Full Title: Association of metabolic syndrome with neuroimaging and cognitive outcomes in the UK Biobank

Short Running Title: Metabolic syndrome, neuroimaging, and cognition

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Twitter Summary: In a study of >37,000 individuals, having metabolic syndrome was associated poorer brain health, characterised by lower brain volumes, greater vascular pathology, and poorer cognitive performance.

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STRUCTURED ABSTRACT

Objective: Metabolic syndrome (MetS) has been previously linked to dementia. This study examines the association of MetS with neuroimaging and cognition in dementia-free adults, offering insight into the impact of MetS on brain health prior to dementia onset.

Research Design and Methods: We included 37,395 dementia-free adults from the UK Biobank. MetS was defined as ≥3 of the following components: elevated waist-circumference, triglycerides, blood-pressure, HbA1c, or reduced HDL-cholesterol. Multivariable-adjusted linear regression was used to assess associations of MetS with structural neuroimaging and cognitive domains.

Results: MetS was associated with lower total brain (Standardised Beta-coefficient (β): -0.06, 95%CI: -0.08, -0.04), grey matter (β: -0.10, 95%CI: -0.12, -0.08) and hippocampal volumes (Left-β: -0.03, 95%CI: -0.05, -0.01; Right-β: -0.04, 95%CI: -0.07, -0.02), and greater white matter hyperintensities (WMH) volume (β: 0.08, 95%CI: 0.06, 0.11). MetS participants performed poorer on cognitive tests of working memory (β: -0.10, 95%CI: -0.13, -0.07), verbal-declarative memory (β: -0.08, 95%CI: -0.11, -0.05), processing speed (β: -0.06, 95%CI: -0.09, -0.04), verbal and numerical reasoning (β: -0.07, 95%CI: -0.09, -0.04), non-verbal reasoning (β: -0.03, 95%CI: -0.05, -0.01), and on executive function, where higher scores indicated poorer performance (β: 0.05, 95%CI: 0.03, 0.08). An increasing number of MetS components were also associated with lower brain volumes, greater WMH, and poorer cognition across all domains.

Conclusions: MetS was associated poorer brain health in dementia-free adults, characterised by lower brain volumes, greater vascular pathology, and poorer cognition. Further research is necessary to understand whether reversal or improvement of MetS can improve brain health.

ARTICLE HIGHLIGHTS

- *Why did we undertake this study?*

  MetS has been previously associated with dementia. We explored links between MetS and preclinical/intermediate markers of dementia by examining associations with structural neuroimaging and cognitive outcomes. This can offer insight into the impact of MetS on brain health prior to dementia onset.

- *What is the specific question(s) we wanted to answer?*

  Is MetS associated with poorer brain health outcomes prior to dementia onset?

- *What did we find?*

  MetS was associated with lower brain volumes, greater vascular pathology, and poorer cognition. An increasing number of MetS components were also associated with these outcomes.

- *What are the implications of our findings?*

  Early identification and management of MetS could help reduce dementia risk. This is especially promising as MetS is amenable to change through lifestyle modifications.

Metabolic syndrome (MetS) has become a serious public health concern, affecting approximately 25% of adults globally.(1) MetS is characterised by a cluster of cardiometabolic and vascular risk factors that tend to co-occur in individuals.(1) Generally, a MetS diagnosis is defined as the presence of ≥3 of the following traits: elevated waist circumference, triglycerides, blood glucose and blood pressure, or reduced high-density lipoprotein (HDL) cholesterol.(1) MetS has been identified as a potentially modifiable risk factor for cardiovascular and cerebrovascular disease(2), making it an important target for disease prevention strategies.

Global dementia incidence has also been rapidly increasing and is expected to triple in the next 30 years.(3) There is currently no definitive cure for dementia, warranting an urgent need to understand and identify which risk factors can be effectively targeted to help prevent or delay its progression. Recent research has linked MetS to an increased risk of dementia.(4; 5) Building on this work by exploring links between MetS and preclinical/intermediate markers of dementia, such as early changes in neuroimaging and cognition, can enhance our understanding of the relationship between MetS and dementia risk. Maintaining both brain structure and cognition – hereafter collectively referred to as brain health – are crucial for healthy aging as loss of both are key indicators of progression towards dementia.(6) Evaluating neuroimaging and cognitive measures can provide distinct insights regarding which aspects of brain health may be affected, such as atrophy, vascular pathology, and global or region-/domain-specific brain and cognitive changes. Different health conditions may influence these markers of brain health in distinct ways; some may exert a widespread effect, impacting multiple aspects of brain health, while others may exert a localised effect.(7) Traditional cardiometabolic and vascular risk factors – such as diabetes, obesity, hypertension, and hyperlipidaemia – have been individually associated with poorer brain

health.(8) However, it is well known that these risk factors are highly correlated with each other, often making it difficult to isolate their individual effects on overall brain health.(8) These relationships remain to be investigated in MetS, which is particularly pertinent, as the clustering of conditions inherent in MetS are more closely in line with real-world representations of known individual risk factors.

In a 2021 meta-analysis of twelve studies (sample sizes ranging: 50-7,000 participants), MetS was consistently associated with lower scores on global tests of cognition; however, its impact on individual cognitive domains was found to be mixed.(9) Moreover, while existing research has examined MetS in relation to either structural neuroimaging outcomes or cognition, few studies have examined this together(7-10), with most research focused on specific populations (e.g., MetS in schizophrenia).(11-13)

Given these knowledge gaps, we sought to investigate the association of MetS with several structural neuroimaging outcomes and cognitive domains in >37,000 participants from the UK Biobank. We also explored the impact of an increasing number of MetS components on these outcomes. To date, this is the largest and most comprehensive study of its kind which incorporates detailed phenotypic data and specific genotypic information on Apolipoprotein (*APOE*)-ε4 carrier status, enabling a robust assessment of these associations.

