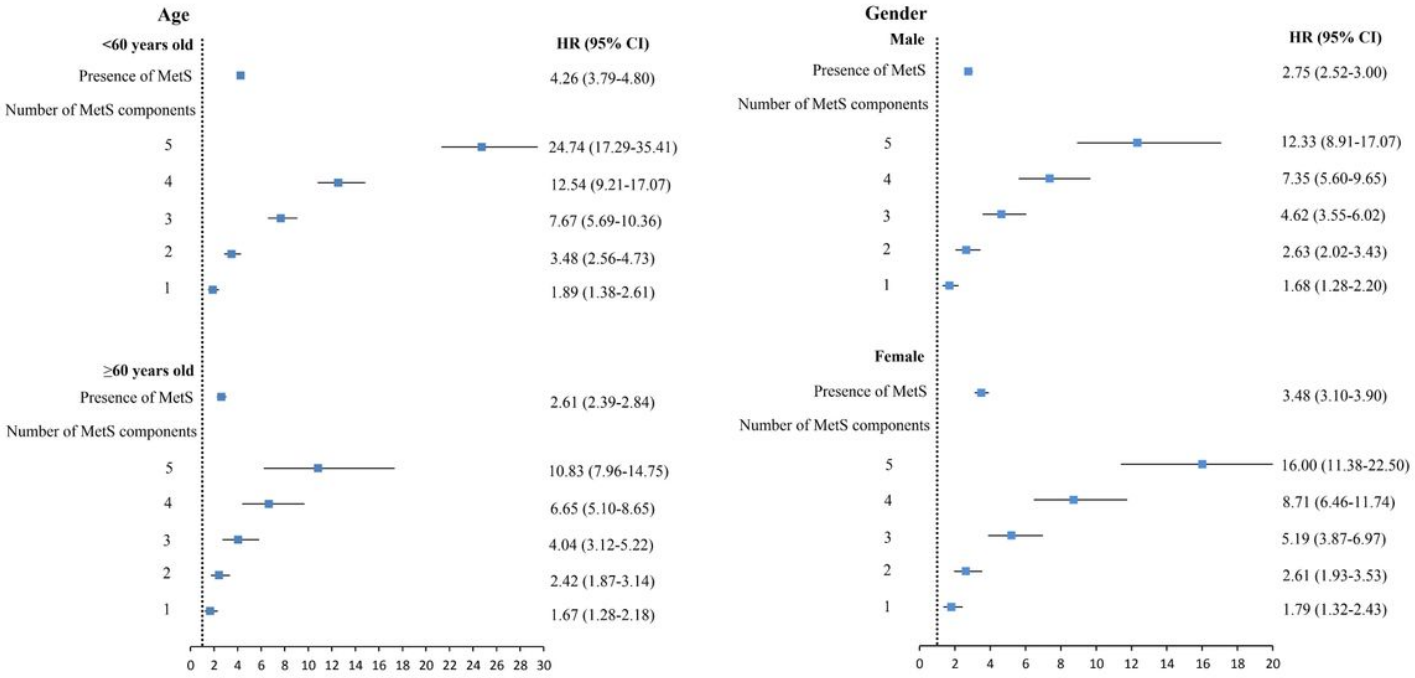

Figure 1

Subgroup analyses for the association between metabolic syndrome and cardiometabolic multimorbidity

Supplementary Files

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- SupplementaryMaterial.docx