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Differential and sex- and age-specific risks of cardiometabolic diseases with unrelated metabolic syndrome dimensions

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Abstract

Objective: This study aimed to investigate whether independent dimensions of metabolic syndrome (MetS) components are associated differentially with incident cardiometabolic diseases.

Methods: Principal components analysis was performed using the five MetS components from 153,073 unrelated European-ancestry participants (55% women) from the UK Biobank. The associations of the principal components (PCs) with incident type 2 diabetes mellitus (T2D), coronary artery disease (CAD), and (ischemic) stroke were analyzed using multivariable-adjusted Cox proportional hazards models in groups stratified by sex and baseline age.

Results: PC1 (40.5% explained variance; increased waist circumference with dyslipidemia) and PC2 (22.7% explained variance; hyperglycemia) were both associated with incident cardiometabolic disease. Hazard ratios for CAD and T2D were higher for PC1 than for PC2 (1.27 [95% CI: 1.25–1.29] vs. 1.06 [95% CI: 1.03–1.08] and 2.09 [95% CI: 2.03–2.16] vs. 1.39 [95% CI: 1.34–1.44], respectively). Furthermore, the association of PC1 with T2D was slightly higher for women than for men, and especially the HRs of PC1 with CAD and T2D attenuated with increasing age (p values for heterogeneity test among subgroups < 0.05).

Conclusions: MetS can be dissected into two distinct presentations characterized by differential sex- and age-associated cardiometabolic disease risk, confirming the loss of information using the dichotomous MetS.

INTRODUCTION

The global epidemic of obesity is driven by the increasing imbalance between energy intake and expenditure in our aging society [1,2]. In addition, obesity is a major cause for the increasing prevalence of a cluster of abnormalities termed the metabolic syndrome (MetS) [1]. MetS is based on five cardiometabolic risk factors: waist circumference, plasma triglycerides, high-density lipoprotein (HDL) cholesterol, blood pressure, and fasting plasma glucose (FPG), and it is defined when at least three out of the five components are beyond population- and sex-specific cutoffs [3]. Importantly, MetS is strongly associated with (incident) cardiometabolic diseases, including type 2 diabetes mellitus (T2D), coronary artery disease (CAD), and (ischemic) stroke [4-7].

The associations of MetS with the risk of cardiometabolic diseases have been reported to vary depending on age and sex [8]. Previous work has shown that the association between MetS and incident cardiovascular disease was weaker in older adults than in younger adults [9]. We previously reported, using Mendelian randomization techniques, that the associations among classical risk factors and CAD

attenuated with increasing age [10] and that genetic associations and causal risk profiles for T2D depended on age [11]. In addition, studies on the risk of cardiometabolic diseases in women and men with MetS have shown inconsistent findings [12,13]. Therefore, additional insight into age- and sex-specific associations among MetS and cardiometabolic diseases is required.

So far, most studies have reported the specific cardiometabolic disease risks of MetS by comparing groups with and without MetS. However, given the intrinsic heterogeneity of the MetS definition, the dichotomous nature of MetS has been frequently criticized [14]. Epidemiological studies have suggested that a composite continuous indicator may be a more robust and effective predictor for cardiometabolic diseases than the generally used dichotomized definition of MetS [15-17]. Moreover, detailed insight in the heterogeneous presentation of MetS components is sparse, including their potential differential risk for cardiometabolic diseases and the potential effect modifications by age and sex.

Principal components analysis (PCA) is a method for dimension reduction to identify largely uncorrelated dimensions of interrelated risk factors [18]. We hypothesized that PCA on the five correlated components of MetS could provide distinct dimensions to further dissect the etiology of specific cardiometabolic disease consequences. We set out to identify the independent dimensions of MetS by PCA and to investigate their age- and sex-specific associations with CAD, (ischemic) stroke, and T2D.

Study Importance

What is already known?

- The global epidemic of obesity is an important cause for the increasing prevalence of the metabolic syndrome (MetS).
- The dichotomous MetS is associated with increased risk for cardiometabolic diseases.

