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Obesity and brain volumes: mediation by cardiometabolic and inflammatory measures

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ABSTRACT

Background This study aimed to investigate the relationship between overall obesity, central obesity and brain volumes, as well as to determine the extent to which cardiometabolic and inflammatory measures act as mediators in the association between body mass index (BMI), waist-hip ratio (WHR) and brain volumes.

Methods In the context of counterfactual framework, mediation analysis was used to explore the potential mediation in which cardiometabolic and inflammatory measures may mediate the relationship between BMI, WHR, and brain volumes.

Results Among 2413 community-dwelling participants, those with high BMI or WHR levels experienced an approximately brain ageing of 4 years. Especially, individuals with high WHR or BMI under the age of 65 exhibited white matter hyperintensity volume (WMHV) differences equivalent to around 5 years of ageing. Conversely, in the high-level WHR population over the age of 65, premature brain ageing in gray matter volume (GMV) exceeded 4.5 years. For GMV, more than 45% of the observed effect of WHR was mediated by glycaemic metabolism indicators. This proportion increases to 78.70% when blood pressure, triglyceride, leucocyte count, and neutrophil count are jointly considered with glycaemic metabolism indicators. Regarding WHR and BMI's association with WMHV, cardiometabolic and inflammatory indicators, along with high-density lipoprotein cholesterol, mediated 35.50% and 20.20% of the respective effects.

Conclusions Overall obesity and central obesity were associated with lower GMV and higher WMHV, a process that is partially mediated by the presence of cardiometabolic and inflammatory measures.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Obesity may be associated with brain structure, but studies investigating the relationship between obesity and brain volumes in Asian populations are limited.

WHAT THIS STUDY ADDS

⇒ This study explored whether body mass index and waist-hip ratio, were associated with brain volumes, and assessed the mediating role of cardiometabolic and inflammatory measures.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Findings of this study provided clues for future studies to identify the causal relationship between obesity and brain volumes, and provided evidence for understanding the mediating role of cardiometabolic and inflammatory measures in the association of obesity and brain volumes.

INTRODUCTION

Obesity is one of the WHO's top 10 global health concerns, affecting more than 30% of adult Chinese citizens,[1] and it has evolved into a public health crisis, particularly among the middle-aged and older population. Previous long-term follow-up studies have found that obesity would increase the risk of dementia onset,[2] and cognitive decline was associated with the deterioration of brain elasticity and accelerated ageing which *may be related to* changes in brain volume.[3–5] However, few studies have shown the associations between different obesity types and brain volumes in Asians.

Both overall obesity and central obesity can lead to systemic low-grade inflammation, impacting molecular metabolism and fat accumulation,[6] where these forms of obesity are also closely linked to neuroinflammation[7] and abnormal glucolipid metabolism, including conditions like hypertension, diabetes and insulin resistance.[8] Moreover, several studies have indicated that disorder in glucolipid metabolism and abnormal inflammatory responses are likely to be associated with brain atrophy.[9] High levels of leucocyte accumulation can result in white thrombi formation in small veins, potentially impairing circulation and leading to the rupture of blood vessel walls in the brain.[10] In the rat model of brain trauma, neutrophil infiltration and accumulation have been associated with structural brain damage.[11] Some studies have shown that both higher white matter hyperintensity volume (WMHV) and smaller gray matter volume (GMV) were associated

with a decreased perceptual speed in older individuals without cognitive impairment.[12] Accordingly, it prompts the hypothesis that cardiometabolic and inflammatory measures may act as mediating factors, providing an indirect pathway through which obesity may be associated with brain volume.

To quantify brain ageing via brain volume differences and explore the association between obesity and brain ageing,[13] we analysed cross-sectional data from the PolyvasculaR Evaluation for Cognitive Impairment and vaScular Events (PRECISE) study. This involved community-dwelling adults aged 50–75, undergoing comprehensive evaluations for vascular events and cognitive assessments. In the present study, we investigated the relationship between overall obesity, central obesity and brain volumes, using univariate and multivariate mediation analysis to assess the mediating role of cardiometabolic and inflammatory measures.

METHODS

Study design and participants

Data for this study were derived from the baseline cross-sectional survey data of the PRECISE study, the details of the project had previously been published.[14] The PRECISE project recruited 3067 dementia-free community-dwelling individuals aged 50–75 from six villages and four communities between May 2017 and September 2019.

According to the purpose of this analysis, participants with a history of stroke (n=87) and both missing information on cardiometabolic and inflammatory measures (n=2) and MRI brain measures (n=565) were excluded. This resulted in a final cross-sectional analysis sample of 2413 participants.

