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ORIGINAL ARTICLE

WILEY

Interactions between age, sex and visceral adipose tissue on brain ageing

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Abstract

Aim: To examine the associations between visceral adipose tissue (VAT) and brain structural measures at midlife and explore how these associations may be affected by age, sex and cardiometabolic factors.

Methods: We used abdominal and brain magnetic resonance imaging data from a population-based cohort of people at midlife in the UK Biobank. Regression modelling was applied to study associations of VAT volume with total brain volume (TBV), grey matter volume (GMV), white matter volume, white matter hyperintensity volume (WMHV) and total hippocampal volume (THV), and whether these associations were altered by age, sex or cardiometabolic factors.

Results: Complete data were available for 17 377 participants (mean age 63 years, standard deviation = 12, 53% female). Greater VAT was associated with lower TBV, GMV and THV ($P < .001$). We found an interaction between VAT and sex on TBV ($P < .001$), such that the negative association of VAT with TBV was greater in men ($\beta = -2.89$, 95% confidence interval [CI] −2.32 to −10.15) than in women ($\beta = -1.32$, 95% CI −0.49 to −3.14), with similar findings for GMV. We also found an interaction between VAT and age (but not sex) on WMHV ($P < .001$). The addition of other cardiometabolic factors or measures of physical activity resulted in little change to the models.

Conclusions: VAT volume is associated with poorer brain health in midlife and this relationship is greatest in men and those at younger ages.

KEYWORDS
weight control, body composition, cohort study, database research, elderly

1 | INTRODUCTION

Obesity at midlife is a risk factor for future dementia.[1–7] It is possible that obesity acts through the promotion of chronic low-grade inflammation[8,9] and cardiovascular risk[10,11] by metabolically active fat such as visceral adipose tissue (VAT). VAT consists of intra-abdominal white adipose tissue located in the mesentery, omentum and retroperitoneum, and plays an important role in energy homeostasis.[9,12–14]

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Greater VAT is associated with poorer cardiometabolic health[10,11] and brain structure,[15–17] and has been causally implicated with lower grey matter volume (GMV),[18] a biomarker of dementia risk.[17] With increasing age, sex differences have been described in the distribution of VAT, as well as for cardiovascular disease and brain structure. Recent work, using data from healthy North Americans aged 18-90 years, has reported some sex differences in the association between visceral fat and brain volume.[19] However, the interplay between VAT, age, sex and cardiovascular factors in explaining the brain structural changes that occur with ageing have not been studied in detail. Examining the associations between VAT and measures of brain health, while accounting for the modifying or mediating effects of age, sex and cardiometabolic factors, is therefore likely to provide solid ground for understanding mechanistic pathways between obesity and the risk of dementia and identifying potentially important target groups for future preventative efforts.

There are challenges in measuring VAT, and to date, different measurement techniques have been attempted, including simple anthropometry (waist circumference),[20–22] computed tomography (CT)[10,23] and bioimpedance.[15,24] Anthropometric and bioimpedance approaches are limited by their ability to accurately measure the volume or location of VAT[25,26] and ionizing radiation (CT) is unsuitable for widespread adoption.[24] On the other hand, abdominal magnetic resonance imaging (MRI), although less widely available, provides excellent characterization of visceral adiposity[24] and is safer to use at a population level than CT. The UK Biobank has collected contemporaneous MRI measures of VAT and brain structure in a large population-based sample of adults at midlife, making the study of VAT and brain health possible on a large scale. We therefore took advantage of these data in the UK Biobank to (i) examine the associations between VAT and brain structure at midlife; and (ii) explore how these associations may be altered by age, sex and cardiometabolic factors.

2 | MATERIALS AND METHODS

2.1 | Study participants and data

The UK Biobank (www.ukbiobank.ac.uk) is an open access resource with data from a population cohort of 500 000 UK volunteers registered with the National Health Service, aged 40-69 years, from across 22 assessment centres in the UK. Data were collected over 5 years from 2006, via computer-based questionnaires and assessments, in-person interviews, biological/genetic sampling and physical measurements. Details of participant recruitment, assessment protocols and other study procedures are available at https://www.ukbiobank.ac.uk/. From 2014, 100 000 participants of the original cohort were invited to undergo imaging assessments, including abdominal and brain MRI. Only participants with abdominal and brain MRI were included in this study.

