www.thelancet.com Vol 44 March, 2024

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

Jing Sun,^{a,e} Na Zeng,^{b,e} Ying Hui,^a Jing Li,^a Wenjuan Liu,^a Xinyu Zhao,^c Pengfei Zhao,^a Shuohua Chen,^d Shouling Wu,^d Zhenchang Wang,^{a,*} and Han Lv^{a,**}

^aDepartment of Radiology, Beijing Friendship Hospital, Capital Medical University, No. 95 Yongan Road, Xicheng District, Beijing 100050, China

^bSchool of Public Health, Peking University, Beijing 100191, China

^cClinical Epidemiology and Evidence-based Medicine Unit, Capital Medical University, No. 95 Yongan Road, Xicheng District, Beijing 100050, China

^dDepartment of Cardiology, Kailuan General Hospital, Tangshan, Hebei 063000, China

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.





The Lancet Regional Health - Western Pacific 2024;44: 101015

Published Online xxx https://doi.org/10. 1016/j.lanwpc.2024. 101015

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.

Funding This study was supported by grants No. 62171297 (Han Lv) and 61931013 (Zhenchang Wang) from the National Natural Science Foundation of China, No. 7242267 from the Beijing Natural Science Foundation (Han Lv), and No. [2015] 160 from the Beijing Scholars Program (Zhenchang Wang).

Copyright © 2024 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

*Corresponding author.

**Corresponding author.

^eThe authors contributed equally to this work.

1

E-mail addresses: cjr.wzhch@vip.163.com (Z. Wang), chrislvhan@126.com (H. Lv).

Keywords: Cohort study; Body mass index; Waist-to-hip ratio; Variability; Brain health; Neuroimaging; Cerebral small vessel disease

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-tohip 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/m²) was calculated as body weight (kg) divided by the square of standing height (m²), 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, susceptibilityweighted 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 ztransformed.

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, 12year 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 (nondrinking, 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 WHRstratified 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/m²; overweight, BMI 23.0-27.5 kg/ m²; and obese, BMI \geq 27.5 kg/m² categories. Four participants were excluded since they were underweight (BMI <18.5 kg/m²). 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 (\geq 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 adult-hood (<45 years), mid-life (45–60 years), and late-life (\geq 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 -0.69to -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,

Articles

	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)		1
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. (%)		5 (1)	(33-7)
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. (%)	299 (2000)	10 (5.2)	205 (45.0)
Sometimes or seldom	568 (51.0)	262 (52.8)	306 (49 5)
	546 (49.0)	234 (47.2)	312 (50 5)
History of hypertension No. (%)	540 (49.0) E40 (48.E)	234 (47.2)	261 (ES 4)
Systelic blood prossure mm Ha	125 1 (116 0 124 2)	1/9 (30.1) 110 0 (113 8 138 E)	128 6 (122 0 127 2)
History of diabates No. (%)	215 (10.2)	62 (12 7)	152 (24 6)
Chalastaval manal/	215 (19.3)	03 (12.7)	152 (24.0)
l'otal cholesterol	4.9 (4.4, 5.5)	4.8 (4.3, 5.4)	5.0 (4.5, 5.5)
	1.4(1.3, 1.7)	1.5 (1.4, 1.7)	1.4 (1.2, 1.6)
	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./)	1.6 (1.2, 2.4)
	140(0/12001.150(5)	1400 ((07.0)	1590.0 (114.0)
	1496.0 (1399.1, 1596.5)	1400.6 (97.0)	1580.9 (114.0)
Brain macrostructural volume, % of TIV			
Brain parenchyma	/3.6 (/0.6, /6.4)	/5./ (/3.3, /8.0)	/1.8 (69.4, /4.2)
Gray matter	39.9 (2./)	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 n	resented as mean (SD), median (IOR), or	r no. (%). ^a Age is calculated at the ti	ime of MR acquisition.

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.