What does this study add?

- The five continuous components of MetS can be dissected into two uncorrelated dimensions, one characterized by waist circumference and dyslipidemia and one characterized by hyperglycemia.
- Both dimensions were associated with incident cardiometabolic disease onset, but with different effect sizes and with reduced effect sizes with increasing age.

How might these results change the direction of research or the focus of clinical practice?

- The dichotomous definition of MetS ignores intrinsic heterogeneity in combinations of its five individual components, which causes loss of information and is thereby not an appropriate indicator for assessing specific disease risk.
- Specific presentations of MetS components are differentially associated with cardiometabolic diseases by sex and age.

METHODS

Study population

The present study was embedded in the prospective UK Biobank, which recruited 502,628 participants aged 40 to 69 years across the entire United Kingdom during the baseline survey between 2006 and 2010. Extensive phenotypic and genotypic details of the participants have been collected since the baseline assessment, including data on sociodemographic factors, lifestyle, and habits from questionnaires, as well as data from physical measures, sample assays, multimodal imaging, genome-wide genotyping, and longitudinal follow-up for a wide range of health-related outcomes. The UK Biobank cohort study was approved by the North-West Multicenter Research Ethics Committee (MREC), and the access for information to invite participants was approved by the Patient Information Advisory Group (PIAG) from England and Wales. All participants provided electronic written informed consent for the study. A detailed description of the UK Biobank cohort study has been presented elsewhere [19].

To minimize ancestry and population stratification bias, we restricted the study participants to 318,734 unrelated individuals of European ancestry, based on the estimated kinship coefficients for all pairs and the self-reported ancestral background [20]. Participants with a history of T2D, CAD, and stroke and those taking cholesterol-lowering medication prior to the baseline survey were excluded from the study. We further excluded participants with newly diagnosed T2D at the baseline assessment according to the World Health Organization (WHO) criteria, i.e., FPG concentration ≥ 7.0 mmoL/L or hemoglobin A_{1c} ≥ 48 mmol/mol (6.5%) [21, 22]. Because of missing values in covariables (details of missingness in each variable are presented in Supporting Information Table S1), particularly in the data on self-reported physical activity level (18.29% missing), and the negligible differences in the baseline characteristics between participants with and without missing data (Supporting Information Table S2), a total 153,073 participants with complete information were ultimately included for analysis. A flowchart displaying the inclusion process of study participants is provided in Supporting Information Figure S1.

Components of MetS

The five continuous components of MetS, namely waist circumference (data-field 48), triglycerides (data-field 30,870, measured on a Beckman Coulter AU5800), HDL cholesterol (data-field 30,760, measured on a Beckman Coulter AU5800), diastolic blood pressure (data-field 4079, measured by Omron device), and glucose (data-field 30,740, measured on a Beckman Coulter AU5800), were collected in

the baseline assessment and used for analysis in this study. Diastolic blood pressure was measured twice in a resting sitting position at the study center, and the average of the two measurements was used. Correcting blood pressure for participants with antihypertensive medication was found to improve analyses and therefore the power of epidemiological studies compared with no medication adjustment or the exclusion of treated individuals [23–26]. In agreement with previous studies, including genomics consortia that aimed to identify genetic variants associated with blood pressure measures [27], if participants reported taking antihypertensive medication, 10 and 5 mm Hg were added to the average measured systolic and diastolic blood pressure, respectively. As samples were collected randomly over the day, and only a minor proportion of the biochemical parameters were measured in the fasting state (>8 hours), both glucose and triglyceride levels were adjusted, using a similar method as previously described [28]. Glucose levels were adjusted by subtracting 1.5, 3.0, 1.0, and 0.3 mmol/L, and there was no correction if the reported fasting time was 0, 1, 2, 3, and >3 hours, respectively. Triglyceride levels were adjusted by subtracting 0.1, 0.2, 0.4, 0.6, 0.65, 0.4, and 0.1 mmol/L, respectively, if the reported fasting time was 1 to 7 hours. Because the triglyceride variable was not normally distributed, it was transformed on a natural log scale.

