Association of variability in body size with neuroimaging metrics of brain health: a population-based cohort study

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Summary

Background The relationship between the fluctuation in body size and brain health is poorly understood. This study aimed to examine the associations of long-term variability in body mass index (BMI) and waist-to-hip ratio (WHR) with neuroimaging metrics that approximate brain health.

Methods This cohort study recruited 1114 participants aged 25–83 years from a multicenter, community-based cohort study in China. We modeled the BMI and WHR trajectories of participants during 2006–2018 and assessed the BMI and WHR variability (direction and speed of change) by calculating the slope. Generalized linear models were applied to investigate the associations of BMI and WHR variability with MRI markers of brain tissue volume, white matter microstructural integrity, white matter hyperintensity (WMH), and cerebral small vessel disease (CSVD).

Findings Progressive weight gain during follow-up was associated with lower global fractional anisotropy (beta = –0.18, 95% confidence interval [CI] –0.34 to –0.02), higher mean diffusivity (beta = 0.15, 95% CI 0.01–0.30) and radial diffusivity (beta = 0.17, 95% CI 0.02–0.32). Weight loss was also associated with a lower burden of periventricular WMH (beta = –0.26, 95% CI –0.48 to –0.03) and a lower risk of moderate-to-severe basal ganglia enlarged perivascular spaces (BG-EPVS, odds ratio [OR] = 0.41, 95% CI 0.20–0.83). Among overweight populations, weight loss was linked with smaller volumes of WMH (beta = –0.47, 95% CI –0.79 to –0.15), periventricular WMH (beta = –0.57, 95% CI –0.88 to –0.26), and deep WMH (beta = –0.36, 95% CI –0.69 to –0.03), as well as lower risk of CSVD (OR = 0.22, 95% CI 0.08–0.62), lacune (OR = 0.12, 95% CI 0.01–0.91) and moderate-to-severe BG-EPVS (OR = 0.24, 95% CI 0.09–0.61). In adults with central obesity, WHR loss was positively associated with larger gray matter volume (beta = 0.50, 95% CI 0.11–0.89), hippocampus volume (beta = 0.62, 95% CI 0.15–1.09), and parahippocampal gyrus volume (beta = 0.85, 95% CI 0.34–1.37). The sex-stratification and age-stratification analyses revealed similar findings with the main results, with the pattern of associations significantly presented in the individuals at mid-life and late-life.

Interpretation Long-term stability of BMI level is essential for maintaining brain health. Progressive weight gain is associated with impaired white matter microstructural integrity. Weight and WHR losses are associated with improved general brain health. Our results contribute to a better understanding of the integrated associations between variations in obesity measures and brain health.

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Research in context

Evidence before this study

We searched PubMed for studies published in English between January 1, 2000 and December 1, 2023, using the search terms "body mass index", "waist-to-hip ratio", "obesity", "variability", "neuroanatomical", and "brain health". These terms were searched in different combinations separately. Higher body mass index (BMI) and waist-to-hip ratio (WHR), the established hallmarks of general and central obesity respectively, were associated with neuroimaging markers indicating negative brain health. However, the relationship between the long-term variability in BMI and WHR and brain health remains underexplored, possibly due to the cross-sectional design and the small sample size of previous studies.

Added value of this study

Long-term stability of BMI level is essential for maintaining brain health. This study shows a significant association of progressive weight gain during follow-up with impaired brain microstructural integrity. Weight and WHR losses are beneficial for better brain health, featured by larger brain tissue volumes, lower white matter hyperintensity burden, and lower risk of cerebral small vessel disease markers. The associations are particularly prominent among individuals who are overweight and central obese, and among individuals in mid-life and late-life.

Implications of all the available evidence

The present study contributes to a better understanding of the integrated relationships between variations in obesity measures and brain health. The understanding of neuroanatomical features linking obesity measures with brain health has important implications in facilitating better brain health status in the general population.

Introduction

Brain health is an evolving concept that is attracting increasing attention from both the academic research area and the wider society. Optimizing brain health improves physical and mental health and creates positive social and economic impacts, and these contribute to greater well-being and the advance of society.[1] The preservation of optimal integrity in brain structures is a key aspect that delineates the definition of brain health.[2]

The obesity epidemic and associated disease burden have become a global public health threat.[3] In recent years, the incidence of general and central obesity has increased rapidly worldwide,[4,5] with the latter being more prevalent in Asian populations.[6] Body mass index (BMI), the most widely recognized indicator of general obesity, has been acknowledged as a critical factor influencing brain health.[7,8] The application of brain magnetic resonance imaging (MRI) examination enables the objective and precise assessments of neuroimaging metrics of brain health in structural domains. Higher BMI is associated with smaller brain volume,[8–10] and lower white matter integrity.[11] Additionally, waist-to-hip ratio (WHR) may be a potential adiposity index for evaluating brain health, as it is a reliable biomarker of central obesity. Several cross-sectional studies have indicated that a higher level of WHR is associated with lower gray matter volume and larger white matter hyperintensity (WMH) volume.[8,12]

However, the weight and WHR levels may fluctuate over time. The association between changes in BMI or WHR and health risks has recently gained increasing attention.[13–15] Cross-sectional studies may not provide state-of-the-art evidence for the impacts of BMI and WHR on brain health. To our knowledge, the clinical significance of long-term variability in BMI and WHR for brain health has not been well documented in populations without a diagnosis of life-limiting illness.

This study primarily aimed to comprehensively evaluate the associations of long-term variability in BMI and WHR with neuroimaging metrics that approximate brain health in a large community population-based cohort in China. We hypothesized that rising levels of obesity measures may negatively affect brain health; conversely, decreasing levels of obesity measures would help maintain better brain health. Our study will provide new insights into the relationship between the variability in body size and brain health, and thus may provide evidence for the preservation of brain health in the general population.

Methods

Study design and participants

This study was embedded within the Kailuan Study, a prospective cohort study conducted in the Kailuan community of Tangshan, Northern China. Participants aged from 18 to 98 years were recruited from June 2006.[16] Demographic questionnaires and clinical and laboratory assessments were implemented biennially from 2006 to 2018 at 11 local hospitals.[17,18] In December 2020, a subset of the Kailuan study, termed the Multimodality MEdical imaging sTudy bAsed on KaiLuan

Study (META-KLS), was established to recruit participants for brain MRI scans. Detailed descriptions of the rationale, design, and database building of META-KLS have been published previously.[19] The primary goal of this cohort was to investigate subclinical brain morphological and functional alterations related to various risk factors and provide high-quality evidence for the prevention and early intervention of neurological diseases and cerebrovascular diseases. As of September 2022, 1195 participants had performed brain MRI examination for once.

In this study, we defined the inclusion criteria as participants who 1) completed three or more clinical visits, with BMI, WHR and other clinical parameters were measured, 2) underwent one brain MRI examination during 2020–2022, and 3) were absence of clinical diagnosed cardiovascular diseases, stroke, dementia, or neuropsychiatric disease such as bipolar disorder. The exclusion criteria were as follows: 1) missing demographic data (e.g., age, self-reported sex), 2) poor neuroimaging quality or incomplete neuroimaging data, and 3) a diagnosis of cancer (Supplementary Fig. S1).

The Medical Ethics Committee of Kailuan General Hospital approved the META-KLS study (IRB number: 2021002). Written informed consent was obtained from all the participants. This study was registered on Clinicaltrials.gov (Clinical Indicators and Brain Image Data: a Study Based on Kailuan Cohort; No. NCT05453877; https://clinicaltrials.gov/ct2/show/NCT05453877). This cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines and principles of the Declaration of Helsinki.