RESEARCH DESIGN AND METHODS

Data Source and Study Population

This study used data from the UK Biobank, a population-based prospective cohort of 0.5M participants aged 40-69 years recruited between 2006-2010 in England, Scotland and Wales.(14) At baseline (2006-2010), participants provided information on sociodemographic, lifestyle, environmental and health-related factors via touch-screen questionnaires and a nurse-led verbal interview, underwent physical examinations, and provided blood samples to measure key biomarkers. Since 2014, participants have been re-invited to attend a follow-up imaging assessment to undergo brain, cardiac, and abdominal magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry and carotid ultrasound. During the imaging assessment, participants also underwent detailed tests of various cognitive domains, and provided repeat measures of baseline assessments (with the exception of biomarker data). The imaging assessments were performed 9.27 ± 2.01 mean years after baseline. Using a standardised imaging protocol, participants were scanned across four imaging centres using Siemens Skyra 3T scanners (software VD13) with a standard 32-channel head coil.

At the time of data analysis (06/2023 to 02/2024), approximately 50,000 participants had undergone an imaging assessment. We excluded participants who were missing data on imaging-related confounders (n=22), and those with prevalent self-reported or diagnosed dementia, Parkinson's disease or any other chronic neurodegenerative condition (e.g., motor neuron disease), brain cancer, brain haemorrhage, brain abscess, aneurysm, cerebral palsy, encephalitis, head injury, nervous system infection, traumatic brain injury, or stroke (n=93). We further excluded those with ≥1 missing value on any of the five MetS components (n=8,888) for the main analyses, and imputed missing MetS components and covariates in sensitivity analyses. See **Supplemental File 1** for the study cohort flow diagram**.**

Ethics Approval

Participants provided electronically signed consent for their data to be used in health-related research. The UK Biobank received ethical approval from the National Health Service (NHS) North West Centre for Research Ethics Committee (Ref: 11/NW/0382).

Metabolic Syndrome

MetS was defined at baseline using the 2009 Harmonized Criteria.(1) The presence of ≥3 of the following components constituted a MetS diagnosis: 1) abdominal obesity (elevated waist circumference: ≥102 cm in males; ≥88 cm in females); 2) elevated triglycerides (≥150 mg/dL or 1.7 mmol/L) or lipid-modifying medications; 3) elevated blood pressure (≥130 mmHg systolic blood pressure and/or ≥85 mmHg diastolic blood pressure) or antihypertensive medication use; 4) elevated fasting blood glucose (≥100 mg/dL or ≥5.6 mmol/L) or drug treatment for elevated blood glucose; and 5) reduced HDL-cholesterol (<40 mg/dL or 1.0 mmol/L in males; <50 mg/dL or 1.3 mmol/L in females). Data on circulating glucose levels were obtained predominantly from non-fasting blood samples, which are more likely to be affected by recent food intake (as compared to fasting samples), potentially leading to high variability in glucose measurements. Therefore, we used glycated hemoglobin (HbA1c) as a proxy measure, based on recommendations from the American Diabetes Association, with a cut-point of HbA1c ≥5.7% (39 mmol/mol) to indicate hyperglycaemia.(15) Medication usage was captured using Anatomical Therapeutic Chemical (ATC) codes, informed by a thorough literature review of previous studies defining MetS using ATC codes, and expert clinical input.(5)

Participants were categorised into two groups: (1) No MetS (reference), and (2) MetS. **Supplemental Files 2-3** contain details regarding variables and medication codes used to define MetS components.

Neuroimaging Measures

Imaging Derived Phenotypes (IDPs) were derived from T1-/T2-weighted brain-MRI scans using an image-processing automated pipeline developed by an external group in collaboration with the UK Biobank.(16)

IDPs were selected based on their relevance to markers of brain health in the context of cognitive decline and/or dementia.(17) These included global grey matter, white matter, and total brain (sum of grey and white matter) volumes, which were segmented using FAST (FMRIB's Automated Segmentation Tool(18)); hippocampal volume (left, right) using FIRST (FMRIB's Integrated Registration and Segmentation Tool(19)), and white matter hyperintensity (WMH) volume from BIANCA(20), which uses both T1-weighted and T2-weighted data. In this study, white matter volume refers to the total volume of white matter in the brain. In contrast, white matter hyperintensities refer areas of white matter that appear hyperintense (i.e., brighter) on brain-MRI, which are often linked to aging, cognitive decline and dementia.(17) Outliers were defined as having a value >8 times the median absolute deviation from the median for any given IDP (N=1,008) and were removed as per previous methods.(16) Full details on the neuroimaging variables are in **Supplemental File 4**.

Cognitive Tests

We chose seven cognitive tests administered at the UK Biobank imaging assessment which assessed different cognitive domains.(21) These included: Trail-Making Tests (TMT) A and B (executive function), Fluid Intelligence Test (verbal and numerical reasoning), Backward Digit Span Task (working memory), Symbol-Digit Substitution Test (complex processing speed), Paired Associate Learning Task (verbal declarative memory), and the Matrix Pattern Completion Test (non-verbal reasoning). Higher scores indicate poorer

cognitive performance for TMT (i.e., time taken to complete test), whereas lower scores reflect poorer performance for all other tests. Individuals with TMT scores of ≤0 were removed from analyses. Detailed descriptions regarding the UK Biobank cognitive tests have been published elsewhere.(21) Full details regarding cognition variables in this study are in **Supplemental File 4**.

