IBRO Neuroscience Reports 18 (2025) 148–157

Contents lists available at ScienceDirect

IBRO Neuroscience Reports

journal homepage: www.sciencedirect.com/journal/IBRO-Neuroscience-Reports

Effects of obesity on aging brain and cognitive decline: A cohort study from the UK Biobank

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ARTICLE INFO

Keywords:
Obesity
Gray matter atrophy
White matter hyper-intensities
Genetic overlap
Mendelian randomization

ABSTRACT

Objective: To investigate the impact of obesity on brain structure and cognition using large neuroimaging and genetic data.

Methods: Associations between body mass index (BMI), gray matter volume (GMV), whiter matter hyper-intensities (WMH), and fluid intelligence score (FIS) were estimated in 30283 participants from the UK Biobank. Longitudinal data analysis was conducted. Genome-wide association studies were applied to explore the genetic loci associations among BMI, GMV, WMH, and FIS. Mendelian Randomization analyses were applied to further estimate the effects of obesity on changes in the brain and cognition.

Results: The observational analysis revealed that BMI was negatively associated with GMV ($r = -0.15$, $p < 1 \times 10^{-24}$) and positively associated with WMH ($r = 0.08$, $p < 1 \times 10^{-16}$). The change in BMI was negatively associated with the change in GMV ($r = -0.04$, $p < 5 \times 10^{-5}$). Genetic overlap was observed among BMI, GMV, and FIS at SBK1 (rs2726032), SGF29 (rs17707300), TUFM (rs3088215), AKAP6 (rs1051695), IL27 (rs4788084), and SPI1 (rs3740689 and rs935914). The MR analysis provided evidence that higher BMI was associated with lower GMV ($\beta = -1119.12$, $p = 5.77 \times 10^{-6}$), higher WMH ($\beta = 42.76$, $p = 6.37 \times 10^{-4}$), and lower FIS ($\beta = -0.081$, $p = 1.92 \times 10^{-23}$).

Conclusions: The phenotypic and genetic association between obesity and aging brain and cognitive decline suggested that weight control could be a promising strategy for slowing the aging brain.

1. Introduction

Obesity has emerged as a chronic metabolic disease that affects almost 20 % of the global population over the past few decades (Wan et al., 2022). The high prevalence of obesity is closely associated with serious diseases such as diabetes, cardiovascular disease, metabolic associated fatty liver disease (MAFLD), chronic kidney disease (CKD) and cerebral disease (Geng et al., 2022). In recent years, aging-associated neurodegeneration has been reported in obesity (Zhang et al., 2023). However, compared to other cognitive-related diseases, limited research exists on the relationship between obesity and the aging brain. It is crucial not to overlook the potential impact of obesity on the aging brain, as it poses a high risk of cognitive dysfunction (Bellocchio and Marsicano, 2022; Hagi et al., 2021). Gaining a thorough understanding of the specific changes in the brain that occur in obesity can prove instrumental in unraveling the underlying mechanism of obesity and develop effective prevention methods.

Cerebral changes and cognitive decline have been found in subjects with obesity or overweight in previous observational studies (Golan Shekhtman et al., 2024). It has been reported that high fat diet can affects brain cortex gene expression in mouse models (Pandit et al., 2024; Honda et al., 2023). Obesity can induce cerebral changes that mediate cognitive impairment (McWhinney et al., 2022). In turn, cognitive dysfunction can have complex interactions with feeding behavior and metabolic system (Rodrigue et al., 2020; Dunn et al., 2023). In addition, a recent large-scale dataset research has found an association between obesity-related genetic variants, such as single nucleotide polymorphisms (SNPs), and regional brain volumes (Pan et al., 2022). However, due to the inherent limitations of observational experimental design, these observational studies cannot tell whether the brain

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https://doi.org/10.1016/j.ibneur.2025.01.001
Received 2 November 2024; Received in revised form 19 December 2024; Accepted 4 January 2025
Available online 5 January 2025

changes are a neural cause or a proxy of obesity. Therefore, it is still unclear the role of cerebral changes in obesity and cognitive decline, though some hypothesis based on the observational results have been made (Miller and Spencer, 2014; Moheet et al., 2015). Recently, two large-scale longitudinal studies have reported that high body mass index (BMI) is associated with accelerated brain aging, specifically, higher BMI is associated with smaller brain parenchyma and gray matter volume (GMV), more cerebrospinal fluid (CSF), and white matter lesions (Lv et al., 2024; Sun et al., 2024).

The genome-wide association studies (GWAS) have been applied in identifying SNPs associated with BMI/obesity and cognition (Singh et al., 2017; Fitzgerald et al., 2020), significantly advancing our understanding of this complex trait. Recently, large-scale cohort studies like the UK Biobank have shed light on genetic variants associated with brain structure (Smith et al., 2021), further enriching the genetic architecture of the human brain. Despite these groundbreaking findings, a critical gap persists in the literature, as there has been a scarcity of studies performing joint analyses to uncover shared genetic signatures underpinning BMI, brain structure, and cognition within the same cohort. Addressing this void is crucial, as it holds the potential to revolutionize our comprehension of the intricate interplay between obesity, brain morphology, and cognitive function, ultimately providing directions for more targeted interventions and therapeutic strategies in these areas.

Mendelian randomization (MR) is an analysis method which leverages the random allocation of genetic variants as instrumental variables to estimate the causal association between exposure and clinical outcomes (Venkatesh et al., 2022; Hashemy et al., 2024). MR provides robust causal inferences and is little affected by residual confounding, as genetic variants are randomly assigned from parents and are generally fixed, meaning they cannot be modulated by the outcomes or confounders. This mimics the random distribution of confounders achieved through randomization in randomized controlled trials (Taschler et al., 2022). Previously, MR analysis has been applied to estimate the causal association between obesity and gastrointestinal diseases (Kim et al., 2023). In this study, our primary aim was to measure the association among body mass index (BMI), brain structure including the GMV and white matter hyper-intensities (WMH), as well as cognitive function in a large cohort from the UK Biobank. Secondarily, we tested the effects of obesity on brain structure and cognitive scores using MR, based on the large available samples with genetic association results.

