Association of metabolic syndrome with incident dementia: role of number and age at measurement of components in a 28-year follow-up of the Whitehall II cohort study

Running title: Association of metabolic syndrome with incident dementia

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ABSTRACT

Objective, Previous research suggests an inconsistent association between Metabolic syndrome (MetS) and incident dementia. We examined the role of number of MetS components and age at their assessment for incident dementia.

Research design and methods, MetS components (fasting glucose, triglycerides, waist circumference, blood pressure, and HDL cholesterol) on 7265, 6660, and 3608 participants at age <60, 60 to <70, and ≥70 years were used to examine associations with incident dementia using cause-specific Cox regression.

Results, Analyses of MetS measured <60, 60 to <70, and ≥70 years involved 393 (5.4%), 497 (7.5%), and 284 (7.9%) dementia cases over a median follow-up of 20.8, 10.4, and 4.2 years respectively. Every additional MetS component before 60 (HR 1.13, 95%CI 1.05-1.23) and 60 to <70 (HR 1.08, 95%CI 1.00-1.16) but not ≥70 years (HR 1.04, 95%CI 0.96-1.13) was associated with higher dementia risk. MetS defined conventionally (≥3 components) before 60 years (HR 1.23, 95%CI 0.96-1.57), between 60-70 years (HR 1.14, 95%CI 0.91, 1.42), or after 70 years (HR 1.10, 95%CI 0.86, 1.40) was not associated with incident dementia. Multi-state models showed higher risk of dementia in those with with ≥1 (HR 1.99, 95%CI 1.08-3.66) and ≥2 MetS components (HR 1.69, 95%CI 1.12, 2.56) before age 60, even when they remained free of cardiovascular disease over the follow-up.

Conclusions, Risk of incident dementia increases with every additional MetS component present in midlife rather than after accumulation of 3 components; only part of this risk is mediated by cardiovascular disease.

Keywords: metabolic syndrome; dementia; abdominal obesity; hdl cholesterol; triglycerides; hypertension; fasting glucose

Metabolic syndrome (MetS) is defined by a cluster of interrelated risk factors, consisting of abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), elevated blood pressure and elevated fasting glucose.(1) It has been shown to be associated with risk of coronary artery disease (1; 2) and stroke,(3) possibly due to a synergistic effect of its components. MetS is amenable to change by lifestyle modification,(4) making it an important target for preventive strategies.

MetS components are included in prevention guidelines for dementia,(5; 6) but whether MetS itself increases the risk of dementia remains uncertain. Most previous studies have used the standard definition of MetS, i.e. the presence of ≥3 risk factors. However, risk of dementia may increase for each additional MetS component,(7) rather than only in those with three or more components. A meta-analysis of longitudinal studies,(4) did not find an association between MetS and all-cause dementia, but there was some evidence of an increased risk of vascular dementia (VaD) although most studies had a follow-up duration of less than ten years as MetS was assessed in late-life. More recent studies with a follow-up of up to ten years show an increased risk of all-cause dementia in individuals with MetS.(7-9) It is possible that like obesity and high blood pressure,(10; 11) late-life MetS may not necessarily increase dementia risk. Two previous studies had a follow-up longer than 20 years, but included only men (12; 13) or were based on a small number of dementia cases.(13)

Besides age at measurement of MetS components and limited follow-up in previous studies, the role of cardiovascular disease (CVD) in the association between MetS and dementia also remains unclear. The aim of our study, using data spanning nearly 30 years, was to examine the role of age at measurement of MetS and its components for incident dementia. Using multi-state models, a further aim was to examine whether MetS was associated with incident dementia in those free of CVD over the follow-up.

RESEARCH DESIGN AND METHODS

Study population

Data were drawn from the ongoing Whitehall II cohort study, established in 1985-1988 among 10,308 London-based civil servants aged 35-55 years.(14) Participants responded to a comprehensive questionnaire and underwent a structured clinical examination at recruitment and thereafter every four to five years. Data on MetS components were first collected during the 1991-1993 study wave, and repeated in 1997-1999, 2002-2004, 2007-2009, 2012-2013 and 2015-2016. In addition, linkage to electronic health records of the UK National Health Service (NHS) was used to record data on health outcomes over the follow-up for all but ten participants until March 31, 2019. Research ethics approval and written informed consent from participants were renewed at each contact; the latest approval was from the Joint UCL/UCLH Committee on the Ethics of Human Research (reference number 85/0938).