The dichotomous MetS in this study was defined by the harmonized criteria proposed in 2009 [3]. In short, a Caucasian person is classified as having MetS when three or more of the following abnormalities are found: waist circumference > 102 cm in men or >88 cm in women; serum triglycerides ≥ 1.7 mmol/L; HDL cholesterol < 1.0 mmol/L in men or <1.3 mmol/L in women; diastolic blood pressure ≥ 85 mm Hg and/or systolic blood pressure ≥ 130 mm Hg or antihypertensive treatment; and FPG ≥ 5.6 mmol/L or antidiabetic treatment.

Outcome definition

Information on the diagnosis of T2D, CAD, and stroke during follow-up was obtained through linkage with the National Health System (NHS) medical records database. Diagnoses were mainly derived from hospital admissions data and were coded according to the *International Classification of Diseases, Tenth Revision* (ICD-10) (summary available at https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=2409). The diagnosis of T2D was based on the date of the first occurrence of "non-insulin-dependent diabetes mellitus (E11)"; CAD was defined as angina pectoris (I20), myocardial infarction (I21 and I22), and acute and chronic ischemic heart disease (I24 and I25); stroke was a broader definition with any type (I60/I61/I62/I63/I64); and ischemic stroke was defined as I63.

Covariates

Covariates used in the study were obtained by baseline measurements, which included age, sex, Townsend deprivation index (consisting of unemployment, owner occupation, car ownership, and household overcrowding and reflecting an overall socioeconomic status of the postcode area where participants live) [29], self-reported smoking status (never, past, and current), frequency of self-reported alcohol consumption (daily or almost daily, three or four times a week, once or twice a week, one to three times a month, special occasions only, and never), and self-reported physical activity (low, moderate, and high), the calculation of which can be found online. (https://biobank.ctsu.ox.ac.uk/crystal/ukb/docs/ipaq_analysis.pdf).

Statistical analysis

PCA

Prior to conducting the PCA, Pearson correlation analyses were performed among the five continuous components of MetS. PCA is one of the methods used in exploratory data analysis and for dimension reduction by projecting each data point onto a new orthogonal coordinate system to obtain lower-dimensional data while capturing as much of the data's variation as possible [18]. In this study, the five continuous components of MetS were first transformed into standardized variables with standard deviation (SD) one and mean zero, and then PCA was performed as a singular value decomposition of the five standardized components matrix. For individual participants, the score of each principal component (PC score) was calculated by summing up the five standardized MetS variables weighted by the respective eigenvectors. The Pearson correlations among the five continuous variables and each PC are represented by loadings, defined as the eigenvector scaled up by the square roots of the eigenvalues of the respective PC [18]. The first two principal components (PC1 and PC2) were identified and used in subsequent analyses given a combination of the eigenvalues-greater-than-one rule [30], variance explained, and interpretability.

Cox regression analysis

Multivariable-adjusted Cox proportional hazards models were used to estimate hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) for the associations of PCs with incident T2D, CAD, stroke, and ischemic stroke separately. Two multivariable-adjusted regression models were fitted: Model 1 was adjusted for age, sex, and the Townsend deprivation index; and Model 2 was additionally adjusted for smoking status, alcohol consumption frequency, and physical activity. To examine potential effect modifiers, analyses were additionally stratified based on the age at enrollment (40–50, 50–60, and 60–70 years) and sex (women and men). Heterogeneity among different strata was assessed using the χ^2 test.