2. Methods

2.1. Study participants

Data from the UK Biobank (the approve number: 94885) were used for the association analysis of BMI (Field ID: 21001 and 23104), brain structure (Category ID: 110 for regional and total gray matter volume; Field ID: 25781 for WMH) and cognitive score (Field ID: 20016). For the current study, 37754 individuals (aged 45–80 years old) of white British ancestry who underwent the T1 and T2 MRI scans were included to investigate the associations among the phenotypes. Then, 3460 subjects were further excluded because they ever had been addicted to or dependent on one or more things, including substances or behaviors (such as gambling) or diagnosed with tumors (Field ID: 20401 and 2453). Next, 2663 subjects were excluded due to missing fluid intelligence score (FIS, Field ID:20016) data which was evaluated at the time point corresponding to the MRI scanning. Furthermore, 1348 subjects were excluded due to missing glucose (Field ID: 26405), living environment score (Field ID: 26417), education score (Field ID: 26414), and income score (Field ID: 26411).

As most of subjects with obesity had hypertension or hyperglycemia, in order to include large samples to improve statistical power, subjects with hypertension or diabetes were not excluded in the main analysis (Li et al., 2019; Fontvieille et al., 2023). Systolic blood pressure (SBP), diastolic blood pressure (DBP), and glucose were included to explore possible effects of hypertension and diabetes on the MRI characteristics and intelligence score (Cox et al., 2019; Newby and Garfield, 2022). Ultimately, a total of 30283 individuals with complete baseline information were included in the phenotype association analyses. The longitudinal analysis was conducted using the longitudinal imaging data of 2734 individuals from 30283 participants.

In order to investigate the genetic loci association among the phenotypes, participants in the entire UK Biobank who underwent similar cohorts' quality control procedures were selected to perform GWAS analyses. After cohorts' quality control, 40375 individuals were selected for GWAS of BMI, 39014 individuals for GWAS of GMV, 37886 for GWAS of WMH, and 102424 individuals for GWAS of FIS. The complete study workflow was shown in Supplement Fig. 1. The UK Biobank study has been approved by the North West Multicenter Research Ethical Committee. All participants have signed the informed consent when joining UK Biobank.

2.2. Phenotypes and covariates

The FIS was chosen as a measure of cognition because it describes the capacity to solve problems that require logic and reasoning ability, independent of acquired knowledge (Siedlinski et al., 2023). In the fluid intelligence test, 13 questions were asked and the answers were collected (see Supplement Table 1 for detail). The FIS was calculated by an unweighted summing of the number of correct answers given to the 13 fluid intelligence questions. Participants who did not answer all of the questions within the allotted 2-minute limit were scored as zero. The living environment score (England) measures the quality of individuals' immediate surroundings both within and outside the home, including four indicators (social and private housing in poor condition, houses with central heating, air quality, and road traffic accidents). The education score measures the extent of deprivation in terms of education, skills and training in an area. The income score measures the proportion of the population in an area experiencing deprivation related to low income. Detail of these variables could be found in the UK Biobank (https://biobank.ndph.ox.ac.uk/showcase/).

The detail of the MRI scanning protocol can be seen at https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id= 25005. In this study, T1-weighted structural imaging data and T2-weighted FLAIR structural imaging data were used to estimate the GMV and WMH. The key protocol parameters for T1-weighted imaging are resolution of $1 \times 1 \times 1$ mm, image matrix of $208 \times 256 \times 256$, duration of 5 minutes with 3D MPRAGE. The key protocol parameters for T2-weighted FLAIR imaging are $1.05 \times 1 \times 1$ mm, imaging matrix of $192 \times 256 \times 256$, duration of 6 minutes with 3D SPACE. For each subject, the raw imaging data were checked, including a semi-automated QC review and manual QC review (Miller et al., 2016).

2.3. Image processing

Our study made use of imaging-derived phenotypes generated by image-processing pipeline developed and run on behalf of UK Biobank (Alfaro-Almagro et al., 2018). The full FOV raw T1-weighted image was cut down to reduce the amount of non-brain tissue using BET (Brain Extraction Tool) and then the brain tissue was extracted using FNIRT (FMRIB's Nonlinear Image Registration Tool). Next, the T1 image was processed by FreeSurfer for segmentation. The regional GMV was extracted with the Desikan-Killiany (DK) atlas. The regional GMV and whole GMV were adjusted for head size. The raw T2-weighted FLAIR image was linearly aligned to the T1-weighted to transform the T2-weighted FLAIR image from the original space into the individual subject's T1-weighted space. Then the transformed T2-weighted FLAIR image was normalized into the MNI standard space using the transform information derived from normalizing individual T1-weighted image to the MNI space. The total volume of WMH is estimated by using the