Metabolic syndrome and its components

MetS was defined using the latest harmonized definition.(1) Participants were classified as having MetS when they met three or more of the following metabolic criteria: a) elevated waist circumference (waist circumference ≥102 cm in men and ≥88 cm in women); b) elevated triglycerides (serum triglycerides level ≥150 mg/dL (1.7 mmol/L), or use of lipid-modifying drugs); c) low HDL-C (<40 mg/dL (1.0 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women, or use of lipid-modifying drugs); d) elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg, or use of antihypertensive drugs); and e) elevated fasting glucose (serum fasting glucose level ≥100 mg/dL (5.6 mmol/L) or use of glucose-lowering drugs).

Waist circumference was measured as the smallest circumference at or below the costal margin. Fasting venous blood samples were collected, centrifuged, and serum was stored in aliquots at −80 °C. Blood pressure was the mean of two measurements using a sphygmomanometer with the participant in a sitting position after five minutes of rest. Use of medication was reported by participants.

MetS components were assessed six times between 1991-1993 and 2015-2016 and for each participant we extracted data on all components at age <60 (range: 40 to 59.9 years), 60 to <70 (range: 60 to 69.9 years), and ≥70 (range: 70 to 84 years). When data were available at several time points within an age range, the measure closest to age 55, 65 and 75 years was chosen for the <60, 60 to <70, and ≥70 age groups, respectively.

Dementia

Dementia cases were ascertained until March 31, 2019, by linkage to three national registers (the national Hospital Episode Statistics (HES), the Mental Health Services Data Set (MHSDS), and the National Statistics Mortality Register) using the unique NHS identification number. ICD-10 codes F00-F03, F05.1, G30, and G31 were used to identify dementia cases. The NHS provides most of the health care in the country, including in- and outpatient care. Assessment of dementia based on HES data has a sensitivity and specificity of 78.0% and 92.0%.(15) The sensitivity in our study is likely to be higher as we also used data from the MHSDS and the mortality register. Date of dementia was set at the first record of dementia diagnosis using all three datasets.

Cardiovascular disease

CVD included stroke (MONICA-Ausburg stroke questionnaire; ICD-10 codes I60–64), coronary heart disease (CHD) (12-lead resting electrocardiogram recording; ICD-10 codes I20–25 or procedures K40–49, K50, K75, U19), and heart failure (ICD10 code I50).

Covariates

Sociodemographic variables included age, sex, ethnicity (white and non-white) and education, (university or higher degree, secondary school, lower secondary school or less). Lifestyle factors included smoking (never, former, and current smoker), alcohol consumption (no consumption, 1-14 units per week, and >14 units per week), consumption of fruits and vegetables (less than daily, once a day, and twice or more a day) and time spent in moderate and vigorous physical activity (hours per

week). Data on covariates were extracted in a similar manner to measure of MetS components, at age <60, 60 to <70, and ≥70.

Statistical analysis

All participants were included in the analyses except those without linkage to electronic health records, incomplete data on MetS components or covariates, and prevalent dementia at the start of follow-up in the three age-based analyses (**Supplemental Figure S1**). Having verified the proportional hazards assumption, we used Cox proportional regression with age as the timescale and incidence of all-cause dementia as the outcome. Age at entry in the follow-up was age at assessment of MetS components and covariates. Participants were censored at date of record of dementia, death, or end of follow-up (March 31, 2019), whichever came first. Cause-specific hazard models were used to account for competing risk of death. All analyses were first adjusted for sex, education, ethnicity and birth-cohort effects using 5-year groups (model 1), and subsequently for smoking, alcohol consumption, fruits and vegetables consumption, and physical activity (model 2).