Sensitivity analysis

To assess whether the dichotomous MetS definition loses information, we compared models fitted with MetS with models fitted with five continuous variables and with PCs (PC1 and PC2) using the

TABLE 1 Baseline characteristics of the population with complete data

		Sex		Age		
Variable	**All**	**Women**	**Men**	**40-50**	**50-60**	**60-70**
n	153,073	84,151	68,922	41,783	54,017	57,273
Age, y, mean (SD)	55.43 (8.04)	55.49 (7.93)	55.37 (8.17)	44.93 (2.74)	54.66 (2.86)	63.83 (2.80)
Sex, men, *n* (%)	68,922 (45.0)	-	68,922	19,471 (46.6)	23,499 (43.5)	25,952 (45.3)
Townsend index, mean (SD)	−1.62 (2.88)	−1.62 (2.85)	−1.62 (2.92)	−1.27 (3.04)	−1.65 (2.85)	−1.85 (2.75)
Risk factors						
Smoking status, *n* (%)						
Never	86,355 (56.4)	50,038 (59.5)	36,317 (52.7)	25,441 (60.9)	30,839 (57.1)	30,075 (52.5)
Previous	51,532 (33.7)	27,013 (32.1)	24,519 (35.6)	10,846 (26.0)	17,691 (32.8)	22,995 (40.1)
Current	15,186 (9.9)	7100 (8.4)	8086 (11.7)	5496 (13.2)	5487 (10.2)	4203 (7.3)
Alcohol status, *n* (%)						
Never	8659 (5.7)	5686 (6.8)	2973 (4.3)	1952 (4.7)	2840 (5.3)	3867 (6.8)
Special occasions only	14,485 (9.5)	10,503 (12.5)	3982 (5.8)	3718 (8.9)	4796 (8.9)	5971 (10.4)
One to three times a month	16,797 (11.0)	10,854 (12.9)	5943 (8.6)	5592 (13.4)	5724 (10.6)	5481 (9.6)
Once or twice a week	40,621 (26.5)	22,664 (26.9)	17,957 (26.1)	12,674 (30.3)	14,283 (26.4)	13,664 (23.9)
Three or four times a week	38,794 (25.3)	19,262 (22.9)	19,532 (28.3)	10,806 (25.9)	14,451 (26.8)	13,537 (23.6)
Daily or almost daily	33,717 (22.0)	15,182 (18.0)	18,535 (26.9)	7041 (16.9)	11,923 (22.1)	14,753 (25.8)
Physical activity group, *n* (%)						
Low	27,109 (17.7)	14,908 (17.7)	12,201 (17.7)	7540 (18.0)	10,707 (19.8)	8862 (15.5)
Moderate	62,472 (40.8)	36,304 (43.1)	26,168 (38.0)	16,421 (39.3)	22,157 (41.0)	23,894 (41.7)
High	63,492 (41.5)	32,939 (39.1)	30,553 (44.3)	17,822 (42.7)	21,153 (39.2)	24,517 (42.8)
MetS and its components						
MetS = 1, *n* (%)	23,640 (15.4)	12,015 (14.3)	11,625 (16.9)	5440 (13.0)	8290 (15.3)	9910 (17.3)
Waist circumference, cm, mean (SD)	88.62 (12.73)	83.06 (11.63)	95.40 (10.54)	87.47 (12.95)	88.62 (12.95)	89.46 (12.30)
Diastolic blood pressure, mm Hg, mean (SD)	82.15 (10.12)	80.34 (9.92)	84.36 (9.93)	80.74 (10.19)	82.69 (10.18)	82.67 (9.92)
Systolic blood pressure, mm Hg, mean (SD)	136.65 (18.48)	133.74 (18.96)	140.21 (17.20)	128.97 (15.58)	135.59 (17.56)	143.26 (18.88)
HDL cholesterol, mmol/L, mean (SD)	1.48 (0.38)	1.63 (0.37)	1.31 (0.31)	1.42 (0.35)	1.50 (0.39)	1.52 (0.39)
TG, mmol/L, mean (SD)	1.30 (0.99)	1.09 (0.81)	1.56 (1.13)	1.25 (1.05)	1.31 (1.00)	1.33 (0.94)
Glucose, mmol/L, mean (SD)	4.47 (0.88)	4.46 (0.87)	4.48 (0.88)	4.28 (0.93)	4.45 (0.87)	4.63 (0.82)
HbA_{1c}, mmol/mol, mean (SD)	34.57 (3.59)	34.64 (3.56)	34.48 (3.62)	33.20 (3.40)	34.62 (3.49)	35.52 (3.50)

Abbreviations: HDL, high-density lipoprotein; MetS, metabolic syndrome; TG, triglycerides.

