Submitted: 11 May, 2024 Accepted: 07 June, 2024 Published: 30 November, 2024 DOI:10.22514/jomh.2024.187

ORIGINAL RESEARCH

JOMH Journal of Men's Health

Structural insights into cortical morphometry and erectile dysfunction: a Mendelian randomization and genetic correlation study

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Abstract

Previous studies have disclosed that abnormal brain dynamics are involved in erectile dysfunction (ED). However, the association of cortical morphometry with ED remains unclear. To investigate the association of the surface area and thickness of the total cerebral cortex and 34 regions with ED, this Mendelian Randomization (MR) study was performed. Summary statistics of the surface area and thickness of cerebral cortex and ED were retrieved from previous genome-wide association studies. Genetic correlations between cortical morphometry and ED were evaluated by high-definition likelihood and linkage disequilibrium score regression (LDSC). Causal inference was made by the inverse variance weighting (IVW) estimator, supplemented by the MR-Egger, Weighted median, Maximum likelihood, MR. robust adjusted profile score, and MR-Pleiotropy Residual Sum and Outlier methods. The effect size of the surface area was scaled according to the standard deviation (SD). For surface area, the IVW estimator showed that a one SD increase of the entorhinal cortex and superior frontal cortex corresponded to a 1.25-fold (95% confidence interval (CI) = 1.03–1.53, $p = 0.026$) and a 1.24-fold (95% CI = 1.02–1.50, $p = 0.031$) risk of ED, respectively. LDSC regression found a significant genetic correlation between the surface area of the entorhinal cortex and ED ($rg = 0.093$, $p < 0.05$). For thickness, the IVW method revealed that genetically proxied one millimeter increase of the inferior temporal cortex and paracentral cortex led to a 6.58-fold (95% CI = 1.16–37.14, $p = 0.033$) and a 7.99-fold (95% CI = 1.17–54.49, $p = 0.034$) risk of ED, respectively. The other five methods also supported these findings. No heterogeneity or pleiotropy was detected in the instrumental variables. This study supports that genetically proxied cortical morphometry is associated with an elevated risk of ED. This study provides new insights into the etiology of ED.

Keywords

Cerebral cortex; Cortical morphometry; Erectile dysfunction; Mendelian randomization; Surface area; Thickness

1. Introduction

Erectile dysfunction (ED) is a prevalent male urological condition characterized by the continual or repeated inability of the penis to become erect and/or achieve satisfactory sexual intercourse [1]. The latest epidemiological systematic review on the prevalence of ED revealed that the global incidence of ED among young men is as high as 30% [2]. Risk factors such as cardiovascular diseases, smoking, obesity, obstructive sleep apnea syndrome, dyslipidemia, diabetes, metabolic syndrome, stress, anxiety, and depression all contribute to an increased incidence of ED [1, 3, 4].

Penile erection is a physiological and psychological event induced by the coordinated regulation of the central nervous system, endocrine system, and peripheral neurovascular system in response to sexual stimulation received by the individual [5]. Sexual stimuli received through sensory modalities such as touch, vision, hearing, and smell are ultimately transmitted to the cerebral cortex and further relayed to the hypothalamic nuclei via the amygdala [6]. The hypothalamus integrates various sexual stimuli and further transmits them to the lower central nervous system-spinal cord (T11–L2 and S2–4), which controls psychologically induced erection via the peripheral nerves [7, 8].

Previous studies using functional magnetic resonance imaging (fMRI) have explored the mechanisms of sexual arousal (SA) and identified several cortical or subcortical activation sites associated with penile erection. These include the prefrontal cortex (PFC), parietal cortex, lateral occipitotemporal cortex, cingulate cortex, inferior temporal cortex, insula, caudate nucleus, putamen, thalamus, amygdala and hypothalamus [9, 10]. The activations within these circuits contribute

to a comprehensive neurobehavioral framework of male SA, encompassing cognitive, incentive, affective, and autonomic elements [11]. Research indicates that in the absence of sexual stimuli, certain brain areas, such as the medial and left lateral orbitofrontal cortex (OFC), angular gyri, lateral temporal cortex, and posterior cingulate cortex are involved in exerting continuous inhibitory control over the SA [9, 12]. Conversely, these areas become less active during the onset of SA to reduce such inhibition [10].