The analyses consisted of first examining the association between each individual component of MetS measured at age <60, 60 to <70, and ≥70 (separate models) with incidence of dementia. Then, the association between the number of MetS components on a scale from zero to five (categorical variable) at age <60, 60 to <70, and ≥70 (separate models) and risk of incident dementia was examined with participants without MetS components as the reference. We repeated these analyses using the number of MetS components as a linear variable to estimate the increase in dementia risk associated with one additional component. We subsequently examined whether alternate cut-off points to define "high metabolic risk" influenced the association with incident dementia using ≥1 component(s) and then ≥2 and ≥3 components (current clinical definition of MetS) at age <60, 60 to <70, and ≥70. We prefer the term "high metabolic risk" rather than MetS as one or even two components cannot be considered to

represent a “syndrome”. In these analyses, the reference was composed of participants without metabolic risk in each definition of “high metabolic risk”.

In the final analyses we used multi-state models (Weibull distribution) to examine the role of CVD (stroke, CHD or heart failure) over the follow-up in the association between “high metabolic risk” and dementia. These analyses were based on participants free of CVD and dementia at baseline and to allow sufficient number of CVD and dementia cases in these analyses they were only undertaken using MetS components assessed at age <60 years. As previously, “high metabolic risk” was defined as presence of ≥1, ≥2 and ≥3 MetS components. The multi-state models allow simultaneous estimation, expressed as a hazard ratio, of the transition from a) “high metabolic risk” to CVD, b) CVD to dementia, and c) “high metabolic risk” to dementia in those free of CVD over the follow-up. Age was used as the timescale, and analyses were adjusted for all covariates.

To examine the robustness of findings we performed several sensitivity analyses. First, the shape of the association between the number of metabolic syndrome components and incidence of dementia was examined using restricted cubic splines with three knots, Stata command xblc, with zero components as the reference. Second, we repeated the primary analyses using inverse probability weighting to account for missing data.(16) This involved first calculating the probability of being included in the analytical sample using logistic regression that included demographic, socioeconomic, behavioral factors, as well as MetS components at the 1991-1993 wave, chronic diseases during the follow-up including dementia, and stepwise-selected interactions between covariates. The inverse of these probabilities were used as weights in the Cox regression.

Multi-state models were performed using R software. All other analyses were undertaken using STATA version 16.1 (StataCorp). A two-sided *P* value <0.05 was considered statistically significant.

RESULTS

Of the 10308 participants recruited to the study in 1985-1988, 159 (1.5%) died before age 40 and 1708 (16.6%) had dropped out of the study when they were 40-59.9 years. We also excluded 1175 (11.4%) participants with missing data on MetS components and one with missing data on covariates, leading to 7265 (70.5%) participants free of dementia in the analyses at <60 years (mean age at clinical examination was 55.1 years, standard deviation (SD)= 2.9 years; flowchart in **Supplemental Figure S1**). Over a mean follow-up 19.6 (SD= 5.9) years, 393 (5.4%) incident dementia cases were recorded. Mean age at dementia diagnosis was 74.7 (SD=6.3) years. **Supplemental Figure S1** also describes the sample selected in the analysis for MetS at age 60 to <70, and ≥70 years. Participants' characteristics at age <60, 60 to <70, and ≥70, overall and according to incident dementia, are shown in **Supplemental Table S1**. In general, participants with dementia had lower education, and were more likely to be women and of non-white ethnicity. There was no interaction between MetS components and sex or ethnicity (all p-values for interaction >0.05), leading to analyses without stratification.

Association of individual MetS components with incident dementia

Table 1 presents the results of the analyses on individual MetS components measured at age <60, 60 to <70, and ≥70 with incident dementia over a mean (SD) follow-up of 19.6 (5.9), 10.9 (5.8), and 5.7 (3.2) years, respectively. When measured <60 years, elevated waist circumference (HR 1.39; 95% CI 1.07, 1.81), low HDL-C (HR 1.30; 95% CI 1.02, 1.66), and elevated blood pressure (HR 1.34; 95% CI 1.09,1.63) were associated with a higher dementia risk in analyses adjusted for all covariates. For MetS components measured at 60 to <70 years, low HDL-C (HR 1.26; 95% CI 1.02, 1.57) and elevated fasting glucose (HR 1.40; 95% CI 1.12, 1.74) were associated with dementia in the fully adjusted analyses. For MetS components measured ≥70 years, only elevated fasting glucose was associated with incident dementia in the fully adjusted analyses (HR 1.38; 95% CI 1.07, 1.79).