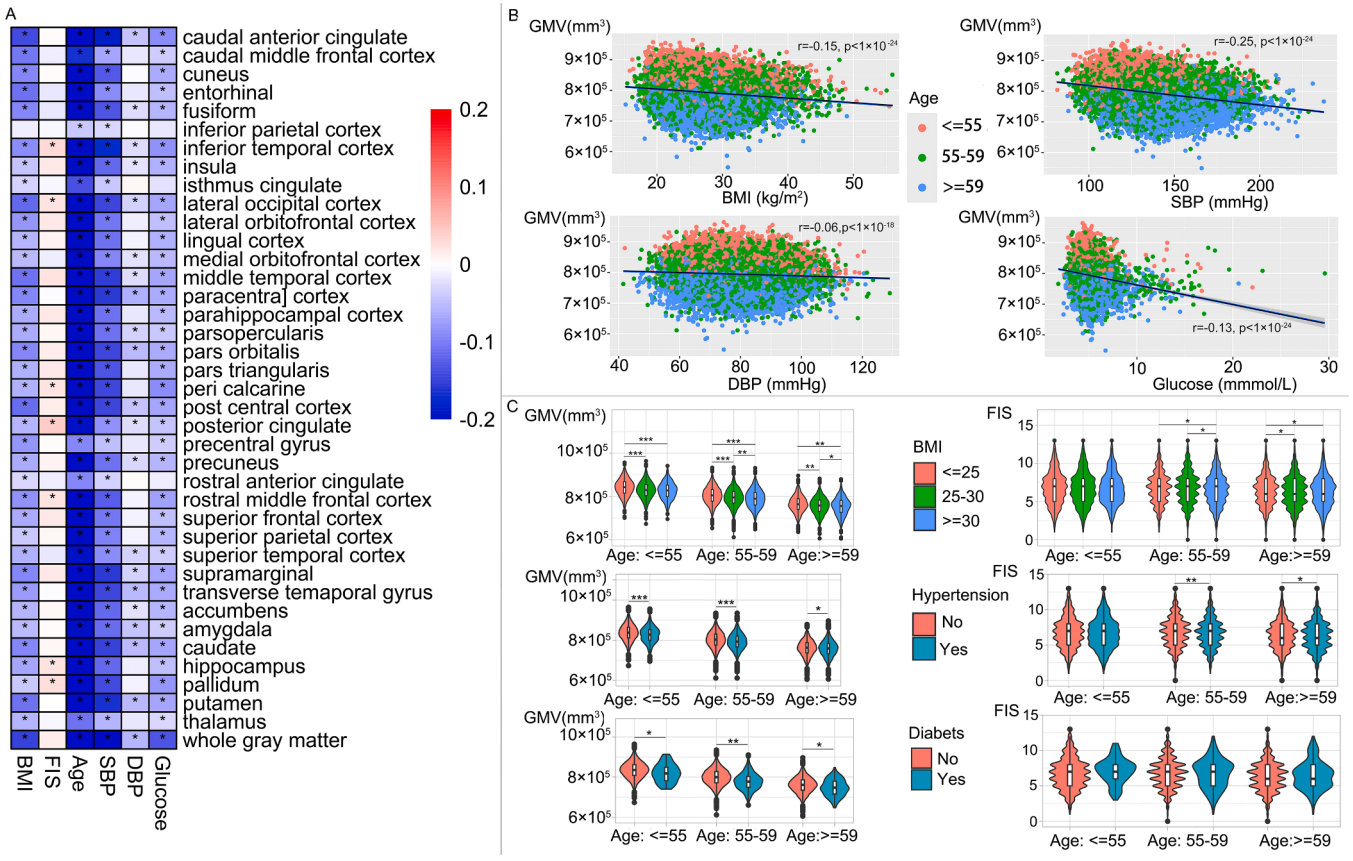

Fig. 1. Observational results for GMV. A represented association between regional GMV and BMI, FIS, Age, SBP, DBP, as well as glucose. B represented association between global GMV and prototypes. C represented group differences for GMV and FIS. Abbreviations: BMI, body mass index; GMV, gray matter volume; FIS, fluid intelligence score, SBP, systolic blood pressure; DBP, diastolic blood pressure. * represented $p < 0.005$, * * represented $p < 5 \times 10^{-10}$, * ** represented $p < 5 \times 10^{-15}$.

Table 1
Study Population characteristics in observational results. SD: standard deviation.

BMI (kg/m^2)	< 25	25–30	> 30
Number	11945	13026	5312
Sex (Male/Female)	7635/4310	5565/7461	2624/2688
Age (Median±SD) [years]	63±7.71	65±7.48	64±7.40
Alcohol Status (Current/Previous/ Never)	11409/219/307	12521/248/257	5038/148/136
Smoking Status (Current/Previous/ Never)	1316/4897/ 5732	1294/5471/ 6261	639/2132/ 2541
Income (Mean±SD)	0.092±0.078	0.098±0.082	0.11±0.093
Living Score (Mean±SD)	16.76±13.93	16.06±13.56	16.97±14.57
Total GMV (Mean±SD) [mm^3]	802100±47539	789449±46658	786500±48022
Total WMH (Mean±SD) [mm^3]	4255±5621	5028±6594	5521±6813
Fluid Intelligence Score (Mean±SD)	6.70±2.03	6.58±2.08	6.43±2.07

Abbreviations: BMI, body mass index; GMV, gray matter volume; WMH, white matter hyperintensities.

BIANCA tool to evaluate the white matter structure.

2.4. Genetic analysis

The detail of the genetic data can be found at the UK Biobank (https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100315). The genetic data process and analysis were performed using the UK Biobank research analysis platform (https://www.ukbiobank.ac.uk/enable-your-research/research-analysis-platform) with the steps referred to the GWAS document (https://dnanexus.gitbook.io/uk-biobank-rap/science-corner/gwas-ex#introduction). In this study, the imputed genotyping data was used to perform the following quality controls (QC) and GWAS analysis on the subset of subjects with BMI, GMV, WMH, and FIS. First, participants were white British ancestry, gender and genetic sex matched, no sex chromosome aneuploidy, no kinship found, and less than 10 % genotype missing. Second, the genetic datasets underwent the following QC process: 1, excluding variants with minor allele frequency less than 0.01; 2, removing variants with imputation INFO score less than 0.8; 3, excluding variants failed the Hardy-Weinberg test at 1×10^{-8} level. Then, the genetic datasets were merged into PLINK format. After merging, the GWAS were performed with two step models by using the software of Regenie. The age, sex, smoking status, and alcohol status were adjusted.

2.5. Mendelian randomization analysis

To further explore relationship between obesity and gray matter atrophy, SNPs associated with exposures were selected as instruments using the threshold of $p < 5 \times 10^{-10}$ for BMI and $p < 5 \times 10^{-6}$ for GMV, and WMH. The threshold for GMV and WMH was relaxed because no SNP reached for $p < 5 \times 10^{-8}$ reference to the strategy applied in previous MR studies (He et al., 2022a). SNPs were excluded with moderate linkage disequilibrium (r^2>0.0001). The linkage disequilibrium across these SNPs were calculated based on the European 1000-Genomers

reference panel. SNPs that had association with outcomes($p < 0.05$) were excluded to obtain the assumption of MR that instrumental variables are strongly associated with exposure and have no direct association with the outcome. In this study, SNPs that were palindromic and had an intermediate allele frequency were also excluded refereed to a previous study (Hemani et al., 2018).

