Metabolic risk and cardiovascular disease: insights from large biobanks with genetic epidemiological approaches

Ao, L.

CHAPTER 6

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

Linjun Ao, Ko Willems van Dijk, Diana van Heemst, Raymond Noordam

Obesity. 2023;31(7):1933-41
The supplemental information for this paper is available online at
https://drive.google.com/drive/folders/1F2qSC68lFi9Vwfx5XvhF3fzihKZecBqZ?usp=drive_link

Study Importance Questions

What is already known about this subject?

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

What are the new findings in your manuscript?

- The five continuous components of metabolic syndrome can be dissected into two uncorrelated dimensions, one characterized by waist circumference and dyslipidemia, and one 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 your results change the direction of research or the focus of clinical practice?

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

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 (PCA) was performed using the five MetS components from 153,073 unrelated European-ancestry participants (55% women) from the UK Biobank. The associations between the principal components (PCs) and incident type 2 diabetes mellitus (T2D), coronary artery diseases (CAD), and (ischemic) stroke were analyzed using multivariable-adjusted Cox proportional hazard 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 (HRs [95% CI]) for CAD and T2D were higher for PC1 than for PC2 (1.27 [1.25, 1.29] versus 1.06 [1.03, 1.08], and 2.09 [2.03, 2.16] versus 1.39 [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.

1. Introduction

The global epidemic of obesity is driven by the increasing disbalance between energy intake and expenditure in our aging society (1, 2). This, in addition, is a major cause for the increasing prevalence of a cluster of abnormalities termed the metabolic syndrome (MetS) (1). The MetS is based on five cardiometabolic risk factors: waist circumference, plasma triglycerides, HDL cholesterol, blood pressure and fasting plasma glucose (FPG), and is defined when at least three out of the five components are beyond population and sex-specific cutoffs (3). Importantly, the MetS is strongly associated with (incident) cardiometabolic diseases, including type 2 diabetes mellitus (T2D), coronary artery diseases (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 showed that the association between MetS and incident cardiovascular disease was weaker in older adults than younger adults (9). We previously reported, using Mendelian Randomization techniques, that the association between 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 disease in women and men with MetS showed inconsistent findings (12, 13). Therefore, additional insight in age and sex specific associations between MetS and cardiometabolic diseases are 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 disease, and the potential effect modifications by age and sex.

Principal component 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.

2. Methods

2.1 Study population

The present study was embedded in the prospective UK Biobank, which recruited 502,628 participants aged 40-69 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 socio-demographic 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, 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 WHO criteria, i.e. fasting plasma glucose concentration ≥ 7.0 mmol/l or HbA1c ≥ 48 mmol/mol (6.5%) (21, 22). Due to missing values in covariables (details of missingness in each variable are presented in 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 (Table S2), 153,073 participants with complete information were ultimately included for analysis. A flowchart displaying the inclusion process of study participants is provided in Figure S1.

2.2 Components of MetS

The five continuous components of MetS, namely waist circumference (data-field 48), triglycerides (data-field 30870, measured on a Beckman Coulter AU5800), HDL-cholesterol (data-field 30760, measured on a Beckman Coulter AU5800), diastolic blood pressure (data-

field 4079, measured by Omron device) and glucose (data-field 30740, 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 hence the power of epidemiological studies compared to 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 mmHg 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 triglycerides levels were adjusted, using a similar method as previously described (28). Glucose levels were adjusted by subtracting 1.5 mmol/L, 3.0 mmol/L, 1.0 mmol/L, 0.3 mmol/L and with no correction if the reported fasting time was 0 hr, 1 hr, 2 hrs, 3 hrs, and >3 hrs, respectively. Triglycerides levels were adjusted by subtracting 0.1 mmol/L, 0.2 mmol/L, 0.4 mmol/L, 0.6 mmol/L, 0.65 mmol/L, 0.4 mmol/L, and 0.1 mmol/L respectively if the reported fasting time was 1 to 7 hrs. Since the triglycerides 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 were 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 mmHg and/or systolic blood pressure ≥ 130 mmHg or antihypertensive treatment, and FPG ≥ 5.6 mmol/L or antidiabetic treatment.