Association between the number of MetS components and incidence of dementia

Table 2 shows the association between the number of MetS components with incident dementia. Treating the MetS scale as a linear variable showed that a 1-point increment in MetS score at age <60 (HR 1.13; 95% CI 1.05, 1.23) and 60 to <70 years (HR 1.08; 95% CI 1.00, 1.16) but not at ≥70 years (HR 1.04; 95% CI 0.96, 1.13) was associated with higher dementia risk in analyses adjusted for all covariates. Linearity of associations using cubic splines was found for Mets component measured at age <60 (**Supplemental Figure S2**, Panel A) and 60 to <70 (**Supplemental Figure S2**, Panel B), but not ≥70 years (**Supplemental Figure S2,** Panel C).

Association between alternate definitions of "high metabolic risk" and incidence of dementia

Analyses on alternative dichotomous definitions of "high metabolic risk" are shown in **Table 3**. "High metabolic risk" defined as the presence of ≥1 component(s) at age <60 (HR 1.38; 95% CI 1.09, 1.74), and 60 to <70 (HR 1.35; 95% CI 1.05, 1.73) was associated with incident dementia compared to those without any MetS components. When "high metabolic risk" was defined as presence of ≥2 components, an increased risk of dementia was observed at age <60, with an HR (95% CI) of 1.32 (1.08, 1.62) but not for "high metabolic risk" in the 60 to <70 and ≥70 years fully adjusted analyses. Analyses of "high metabolic risk" defined as presence ≥3 components (the current definition of MetS) showed no association with incident dementia in the fully adjusted analyses, irrespective of the age of measurement of MetS components. Changing the reference group to those with no MetS components, showed MetS (≥3 components) at <60 years (HR 1.50; 95% CI 1.11, 2.02) and 60 to <70 years (HR 1.40; 95% CI 1.04, 1.89) to be associated with higher risk of dementia (**Supplemental Table S2**).

Role of CVD in the association between MetS at age <60 and incident dementia

Results from the multi-state analyses (**Figure 1**) showed "high metabolic risk" at age <60 years defined as prevalence of ≥1 (HR 1.99, 95% CI 1.08, 3.66) and ≥2 (HR 1.69, 95% CI 1.12, 2.56) components, but not MetS itself (≥3 components, HR 1.51, 95% CI 0.99, 2.29) to be associated with higher risk of dementia in those free of CVD during the follow-up. As expected, "high metabolic risk"

was associated with higher risk of incident CVD, irrespective of the number of components used to define risk (pathway A, Figure 2).

Additional analyses

Inverse probability weighting to account for missing data yielded results similar to those in main analyses (**Supplemental Figure S3**, and **Supplemental Tables S3, S4,** and **S5**)**.**

CONCLUSIONS

This longitudinal study using repeated measures of MetS components and incidence of dementia presents three key findings. First, the conventional case definition of MetS that requires three or more of five risk components was not associated with incident dementia, irrespective of age at assessment of MetS. The five MetS components measured before 70 years, considered on a continuous scale showed the risk of dementia to increase with each additional component. Second, individual MetS components were more strongly associated with incident dementia when measured before 60 years rather than after 70 years. Third, the association between "high metabolic risk", defined as one or two components at high risk, and dementia was partly mediated by CVD but the association was also present in those free of CVD over the follow-up. Taken together, these results highlight the importance of controlling MetS risk factors in midlife, particularly when the interest is in dementia at older ages.

The current evidence on the association between MetS and dementia is characterized by a single assessment of MetS,(9; 12; 13; 17-21) primarily in older adults.(17-20). The follow-up in these studies was less than ten years (4; 7-9; 17-22). Given the long preclinical phase of dementia,(23) the results from these studies may be prone to reverse causation biases as changes in multiple metabolic processes may occur during this phase. A long follow-up, such as in the present study spanning 28 years, allows the assessments of MetS and onset of dementia to be separated by over two decades minimizing the risk of reverse causation bias. A 25-year follow-up study on 3555 men aged 45-68 years at baseline