2.6. Statistical analyses

The Spearman correlation coefficient between BMI and GMV was calculated to test whether BMI was associated with GMV. According to the age range, participants were divided into three groups: range from 40 to 49 years old for the first group, range from 50 to 59 years old for the second group, greater than or equal to 60 years old for the last group. The *t*-test was applied to evaluate the differences in GMV among obesity, overweight, and normal weight in each age group. Sensitivity analyses were conducted to examine whether the impact of obesity on the aging brain and cognition decline still exists by excluding the participants ever had hypertension, diabetes, neurological and psychiatric disorders (including dementia, delirium, Parkinson's disease, Alzheimer's disease, multiple sclerosis, epilepsy, migraine, and sleep disorders), and cerebrovascular diseases (including cerebral infarction, stroke, other cerebrovascular diseases, and atherosclerosis). The detail of sensitivity analyses was presented in the Supplementary File.

In the longitudinal correlation analysis, the Spearman correlation coefficient between changes in GMV, BMI, WMH, SBP, and DBP was evaluated. The changes in WMH and GMV were categorized as low change (Q1), medium change (Q2), and high change (Q3). The differences in changed GMV and WMH were compared between the BMI increase and decrease group, between the SBP increase and decrease group, between the DBP increase and decrease group, as well as the FIS increase and decrease group.

To test whether shared genetic effects among the BMI, GMV, WMH, and FIS, significant genetic variants were firstly identified with linkage disequilibrium (LD) < 0.1 and $P < 5 \times 10^{-7}$. Then the association lookups for the identified genetic variants were performed.

To examine whether the association is likely causal, inverse-variance weighted (IVW) two-sample MR with random-effects was applied as our main analysis to estimate the effect of a 1-standard deviation (SD) increase in BMI on changes in the volume of cerebral cortex. The IVW method provides most accurate estimate in the absence of horizontal pleiotropy (when the genetic variants are associated with the outcome through pathways other than the exposure). Thus, several sensitivity analyses, including MR-Egger, weighted median, simple mode, and weighted mode, were performed to assess an account for potential heterogeneity and horizontal pleiotropy. The p-value for intercept in MR-Egger model was used to detect the extent of horizontal pleiotropy. The Q and I^2 statistics were calculated to evaluate the degree of heterogeneity. To validate the association between BMI and GMV, the same MR methods were further applied to the GWAS summary statistics of Obesity and GMV. In addition, the Wald ratio method was applied to examine the association (He et al., 2022b). All the analyses were performed using the 'TwoSampleMR' package in R.

3. Results

3.1. Association among BMI, brain structure and cognition

In our observation results, characteristics of 30283 individuals of observational population were shown in Table 1. In addition to the inferior parietal cortex, the GMV in other brain regions as well as the overall GMV of the brain were negatively correlated with BMI after correction for multiple testing ($p < 0.00128$ after Bonferroni-corrected). Both the regional and whole GMV were negatively associated with age after correction for multiple testing. The regional GMV of inferior temporal gyrus, lateral occipital cortex, peri calcarine gyrus, posterior cingulate, rostral middle frontal cortex, hippocampus, pallidum cortex, as well as the whole GMV were positively associated with FIS ($p < 0.00128$ after Bonferroni-corrected). Significant group differences ($p < 5 \times 10^{-4}$) were found among normal weight, over-weight, and obesity in each age group (Fig. 1A). Similar to BMI, blood pressure and glucose were negatively associated with gray matter volume ($p < 0.00128$ after Bonferroni-corrected).

The association between BMI and WMH was shown in Fig. 2. The BMI was positively associated with WMH ($r = 0.08$, $p < 1 \times 10^{-16}$). In each sub-age group, the WMH of the obese population is higher ($p < 0.0005$) than that of the overweight population, and the WMH of the overweight population is higher ($p < 0.0005$) than that of the normal weight population (Fig. 2B). In addition, blood pressure and glucose were positively associated with WMH ($r = 0.07$, 0.21, and 0.07 for DBP, SBP, and glucose respectively, $p < 1 \times 10^{-16}$).

The longitudinal analysis result showed that the changes of BMI was significantly ($p < 5 \times 10^{-5}$) associated with the changes of total GMV, SBP, and DBP (Fig. 3A). The changes of WMH were significantly ($p < 0.003$) associated with the changes of SBP. The population with increased BMI had more gray matter reduction ($p = 0.015$) than the population with decreased BMI (Fig. 3B and Supplement figure). The population with increased SBP and DBP had more WMH increase ($p = 7 \times 10^{-5}$ and 0.017 respectively) than the population with decreased SBP and DPB.

After excluding participants with hypertension, diabetes, neurological and psychiatric disorders, and cerebrovascular diseases before MRI scanning, there was still significant positive correlations between BMI and GMV, as well as significant negative correlations between BMI and WMH (Supplement Figs. 2A, 3A, and 4A). Furthermore, after excluding disease factors that have occurred before the MRI scanning, the differences in GMV and WMH among obese, overweight, and normal-weight groups remained significant (Supplement Figs. 2B, 3B, and 4B).

3.2. Genetic correlations among BMI, brain structure and cognition

The GWAS results for BMI, GMV, WMH, and FIS were shown in Supplement Figure 6. Our results tagged genetic variants that were linked to the four phenotypes (Fig. 4). The rs34811474 (ANAPC4), rs4524616, rs62422661, rs1487445, rs1051695 (AKAP6), rs2726032 (SBK1), rs4788084 (IL27), rs17707300 (SGF29), rs3088215 (TUFM), rs56186137 (ATXN2L), rs72793809 (ATXN2L), rs8049439 (ATXN2L), rs12443881 (ATXN2L), and rs4788101 were significantly associated with both BMI and FIS. The rs34974290 (TRIM65) and rs7222757 (TRIM65) were significantly associated ($p < 5 \times 10^{-8}$) with WMH and almost significantly associated ($p = 1.39 \times 10^{-7}$ for rs3499429 and $p = 8.9 \times 10^{-7}$ for rs7222757) with BMI. The rs116969588 significantly associated with GMV ($p = 3.37 \times 10^{-8}$) was loci associated ($r^2 < 0.0001$) with rs948094 which was significantly associated ($p = 4.84 \times 10^{-12}$) with BMI. In addition, the rs3740689 almost associated with GMV ($p = 7.02 \times 10^{-8}$) had functional overlap with the rs935914 significantly associated with BMI ($p = 9.85 \times 10^{-12}$), both of them belong to the SPI1 gene.