Baseline data collection

Face-to-face interviews were conducted by qualified neurologists from Lishui Hospital to collect basic characteristic data including age, sex, ethnicity, education level, medical history, self-reported medication use, medical history, smoking and drinking status, physical examination and laboratory tests. Brain MRI measures were performed at enrolment using a standard data collection technique established by the steering committee.

Laboratory tests

Fasting blood samples were collected and sent to the laboratory of the Lishui Hospital, where they were centrifuged to extract serum, plasma and leucocytes, and all serum markers were measured by an automated analyzer (ARCH ITECT c16000, Illinois, USA). Fasting glucose was measured by the enzymatic hexokinase method; the homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated as (fasting insulin (μU/mL)×fasting glucose (mmol/L))/22.5, of which insulin was determined by radioimmunoassay; triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were determined by an enzymatic assay.

Obesity measures

Body mass index (BMI) and waist-hip ratio (WHR) were measured by physicians using standard procedures. BMI was calculated by dividing weight in kilograms by height in metres squared and divided into three groups: normal BMI group, BMI<24.0 kg/m^2; overweight group, BMI: 24.0–27.9 kg/m^2; and obese group, BMI≥28.0 kg/m^2.[15] WHR was estimated as the ratio of waist to hip circumference in centimetres and divided into three groups: low level: <0.85 (female), <0.90 (male); medium level: 0.85–1.00 (female), 0.90–1.00 (male); high level: >1.00 (female), >1.00 (male).[16 17] Additionally, this study used the Chinese visceral adiposity index (CVAI), which is a recent index for assessing abdominal obesity in Chinese adults.[18] Males: CVAI=−267.93+0.68×age+0.03×BMI+4.00×waist circumference+22.00×Log10TG−16.32×HDL-C. Females: CVAI=−187.32+1.71×age+4.23×BMI+1.12×waist circumference+39.76×Log10TG−11.66×HDL-C.

Medical examinations

Hypertension was defined as prior diagnosis by medical practitioners, the present utilisation of antihypertensive medications, or systolic blood pressure (SBP) ≥140 mm Hg, or diastolic blood pressure (DBP) ≥90 mm Hg.[19] Diabetes was ascertained through self-reported physician-diagnosed diabetes, current utilisation of antidiabetic medications, fasting plasma glucose (FPG) levels at or above 7.0 mmol/L, 2-hour post-load glucose levels at or above 11.1 mmol/L, or HbA1c levels above 6.5% (48 mmol/mol).[20] History of dyslipidaemia was identified by self-reported prior diagnosis of dyslipidaemia by a physician[21] or current use of lipid-lowering medication.

Imaging data collection

Employing the default processing pipeline of FreeSurfer (V.7.0), each T1-weighted magnetisation-prepared rapid-acquisition gradient-echo (3D T1w MPRAGE) was meticulously processed. The White matter Hyperintensities Analysis Tools software was subsequently used, providing a summarised representation of WMHV data.[22] High-resolution imaging via a 3.0T MRI scanner (Ingenia 3.0T, Philips, Best, The Netherlands) was conducted in the Lishui Hospital Medical Centre, and delivered to the imaging research centre at Beijing Tiantan Hospital for additional investigation.

Using multispectral MRI and an automated image analysis pipeline, we generated independent measurements for the volumes of total cerebral brain (TCBV), GMV, white matter (WMV) and WMHV. All brain MRI measures were quantified using the residual method (regression-based predicted brain tissue volumes evaluated with intracranial volume (ICV) as a proxy for head size) to compensate for differences in head size among participants. We applied a logarithmic transformation to address the non-normal distribution of structural brain MRI measures. Subsequently, we standardised those measures using z-transformation to conduct the mean and SD specific to each region. In addition, we employed the

proportion method, which involves calculating tissue-ICV proportion, as another common method for quantifying brain volume. In this method, all brain volumes underwent equal logarithmic transformations.

Statistical analysis

According to a previous study, the mean GMV and SD for individual with normal low-level BMI (BMI: <25 kg/m^2), overweight (25 kg/m^2≤BMI<30 kg/m^2), and obesity (BMI≥30 kg/m^2) were 805±41 cm^3, 790±41 cm^3 and 780±41 cm^3, respectively.[23] Based on the sample size calculation formula for cross-sectional surveys, the adequacy of the sample size was assessed by estimating mean difference in GMV between BMI groups for primary general linear model incorporating assumptions that 50% of individuals had normal BMI (BMI: <24 kg/m^2), 40% were overweight (24 kg/m^2≤BMI<28 kg/m^2), and 10% were obese (BMI≥28 kg/m^2) among Chinese middle-aged and older residents. Considering the necessity for multiple comparison corrections for significance level and accounting for a 10% non-response rate, our study population is sufficient for statistical analysis. It achieved a desired power of over 99% with a two-sided α value of 5%.

