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ORIGINAL RESEARCH

The Impact of Brain Morphometry on Low Back Pain Risk: A Mendelian Randomization Study

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Background: Low back pain (LBP) is a major global health concern with genetic and central nervous system factors. Recent studies have indicated associations between brain morphometry and LBP, but the causal relationships remain unclear.

Methods: We conducted a two-sample Mendelian randomization (MR) analysis to investigate the causal effects of brain morphometric features on LBP, leveraging genome-wide association study (GWAS) summary statistics. Genetic instruments for cortical structure were obtained from the ENIGMA consortium, while instruments for regional brain volumes were derived from UK Biobank imaging data; sulcal morphology traits were obtained from a large neuroimaging GWAS. LBP summary statistics were sourced from the FinnGen consortium. The inverse variance weighted (IVW) method was used as the primary analysis, complemented by multiple sensitivity analyses, including MR-Egger regression, weighted median estimation, and MR-PRESSO, to evaluate the core MR assumptions and assess robustness.

Results: After false discovery rate correction, ten brain morphometric traits were identified as being causally associated with LBP. These associations primarily involved greater global cortical surface area and larger volumes in frontal and temporal regions, the cingulate cortex, and the thalamus, indicating consistent protective effects. In contrast, no causal associations were observed for sulcal morphology traits.

Conclusion: Genetically reduced global cortical surface area and frontal–thalamic brain volumes were causally associated with an increased risk of LBP, providing novel evidence for a central neuroanatomical contribution to pain vulnerability.

Keywords: brain morphometry, brain volumes, brain cortical structure, brain sulcal morphology, low back pain, mendelian randomization

Introduction

Low back pain (LBP) is highly prevalent and significantly impacts individuals' quality of life, contributing substantially to global productivity loss. Approximately 50–80% of adults experience LBP at some point during their lifetime.[1] In older populations, LBP is further associated with reduced functional capacity, impaired physical performance, and an increased risk of falls, underscoring its substantial clinical and societal burden.[2] The etiology of LBP is complex and multifaceted, reflecting a complex interplay between biomechanical, genetic, and neurobiological factors.[3,4] In recent years, increasing attention has been directed toward central nervous system mechanisms, as accumulating evidence suggests that brain structure and function play important roles in pain perception, modulation, and chronification.[5]

Structural and functional changes in the brain are often observed in patients with pain. Studies[6,7] have reported structural alterations in multiple brain regions among individuals with LBP, including changes in cortical thickness, surface area, and subcortical volumes. These regions often overlap with networks involved in emotional regulation, cognitive control, and sensory processing, such as frontal cortical areas, the cingulate cortex, and the thalamus. However, most existing evidence is derived from observational studies, which are inherently susceptible to confounding and reverse causation. As a result, it remains unclear whether observed brain morphometric differences contribute to the development of LBP or instead represent secondary adaptations to persistent pain. Moreover, brain morphometry is

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a multidimensional construct encompassing cortical thickness, surface area, regional brain volumes, and sulcal morphology, each reflecting distinct neurodevelopmental and biological processes.[8–10] Whether these different morphometric features exert differential causal effects on LBP susceptibility has not been systematically investigated.

Mendelian randomization (MR) offers a new method to tackle these challenges by using genetic variants as tools to estimate causal relationships. As these variants are randomly assigned at conception, MR avoids confounding factors and measurement errors, providing more reliable causal analysis compared to traditional epidemiological methods.[11] Importantly, brain morphometric traits, including cortical surface area and regional brain volumes, have been shown to be moderately to highly heritable, making them well suited for MR-based causal investigation.[12] Previous studies have begun to explore causal relationships between brain structure and pain-related phenotypes, but comprehensive evaluations across multiple brain morphometry domains remain limited.

In this study, we utilized three independent publicly available genome-wide association study (GWAS) datasets, each describing brain cortical structure, brain volumes, and sulcal morphology, respectively, to characterize brain morphometry. We conducted a two-sample MR analysis to explore the potential causal relationship between brain morphometry and LBP. Specifically, we sought to test whether genetically determined differences in brain morphometric traits, particularly within pain-related cortical and subcortical regions, are causally associated with LBP risk. By applying multiple MR methods and sensitivity analyses, we aimed to identify robust causal associations and to clarify the role of central neural architecture in LBP susceptibility.

Methods

Study Design

The design of our study was outlined in Figure 1. We performed a series of two-sample MR analyses to investigate the potential causal relationships between distinct aspects of brain morphometry and the risk of LBP. Specifically, we treated three independent brain structural traits—cortical structure (including cortical surface area and thickness), regional brain volumes, and sulcal morphology—as exposures. For each exposure dataset, we conducted a separate two-sample MR analysis using GWAS summary statistics for LBP as the outcome. MR analysis must satisfy three core assumptions: (I) the relevance assumption: the genetic variant is strongly associated with the exposure of interest; (II) the independence assumption: the genetic variant is not influenced by any confounding factors; (III) the exclusion restriction: the genetic variant affects the outcome only through the exposure.[13]

GWAS Summary Data

The GWAS summary results for LBP were acquired from the FinnGen consortium (https://www.finngen.fi/fi). This dataset encompasses 32,845 cases and 294,770 controls. LBP diagnosis was based on the International Classification of Diseases, specifically ICD-10 (M54.5), ICD-9 7242, and ICD-8 72870 coding standards.