3.3. Effects of BMI on brain structure and cognition

The two-sample IVW MR provided evidence for a role of increased BMI in risk of gray matter atrophy (Table 2: β=-1119.12, SE=246.79 $p = 5.77 \times 10^{-6}$); that was 1119.12 ×log(BMI) decrease of GMV per 1 standard deviation (SD) increase of BMI. Sensitivity analyses using the MR Egger (β=-2372.70, $p = 7.21 \times 10^{-3}$), weighted median (β=-1510.42, $p = 2.81 \times 10^{-5}$), simple mode (β=-1888.59, $p = 8.70 \times 10^{-2}$), and weighted mode (β=-2028.87, $p = 2.10 \times 10^{-2}$) showed the similar results. There was no evidence of horizontal pleiotropy and heterogeneity in the MR Egger (Table 2: EI=5.42 [$p = 0.91 > 0.05$], Q=102.04 [$p = 0.97 > 0.05$], I^2=0.29). Our MR results also showed that the increased BMI had effect on increased WMH

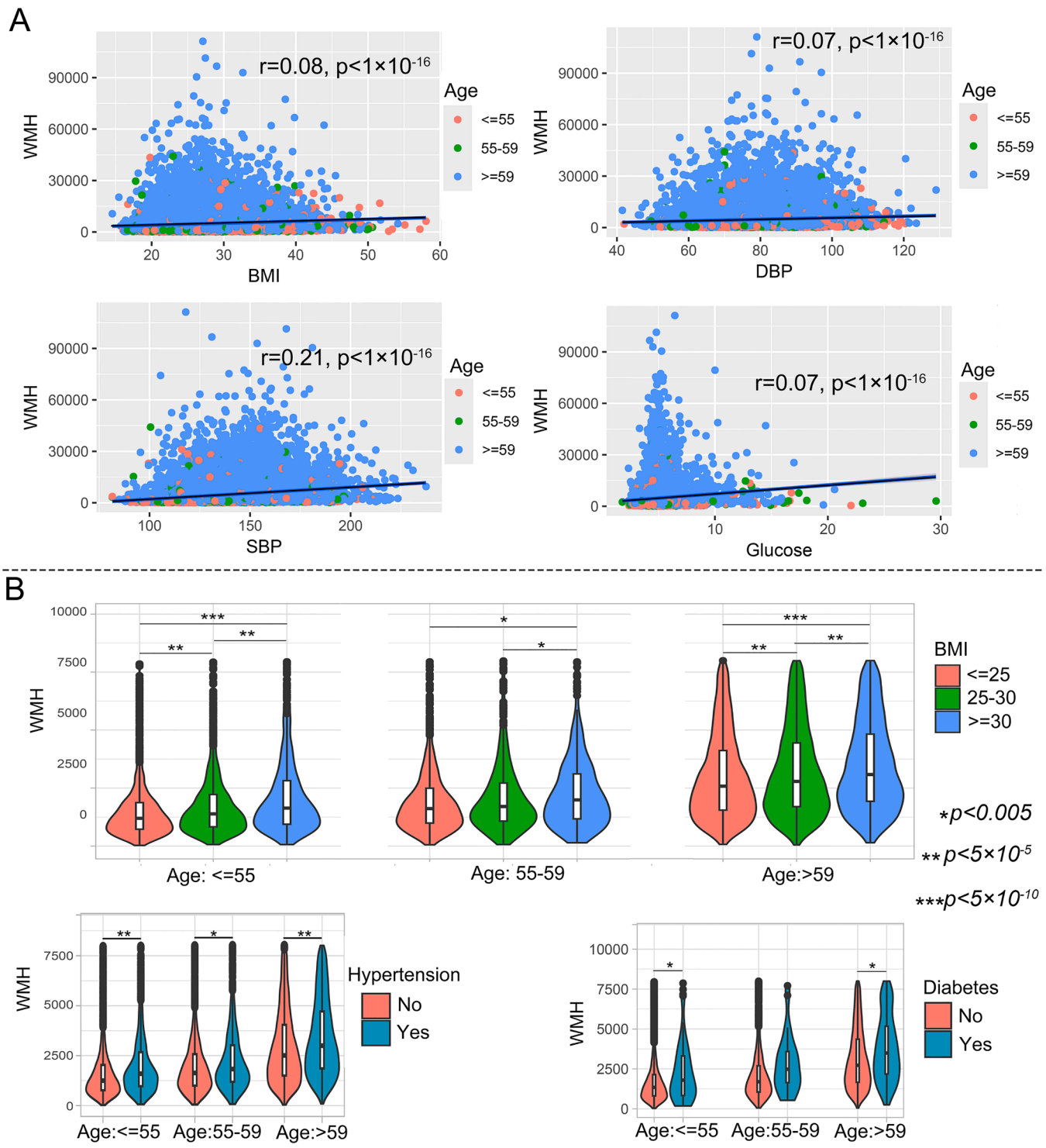

Fig. 2. Observational results for WMH. A represented association between WMH and BMI, SBP, DBP, as well as glucose. B represented group differences for WMH. Abbreviations: BMI, body mass index; WMH, white-matter hyperintensities; FIS, fluid intelligence score, SBP, systolic blood pressure; DBP, diastolic blood pressure.

(β=42.76, $p = 6.37 \times 10^{-4}$) and decreased FIS (β=-0.081, $p = 1.92 \times 10^{-23}$). The effects of single SNP were shown in Supplement Figure 7.

4. Discussion

This study provided genetic evidence demonstrating an effect of higher BMI on brain atrophy using large samples from the UK Biobank. To the best of our knowledge, few studies explored the role of obesity on changes in the aging brain. Our findings not only shed light on the clinical observations linking obesity in middle-aged adults to risk of cognitive decline (Quaye et al., 2023; Batsis et al., 2021), but also to an enhanced understanding the damaging effects of obesity on the brain. These results underscore the importance and necessity of weight control.