2.2 | Covariables

Age and physical measurement data recorded at the time of MRI attendance were used. Covariables such as ethnicity, educational qualification, smoking and alcohol use were based on participant self-report. Socioeconomic status was based on the Townsend Deprivation Index. Cardiometabolic factors were collected from baseline and at imaging assessments using a combination of self-reported diagnosis, medication use and International Classification of Diseases (ICD)-10 codes. Diabetes was identified from a self-reported diagnosis, use of insulin or other medication for diabetes and/or an ICD-10 code for diabetes. Hypertension was identified from a self-reported diagnosis, medication for hypertension and/or an ICD-10 code for hypertension. Ischaemic heart disease (IHD) and stroke were identified from a self-reported diagnosis and/or an ICD-10 code for IHD and stroke, respectively. Dyslipidaemia was identified from medications for dyslipidaemia and/or an ICD-10 code for dyslipidaemia. Apolipoprotein E ε4 carrier (APOE4) status, a risk factor for dementia, was identified from genotyping of participants through a UK BiLEVE array or UK Biobank Axiom array. Physical activity (overall average physical activity, m*g*) was recorded from accelerometer data, using only those with good wear and calibration quality.[27] Participant data were classified as 'missing' if results were not available or the participant had selected 'prefer not to answer' or 'not sure'.

2.3 | MRI acquisition and processing

Brain MRI was performed on a Siemens Skyra 3-T (VD13A SP4) scanner with a standard Siemens 32-channel RF receive head coil. The acquisition protocol can be viewed in full at https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/bmri_V4_23092014.pdf. Brain imaging data were processed through UK Biobank-specific acquisition protocols and automated processing pipelines, generating the imaging-derived phenotypes such as structural volumes.[28] Using the external surface of the skull estimated from T1 imaging, brain tissue volumes could be normalized for head size, generating distinct normalized and non-normalized imaging-derived phenotypes using a SIENAX analysis.[29] We used T1 total brain (grey + white matter) volume (TBV), total GMV and total white matter volume (WMV), all normalized for head size. Total hippocampal volume (THV; right + left hippocampus) was generated using FMRIB's Integrated Registration and Segmentation Tool (FIRST). Hippocampal volumes were normalized for head size using a scaling factor, calculated by dividing the normalized total brain volume imaging-derived phenotype by the non-normalized phenotype. Total white matter hyperintensity volume (WMHV) was measured using T1 and T2 FLAIR imaging. WMHV was log-transformed given its skewed distribution (Figure S1).

VAT measures for the UK Biobank were derived by abdominal MRI on a Siemens MAGNETOM Aera 1.5-T MRI scanner (Syngo MR D13) using a dual-echo Dixon Vibe protocol scanning from neck to knees and according to a magnetic resonance body composition analysis[30] (in AMRA Profiler), which can be viewed in full at https://

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biobank.ndph.ox.ac.uk/ukb/ukb/docs/AbdoBodyCompMethod.pdf. The image volumes were corrected and calibrated through an algorithm using adipose tissue as the internal signal reference before being processed and merged into a composite of fat and water image volumes.[31,32] Using non-rigid registration, quality-controlled ground-truth labelled atlases for fat and muscle compartments were registered to the acquired imaging volumes using an atlas database of both genders from a range of phenotypes.[30,33] VAT was defined as adipose tissue within the abdomen posterior to abdominal muscles and anterior to the spine and back muscles. Tissue volumes were quantified through an automatic segmentation process, adjusted by a trained operator and calculated through integration of the calibrated adipose tissue imaging.[30,34]

2.4 | Standard protocol approvals, registrations and patient consents

Written informed consent was obtained from all participants. The UK Biobank approved this study (project ID 24954) and ethics approval was obtained from the UK Biobank Research Ethics Committee (reference 11/NW/0382), as well as the Monash University Human Research Ethics Committee (project ID 18734).