showed higher dementia risk in participants with a cluster of cardiometabolic risk factors.(12) However, that study did not use a standardized definition of MetS and competing risk of death was not considered. Another study on 1225 men, mean age 52.8 years at baseline, showed an imprecisely estimated, statistically non-significant association between MetS (using the International Diabetes Federation definition) and incident dementia over a 20-year follow-up, possibly due to small number of dementia cases (N < 100) in the analyses.(13) Studies with a short follow-up that have shown an association with dementia used a retrospective measure of history of MetS (22) or were based on Asian populations.(7-9) The typical approach consists of including participants with a wide age range at baseline. The disadvantage of this approach is that older participants at baseline who are more likely to develop dementia during the short follow-up are also more likely to be in the preclinical phase of dementia. Two previous studies performed age-stratified analyses;(8; 20) one showed no association between MetS and all-cause dementia before or after age 75(20) and the other study on 4,106,590 Korean participants found higher dementia, AD, and VaD risk in participants younger and older than 65 years.(8)

The present study adds to the understanding of the association between MetS and dementia due to three novel features. First, alternative thresholds to define "high metabolic risk" were used, and findings show increased risk of dementia to start with the presence of one MetS component. Second, assessment of MetS components in midlife and later life allowed the examination of the role of age at prevalence of metabolic risk for incident dementia at older ages. Third, the use of multi-state models permitted the role of CVD in the association between "high metabolic risk" and incident dementia to be examined.

Our results suggest that the current definition of the MetS, i.e. presence of three or more components, may not be optimal to define dementia risk as it is already present in those with one or two risk factors. The comparison group, in studies using the conventional MetS definition, involves

comparing incidence of dementia in those with three or more risk factors to those with zero to two risk factors. The heterogeneity in metabolic risk in the reference category offers a possible explanation for inconsistent results in previous studies on MetS and risk of dementia, irrespective of the age at assessment of MetS. (4; 13; 17-21) A previous study on 1,492,776 Korean adults, mean age 53.1 years at baseline, also found higher risk of dementia in those with one or more MetS components.(7) Our results showed an increased risk of dementia with an increasing number of MetS components starting with one component, notably at age <60 years, highlighting the importance of all MetS components in midlife for risk of dementia at older ages.

Individual components of MetS have previously been associated with dementia, notably when assessed in midlife, highlighting the role of age in the association between cardiometabolic risk factors and the risk of late-life dementia. In the present study, high waist circumference, decreased HDL-C and elevated blood pressure, when prevalent before 60 years but not after 70 years, were associated with risk of dementia when considered individually. Obesity/high waist circumference(11; 24) and hypertension(10) in mid- but not late-life are known to be associated with an increased dementia risk. Similar to our results, a study of over 8000 men and women found higher dementia risk among those with elevated systolic blood pressure at age 50 but not at age 70.(25) Obesity and central obesity, defined by high BMI and elevated waist circumference respectively, have also been shown to be associated with a higher risk of late-onset dementia when measured at age 50 but not after 60 years.(11) Our results show low HDL-C, but not elevated triglycerides, to be associated with incident dementia. Although dyslipidemia, particularly in midlife, has been associated with an increased risk of dementia in previous studies,(7-9; 12; 18) the precise blood lipid that is pertinent for dementia remains the subject of debate.(26) An increment of 15 mg/dL in blood glucose measured during middle (51 to 60 years) but not in late adulthood (≥61 years) has previously been associated with higher risk of Alzheimer's disease.(27) Nevertheless, elevated fasting glucose in our analyses was associated with

dementia only after age 60; it is possible that the explanation lies in the threshold for fasting glucose used in MetS definition that combines individuals with prediabetes and diabetes. There is now robust evidence that diabetes, but not prediabetes is associated with risk of dementia,(5; 28) possibly driven by poor glycemic control.(29)

Given the increased risk of dementia among those free of CVD during follow-up, our results suggest that the association between MetS and dementia is not fully explained by CVD. The mechanisms linking MetS and dementia are likely to be due to multifactorial pathogenesis linked to its components and based on both vascular injury and neurodegeneration.(30) All MetS components may jointly contribute to dementia through the development of atherosclerotic lesions and/or microvascular dysfunction.(30; 31) Both elevated glucose and obesity have been associated with insulin resistance, as well as with low-grade systemic inflammation, which could increase the expression of pro-inflammatory cytokines, contributing to neurodegeneration, neurotoxicity leading to dementia (30; 32)

The strengths of this study include repeated, objective measures of MetS components from midlife to late-life, long follow-up duration for incident dementia, and linkage to multiple electronic health records for dementia ascertainment. A further strength was the use of inverse probability weighting to account for missing data.