Covariates

Covariates included factors considered to be potential confounders in the relationship between the exposure (MetS) and outcomes (neuroimaging and cognition).(3; 9; 17; 22)

Age in years was calculated as the interval between date of birth and the date of attending an imaging assessment centre. Location of imaging assessment centre ('Cheadle', 'Reading', 'Newcastle', 'Bristol') was defined as attendance at the imaging site. The Townsend deprivation index was used as a proxy for socio-economic deprivation and was assigned to each study participant using their residential postal code at baseline, and was categorised into fifths (1-5: least deprived to most deprived).(23) Sex ('male', 'female') was defined using NHS records and/or self-reported data. Self-reported ethnicity ('white', 'non-white'), education level ('primary', 'secondary', 'post-secondary non-tertiary', 'tertiary'), household income in GBP (less than 18,000', '18,000-30,999', '31,000-51,999', '52,000-100,000', 'greater than 100,000'), smoking status ('never', 'previous', 'current'), and alcohol intake ('never', 'former drinker', 'infrequent' [special occasions only/1-3 times per month], '1-2 times per week', '3-4 times per week', 'daily or almost daily') were measured via touchscreen questionnaires. Physical activity level ('low' – metabolic equivalent (MET) minutes ≤1200, 'high' – MET >1200) was derived from touchscreen questionnaire items which were adapted to the validated short International Physical Activity Questionnaire (24);

time spent conducting vigorous, moderate, and walking activity was weighted by the amount of energy expended which allowed us to derive total MET minutes/week. *APOE*-ε4 carrier status ('ε4 non-carrier', 'ε4 carrier') was derived using rs429358 and rs7412 single nucleotide polymorphisms, which were directly genotyped.(25) Participants with any missing covariate data, or who responded with "prefer not to answer/do not know" were assigned as a separate category for each categorical variable.

We also incorporated several imaging-related confounders. These included: 1) head size (i.e., intracranial volume); 2) head position (using x-,y-, and z-axis position coordinates); and 3) head motion.(16)

Statistical Analysis

Descriptive statistics were used to compare baseline characteristics between participants with and without MetS; mean and standard deviation was calculated for normally distributed variables, and median and interquartile range for skewed variables. Skewness was assessed for outcomes by visually inspecting their distributions through histograms. Skewed variables (TMT A/B, WMH) were normalised using natural logarithm transformations.(21) All outcomes were then standardised (mean=0, standard deviation=1), to permit comparison of effect size across outcomes. Therefore, we report standardised beta-coefficients (β) and 95% confidence intervals throughout the results.

Separate multivariable linear regression models were used to estimate the association of MetS with neuroimaging and cognitive outcomes. Models were adjusted for age, sex, ethnicity, education, Townsend deprivation index, household income, smoking status, alcohol intake, physical activity level, and *APOE*-ε4 carrier status. To correct for interactions between age and sex, analyses were also adjusted for age^2 (non-linear effects), sex*age and

sex*age^2. As per previous recommendations, we included quadratic age terms in our models (age^2) to account for non-linear age effects across all outcomes.(26) This decision was further supported by ANOVA tests comparing models with and without the age^2 term, which demonstrated that its inclusion significantly improved model fit. Similarly, age-sex interaction terms were included to comprehensively account for their potential joint effects on brain health. Age and sex are known to interact in non-additively in the context of brain health outcomes, and thus the product of these two confounders must be considered.(26) For neuroimaging analyses only, we further adjusted for the following imaging-related confounders (i.e., precision variables): head size, head position, and head motion.(26)

In secondary analyses, we examined associations of 1) individual MetS components and 2) the categorical number of MetS components present (0-5), with each neuroimaging and cognitive outcome. In a sensitivity analysis, we repeated the main analysis using multiple imputation to investigate the impact of missing data for the exposure and covariates. We also examined the interaction between 1) MetS and age ("<65 years", "65+ years"), and 2) MetS and sex ("female", "male") due to prior evidence indicating differences in structural neuroimaging and cognition based on these factors.(17; 27-29)

All p-values were two sided, with statistical significance set at $p < 0.05$. All analyses were performed using RStudio version 4.2.2.

Data & Resource Availability Statement

The UK Biobank Resource (Application #: 33952) holds the data used in this article. Data can be requested by researchers at: www.ukbiobank.ac.uk/register-apply.

RESULTS

We identified 37,395 participants (mean age: 55.01 ± 7.55 years), among which 7,945 (21.2%) had MetS. The average time between baseline and follow-up imaging assessment was similar between participants with and without MetS (MetS: 9.21 ± 2.04 years; No MetS: 9.28 ± 2.0 years). Compared to no MetS, those with MetS were more likely to be older, male, of non-white ethnicity, have lower education, have lower household income, reside in more socioeconomically deprived areas, previous smokers, less physically active, and *APOE*-ε4 carriers (**Table 1**). Among those with MetS, 65.7%, 27.4%, and 6.9% had three, four, and five MetS components, respectively. Among MetS participants, the most prevalent component was elevated blood pressure (93.2%), followed by elevated triglycerides (83.7%), elevated waist circumference (72.0%), reduced HDL-cholesterol (54.6%), and elevated HbA1c (37.7%).

MetS and Neuroimaging Outcomes

Compared to no MetS, the presence of MetS was associated with lower total brain (β: -0.06, 95%CI: -0.08, -0.04) and grey matter volume (β: -0.10, 95%CI: -0.12, -0.08), as well as increased WMH volume (β: 0.08, 95%CI: 0.06, 0.11) **(Table 2)**. MetS was also associated with lower left (β: -0.03, 95%CI: -0.05, -0.01) and right hippocampal volumes (β: -0.04, 95%CI: -0.07, -0.02). No significant association was observed between MetS and white matter volume. Results remained similar after performing multiple imputation for missing exposure and covariate data **(Supplemental File 5)**.