Anthropometric measurement

The anthropometric parameters of participants were measured by well-trained medical staff following standard instruments and protocols.[19,20] While the participants stood barefoot in light clothing, body weight was measured to the precision of 0.1 kg using a calibrated platform scale. Standing height was accurate to the precision of 0.1 cm using a platform scale altimeter. Waist circumference was measured at the midpoint between the lowest rib margin and the iliac crest and was accurate to 0.1 cm. Hip circumference was measured at the maximum circumference over the buttocks and was accurate to 0.1 cm. BMI (kg/m^2) was calculated as body weight (kg) divided by the square of standing height (m^2), and WHR was calculated as waist circumference divided by hip circumference.

Body mass index and waist-to-hip ratio variability

For BMI and WHR variability separately, we constructed a general linear model by incorporating all BMI and WHR assessments of each participant from 2006 to 2018 to calculate the slope value and corresponding p value. We used the slope method based on the least squares method to determine the trend (including direction and speed) of variability during the follow-up period.[21] Slope based on the least squares method is a classic trend detection method.[22] It fits the time series data by using least squares methods, and then judges the trend of the sequence according to the slope and corresponding p value. When slope > 0 and $p < 0.05$, it represents a significant rising trend; conversely, when slope < 0 and $p < 0.05$, it indicates a significant decreasing trend; and when $p > 0.05$, it suggests no statistically significant evidence of a trend. This method considers all the measurements of each participant, which can reflect the variability of each individual and is easy to use. We divided the subjects into three groups based on the calculated slope and p value of BMI and WHR in each participant. The groups were separately categorized by BMI and WHR.

Imaging metrics of brain health

The neuroimaging data collection has been described in detail elsewhere.[19] All brain MRI examinations were performed using a 3.0 T MRI scanner (GE Healthcare 750 W, Milwaukee, Wisconsin, USA). Briefly, the sequences used in this cohort study were three-dimensional (3D) brain volume for brain macrostructural volume evaluation based on high-resolution T1-weighted imaging (T1WI), diffusion tensor imaging (DTI) for brain microstructural integrity assessment, 3D fluid-attenuated inversion recovery (FLAIR) for the evaluation of WMH, susceptibility-weighted angiography (SWAN) for cerebral microbleeds (CMB), T2-weighted imaging (T2WI) and diffusion weighted imaging (DWI) (with FLAIR together) for the detection of enlarged perivascular spaces (EPVS) and lacune. The parameter settings for the corresponding sequences were reported in Supplementary Table S1.

Brain macrostructural volume

Global brain macrostructural volumes were calculated using the 3D-BRAVO-T1WI sequences. The volumes of the supratentorial brain tissue, including the gray matter, white matter, and the volume of cerebrospinal fluid (CSF), as well as the total intracranial volume (TIV), were quantified using an automatic pipeline based on the Statistical Parametric Mapping (SPM) software and CAT12 package (http://www.neuro.uni-jena.de). The cerebral parenchyma is the sum of the gray and white matter. Additionally, we calculated the volumes of Alzheimer's-related regions, including the hippocampus and parahippocampal gyrus, according to the AAL_90 atlas.[23,24] To normalize for head size, these brain volumetric measures were expressed as percentages of TIV. Continuous outcomes were converted to z-scores to fit the normal distribution.

Brain microstructural integrity

To assess early-stage microstructural changes in brain white matter, we examined four DTI markers that

reflect global white matter microstructural integrity. The data were pre-processed using a standardized and validated pipeline.[19] Specifically, fractional anisotropy (FA) represents the coherence of the diffusion direction of water molecules. Mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were used to assess the magnitude of water molecule diffusion. MD measures the average diffusion that is unrelated to tissue-based directionality; AD and RD measure apparent diffusivity in the directions parallel and perpendicular to the white matter tract, respectively, representing axonal and myelin integrity.[25,26] The results were z-transformed. Generally, lower FA and higher MD, AD, and RD values indicate impaired white matter microstructural integrity.

White matter hyperintensity

WMH indicates white matter lesions that exhibit hyperintensity on T2WI and FLAIR images. We quantified the volumes of WMH, as well as the volumes of periventricular white matter hyperintensity (PWMH) and deep white matter hyperintensity (DWMH), based on 3D FLAIR sequences using a widely used unsupervised pipeline of Lesion Prediction Algorithm.[27] The volumetric results were then corrected for TIV and z-transformed.

Cerebral small vessel disease

Imaging assessment of cerebral small vessel disease (CSVD) markers was performed independently by two well-trained neuroradiologists (Jing Li and Ying Hui, 12-year experience) and further confirmed by a third neuroradiologist (Wenjuan Liu, 10-year experience), who was blinded to the clinical information of all participants. CMB is identified as a lesion with extremely low signal intensity and a diameter of 2–15 mm on T2*-weighted, sensitivity-weighted, or gradient-recalled echo (GRE) images.[28] EPVS are small punctate or linear spaces displayed as CSF signals on T2 images.[29] A lacune is defined as an ovoid or round-shape lesion of the CSF signal, with a diameter of 3–15 mm and a hyperintense rim on FLAIR images.[29] We evaluated the presence of CSVD, CMBs, moderate-to-severe basal ganglia EPVS (BG-EPVS), and lacune referring to the widely accepted validated method developed by Wardlaw's group.[30]

Statistical analysis

Associations between BMI variability and the MRI markers of brain volume, white matter microstructural integrity, and WMH were assessed using the generalized linear model. We performed a binary logistic regression analysis to examine the impact of BMI variability on the presence of CSVD, CMBs, EPVS, and lacune. The same method was used to analyze WHR variability as the independent variable and MRI metrics of brain health as the dependent variables.

Three models were performed to analyze the associations of BMI and WHR variability with the MRI markers of brain health. In model 1, the effects of BMI and WHR variability on brain MRI markers were estimated without any confounder adjustment. In model 2, we included age, sex, smoking status (non-smoking, former smoker, and current smoker), alcohol use (non-drinking, former drinker, and current drinker), physical activity (exercising ≥3 times/week for ≥30 min each time), systolic blood pressure, history of diabetes, and total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels. Model 3, as the fully adjusted model, was additionally adjusted for average BMI or WHR levels on the basis of model 2. The group with no significant weight or WHR change was used as the reference. For the clinical interpretation of the findings, the results were reported as the fully adjusted difference in outcome between the weight/WHR loss group and the reference group, as well as the weight/WHR gain group and the reference group.

In addition to the overall analysis of the total population, we further performed BMI-stratified and WHR-stratified analyses based on different BMI and WHR levels. We first calculated the mean value of BMI and WHR measurements during the follow-up period for each subject. According to the World Health Organization (WHO) criteria for obesity in Asian populations,[6] the participants were classified into normal weight, BMI 18.5–23.0 kg/m^2; overweight, BMI 23.0–27.5 kg/m^2; and obese, BMI ≥27.5 kg/m^2 categories. Four participants were excluded since they were underweight (BMI <18.5 kg/m^2). According to the WHO recommendation on the sex-specific cut-off points for WHR,[31] we divided all participants into normal WHR (<0.90 for males, <0.85 for females) and abdominal obesity (≥0.90 for males, ≥0.85 for females) groups.

To test the robustness of the main findings, we also conducted sensitivity analyses stratified by age and sex respectively. We divided the subjects into young adulthood (<45 years), mid-life (45–60 years), and late-life (≥60 years).[32] The sex-stratification analysis was performed according to the self-reported sex as female and male. In addition, considering that well-established evidence has indicated the associations between hypertension and negative brain health,[33] a sensitivity analysis was conducted in the subjects without hypertension.