2.5 | Statistical analysis

Simple summary statistics were used to describe the sample. We used multivariable linear regression to examine the associations between VAT and each of the normalized brain volume measures, namely, total brain, grey matter, white matter, white matter hyperintensity and hippocampal volume. In previously published work using UK Biobank data, we identified an interaction between age and sex on TBV, GMV, WMV, WMHV and THV,[35] and therefore added this term first to univariable models (Model 2) before examining for the presence of additional VAT × sex or VAT × age interaction terms. Interactions were assessed using a product term and those identified were further explored through plots. Interactions involving age were plotted using tertiles based on the distribution of age. The 'simple_slopes' command within the R package 'reghelper' was used to estimate associations within models, including an interaction term. To assist with understanding the scale of any interactions, the interaction was additionally reported relative to size of the univariable association of age with the outcome variable. Associations were then examined for whether they were altered by the addition of ethnicity, socioeconomic status (Townsend Deprivation Index), ever smoked, ever consumed alcohol, cardiometabolic factors (hypertension, diabetes, dyslipidaemia, stroke, IHD) and APOE4 status. We performed sensitivity analyses, limited to those with physical activity data available, to examine their potential influence on identified associations. All statistical analyses were performed using RStudio (version 1.4.1717) in R (version 4.1.1).

3 | RESULTS

3.1 | Sample characteristics

Complete data were available for 17 377 participants. Table 1 describes the sample characteristics with further stratification by age and sex presented in Tables S1 and S2, respectively. The median age was 63 years (interquartile range [IQR] = 12) and 53% (9145) were women. Overall, 93% of participants self-identified as British. The median Townsend Deprivation Index was −2.7 (IQR = 3.2). The mean body mass index (BMI) was 26.6 kg/m^2 (SD = 4.4), the mean waist and hip circumferences were 87.9 cm (SD = 12.4) and 101.3 cm (SD = 8.7), respectively. Almost all participants reported consuming alcohol (96%) and 37% (n = 6434) smoking tobacco in the past. The prevalence of hypertension was 43% (n = 7426), with participants having a mean systolic blood pressure of 139 mmHg (SD = 19) and mean diastolic blood pressure of 79 mmHg (SD = 11). Also, 25.1% of participants had dyslipidaemia (n = 4356), 5.9% had diabetes (n = 1024), 7.5% had IHD (n = 1303), 5.7% had stroke (n = 991) and 26.6% had at least one APOE4 allele (n = 2183). A smaller number of people (n = 7708) had good quality accelerometer data available. The overage average physical activity of these participants was 27.4 mg (IQR = 10.0). The characteristics of those with accelerometer data available were similar to those of the whole group.

3.2 | VAT, age, sex and brain volumes

Table 2 describes the associations between VAT and normalized brain volumes. Similar to our previously published work,[35] we confirmed an interaction between age and sex on TBV, GMV, THV and WMHV (*P* for interaction < .001) (Table S3).

3.2.1 | Total brain volume

Greater VAT was associated with lower TBV (beta coefficient [β] = −5.95, 95% confidence interval [CI] −6.43 to −5.48, *P* < .001) and this persisted following the inclusion of a statistically significant age × sex interaction term (β = −2.39, 95% CI −2.86 to −1.93, *P* < .001). We additionally found an interaction between VAT and sex (β = −1.57, 95% CI −2.57 to −0.58, *P* < .001), but not between VAT and age (β = 0.001, 95% CI −0.05 to 0.07, *P* = .77) in explaining TBV. Figure 1 presents the nature of this VAT × sex interaction. The negative association between VAT and TBV was greater in men (β = −2.89, 95% CI −2.32 to −10.15, *P* < .001) than in women (β = −1.32, 95% CI −0.49 to −3.14, *P* < .002), irrespective of the age × sex interaction (*P* for difference .002). The magnitude of these interactions (equivalent in scale to approximately 3.5 months of life) changed very little when cardiometabolic factors were included as covariables (Table S4). Restricting the dataset to those with available physical activity data altered the point estimate and statistical

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TABLE 1 Participant characteristics.