PPP <th< th=""><th>Index of brain health</th><th colspan="2">Weight loss</th><th>Reference</th><th colspan="2">Weight gain</th></th<>	Index of brain health	Weight loss		Reference	Weight gain	
Intermentational values (not server)N + 53N + 93Orchal parmalysma-021 (-045 non)0.1410 (nd)0.05 (-0.027 no.051)0.035Madal 20.011 (-0.77 no.151)0.0460.064-0.05 (-0.27 no.051)0.035Madal 20.011 (-0.17 no.151)0.0460.0640.0550.010Madal 10.021 (-0.15 no.051)0.0150.0100.0120.0100.010Madal 10.021 (-0.15 no.051)0.0120.0100.0100.0100.010Madal 20.011 (-0.15 no.011)0.0150.0100.0110.0100.010Madal 30.012 (-0.15 no.011)0.0120.0120.0120.0120.011Madal 30.012 (-0.15 no.011)0.0120.0110.0120.0120.011Madal 30.012 (-0.012 no.011)0.0120.0120.0110.0120.011Madal 30.012 (-0.012 no.011)0.0210.0210.0210.0210.021Madal 10.0120.0210.0210.0210.0210.0210.021Madal 30.0120.0210.0210.0210.0210		β	p value	β	β	p value
General parandoms -021 (-0.48 to 6.07) 0.148 0 (ref) 0.01 (-0.12 to 0.28) 0.478 Model 1 0.021 (-0.16 to 0.13) 0.936 0 (ref) -0.05 (-0.127 to 0.05) 0.370 Model 1 -0.07 (-0.16 to 0.13) 0.936 0 (ref) 0.02 (-0.11 to 0.15) 0.109 Model 1 -0.07 (-0.17 to 0.15) 0.109 0 (ref) 0.02 (-0.11 to 0.12) 0.046 Model 2 0.02 (-0.15 to 0.15) 0.109 0 (ref) 0.02 (-0.01 to 0.12) 0.045 Model 1 -0.011 (-0.19 to 0.15) 0.490 0 (ref) -0.01 (-0.13 to 0.23) 0.652 Model 1 -0.017 (-0.02 to 0.02) 0.940 0 (ref) -0.01 (-0.03 to 0.02) 0.946 Model 1 0.022 (-0.13 to 0.12) 0.938 0 (ref) -0.01 (-0.03 to 0.02) 0.966 Model 1 0.021 (-0.02 to 0.02) 0.940 0 (ref) -0.01 (-0.03 to 0.02) 0.966 Model 1 -0.027 (-0.03 to 0.02) 0.952 0 (ref) -0.01 (-0.03 to 0.23) 0.264 Model 1 -0.027 (-0.23 to 0.13) 0.572 <	Brain macrostructural volume (in z-score)	N = 53		N = 825	N = 133	
Medel 1 -0.21 (4.048 to 0.07) 0.14j 0 (ref) 0.01 (4.027 to 0.18) 0.049 Medel 3 0.02 (0.16 to 0.02) 0.886 0.07 0.03 (4.05 to 0.05) 0.017 Medel 1 -0.03 (4.05 to 0.05) 0.190 0.017 0.020 0.020 Medel 2 0.01 (-0.17 to 0.18) 0.393 0.074 0.020 to 0.01 (0.020 to 0.14) 0.657 Medel 3 0.01 (-0.17 to 0.18) 0.393 0.074 0.020 to 0.01 (0.020 to 0.14) 0.657 Medel 1 0.01 (-0.23 to 0.24) 0.920 0.021 (0.020 to 0.14) 0.657 Medel 2 0.120 (23 to 2.24) 0.920 0.021 (-0.25 to 0.03) 0.056 Medel 3 0.120 (20 to 0.43) 0.124 0.020 (0.014 to 0.05) 0.164 Medel 1 0.124 (0.25 to 0.13) 0.956 0.167 0.124 (0.25 to 0.13) 0.567 Medel 1 0.124 (0.25 to 0.13) 0.557 0.077 0.014 0.024 (0.027 to 0.13) 0.57 Medel 2 0.021 (-0.25 to 0.13) 0.557 0.077 0.014 (-0.027 to 0.13) 0.57 <tr< td=""><td>Cerebral parenchyma</td><td></td><td></td><td></td><td></td><td></td></tr<>	Cerebral parenchyma					
Madel 1 DDI (-D.T. yo. DB) DDB (Orde(-D.T. yo. DB) DDS (DDS (<thds (<="" th=""> DDS (DDS (<</thds>	Model 1	-0.21 (-0.48 to 0.07)	0.143	0 (ref)	0.16 (-0.02 to 0.35)	0.079
Model j 0.02 (-0.26 to 0.39) 0.87 0 (ref) 0.03 (-0.27 to 0.66) 0.20 Model 1 -0.32 (-0.56 to 0.05) 0.09 0 (ref) 0.21 (0.03 - 0.01) 0.65 Model 2 0.01 (-0.17 to 0.18) 0.393 0 (ref) 0.03 (-0.01 to 0.31) 0.657 Model 3 0.02 (-0.13 to 0.20) 0.944 0 (ref) 0.04 (-0.14 to 0.32) 0.657 Model 1 0.01 (-0.37 to 0.24) 0.944 0 (ref) -0.01 (-0.25 to 0.05) 0.056 Model 2 0.01 (-0.23 to 0.24) 0.942 0 (ref) -0.01 (-0.25 to 0.05) 0.056 Model 1 0.21 (-0.23 to 0.21) 0.952 0 (ref) 0.01 (-0.35 to 0.31) 0.667 Model 1 -0.02 (-0.35 to 0.31) 0.057 0 (ref) -0.03 (-0.05 to 0.31) 0.674 Model 2 -0.03 (-0.02 to 0.03) 0.552 0 (ref) -0.03 (-0.35 to 0.31) 0.674 Model 1 -0.02 (-0.23 to 0.21) 0.572 0 (ref) -0.03 (-0.35 to 0.31) 0.674 Model 2 -0.03 (-0.35 to 0.31) 0.574 0 (ref) <t< td=""><td>Model 2</td><td>0.01 (-0.17 to 0.18)</td><td>0.948</td><td>0 (ref)</td><td>-0.04 (-0.15 to 0.08)</td><td>0.538</td></t<>	Model 2	0.01 (-0.17 to 0.18)	0.948	0 (ref)	-0.04 (-0.15 to 0.08)	0.538
Gray matrixUnder 10-33 (-625 ho.02)0.1990.1970.21 (0.03-4.0)0.201Model 20.01 (-1.17 ho.13)0.3980 (ref)0.03 (-0.19 ho.0.1)0.457Model 30.02 (-1.13 ho.0.2)0.9480 (ref)0.04 (-1.14 ho.0.2)0.527Model 10.01 (-0.39 ho.0.4)0.9540 (ref)0.01 (-0.14 ho.0.2)0.528Model 30.01 (-0.23 ho.0.4)0.9540 (ref)-0.11 (-0.25 ho.0.5)0.568Model 30.01 (-0.23 ho.0.4)0.9540 (ref)-0.11 (-0.25 ho.0.5)0.568Model 30.02 (-0.13 ho.0.1)0.5840 (ref)-0.01 (-0.25 ho.0.1)0.568Model 30.02 (-0.13 ho.0.1)0.5840 (ref)0.01 (-0.68 ho.0.2)0.564Model 3-0.02 (-0.13 ho.0.1)0.5840 (ref)0.01 (-0.68 ho.0.2)0.564Model 3-0.02 (-0.13 ho.0.1)0.5610.5770.04 (-0.10 ho.0.1)0.564Model 1-0.03 (-0.12 ho.0.1)0.5620 (ref)0.01 (-0.38 ho.0.2)0.564Model 2-0.07 (-0.29 ho.0.1)0.5520 (ref)-0.04 (-0.10 ho.0.1)0.564Model 3-0.07 (-0.29 ho.0.1)0.5620 (ref)-0.03 (-0.13 ho.0.1)0.564Model 1-0.03 (-0.13 ho.0.1)0.5640.5770.67-0.04 (-0.10 ho.0.1)0.564Model 2-0.03 (-0.13 ho.0.1)0.5640.27 (-0.24 ho.0.1)0.770.7640.16 (-0.15 ho.0.23 ho.0.1)0.77Model 10.06 (-0.21 ho.0.1)0.3520 (ref)-0	Model 3	0.02 (-0.16 to 0.19)	0.836	0 (ref)	-0.05 (-0.17 to 0.06)	0.370
Model 1-0.22 (-0.30 to 0.05)0.190 (ref)0.21 (0.03-0.49)0.020Model 20.02 (-0.15 to 0.20)0.7340 (ref)0.03 (-0.10 to 0.13)0.557Model 10.01 (-0.15 to 0.12)0.9420.9440 (ref)0.04 (-0.14 to 0.23)0.557Model 20.02 (-0.15 to 0.20)0.9420.9440 (ref)-0.11 (-0.25 to 0.05)0.161Model 30.023 to 0.24)0.9420.9440 (ref)-0.11 (-0.25 to 0.05)0.161Model 10.21 (-0.70 to 0.49)0.1380 (ref)-0.11 (-0.25 to 0.05)0.464Model 10.21 (-0.17 to 0.15)0.5520 (ref)0.02 (-0.07 to 0.16)0.54Model 10.22 (-0.31 to 0.10)0.5520 (ref)0.01 (-0.03 to 0.01)0.564Model 1-0.02 (-0.10 to 0.15)0.5520.16-0.03 (-0.03 to 0.01)0.567Model 1-0.03 (-0.40 to 0.15)0.570.16-0.03 (-0.13 to 0.10)0.567Model 20.021 (-0.24 to 0.24)0.3430.1640.05 (-0.03 to 0.31)0.564Model 1-0.03 (-0.40 to 0.15)0.3510.1640.05 (-0.03 to 0.31)0.574Model 10.01 (-0.23 to 0.25)0.9430.1640.02 (-0.14 to 0.31)0.574Model 10.01 (-0.23 to 0.25)0.9430.1640.02 (-0.24 to 0.24)0.264Model 10.01 (-0.23 to 0.25)0.5540.1640.032 (-0.25 to 0.23)0.574Model 10.01 (-0.23 to 0.25)0.5540.1640.052 (-0.20 to 0.23) <t< td=""><td>Gray matter</td><td></td><td></td><td></td><td></td><td></td></t<>	Gray matter					