Our observational findings were consistent with results from traditional neuroimaging studies that decreased GMV and increased WMH in obesity as well as brain atrophy in the older (Pflanz et al., 2022; Zheng et al., 2023). Recently, longitudinal cohort studies have attempted to

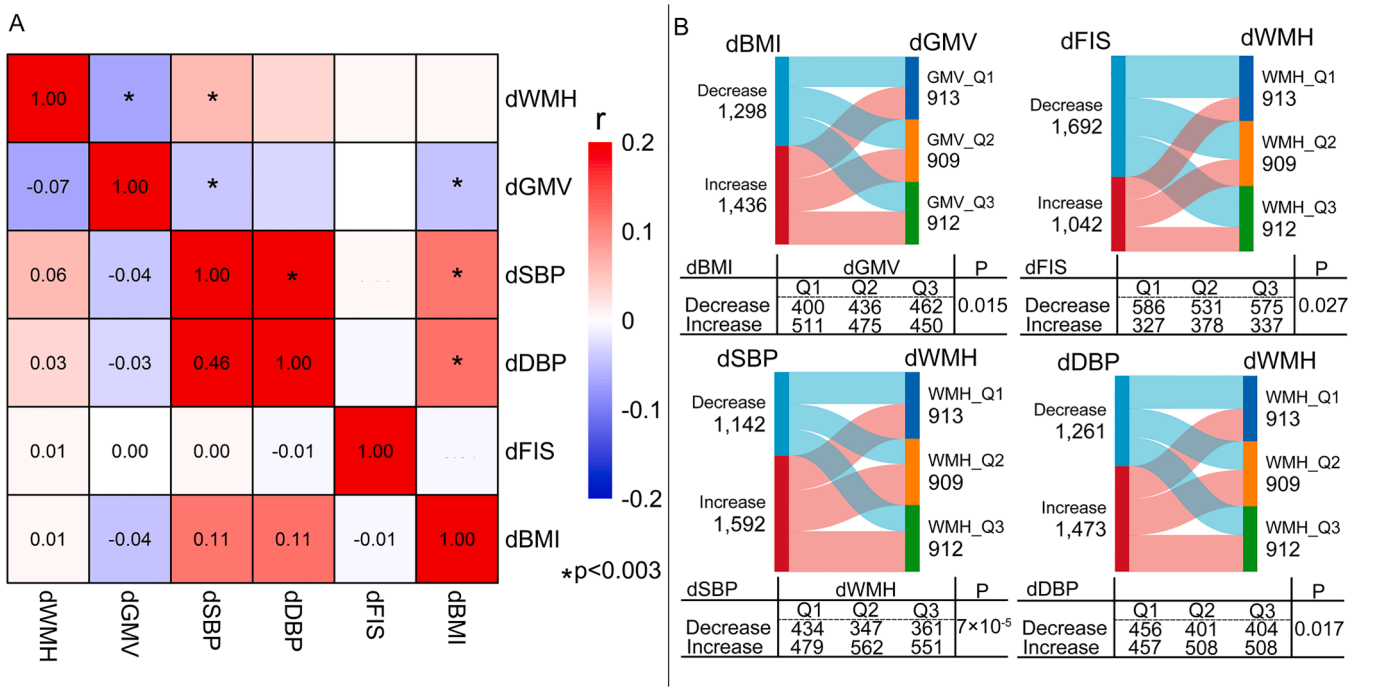

Fig. 3. Longitudinal analysis results. A represented association changes in WMH, GMV, SBP, DBP, FIS and BMI. B represented group differences in changes in GMV and WMH between the BMI increase group and BMI decrease group, as well as between the blood pressure increase group and blood pressure decrease group. The Q1, Q2, and Q3 represented low level of change, medium level of change, and high level of change. Abbreviations: BMI, body mass index; WMH, white-matter hyperintensities; FIS, fluid intelligence score, SBP, systolic blood pressure; DBP, diastolic blood pressure.

reveal behind the correlation in obesity-brain research (Ma et al., 2019; McWhinney et al., 2021). However, according to the bias of little sample-size, finite time-points data, and image artifact, the neurobiological results regarding how obesity contributes to accelerated brain aging have not always been consistent (Medawar and Witte, 2022). In this research, large datasets from the UK Biobank were utilized to improve the statistical power. In addition, the association still existed after excluding confounder such as several neurological and mental disorders, hypertension, diabetes, and cerebrovascular diseases. In our MR analysis, all selected SNPs meet the three assumptions of MR, that instruments are: strongly associated with exposure (BMI and obesity); but have no direct association with the outcome (GMV and FIS); and have no heterogeneity and horizontal pleiotropy (Richmond and Smith, 2022).

Our results provide the first genetic evidence that the increased BMI may be related to accelerated brain aging. The potential mechanisms responsible for the association of increased BMI and aging-associated brain atrophy remain to be determined. Chronic hyper insulinemia and insulin resistance in the periphery primarily caused by obesity tend to accelerate age-related arterial stiffening (Gagliardino et al., 2021), leading to increased blood-brain barrier (BBB) permeability, cerebral hypoperfusion and cortical atrophy (Winder et al., 2021; Baradaran and Gupta, 2022). Our GWAS results revealed that the genetic variants associated with BMI and FIS regarding cell metabolism and cardiac function. For example, the SBK1 (rs2726032) mainly expression in brain, SGF29 (rs17707300), and TUFM (rs3088215) play crucial roles various physiological processes, including cycle regulation, apoptosis, and signal transduction (Auburger et al., 2022); the AKAP6 (rs1051695) mainly expression in brain and heart, playing important roles in cardiovascular function (Vergarajauregui et al., 2020). Abnormal expression of these genes has been found associated with the occurrence and development of various diseases such as tumors, diabetes, and neurological disorders (Zhong et al., 2021; Kurabe et al., 2015).

Another possible neurological mechanism is the heightened inflammation in subjects with obesity (Herrera-Martínez et al., 2022). Our results indicate that some SNPs associated with immune response, such as rs4788084 (IL27), rs3740689 and rs935914 (SPI1), were simultaneously correlated with BMI and brain structure. It has been well known that the excess adipose tissue, especially the increased white fat can activate immune cells, which secrete inflammatory cytokines and hormone, like interleukin (IL)-1β, tumor necrosis factor-alpha (TNF-α), IL-6, and adrenocorticotropic hormone (ACTH), causing the apoptosis of neurons and decreasing the number of dendritic columns, synapses, glial cells, and dendritic atrophy (Medjerab et al., 2019; Yang et al., 2019; Li et al., 2021). Also, these factors are not isolated, but interact with each other. For example, recent evidence has shown that oxidative stress in obesity could induce apoptosis and neuro-degeneration by contributing to system chronic inflammatory and insulin resistance (Santana et al., 2021; Jakubiak et al., 2022; Andreadi et al., 2022; Panova-Noeva et al., 2024).