The Kolmogorov–Smirnov test was performed to evaluate whether continuous variables were normally distributed. Continuous variables with a normal distribution were expressed as mean (standard deviation, SD), whereas non-normal variables were described as median (interquartile range, IQR). Categorical variables were presented as absolute frequencies (relative percentages). All analyses were performed using IBM SPSS Statistics 27 (IBM Corp., Armonk, NY, USA) and R 4.2.2 (R Development Core Team). The *p*-values presented are

two-sided, and after correcting for multiple testing, p-value <0.05 determined by least significance difference was considered statistically significant.

Role of the funding source

The funder had no role in the design and conduct of the study, nor in the writing of the manuscript or the decision to submit it for publication. The authors have not been paid to write this article by any agency. As the corresponding author, I state that the authors were not precluded from accessing data in the study, and they accept responsibility to submit for publication.

Results

A total of 1114 individuals aged between 25 and 83 years were eligible for this study. The median (IQR) age was 56 (47–65) years, and 496 (44.5%) participants were females. Table 1 summarizes the demographic, clinical characteristics, and neuroimaging metrics of included participants.

BMI variability and brain health

Table 2, Fig. 1, and Supplementary Fig. S2 present the multivariate-adjusted associations between BMI variability and brain health in the general population. After full adjustments, progressive weight gain was associated with lower global FA (beta = –0.18, 95% confidence interval [CI] –0.34 to –0.02, p = 0.032) and higher MD (beta = 0.15, 95% CI 0.01–0.30, p = 0.043) and RD value (beta = 0.17, 95% CI 0.02–0.32, p = 0.025). Weight loss was associated with a lower PWMH burden (beta = –0.26, 95% CI –0.48 to –0.03, p = 0.024). Additionally, a lower risk for the presence of moderate-to-severe BG-EPVS was observed with weight loss (odds ratio [OR] = 0.41, 95% CI 0.20–0.83, p = 0.012).

WHR variability and brain health

As summarized in Table 3, Fig. 2, and Supplementary Fig. S3, WHR loss was associated with a larger gray matter volume (beta = 0.37, 95% CI 0.05–0.70, p = 0.023), as well as the volume of parahippocampal gyrus (beta = 0.54, 95% CI 0.11–0.98, p = 0.015).

The associations of waist circumference variability with neuroimaging markers were also explored with the generalized linear model. Results showed that the reduction in waist circumference level during follow up was associated with larger hippocampus volume (beta = 0.27, 95% CI 0.01–0.53, p = 0.041) (Supplementary Table S2).

BMI-stratified analysis

In the BMI-stratified analysis among individuals who were overweight, participants with weight loss exhibited a lower burden of WMH (beta = –0.47, 95% CI –0.79 to –0.15, p = 0.004) than those with no significant weight change (Supplementary Table S3 and Fig. 3). A similar association with weight loss was observed for lower PWMH (beta = –0.57, 95% CI –0.88 to –0.26, p < 0.001) and DWMH burden (beta = –0.36, 95% CI –0.69 to –0.03, p = 0.033), with the higher magnitudes of association for PWMH than for DWMH. The odds of developing any of the CSVD markers were lower with weight loss among individuals who were overweight (OR = 0.22, 95% CI 0.08–0.62, p = 0.004). More specifically, weight loss was suggestively associated with a lower risk of lacune (OR = 0.12, 95% CI 0.01–0.91, p = 0.041) and moderate-to-severe BG-EPVS (OR = 0.24, 95% CI 0.09–0.61, p = 0.003). However, we did not find any evidence of a significant association between weight loss during follow-up and the risk of CMBs.

WHR-stratified analysis

Supplementary Table S4 and Fig. 4 summarize the associations between WHR variability and brain health indices in the normal WHR and abdominal obesity groups. In individuals with abdominal obesity, compared with participants with no significant WHR change during follow-up, those undergoing WHR loss were associated with a larger gray matter volume (beta = 0.50, 95% CI 0.11–0..89, p = 0.012). Furthermore, WHR loss was also associated with larger hippocampus (beta = 0.62, 95% CI 0.15–1.09, p = 0.010) and parahippocampal gyrus volumes (beta = 0.85, 95% CI 0.34–1.37, p = 0.001).

Age-stratified analysis

The results revealed significant age-dependent relationship between BMI or WHR variability and brain health (Supplementary Tables S5 and S6). For individuals at late-life, progressively weight gain was associated with smaller hippocampus volume (beta = –0.44, 95% CI –0.73 to –0.15, p = 0.003), higher MD (beta = 0.46, 95% CI 0.09–0.83, p = 0.015), AD (beta = 0.42, 95% CI 0.07–0.78, p = 0.019) and RD value (beta = 0.45, 95% CI 0.06–0.84, p = 0.025), and weight loss was associated with a lower risk of moderate-to-severe BG-EPVS (OR = 0.29, 95% CI 0.09–0.94, p = 0.040). For individuals at mid-life, WHR loss was linked with a larger gray matter volume (beta = 0.47, 95% CI 0.02–0.92, p = 0.041). These findings were similar to the main findings of the total population.

Sex-stratified analysis

The sex-stratified analysis indicated that in male participants, progressively weight gain was correlated with higher MD (beta = 0.27, 95% CI 0.03–0.51, p = 0.026) and RD value (beta = 0.29, 95% CI 0.04–0.53, p = 0.024), and weight loss was observed with lower PWMH burden (beta = –0.32, 95% CI –0.63 to –0.01, p = 0.045) and lower risk of moderate-to-severe BG-EPVS (OR = 0.33, 95% CI 0.15–0.74, p = 0.007) and lacune (OR = 0.32, 95% CI 0.10–0.98, p = 0.046) (Supplementary Table S7). WHR loss was associated with a larger gray matter volume in males (beta = 0.40,