Continuous variables are expressed as means and SD or medians or IQR, and categorical variables are expressed as frequencies and percentages. We compared the baseline characteristics among BMI groups and WHR groups using χ^2 test for categorical variables or one-way analysis of variance for continuous variables. Covariates potentially associated with obesity groups and brain volumes were adjusted in all models, including age, sex, current smoking, current drinking, ethnicity, educational level. In this study, the residual method and z-transformation was primarily used to normalise the ICV, with the proportion method serving as online supplemental material.[24] Stratified by age group and using the BMI<24.0 kg/m^2 group or low level WHR group as a reference, we investigated brain volume differences and correspondent years of brain ageing in higher BMI or WHR groups.[25] Calculation of years of brain ageing was based on regressing MRI brain measures onto age at time of MRI examination, where the slope is the estimate of the change in MRI brain measures per year of age. Mean brain volumes specific to age groups (<60, 60–64 and ≥65 years) was calculated for those with different BMI or WHR levels. For each age group, we then calculated the years of brain ageing due to obesity through the difference between the mean brain volumes among those with different BMI or WHR levels divided by the β coefficient. Because the association between age and the MRI measures might be different among different age groups, the estimations of years of brain ageing due to overweight and obesity were performed by age groups. The slopes of the different brain volumes in our study were calculated based on our data. When using BMI as a measure of overall obesity, the slope was the estimate of the difference in residual adjusted brain volume per year of age (TCBV=−3.0505×age; GMV=−1.3832×age; WMV=−1.6673×age; WMHV=0.3015×age); and when using WHR as a measure of central obesity, the slope was the estimate of the difference in residual adjusted brain volume per year of age (TCBV=−3.0375×age; GMV=−1.3579×age; WMV=−1.6796×age; WMHV=0.2963×age).

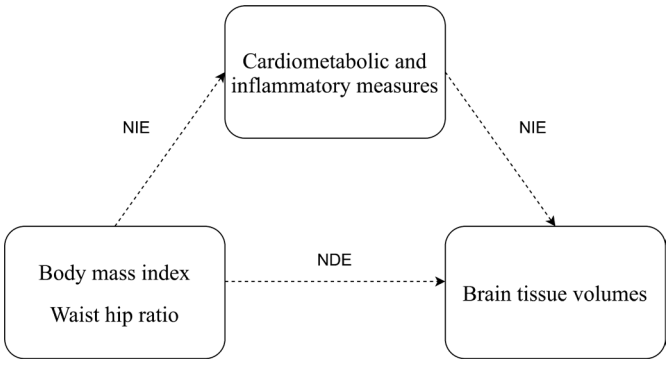

Figure 1 Mediation model of the hypothetical causal pathway. Arrows indicate the causal direction or possible association. Total effect=NDE+NIE. NDE, natural direct effect; NIE, natural indirect effect.

To assess the extent of associations of BMI and WHR with brain volumes mediated by cardiometabolic and inflammatory measures, we performed mediation analysis based on the counterfactual outcome framework (figure 1). Within this framework, we determined the total, natural direct and natural indirect effects using a regression-based method. In this context, the total association of obesity on brain volumes is composed of natural indirect effect (or mediated effect) and natural direct effect, and all are presented in regression coefficient (β) with corresponding p values. The indirect effect represents the impact of obesity on brain volumes mediated through cardiometabolic and inflammatory measures, while the direct effect encompasses pathways not involving these markers. β is usually calculated using structural equation modelling, and β of the direct effect represents the coefficient of the path of the direct effect from the independent variable to the dependent variable. β of the indirect effect represents the product of the path coefficient of the independent variable to the mediator variable and the path coefficient of the mediator variable to the dependent variable. P value tests whether the path coefficient for indirect/direct effect (β) is equal to 0 and an indirect/direct effect is considered to exist when p<0.05. This method could yield valid estimates under the condition that the baseline covariates adequately address exposure-outcome, mediator-outcome and exposure-mediator confounding. First, we evaluated the relationship between obesity, cardiometabolic, and inflammatory measures, and brain volume while accounting for aforementioned confounders. Logarithmic transformation was performed for BMI, WHR, all cardiometabolic and inflammatory measures, as well as residual adjusted brain volumes. Second, we conducted individual mediation analyses to elucidate the relationship between each cardiometabolic and inflammatory measures and brain volumes. To evaluate the collective mediation effect of

cardiometabolic and inflammatory measures, we considered markers indicating mediation in multiple analyses based on individual mediator analyses. The proportion mediated by cardiometabolic and inflammatory measures, was calculated by dividing the natural indirect effect (mediated effect) by the total effect.[26] Brain volumes were residual-adjusted and normalised. We also used proportional brain volume for mediation analysis.