2.3 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 edition 10 (ICD-10), summary information of which could be found online (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 (MI) (I21 and I22), and acute and chronic ischemic heart disease (IHD) (I24 and I25); Stroke was a broader definition with any type (I60/I61/I62/I63/I64), and ischemic stroke was defined as I63.

2.4 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/never], and self-reported physical activity [low/moderate/high], the calculation of which can be found online

(https://biobank.ctsu.ox.ac.uk/crystal/ukb/docs/ipaq_analysis.pdf).

2.5 Statistical analysis

Principal component analysis

Prior to conducting the PCA, Pearson correlation analyses were performed between the five continuous components of the 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 one and mean zero, and then PCA was performed as a singular value decomposition (SVD) 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 between the five continuous variables and each PC is 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 (see more details in the Results section).

Cox regression analysis

Multivariable adjusted Cox proportional hazard models were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (95% CI) for the association between PCs and 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; 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 enrolment (40-50 years, 50-60 years, and 60-70 years) and sex (women and men). Heterogeneity among different strata was assessed using the chi square (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 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 (Table S2), to detect and reduce the potential selection bias due to missing values, we performed multiple imputation (MI) 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 the R (version 4.0.2) software, with 'prcomp', 'mice' and 'survival' packages for PCA, MI, and Cox regression analyses respectively.

3. Results

3.1 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, T2D and 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% versus 14.3%, and 17.3% versus 15.3% versus 13.0%, 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.

Table 1 Baseline characteristics of the population with complete data

		Sex		Age		
	All	**Women**	**Men**	**40 ~ 50**	**50 ~ 60**	**60 ~ 70**
n	153073	84151	68922	41783	54017	57273
Age, 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 (%)	68922 (45.0)	-	68922	19471 (46.6)	23499 (43.5)	25952 (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)
Smoking status, N (%)						
Never	86355 (56.4)	50038 (59.5)	36317 (52.7)	25441 (60.9)	30839 (57.1)	30075 (52.5)
Previous	51532 (33.7)	27013 (32.1)	24519 (35.6)	10846 (26.0)	17691 (32.8)	22995 (40.1)
Current	15186 (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	14485 (9.5)	10503 (12.5)	3982 (5.8)	3718 (8.9)	4796 (8.9)	5971 (10.4)
One to three times a month	16797 (11.0)	10854 (12.9)	5943 (8.6)	5592 (13.4)	5724 (10.6)	5481 (9.6)
Once or twice a week	40621 (26.5)	22664 (26.9)	17957 (26.1)	12674 (30.3)	14283 (26.4)	13664 (23.9)
Three or four times a week	38794 (25.3)	19262 (22.9)	19532 (28.3)	10806 (25.9)	14451 (26.8)	13537 (23.6)
Daily or almost daily	33717 (22.0)	15182 (18.0)	18535 (26.9)	7041 (16.9)	11923 (22.1)	14753 (25.8)
Physical activity group, N (%)						
Low	27109 (17.7)	14908 (17.7)	12201 (17.7)	7540 (18.0)	10707 (19.8)	8862 (15.5)
Moderate	62472 (40.8)	36304 (43.1)	26168 (38.0)	16421 (39.3)	22157 (41.0)	23894 (41.7)
High	63492 (41.5)	32939 (39.1)	30553 (44.3)	17822 (42.7)	21153 (39.2)	24517 (42.8)
MetS = 1, N (%)	23640 (15.4)	12015 (14.3)	11625 (16.9)	5440 (13.0)	8290 (15.3)	9910 (17.3)
Waist circumference, 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, 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, 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, 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, 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, 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)
HbA1c, 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: MetS: metabolic syndrome; HDL: high-density lipoprotein; TG: triglycerides; SD: standard deviation.

3.2 Principal component analysis

The intercorrelations between the components of the MetS are presented in Table S3. The first two PCs had eigenvalues greater than one (Table S4), and the loadings are shown in **Figure 1** (see 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.