Characteristics	Overall	Female	Male
Demographic and clinical characteristics			
Age, years[a]	56.0 (47.0, 65.0)	53.0 (43.0, 61.8)	58.0 (50.0, 66.0)
Female, No. (%)	496 (44.5)	/	/
BMI variability, kg/m^2/2 years	0.03 (−0.09, 0.16)	0.06 (−0.07, 0.18)	0.01 (−0.11, 0.14)
WHR variability	0.00 (0.00, 0.01)	0.00 (0.01)	0.00 (0.00, 0.00)
Smoking habits, No. (%)			
Never	676 (60.7)	487 (98.2)	189 (30.6)
Past	212 (19.0)	4 (0.8)	208 (33.7)
Current	226 (20.3)	5 (1.0)	221 (35.8)
Alcohol habits, No. (%)			
Never	667 (59.9)	458 (92.3)	209 (33.8)
Past	148 (13.3)	22 (4.4)	126 (20.4)
Current	299 (26.8)	16 (3.2)	283 (45.8)
Physical activity habits, No. (%)			
Sometimes or seldom	568 (51.0)	262 (52.8)	306 (49.5)
Usually	546 (49.0)	234 (47.2)	312 (50.5)
History of hypertension, No. (%)	540 (48.5)	179 (36.1)	361 (58.4)
Systolic blood pressure, mm Hg	125.1 (116.9, 134.3)	119.9 (112.8, 128.5)	128.6 (122.0, 137.3)
History of diabetes, No. (%)	215 (19.3)	63 (12.7)	152 (24.6)
Cholesterol, mmol/L			
Total cholesterol	4.9 (4.4, 5.5)	4.8 (4.3, 5.4)	5.0 (4.5, 5.5)
High density lipoprotein cholesterol	1.4 (1.3, 1.7)	1.5 (1.4, 1.7)	1.4 (1.2, 1.6)
Low density lipoprotein cholesterol	2.6 (2.2, 3.0)	2.6 (2.2, 3.0)	2.7 (0.6)
Triglyceride, mmol/L	1.4 (1.1, 2.1)	1.2 (0.9, 1.7)	1.6 (1.2, 2.4)
MRI profiles			
TIV, cm^3	1496.0 (1399.1, 1596.5)	1400.6 (97.0)	1580.9 (114.0)
Brain macrostructural volume, % of TIV			
Brain parenchyma	73.6 (70.6, 76.4)	75.7 (73.3, 78.0)	71.8 (69.4, 74.2)
Gray matter	39.9 (2.7)	41.4 (2.5)	38.6 (2.2)
White matter	33.5 (32.1, 34.9)	34.1 (32.7, 35.2)	33.0 (2.1)
Cerebrospinal fluid	26.3 (23.5, 29.2)	24.1 (21.9, 26.5)	28.2 (3.6)
Hippocampus	0.2 (0.2, 0.3)	0.3 (0.2, 0.3)	0.2 (0.2, 0.2)
Parahippocampal gyrus	0.2 (0.0)	0.2 (0.0)	0.2 (0.0)
Brain microstructural integrity			
Fractional anisotropy	0.46 (0.45, 0.47)	0.46 (0.02)	0.46 (0.44, 0.47)
Mean diffusivity, 10^{-3} mm^2/s	0.81 (0.80, 0.84)	0.80 (0.79, 0.82)	0.82 (0.80, 0.85)
Axial diffusivity, 10^{-3} mm^2/s	1.26 (1.25, 1.28)	1.25 (1.24, 1.27)	1.27 (1.25, 1.29)
Radial diffusivity, 10^{-3} mm^2/s	0.59 (0.57, 0.62)	0.58 (0.56, 0.60)	0.60 (0.58, 0.63)
White matter hyperintensity, % of TIV			
White matter hyperintensity	0.23 (0.11, 0.55)	0.16 (0.07, 0.38)	0.32 (0.16, 0.76)
Periventricular white matter hyperintensity	0.14 (0.06, 0.33)	0.10 (0.05, 0.24)	0.18 (0.09, 0.42)
Deep white matter hyperintensity	0.09 (0.03, 0.22)	0.05 (0.02, 0.14)	0.12 (0.05, 0.30)
Cerebral small vessel disease			
Presence of cerebral small vessel disease	701 (62.9)	265 (53.4)	436 (70.6)
Presence of cerebral microbleeds	278 (25.0)	84 (16.9)	194 (31.4)
Presence of moderate-to-severe basal ganglia enlarged perivascular spaces	614 (55.1)	217 (43.8)	397 (64.2)
Presence of lacune	172 (15.4)	34 (6.9)	138 (22.3)

BMI, body mass index; WHR, waist-to-hip ratio; TIV, total intracranial volume. Values are presented as mean (SD), median (IQR), or no. (%). [a]Age is calculated at the time of MR acquisition.

Table 1: **Demographic, clinical characteristics, and neuroimaging metrics of participants.**

95% CI 0.02–0.79, $p = 0.040$). And in female individuals, WHR loss was associated with larger hippocampus (beta = 0.81, 95% CI 0.17–1.46, $p = 0.014$) and parahippocampal gyrus volumes (beta = 1.11, 95% CI 0.36–1.86, $p = 0.004$) (Supplementary Table S8). These findings were also largely in line with the main results.

Index of brain health	Weight loss		Reference	Weight gain	
	β	*p* value	β	β	*p* value
Brain macrostructural volume (in z-score)	N = 53		N = 825	N = 133	
Cerebral parenchyma					
Model 1	−0.21 (−0.48 to 0.07)	0.143	0 (ref)	0.16 (−0.02 to 0.35)	0.079
Model 2	0.01 (−0.17 to 0.18)	0.948	0 (ref)	−0.04 (−0.15 to 0.08)	0.538
Model 3	0.02 (−0.16 to 0.19)	0.836	0 (ref)	−0.05 (−0.17 to 0.06)	0.370
Gray matter					
Model 1	−0.23 (−0.50 to 0.05)	0.109	0 (ref)	**0.21 (0.03–0.40)**	**0.020**
Model 2	0.01 (−0.17 to 0.18)	0.938	0 (ref)	0.03 (−0.09 to 0.14)	0.667
Model 3	0.02 (−0.15 to 0.20)	0.794	0 (ref)	0.00 (−0.11 to 0.12)	0.945
White matter					
Model 1	−0.11 (−0.39 to 0.16)	0.420	0 (ref)	0.04 (−0.14 to 0.23)	0.652
Model 2	0 (−0.23 to 0.24)	0.984	0 (ref)	−0.11 (−0.26 to 0.05)	0.180
Model 3	0.01 (−0.23 to 0.24)	0.962	0 (ref)	−0.11 (−0.26 to 0.05)	0.164
Cerebrospinal fluid					
Model 1	0.21 (−0.07 to 0.49)	0.138	0 (ref)	−0.17 (−0.35 to 0.01)	0.066
Model 2	0 (−0.18 to 0.17)	0.966	0 (ref)	0.03 (−0.09 to 0.14)	0.640
Model 3	−0.02 (−0.19 to 0.16)	0.854	0 (ref)	0.04 (−0.07 to 0.16)	0.454
Hippocampus					
Model 1	−0.25 (−0.53 to 0.03)	0.076	0 (ref)	0.10 (−0.08 to 0.28)	0.274
Model 2	−0.07 (−0.29 to 0.15)	0.552	0 (ref)	−0.03 (−0.18 to 0.11)	0.647
Model 3	−0.06 (−0.28 to 0.16)	0.577	0 (ref)	−0.04 (−0.19 to 0.11)	0.596
Parahippocampal gyrus					
Model 1	−0.13 (−0.40 to 0.15)	0.363	0 (ref)	0.15 (−0.03 to 0.33)	0.104
Model 2	0 (−0.24 to 0.24)	0.988	0 (ref)	0.03 (−0.13 to 0.19)	0.686
Model 3	0.01 (−0.23 to 0.25)	0.943	0 (ref)	0.02 (−0.14 to 0.18)	0.770
Brain microstructural integrity (in z-score)	**N = 54**		**N = 858**	**N = 130**	
Fractional anisotropy					
Model 1	0.08 (−0.20 to 0.35)	0.585	0 (ref)	−0.05 (−0.24 to 0.13)	0.573
Model 2	0.12 (−0.13 to 0.36)	0.352	0 (ref)	**−0.19 (−0.35 to −0.02)**	**0.025**
Model 3	0.11 (−0.13 to 0.35)	0.373	0 (ref)	**−0.18 (−0.34 to −0.02)**	**0.032**
Mean diffusivity					
Model 1	−0.03 (−0.30 to 0.25)	0.841	0 (ref)	−0.02 (−0.20 to 0.16)	0.835
Model 2	−0.13 (−0.35 to 0.09)	0.236	0 (ref)	**0.16 (0.01–0.31)**	**0.034**
Model 3	−0.13 (−0.35 to 0.09)	0.253	0 (ref)	**0.15 (0.01–0.30)**	**0.043**
Axial diffusivity					
Model 1	0.01 (−0.26 to 0.28)	0.941	0 (ref)	−0.08 (−0.26 to 0.10)	0.394
Model 2	−0.12 (−0.34 to 0.11)	0.311	0 (ref)	0.09 (−0.07 to 0.24)	0.264
Model 3	−0.11 (−0.34 to 0.11)	0.330	0 (ref)	0.08 (−0.07 to 0.23)	0.302
Radial diffusivity					
Model 1	−0.04 (−0.32 to 0.23)	0.759	0 (ref)	0 (−0.18 to 0.19)	0.965
Model 2	−0.13 (−0.35 to 0.09)	0.241	0 (ref)	**0.18 (0.03–0.33)**	**0.019**
Model 3	−0.13 (−0.35 to 0.09)	0.257	0 (ref)	**0.17 (0.02–0.32)**	**0.025**
White matter hyperintensity (in z-score)	**N = 52**		**N = 805**	**N = 129**	
White matter hyperintensity					
Model 1	0.01 (−0.26 to 0.29)	0.942	0 (ref)	−0.11 (−0.29 to 0.07)	0.242
Model 2	−0.13 (−0.37 to 0.11)	0.286	0 (ref)	0.06 (−0.10 to 0.22)	0.473
Model 3	−0.15 (−0.38 to 0.09)	0.232	0 (ref)	0.08 (−0.08 to 0.24)	0.324
Periventricular white matter hyperintensity					
Model 1	−0.10 (−0.37 to 0.18)	0.485	0 (ref)	−0.11 (−0.29 to 0.07)	0.246
Model 2	**−0.24 (−0.47 to −0.02)**	**0.033**	0 (ref)	0.08 (−0.07 to 0.22)	0.322
Model 3	**−0.26 (−0.48 to −0.03)**	**0.024**	0 (ref)	0.09 (−0.05 to 0.24)	0.215