A dose-response relationship was observed between the number of MetS components present and several neuroimaging measures **(Figure 1, Supplemental File 6)**. Specifically, an increasing number of MetS components were associated with lower total brain (β range: -0.02 to -0.21, *p-trend<0.001*) and grey matter volume (β range: -0.03 to -0.31, *p-trend<0.001*), and greater WMH volume (β range: 0.13 to 0.30, *p-trend <0.001*). An increasing number of MetS components also showed a dose-response association with lower left (β range: 0.00 to -0.11, *p-trend=0.003*) and right hippocampal volume (β range: 0.00 to -0.09, *p-trend=0.002*). No association was observed with white matter volume.

In analysis of individual components, elevated waist circumference and HbA1c were significantly associated with lower total brain and grey matter volumes, while having elevated blood pressure showed the strongest association with greater WMH volume **(Supplemental File 7)**.

Associations between MetS and neuroimaging outcomes were consistent amongst younger (<65) and older (65+) participants. However, there was a significant interaction (*p<0.001*) of age with MetS and WMH volume, with the strength of the association being greater among younger participants (<65: β: 0.09, 95%CI: 0.07, 0.11 vs. 65+: β: 0.04, 95%CI: -0.02, 0.11) **(Supplemental File 8)**. Moreover, there was a significant interaction of sex with MetS and total brain, grey matter and white matter volumes (*p<0.001*), with the strength of these associations being greater in males. Associations among other neuroimaging outcomes remained similar **(Supplemental File 9)**.

MetS and Cognitive Outcomes

MetS participants performed significantly poorer on tests measuring several different cognitive domains, including working memory (β: -0.10, 95%CI: -0.13, -0.07), verbal declarative memory (β: -0.08, 95%CI: -0.11, -0.05), processing speed (β: -0.06, 95%CI: -0.09, -0.04), verbal and numerical reasoning (β: -0.07, 95%CI: -0.09, -0.04), non-verbal reasoning (β: -0.03, 95%CI: -0.05, -0.01), and executive function (TMT B - β: 0.05, 95%CI: 0.03, 0.08; TMT A - β: 0.03, 95%CI: 0.01, 0.06) **(Table 2)**. Results remained similar after performing multiple imputation for missing exposure and covariate data **(Supplemental File 5)**.

We also observed a dose-response relationship between the number of MetS components present and cognitive performance across several domains **(Figure 2, Supplemental File 10)**. An increasing number of MetS components were associated with poorer cognitive performance on tests of working memory (β range: -0.05 to -0.27, *p-trend<0.001*), verbal declarative memory (β range: -0.05 to -0.22, *p-trend<0.001*), processing speed (β range: -0.02 to -0.15, *p-trend<0.001*), executive function (TMT A or TMT B - β range: 0.01 to 0.16, *p-trend<0.001*), and verbal and numerical reasoning (β range: -0.04 to -0.13, *p-trend<0.001*). Increasingly poorer performance was also noted for non-verbal reasoning, although less pronounced (β range: -0.03 to -0.13, *p-trend=0.016*).

Regarding individual components, elevated blood pressure was consistently associated with significantly poorer performance across all cognitive domains **(Supplemental File 7)**.

Associations of MetS with poor cognitive performance were generally consistent amongst younger (<65) and older (65+) participants. However, no significant interaction of

age with MetS and cognition was observed for any of the cognitive domains. **(Supplemental File 11)**. In contrast, there was a significant interaction of sex with MetS and verbal and numerical reasoning (*p=0.023*), where the strength of the association was greater among males. Associations among other cognitive outcomes remained similar when comparing by sex **(Supplemental File 12)**.

CONCLUSIONS

In this large population-based cohort of more than 37,000 mid-to-late-life dementia-free adults, MetS was associated with lower brain volumes, greater vascular pathology, and poorer cognition. There was a dose-response relationship between an increasing number of MetS components and lower brain volume, vascular pathology and poorer cognition. These findings suggest that MetS is associated with poorer global brain health rather than having region- or domain-specific effects, which might have implications for understanding previously observed relationships between MetS and dementia.

Several studies have previously associated MetS with several brain abnormalities, including lower total brain volume, silent brain infarcts, decreased grey matter volume in specific brain regions, and increased WMHs.(7; 8) However, other research studies have shown inconsistent findings. Cavalieri et al., found no significant differences in total brain volume between those with and without MetS in 819 dementia-free participants.(27) Additionally, Sala et al., found no association between MetS and grey and white matter volumes among elderly participants from families with a history of longevity.(30) Another study by Tiehuis et al., found that MetS was associated with smaller brain volumes but not increased WMHs in 1,232 patients with manifest arterial disease.(13) Similarly, evidence

regarding MetS and cognitive performance has been equally varied. While previous studies have been relatively consistent in demonstrating an association between MetS and impaired global cognition scores, its impact on individual cognitive domains remains largely inconsistent.(10) Inconsistencies could be due to several methodological issues including: 1) most studies comprise of relatively small samples; 2) most studies focus on specific disease populations (e.g., MetS in those with mental disorders), limiting generalisability; 3) exposure misclassification resulting from heterogeneity in components and cut-offs used to define MetS; 4) the vast number of cognitive tests used to assess the same cognitive domain, with each having different sensitivity which could affect the ability to detect minor cognitive deficits; 5) large variation in sample characteristics (i.e., age, sex, education), and covariate adjustment. Findings from our study contribute to this existing body of research by providing a more robust and comprehensive evaluation of the influence of MetS on various neuroimaging and cognitive measures in a large sample.