Model 2 0.01 (-0.17 to 0.18) 0.938 0 (ref) 0.03 (-0.09 to 0.14) 0.494 Model 3 0.02 (-0.15 to 0.20) 0.744 0 (ref) 0.00 (-0.11 to 0.21) 0.494 Model 1 -0.11 (-0.25 to 0.20) 0.404 0.004 -0.011 (-0.25 to 0.03) 0.550 Model 3 0.01 (-0.25 to 0.24) 0.954 0 (ref) -0.011 (-0.25 to 0.03) 0.054 Model 3 0.01 (-0.25 to 0.24) 0.954 0 (ref) -0.011 (-0.25 to 0.03) 0.056 Model 3 0.01 (-0.12 to 0.17) 0.66 0.66 0.67 0.021 (-0.03 to 0.14) 0.640 Model 1 0.21 (-0.23 to 0.21) 0.551 0.067 0.041 (-0.05 to 0.03) 0.640 Model 3 -0.02 (-0.13 to 0.17) 0.660 0.670 0.041 (-0.05 to 0.13) 0.541 Model 1 -0.02 (-0.13 to 0.17) 0.552 0 (ref) -0.03 (-0.13 to 0.13) 0.144 Model 1 -0.02 (-0.21 to 0.13) 0.516 0.573 0 (ref) 0.03 (-0.31 to 0.3) 0.144 Model 1 -0.03 (-0.21 to 0.31) 0	Model 1	-0.23 (-0.50 to 0.05)	0.109	0 (ref)	0.21 (0.03-0.40)	0.020
Model 3 0.00 (-0.15 to 0.20) 0.794 0 (ref) 0.00 (-0.11 to 0.12) 0.945 Model 1 -0.01 (-0.39 to 0.16) 0.420 0 (ref) 0.014 (-0.24 to 0.03) 0.369 Model 2 0 (-0.25 to 0.24) 0.954 0 (ref) -0.01 (-0.26 to 0.05) 0.056 Model 1 0.01 (-0.25 to 0.02) 0.054 0 (ref) -0.01 (-0.26 to 0.05) 0.056 Model 1 0.21 (-0.07 to 0.4) 0.138 0 (ref) -0.01 (-0.26 to 0.05) 0.056 Model 1 0.22 (-0.07 to 0.4) 0.354 0 (ref) -0.01 (-0.26 to 0.05) 0.056 Model 2 0 (-0.18 to 0.17) 0.966 0 (ref) -0.01 (-0.26 to 0.02) 0.056 Model 3 -0.02 (-0.139 to 0.15) 0.356 0 (ref) -0.01 (-0.08 to 0.27) 0.747 Model 1 -0.02 (-0.238 to 0.15) 0.957 0 (ref) -0.04 (-0.198 to 1.1) 0.556 Parbippoznapul grus -0.01 (-0.240 to 0.23) 0.958 0 (ref) 0.02 (-0.218 to 1.1) 0.573 Model 1 -0.01 (-0.240 to 0.23) 0.585 0 (ref	Model 2	0.01 (-0.17 to 0.18)	0.938	0 (ref)	0.03 (-0.09 to 0.14)	0.667
White matter White matter Nodel 1 0.01 (-0.23 to 0.24) 0.964 0. (ref) 0.04 (-0.14 to 0.25) 0.652 Model 1 0.01 (-0.23 to 0.24) 0.964 0. (ref) -0.01 (-0.25 to 0.05) 0.180 Model 1 0.21 (-0.27 to 0.04) 0.183 0. (ref) -0.11 (-0.25 to 0.05) 0.164 Model 1 0.21 (-0.07 to 0.04) 0.138 0. (ref) 0.07 (-0.35 to 0.01) 0.664 Model 2 -0.02 (-0.18 to 0.17) 0.565 0.(ref) 0.01 (-0.08 to 0.28) 0.274 Model 1 -0.25 (-0.53 to 0.03) 0.076 0.01 (-0.08 to 0.28) 0.274 Model 2 -0.07 (-0.29 to 0.15) 0.52 0.(ref) 0.01 (-0.08 to 0.28) 0.274 Model 2 0.66 (-28 to 0.15) 0.57 0.(ref) 0.01 (-0.18 to 0.13) 0.052 Model 1 -0.03 (-0.24 to 0.24) 0.98 0.ref) 0.01 (-0.38 to 0.3) 0.676 Bain microtactural integrity (in z-score) M < 54	Model 3	0.02 (-0.15 to 0.20)	0.794	0 (ref)	0.00 (-0.11 to 0.12)	0.945
Model 1 -0.11 (-0.23 to 0.24) 0.44 0.044 (-0.24 to 0.23) 0.552 Model 3 0.01 (-0.23 to 0.24) 0.952 0.(ef) -0.11 (-0.26 to 0.05) 0.164 Model 1 0.01 (-0.23 to 0.24) 0.952 0.(ef) -0.11 (-0.26 to 0.05) 0.164 Model 1 0.01 (-0.23 to 0.24) 0.956 0.(ef) -0.17 (-0.35 to 0.01) 0.646 Model 2 0.02 (-0.13 to 0.17) 0.956 0.(ef) -0.03 (-0.08 to 0.18) 0.464 Model 2 0.02 (-0.13 to 0.16) 0.854 0.(ef) -0.03 (-0.18 to 0.18) 0.747 Model 3 -0.07 (-0.29 to 0.15) 0.552 0.(ef) -0.03 (-0.18 to 0.18) 0.747 Model 3 -0.07 (-0.29 to 0.15) 0.563 0.676 0.(ef) -0.03 (-0.18 to 0.18) 0.747 Model 3 -0.07 (-0.29 to 0.15) 0.563 0.677 0.(ef) -0.03 (-0.18 to 0.18) 0.747 Model 3 -0.07 (-0.29 to 0.15) 0.541 0.(ef) 0.051 (-0.15 to 0.18) 0.144 Model 1 -0.01 (-0.28 to 0.28) 0.953	White matter					
Model 2 0 (-0.21 to 0.24) 0.984 0 (ref) -0.11 (-0.26 to 0.05) 0.180 Model 1 0.21 (-0.07 to 0.49) 0.382 0 (ref) -0.17 (-0.35 to 0.01) 0.066 Model 1 0.21 (-0.07 to 0.49) 0.383 0 (ref) -0.02 (-0.07 to 0.49) 0.644 Model 3 -0.02 (-0.19 to 0.16) 0.854 0 (ref) -0.02 (-0.07 to 0.49) 0.644 Model 1 -0.02 (-0.19 to 0.16) 0.854 0 (ref) -0.02 (-0.00 to 0.02) 0.644 Model 1 -0.02 (-0.29 to 0.15) 0.522 0 (ref) -0.04 (-0.19 to 0.11) 0.564 Model 1 -0.06 (-0.28 to 0.15) 0.577 0 (ref) 0.04 (-0.07 to 0.31) 0.104 Model 1 -0.06 (-0.28 to 0.15) 0.563 0 (ref) 0.01 (-0.08 to 0.33) 0.104 Model 1 -0.01 (-0.02 to 0.21) 0.548 0 (ref) 0.03 (-0.31 to 0.33) 0.170 Brain microstructural integrity (re zsccre) N = 54 N = 898 N = 302 N = 302 Fractional anisotropy Model 1 0.02 (-0.21 to 0.31) 0.512	Model 1	-0.11 (-0.39 to 0.16)	0.420	0 (ref)	0.04 (-0.14 to 0.23)	0.652
Model 3 OD1 (-0.23 to 0.24) 0.962 0 (re) -0.11 (-0.26 to 0.05) 0.154 Cerbrospnal fluid 0.21 (-0.07 to 0.49) 0.138 0 (ref) -0.17 (-0.35 to 0.01) 0.666 Model 1 0.02 (-1.09 to 0.49) 0.338 0 (ref) 0.04 (-0.07 to 0.16) 0.644 Model 1 -0.02 (-0.19 to 0.15) 0.552 0 (ref) 0.04 (-0.07 to 0.16) 0.647 Model 1 -0.05 (-0.25 to 0.03) 0.577 0 (ref) -0.04 (-0.09 to 0.13) 0.667 Model 1 -0.05 (-0.28 to 0.15) 0.572 0 (ref) 0.04 (-0.09 to 0.13) 0.667 Model 1 -0.05 (-0.28 to 0.15) 0.573 0 (ref) 0.02 (-0.18 to 0.13) 0.561 Model 1 -0.16 (-0.24 to 0.13) 0.573 0 (ref) 0.02 (-0.14 to 0.13) 0.570 Bain microstructural integrity (in zecore) Pat Pat Pat Pat Pat Model 1 -0.02 (-0.24 to 0.23) 0.414 0.16 (-0.24 to 0.23) 0.267 0.414 to 0.13) 0.573 Model 1 0.02 (-0.24 to 0.23) 0.274	Model 2	0 (-0.23 to 0.24)	0.984	0 (ref)	-0.11 (-0.26 to 0.05)	0.180