	Whole group Mean ± SD or median (IQR) or n (%)	Accelerometer data available Mean ± SD or median (IQR) or n (%)
N	17 377	7708
Age (y)	63 ± 12	63 ± 8
Female	9145 (53%)	4253 (55%)
Tertiary degree	8119 (47%)	3620 (47%)
British ethnicity	16 066 (93%)	7194 (93%)
Townsend Deprivation Index	−2.7 (IQR 3.2)	−2.7 (IQR 3.1)
Body mass index (kg/m^2)	26.6 ± 4.4	26.5 ± 4.4
Waist circumference (cm)	87.9 ± 12.4	87.3 ± 12.5
Hip circumference (cm)	101.3 ± 8.7	101.1 ± 8.7
Ever smoked	6434 (37%)	2821 (37%)
Ever drunk alcohol	16 704 (96%)	7424 (96%)
Hypertension	7426 (43%)	3321 (43%)
Diabetes	1024 (5.9%)	428 (5.6%)
Ischaemic heart disease	1303 (7.5%)	570 (7.4%)
Dyslipidaemia	4356 (25.1%)	1888 (24.5%)
Stroke	991 (5.7%)	436 (5.7%)
Systolic blood pressure (mmHg)	139 ± 19	139 ± 19
Diastolic blood pressure (mmHg)	79 ± 11	79 ± 11
Apolipoprotein E ε4 carrier	2183 (26.6%)	2068 (26.8%)
Overall average physical activity (mg)	27.4 (IQR 10.0)	27.4 (IQR 10.0)
Visceral adipose tissue (mL)	3285 (IQR 3071)	3594 (IQR 3025)
Total brain volume (mL)	1501.7 ± 73	1503 ± 73
Grey matter volume (mL)	795.3 ± 48.1	795.9 ± 47.9
White matter volume (mL)	706.4 ± 40.9	706.9 ± 41.3
White matter hyperintensity volume (mL)	2.7 (IQR 3.8)	4.6 (IQR 3.8)
Total hippocampal volume (mL)	9.95 ± 1.1	9.97 ± 1.1

Abbreviations: IQR, interquartile range; n, number; SD, standard deviation.

strength of the VAT × sex interaction (β = −1.26, P = .09) (Table S5). Including physical activity as a covariable resulted in minimal additional change (VAT × sex interaction β = −1.34, P = .07).

3.2.2 | Grey matter volume

Greater VAT was associated with lower GMV (β = −6.32, 95% CI −6.62 to −6.01, P < .001) and persisted following the inclusion of the statistically significant age × sex interaction term (β = −2.27, 95% CI −2.55 to −2.00). There was an additional interaction between VAT and sex (β = −1.02, 95% CI −1.62 to −0.43), but not VAT and age (P = .17) in explaining GMV. Figure 2 presents the nature of this VAT and sex interaction. The negative association between VAT and GMV was greater in men (β = −2.60, P < .001) than in women (β = −1.58, P < .001), irrespective of any age × sex interaction (P for difference < .001). The magnitude of these interactions (equivalent in scale to approximately 3.2 months of life) changed very little when cardiometabolic factors were included as covariables (Table S4). Restricting the dataset to those with available physical activity data substantially changed the point estimate and statistical strength of the VAT × sex interaction (β = −0.50, P = .26) (Table S5). Including physical activity as a covariable resulted in minimal additional change (VAT × sex interaction β = −0.52, P = .24).

3.2.3 | White matter volume

Greater VAT was associated with greater WMV (β = 0.36, 95% CI 0.09 to 0.63), but this association no longer remained following the addition of the age × sex interaction term (Table 2). Additional adjustments for other covariables resulted in minimal change in the above associations (Tables S4 and S5).

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TABLE 2 Associations and interactions between VAT, age and sex on brain volumes.