In our study, MetS was associated with several neuroimaging and cognitive indicators of poor brain health. Specifically, we found that MetS was linked to lower total brain and grey matter volumes, including hippocampal volume, as well as increased WMHs, which were paralleled by cognitive deficits across several domains including memory, reasoning, processing speed and executive function. Collectively, these findings suggest that rather than having a localised effect, MetS appears to have a more widespread effect on brain health. These findings align with and build upon our previous study from the UK Biobank as well as other dementia research studies from Europe and Asia, which demonstrate consistent associations of MetS with increased dementia risk, irrespective of the dementia subtype.(5; 31-34)

We also found that an increasing number MetS components were associated with greater reductions across several measures of brain volume and poorer performance on various cognitive domains. While several studies have reported similar findings in relation to the number of MetS components and cognitive outcomes(9; 10), few comparable studies have explored these relationships with structural neuroimaging outcomes, yielding inconsistent findings.(30; 35; 36) Our study also provides a detailed evaluation of various cognitive domains in relation to the number of MetS components present, showing that the presence of a greater number of components incrementally increases cognitive deficits in areas of memory, processing, and executive function. Taken together, these results indicate that the impact of MetS on brain health is characterised by a dose-response relationship. Therefore, considering the overall number of MetS components present, rather than focusing solely on its threshold effect (i.e., presence of ≥3 components) may prove useful for devising prevention strategies to mitigate cognitive decline and dementia.

Interventional studies show promising results in managing MetS components to improve brain health. The SPRINT-MIND trial demonstrated that aggressive blood pressure control reduced WMH progression.(37; 38) The Sydney Memory and Aging Study observed that diabetics on metformin experienced less cognitive decline and dementia versus those not treated.(38) Moreover, physical activity was shown to improve cognition in diabetics.(37) The ACCORDION-MIND trial noted short-term increases in brain volume from intensive hyperglycaemia management, though benefits did not persist in the long-term.(37) Conversely, trials targeting hypercholesterolemia did not show benefits for brain health.(37) Perhaps the most promising findings come from the FINGER trial – a multidomain intervention involving a diet, exercise, cognitive training, and vascular risk monitoring program in older adults with high rates of MetS-related components.(37; 38) Results from

FINGER indicated that the intervention group exhibited significantly less cognitive decline than controls (although no significant changes in brain volume or WMHs).(37; 38) Further large-scale intervention studies with longer follow-up are necessary to understand how reversal of MetS as a whole, or its components, might impact overall brain health and dementia risk.

Key strengths of this study include a comprehensive evaluation of the relationship of MetS with several neuroimaging measures and validated domain-specific cognitive outcomes.(21) This is also the largest study of its kind, incorporating extensive phenotypic data and specific genotypic information on *APOE*-ε4 carrier status, allowing for a robust assessment of these associations. The present study also has several limitations. First, MetS was defined using baseline measurements (due to lack of biomarker data at the follow-up assessment) with neuroimaging and cognitive outcomes assessed several years later, limiting our ability to account for variability in MetS status over time. However, the validity of incorporating baseline biomarker data is supported by previous work demonstrating their high stability over time.(39) Second, we used HbA1c as a proxy for fasting glucose (given the low number of fasting samples), which varies from the Harmonized Criteria for MetS. However, previous recommendations from the American Diabetes Association support use of this measure as a suitable proxy for glucose.(15) Third, our study was limited by lack of information on the severity and duration of MetS and its individual components. Fourth, while we excluded prevalent dementia, some cases may have gone undetected; this could introduce selection bias, particularly if the prevalence of undetected cases varies between those with and without MetS. Fifth, the design of this work makes our findings susceptible to residual confounding from unmeasured factors which is an inherent limitation of all observational studies. Moreover, we did not adjust for multiple comparisons, increasing the

potential for Type-I error. Additionally, UK Biobank participants are known to be healthier than the general population, especially among those who attended the follow-up imaging assessment (i.e., healthy-volunteer bias). Thus, it is possible that our findings may underestimate the true magnitude of the association between MetS and brain health.(40) Moreover, findings from the UK Biobank may not be broadly generalizable. Finally, due to the nature of data availability, we were unable to assess how MetS influences changes in neuroimaging and cognition over time.

In conclusion, we found that MetS, a cluster of risk factors associated with cognitive decline and dementia, was linked to significantly lower brain volumes and greater vascular pathology, which were paralleled by impaired performance across a range of cognitive domains. These findings demonstrate that MetS is related to poorer global brain health, aligning with previously observed associations between MetS and increased risk of several dementia subtypes.(5; 31-34) Further research is necessary to understand whether reversal or improvement of MetS (and its components) can improve brain health and reduce risk for dementia.