All analyses were conducted with SAS V.9.4 (SAS Institute, Cary, NC) and R V.4.2.2 (R Development Core Team). The %mediate SAS macro and 'lavaan' package were applied for mediation analysis. Two-sided p less than 0.05 was considered to be statistically significant.

Patient and public involvement

The public is concerned about the current state of the epidemiology of cerebrovascular disease and dementia and risk factors in the elderly population, and their concerns informed our research questions. Although participants were not involved in the study design, they played a central role in the conduct of the study by completing baseline, 2-year and 4-year follow-up surveys and imaging in our cohort, and we thank them for their contributions. We were unable to directly involve members of the public in this study due to the lack of allocated funds and time for patient and public involvement.

RESULTS

Study participants and characteristics

A total of 3067 community-dwelling adults were enrolled in the PRECISE study. After excluding 654 participants due to a history of stroke, MRI imaging quality, invalid data on cardiometabolic and inflammatory measures, the final analysis included 2413 participants (figure 2). The included patients were older and had a higher proportions of blood pressure and glycolipid abnormalities than the excluded patients (online supplemental table 1). At baseline, 2413 participants had a mean (SD) age of 61.3 (6.6) years, with 53.9% being female, and over 95% being Han. Approximately 30% of individuals had a high school education or above, and around 20% of the participants reported currently smoking or drinking alcohol.

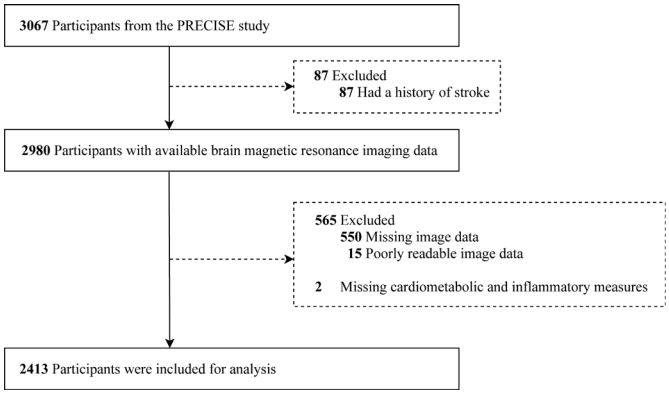

Figure 2 Flow chart of study population. PRECISE, PolyvasculaR Evaluation for Cognitive Impairment and vaScular Events.

Baseline characteristics and brain volume differences by BMI and WHR level

The median BMI was 23.73 (IQR: 21.91–25.80 kg/m²), and the median WHR was 0.91 (IQR: 0.87–0.95). Compared with individuals with BMI<24.0 kg/m^2, participants with higher BMI were less likely to be current smokers or drinkers, had a higher prevalence of abnormal blood pressure and glycolipid. In contrast, compared with individuals with a low WHR, participants with higher WHR were more likely to be older and drinkers (table 1).

In the overall population, compared with individuals with BMI<24.0 kg/m^2, overweight and obese participants had a 1.13 cm^3 and 3.27 cm^3 reduction in GMV, corresponding to 0.8 and 2.4 years earlier brain ageing; while a 0.66 cm^3 and 1.22 cm^3 increase in WMHV, indicating 2.2 and 4.0 years earlier brain ageing. In the three different groups of under 60 years, 60–64 years and above 65 years, the premature brain ageing corresponding to WMHV differences was 4.5, 3.4 and 3.1 years, respectively (table 2). However, compared with individuals with a low WHR, those with a high WHR showed premature brain ageing corresponding to GMV and WMHV differences of 3.7 and 2.2 years, respectively. High WHR individuals displayed evident premature brain ageing, with WMHV differences reaching 4.8 years in the 60–64 years age group and GMV differences reaching 4.6 years in those aged 65 years or older (table 3). Additionally, the results of the proportion method were similar (online supplemental tables 2 and 3). In addition, we found differences in brain ageing across age groups for men and women with different levels of obesity. It is noteworthy that in women over 65 years old with abdominal obesity, the reduction in GMV represented an ageing effect of approximately 8.5 years (online supplemental table 4).