This study also has several limitations. First, data come from the Whitehall II study, a longitudinal cohort study where participants are known to be healthier than the general population. While this setting precludes estimation of the incidence and prevalence of risk factors and disease outcomes, it is unlikely to affect associations between risk factors and disease of interest,(33) as has been previously using these data.(34) Second, data on dementia subtypes were incomplete and did not allow analyses of MetS and its components. Third, analyses on MetS components measured after 70 years and subsequent dementia were based on a relatively small number of events, which may have led

to an imprecise estimates. Fourth, we cannot exclude the possibility of residual confounding although the analyses were adjusted for a broad range of sociodemographic and behavioral covariates.

In conclusion, the present study suggests that MetS components when present before age 60 are associated with an increased risk of late-onset dementia. Our results also suggest that the conventional definition of MetS, requiring the prevalence of three or more components, is not optimal as risk for dementia is linear with risk accumulating over the entire scale of MetS components. Dementia is a public health problem with tremendous personal and societal implications; our results show the importance of targeting all metabolic risk factors rather than the presence of metabolic risk clusters.

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The authors report no conflicts of interest.

Author contributions

Conceptualization: MDM-F, SS, ASM.

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Investigation: MDM-F, AF, MSY, TvS, AT, MK, SS, ASM.

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Formal analysis: MDM-F, AF.

Access and verified the data: MDM-F, AF.

Data Curation: AF.

Writing –original draft preparation: MDM-F, ASM.

Writing –review and editing: MDM-F, AF, MSY, TvS, AT, MK, SS, ASM.

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Supervision: SS, ASM.

Funding acquisition: MK, ASM.

ASM is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY

Whitehall II data cannot be shared publicly because of constraints dictated by the study's ethics approval and IRB restrictions. The Whitehall II data are available for sharing within the scientific community. Researchers can apply for data access at https://www.ucl.ac.uk/epidemiology-health-care/research/epidemiology-and-public-health/research/whitehall-ii/data-sharing.

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Table 1. Association between individual metabolic syndrome components at <60, 60 to <70, and ≥70 years and incidence of dementia.

	Elevated WC		Elevated triglycerides		Low HDL-C		Elevated blood pressure		Elevated fasting glucose	
	No	Yes	No	Yes	No	Yes	**No**	Yes	No	Yes
At age <60 years*, Median (IQR) follow-up 20.8 (15.5, 26.2) years										
Dementia cases/total, N	322/5979	71/1286	270/5102	123/2163	306/5954	87/1311	184/4072	209/3193	293/5603	100/1662
Rate/1000 person-years	2.69	3.11	2.68	2.95	2.60	3.47	2.28	3.37	2.65	3.13
Cox regression, HR (95% CI)										
Model 1§	1 (Ref.)	1.45 (1.12, 1.89)	1 (Ref.)	1.10 (0.89, 1.36)	1 (Ref.)	1.33 (1.04, 1.68)	1 (Ref.)	1.36 (1.11, 1.66)	1 (Ref.)	1.18 (0.94, 1.49)
Model 2‖	1 (Ref.)	1.39 (1.07, 1.81)	1 (Ref.)	1.04 (0.84, 1.29)	1 (Ref.)	1.30 (1.02, 1.66)	1 (Ref.)	1.34 (1.09, 1.63)	1 (Ref.)	1.18 (0.94, 1.49)
At age 60 to <70 years†, Median (IQR) follow-up 10.4 (6.4, 15.6) years										
Dementia cases/total, N	318/4760	99/1900	269/4052	148/2608	295/4551	122/2109	172/2784	245/3876	298/4945	119/1715
Rate/1000 person-years	5.87	5.31	5.75	5.68	5.60	6.05	5.67	5.77	5.41	6.71
Cox regression, HR (95% CI)										
Model 1§	1 (Ref.)	1.06 (0.84, 1.33)	1 (Ref.)	1.20 (0.98, 1.47)	1 (Ref.)	1.32 (1.07, 1.64)	1 (Ref.)	0.99 (0.81, 1.20)	1 (Ref.)	1.41 (1.14, 1.76)
Model 2‖	1 (Ref.)	1.00 (0.79, 1.26)	1 (Ref.)	1.16 (0.95, 1.42)	1 (Ref.)	1.26 (1.02, 1.57)	1 (Ref.)	0.97 (0.80, 1.18)	1 (Ref.)	1.40 (1.12, 1.74)
At age ≥70 years‡, Median (IQR) follow-up 4.2 (3.1, 7.1) years										
Dementia cases/total, N	177/2327	87/1281	122/1685	142/1923	133/1798	131/1810	69/1006	195/2602	172/2631	92/977
Rate/1000 person-years	12.95	12.35	12.38	13.08	12.52	12.99	12.31	12.91	11.41	16.33
Cox regression, HR (95% CI)										
Model 1§	1 (Ref.)	1.01 (0.77, 1.32)	1 (Ref.)	1.08 (0.85, 1.38)	1 (Ref.)	1.08 (0.85, 1.38)	1 (Ref.)	0.99 (0.75, 1.31)	1 (Ref.)	1.39 (1.08, 1.80)
Model 2‖	1 (Ref.)	1.00 (0.76, 1.30)	1 (Ref.)	1.06 (0.83, 1.35)	1 (Ref.)	1.06 (0.83, 1.30)	1 (Ref.)	0.96 (0.73, 1.27)	1 (Ref.)	1.38 (1.07, 1.79)