The summary statistics for brain cortical structure came from a meta-analysis conducted by the ENIGMA consortium, involving 33,992 individuals of European descent.[14] Measurements of cortical structure primarily include surface area (SA) and thickness of global and regional brain cortex obtained through MRI scans. This GWAS data can be accessed upon request from https://enigma.ini.usc.edu/research/download-enigma-gwas-results/.

The GWAS data for brain volumes were obtained from a study of 36,778 "European participants", aged 40.0 to 81.8 years (54% female), from the UK Biobank.[15] This study measured cortical and subcortical grey matter volumes in 33 cortical Desikan-Killiany regions[16] in each hemisphere, 8 subcortical regions in each hemisphere and brain stem. The summary data can be obtained from GWAS Catalog (https://www.ebi.ac.uk/gwas/) (ID: GCST90085819-GCST90085901).

The summary data for brain sulcal morphology came from a study involving 18,101 participants.[17] This study extracted T1-weighted MRI data to quantify sulcal parameters, investigating 44 different brain sulcal morphologies, including sulcal opening and depth features. Sulcal opening was defined as the average distance between both banks of the pial surface. Sulcal depth indicated the average geodesic distance from the convex hull to the bottom line of the sulcus medial surface.

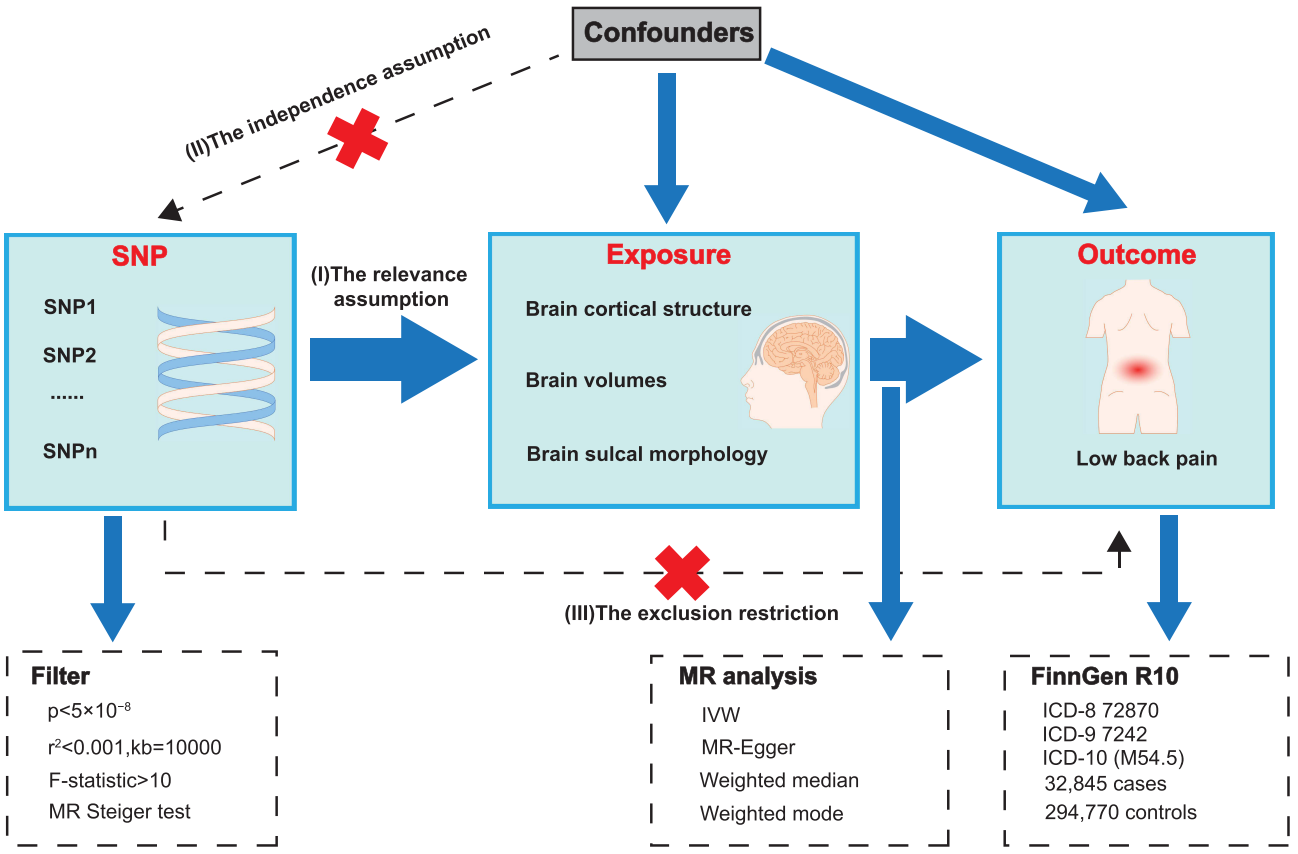

Figure 1 Schematic presentation of MR analysis.