(Table 2 continues on next page)

Index of brain health	Weight loss		Reference	Weight gain	
	β	*p* value	β	β	*p* value
Brain macrostructural volume (in z-score)	N = 53		N = 825	N = 133	
(Continued from previous page)					
Deep white matter hyperintensity					
Model 1	0.09 (−0.19 to 0.36)	0.546	0 (ref)	−0.10 (−0.28 to 0.08)	0.283
Model 2	−0.04 (−0.29 to 0.22)	0.764	0 (ref)	0.04 (−0.13 to 0.21)	0.633
Model 3	−0.05 (−0.31 to 0.20)	0.675	0 (ref)	0.06 (−0.11 to 0.23)	0.465
Cerebral small vessel disease	**N = 49**		**N = 836**	**N = 130**	
Presence of cerebral small vessel disease					
Model 1	0.95 (0.51–1.78)	0.874	1.00 (ref)	**0.63 (0.43–0.92)**	**0.017**
Model 2	0.59 (0.27–1.28)	0.179	1.00 (ref)	1.07 (0.66–1.74)	0.776
Model 3	0.59 (0.27–1.27)	0.175	1.00 (ref)	1.10 (0.68–1.78)	0.707
Presence of cerebral microbleeds					
Model 1	**1.85 (1.03–3.34)**	**0.041**	1.00 (ref)	0.84 (0.55–1.29)	0.428
Model 2	1.67 (0.88–3.16)	0.118	1.00 (ref)	1.12 (0.69–1.81)	0.646
Model 3	1.68 (0.88–3.19)	0.113	1.00 (ref)	1.11 (0.68–1.79)	0.684
Presence of moderate-to-severe basal ganglia enlarged perivascular spaces					
Model 1	0.73 (0.41–1.31)	0.289	1.00 (ref)	**0.56 (0.39–0.81)**	**0.002**
Model 2	**0.41 (0.21–0.83)**	**0.013**	1.00 (ref)	0.89 (0.56–1.43)	0.631
Model 3	**0.41 (0.20–0.83)**	**0.012**	1.00 (ref)	0.94 (0.59–1.52)	0.811
Presence of lacune					
Model 1	0.76 (0.34–1.73)	0.516	1.00 (ref)	0.60 (0.34–1.05)	0.074
Model 2	0.50 (0.19–1.29)	0.151	1.00 (ref)	0.74 (0.36–1.50)	0.399
Model 3	0.50 (0.19–1.30)	0.153	1.00 (ref)	0.73 (0.36–1.49)	0.393

BMI, body mass index. The group with no significant weight change was used as the reference. Model 1 did not correct for any covariates. Model 2 was adjusted for age, sex, smoking status, alcohol use, physical activity, systolic blood pressure, history of diabetes, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. Model 3 was additionally adjusted for average BMI level based on Model 2. Bold values indicated that *p*-value < 0.05.

Table 2: **Association of BMI variability with brain macrostructural volume, brain microstructural integrity, white matter hyperintensity, and cerebral small vessel disease.**

Sensitivity analysis in subjects without hypertension

The main findings largely remained significant in subjects without hypertension after full adjustment, especially regarding the WHR (Supplementary Tables S9 and S10). Several results regarding the BMI remained in the same direction but without statistical significance. We consider that this may be due to the largely reduced sample size. These results further proved the robustness of the main analysis.

Discussion

In this population-based cohort study, we investigated the association of changes in body size indicators with a wide range of established neuroimaging markers of brain health. The primary findings indicated that weight gain was associated with poor white matter microstructural integrity, including lower global FA values and higher MD and RD values. Weight loss was associated with a lower burden of PWMH and lower risk of moderate-to-severe BG-EPVS. We also observed associations between WHR loss and larger gray matter volume and parahippocampal gyrus volume. In summary, our findings emphasized the detrimental effects of weight gain as well as the protective effects of weight and WHR loss on brain health.

There are several strengths in this study. First, it was a large community population-based study, with the enrollment of subjects of a wide range of ages in nearly the life course. The findings may be well generalized to the general population in Northern China. Second, multimodal neuroimaging enables objective and precise quantitative assessments of brain structures from distinct aspects. This provides a comprehensive framework for assessing the state of brain health. Third, We repeatedly collected information on BMI and WHR for multiple times over a 12-year follow-up period, which may have reduced random errors associated with the cross-sectional studies. The high-quality longitudinal measurement data allowed for the exploration of the impact of BMI and WHR variations on brain health. Most importantly, we performed comprehensive sensitivity analyses in BMI and WHR-stratified, age-stratified, sex-stratified, and nonhypertension groups respectively. These analyses revealed largely consistent findings with the main results, with the associations significantly present in the individuals at mid-life and late-life.