Creational fluid 021 (-0.07 to 0.49) 0.18 0 (ref) 0.012 (-0.33 to 0.01) 0.066 Model 1 0.02 (-0.19 to 0.16) 0.854 0 (ref) 0.03 (-0.09 to 0.14) 0.640 Model 3 0 (ref) 0.03 (-0.09 to 0.14) 0.640 Model 1 -0.57 (-0.53 to 0.03) 0.076 0 (ref) 0.012 (-0.08 to 0.28) 0.274 Model 1 -0.57 (-0.53 to 0.03) 0.076 0 (ref) 0.012 (-0.18 to 0.28) 0.274 Model 1 -0.57 (-0.53 to 0.03) 0.076 0 (ref) 0.04 (-0.18 to 0.28) 0.257 Model 2 -0.07 (-0.28 to 0.15) 0.577 0 (ref) 0.04 (-0.18 to 0.28) 0.18 Model 1 -0.31 (-0.40 to 0.15) 0.363 0 (ref) 0.05 (-0.28 to 0.23) 0.140 Model 2 0 (ref) -0.03 (-0.31 to 0.39 0.37 0 (ref) -0.03 (-0.31 to 0.39 0.37 Model 1 0.01 (-0.23 to 0.23) 0.130 0.33 0.130 0.33 0.130 Model 1 0.01 (-0.33 to 0.39) 0.35 0 (ref) -0.05 (-0.24 to 0.13) </td <td>Model 3</td> <td>0.01 (-0.23 to 0.24)</td> <td>0.962</td> <td>0 (ref)</td> <td>-0.11 (-0.26 to 0.05)</td> <td>0.164</td>	Model 3	0.01 (-0.23 to 0.24)	0.962	0 (ref)	-0.11 (-0.26 to 0.05)	0.164
Model 1 0.21 (-0.07 to 0.49) 0.38 0 (m) -0.17 (-0.35 to 0.01) 0.066 Model 2 0.00 (1.01 to 0.17) 0.966 0 (m) 0.03 (-0.09 to 0.14) 0.640 Hippocampus -0.22 (-0.19 to 0.15) 0.854 0 (m) 0.04 (-0.09 to 0.14) 0.640 Model 1 -0.52 (-0.53 to 0.03) 0.07 0 (m) -0.03 (-0.18 to 0.11) 0.647 Model 2 -0.07 (-0.29 to 0.15) 0.552 0 (m) -0.03 (-0.18 to 0.11) 0.657 Model 3 -0.07 (-0.29 to 0.15) 0.363 0 (m) 0.03 (-0.01 to 0.13) 0.144 Model 2 -0.03 (-0.01 to 0.21) 0.363 0 (m) 0.03 (-0.01 to 0.13) 0.144 Model 2 0.01 (-0.21 to 0.21) 0.363 0 (m) 0.02 (-0.14 to 0.13) 0.573 Model 1 -0.01 (-0.21 to 0.23) 0.441 0 (m) -0.016 (-0.32 to 0.23) 0.681 Model 2 0.02 (-0.14 to 0.13) 0.573 0 (m) -0.016 (-0.32 to 0.23) 0.632 Model 1 0.03 (-0.13 to 0.31) 0.141 0.169 -0.016 (-0	Cerebrospinal fluid					
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 Model 1 -0.52 (-0.53 to 0.03) 0.76 0 (ref) 0.01 (-0.08 to 0.28) 0.274 Model 2 -0.07 (-0.29 to 0.15) 0.557 0 (ref) -0.04 (-0.13 to 0.11) 0.556 Parahippocampal grus -0.05 (-0.28 to 0.16) 0.577 0 (ref) 0.02 (-0.18 to 0.13) 0.104 Model 2 0.12 (-0.40 to 0.15) 0.363 0 (ref) 0.02 (-0.18 to 0.13) 0.568 Model 3 0.01 (-0.23 to 0.23) 0.154 0.02 0.02 (-0.14 to 0.18) 0.770 Parahipocampal grus N = 52 N = 58 N = 130 777 Factional anisotropy N = 55 N = 130 0.573 0.026 (-0.24 to 0.13) 0.573 Model 1 0.08 (-0.20 to 0.35) 0.585 0 (ref) -0.016 (-0.34 to -0.20) 0.022 Model 1 0.03 (-0.37 to 0.37) 0 (ref) -0.02 (-0.20 to 0.15) 0.635	Model 1	0.21 (-0.07 to 0.49)	0.138	0 (ref)	-0.17 (-0.35 to 0.01)	0.066
Inded 3 -0.0 (-0.19 to 0.16) 0.854 0 (ref) 0.04 (-0.07 to 0.16) 0.04 (-0.07 to 0.16) Hippcompus Model 1 -0.25 (-0.53 to 0.03) 0.055 0 (ref) -0.03 (-0.31 to 0.13) 0.647 Model 2 -0.06 (-0.28 to 0.15) 0.525 0 (ref) -0.04 (-0.13 to 0.13) 0.647 Model 3 -0.66 (-0.28 to 0.15) 0.563 0 (ref) -0.04 (-0.13 to 0.13) 0.647 Model 1 -0.13 (-0.40 to 0.13) 0.463 0 (ref) 0.015 (-0.03 to 0.33) 0.164 Model 2 0 (0.24 to 0.24) 0.988 0 (ref) 0.02 (-0.14 to 0.38 0.767 Model 3 0.01 (-0.23 to 0.25) 0.43 0 (ref) -0.05 (-0.24 to 0.33) 0.573 Model 3 0.01 (-0.31 to 0.35) 0.555 0 (ref) -0.03 (-0.33 to -0.30) 0.573 Model 3 0.11 (-0.13 to 0.36) 0.552 0 (ref) -0.045 (-0.24 to 0.33) 0.573 Model 3 0.11 (-0.33 to 0.39) 0.565 0 (ref) -0.045 (-0.24 to 0.31) 0.510 Model 3 0.11 (-0.31 to 0.350 0.573 0 (ref) -0.05 (-0.24 to 0.31) 0.510 <	Model 2	0 (-0.18 to 0.17)	0.966	0 (ref)	0.03 (-0.09 to 0.14)	0.640
Hippocample Model 1 -0.27 (-0.53 to 0.03) 0.076 0.076 0.076 0.076 0.076 0.076 0.076 0.076 0.076 0.076 0.076 0.076 0.076 0.076 0.076 0.076 0.076 0.037 0.075 0.076 0.037 0.076 0.037 0.076 0.037 0.076 0.037 0.076 0.037 0.076 0.037 0.076 0.037 0.	Model 3	-0.02 (-0.19 to 0.16)	0.854	0 (ref)	0.04 (-0.07 to 0.16)	0.454
Model 1 -0.25 (-0.35 to 0.03) 0.076 0 (ref) 0.10 (-0.08 to 0.28) 0.274 Model 2 -0.06 (-0.28 to 0.31) 0.575 0 (ref) -0.03 (-0.18 to 0.11) 0.547 Model 3 -0.06 (-0.28 to 0.16) 0.577 0 (ref) -0.03 (-0.18 to 0.11) 0.595 Parahippocampal gyrus 0 (-0.24 to 0.24) 0.988 0 (ref) 0.03 (-0.13 to 0.13) 0.164 Model 3 0 (0.1 (-0.23 to 0.25) 0.943 0 (ref) 0.03 (-0.13 to 0.13) 0.166 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 0.027 Model 3 0.12 (-0.13 to 0.36) 0.352 0 (ref) -0.03 (-0.32 to 0.02) 0.021 Model 3 0.11 (-0.13 to 0.36) 0.352 0 (ref) -0.16 (-0.34 to -0.02) 0.032 Model 1 -0.03 (-0.30 to 0.25) 0.841 0 (ref) 0.16 (0.01-0.31) 0.835 Model 1 -0.03 (-0.35 to 0.02) 0.254 0 (ref)	Hippocampus					
Model 2 -0.07 (-0.29 to 0.15) 0.577 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) 0.595 Parahippocampal grus -0.03 (-0.40 to 0.15) 0.363 0 (ref) 0.51 (-0.03 to 0.23) 0.104 Model 2 0.01 (-0.21 to 0.24) 0.984 0 (ref) 0.02 (-0.14 to 0.13) 0.770 Brain microstructural integrity (in z-score) N = 54 N = 858 N = 30 Fractional anisotropy -0.03 (-0.13 to 0.30) 0.352 0 (ref) -0.02 (-0.24 to 0.13) 0.575 Model 2 0.12 (-0.13 to 0.35) 0.352 0 (ref) -0.03 (-0.24 to 0.13) 0.575 Model 3 0.12 (-0.13 to 0.35) 0.352 0 (ref) -0.03 (-0.24 to 0.13) 0.575 Model 1 -0.03 (-0.30 to 0.25) 0.841 0 (ref) -0.02 (-0.24 to 0.13) 0.634 Model 3 -0.13 (-0.35 to 0.09) 0.253 0 (ref) 0.16 (0.01-0.30) 0.544 Model 1 -0.01 (-0.24 to 0.11) 0.311 0 (ref) 0.0	Model 1	-0.25 (-0.53 to 0.03)	0.076	0 (ref)	0.10 (-0.08 to 0.28)	0.274
Model 3 -0.06 (-0.28 to 0.16) 0.577 0 (ref) -0.04 (-0.19 to 0.11) 0.596 Parahipporampal grus 0.03 (-0.40 to 0.15) 0.363 0 (ref) 0.15 (-0.03 to 0.33) 0.104 Model 1 0 (-0.24 to 0.24) 0.988 0 (ref) 0.03 (-0.13 to 0.19) 0.666 Model 2 0.01 (-0.25 to 0.25) 0.987 0 (ref) 0.02 (-0.14 to 0.18) 0.7070 Brain microstructural integrity (in z-score) N 54 N = 130 - - Fractional anisotropy - N = 58 N = 130 - 0.032 0 (ref) -0.013 (-0.23 to -0.02) 0.025 Model 1 0.08 (-0.20 to 0.35) 0.585 0 (ref) -0.02 (-0.20 to 0.16) 0.032 Model 3 0.12 (-0.13 to 0.35) 0.373 0 (ref) -0.03 (-0.32 to -0.02) 0.032 Model 1 -0.03 (-0.32 to 0.25) 0.414 0 (ref) -0.02 (-0.20 to 0.16) 0.835 Model 1 -0.03 (-0.35 to 0.09) 0.236 0 (ref) 0.16 (0.04 -0.31) 0.314 Model 1 0.01(-0.26 to 0.28)	Model 2	-0.07 (-0.29 to 0.15)	0.552	0 (ref)	-0.03 (-0.18 to 0.11)	0.647