Both the exposure and outcome GWAS were conducted in individuals of European ancestry, which minimizes potential bias due to population structure and supports the assumption that SNP-exposure associations are comparable across datasets. The LBP GWAS was derived from the FinnGen consortium, while the brain morphometry GWAS data were obtained from ENIGMA and UK Biobank imaging studies, which are independent cohorts and do not include FinnGen participants. Therefore, there was no sample overlap between the exposure and outcome datasets.

Instrumental Variable Selection

Single nucleotide polymorphisms (SNPs) associated with each exposure at genome-wide significance ($P<5\times10^{-8}$) were selected as instrumental variables. To ensure numerical stability and scale comparability across traits, beta coefficients for brain volume GWAS were Z-score normalized prior to MR analysis, as these traits were measured on substantially larger absolute scales compared with other morphometric phenotypes.

Linkage disequilibrium (LD) clumping was performed to ensure independence among SNPs, excluding variants with pairwise LD $r^2\geq0.001$ within a 10 Mb window, using the European reference panel from the 1000 Genomes Project. Palindromic SNPs with intermediate allele frequencies (minor allele frequency between 0.42 and 0.58) were excluded to avoid strand ambiguity. To avoid weak instrument bias, we validated the strength of individual SNPs using the F-statistic,[18] calculated as $F=(beta/SE)^2$ and included only those with an F-statistic value greater than 10. The MR Steiger test was used to filter out SNPs with reverse causality. Detailed information and the SNPs used for our analysis were presented in Supplementary Table 1.

Statistical Analysis

We used R statistical software (version 4.3.3) with the "TwoSampleMR" package (version 0.6.3) and the MR-PRESSO package for our statistical analysis. Exposure and outcome GWAS summary statistics were harmonized to ensure consistent alignment of

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effect alleles. SNPs with missing effect estimates or absent from either dataset were excluded during harmonization. Ambiguous palindromic SNPs (A/T or C/G) with intermediate allele frequencies were removed. The inverse variance weighted (IVW) method[19] was used as the primary analysis method for the two-sample MR to verify the causal relationship between brain morphometry and LBP. Additionally, MR-Egger,[20] weighted mode,[21] and weighted median[22] methods were applied to ensure the robustness of our results. Sensitivity analyses, including leave-one-out analysis,[23] Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO),[24] and MR-Egger intercept,[20] were conducted to evaluate potential biases in the MR analysis results. Cochran's Q test[25] was used to assess heterogeneity. For multiple testing correction across multiple exposure–outcome comparisons, the Benjamini-Hochberg false discovery rate (FDR) method was applied.

Results

Using the IVW method as the primary analysis, we found that two cortical structure traits and seventeen brain volume traits were associated with LBP (P<0.05) (Figure 2). No causal relationship was found between brain sulcal morphology

Exposure	Sample size	OR (95% CI)	P	P_{FDR}
Brain cortical structure	33992			
Global cortical SA		0.799 (0.717 to 0.891)	5.67e–05	1.13e-04
Entorhinal SA		0.713 (0.509 to 0.998)	0.048	0.734
Brain volumes	36778			
Left caudal middle frontal gyrus volume		0.764 (0.688 to 0.848)	4.44e–07	3.51e–05
Left lateral orbitofrontal cortex volume		0.840 (0.775 to 0.911)	2.76e–05	0.001
Right superior frontal gyrus volume		0.859 (0.789 to 0.936)	4.78e-04	0.009
Right lateral orbitofrontal cortex volume		0.877 (0.810 to 0.950)	0.001	0.020
Left superior temporal gyrus volume		0.801 (0.693 to 0.925)	0.003	0.031
Left medial orbitofrontal cortex volume		0.766 (0.643 to 0.912)	0.003	0.031
Right paracentral lobule volume		0.656 (0.496 to 0.867)	0.003	0.031
Left rostral anterior cingulate cortex volume		0.816 (0.710 to 0.936)	0.004	0.031
Right thalamus proper volume		0.894 (0.829 to 0.965)	0.004	0.031
Right inferior temporal volume		0.852 (0.753 to 0.965)	0.012	0.071
Brain stem volume		0.944 (0.902 to 0.988)	0.013	0.075
Right hippocampus volume		0.931 (0.871 to 0.995)	0.035	0.125
Right precuneus volume		0.923 (0.853 to 0.998)	0.044	0.150
Left middle temporal volume		0.885 (0.784 to 0.999)	0.048	0.156
Right insula volume		0.847 (0.750 to 0.957)	0.008	0.053
Left superior frontal volume		0.873 (0.781 to 0.976)	0.017	0.077
Left inferior temporal volume		0.842 (0.730 to 0.972)	0.019	0.081
Brain sulcal morphology structure	18101			
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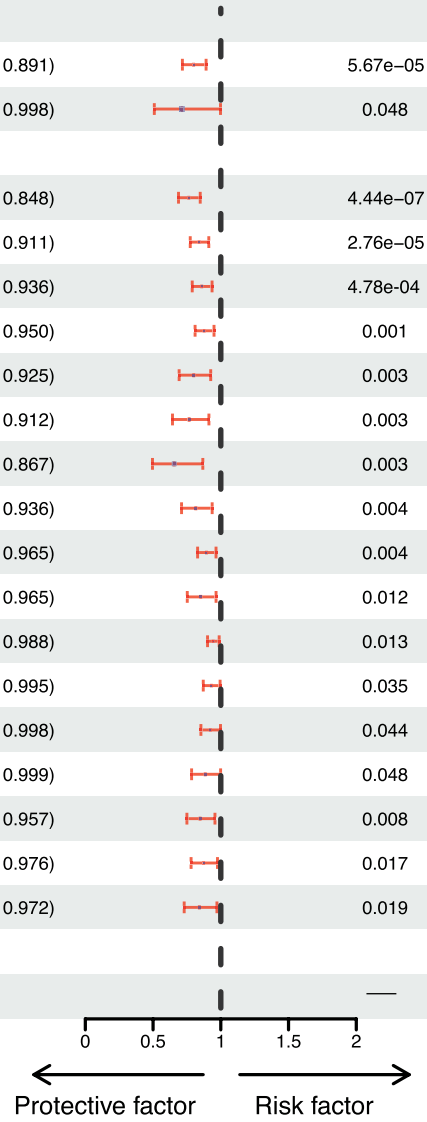