The present study elucidated the clinical relevance of BMI and WHR variability with brain macrostructural

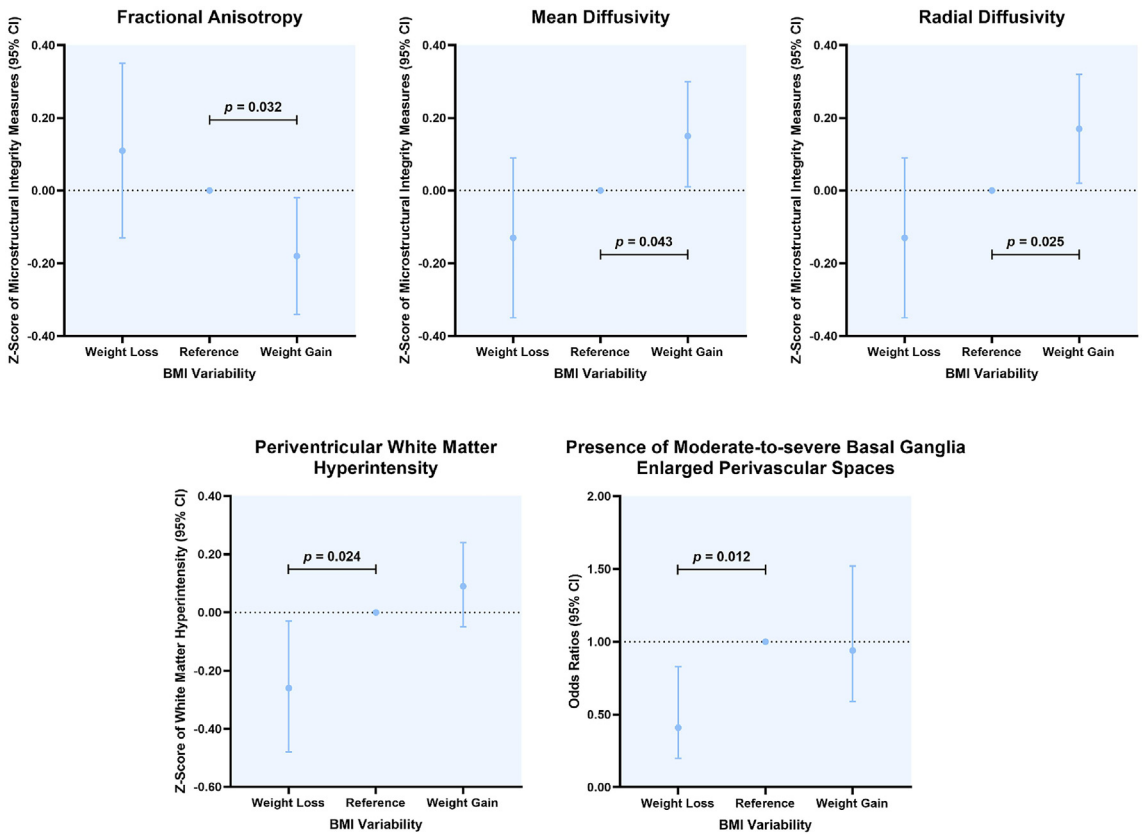

Fig. 1: The association of BMI variability with neuroimaging metrics of brain health. The BMI variability was categorized into weight loss, no significant change (reference), and weight gain groups. Associations were estimated after adjusting for age, sex, smoking and alcohol use status, physical activity, systolic blood pressure, history of diabetes, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and average BMI level. Abbreviations: BMI, body mass index.

and microstructural metrics. However, it is worth noting that our findings reveal that the aspects of brain structural alterations susceptible to BMI and WHR variations are significantly different. In our study, long-term BMI variations primarily affect white matter microstructural integrity, WMH, and CSVD, whereas WHR variations are mainly associated with brain volumetric alterations. This phenomenon was in line with a meta-analysis of 45 observational epidemiological studies of obesity and brain structures by Han et al.[34] Our study provided additional evidence to investigate the different effects of BMI and WHR variations on brain structures.

In this cohort study, we reported that progressive weight gain during long-term follow-up period was associated with disrupted microstructural integrity. This suggests that white matter injuries are sensitive to weight changes at the microstructural level, which may present prior to the macrostructural volume alterations. This finding was consistent with the evidence from a previous study showing that elevated BMI levels were associated with impaired white matter integrity.[11] The age-stratification analyses also yielded similar findings to the main results in late-life regarding to progressively increased BMI. Our study emphasizes that long-term weight control is critical for brain health especially during late life.

Emerging evidence from the analysis among participants who were overweight suggested that weight loss during the 12-year follow-up was associated with neuroimaging features associated with better brain health. Except for several identical findings with the main analysis, additional significant results included smaller volumes of WMH, and DWMH, as well as a lower risk of CSVD, and the presence of lacune. In adults featured by central obesity, WHR loss was also positively associated with larger gray matter, hippocampus, and parahippocampal gyrus volumes. These findings suggest that loss of adiposity may play an essential role in maintaining brain health, with the effect being particularly pronounced in subjects who are overweight and central obese.

A previous cohort study based on UK Biobank has observed a positive correlation between waist

Index of brain health	WHR loss		Reference	WHR gain	
	β	*p* value	β	β	*p* value
Brain macrostructural volume (in z-score)	N = 15		N = 944	N = 52	
Cerebral parenchyma					
Model 1	0.03 (−0.48 to 0.54)	0.906	0 (ref)	0.28 (0–0.55)	0.051
Model 2	0.07 (−0.24 to 0.39)	0.648	0 (ref)	0.02 (−0.16 to 0.20)	0.829
Model 3	0.09 (−0.23 to 0.41)	0.592	0 (ref)	0.02 (−0.16 to 0.19)	0.838
Gray matter					
Model 1	0.30 (−0.21 to 0.80)	0.251	0 (ref)	**0.32(0.04–0.59)**	**0.026**
Model 2	**0.36(0.04–0.68)**	**0.028**	0 (ref)	0.02 (−0.16 to 0.20)	0.839
Model 3	**0.37(0.05–0.70)**	**0.023**	0 (ref)	0.02 (−0.16 to 0.19)	0.848
White matter					
Model 1	−0.33 (−0.84 to 0.18)	0.209	0 (ref)	0.14 (−0.14 to 0.42)	0.340
Model 2	−0.33 (−0.75 to 0.10)	0.133	0 (ref)	0.01 (−0.22 to 0.25)	0.905
Model 3	−0.32 (−0.74 to 0.11)	0.145	0 (ref)	0.01 (−0.22 to 0.25)	0.910
Cerebrospinal fluid					
Model 1	−0.04 (−0.54 to 0.47)	0.886	0 (ref)	−0.28 (−0.55 to 0)	0.052
Model 2	−0.08 (−0.40 to 0.24)	0.616	0 (ref)	−0.02 (−0.20 to 0.16)	0.836
Model 3	−0.09 (−0.41 to 0.23)	0.563	0 (ref)	−0.02 (−0.19 to 0.16)	0.846
Hippocampus					
Model 1	0.25 (−0.26 to 0.75)	0.344	0 (ref)	0.27 (−0.01 to 0.55)	0.055
Model 2	0.28 (−0.12 to 0.68)	0.167	0 (ref)	0.03 (−0.19 to 0.25)	0.816
Model 3	0.30 (−0.10 to 0.70)	0.141	0 (ref)	0.03 (−0.20 to 0.24)	0.826
Parahippocampal gyrus					
Model 1	0.51 (0–1.01)	0.050	0 (ref)	0.12 (−0.16 to 0.39)	0.412
Model 2	**0.52(0.08–0.96)**	**0.019**	0 (ref)	−0.04 (−0.28 to 0.20)	0.726
Model 3	**0.54(0.11–0.98)**	**0.015**	0 (ref)	−0.05 (−0.28 to 0.20)	0.714
Brain microstructural integrity (in z-score)	**N = 16**		**N = 973**	**N = 53**	
Fractional anisotropy					
Model 1	0 (−0.50 to 0.49)	0.987	0 (ref)	0.12 (−0.16 to 0.39)	0.398
Model 2	−0.02 (−0.46 to 0.41)	0.921	0 (ref)	0.04 (−0.21 to 0.28)	0.782
Model 3	−0.03 (−0.47 to 0.41)	0.892	0 (ref)	0.04 (−0.21 to 0.28)	0.781
Mean diffusivity					
Model 1	0.12 (−0.37 to 0.61)	0.637	0 (ref)	−0.21 (−0.49 to 0.06)	0.133
Model 2	0.11 (−0.28 to 0.50)	0.590	0 (ref)	−0.02 (−0.24 to 0.20)	0.863
Model 3	0.11 (−0.28 to 0.50)	0.590	0 (ref)	−0.02 (−0.24 to 0.20)	0.863
Axial diffusivity					
Model 1	0.20 (−0.29 to 0.69)	0.424	0 (ref)	−0.26 (−0.53 to 0.02)	0.065
Model 2	0.17 (−0.23 to 0.57)	0.400	0 (ref)	−0.03 (−0.25 to 0.20)	0.823
Model 3	0.17 (−0.24 to 0.57)	0.420	0 (ref)	−0.03 (−0.25 to 0.20)	0.823
Radial diffusivity					
Model 1	0.08 (−0.41 to 0.57)	0.753	0 (ref)	−0.18 (−0.46 to 0.09)	0.192
Model 2	0.07 (−0.32 to 0.47)	0.714	0 (ref)	−0.02 (−0.24 to 0.21)	0.885
Model 3	0.08 (−0.32 to 0.47)	0.704	0 (ref)	−0.02 (−0.24 to 0.21)	0.884
White matter hyperintensity (in z-score)	**N = 14**		**N = 922**	**N = 50**	
White matter hyperintensity					
Model 1	0.09 (−0.43 to 0.60)	0.748	0 (ref)	−0.12 (−0.40 to 0.16)	0.410
Model 2	0.04 (−0.41 to 0.48)	0.876	0 (ref)	0 (−0.25 to 0.24)	0.974
Model 3	0.02 (−0.43 to 0.47)	0.925	0 (ref)	0 (−0.24 to 0.24)	0.985
Periventricular white matter hyperintensity					
Model 1	0.16 (−0.35 to 0.68)	0.536	0 (ref)	−0.06 (−0.33 to 0.22)	0.689
Model 2	0.13 (−0.29 to 0.55)	0.552	0 (ref)	0.06 (−0.17 to 0.28)	0.612
Model 3	0.11 (−0.30 to 0.53)	0.593	0 (ref)	0.06 (−0.17 to 0.29)	0.601