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REFERENCES

1. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart J-C, James WPT, Loria CM, Smith Jr SC. 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;120:1640-1645
2. Rodriguez-Colon SM, Mo J, Duan Y, Liu J, Caulfield JE, Jin X, Liao D. Metabolic syndrome clusters and the risk of incident stroke: the atherosclerosis risk in communities (ARIC) study. Stroke 2009;40:200-205
3. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. The Lancet 2020;396:413-446
4. Atti AR, Valente S, Iodice A, Caramella I, Ferrari B, Albert U, Mandelli L, De Ronchi D. Metabolic syndrome, mild cognitive impairment, and dementia: a meta-analysis of longitudinal studies. The American Journal of Geriatric Psychiatry 2019;27:625-637
5. Qureshi D, Collister J, Allen NE, Kuźma E, Littlejohns T. Association between metabolic syndrome and risk of incident dementia in UK Biobank. Alzheimer's & Dementia 2023;
6. Ávila-Villanueva M, Marcos Dolado A, Gómez-Ramírez J, Fernández-Blázquez M. Brain structural and functional changes in cognitive impairment due to Alzheimer's disease. Frontiers in psychology 2022;13:886619
7. Vergoossen LW, Jansen JF, Backes WH, Schram MT. Cardiometabolic determinants of early and advanced brain alterations: Insights from conventional and novel MRI techniques. Neuroscience & Biobehavioral Reviews 2020;115:308-320
8. Friedman JI, Tang CY, de Haas HJ, Changchien L, Goliasch G, Dabas P, Wang V, Fayad ZA, Fuster V, Narula J. Brain imaging changes associated with risk factors for cardiovascular

and cerebrovascular disease in asymptomatic patients. JACC: cardiovascular imaging 2014;7:1039-1053
9. González-Castañeda H, Pineda-García G, Serrano-Medina A, Martínez AL, Bonilla J, Ochoa-Ruíz E. Neuropsychology of metabolic syndrome: A systematic review and meta-analysis. Cogent Psychology 2021;8:1913878
10. Alcorn T, Hart E, Smith AE, Feuerriegel D, Stephan BC, Siervo M, Keage HA. Cross-sectional associations between metabolic syndrome and performance across cognitive domains: A systematic review. Applied Neuropsychology: Adult 2019;26:186-199
11. Bora E, Akdede B, Alptekin K. The relationship between cognitive impairment in schizophrenia and metabolic syndrome: a systematic review and meta-analysis. Psychological medicine 2017;47:1030-1040
12. Bora E, McIntyre RS, Ozerdem A. Neurococognitive and neuroimaging correlates of obesity and components of metabolic syndrome in bipolar disorder: a systematic review. Psychological medicine 2019;49:738-749
13. Tiehuis AM, Van Der Graaf Y, Mali WP, Vincken K, Muller M, Geerlings MI. Metabolic syndrome, prediabetes, and brain abnormalities on mri in patients with manifest arterial disease: the SMART-MR study. Diabetes care 2014;37:2515-2521
14. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS medicine 2015;12:e1001779
15. Association AD. Standards of medical care in diabetes—2010. Diabetes care 2010;33:S11-S61
16. Alfaro-Almagro F, Jenkinson M, Bangerter NK, Andersson JL, Griffanti L, Douaud G, Sotiropoulos SN, Jbabdi S, Hernandez-Fernandez M, Vallee E. Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. Neuroimage 2018;166:400-424
17. Yates KF, Sweat V, Yau PL, Turchiano MM, Convit A. Impact of metabolic syndrome on cognition and brain: a selected review of the literature. Arteriosclerosis, thrombosis, and vascular biology 2012;32:2060-2067
18. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE transactions on medical imaging 2001;20:45-57
19. Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage 2011;56:907-922
20. Griffanti L, Zamboni G, Khan A, Li L, Bonifacio G, Sundaresan V, Schulz UG, Kuker W, Battaglini M, Rothwell PM. BIANCA (Brain Intensity AbNormality Classification Algorithm): A new tool for automated segmentation of white matter hyperintensities. Neuroimage 2016;141:191-205
21. Fawns-Ritchie C, Deary IJ. Reliability and validity of the UK Biobank cognitive tests. PloS one 2020;15:e0231627
22. Koutsonida M, Markozannes G, Bouras E, Aretouli E, Tsilidis KK. Metabolic syndrome and cognition: A systematic review across cognitive domains and a bibliometric analysis. Frontiers in Psychology 2022;13:981379
23. Townsend P, Phillimore P, Beattie A. *Health and deprivation: inequality and the North*. Routledge, 1988
24. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF. International physical activity questionnaire: 12-country reliability and validity. Medicine and science in sports and exercise 2003;35:1381-1395

25. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D, Delaneau O, O'Connell J. The UK Biobank resource with deep phenotyping and genomic data. Nature 2018;562:203-209
26. Alfaro-Almagro F, McCarthy P, Afyouni S, Andersson JL, Bastiani M, Miller KL, Nichols TE, Smith SM. Confound modelling in UK Biobank brain imaging. NeuroImage 2021;224:117002
27. Cavalieri M, Ropele S, Petrovic K, Pluta-Fuerst A, Homayoon N, Enzinger C, Grazer A, Katschnig P, Schwingenschuh P, Berghold A. Metabolic syndrome, brain magnetic resonance imaging, and cognition. Diabetes care 2010;33:2489-2495
28. Kotkowski E, Price LR, DeFronzo RA, Franklin CG, Salazar M, Garrett AS, Woolsey M, Blangero J, Duggirala R, Glahn DC. Metabolic syndrome predictors of brain gray matter volume in an age-stratified community sample of 776 Mexican-American adults: Results from the genetics of brain structure image archive. Frontiers in Aging Neuroscience 2022;14:999288
29. Laudisio A, Marzetti E, Pagano F, Cocchi A, Franceschi C, Bernabei R, Zuccalà G. Association of metabolic syndrome with cognitive function: the role of sex and age. Clinical Nutrition 2008;27:747-754
30. Sala M, de Roos A, van den Berg A, Altmann-Schneider I, Slagboom PE, Westendorp RG, van Buchem MA, de Craen AJ, van der Grond J. Microstructural brain tissue damage in metabolic syndrome. Diabetes care 2014;37:493-500
31. Fan YC, Chou CC, You SL, Sun CA, Chen CJ, Bai CH. Impact of worsened metabolic syndrome on the risk of dementia: a nationwide cohort study. Journal of the American Heart Association 2017;6:e004749
32. Lee JE, Shin DW, Han K, Kim D, Yoo JE, Lee J, Kim S, Son KY, Cho B, Kim MJ. Changes in metabolic syndrome status and risk of dementia. Journal of Clinical Medicine 2020;9:122
33. Raffaitin C, Gin H, Empana J-P, Helmer C, Berr C, Tzourio C, Portet F, Dartigues J-F, Alpérovitch A, Barberger-Gateau P. Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia: the Three-City Study. Diabetes care 2009;32:169-174
34. Solfrizzi V, Scafato E, Capurso C, D'Introno A, Colacicco AM, Frisardi V, Vendemiale G, Baldereschi M, Crepaldi G, Di Carlo A. Metabolic syndrome and the risk of vascular dementia: the Italian Longitudinal Study on Ageing. Journal of Neurology, Neurosurgery & Psychiatry 2010;81:433-440
35. Alkan E, Taporoski T, Sterr A, von Schantz M, Vallada H, Krieger J, Pereira A, Alvim R, Horimoto A, Pompéia S. Metabolic syndrome alters relationships between cardiometabolic variables, cognition and white matter hyperintensity load. Scientific reports 2019;9:4356
36. Choi HS, Cho YM, Kang JH, Shin CS, Park KS, Lee HK. Cerebral white matter hyperintensity is mainly associated with hypertension among the components of metabolic syndrome in Koreans. Clinical endocrinology 2009;71:184-188
37. Kivipelto M, Palmer K, Hoang TD, Yaffe K. Trials and treatments for vascular brain health: risk factor modification and cognitive outcomes. Stroke 2022;53:444-456
38. Gottesman RF, Seshadri S. Risk factors, lifestyle behaviors, and vascular brain health. Stroke 2022;
39. Allen NE, Arnold M, Parish S, Hill M, Sheard S, Callen H, Fry D, Moffat S, Gordon M, Welsh S. Approaches to minimising the epidemiological impact of sources of systematic and random variation that may affect biochemistry assay data in UK Biobank. Wellcome Open Research 2020;5
40. Lyall DM, Quinn T, Lyall LM, Ward J, Anderson JJ, Smith DJ, Stewart W, Strawbridge RJ, Bailey ME, Cullen B. Quantifying bias in psychological and physical health in the UK Biobank imaging sub-sample. Brain communications 2022;4:fcac119

Table 1: Study Cohort Characteristics by MetS Status

Characteristic	No MetS (N= 29,450)	MetS (N= 7,945)	Overall (N= 37,395)
Age – mean (SD)	54.60 (7.58)	56.53 (7.22)	55.01 (7.55)
Sex			
Female	16,010 (54%)	3,555 (45%)	19,565 (52%)
Male	13,440 (46%)	4,390 (55%)	17,830 (48%)
Ethnicity			
White	28,557 (97%)	7,655 (96%)	36,212 (97%)
Non-White	809 (2.7%)	266 (3.3%)	1,075 (2.9%)
Missing*	84 (0.3%)	24 (0.3%)	108 (0.3%)
Education level			
Primary	1,722 (5.8%)	700 (8.8%)	2,422 (6.5%)
Secondary	5,495 (19%)	1,648 (21%)	7,143 (19%)
Post-secondary non-tertiary	3,659 (12%)	1,063 (13%)	4,722 (13%)
Tertiary	18,489 (63%)	4,502 (57%)	22,991 (62%)
Missing*	85 (0.3%)	32 (0.4%)	117 (0.3%)
Townsend deprivation index			
1 (less deprived)	6,032 (20%)	1,441 (18%)	7,473 (20%)
2	5,979 (20%)	1,493 (19%)	7,472 (20%)
3	5,890 (20%)	1,582 (20%)	7,472 (20%)
4	5,814 (20%)	1,658 (21%)	7,472 (20%)
5 (more deprived)	5,709 (19%)	1,763 (22%)	7,472 (20%)
Missing	26 (<0.1%)	8 (0.1%)	34 (<0.1%)
Household income (GBP)			
Less than 18,000	2,918 (9.9%)	1,089 (14%)	4,007 (11%)
18,000 to 30,999	5,703 (19%)	1,816 (23%)	7,519 (20%)
31,000 to 51,999	8,069 (27%)	2,231 (28%)	10,300 (28%)
52,000 to 100,000	7,945 (27%)	1,759 (22%)	9,704 (26%)
Greater than 100,000	2,316 (7.9%)	365 (4.6%)	2,681 (7.2%)
Missing*	2,499 (8.5%)	685 (8.6%)	3,184 (8.6%)
Alcohol intake			
Never	856 (2.9%)	349 (4.4%)	1,205 (3.2%)
Former	876 (3.0%)	374 (4.7%)	1,250 (3.3%)
Infrequent[†]	5,883 (20%)	2,325 (29%)	8,208 (22%)
1-2 times per week	7,779 (26%)	2,037 (26%)	9,816 (26%)
3-4 times per week	8,665 (29%)	1,772 (22%)	10,437 (28%)
Daily or almost daily	5,180 (18%)	1,024 (13%)	6,204 (17%)
Missing*	211 (0.7%)	64 (0.8%)	275 (0.7%)
Smoking status			
Never	18,324 (62%)	4,389 (55%)	22,713 (61%)
Previous	9,362 (32%)	2,918 (37%)	12,280 (33%)
Current	1,706 (5.8%)	617 (7.8%)	2,323 (6.2%)
Missing*	58 (0.2%)	21 (0.3%)	79 (0.2%)
Physical activity level			
Low (MET minutes ≤ 1200)	8,617 (29%)	2,883 (36%)	11,500 (31%)
High (MET minutes > 1200)	16,428 (56%)	3,688 (46%)	20,116 (54%)
Missing	4,405 (15%)	1,374 (17%)	5,779 (15%)
***APOE*-ε4 carrier status**			
Non-carrier	21,185 (72%)	5,631 (71%)	26,816 (72%)
ε4 carrier	7,398 (25%)	2,045 (26%)	9,443 (25%)
Missing	867 (2.9%)	269 (3.4%)	1,136 (3.0%)
Elevated waist circumference	3,552 (12%)	5,721 (72%)	9,273 (25%)
Elevated triglycerides[‡]	6,712 (23%)	6,651 (84%)	13,363 (36%)
Elevated blood pressure[‡]	16,736 (57%)	7,410 (93%)	24,146 (65%)
Elevated HbA1c[‡]	1,666 (5.7%)	2,992 (38%)	4,658 (12%)
Reduced HDL-cholesterol	2,397 (8.1%)	4,336 (55%)	6,733 (18%)