Figure 2 Forest plot showing the causal associations between genetically predicted brain morphometric traits and low back pain. Odds ratios (ORs) less than 1 indicate a protective effect, with ORs ranging from 0.65 to 0.89, corresponding to approximately 11–35% lower risk of low back pain.

and LBP. However, after FDR adjustment, only one cortical structure trait and nine brain volume traits remained significantly associated with LBP (P_{FDR}<0.05) (Figure 3). The complete results are presented in Supplementary Table 2.

Effect of Brain Cortical Structure on LBP

To investigate the causal relationship between brain cortical structure and LBP, we conducted the IVW method as the primary analysis approach. At the global level, increased cortical SA was significantly associated with a lower risk of LBP (OR=0.799; 95% CI: 0.717–0.891; $P=5.67\times10^{-5}$; $P_{FDR}=1.13\times10^{-4}$), suggesting a protective effect of greater overall cortical expansion. Consistency analysis using MR-Egger, weighted mode, and weighted median methods produced beta coefficients in the same direction (Table 1). At the regional level, no cortical SA or thickness measures survived FDR correction. However, entorhinal SA showed a nominal association with LBP (OR=0.713; 95% CI: 0.509–0.998) indicating a potential region-specific effect that did not withstand multiple testing correction.

Effect of Brain Volumes on LBP

We analyzed the causal relationship between brain volumes and LBP. After FDR adjustment, nine brain volume traits showed a significant causal relationship with LBP, with ORs ranging from 0.656 to 0.894 (P_{FDR}<0.05). These regions could be thematically grouped into functionally relevant brain systems: prefrontal regions (left lateral orbitofrontal, right lateral orbitofrontal, left medial orbitofrontal, right superior frontal, and left caudal middle frontal volumes), limbic and paralimbic regions (left rostral anterior cingulate and left superior temporal volumes), sensorimotor-related regions (right paracentral volume), and subcortical structures (right thalamus proper volume) (Table 2).

Effect directions from MR-Egger, weighted median, and weighted mode analyses were consistent with those obtained using the IVW method.

Effect of Brain Sulcal Morphology on LBP

We further explored the potential relationship between brain sulcal morphology and LBP. At both P<0.05 and P_{FDR}<0.05 levels, no causal relationship was found between brain sulcal morphology and LBP. This lack of detectable association may reflect the relatively smaller sample size of the sulcal morphology GWAS, as well as the lower inter-individual variability of sulcal parameters compared with cortical surface area or volumetric measures, potentially limiting statistical power in MR analyses.

Sensitivity Analysis

Heterogeneity and horizontal pleiotropy in the above three components of brain morphometry related to LBP were assessed using Cochran's Q test, MR-Egger intercept test, and MR-PRESSO. No evidence of heterogeneity or horizontal pleiotropy was detected (all P>0.05) (Table 3). Additionally, leave-one-out analysis did not reveal any significant changes in the causal relationships (Figure 4), underscoring the consistency and robustness of our results.

Discussion

The relationship between brain morphometry and LBP is complex. Although many previous studies have observed a relationship between brain morphology and low back pain,[26,27] limitations such as modest sample sizes and observational designs have hindered definitive conclusions regarding causality. In the present study, we applied Mendelian randomization to investigate the causal effects of multiple domains of brain morphometry on LBP, thereby reducing confounding and reverse causation inherent to conventional epidemiological studies. Large-scale GWAS datasets were leveraged to ensure sufficient statistical power, and stringent SNP selection criteria were applied. Multiple complementary MR methods and sensitivity analyses were used to assess the robustness of the findings and potential violations of MR assumptions. To minimize bias, we evaluated heterogeneity and horizontal pleiotropy using MR-Egger regression, weighted median, and MR-PRESSO, applied false discovery rate correction for multiple testing, and performed MR Steiger filtering to exclude reverse causation. Collectively, these approaches provide reassurance that the observed associations are unlikely to be driven by directional pleiotropy or weak instruments, although residual pleiotropic effects