Pachippocampal gyns -0.13 (-0.40 to 0.15) 0.363 0 (ref) 0.15 (-0.03 to 0.33) 0.104 Model 1 -0.12 (-0.24 to 0.24) 0.988 0 (ref) 0.32 (-0.13 to 0.33) 0.164 Model 3 0.01 (-0.23 to 0.25) 0.943 0 (ref) 0.02 (-0.14 to 0.18) 0.700 Braincrostructural integrity (in z-score) N = 54 N = 858 N = 30 Fractional anisotropy 0.02 (-0.14 to 0.13) 0.575 0 (ref) -0.05 (-0.24 to 0.13) 0.575 Model 3 0.12 (-0.13 to 0.36) 0.585 0 (ref) -0.03 (-0.34 to -0.02) 0.022 Model 3 0.11 (-0.13 to 0.35) 0.373 0 (ref) -0.03 (-0.24 to 0.13) 0.585 Model 2 -0.03 (-0.30 to 0.25) 0.841 0 (ref) -0.02 (-0.20 to 0.16) 0.831 Model 3 -0.03 (-0.35 to 0.09) 0.236 0 (ref) 0.16 (0.01-0.31) 0.034 Model 3 -0.11 (-0.34 to 0.11) 0.311 0 (ref) -0.08 (-0.26 to 0.10) 0.334 Model 3 -0.12 (-0.34 to 0.12) 0.320 0 (ref) -0.16 (0	Model 3	-0.06 (-0.28 to 0.16)	0.577	0 (ref)	-0.04 (-0.19 to 0.11)	0.596
Madel 1 -0.33 (-0.40 to 0.15) 0.363 0 (ref) 0.15 (-0.03 to 0.33) 0.104 Madel 2 0.(-0.21 to 0.24) 0.988 0 (ref) 0.32 (-0.13 to 0.13) 0.686 Madel 3 0.01 (-0.23 to 0.25) 0.983 0 (ref) 0.02 (-0.14 to 0.18) 0.700 Brain microstructural integrity (in z-score) N = 54 N = 858 N = 130 Fractional anisotropy 0.02 (-0.13 to 0.35) 0.352 0 (ref) -0.05 (-0.24 to 0.13) 0.573 Model 1 0.08 (-0.20 to 0.35) 0.352 0 (ref) -0.12 (-0.35 to -0.02) 0.025 Model 3 0.11 (-0.13 to 0.35) 0.373 0 (ref) -0.02 (-0.20 to 0.16) 0.835 Model 1 0.03 (-0.35 to 0.09) 0.263 0 (ref) 0.16 (0.01-0.31) 0.034 Model 3 -0.01 (-0.26 to 0.28) 0.941 0.16 (0.01-0.31) 0.034 Model 3 -0.01 (-0.26 to 0.28) 0.941 0.08 (-0.07 to 0.24) 0.264 Model 3 -0.01 (-0.26 to 0.29) 0.31 0.026 0.016 0.034 (-0.37 to 0.31) 0.304 <td>Parahippocampal gyrus</td> <td></td> <td></td> <td></td> <td></td> <td></td>	Parahippocampal gyrus					
Model 2 0 (-0.24 to 0.24) 0.988 0 (ref) 0.03 (-0.13 to 0.19) 0.686 Model 3 0 (ref) 0.02 (-0.14 to 0.18) 0.770 Brain microstructural integrity (in z-score) N - 54 N - 858 N - 130 Fractional miscotropy N N N N N N N N N Model 1 0.08 (-0.20 to 0.35) 0.585 0 (ref) -0.05 (-0.24 to 0.13) 0.573 Model 2 0.22 (-0.13 to 0.35) 0.585 0 (ref) -0.01 (-0.35 to -0.02) 0.032 Model 3 0.11 (-0.13 to 0.35) 0.581 0 (ref) -0.02 (-0.20 to 0.16) 0.835 Model 1 -0.03 (-0.35 to 0.09) 0.236 0 (ref) 0.16 (0.01-0.31) 0.034 Model 1 0.01 (-0.25 to 0.28) 0.941 0 (ref) -0.88 (-0.25 to 0.23) 0.83 Model 1 0.01 (-0.25 to 0.28) 0.941 0 (ref) -0.86 (-0.25 to 0.23) 0.30 Model 1 0.01 (-0.25 to 0.23) 0.951 0 (ref) 0.16 (0.01-0.31) 0.302	Model 1	-0.13 (-0.40 to 0.15)	0.363	0 (ref)	0.15 (-0.03 to 0.33)	0.104
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 N N 9.858 0 (ref) -0.05 (-0.24 to 0.13) 0.573 Model 1 0.08 (-0.20 to 0.35) 0.585 0 (ref) -0.018 (-0.35 to -0.02) 0.025 Model 2 0.11 (-0.13 to 0.35) 0.373 0 (ref) -0.018 (-0.35 to -0.02) 0.025 Model 3 0.11 (-0.13 to 0.35) 0.373 0 (ref) -0.018 (-0.35 to -0.02) 0.025 Model 1 -0.03 (-0.30 to 0.25) 0.841 0 (ref) -0.02 (-0.20 to 0.16) 0.835 Model 3 -0.13 (-0.35 to 0.09) 0.25 0 (ref) 0.16 (0.01-0.31) 0.034 Model 3 -0.11 (-0.34 to 0.11) 0.311 0 (ref) 0.08 (-0.07 to 0.24) 0.264 Model 3 -0.11 (-0.34 to 0.11) 0.311 0 (ref) 0.08 (-0.07 to 0.23) 0.302 Model 3 -0.01 (-0.37 to 0.32) 0.257 0 (ref) 0.11 (-0.29 t	Model 2	0 (-0.24 to 0.24)	0.988	0 (ref)	0.03 (-0.13 to 0.19)	0.686
Brain microstructural integrity (in 2-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) -0.013 (-0.35 to -0.02) 0.022 Model 3 0.11 (-0.13 to 0.35) 0.373 0 (ref) -0.02 (-0.20 to 0.16) 0.835 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) 0.253 0 (ref) 0.02 (-0.20 to 0.16) 0.831 Model 3 -0.13 (-0.35 to 0.09) 0.253 0 (ref) 0.015 (0.01-0.31) 0.931 Model 1 0.01 (-0.26 to 0.28) 0.941 0 (ref) 0.08 (-0.07 to 0.24) 0.264 Model 2 -0.11 (-0.34 to 0.11) 0.311 0 (ref) 0.08 (-0.07 to 0.23) 0.302 Model 3 -0.13 (-0.35 to 0.09) 0.241 0 (ref) 0.11 (0.02 - 0.32) 0.302 Model 1 -0.04 (-0.32 to 0.23) 0.759 0.769	Model 3	0.01 (-0.23 to 0.25)	0.943	0 (ref)	0.02 (-0.14 to 0.18)	0.770
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) -0.03 (-0.32 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 -0.03 (-0.30 to 0.25) 0.841 0 (ref) -0.02 (-0.20 to 0.16) 0.835 Model 2 -0.31 (-0.35 to 0.09) 0.236 0 (ref) 0.16 (0.01-0.31) 0.034 Model 3 -0.03 (-0.25 to 0.09) 0.236 0 (ref) 0.026 (-0.20 to 0.16) 0.835 Model 3 -0.31 (-0.25 to 0.09) 0.236 0 (ref) 0.16 (0.01-0.31) 0.034 Model 3 -0.13 (-0.25 to 0.02) 0.941 0 (ref) 0.08 (-0.07 to 0.24) 0.264 Model 2 -0.12 (-0.34 to 0.11) 0.311 0 (ref) 0.08 (-0.07 to 0.24) 0.264 Model 3 -0.01 (-0.26 to 0.23) 0.759 0 (ref) 0.164 (0.03-0.33) 0.019 Model 3 -0.03 (-0.35 to 0.09) 0.241 0 (ref) 0.18 (0.03-0.33) 0.019	Brain microstructural integrity (in z-score)	N = 54		N = 858	N = 130	
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) 0.370 0 (ref) -0.19 (-0.35 to -0.02) 0.032 Mean diffusivity -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) 0.256 0 (ref) 0.16 (0.01-0.31) 0.034 Model 3 -0.03 (-0.25 to 0.09) 0.256 0 (ref) 0.16 (0.01-0.31) 0.034 Model 2 -0.13 (-0.25 to 0.28) 0.941 0 (ref) 0.06 (-0.26 to 0.10) 0.394 Model 3 -0.01 (-0.26 to 0.28) 0.941 0 (ref) 0.09 (-0.07 to 0.24) 0.264 Model 3 -0.11 (-0.34 to 0.11) 0.311 0 (ref) 0.96 (-0.07 to 0.23) 0.302 Radial diffusivity Model 1 -0.04 (-0.32 to 0.23) 0.759 0 (ref) 0.18 (0.03-0.33) 0.019 Model 1 -0.03 (-0.35 to 0.09) 0.2	Fractional anisotropy					