Association between obesity, cardiometabolic and inflammatory measures and brain volumes

BMI was significantly associated with WMHV (β=1.55, 95% CI 1.26 to 1.84, p<0.001, online supplemental table 5), whereas WHR was significantly associated with both GMV and WMHV (β=−0.68, 95% CI −1.22 to −0.14, p=0.01; β=2.12, 95% CI 1.58 to 2.65, p<0.001, respectively, online supplemental table 6). SBP, DBP, FPG, HOMA-IR, TG, leucocyte count and neutrophil count were linearly correlated with GMV and WMHV, whereas, HDL-C were exclusively related to increased WMHV (online supplemental table 7). When GMV was expressed by percentage of total cranial volume, there was a linear correlation between BMI and GMV, whereas no linear correlation was observed between HOMA-IR, TG and GMV (online supplemental tables 8 and 9). We also found differences in brain volume (expressed in both absolute volume and percentage) among populations with different obesity phenotypes. Individuals with high levels of both BMI and WHR exhibited a greater proportion of WMHV relative

Table 1 Baseline characteristics according to BMI and WHR

Characteristics	Total (n=2413)	BMI			WHR		
		<24.0 kg/m^2 (n=1278)	24.0–27.9 kg/m^2 (n=907)	≥28.0 kg/m^2 (n=228)	Low level* (n=629)	Medium level* (n=1585)	High level* (n=199)
Age, mean±SD	61.3±6.6	61.4±6.7	61.3±6.4	60.9±6.8	60.5±6.4	61.3±6.6	63.6±6.7
Female, n (%)	1300 (53.9)	693 (54.2)	483 (53.3)	124 (54.4)	269 (42.8)	937 (59.1)	94 (47.2)
Han ethnicity, n (%)	2329 (96.5)	1232 (96.4)	876 (96.6)	221 (96.9)	603 (95.9)	1533 (96.7)	193 (97.0)
Educational level, n (%)							
Illiteracy	389 (16.1)	201 (15.7)	146 (16.1)	42 (18.4)	69 (11.0)	271 (17.1)	49 (24.6)
Primary school	594 (24.6)	309 (24.2)	227 (25.0)	58 (25.4)	149 (23.7)	393 (24.8)	52 (26.1)
Junior school	732 (30.3)	369 (28.9)	289 (31.9)	74 (32.5)	193 (30.7)	478 (30.2)	61 (30.7)
High school	510 (21.1)	285 (22.3)	184 (20.3)	41 (18.0)	151 (24.0)	327 (20.6)	32 (16.1)
College school	188 (7.8)	114 (8.9)	61 (6.7)	13 (5.7)	67 (10.7)	116 (7.3)	5 (2.5)
Current smoker, n (%)	482 (20.0)	287 (22.5)	156 (17.2)	39 (17.1)	165 (26.2)	265 (16.7)	52 (26.1)
Current drinker, n (%)	437 (18.1)	237 (18.5)	162 (17.9)	38 (16.7)	122 (19.4)	270 (17.0)	45 (22.6)
Medical history, n (%)							
Hypertension	1047 (43.4)	442 (34.6)	458 (50.5)	147 (64.5)	190 (30.2)	739 (46.6)	118 (59.3)
Diabetes mellitus	536 (22.2)	231 (18.1)	224 (24.7)	81 (35.5)	86 (13.7)	377 (23.8)	73 (36.7)
Dyslipidaemia	524 (21.7)	227 (17.8)	230 (25.4)	67 (29.4)	97 (15.4)	373 (23.5)	54 (27.1)
Coronary artery disease	10 (0.4)	6 (0.5)	3 (0.3)	1 (0.4)	3 (0.5)	4 (0.3)	3 (1.5)
Atrial fibrillation	19 (0.8)	8 (0.6)	9 (1.0)	2 (0.9)	4 (0.6)	13 (0.8)	2 (1.0)
Cardiometabolic and inflammatory measures							
SBP, mm Hg	129.8±16.2	127.3±16.2	131.9±15.9	135.8±14.9	125.4±16.0	131.1±16.1	133.3±15.4
DBP, mm Hg	75.5±9.0	74.0±8.7	76.7±8.9	78.6±8.9	73.6±9.2	76.1±8.8	76.4±8.4
FPG, mmol/L	6.0±1.6	5.8±1.4	6.2±1.7	6.5±1.8	5.6±1.0	6.1±1.6	6.6±2.2
HOMA-IR	1.7 (1.2–2.5)	1.3 (1.0–1.9)	2.0 (1.5–2.9)	1.7 (1.2–2.5)	1.2 (0.9–1.7)	1.8 (1.3–2.6)	2.4 (1.7–4.0)
TC, mmol/L	5.4±1.0	5.3±1.0	5.4±1.0	5.4±1.0	5.3±1.0	5.4±1.0	5.3±0.9
TG, mmol/L	1.8±1.3	1.6±1.2	2.1±1.4	1.8±1.3	1.5±1.0	1.9±1.3	2.1±1.4
LDL-C, mmol/L	2.8±0.8	2.8±0.8	2.9±0.8	2.8±0.8	2.8±0.8	2.8±0.8	2.8±0.8
HDL-C, mmol/L	1.4±0.3	1.5±0.4	1.3±0.3	1.4±0.3	1.5±0.3	1.4±0.3	1.2±0.3
Leucocyte count, ×10^9/L	6.2±1.6	6.0±1.6	6.3±1.6	6.2±1.6	6.0±1.6	6.2±1.6	6.7±1.8
Neutrophil count, ×10^9/L	3.5±1.2	3.5±1.3	3.6±1.2	3.5±1.2	3.4±1.3	3.6±1.2	3.8±1.5
Neutrophil ratio, %	56.3±8.3	56.3±8.5	56.2±8.1	56.3±8.3	56.2±8.4	56.3±8.2	56.6±9.1
Medication use, n (%)							