(Table 3 continues on next page)

Index of brain health	WHR loss		Reference	WHR gain	
	β	*p* value	β	β	*p* value
Brain macrostructural volume (in z-score)	N = 15		N = 944	N = 52	
(Continued from previous page)					
Deep white matter hyperintensity					
Model 1	0.02 (−0.50 to 0.54)	0.934	0 (ref)	−0.15 (−0.43 to 0.13)	0.295
Model 2	−0.03 (−0.51 to 0.44)	0.893	0 (ref)	−0.05 (−0.30 to 0.21)	0.715
Model 3	−0.05 (−0.52 to 0.43)	0.849	0 (ref)	−0.05 (−0.30 to 0.21)	0.724
Cerebral small vessel disease	**N = 14**		**N = 948**	**N = 53**	
Presence of cerebral small vessel disease					
Model 1	2.67 (0.59–12.01)	0.200	1.00 (ref)	0.73 (0.41–1.30)	0.290
Model 2	2.60 (0.48–14.19)	0.270	1.00 (ref)	0.99 (0.48–2.03)	0.978
Model 3	2.57 (0.47–14.06)	0.277	1.00 (ref)	0.99 (0.48–2.03)	0.979
Presence of cerebral microbleeds					
Model 1	1.49 (0.49–4.48)	0.482	1.00 (ref)	1.06 (0.57–1.95)	0.863
Model 2	1.43 (0.44–4.67)	0.551	1.00 (ref)	1.59 (0.80–3.14)	0.183
Model 3	1.45 (0.44–4.74)	0.539	1.00 (ref)	1.59 (0.80–3.14)	0.183
Presence of moderate-to-severe basal ganglia enlarged perivascular spaces					
Model 1	2.39 (0.66–8.62)	0.183	1.00 (ref)	0.79 (0.45–1.37)	0.400
Model 2	2.26 (0.51–10.10)	0.286	1.00 (ref)	1.21 (0.61–2.40)	0.595
Model 3	2.18 (0.48–9.82)	0.310	1.00 (ref)	1.20 (0.60–2.40)	0.597
Presence of lacune					
Model 1	0.80 (0.18–3.62)	0.775	1.00 (ref)	0.73 (0.33–1.65)	0.454
Model 2	0.59 (0.11–3.10)	0.529	1.00 (ref)	1.52 (0.55–4.16)	0.419
Model 3	0.58 (0.11–3.03)	0.515	1.00 (ref)	1.52 (0.55–4.19)	0.414

WHR, waist-to-hip ratio. The group with no significant WHR change was used as the reference. Model 1 did not correct for any covariates. Model 2 was adjusted for age, sex, smoking status, alcohol use, physical activity, systolic blood pressure, history of diabetes, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. Model 3 was additionally adjusted for average WHR level based on Model 2. Bold values indicated that *p*-value < 0.05.

Table 3: **Association of WHR variability with brain macrostructural volume, brain microstructural integrity, white matter hyperintensity, and cerebral small vessel disease.**

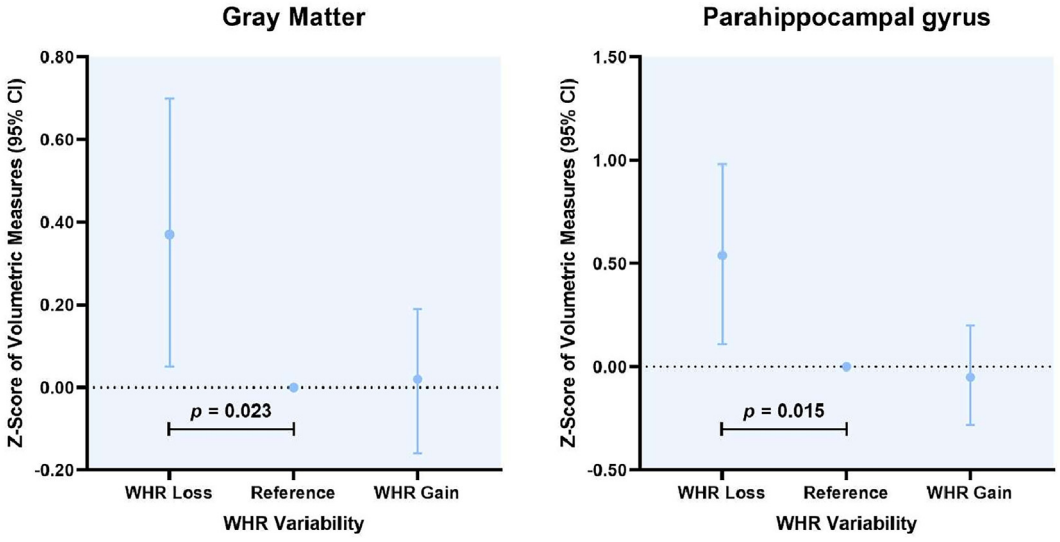

Fig. 2: The association of WHR variability with neuroimaging metrics of brain health. The WHR variability was categorized into WHR loss, no significant change (reference), and WHR gain groups. Associations were estimated after adjusting for age, sex, smoking and alcohol use status, physical activity, systolic blood pressure, history of diabetes, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and average WHR level. Abbreviations: WHR, waist-to-hip ratio.