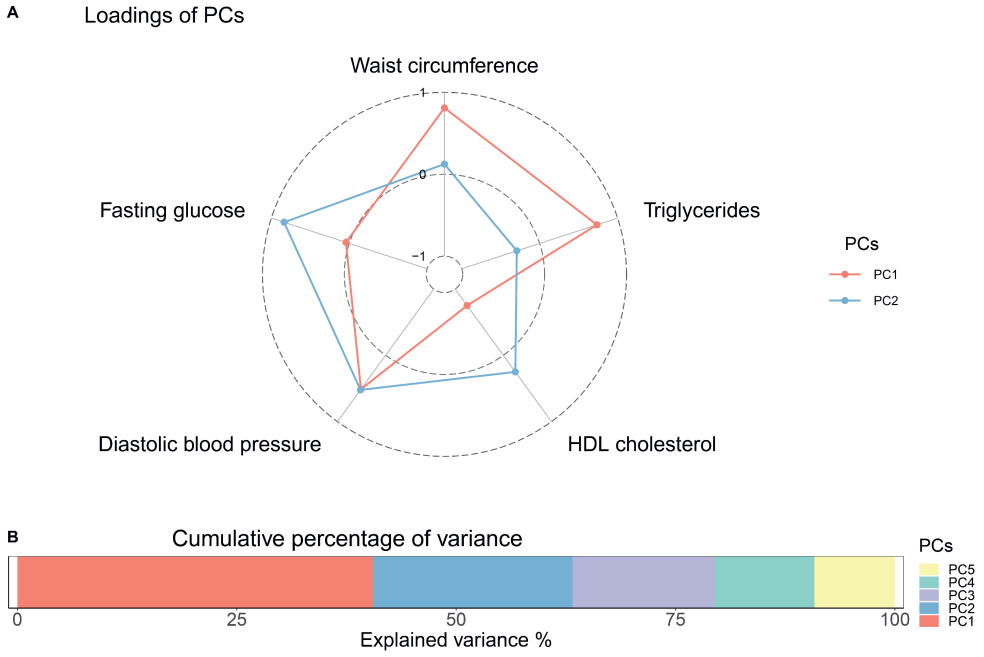

Figure 1. Loadings and explained variance of PCs for the five components of MetS. (A) Spider plot of the loadings of the PCs, and (B) explained variance of the PCs for MetS components. PC1, PC2, PC3, PC4 and PC5 indicate the first, second, third, fourth and fifth principal component respectively.

3.3 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 [95% CI] for per one-SD increase in PC1 was 1.27 [1.25, 1.29], 1.17 [1.12, 1.22], 1.13 [1.09, 1.17] and 2.09 [2.03, 2.16] for the risk of CAD, ischemic stroke, stroke, and T2D, respectively; the HRs [95% CI] for per one-SD increase in PC2 was 1.06 [1.03, 1.08], 1.13 [1.08, 1.19], 1.13 [1.09, 1.18], and 1.39 [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 (HRs [95% CI]: 2.19 [2.10, 2.28] for men *versus* 2.01 [1.93, 2.09] for women, Figure S2). Notably, the age-stratified analyses showed that the risks of developing CAD and T2D associated with PC1 both decreased with increasing age (χ^2 = 44.92 and *P* = 1.76e-10 for CAD; χ^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 for per one-SD increase in PC1; In addition, the association between PC2 and incident CAD also attenuated with increasing age (χ^2 = 8.44 and *P* = 0.01, Figure 2), but not with T2D (χ^2 = 0.38 and *P* = 0.83, Figure 2). No statistical support was found for possible heterogeneity in the association between PCs and 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 (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 association between PC1 and both CAD and T2D (Table S7, Figure S3-S5).

Table 2 Hazard Ratios (95% CI) for incident CAD, Ischemic Stroke, Stroke and T2D according to changes in principal components

		CAD	Ischemic Stroke	Stroke	T2D
Events (n)	-	8467	1607	2527	3696
Incidence rates*	-	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)

*: Incidence rate of per 100,000 person-years

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

CAD: coronary artery disease; T2D: type 2 diabetes; 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.