Except the genetic variants regarding metabolism and immune, some genes can directly affect the brain. For example, rs56186137, rs72793809, rs8049439, and rs12443881 belong to the ATXN2L gene, while rs34974290 and rs7222757 belong to TRIM65. Both the two genes have been found regarding in the function of nerve cells and relating to nervous system disease (Key et al., 2020; Lopez et al., 2015; Liu et al., 2021). Though some of these genetic variants are still being explored, our results suggested a genetic association between obesity, brain atrophy, and cognitive decline. To further investigate the relationships among them, the SNPs extracted from the GWAS results were used as instruments in MR analyses. Our results showed that the increased BMI had a role in brain atrophy and cognitive decline.

Several limitations in this study should be noted. First, it should be noted that our findings were based on cohorts of European from UKB study, which was not a representation of the general European population (Zhao et al., 2023). It can be expected that some of the genetic variants found in this study may be population specific or UKB specific. more researches were still needed to confirm the generalizability and reproducibility of our findings in other populations, particularly in non-European populations. Second, it should be noted that the datasets

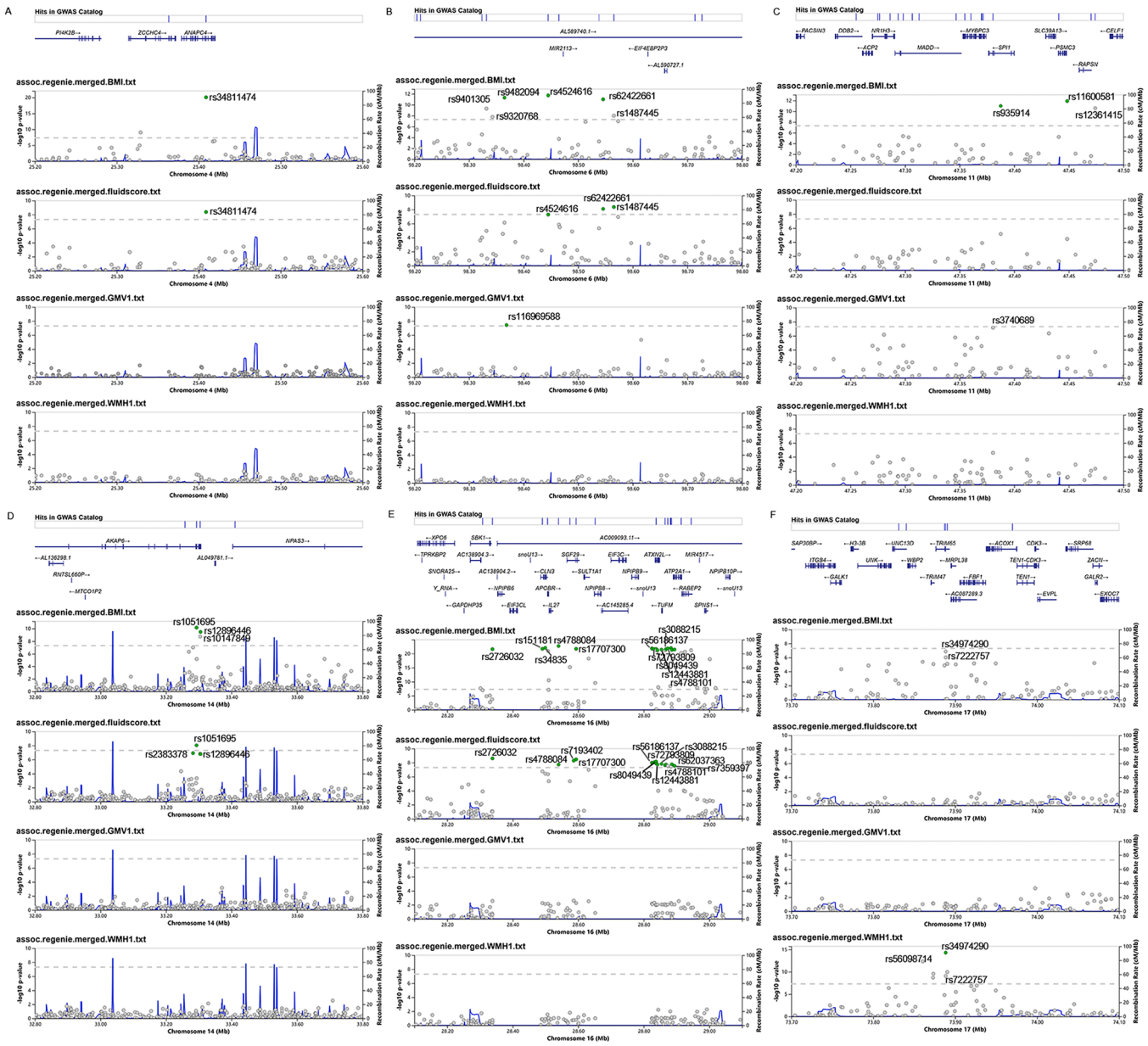

Fig. 4. Genetic loci overlap among BMI, GMV, WMH, and fluid intelligence score. A-F represented the loci overlap in different Chrome.

used in brain structure GWAS and fluid intelligence GWAS were subsets of datasets used in BMI GWAS, as only about fifty thousand underwent brain MRI and only about two hundred and twenty thousand underwent fluid intelligence test, which was available in the UK Biobank. More open and large-scale imaging-gene datasets may enable a better picture of obesity and the aging brain as well as to help to identify genetic associations among obesity, brain atrophy, and cognitive decline in globally diverse populations and quantify population-specific heterogeneity of genetic effects. Third, this study specifically focused on the effect of obesity on brain atrophy. Although similar effects on the brain and cognition were found in hypertension, diabetes, and obesity, and even after excluding hypertension and diabetes, the impact of obesity on the brain and cognition still existed. However, our research cannot determine the reasons for the similarities and differences in the effects of obesity, hypertension, and diabetes on the brain and cognition. More prospective researches were needed to reveal the complex relationship among them. Fourth, though the MR method provide causal evidence, it should be careful for causal conclusion. Although several sensitivity analyses were applied to ensure the instruments obtain the hypotheses of MR, the relaxing p-value thresholds for instruments selection especially for GMV and WMH may include SNPs that were not actually associated with the exposure factors, or introduce SNPs that have heterogeneous effects on the exposure factors or were associated with multiple outcomes and pleiotropic effects, may bias the estimation of causal effects.