Continued

Table 1 Continued

Characteristics	Total (n=2413)	BMI			WHR		
		<24.0 kg/m^2 (n=1278)	24.0–27.9 kg/m^2 (n=907)	≥28.0 kg/m^2 (n=228)	Low level* (n=629)	Medium level* (n=1585)	High level* (n=199)
Antihypertensive	628 (26.0)	235 (18.4)	293 (32.3)	628 (26.0)	104 (16.5)	443 (27.9)	81 (40.7)
Antidiabetic	228 (9.4)	91 (7.1)	100 (11.0)	228 (9.4)	27 (4.3)	164 (10.3)	37 (18.6)
Lipid-lowering	93 (3.9)	49 (3.8)	30 (3.3)	93 (3.9)	16 (2.5)	70 (4.4)	7 (3.5)
Anticoagulants	1 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
MRI brain measures							
TCBV, %†	68.8±3.0	68.9±3.0	68.7±2.9	68.6±3.2	68.8±3.0	68.8±2.9	68.1±2.9
GMV, %†	38.7±2.0	38.8±2.0	38.6±1.9	38.5±2.0	38.7±2.0	38.7±2.0	38.1±1.8
WMV, %†	30.1±1.9	30.1±1.8	30.1±1.9	30.1±1.9	30.1±1.9	30.1±1.9	30.0±1.9
WMHV, %†	0.1 (0.0–0.2)	0.1 (0.0–0.2)	0.1 (0.1–0.3)	0.1 (0.1–0.3)	0.1 (0.0–0.2)	0.1 (0.0–0.2)	0.2 (0.1–0.4)
TCBV, cm^3‡	1032.8±41.4	1033.2±40.9	1032.7±41.0	1030.9±45.4	582.6±24.9	580.2±24.8	572.6±24.3
GMV, cm^3‡	580.2±24.9	580.9±25.0	579.7±24.5	578.1±26.5	1035.3±42.1	1033.0±40.9	1023.4±41.7
WMV, cm^3‡	452.6±28.2	452.3±27.3	452.9±29.2	452.8±28.9	452.7±28.2	452.8±28.1	450.9±28.9
WMHV, cm^3‡	3.1±5.2	2.8±5.7	3.4±4.5	3.8±4.5	2.6±5.3	3.2±5.2	4.1±4.7

*WHR groups: low level: <0.85 (female), <0.90 (male); medium level: 0.85–1.00 (female), 0.90–1.00 (male); high level: >1.00 (female), >1.00 (male).
†Expressed by proportion method.
‡Expressed by residual method.
BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GMV, gray matter volume; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TCBV, total cerebral brain volume; TG, triglyceride; WHR, waist-hip ratio; WMHV, white matter hyperintensity volume; WMV, white matter volume.

Table 2 Difference in brain volumes and brain ageing years in BMI groups of different age groups

Age group, year	N	MRI brain measures*	Mean brain volume, cm^3†			Years of brain ageing‡	
			BMI: <24.0 kg/m^2	BMI: 24.0–27.9 kg/m^2	BMI: ≥28.0 kg/m^2	BMI: 24.0–27.9 kg/m^2	BMI: ≥28.0 kg/m^2
<60	1112	TCBV	1049.46	1052.46	1048.05	−1.0	0.5
		GMV	588.97	589.10	586.73	−0.1	1.6
		WMV	460.49	463.36	461.32	−1.7	−0.5
		WMHV	1.29	1.87	2.65	1.9	4.5
60–64	571	TCBV	1035.02	1030.62	1031.80	1.4	1.1
		GMV	580.60	577.58	576.97	2.2	2.6
		WMV	454.42	453.05	454.84	0.8	−0.3
		WMHV	2.19	2.90	3.21	2.4	3.4
≥65	730	TCBV	1006.98	1004.45	1002.43	0.8	1.5
		GMV	568.92	567.22	564.63	1.2	3.1
		WMV	438.05	437.24	437.80	0.5	0.1
		WMHV	5.38	6.17	6.32	2.6	3.1
All participants	2413	TCBV	1033.33	1032.80	1029.78	0.2	1.2
		GMV	580.93	579.80	577.66	0.8	2.4
		WMV	452.40	453.00	452.12	−0.4	0.2
		WMHV	2.74	3.40	3.96	2.2	4.0