Akaike information criterion (AIC) [31]. With respect to interpretation of the AIC, the lower the AIC, the better the model. Even though the differences of the baseline characteristics between participants with and without complete data were negligible (Supporting Information Table S2), to detect and reduce the potential selection bias due to missing values, we performed multiple imputation by the chained equations method [32, 33] on 251,794 participants and repeated the main analysis with the imputed data in a bigger sample.

All statistical analyses were performed in R software (version 4.0.2), with "prcomp," "mice," and "survival" packages for PCA, multiple imputation, and Cox regression analyses, respectively.

RESULTS

Characteristics of the study population

The general baseline characteristics of the study participants are presented in Table 1 by sex and age strata. A total of 153,073 unrelated European-ancestry participants without history of CAD, stroke, and T2D and who were not using cholesterol-lowing therapy at baseline were eligible for analyses in this study. The prevalence of MetS was higher in men and older adults than in women and younger adults (16.9% vs. 14.3% in men vs. women and 17.3% vs. 15.3% vs. 13.0%, by age group, respectively).

During up to 13.7 years of follow-up, 3696 participants developed T2D, 8467 participants developed CAD, 2527 participants developed any kind of stroke, and 1607 developed ischemic stroke, with incidence rates of 209 (95% CI: 202–216), 487 (95% CI: 475–496), 142 (95% CI: 137–148), and 90 (95% CI: 86–95) per 100,000 person-years, respectively.

PCA

The intercorrelations among the components of MetS are presented in Supporting Information Table S3. The first two PCs had eigenvalues greater than one (Supporting Information Table S4), and the loadings are shown in Figure 1 (see Supporting Information Table S5 for detailed eigenvector and loadings). PC1 (40.5% explained variance) was mainly correlated with higher waist circumference and triglycerides and lower HDL cholesterol, with absolute loadings greater than 0.7. PC2 (22.7% explained variance) was mainly correlated with higher glucose, with a loading of 0.84. Blood pressure contributed similarly to PC1 and PC2, with moderate loadings of 0.51 and 0.52, respectively.

Prospective analyses on incident cardiometabolic disease

Both PCs (PC1 and PC2) were associated with the risk of all examined incident cardiometabolic diseases (Table 2). After adjusting for all considered confounders (Model 2), the HRs per one-SD increase in PC1