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) -0.08 (-0.34 to -0.02) 0.032 Mean diffusivity -0.03 (-0.30 to 0.25) 0.841 0 (ref) -0.02 (-0.20 to 0.16) 0.834 Model 1 -0.03 (-0.35 to 0.09) 0.236 0 (ref) 0.16 (0.01-0.31) 0.034 Model 2 -0.13 (-0.35 to 0.09) 0.253 0 (ref) 0.15 (0.01-0.30) 0.043 Avail diffusivity -0.12 (-0.34 to 0.11) 0.311 0 (ref) -0.08 (-0.26 to 0.10) 0.394 Model 2 -0.12 (-0.34 to 0.11) 0.311 0 (ref) -0.08 (-0.26 to 0.10) 0.394 Model 3 -0.11 (-0.34 to 0.11) 0.311 0 (ref) 0.086 (-0.07 to 0.24) 0.264 Model 3 -0.11 (-0.34 to 0.11) 0.311 0 (ref) 0.18 (0.03-0.33) 0.019 Model 1 -0.04 (-0.32 to 0.23) 0.759 0 (ref) 0.14 (0.03-0.33) 0.019 Model 3 -0.13 (-0.35 to 0.09) 0.257 N = 805	Model 1	0.08 (-0.20 to 0.35)	0.585	0 (ref)	-0.05 (-0.24 to 0.13)	0.573
Model 3 0.11 (-0.13 to 0.35) 0.373 0 (ref) -0.18 (-0.34 to -0.02) 0.032 Mean diffusivity -0.03 (-0.30 to 0.25) 0.841 0 (ref) -0.02 (-0.20 to 0.16) 0.835 Model 1 -0.03 (-0.35 to 0.09) 0.253 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) 0.034 Axial diffusivity -0.12 (-0.34 to 0.11) 0.311 0 (ref) -0.08 (-0.26 to 0.10) 0.394 Model 2 -0.12 (-0.34 to 0.11) 0.311 0 (ref) 0.08 (-0.07 to 0.24) 0.264 Model 3 -0.04 (-0.32 to 0.21) 0.391 0 (ref) 0.048 (-0.07 to 0.23) 0.392 Radial diffusivity -0.04 (-0.32 to 0.23) 0.575 0 (ref) 0.18 (0.03-0.33) 0.019 Model 2 -0.31 (-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	Model 2	0.12 (-0.13 to 0.36)	0.352	0 (ref)	-0.19 (-0.35 to -0.02)	0.025
Mean diffusivity Nodel 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) 0.25 0 (ref) 0.16 (0.01-0.31) 0.034 Model 3 -0.3 (-0.35 to 0.09) 0.253 0 (ref) 0.15 (0.01-0.31) 0.034 Axial diffusivity -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 - - - 0.01 (-0.25 to 0.23) 0.759 0 (ref) 0.18 (0.03-0.33) 0.019 Model 1 -0.04 (-0.32 to 0.23) 0.759 0 (ref) 0.18 (0.03-0.33) 0.019 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) 0.11 (-0.29 to 0.07) 0.242 Model 1	Model 3	0.11 (-0.13 to 0.35)	0.373	0 (ref)	-0.18 (-0.34 to -0.02)	0.032
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 -0.01 (-0.26 to 0.28) 0.941 0 (ref) -0.08 (-0.26 to 0.10) 0.394 Model 1 0.01 (-0.26 to 0.28) 0.941 0 (ref) 0.08 (-0.07 to 0.24) 0.263 Model 3 -0.11 (-0.34 to 0.11) 0.310 0 (ref) 0.09 (-0.07 to 0.24) 0.264 Model 1 -0.04 (-0.32 to 0.23) 0.759 0 (ref) 0.618 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 -0.33 (-0.35 to 0.09) 0.257 0 (ref) 0.18 (0.03-0.33) 0.019 Model 2 -0.33 (-0.37 to 0.11) 0.284 0 (ref) 0.11 (-0.29 to 0.07) 0.242 Model 3 -0.11 (-0.29 to 0.07) 0.244 0.232 0 (r	Mean diffusivity	x		. ,	, ,	
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 0.01 (-0.26 to 0.28) 0.941 0 (ref) -0.08 (-0.26 to 0.10) 0.394 Model 1 0.01 (-0.26 to 0.28) 0.941 0 (ref) 0.09 (-0.07 to 0.24) 0.264 Model 3 -0.12 (-0.34 to 0.11) 0.311 0 (ref) 0.09 (-0.07 to 0.24) 0.304 Model 3 -0.12 (-0.34 to 0.11) 0.311 0 (ref) 0.08 (-0.07 to 0.24) 0.302 Model 3 -0.04 (-0.32 to 0.23) 0.759 0 (ref) 0.16 (0.03-0.33) 0.019 Model 1 -0.04 (-0.32 to 0.23) 0.759 0 (ref) 0.18 (0.03-0.33) 0.019 Model 2 -0.13 (-0.35 to 0.09) 0.241 0 (ref) 0.17 (0.02-0.32) 0.025 Model 3 -0.13 (-0.35 to 0.09) 0.257 0 (ref) 0.11 (-0.29 to 0.07) 0.242 Model 2 -0.13 (-0.27 to 0.11) 0.268 0 (ref) </td <td>Model 1</td> <td>-0.03 (-0.30 to 0.25)</td> <td>0.841</td> <td>0 (ref)</td> <td>-0.02 (-0.20 to 0.16)</td> <td>0.835</td>	Model 1	-0.03 (-0.30 to 0.25)	0.841	0 (ref)	-0.02 (-0.20 to 0.16)	0.835
Model 3 -0.13 (-0.35 to 0.09) 0.253 0 (ref) 0.15 (0.01-0.30) 0.043 Axial diffusivity 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 Radia diffusivity -0.11 (-0.34 to 0.11) 0.330 0 (ref) 0.401 to 0.51 to 0.13) 0.302 Model 1 -0.04 (-0.32 to 0.23) 0.759 0 (ref) 0.10 (-0.18 to 0.19) 0.965 Model 3 -0.13 (-0.35 to 0.09) 0.241 0 (ref) 0.14 (0.02-0.32) 0.025 Model 3 -0.33 (-0.35 to 0.09) 0.247 0 (ref) 0.17 (0.02-0.32) 0.025 Model 3 -0.13 (-0.37 to 0.13) 0.865 N = 12 V V White matter hyperintensity Model 2 0.01 (-0.26 to 0.29) 0.942 0 (ref) -0.01 (-0.29 to 0.07) 0.242 Model 3 -0.15 (-0.38 to 0.09) 0.232 <td>Model 2</td> <td>-0.13 (-0.35 to 0.09)</td> <td>0.236</td> <td>0 (ref)</td> <td>0.16 (0.01-0.31)</td> <td>0.034</td>	Model 2	-0.13 (-0.35 to 0.09)	0.236	0 (ref)	0.16 (0.01-0.31)	0.034
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 -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 1 0.01 (-0.26 to 0.29) 0.942 0 (ref) 0.06 (-0.01 to 0.22) 0.473 Model 3 -0.15 (-0.38 to 0.09) 0.232 0 (ref) 0.06 (-0.01 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 <	Model 3	-0.13 (-0.35 to 0.09)	0.253	0 (ref)	0.15 (0.01-0.30)	0.043
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 -0.04 (-0.32 to 0.23) 0.759 0 (ref) 0 (-0.18 to 0.19) 0.965 Model 2 -0.03 (-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) 0.011 (-0.29 to 0.07) 0.242 Model 1 0.01 (-0.26 to 0.29) 0.942 0 (ref) 0.011 (-0.29 to 0.07) 0.242 Model 3 -0.15 (-0.38 to 0.09) 0.232 0 (ref) 0.08 (-0.08 to 0.24) 0.324 Model 3 -0.10 (-0.37 to 0.18) 0.485 0 (ref)	Axial diffusivity					
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 -0.01 (-0.34 to 0.11) 0.330 0 (ref) 0.08 (-0.07 to 0.23) 0.302 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 0.01 (-0.26 to 0.29) 0.942 0 (ref) -0.11 (-0.29 to 0.07) 0.242 Model 1 0.01 (-0.37 to 0.11) 0.286 0 (ref) 0.06 (-0.00 to 0.22) 0.473 Model 3 -0.10 (-0.37 to 0.18) 0.485 0 (ref) 0.08 (-0.07 to 0.22) 0.242 Model 3 -0.10 (-0.37 to 0.18) 0.485 0 (ref) -0.11 (-0.29	Model 1	0.01 (-0.26 to 0.28)	0.941	0 (ref)	-0.08 (-0.26 to 0.10)	0.394