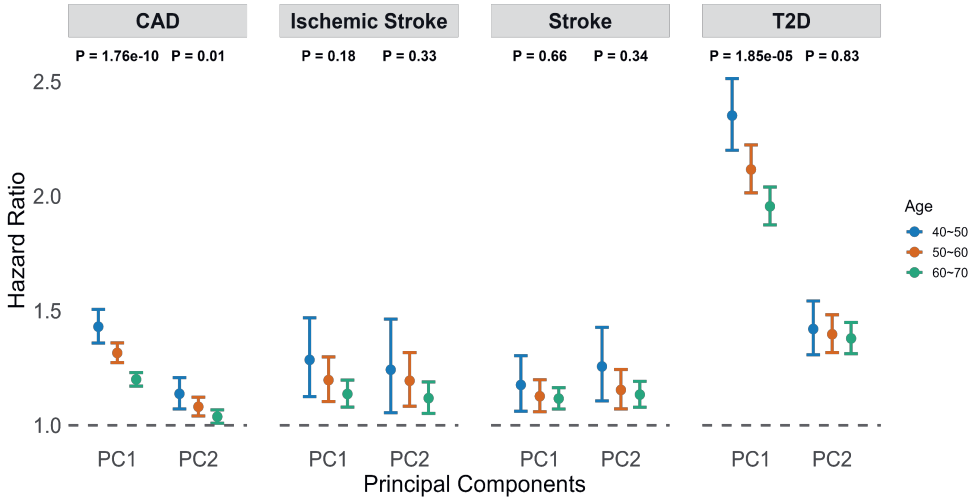

Figure 2. Hazard Ratios (95% CI) for incident CAD, Ischemic Stroke, Stroke and T2D according to changes in principal components stratified by age. CAD: coronary artery disease; T2D: type 2 diabetes. The blue color indicates the 40-50 age group, orange indicates the 50-60 age group, and green indicates the 60-70 age group. The P values show the results of chi-square tests between three age groups, with P <0.05 indicating statistically significant heterogeneity of risks among groups.

4. 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. While both PCs 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 found similar contributions of each component of the 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 multi-ethnic study population in one study (17), or potential patient stratification bias in the other study (34). Similar to our findings, some studies 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 is largely determined by waist circumference, triglycerides and HDL cholesterol, the absolute HR for T2D is higher as compared to 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 confidence intervals, 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 hazard ratio 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 hazard ratios 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 the MetS and the MetS itself with cardiovascular diseases declined with age (9, 10, 42, 43). Moreover, recent 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 only based 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.