	Total brain volume β (95% CI)	Grey matter volume β (95% CI)	White matter volume β (95% CI)	Total hippocampal volume β (95% CI)	White matter hyperintensity volume β (95% CI)
Model 1 (univariable)					
VAT	−5.95 (−6.43 to −5.48)*	−6.32 (−6.62 to −6.01)*	0.36 (0.09 to 0.63)*	−0.10 (−0.11 to −0.09)*	0.04 (0.03 to 0.04)*
Model 2 (VAT + age + sex + age × sex)					
VAT	−2.39 (−2.86 to −1.93)*	−2.27 (−2.55 to −2.00)*	−0.12 (−0.42 to 0.18)	−0.02 (−0.03 to −0.01)*	0.03 (0.02 to 0.03)*
Age × sex	0.86 (0.62 to 1.10)	0.53 (0.39 to 0.68)*	0.32 (0.17 to 0.48)*	−0.02 (−0.02 to −0.01)*	−0.004 (−0.01 to −0.003)*
Model 3 (VAT + age + sex + age × sex + VAT × sex)					
Age × sex	0.89 (0.65 to 1.13)*	0.56 (0.41 to 0.70)*	0.34 (0.18 to 0.49)*	−0.02 (−0.02 to −0.01)*	−0.004 (−0.01 to −0.003)*
VAT × sex	−1.57 (−2.57 to −0.58)*	−1.02 (−1.62 to −0.43)*	−0.55 (−1.20 to 0.09)	0.01 (−0.004 to 0.03)	−0.0001 (−0.006 to 0.006)
Model 4 (VAT + age + sex + age × sex + VAT × age)					
Age × sex	0.86 (0.58 to 1.14)*	0.61 (0.44 to 0.77)*	0.25 (0.07 to 0.43)*	−0.02 (−0.2 to −0.01)*	−0.002 (−0.004 to −0.0004)*
VAT × age	−0.004 (−0.06 to 0.06)	−0.3 (−0.07 to 0.005)	0.03 (−0.01 to 0.07)	0.0003 (−0.007 to 0.001)	−0.001 (−0.001 to −0.001)*
Model 5 (VAT + age + sex + age × sex + VAT × age + VAT × sex)					
Age × sex	0.87 (0.59 to 1.15)*	0.61 (0.45 to 0.78)*	0.25 (0.08 to 0.44)*	−0.02 (−0.02 to −0.01)*	−0.002 (−0.004 to −0.0005)*
VAT × age	0.009 (−0.05 to 0.07)	−0.03 (−0.06 to 0.01)	0.04 (−0.005 to 0.08)	0.0003 (−0.001 to 0.001)	−0.001 (−0.001 to −0.001)*
VAT × sex	−1.59 (−2.59 to −0.59)*	−0.98 (−1.58 to −0.38)*	−0.61 (−1.26 to 0.04)	0.01 (−0.004 to 0.03)	0.001 (−0.005 to 0.01)

Abbreviations: CI, confidence interval; VAT, visceral adipose tissue.
*$P < .05$.