*Expressed by residual method.
†Adjusted for age, sex, current smoking, current drinking, ethnicity and educational level.
‡Calculation of years of brain ageing is based on regressing each brain volume onto age at MRI, where the slope is the estimate of the change in residual adjusted brain volume per year of age (TCBV=−3.0505×age; GMV=−1.3832×age; WMV=−1.6673×age; WMHV=0.3015×age).
BMI, body mass index; GMV, gray matter volume; TCBV, total cerebral brain volume; WMHV, white matter hyperintensity volume; WMV, white matter volume.

to ICV compared with those with low levels of both BMI and WHR (online supplemental table 10).

Mediating effect of cardiometabolic and inflammatory measures

Online supplemental table 11 showed the mediation effect of cardiometabolic and inflammatory measures on the relationship between obesity indices and brain volumes. The proportion of the effect of WHR on GMV jointly mediated by all mediators was 78.70% (95% CI 4.60% to 99.70%, p<0.001). Furthermore, the combined mediation effect of all markers on WHR-WMHV was 35.50% (95% CI 21.90% to 51.90%, p<0.001). Similar results were observed when MRI brain measures were reported by proportion (online supplemental table 12). We also observed an association between CVAI and WMHV, with approximately 10% of the mediation effect attributed to DBP and SBP (online supplemental tables 13 and 14).

DISCUSSION

Higher BMI and WHR were associated with premature brain ageing and brain volume impairment in this population-based cross-sectional investigation. Note that WMHV and GMV in high-BMI and high-WHR populations displayed brain ageing 4 years earlier than normal BMI (BMI≤24 kg/m^2) or low WHR populations. This study contributes to quantifying the effect of cardiometabolic and inflammatory factors in the association between obesity and brain volume in middle-aged and older residents.

Substantial research suggests that obesity may accelerate the ageing process, induce neurodegenerative lesions, affecting global cognitive function, psychomotor speed and memory.[2 3 27] Changes in brain volumes could lead to brain age gaps,[4] and ageing could ultimately cause cognitive dysfunction by destroying brain elasticity.[5 28] In our study, participants older than 65 years with central obesity (WHR>1.0) and overall obesity (BMI≥28.0 kg/m^2) exhibited brain ageing, as indicated by changes in GMV according to increases of 3.1 and 4.6 years, respectively. In the LIFE study, elevated WHR independently related to lower GMV in a multimodal network that negatively correlated with ageing and memory function.[29] In combination with their findings, our results indicated that obesity appeared to affect brain ageing as represented by GMV in participants over 65 years of age, while brain ageing as represented by WMHV was more pronounced in obese people under 65 years of age. This suggested that a single measure of obesity may be sufficient to assess the

Table 3 Difference in brain volumes and brain ageing years in WHR groups of different age groups

Age group, year	N	MRI brain measures*	Mean brain volume, cm³†			Years of brain ageing‡	
			Low level WHR§	Medium level WHR§	High level WHR§	Medium level WHR§	High level WHR§
<60	1112	TCBV	1051.18	1050.42	1047.21	0.3	1.3
		GMV	590.48	588.21	586.83	1.7	2.7
		WMV	460.70	462.22	460.38	−0.9	0.2
		WMHV	1.39	1.73	2.11	1.1	2.4
60–64	571	TCBV	1030.53	1034.42	1031.25	−1.3	−0.2
		GMV	578.32	580.23	573.86	−1.4	3.3
		WMV	452.21	454.19	457.39	−1.2	−3.1
		WMHV	2.10	2.58	3.51	1.6	4.8
≥65	730	TCBV	1007.15	1005.05	1006.00	0.7	0.4
		GMV	569.52	568.17	563.26	1.0	4.6
		WMV	437.63	436.88	442.74	0.4	−3.0
		WMHV	5.37	5.93	5.53	1.9	0.5
All participants	2413	TCBV	1033.10	1032.84	1031.45	0.1	0.5
		GMV	581.36	580.21	576.40	0.8	3.7
		WMV	451.74	452.63	455.05	−0.5	−2.0
		WMHV	2.75	3.21	3.40	1.6	2.2