IQR: interquartile range; WC: waist circumference; HDL-C: high density lipoprotein-cholesterol

* Mean (SD) age at assessment=55.1 (2.9) years

† Mean (SD) age at assessment=65.0 (1.5) years

‡ Mean (SD) age at assessment=73.9 (1.9) years

§ Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)

‖ Model 2: Model 1 plus adjustment for health behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

Table 2. Association between the number of MetS components at <60, 60 to <70, and ≥70 years and incidence of dementia.

Number of components	N Dementia cases/ Total	Rate of dementia/ 1000 person-years	HR (95% CI)		HR (95% CI) per component increment	
			Model 1[§]	Model 2[e]	Model 1[§]	Model 2[‖]
At age <60 years*, Median follow-up 20.8 (IQR 15.5, 26.2) years						
0	97/2325	2.08	1 (Ref.)	1 (Ref.)		
1	123/2145	2.85	1.28 (0.99, 1.68)	1.25 (0.96, 1.63)		
2	92/1493	3.21	1.57 (1.18, 2.09)	1.48 (1.11, 1.98)	1.15 (1.06, 1.24)	1.13 (1.05, 1.23)
3	47/823	2.98	1.38 (0.97, 1.96)	1.31 (0.92, 1.85)		
4	28/380	4.12	1.99 (1.30, 3.04)	1.92 (1.25, 2.93)		
5	6/99	3.48	1.90 (0.83, 4.35)	1.73 (0.76, 3.97)		
At age 60 to <70 years†, Median follow-up 10.4 (IQR 6.4, 15.6) years						
0	75/1409	4.65	1 (Ref.)	1 (Ref.)		
1	127/1753	6.20	1.30 (0.98, 1.73)	1.28 (0.96, 1.71)		
2	100/1387	6.31	1.42 (1.05, 1.92)	1.38 (1.02, 1.86)	1.10 (1.02, 1.18)	1.08 (1.00, 1.16)
3	68/1089	6.03	1.46 (1.05, 2.03)	1.39 (1.00, 1.94)		
4	33/696	5.20	1.51 (0.99, 2.29)	1.38 (0.91, 2.10)		
5	14/326	5.12	1.64 (0.92, 2.93)	1.54 (0.86, 2.76)		
At age ≥70 years‡, Median follow-up 4.2 (IQR 3.1, 7.1) years						
0	23/442	8.90	1 (Ref.)	1 (Ref.)		
1	57/729	13.26	1.50 (0.92, 2.42)	1.44 (0.88, 2.34)		
2	48/650	12.81	1.50 (0.91, 2.47)	1.45 (0.88, 2.39)	1.05 (0.97, 1.14)	1.04 (0.96, 1.13)
3	68/844	13.95	1.56 (0.97, 2.50)	1.49 (0.93, 2.40)		
4	50/683	13.45	1.57 (0.96, 2.59)	1.53 (0.93, 2.51)		
5	18/260	12.12	1.38 (0.75, 2.57)	1.27 (0.68, 2.37)		