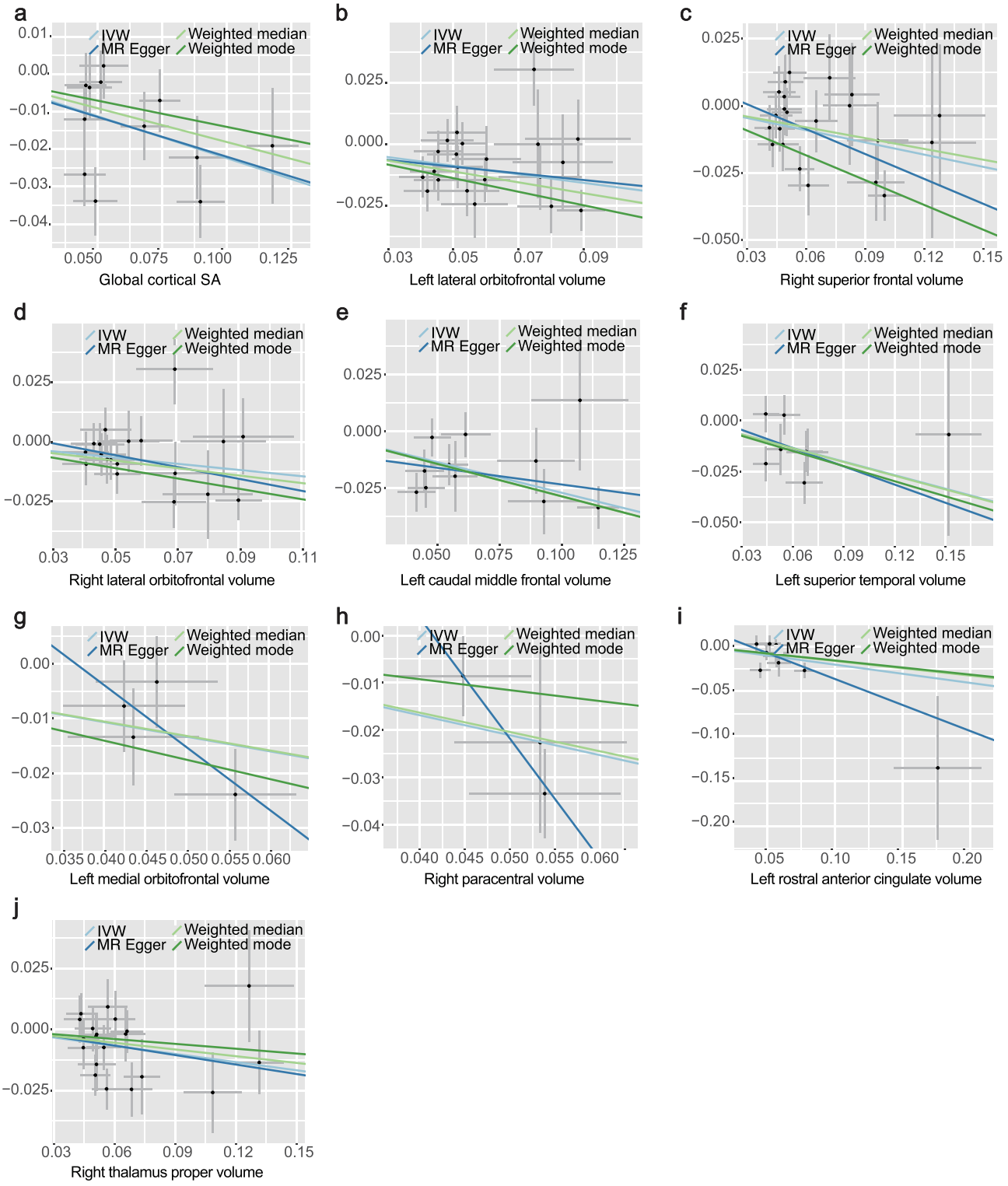

Figure 3 Scatter plot of the causal relationship between SNP effects and brain morphometry. Scatter plot of the causal relationship between SNP effects and (**a**) global cortical SA, (**b**) left lateral orbitofrontal volume, (**c**) right superior frontal volume, (**d**) right lateral orbitofrontal volume, (**e**) left caudal middle frontal volume, (**f**) left superior temporal volume, (**g**) left medial orbitofrontal volume, (**h**) right paracentral volume, (**i**) left rostral anterior cingulate volume, (**j**) right thalamus proper volume. The slope of each line represents the causal relationship of each method.

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Table 1 Causal Effects of Brain Cortical Structure on Low Back Pain

Exposure	Outcome	Method	Beta	OR (95% CI)	*P*	P_{FDR}
Global cortical SA	Low back pain	IVW	−0.224	0.799 (0.717–0.891)	5.67×10^{-5}	1.13×10^{-4}
		MR-Egger	−0.213	0.808 (0.547–1.194)	0.310	0.620
		Weighted median	−0.181	0.834 (0.738–0.944)	0.004	0.008
		Weighted mode	−0.141	0.869 (0.725–1.042)	0.157	0.315

Abbreviations: SA, surface area; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval; P_{FDR}, P value after FDR adjustment.