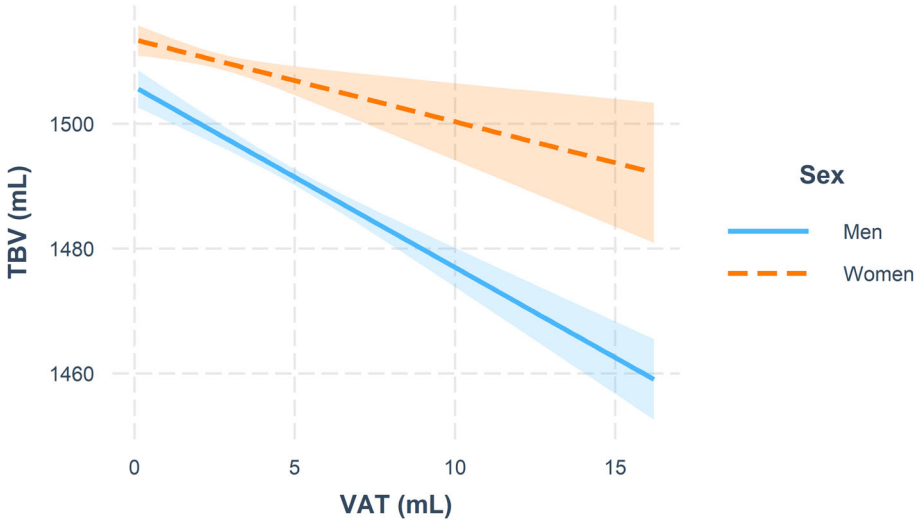

FIGURE 1 Association between visceral adipose tissue (VAT) and predicted total brain volume (TBV) by sex. Key: shaded bands represent 95% confidence intervals (CIs) of the model including an age × sex interaction.

3.2.4 | Total hippocampal volume

Greater VAT was associated with lower THV (β = −0.10, 95% CI −0.11 to −0.09, $P < 2 \times 10^{-16}$), and this association persisted with the inclusion of the age × sex interaction term (β = −0.02, 95% CI −0.03 to −0.01) (Table 2). We did not find an interaction between VAT and sex or VAT and age (Tables 2, S4 and S5). The introduction of cardiometabolic factors resulted in minimal change to the

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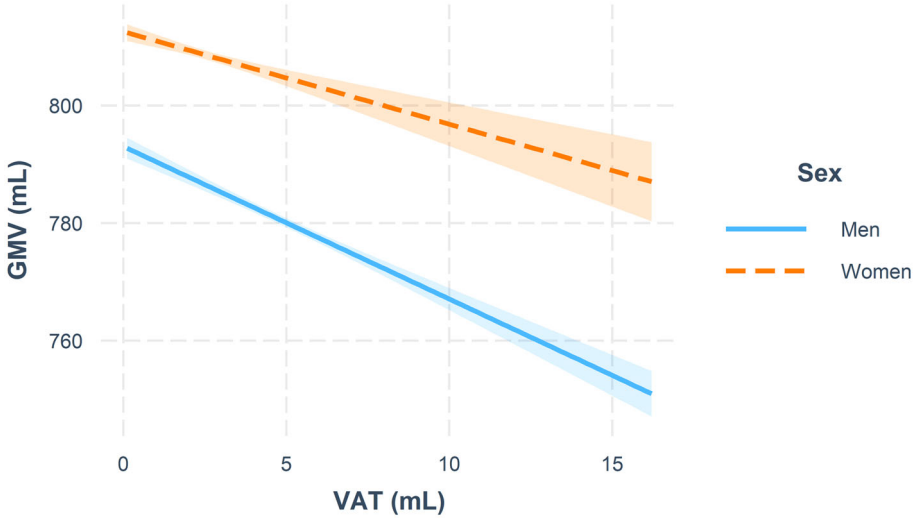

FIGURE 2 Association between visceral adipose tissue (VAT) and predicted grey matter volume (GMV) by sex. Key: shaded bands represent 95% confidence intervals (CIs) of the model including an age × sex interaction.