In this study, the cross-sectional and genetic results revealed an association between obesity and brain atrophy and cognitive decline. The longitudinal results showed that the BMI decrease group had lower GMV reduction and WMH increasing compared to the BMI increase group. Based on our results, it was suggested that weight control such as dietary adjustment, physical exercise and behavioral therapy would be a promising strategy for preventing or slowing changes to the aging brain.

What is already known?

- Obesity is associated with aging brain and cognitive decline; however, it is uncertain the causal relationship among them.

Table 2
Results of the MR.

Analysis	β	SE	*p*	Horizontal Pleiotropy: EI	Heterogeneity: Q	Heterogeneity: I^2
BMI VS GMV: number of SNP= 132						
MR Egger	−2372.70	869.02	7.21×10^{-3}	5.42, $p = 0.91$	102.04, $p = 0.97$	0.27
Weighted Median	−1510.42	360.59	2.81×10^{-5}			
Inverse Variance Weighted	−1119.12	246.79	5.77×10^{-6}		104.30, $p = 0.96$	0.26
Simple Mode	−1888.59	1095.28	8.70×10^{-2}			
Weighted Mode	−2028.87	868.75	2.10×10^{-2}			
BMI VS WMH: number of SNP= 224						
MR Egger	131.92	29.96	1.66×10^{-5}	−14.42, $p = 0.0012$	223.88, $p = 0.79$	0.08
Weighted Median	87.14	20.14	1.52×10^{-5}			
Inverse Variance Weighted	42.76	9.88	6.37×10^{-4}		260.99, $p = 0.20$	0.07
Simple Mode	50.88	46.45	3.13×10^{-1}			
Weighted Mode	91.21	24.40	2.89×10^{-4}			
BMI VS fluid intelligence score: number of SNP= 125						
MR Egger	−0.028	0.027	3.01×10^{-1}	−0.0068, $p = 0.042$	31.92, $p = 1.00$	2.85
Weighted Median	−0.070	0.011	1.03×10^{-9}			
Inverse Variance Weighted	−0.081	0.0080	1.92×10^{-23}		36.14, $p = 1.00$	2.43
Simple Mode	−0.069	0.028	1.56×10^{-2}			
Weighted Mode	−0.062	0.021	3.45×10^{-3}			
GMV VS Fluid intelligence score: number of SNP= 13						
MR Egger	-2.06×10^{-6}	6.75×10^{-6}	0.77	2.90, $p = 0.95$	6.76, $p = 0.99$	0.60
Weighted Median	-2.87×10^{-6}	2.16×10^{-6}	0.19			
Inverse Variance Weighted	-3.35×10^{-6}	1.65×10^{-6}	0.04		6.81, $p = 0.99$	0.62
Simple Mode	-3.10×10^{-6}	3.83×10^{-6}	0.43			
Weighted Mode	-2.92×10^{-6}	3.83×10^{-6}	0.46			
WMH VS Fluid intelligence score: number of SNP= 12						
MR Egger	4.25×10^{-5}	1.11×10^{-4}	0.71	−0.0094, $p = 0.68$	13.83, $p = 0.18$	0.28
Weighted Median	-1.67×10^{-5}	2.70×10^{-5}	0.54			
Inverse Variance Weighted	-3.30×10^{-5}	2.16×10^{-5}	0.88		14.08, $p = 0.23$	0.22
Simple Mode	-1.50×10^{-5}	4.43×10^{-5}	0.74			
Weighted Mode	-1.89×10^{-5}	3.67×10^{-5}	0.62			

Abbreviations: MR, Mendelian randomization;β, effect coefficient; SE, stand error; EI, intercept of MR Egger; BMI, body mass index; GMV, gray matter volume; WMH, white matter hyperintensities.

- Genes related to obesity have been found; however, it is unclear whether genetic overlap among obesity, aging brain, and cognition decrease.

What does this study add?

- The phenotypic and genetic associations among obesity, aging brain, and cognitive decline were found by analyzing the large neuroimaging data and genetic data from the UK Biobank.
- Causal effect of obesity on aging brain was observed by Mendelian Randomization analyses.

How might these results change the direction of research or the focus of clinical practice?

- Excessive energy surplus in the body may accelerate the aging brain, leading to cognitive decline especially for high genetic risk subjects.
- The genetic overlap focused on certain SNPs associated with immune response suggests heightened inflammation may be a mechanism for brain atrophy in obesity.

Funding

This work was supported by the National Natural Science Foundation of Henan (222300420376), the Doctoral Research Start-up Foundation of Zhengzhou University of Light Industry (2020BSJJ007), the National Natural Science Foundation of China (82071282 and 82270463), the Rare Disease Registration Platform of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (JYHJB08), the project of Tianjian Laboratory of Advanced Biomedical Sciences, Zhengzhou University, the Henan Provincial Medical Science and Technology Research Project (LHGJ20230069), and Postdoctoral Research Funding of Henan Province.

Ethical statement

The UK Biobank study obtained approval from the Northwest Multicentre Research Ethics Committee. Each of the participants offered knowledgeable written informed consent. This study was performed in accordance with the principles of the Declaration of Helsinki.

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Yuan Qiao: Writing – review & editing, Visualization, Validation, Software, Investigation, Data curation. **Min Liu:** Writing – review & editing, Visualization, Validation, Software, Investigation, Formal analysis. **Jingjing Su:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization. **Dandan Tian:** Writing – review & editing, Validation, Supervision, Resources, Funding acquisition, Conceptualization. **Xirui Zhu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Chun Huang:** Writing – review & editing, Visualization, Validation, Software, Resources, Investigation, Formal analysis. **Shan Tian:** Writing – review & editing, Visualization, Validation, Software, Investigation, Data curation. **Yuna Li:** Writing – review & editing, Visualization, Validation, Software, Investigation, Data curation. **Panlong Li:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ibneur.2025.01.001.

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