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 2	-0.12 (-0.34 to 0.11)	0.311	0 (ref)	0.09 (-0.07 to 0.24)	0.264
Radial diffusivity -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 0.01 (-0.26 to 0.29) 0.942 0 (ref) -0.11 (-0.29 to 0.07) 0.242 Model 1 0.01 (-0.26 to 0.29) 0.942 0 (ref) -0.011 (-0.29 to 0.07) 0.242 Model 2 -0.13 (-0.37 to 0.11) 0.286 0 (ref) 0.08 (-0.08 to 0.24) 0.324 Model 3 -0.15 (-0.38 to 0.09) 0.232 0 (ref) 0.08 (-0.08 to 0.24) 0.324 Model 1 -0.10 (-0.37 to 0.18) 0.485 0 (ref) -0.01 (-0.29 to 0.07) 0.246 Model 2 -0.24 (-0.47 to -0.02) 0.033 0 (ref) -0.01 (-0.29 to 0.07) 0.246 Model 3 -0.26 (-0.48 to -0.03) 0.024 0 (ref) 0.09 (-0.05 to 0.24) 0.322 Model 3 -0.26 (-0.48 to -0.03) </td <td>Model 3</td> <td>-0.11 (-0.34 to 0.11)</td> <td>0.330</td> <td>0 (ref)</td> <td>0.08 (-0.07 to 0.23)</td> <td>0.302</td>	Model 3	-0.11 (-0.34 to 0.11)	0.330	0 (ref)	0.08 (-0.07 to 0.23)	0.302
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 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) 0.066 (-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 Model 3 -0.10 (-0.37 to 0.18) 0.485 0 (ref) -0.11 (-0.29 to 0.07) 0.242 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 Model 2 -0.26 (-0.48 to -0.03) <	Radial diffusivity			. ,		
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 0.01 (-0.26 to 0.29) 0.942 0 (ref) -0.11 (-0.29 to 0.07) 0.242 Model 1 0.01 (-0.26 to 0.29) 0.942 0 (ref) 0.010 (-0.29 to 0.07) 0.242 Model 2 -0.13 (-0.37 to 0.11) 0.286 0 (ref) 0.066 (-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 -0.10 (-0.37 to 0.18) 0.485 0 (ref) -0.11 (-0.29 to 0.07) 0.246 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 Model 3	Model 1	-0.04 (-0.32 to 0.23)	0.759	0 (ref)	0 (-0.18 to 0.19)	0.965
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 -0.10 (-0.37 to 0.18) 0.485 0 (ref) -0.011 (-0.29 to 0.07) 0.246 Model 1 -0.01 (-0.37 to 0.18) 0.485 0 (ref) -0.011 (-0.29 to 0.07) 0.246 Model 1 -0.01 (-0.37 to 0.18) 0.485 0 (ref) -0.011 (-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	Model 2	-0.13 (-0.35 to 0.09)	0.241	0 (ref)	0.18 (0.03-0.33)	0.019
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 1 0.01 (-0.26 to 0.29) 0.942 0 (ref) 0.06 (-0.10 to 0.22) 0.473 Model 2 -0.13 (-0.37 to 0.11) 0.286 0 (ref) 0.08 (-0.08 to 0.24) 0.324 Periventricular white matter hyperintensity -0.10 (-0.37 to 0.18) 0.485 0 (ref) -0.11 (-0.29 to 0.07) 0.246 Model 1 -0.010 (-0.37 to 0.18) 0.485 0 (ref) 0.08 (-0.08 to 0.24) 0.324 Periventricular white matter hyperintensity -0.24 (-0.47 to -0.02) 0.033 0 (ref) 0.08 (-0.07 to 0.22) 0.322 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	Model 3	-0.13 (-0.35 to 0.09)	0.257	0 (ref)	0.17 (0.02-0.32)	0.025
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 -0.10 (-0.37 to 0.18) 0.485 0 (ref) -0.11 (-0.29 to 0.07) 0.246 Model 1 -0.10 (-0.37 to 0.18) 0.485 0 (ref) -0.011 (-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	White matter hyperintensity (in z-score)	N = 52		N = 805	N = 129	
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 -0.10 (-0.37 to 0.18) 0.485 0 (ref) -0.011 (-0.29 to 0.07) 0.246 Model 1 -0.10 (-0.37 to 0.18) 0.485 0 (ref) -0.011 (-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	White matter hyperintensity					
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 -0.10 (-0.37 to 0.18) 0.485 0 (ref) -0.11 (-0.29 to 0.07) 0.246 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	Model 1	0.01 (-0.26 to 0.29)	0.942	0 (ref)	-0.11 (-0.29 to 0.07)	0.242
Model 3 -0.15 (-0.38 to 0.09) 0.232 0 (ref) 0.08 (-0.08 to 0.22) 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	Model 2	-0.13 (-0.37 to 0.11)	0.286	0 (ref)	0.06 (-0.10 to 0.22)	0.473
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	Model 3	-0.15 (-0.38 to 0.00)	0.232	0 (ref)	0.08 (-0.08 to 0.22)	0.324
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	Periventricular white matter hyperintensity	0.19 (0.90 to 0.09)	0.232		0.00 (0.00 to 0.24)	0.524
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	Model 1	-0.10 (-0.37 to 0.18)	0.485	0 (ref)	-0.11 (-0.29 to 0.07)	0.246
Model 3 -0.26 (-0.48 to -0.03) 0.024 0 (ref) 0.09 (-0.05 to 0.24) 0.215 (Table 3 continues on part page)	Model 2	-0.24 (-0.47 to -0.02)	0.022	0 (ref)	0.08(-0.07 to 0.27)	0 277
(Table 2 continues on next name)	Model 3	-0.26 (-0.48 to -0.02)	0.024	0 (ref)	0.09(-0.05 to 0.22)	0.215
	induci y	0.20 (0.40 to -0.03)	0.024		(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, longterm 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	ealth 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	0.11 (0.20 to 0.50)	0.550	0 (101)	0.02 (0.24 10 0.20)	0.005
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 2	0.17 (-0.24 to 0.57)	0.420	0 (ref)	-0.02 (-0.25 to 0.20)	0.822
Radial diffusivity	0.17 (-0.24 10 0.37)	0.420	0 (101)	-0.05 (-0.25 10 0.20)	0.025
Model 1	$0.08(-0.41 \pm 0.57)$	0.752	0 (ref)	$-0.18(-0.46 \pm 0.00)$	0 102
Model 2	0.00(-0.41 to 0.57)	0.755	0 (ref)	$-0.10(-0.40\ to\ 0.09)$	0.192
Model 2	0.07 (-0.32 to 0.47)	0.714	0 (ref)	-0.02 (-0.24 to 0.21)	0.005
White matter hyperintensity (in z score)	$0.00(-0.32 \ 10 \ 0.47)$	0.704	0 (iei)	-0.02(-0.24(0)0.21)	0.004
white matter hyperintensity (in 2-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 or	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 populationbased studies and animal experiments. Activation of reward circuits,^{39,40} and demyelination or axonal loss⁴¹ 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