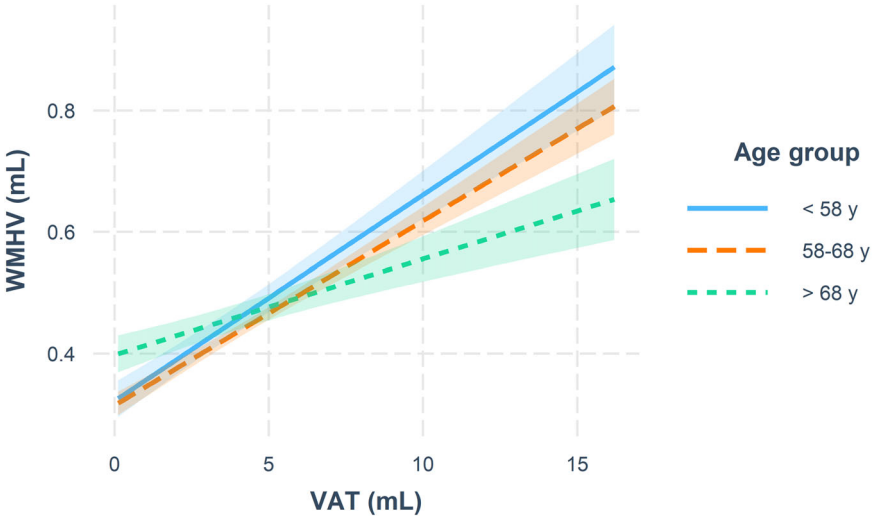

FIGURE 3 Association between visceral adipose tissue (VAT) and predicted white matter hyperintensity volume (WMHV) by age. Key: shaded bands represent 95% confidence intervals (CIs).

association between VAT and THV (β = −0.03, 95% CI −0.03 to −0.01, $P = 2 \times 10^{-6}$). Restricting the dataset to those with physical activity data available, the association between VAT and THV remained similar (β = −0.03, 95% CI −0.05 to −0.01, $P < .002$). Including physical activity as a covariable resulted in minimal additional change (β = −0.03, 95% CI −0.05 to −0.005, $P = .01$).

3.2.5 | White matter hyperintensity volume

Greater VAT was associated with greater WMHV (β = 0.04, 95% CI 0.03 to 0.04, $P < 2 \times 10^{-16}$) and this association persisted following the inclusion of the statistically significant age × sex interaction term (β = 0.03, 95% CI 0.02 to 0.03, $P < 2 \times 10^{-16}$) (Table 2). We found an interaction between VAT and age (β = −0.001, $P < 5 \times 10^{-6}$), but not between VAT and sex ($P = .97$), in explaining WMHV. Figure 3 presents the nature of this VAT × age interaction using predicted plots derived from Model 4. When compared with those aged younger than 58 years, the positive association between VAT and WMHV was less in those aged older than 68 years (P for difference $< 4 \times 10^{-6}$), but similar to those aged 58-68 years (P for difference = .27). The magnitude of these interactions (equivalent in scale to approximately 0.4 months of life) changed very little when cardiometabolic factors were included as covariables (Table S4). Restricting the dataset to those with physical activity data available, minimally changed the interaction between VAT and age (Table S5). Including physical activity as a covariable resulted in minimal additional change (VAT × age interaction β = −0.0008, $P = .007$).

4 | DISCUSSION

In this large population-based sample, we found that the association between visceral adiposity and MRI measures of brain ageing were modified by sex for TBV and GMV, and by age for WMHV. The negative associations of visceral adiposity with TBV and GMV were greater in men than in women. The positive association of visceral adiposity with WMHV was greatest in those in the youngest age group.

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Such novel results suggest that interventions targeting reductions in VAT may have the greatest benefit in men and in those before they reach older ages. Clinical trials are required to test these hypotheses.

Our results differ from the one previous study (of which we are aware) that has examined the association between MRI measures of visceral fat and brain volumes.[19] In that study, the authors also reported sex differences in the association between visceral fat and brain volumes, but partial correlations between greater visceral fat and lower brain volumes were greater in women than in men. Although the reasons for the different results reported by our studies are not clear, the average age of participants in the previously published work was 10 years younger than those in our study and included people aged 18-90 years. Our study focused on people in mid-later life, and may have been better powered to identify age and sex differences occurring in mid-later life rather than across the lifespan. Additionally, reflecting our aims, we adopted a very detailed analytical exploration of the potential for age and sex to interact on brain volumes based on our previous work,[35] an approach not used in the previously published study.[19] Taken together, both studies highlight the importance for future work to explore how sex and age interact when influencing brain volumes.