Table 2 Causal Effects of Brain Volumes on Low Back Pain

Exposure	Outcome	Method	Beta	OR (95% CI)	*P*	P_{FDR}
Left caudal middle frontal volume	Low back pain	IVW	−0.270	0.764(0.688–0.848)	4.44×10^{-7}	3.51×10^{-5}
		MR-Egger	−0.147	0.863(0.646–1.154)	0.346	0.895
		Weighted median	−0.286	0.751(0.659–0.857)	2.19×10^{-5}	0.002
		Weighted mode	−0.285	0.752(0.647–0.873)	0.004	0.145
Left lateral orbitofrontal volume	Low back pain	IVW	−0.174	0.840(0.775–0.911)	2.76×10^{-5}	0.001
		MR-Egger	−0.135	0.873(0.631–1.209)	0.424	0.942
		Weighted median	−0.221	0.802(0.721–0.892)	4.69×10^{-5}	0.002
		Weighted mode	−0.275	0.759(0.655–0.880)	0.002	0.120
Left medial orbitofrontal volume	Low back pain	IVW	−0.266	0.766(0.643–0.912)	0.003	0.031
		MR-Egger	−1.140	0.320(0.067–1.517)	0.288	0.895
		Weighted median	−0.264	0.768(0.620–0.953)	0.016	0.153
		Weighted mode	−0.351	0.704(0.514–0.966)	0.118	0.701
Left rostral anterior cingulate volume	Low back pain	IVW	−0.204	0.816(0.710–0.936)	0.004	0.031
		MR-Egger	−0.581	0.560(0.291–1.075)	0.119	0.811
		Weighted median	−0.163	0.850(0.716–1.009)	0.063	0.275
		Weighted mode	−0.157	0.854(0.655–1.114)	0.275	0.889
Left superior temporal volume	Low back pain	IVW	−0.222	0.801(0.693–0.925)	0.003	0.031
		MR-Egger	−0.298	0.742(0.364–1.515)	0.444	0.942
		Weighted median	−0.225	0.799(0.667–0.956)	0.014	0.153
		Weighted mode	−0.247	0.781(0.582–1.049)	0.144	0.701
Right lateral orbitofrontal volume	Low back pain	IVW	−0.131	0.877(0.810–0.950)	0.001	0.020
		MR-Egger	−0.250	0.779(0.576–1.054)	0.124	0.811
		Weighted median	−0.157	0.855(0.762–0.959)	0.007	0.110
		Weighted mode	−0.218	0.804(0.681–0.948)	0.019	0.347
Right paracentral volume	Low back pain	IVW	−0.422	0.656(0.496–0.867)	0.003	0.031
		MR-Egger	−2.554	0.078(0.006–1.040)	0.304	0.895
		Weighted median	−0.408	0.665(0.485–0.911)	0.011	0.137
		Weighted mode	−0.232	0.793(0.490–1.284)	0.445	0.996
Right superior frontal volume	Low back pain	IVW	−0.152	0.859(0.789–0.936)	4.78×10^{-4}	0.009
		MR-Egger	−0.310	0.734(0.557–0.966)	0.039	0.811
		Weighted median	−0.134	0.875(0.781–0.979)	0.020	0.169
		Weighted mode	−0.308	0.735(0.601–0.899)	0.007	0.171
Right thalamus proper volume	Low back pain	IVW	−0.111	0.894(0.829–0.965)	0.004	0.031
		MR-Egger	−0.129	0.879(0.682–1.133)	0.331	0.895
		Weighted median	−0.092	0.912(0.817–1.019)	0.103	0.275
		Weighted mode	−0.066	0.936(0.799–1.096)	0.422	0.989

Abbreviations: IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval; P_{FDR}, P value after FDR adjustment.

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Table 3 Results of Sensitivity Analysis of Brain Morphometry on Low Back Pain

Exposure	MR-Egger Intercept Test		Cochran's Q test		MR-PRESSO	
	Egger-Intercept	*P*	Q	Q_*P*	Outlier	*P*
Global cortical SA	−0.001	0.955	19.151	0.058	0	0.083
Left caudal middle frontal volume	−0.009	0.397	12.525	0.251	0	0.348
Left lateral orbitofrontal volume	−0.002	0.812	23.714	0.2551	0	0.278
Left medial orbitofrontal volume	0.042	0.384	2.566	0.4634	0	0.484
Left rostral anterior cingulate volume	0.022	0.281	13.949	0.124	0	0.143
Left superior temporal volume	0.004	0.838	9.017	0.251	0	0.278
Right lateral orbitofrontal volume	0.007	0.435	17.330	0.501	0	0.481
Right paracentral volume	0.106	0.352	2.818	0.244	N/A	N/A
Right superior frontal volume	0.010	0.252	27.618	0.151	0	0.145
Right thalamus proper volume	0.001	0.888	20.357	0.373	0	0.390

Abbreviations: SA, surface area; N/A, Not Available.

cannot be entirely excluded. Our results demonstrated that larger global cortical surface area and volumes of specific cortical and subcortical regions were associated with a reduced risk of LBP, whereas no causal relationship was observed for sulcal morphology. These findings highlight a potential protective role of specific brain structural traits in LBP susceptibility.