*Expressed by residual method.
†Adjusted for age, sex, current smoking, current drinking, ethnicity and educational level.
‡Calculation of years of brain ageing is based on regressing each brain volume onto age at MRI, where the slope is the estimate of the change in residual adjusted brain volume per year of age (TCBV=−3.0375×age; GMV=−1.3579×age; WMV=−1.6796×age; WMHV=0.2963×age).
§WHR groups: low level: <0.85 (female), <0.90 (male); medium level: 0.85–1.00 (female), 0.90–1.00 (male); high level: >1.00 (female), >1.00 (male).
GMV, gray matter volume; TCBV, total cerebral brain volume; WHR, waist-hip ratio; WMHV, white matter hyperintensity volume; WMV, white matter volume.

impact on brain ageing in middle-aged and older adults of different age groups.

The association between obesity and differences in brain volume is controversial at present.[30] Higher BMI and WHR were found to be associated with smaller GMV but not with WMV in the UK Biobank study,[23] contradicting a small-sample study that found morbid obesity was associated with white matter atrophy.[31] In the IDCD study, researchers failed to observe an association between obesity and total GMV among type 2 diabetes participants.[32] However, in our study, we found associations between BMI, WHR, WMHV and GMV, mediated by cardiometabolic and inflammatory factors. This suggested central obesity may closely relate to GMV and WMHV, warranting attention for metabolic and inflammatory abnormalities, especially in glucose metabolism and blood pressure. Several factors cause these differences. First, race may influence diet and ethnic genetics, potentially affecting outcomes. Second, sample size, population sources, age distribution, imaging methods and indicator definitions may affect extrapolation across studies. Third, metabolic diseases that cause abdominal fat accumulation could render central obesity assessment more significant for older adults.

Obesity may play a significant role in energy and substrate metabolism as well as systemic and tissue-specific inflammation.[33] We focused on critically important cardiometabolic and inflammatory indicators related to glycolipid metabolism, leucocyte and neutrophil count, since they are easier to collect in clinical practice and may be overlooked by investigators.[34] Generally, obesity was considered to be related to fatty liver disease, insulin resistance and type 2 diabetes.[35] BMI was directly linked with total leucocyte count and neutrophil count among apparently healthy and non-smoking men in ACLS study,[36] which in turn may be associated with slower processing speed.[37] Previous studies suggested that the association between obesity and dementia was mediated through metabolites, inflammatory cells and structural brain abnormalities.[38] One conceivable explanation is that obesity induces more aberrant cardiometabolic and inflammatory reactions,[39] which could then lead to poorer maintenance of brain volume and structure.[40] However, investigations on the mediation analysis of the relationship between BMI, WHR and brain volume in Asian populations are limited. We found that FPG and HOMA-IR mediated glucose metabolism by 45%–60%, followed by blood pressure and inflammatory cell count. Multiple cardiometabolic

and inflammatory measures mediated the association of WHR with GMV or WMHV by 1.3- to 1.5-folds compared with an individual mediator. Our findings supported the hypothesis that abnormal cardiometabolic and inflammatory processes could mediate the association between central obesity and brain volume variations.

Obesity is a major threat to public health. Our findings on obesity and brain volumes suggested that maintaining a lower BMI and WHR may protect brain structure. A small sample study of 50 extremely obese adults found that losing weight could result in increased GMV and WMV,[41] emphasising the importance of obesity as a modifiable factor in brain volume and supporting the findings of our study. In addition, cardiometabolic and inflammatory factors can partially explain the relationship between different types of obesity and brain volume differences, further investigation is needed to explore other mechanisms and pathways.

There are limitations in the present study. First, potential selection bias was unavoidable as the study was conducted in rural communities and excluded nearly one-fifth of the population due to unavailable data. Second, the cross-sectional design prevents determining causation. A further longitudinal investigation with representative participants is needed to confirm the findings. Third, our study sample was generally older, the effect of obesity in early life or in middle age on brain volume cannot be explored. Finally, the findings are limited to the Chinese Han population in rural areas and may not apply to other ethnic groups or populations.

CONCLUSIONS

BMI and WHR were associated with lower GMV and higher WMHV, potentially accelerating brain ageing by 4 years. In Chinese middle-aged and older people, 78.70% and 35.50% of cardiometabolic and inflammatory factors mediated the relationship between WHR and GMV or WMHV. Our findings suggested that normal BMI and WHR may preserve brain anatomy, with cardiometabolic and inflammatory measures mediating this effect.

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