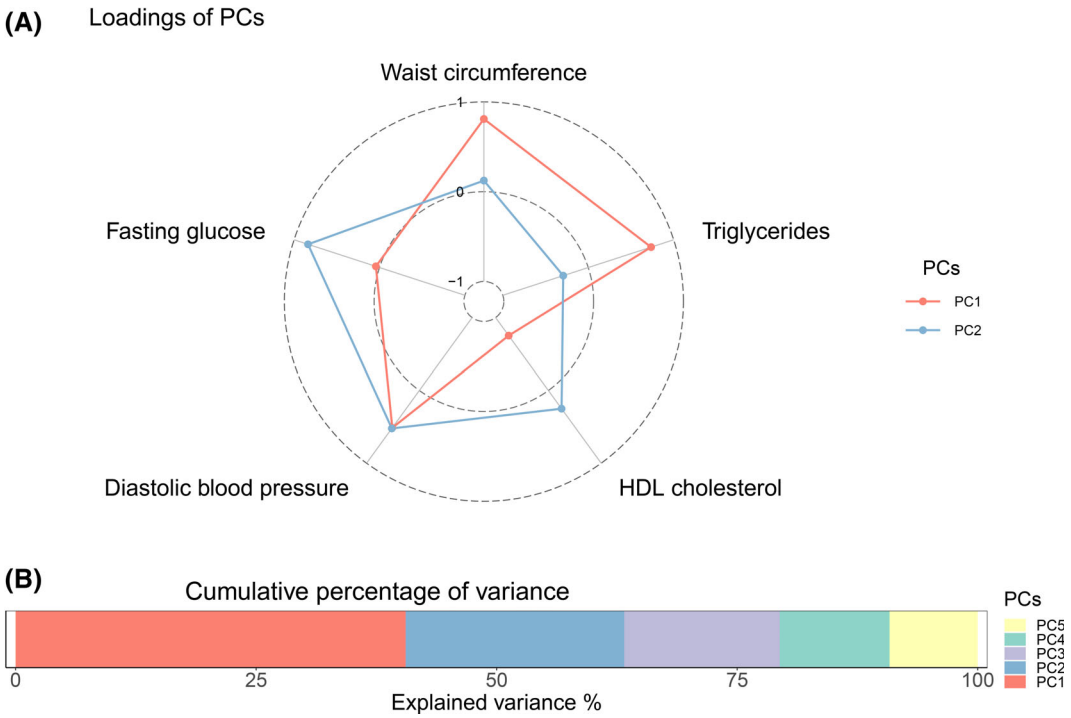

FIGURE 1 Loadings and explained variance of PCs for the five components of MetS. (A) Spider plot of the loadings of the PCs and (B) explained variance of the PCs for MetS components. PC1, PC2, PC3, PC4, and PC5 indicate the first, second, third, fourth, and fifth PC, respectively. MetS, metabolic syndrome; PC, principal component [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Hazard ratios (95% CI) for incident CAD, ischemic stroke, stroke, and T2D according to changes in PCs

	Variable	CAD	Ischemic stroke	Stroke	T2D
Events (*n*)	-	8467	1607	2527	3696
Incidence rates[a]	-	486.71 (475.42–496.17)	90.38 (86.01–94.91)	142.41 (136.91–148.08)	209.05 (202.37–215.91)
Model 1	PC1	1.29 (1.27–1.31)	1.17 (1.13–1.22)	1.14 (1.10–1.17)	2.19 (2.13–2.25)
	PC2	1.04 (1.02–1.06)	1.12 (1.06–1.17)	1.12 (1.07–1.16)	1.34 (1.30–1.39)
Model 2	PC1	1.27 (1.25–1.29)	1.17 (1.12–1.22)	1.13 (1.09–1.17)	2.09 (2.03–2.16)
	PC2	1.06 (1.03–1.08)	1.13 (1.08–1.19)	1.13 (1.09–1.18)	1.39 (1.34–1.44)

Note: Model 1 was adjusted for sex, age, and Townsend index. Model 2 was Model 1 additionally adjusted for smoking status, alcohol consumption frequency, and physical activity.

Abbreviations: CAD, coronary artery disease; HDL, high-density lipoprotein; PC1, the first principal component representing a phenotype of higher waist circumference and triglycerides and lower HDL cholesterol; PC2, the second principal component representing a phenotype of higher glucose level; T2D, type 2 diabetes.

[a]Incidence rate per 100,000 person-years.