Accumulating evidence has linked brain morphometry to diverse physiological and pathological states, including cognition, aging, sex differences, and neurological disorders.[28–31] In LBP, prior studies have reported widespread cortical and subcortical alterations.[27,32,33] However, these studies have reported inconsistent directions of effect, including both reductions and increases in gray matter volume or thickness. Our MR results suggest that not all morphometric features exert equivalent causal relevance to LBP risk. Notably, global cortical SA—but not cortical thickness—showed a robust causal association with LBP risk. Cortical surface area and thickness reflect partially distinct neurobiological processes. Surface area and cortical thickness are shaped by distinct neurodevelopmental processes. Surface area is strongly influenced by early neurodevelopmental events including progenitor cell proliferation and cortical folding, whereas cortical thickness appears more susceptible to later environmental influences, aging, and experience-dependent plasticity, reflecting their different developmental origins and trajectories. This distinction has been demonstrated in prior studies showing independent genetic influences and developmental patterns for surface area and thickness.[34–36] Thus, genetically determined variation in SA may capture stable, lifelong neurodevelopmental characteristics that confer vulnerability or resilience to pain, whereas cortical thickness may reflect downstream or state-dependent responses to chronic pain. This distinction may explain why SA, but not thickness, emerged as causally relevant in the present analysis.

From the perspective of neuroanatomical biomarkers, our results suggest that reduced brain volumes and surface area primarily reflect markers of vulnerability or resilience rather than direct therapeutic targets. While these traits are partly genetically determined, brain structure retains a degree of plasticity across the lifespan. Consequently, the identified morphometric features may represent both inherited risk markers and modifiable correlates influenced by behavioral and environmental factors, such as physical activity, cognitive engagement, and pain-related coping strategies. This interpretation emphasizes their relevance for risk stratification and understanding pain susceptibility rather than implying straightforward structural targets for intervention.

The functional relevance of the identified regions can be interpreted within the Neuromatrix Theory of pain, which conceptualizes pain as an integration of sensory, emotional, and cognitive components.[14,26] Rather than isolated regional effects, the associated brain volumes clustered within functionally coherent systems, including prefrontal, limbic/paralimbic, sensorimotor, and subcortical networks. Sensorimotor-related structures, such as the paracentral lobule, are closely linked to somatosensory processing and bodily awareness; experimental studies have demonstrated pain-related activation of the primary somatosensory cortex and paracentral lobule following peripheral stimulation.[37] Frontal and orbitofrontal regions contribute to cognitive appraisal, emotional regulation, and top-down modulation of pain, with evidence that reward-related activation of the orbitofrontal cortex can attenuate pain perception.[38–41] In parallel, temporal and cingulate