Abbreviations: APOE, apolipoprotein E; GBP, British pound sterling; MET, metabolic equivalent of task; SD, standard deviation. HbA1c = hemoglobin A1c, HDL = high density lipoprotein.

Note: Percentages do not add up to 100 due to rounding.

***Includes 'Prefer not to answer' and/or 'Do not know'.**

† **Special occasions only or 1-3 times per month.**
‡ **Includes medication use.**

Table 2: Multivariable linear regression analyses examining association between the presence of MetS and A) standardised neuroimaging measures and B) standardised cognitive test scores

	Standardised Beta	95% CI	*P*
A) Neuroimaging Measures*			
Total Brain Volume	-0.06	-0.08, -0.04	<**0.001**
Grey Matter Volume	-0.10	-0.12, -0.08	<**0.001**
White Matter Volume	0.01	-0.01, 0.04	0.2
Left Hippocampal Volume	-0.03	-0.05, -0.01	**0.009**
Right Hippocampal Volume	-0.04	-0.07, -0.02	<**0.001**
WMH Volume	0.08	0.06, 0.11	<**0.001**
B) Cognitive Test Measures			
Executive Function (TMT A)	0.03	0.01, 0.06	**0.029**
Executive Function (TMT B)	0.05	0.03, 0.08	<**0.001**
Verbal & Numerical Reasoning (FI)	-0.07	-0.09, -0.04	<**0.001**
Working Memory (BDS)	-0.10	-0.13, -0.07	<**0.001**
Processing Speed (SDS)	-0.06	-0.09, -0.04	<**0.001**
Verbal Declarative Memory (PAL)	-0.08	-0.11, -0.05	<**0.001**
Non-Verbal Reasoning (MPC)	-0.03	-0.05, -0.01	**0.032**

Abbreviations: CI, Confidence Interval; WMH, White Matter Hyperintensity; TMT, Trail Making Test; FI, Fluid Intelligence Score; BDS, Backward Digit Span Task; SDS, Symbol Digit Substitution Task; PAL, Paired Associate Learning Task; MPC, Matrix Pattern Completion Test.

All models adjusted for: age, sex, age^2, age*sex, age^2*sex, ethnicity, education level, Townsend deprivation index, household income, alcohol intake, smoking status, physical activity level, and APOE-ε4 carrier status, assessment centre, time between baseline and follow-up imaging assessment.

*Neuroimaging models (only) were further adjusted for imaging-related confounders: head size, head position, head motion.

WMH, TMT A, and TMT B were log-transformed. All outcomes were standardised (mean = 0, standard deviation = 1, to permit comparison of effect size across outcomes. Higher scores indicate poorer cognitive performance for TMT (as it measures time taken to complete the test), whereas lower scores reflect poorer performance for all other tests.

FIGURE LEGENDS

Figure 1: Multivariable linear regression analyses examining the association between the number of MetS components and standardised neuroimaging measures

- Abbreviations: MetS, Metabolic Syndrome; WMH, White Matter Hyperintensity
- Models adjusted for: age, sex, age^2, age*sex, age^2*sex, ethnicity, education level, Townsend deprivation index, household income, alcohol intake, smoking status, physical activity level, and *APOE*-ε4 carrier status, assessment centre, time between baseline and follow-up imaging assessment, head size, head size, head position, head motion.
- WMH was log-transformed. All outcomes were standardised (mean = 0, standard deviation = 1), to permit comparison of effect size across outcomes.
- Red denotes unfavourable direction (i.e., potential challenge or risk to brain health). Blue denotes favourable direction (i.e., potential neutral or protective effect on brain health).

Figure 2: Multivariable linear regression analyses examining the association between the number of MetS components and standardised cognitive test scores

- Abbreviations: MetS, Metabolic Syndrome; TMT, Trail Making Test; FI, Fluid Intelligence Score; BDS, Backward Digit Span Task; SDS, Symbol Digit Substitution Task; PAL, Paired Associate Learning Task; MPC, Matrix Pattern Completion Test
- Models adjusted for: age, sex, age^2, age*sex, age^2*sex, ethnicity, education level, Townsend deprivation index, household income, alcohol intake, smoking status, physical activity level, and *APOE*-ε4 carrier status, assessment centre, time between baseline and follow-up imaging assessment.
- TMT A and B were log-transformed. All outcomes were standardised (mean = 0, standard deviation = 1), to permit comparison of effect size across outcomes.
- Red denotes poor performance (i.e., potentially indicative of challenges in cognitive function). Blue denotes good performance.