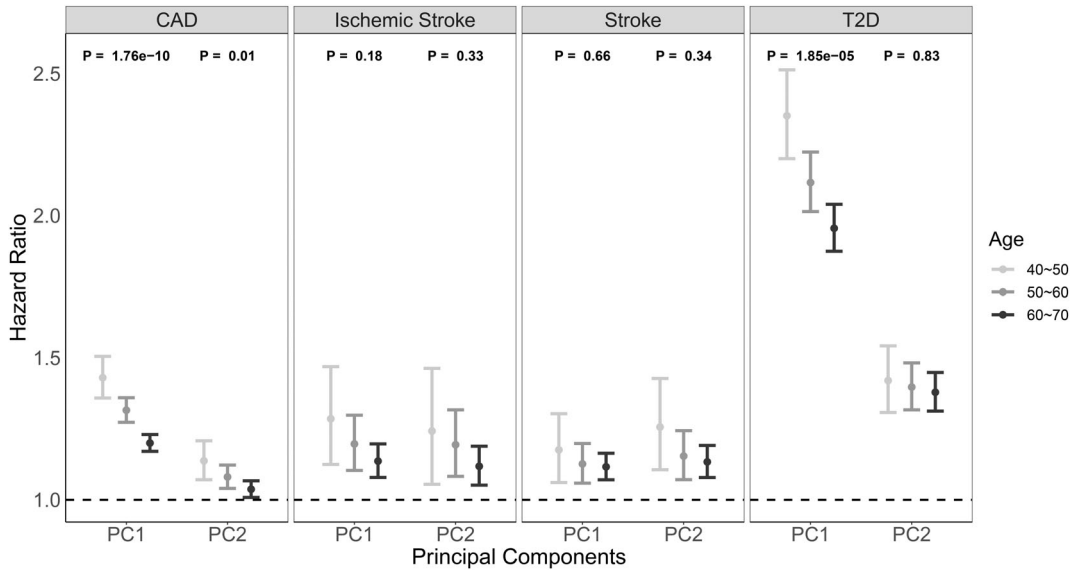

FIGURE 2 Hazard ratios (95% CI) for incident CAD, ischemic stroke, stroke, and T2D according to changes in PCs stratified by age. The *p* values show the results of χ^2 tests among the three age groups, with $p < 0.05$ indicating statistically significant heterogeneity of risks among groups. CAD, coronary artery disease; PC, principal component; T2D, type 2 diabetes

were 1.27 (95% CI: 1.25–1.29), 1.17 (95% CI: 1.12–1.22), 1.13 (95% CI: 1.09–1.17), and 2.09 (95% CI: 2.03–2.16) for the risk of CAD, ischemic stroke, stroke, and T2D, respectively; the HRs per one-SD increase in PC2 were 1.06 (95% CI: 1.03–1.08), 1.13 (95% CI: 1.08–1.19), 1.13 (95% CI: 1.09–1.18), and 1.39 (95% CI: 1.34–1.44) for the risk of CAD, ischemic stroke, stroke, and T2D, respectively.

In the sex-stratified analyses, a small risk difference was observed in the association between PC1 and T2D (HR: 2.19 [95% CI: 2.10–2.28] for women vs. HR: 2.01 [95% CI: 1.93–2.09] for men; Supporting Information Figure S2). Notably, the age-stratified analyses showed that the risks of developing CAD and T2D associated with PC1 both decreased with increasing age ($\chi^2 = 44.92$ and $p = 1.76e{-}10$ for CAD; $\chi^2 = 21.79$ and $p = 1.85e{-}05$ for T2D; Figure 2). Specifically, the risk of CAD and T2D was 1.19 (95% CI: 1.16–1.23) and 1.20 (95% CI: 1.18–1.23) times higher in the youngest adults than in the oldest adults per one-SD increase in PC1. In addition, the association between PC2 and incident CAD also attenuated with increasing age ($\chi^2 = 8.44$ and $p = 0.01$; Figure 2), but not between PC2 and T2D ($\chi^2 = 0.38$ and $p = 0.83$; Figure 2). No statistical support was found for possible heterogeneity in the associations of PCs with the risk of stroke and ischemic stroke across sex groups or age groups.

The model fitted with MetS had the largest AIC, and the model fitted with PCs had a similar AIC to the model fitted with the five continuous MetS variables (Supporting Information Table S6). Sensitivity analyses with multiple imputed data yielded similar results as our main analysis, except that a difference in risk between women and men was observed in the associations of PC1 with both CAD and T2D (Supporting Information Table S7 and Figures S3–S5).