The mechanisms through which VAT may contribute to brain atrophy are unclear, but are probably the result of complex interactions between adipose tissue-driven inflammation and hormones.[9,18,36–38] The relationship between lipids and VAT is unclear, with some studies highlighting that obesity is not always associated with lipid abnormalities,[18] and that the metabolic effects of visceral adiposity may be independent of lipid pathways.[9,18] VAT is a strong driver of inflammatory cytokines, which have been associated with an increased risk of cardiovascular disease[9,13,36] and, more recently, poorer cognition.[37] There is plausible evidence that this complex relationship is further influenced by sex.[36,37] Sex hormones may be neuroprotective, with oestrogen and oestrogen receptors potentially playing an important role in dampening the negative effects of inflammatory pathways in women,[9,39] potentially explaining the sex differences we observed. The loss of this protective effect of oestrogen following menopause also may explain the known increased risk of dementia in women compared with men in older age.[35,40] The effects of a transition to a postmenopausal pro-inflammatory state coupled with a loss of neuroprotection may simply not yet be observable in our comparatively young sample. Further, longitudinal work is required to better understand whether these pathways accelerate over time in women postmenopause. Our results suggest that interventions to reduce visceral adiposity for preserving brain volume may have different impacts in men and women, and that middle-aged men in particular may benefit from such interventions. However, clinical trials will be required to test this hypothesis.

Consistent with prior work using measures such as BMI and waist–hip ratio,[41] we found that there was a negative association between VAT and WMHV. The potential for obesity to have a greater negative effect on health outcomes during earlier stages of life has been previously described. This obesity paradox describes the phenomenon that obesity in early to midlife may be associated with a higher risk of disease in later life, but that obesity in later life may actually be associated with positive outcomes.[42–44] The mechanisms linking visceral adiposity with greater WMHV are not well understood, but adiposity-driven chronic low-grade inflammation and disease of cerebral small vessels are both plausible explanations that may act independently or in conjunction.[41] Our results provide further support for The Lancet Commission, which highlighted the contribution of midlife risk factors (including obesity) to the risk of dementia in later life,[45] and additionally highlights the mechanistic and potential therapeutic importance of VAT.

The strengths of this study include the use of a very large population-based cohort at midlife with sensitive brain and adiposity MRI data, thus allowing exploration of sex differences and other potential biological interactions with sufficient power.[46] However, the current study also has limitations. UK Biobank participants are volunteers and, as such, may reflect healthier or more health-literate members of the community. This is supported by the comparatively low prevalence of cardiometabolic factors and low BMI of the cohort, which limits the generalizability of our findings. It is also possible that the associations we report may differ further in those with greater BMI. However, it is possible that the associations we describe may be more prominent in a sample with larger variability in relevant exposures and outcomes. We were also unable to fully explore the role of physical activity as a potential mediator or modifier of the associations we report. Because only approximately 40% of our analytical sample had accelerometer data available, we frequently found that our primary associations were no longer statistically robust when restricted to a sample with complete data. We therefore lacked the statistical power to explore the role of physical activity across age and sex subgroups. Such work is important for the future because it will help inform interventions targeting reductions in VAT. The cross-sectional nature of these analyses prevents confirmation of causality, but analyses of longitudinal data becoming available within the UK Biobank are planned. Similarly, using our findings and analytical approach to drive exploration of the available granular brain structural (e.g. hippocampal subfields) and cognitive data will assist with understanding the functional implications of our results.

In conclusion, through middle age, the association of VAT with lower GMV and TBV is modified by sex. VAT is also adversely associated with other measures of brain structure, with age-modification evident in its association with WMHV. Future work is required to examine longitudinal relationships, clarify biological mechanisms driving these relationships, and to explore whether interventions to reduce visceral adiposity need to be different for men and women to reduce their future risk of cognitive decline and dementia.

AUTHOR CONTRIBUTIONS

CM was responsible for study ideation, analytical design, analysis and writing of the manuscript. JH contributed to writing the manuscript, analysis and interpretation of results. ST contributed to obtaining the dataset, analysis, interpretation of results and writing the manuscript. TC contributed to analytical design, interpretation of results and writing the manuscript. RB contributed to obtaining the dataset, analysis,

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interpretation of results and writing the manuscript. SS contributed to interpretation of results and writing the manuscript. VS was responsible for study ideation and access to the dataset. VS contributed to analytical design, interpretation of results and writing the manuscript.

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CONFLICT OF INTEREST STATEMENT

None declared.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15727.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from UK Biobank on reasonable request.

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