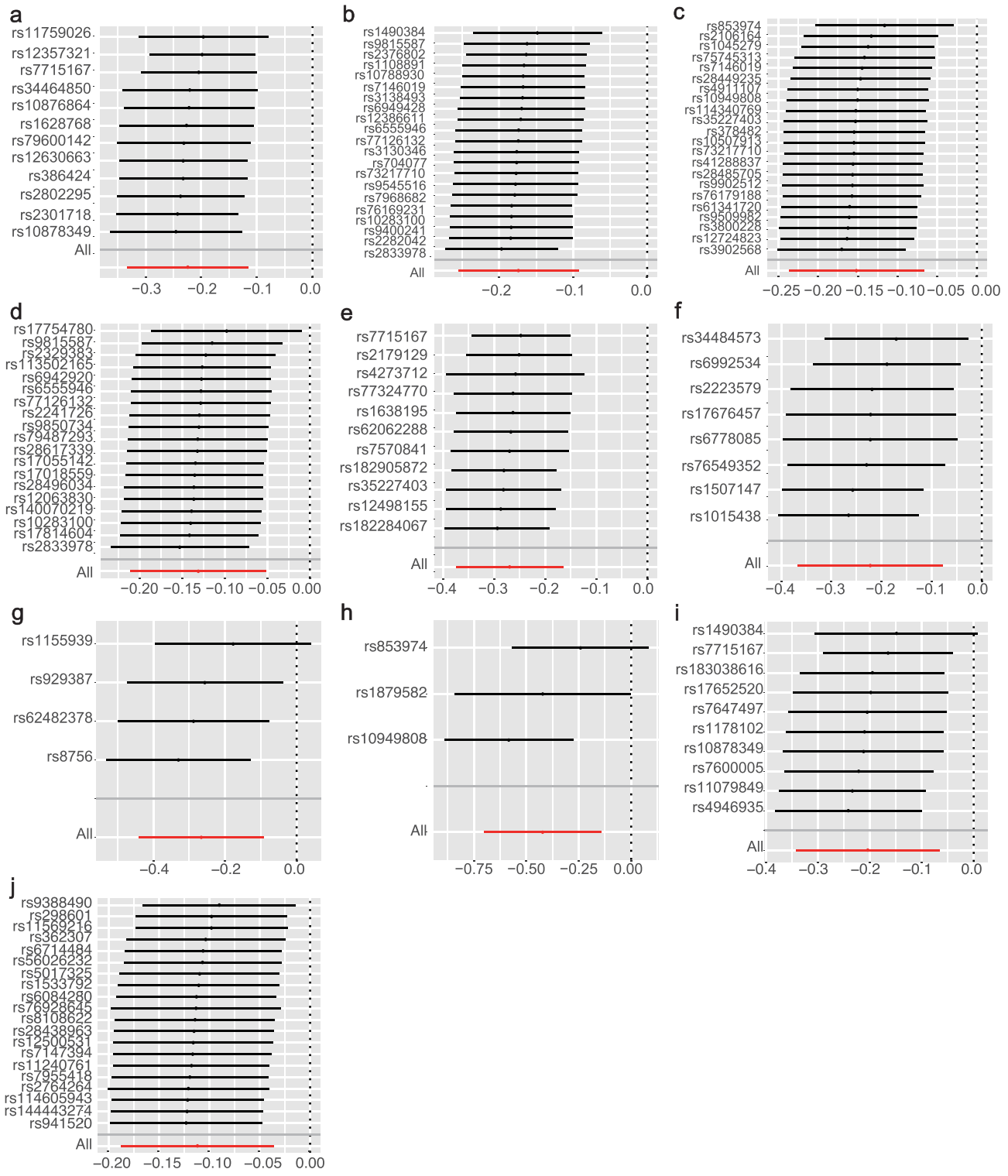

Figure 4 Leave-one-out analysis results. Leave-one-out plot of the causal relationship between SNP effects and (**a**) global cortical SA, (**b**) left lateral orbitofrontal volume, (**c**) right superior frontal volume, (**d**) right lateral orbitofrontal volume, (**e**) left caudal middle frontal volume, (**f**) left superior temporal volume, (**g**) left medial orbitofrontal volume, (**h**) right paracentral volume, (**i**) left rostral anterior cingulate volume, (**j**) right thalamus proper volume.

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regions are implicated in pain-related cognition, emotional memory, and attentional processes, with altered gray matter volume associated with heightened pain sensitivity and maladaptive cognitive strategies.[42–45] The anterior cingulate cortex and thalamus play central roles in integrating sensory input with affective and motivational responses.[46–50] Together, these systems provide a biologically plausible framework linking brain morphometry to pain vulnerability.

Alternative explanations for the observed associations should be considered. Although MR reduces confounding by measured and unmeasured environmental factors, shared genetic pathways influencing both brain morphometry and pain-related traits may contribute to the observed effects, independent of a direct causal pathway. For example, pleiotropic genetic variants involved in neurodevelopment, neurotransmission, or stress responsivity could influence both brain structure and pain susceptibility. While our sensitivity analyses did not detect substantial horizontal pleiotropy, such mechanisms cannot be entirely ruled out and should be explored in future studies integrating genetic, transcriptomic, and functional data.

The absence of causal associations for sulcal morphology may reflect limited statistical power due to smaller GWAS sample sizes and lower inter-individual variability of sulcal features, rather than a true lack of biological relevance. Compared with cortical surface area and volume, sulcal parameters may capture subtler anatomical characteristics that require larger samples or alternative analytical approaches to detect causal effects.

From a clinical perspective, our findings underscore the relevance of central nervous system architecture in LBP susceptibility. Identifying brain morphometric traits associated with reduced LBP risk may contribute to the development of neuroanatomical biomarkers for risk stratification. The results are conceptually consistent with active physiotherapy and exercise-based interventions, which are thought to engage frontal, cingulate, and sensorimotor networks involved in pain modulation. A recent study[51] demonstrated that active physiotherapy is significantly more effective than passive modalities in the treatment of chronic low back pain. Active exercise interventions engage motor control, cognitive processing, and emotional regulation networks, which overlap substantially with the brain regions identified in our MR analysis. This convergence suggests that active physiotherapy may exert its superior therapeutic effects precisely by modulating the structure and function of these protective brain networks, rather than acting solely on peripheral musculoskeletal mechanisms. Several limitations merit consideration. The analysis was restricted to individuals of European ancestry, limiting generalizability to other populations. MR estimates reflect lifelong genetically influenced exposures and may not translate directly to short-term interventions. Additionally, MR assumes linear exposure–outcome relationships, which may not capture complex nonlinear dynamics. Despite these limitations, the present study provides novel causal evidence linking specific brain morphometric traits to LBP risk and highlights the importance of central neural mechanisms in pain susceptibility.

Conclusion

This Mendelian randomization study provides robust evidence that specific brain morphometric features are causally associated with low back pain. Notably, smaller global cortical surface area and reduced volumes in frontal–thalamic regions were associated with a higher risk of LBP, whereas no causal relationship was identified between brain sulcal morphology and LBP. These findings highlight the importance of central nervous system architecture in LBP susceptibility and suggest that central mechanisms should be considered in the clinical understanding and management of low back pain.

Abbreviations

LBP, low back pain; MR, Mendelian randomization; GWAS, genome-wide association study; SA, surface area; SNPs, single nucleotide polymorphisms; IVW, inverse variance weighted; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier; FDR, false discovery rate.

Data Sharing Statement

All data generated or analysed during this study are included in this published article and its supplementary information files.

Ethics Approval and Consent to Participate

All GWAS summary statistics included in this study are publicly available and have received prior approval from the respective ethics review boards. According to item 1 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China, this study did not require separate ethical approval.

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Disclosure

The authors declare that they have no competing interests.

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