DISCUSSION

We performed PCA on the five continuous components of MetS and found that the first two PCs explained 63.4% of the total variance, in which PC1 (40.5%) was predominantly determined by waist circumference, HDL cholesterol, and triglycerides, and PC2 (22.7% variance) was predominantly determined by glucose. Whereas both PCs were associated with all examined incident cardiometabolic disease outcomes, PC1 was associated with CAD and T2D to a greater extent than PC2. Furthermore, the association between PC1 and T2D was higher in women than in men, and the association of especially PC1 with incident CAD and T2D attenuated with increasing age.

In contrast to previous studies that have found similar contributions of each component of MetS to the first PC [17, 34], our study found that PC1 was predominantly determined by central obesity and dyslipidemia, whereas PC2 was predominantly determined by hyperglycemia (Figure 1). This discrepancy may be explained by heterogeneity of the multiethnic study population in one study [17] or potential patient stratification bias in the other study [34]. Similar to our findings, some studies have also found that the first PC was more correlated with waist circumference and triglycerides [35, 36].

Earlier studies have found that the risk of developing T2D associated with the presence of MetS was higher than the risk of CAD [7,12,36-38]. A meta-analysis revealed that individuals diagnosed with MetS have a relative risk (RR) of 2.35 (95% CI: 2.02–2.73) for developing cardiovascular diseases [12]. However, the estimated RR for the association of MetS according to similar criteria with incident T2D was 3.53 (95% CI: 2.84–4.93) [38]. A similar pattern was found in this study, confirming that the risk of developing T2D was higher than the risk of developing CAD for both PCs. Nevertheless, although PC1 was largely determined by waist circumference, triglycerides, and HDL cholesterol, the absolute HR for T2D was higher compared with PC2. This confirms that multiple, more or less independent pathways lead to T2D.

Our main analyses stratified for sex did not reveal a difference in CAD risk. Previous studies have suggested that CAD associated with MetS in women does not appear to exceed that for men after excluding or adjusting for T2D [39, 40]. Interestingly, a sex difference in the association of PC1 with incident CAD was found after replacing complete data with multiple imputed data. This is likely due to increased power and associated narrower CI, emphasizing the weak sex difference in the original analysis. Few studies have examined the sex-specific risks for incident T2D associated with MetS and confirmed that women had a significantly higher HR with every single unit increase in exposure [41]. Even though our study found that the association between PC1 and the risk of developing T2D in women was consistently higher than in men across the main and sensitivity analyses, the HRs did not differ much, and the statistically significant difference may be due to the large power.

Previous studies have shown that the strength of the association of most of the components of MetS and MetS itself with cardiovascular diseases declined with age [9, 10, 42, 43]. Moreover, randomized clinical trials have found that the effectiveness of cholesterol-lowering treatment and antihypertensive treatment on (primary) CAD risk decreased with increasing age [44, 45]. In line with these findings, we also found that the association between PC1 and the risk of developing T2D and CAD decreased with increasing age. However, the mechanisms underlying this specific age-dependent risk trend remain unclear.

The main strength of this study is that it was embedded in the UK Biobank cohort, with a large population providing ample statistical power. There are also some limitations in our study. First, our analyses were based only on European-ancestry individuals, which cannot be extrapolated to individuals of non-European ancestry. Second, this study may suffer from some inevitable limitations of observational study design, such as residual confounding. More studies addressing the causality question are required to further characterize the independent dimensions of MetS and investigate their cardiometabolic risk profiles.

CONCLUSION

The five correlated components of MetS can be dissected primarily into two independent dimensions, one representing a phenotype characterized by increased waist circumference and dyslipidemia and the other representing a phenotype characterized by hyperglycemia, which are both characterized by differential age- and sex-dependent cardiometabolic disease risk. This study emphasizes the heterogenous presentation of MetS components and the need for careful application of the dichotomous MetS definition when assessing the risk of cardiometabolic diseases.O

AUTHOR CONTRIBUTIONS

Raymond Noordam has full access to all data in the study. All authors conceptualized and designed the study. Linjun Ao is responsible for the statistical analyses and writing, original draft. All authors contributed to the data interpretation and writing, review and editing and approved the final version of manuscript as submitted.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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