IQR: interquartile range; * Mean (SD) age at assessment=55.1 (2.9) years

† Mean (SD) age at assessment=65.0 (1.5) years

‡ Mean (SD) age at assessment=73.9 (1.9) years

§ Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)

‖ Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

Table 3. Alternate cut-off points to define "high metabolic risk" at <60, 60 to <70, and ≥70 years and incidence of dementia.

Metabolic risk	N Dementia cases/Total	Rate of dementia/ 1000 person-years	HR (95% CI)	
			Model 1[§]	Model 2[‖]
High metabolic risk defined as presence of ≥1 MetS component				
At age <60 years[*]				
No risk	97/2325	2.08	Ref.	Ref.
High risk	296/4940	3.08	1.44 (1.14, 1.81)	1.38 (1.09, 1.74)
At age 60 to <70 years[†]				
No risk	75/1409	4.65	Ref.	Ref.
High risk	342/5251	6.03	1.39 (1.08, 1.79)	1.35 (1.05, 1.73)
At age ≥70 years[‡]				
No risk	23/442	8.90	Ref.	Ref.
High risk	241/3166	13.30	1.52 (0.99, 2.33)	1.46 (0.95, 2.24)
High metabolic risk defined as presence of ≥2 MetS components				
At age <60 years[*]				
No risk	220/4470	2.45	Ref.	Ref.
High risk	173/2795	3.27	1.37 (1.12, 1.68)	1.32 (1.08, 1.62)
At age 60 to <70 years[†]				
No risk	202/3162	5.52	Ref.	Ref.
High risk	215/3498	5.94	1.26 (1.03, 1.52)	1.19 (0.98, 1.46)
At age ≥70 years[‡]				
No risk	80/1171	11.62	Ref.	Ref.
High risk	184/2437	13.31	1.17 (0.90, 1.52)	1.15 (0.88, 1.49)
High metabolic risk defined as presence of ≥3 MetS components (current clinical MetS definition)				
At age <60 years[*]				
No risk (non-MetS)	312/5963	2.64	Ref.	Ref.
High risk (MetS)	81/1302	3.34	1.27 (0.99, 1.62)	1.23 (0.96, 1.57)
At age 60 to <70 years[†]				
No risk (non-MetS)	302/4549	5.76	Ref.	Ref.
High risk (MetS)	115/2111	5.65	1.20 (0.96, 1.49)	1.14 (0.91, 1.42)
At age ≥70 years[‡]				
No risk (non-MetS)	128/1821	12.04	Ref.	Ref.
High risk (MetS)	136/1787	13.49	1.12 (0.88, 1.43)	1.10 (0.86, 1.40)

MetS: Metabolic syndrome.

[*] Mean (SD) age at assessment=55.1 (2.9) years; median (IQR) follow-up 20.8 (15.5, 26.2) years

[†] Mean (SD) age at assessment=65.0 (1.5) years; median (IQR) follow-up 10.4 (6.4, 15.6) years

[‡] Mean (SD) age at assessment=73.9 (1.9) years) years; median (IQR) follow-up 4.2 (3.1, 7.1) years

[§] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)

[‖] Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

FIGURE LEGENDS

Figure 1

Role of "high metabolic risk" (defined as presence of ≥1, ≥2, or ≥3 MetS components) at age <60 years in the transition from: A) healthy state to incident cardiovascular disease (stroke, coronary heart disease or heart failure); B) cardiovascular disease (stroke, coronary heart disease or heart failure) to incident dementia; C) healthy state to incident dementia in those free of cardiovascular disease (stroke, coronary heart disease or heart failure) over the follow-up. Analyses with age as timescale and adjusted for sex, education, ethnicity, birth cohort (5-year groups), and health-related behaviors at age <60 years (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)