Conceptualisation: Jing Sun, Zhenchang Wang, and Han Lv.

- Data curation: Jing Sun, Ying Hui, Jing Li, Wenjuan Liu, Xinyu Zhao, Pengfei Zhao, Shuohua Chen, Shouling Wu, Zhenchang Wang, and Han Lv.
 - Investigation: Na Zeng, Jing Sun, and Han Lv.
 - Writing—original draft: Jing Sun and Han Lv.
 - Writing—review & editing: Jing Sun, Na Zeng, and Han Lv. Project administration: Shouling Wu and Zhenchang Wang.

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.

Acknowledgements

The authors would like to thank all participating investigators, doctors, nurses, and technicians for their contributions to this cohort study.

Appendix A. Supplementary data

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

References

- Optimizing brain health across the life course: WHO position paper. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO; https://creativecommons.org/licenses/by-nc-sa/3.0/igo/.
- 2 Wang Y, Pan Y, Li H. What is brain health and why is it important? BMJ. 2020;371:m3683.
- 3 Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894(ixii):1–253.
- 4 Collaboration NCDRF. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet.* 2017;390(10113): 2627–2642.
- 5 Wong MCS, Huang J, Wang J, et al. Global, regional and time-trend prevalence of central obesity: a systematic review and meta-analysis of 13.2 million subjects. Eur J Epidemiol. 2020;35(7):673–683.
- 6 Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet.* 2004;363(9403):157–163.
- 7 Bobb JF, Schwartz BS, Davatzikos C, Caffo B. Cross-sectional and longitudinal association of body mass index and brain volume. *Hum Brain Mapp.* 2014;35(1):75–88.
- 8 Hamer M, Batty GD. Association of body mass index and waist-tohip ratio with brain structure: UK Biobank study. *Neurology*. 2019;92(6):e594–e600.
- 9 Taki Y, Kinomura S, Sato K, et al. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. *Obesity*. 2008;16(1):119–124.
- 10 Raji CA, Ho AJ, Parikshak NN, et al. Brain structure and obesity. Hum Brain Mapp. 2010;31(3):353–364.
- Repple J, Opel N, Meinert S, et al. Elevated body-mass index is associated with reduced white matter integrity in two large independent cohorts. *Psychoneuroendocrinology*. 2018;91:179–185.
- 12 Lampe L, Zhang R, Beyer F, et al. Visceral obesity relates to deep white matter hyperintensities via inflammation. Ann Neurol. 2019;85(2):194–203.
- 13 Hussain SM, Newman AB, Beilin LJ, et al. Associations of change in body size with all-cause and cause-specific mortality among healthy older adults. *JAMA Netw Open.* 2023;6(4): e237482.
- 14 Kaze AD, Santhanam P, Erqou S, Ahima RS, Bertoni AG, Echouffo-Tcheugui JB. Body weight variability and risk of cardiovascular outcomes and death in the context of weight loss intervention among patients with type 2 diabetes. JAMA Netw Open. 2022;5(2): e220055.
- 15 Khan SS, Shah SJ, Colangelo LA, et al. Association of patterns of change in adiposity with diastolic function and systolic myocardial mechanics from early adulthood to middle age: the coronary artery risk development in young adults study. J Am Soc Echocardiogr. 2018;31(12):1261–1269.e8.
- 16 Wu S, An S, Li W, et al. Association of trajectory of cardiovascular health score and incident cardiovascular disease. JAMA Netw Open. 2019;2(5):e194758.
- 17 Zhang Q, Zhou Y, Gao X, et al. Ideal cardiovascular health metrics and the risks of ischemic and intracerebral hemorrhagic stroke. *Stroke.* 2013;44(9):2451–2456.

- 18 Zhang H, Gu Z, Yao C, et al. Risk factors for possible REM sleep behavior disorders: a community-based study in Beijing. *Neurology*. 2020;95(16):e2214–e2224.
- 19 Sun J, Hui Y, Li J, et al. Protocol for Multi-modality MEdical imaging sTudy bAsed on KaiLuan Study (META-KLS): rationale, design and database building. *BMJ Open*. 2023;13(2):e067283.
- 20 Jia Z, Zhou Y, Liu X, et al. Comparison of different anthropometric measures as predictors of diabetes incidence in a Chinese population. *Diabetes Res Clin Pract*. 2011;92(2):265–271.
- 21 Hindman BJ, Dexter F, Gadomski BC, Puttlitz CM. Relationship between glottic view and intubation force during macintosh and airtraq laryngoscopy and intubation. *Anesth Analg.* 2022;135(4):815–819.
- 22 Manolov R, Solanas A. A comparison of mean phase difference and generalized least squares for analyzing single-case data. J Sch Psychol. 2013;51(2):201–215.
- 23 Burgess N, Maguire EA, O'Keefe J. The human hippocampus and spatial and episodic memory. *Neuron.* 2002;35(4):625–641.
- 24 West MJ, Coleman PD, Flood DG, Troncoso JC. Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease. *Lancet.* 1994;344(8925):769–772.
- 25 Alexander AL, Hurley SA, Samsonov AA, et al. Characterization of cerebral white matter properties using quantitative magnetic resonance imaging stains. *Brain Connect.* 2011;1(6):423–446.
- 26 Rosas HD, Lee SY, Bender AC, et al. Altered white matter microstructure in the corpus callosum in Huntington's disease: implications for cortical "disconnection". *Neuroimage*. 2010;49(4):2995–3004.
- 27 Schmidt P. Bayesian inference for structured additive regression models for large-scale problems with applications to medical imaging. Dissertation. Ludwig-Maximilians Universitat Munchen; 2017.
- 28 Greenberg SM, Vernooij MW, Cordonnier C, et al. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol.* 2009;8(2):165–174.
- 29 Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol.* 2013;12(8):822–838.
- 30 Staals J, Makin SD, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology*. 2014;83(14):1228–1234.
- 31 World Health Organization. Waist circumference and waist-hip ratio : report of a WHO expert consultation, Geneva, 8-11 December 2008. 2011.

- **32** Jiang R, Noble S, Sui J, et al. Associations of physical frailty with health outcomes and brain structure in 483 033 middle-aged and older adults: a population-based study from the UK Biobank. *Lancet Digit Health.* 2023;5(6):e350–e359.
- 33 Lane CA, Barnes J, Nicholas JM, et al. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. *Lancet Neurol.* 2019;18(10):942–952.
- 34 Han YP, Tang X, Han M, et al. Relationship between obesity and structural brain abnormality: accumulated evidence from observational studies. Ageing Res Rev. 2021;71:101445.
- 35 Pillay P, Lewington S, Taylor H, Lacey B, Carter J. Adiposity, body fat distribution, and risk of major stroke types among adults in the United Kingdom. JAMA Netw Open. 2022;5(12):e2246613.
- 36 Yuan Y, Liu K, Zheng M, et al. Analysis of changes in weight, waist circumference, or both, and all-cause mortality in Chinese adults. JAMA Netw Open. 2022;5(8):e2225876.
- 37 Kaltenhauser S, Weber CF, Lin H, et al. Association of body mass index and waist circumference with imaging metrics of brain integrity and functional connectivity in children aged 9 to 10 Years in the US, 2016-2018. JAMA Netw Open. 2023;6(5):e2314193.
- 38 Garcia-Garcia I, Michaud A, Jurado MA, Dagher A, Morys F. Mechanisms linking obesity and its metabolic comorbidities with cerebral grey and white matter changes. *Rev Endocr Metab Disord*. 2022;23(4):833–843.
- 39 Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. *Nat Rev Neurosci.* 2005;6(9):691–702.
- 40 Stice E, Burger K. Neural vulnerability factors for obesity. Clin Psychol Rev. 2019;68:38–53.
- 41 Bouhrara M, Khattar N, Elango P, Resnick SM, Ferrucci L, Spencer RG. Evidence of association between obesity and lower cerebral myelin content in cognitively unimpaired adults. *Int J Obes.* 2021;45(4):850–859.
- 42 Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. *Nat Rev Endocrinol.* 2017;13(11):633-643.
- 43 Longo M, Zatterale F, Naderi J, et al. Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. Int J Mol Sci. 2019;20(9):2358.
- 44 Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. J Clin Invest. 2011;121(6):2111–2117.