Reference

1. Saklayen M. G. The Global Epidemic of the Metabolic Syndrome. Curr Hypertens Rep. 2018;20(2):12.
2. Stout M. B., Justice J. N., Nicklas B. J., Kirkland J. L. Physiological Aging: Links Among Adipose Tissue Dysfunction, Diabetes, and Frailty. Physiology (Bethesda). 2017;32(1):9-19.
3. Alberti K. G., Eckel R. H., Grundy S. M., Zimmet P. Z., Cleeman J. I., Donato K. A., et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-5.
4. Roth G. A., Mensah G. A., Johnson C. O., Addolorato G., Ammirati E., Baddour L. M., et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982-3021.
5. Gami A. S., Witt B. J., Howard D. E., Erwin P. J., Gami L. A., Somers V. K., et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol. 2007;49(4):403-14.
6. Lee M. K., Han K., Kim M. K., Koh E. S., Kim E. S., Nam G. E., et al. Changes in metabolic syndrome and its components and the risk of type 2 diabetes: a nationwide cohort study. Sci Rep. 2020;10(1):2313.
7. Ford E. S., Li C., Sattar N. Metabolic syndrome and incident diabetes: current state of the evidence. Diabetes Care. 2008;31(9):1898-904.
8. Ford Earl S. Risks for All-Cause Mortality, Cardiovascular Disease, and Diabetes Associated With the Metabolic Syndrome: A summary of the evidence. Diabetes Care. 2005;28(7):1769-78.
9. Lind L., Sundstrom J., Arnlov J., Riserus U., Lampa E. A longitudinal study over 40 years to study the metabolic syndrome as a risk factor for cardiovascular diseases. Sci Rep. 2021;11(1):2978.
10. Jansen S. A., Huiskens B., Trompet S., Jukema J., Mooijaart S. P., Willems van Dijk K., et al. Classical risk factors for primary coronary artery disease from an aging perspective through Mendelian Randomization. Geroscience. 2022;44(3):1703-13.
11. Noordam Raymond, Läll Kristi, Smit Roelof A.J., Laisk Triin, Metspalu Andres, Esko Tõnu, et al. Stratification of Type 2 Diabetes by Age of Diagnosis in the UK Biobank Reveals Subgroup-Specific Genetic Associations and Causal Risk Profiles. Diabetes. 2021;70(8):1816-25.
12. Mottillo S., Filion K. B., Genest J., Joseph L., Pilote L., Poirier P., et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol. 2010;56(14):1113-32.
13. McNeill Ann Marie, Rosamond Wayne D., Girman Cynthia J., Golden Sherita Hill, Schmidt Maria I., East Honey E., et al. The Metabolic Syndrome and 11-Year Risk of Incident Cardiovascular Disease in the Atherosclerosis Risk in Communities Study. Diabetes Care. 2005;28(2):385-90.
14. Kahn Richard, Buse John, Ferrannini Ele, Stern Michael. The Metabolic Syndrome: Time for a Critical Appraisal: Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2005;28(9):2289-304.
15. Janghorbani M., Amini M. Utility of Continuous Metabolic Syndrome Score in Assessing Risk of Type 2 Diabetes: The Isfahan Diabetes Prevention Study. Ann Nutr Metab. 2016;68(1):19-25.
16. Kang G. D., Guo L., Guo Z. R., Hu X. S., Wu M., Yang H. T. Continuous metabolic syndrome risk score for predicting cardiovascular disease in the Chinese population. Asia Pac J Clin Nutr. 2012;21(1):88-96.
17. Agarwal S., Jacobs D. R., Jr., Vaidya D., Sibley C. T., Jorgensen N. W., Rotter J. I., et al. Metabolic Syndrome Derived from Principal Component Analysis and Incident Cardiovascular Events: The Multi Ethnic Study of Atherosclerosis (MESA) and Health, Aging, and Body Composition (Health ABC). Cardiol Res Pract. 2012;2012:919425.
18. Jolliffe I. T., Cadima J. Principal component analysis: a review and recent developments. Philos Trans A Math Phys Eng Sci. 2016;374(2065):20150202.
19. Sudlow C., Gallacher J., Allen N., Beral V., Burton P., Danesh J., et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779.
20. Bycroft C., Freeman C., Petkova D., Band G., Elliott L. T., Sharp K., et al. The UK Biobank resource with deep phenotyping and genomic data. Nature. 2018;562(7726):203-9.
21. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. 2006.
22. World Health Organization. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. 2011.