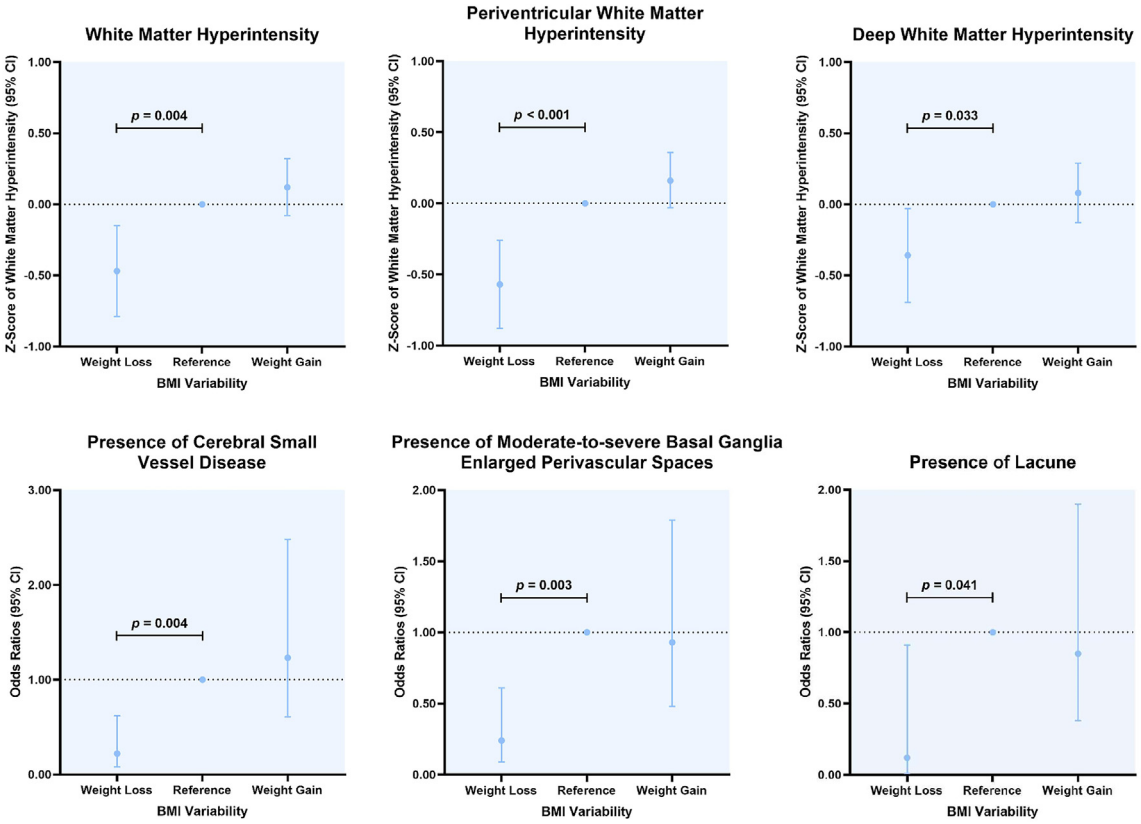

Fig. 3: The association of BMI variability with neuroimaging metrics of brain health among overweight adults. The BMI variability was categorized into weight loss, no significant change (reference), and weight gain groups. Associations were estimated after adjusting for age, sex, smoking and alcohol use status, physical activity, systolic blood pressure, history of diabetes, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and average BMI level. Abbreviations: BMI, body mass index.

circumference and the risk of ischemic stroke and intracerebral hemorrhage.[35] Furthermore, the variability in waist circumference is significantly linked with a higher risk of all-cause mortality,[13,14,36] cancer mortality,[13] and cardiovascular disease mortality.[14] However, there is still limited evidence regarding the relationship between changes in central adiposity indicators and neuroimaging metrics.[37] Our study reported for the first time that decreased waist circumference level was associated with larger hippocampus volume, and decreased WHR

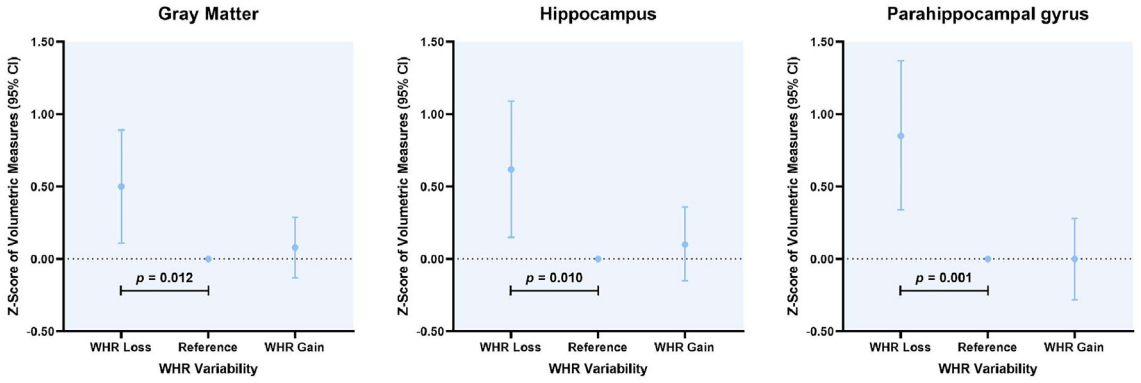

Fig. 4: The association of WHR variability with neuroimaging metrics of brain health among individuals with abdominal obesity. The WHR variability was categorized into WHR loss, no significant change (reference), and WHR gain groups. Associations were estimated after adjusting for age, sex, smoking and alcohol use status, physical activity, systolic blood pressure, history of diabetes, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and average WHR level. Abbreviations: WHR, waist-to-hip ratio.

was linked with larger gray matter volume and parahippocampal gyrus volume. The findings provide novel evidence on the relationship between long-term variability in central adiposity indicators with brain macrostructural features.

There are emerging evidences regarding the mechanism that links the body size and neuroimaging features.[38] Several hypotheses were proposed according to population-based studies and animal experiments. Activation of reward circuits,[39,40] and demyelination or axonal loss[41] may be possible reasons for brain macro- and microstructural changes. Especially for excessive accumulation of adipose tissue, complex endocrine and metabolic regulations may be associated with systemic chronic, low-grade inflammations that are featured by elevated interleukine-6 and high-sensitivity C-reactive protein.[42] Possible mechanisms may involve enlargement of mature adipocytes and impaired adipogenesis, increased number of immune cells infiltrating adipose tissue, changes in the cellular composition of adipose tissue and fibrosis, and altered secretion of proinflammatory cytokines.[43] These inflammatory responses may have a harmful impact on the brain.[44] Further studies based on the large populations are still needed to explore the mechanisms.

This study has a few limitations. First, the participants of META-KLS had completed the brain MRI examination for once. Longitudinal brain MRI data are warranted to analyze changes in neuroimaging features over time in the future. Second, examinations such as dual-energy X-ray absorptiometry, which can quantify the proportion of muscle and adipose tissue, were not used in this study. Thus, we may not determine the muscular proportion of the subjects. Third, the findings on BMI and WHR variability over a period of years may not be generalizable to variability over shorter periods.

Conclusions

Long-term stability of BMI level is essential for maintaining brain health. Progressive weight gain is associated with damaged white matter microstructural integrity. Weight and WHR losses are suggestively associated with improved brain health, manifested as larger volumes of brain tissues, lower WMH burden, and lower risk of CSVD markers. The present study contributes to a better understanding of the integrated relationship between variations in obesity measures and brain health.

Contributors

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Data sharing statement

Clinical data will be available for other research groups whose proposed use of the data has been approved by an independent review committee identified for this purpose. Requests for data should be directed to the principal investigator, Dr. Zhenchang Wang (cjr.wzhch@vip.163.com).

Declaration of interests

The authors report no conflicts of interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101015.

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