23. Tobin M. D., Sheehan N. A., Scurrah K. J., Burton P. R. Adjusting for treatment effects in studies of quantitative traits: antihypertensive therapy and systolic blood pressure. Stat Med. 2005;24(19):2911-35.
24. Hunt S. C., Ellison R. C., Atwood L. D., Pankow J. S., Province M. A., Leppert M. F. Genome scans for blood pressure and hypertension: the National Heart, Lung, and Blood Institute Family Heart Study. Hypertension. 2002;40(1):1-6.
25. Wu J., Kraja A. T., Oberman A., Lewis C. E., Ellison R. C., Arnett D. K., et al. A summary of the effects of antihypertensive medications on measured blood pressure. Am J Hypertens. 2005;18(7):935-42.
26. Cui J. S., Hopper J. L., Harrap S. B. Antihypertensive treatments obscure familial contributions to blood pressure variation. Hypertension. 2003;41(2):207-10.
27. Simino J., Shi G., Bis J. C., Chasman D. I., Ehret G. B., Gu X., et al. Gene-age interactions in blood pressure regulation: a large-scale investigation with the CHARGE, Global BPgen, and ICBP Consortia. Am J Hum Genet. 2014;95(1):24-38.
28. Lind L. Genetic Determinants of Clustering of Cardiometabolic Risk Factors in U.K. Biobank. Metab Syndr Relat Disord. 2020;18(3):121-7.
29. Townsend Peter. Deprivation. Journal of Social Policy. 1987;16(2):125-46.
30. Kaiser Henry F. The Application of Electronic Computers to Factor Analysis. Educational and Psychological Measurement. 1960;20(1):141-51.
31. Akaike Hirotogu. Information Theory and an Extension of the Maximum Likelihood Principle. In: Petrov. BN, Csaki F, editors. 2nd International Symposium on Information Theory Budapest, Hungary Akadémiai Kiadó 1973. p. 267-81
32. White I. R., Royston P., Wood A. M. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30(4):377-99.
33. van Buuren Stef, Groothuis-Oudshoorn Karin. mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software. 2011;45(3):1 - 67.
34. Dusseault-Belanger F., Cohen A. A., Hivert M. F., Courteau J., Vanasse A. Validating metabolic syndrome through principal component analysis in a medically diverse, realistic cohort. Metab Syndr Relat Disord. 2013;11(1):21-8.
35. Wijndaele K., Beunen G., Duvigneaud N., Matton L., Duquet W., Thomis M., et al. A continuous metabolic syndrome risk score: utility for epidemiological analyses. Diabetes Care. 2006;29(10):2329.
36. Hillier T. A., Rousseau A., Lange C., Lépinay P., Cailleau M., Novak M., et al. Practical way to assess metabolic syndrome using a continuous score obtained from principal components analysis. Diabetologia. 2006;49(7):1528-35.
37. Sattar Naveed, McConnachie Alex, Shaper A. Gerald, Blauw Gerard J., Buckley Brendan M., de Craen Anton J., et al. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. The Lancet. 2008;371(9628):1927-35.
38. Shin J. A., Lee J. H., Lim S. Y., Ha H. S., Kwon H. S., Park Y. M., et al. Metabolic syndrome as a predictor of type 2 diabetes, and its clinical interpretations and usefulness. J Diabetes Investig. 2013;4(4):334-43.
39. Schillaci G., Pirro M., Vaudo G., Gemelli F., Marchesi S., Porcellati C., et al. Prognostic value of the metabolic syndrome in essential hypertension. J Am Coll Cardiol. 2004;43(10):1817-22.
40. Pucci G., Alcidi R., Tap L., Battista F., Mattace-Raso F., Schillaci G. Sex- and gender-related prevalence, cardiovascular risk and therapeutic approach in metabolic syndrome: A review of the literature. Pharmacol Res. 2017;120:34-42.
41. Joseph J., Svartberg J., Njolstad I., Schirmer H. Risk factors for type 2 diabetes in groups stratified according to metabolic syndrome: a 10-year follow-up of the Tromso Study. Eur J Epidemiol. 2011;26(2):117-24.
42. Lind L., Sundstrom J., Arnlov J., Lampa E. Impact of Aging on the Strength of Cardiovascular Risk Factors: A Longitudinal Study Over 40 Years. J Am Heart Assoc. 2018;7(1).
43. Devers M. C., Campbell S., Simmons D. Influence of age on the prevalence and components of the metabolic syndrome and the association with cardiovascular disease. BMJ Open Diabetes Res Care. 2016;4(1):e000195.
44. Murad M. H., Larrea-Mantilla L., Haddad A., Spencer-Bonilla G., Serrano V., Rodriguez-Gutierrez R., et al. Antihypertensive Agents in Older Adults: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. J Clin Endocrinol Metab. 2019;104(5):1575-84.
45. Armitage Jane, Baigent Colin, Barnes Elizabeth, Betteridge D. John, Blackwell Lisa, Blazing Michael, et al. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. The Lancet. 2019;393(10170):407-15.