In the realm of male sexual dysfunction, several functional neuroimaging investigations have identified anomalies in the central mechanisms governing male sexual functioning [13, 14]. Specifically, individuals with psychogenic ED have exhibited abnormal increases or prolongations of activity in brain areas such as the OFC [10], the medial and basal PFC [15], the lateral hypothalamus [16], and the anterior middle cingulate cortex [17], which are recognized to regulate the inhibitory processes underlying male SA [10]. Conversely, there was reduced activity in the inferior temporal cortex, which is implicated in the cognitive aspects of male SA [18, 19], as well as in the insula, hippocampus and anterior cingulate cortex, which are implicated in modulating autonomic, cognitive, and motivational aspects related to male SA [13]. Although ED is predominantly viewed as a functional issue, its neuroanatomical underpinnings have received limited consideration [10]. Nonetheless, a structural MRI study concentrating on subcortical structures detected gray matter atrophy in the nucleus accumbens and hypothalamus among individuals with ED, which is thought to impact the motivational aspect of male sexual arousal [20]. Another investigation employing diffusion-based imaging disclosed microstructural alterations in white matter tracts across several regions in ED patients, suggesting deficits in neuroanatomical connectivity in ED patients [21]. Zhao *et al*. [11] investigated brain structure in 40 ED patients and 39 healthy controls, and revealed that reduced cortical thickness in regions associated with disrupted male SA, which correlated with diminished sexual functioning in males. These findings suggest that in addition to functional deficits, structural changes in the brain may play a role in ED.

Observational studies can only reflect whether there is an association between the two, making it challenging to elucidate the complex causal interplay between cortical morphology and ED in a clear and intuitive manner [22]. Mendelian randomization (MR) serves as a technique for evaluating causal relationships [23]. MR utilizes genetic variants as instrumental tools to overcome confounding factors and reverse causation issues encountered in traditional observational epidemiological research because alleles follow Mendel's random allocation law during gamete formation, and the relationship between genes and outcomes remains unaffected by common confounding variables such as postnatal environmental factors and behavioral lifestyles [24]. Additionally, it meets the temporal requirement of causality inference, known as the "cause precedes effect", making it a natural randomized controlled trial [25]. Therefore, we employed a two-sample MR approach using genome-wide association study (GWAS) databases to investigate potential causal relationships between cortical morphometry and ED.

2. Materials and methods

2.1 Study design and included samples

The study design and schematic diagram are illustrated in Fig. 1. The total surface area (mm^2) and average thickness (mm) of the total cerebral cortex and 34 regions were used as exposures and ED was used as an outcome.

Summary-level data regarding the surface area and thickness of the total cerebral cortex and 34 regions were retrieved from Grasby KL's study [26]. This consortium collected data from 60 cohorts globally and increased the sample size to 51,665 individuals. Of them, 94% were of European descent. To avoid bias from the mixed population, we only used the data from individuals of European descent (33,992 participants) as exposures. The 33,992 participants included 23,909 individuals from 49 cohorts participating in the Enhancing NeuroImaging Genetics through Meta-Analysis Consortium (ENIGMA) and 10,083 individuals from the UK Biobank. The surface area and thickness of the human cerebral cortex were detected by structural brain magnetic resonance imaging. The 34 regions were defined by the Desikan-Killiany atlas, which is commonly used in clinics. For one specific region, the global measure of surface area or thickness was adjusted to identify region-specific genetic variants. Finally, 35 phenotypes for surface area and 35 phenotypes for thickness were generated. Detailed information about these data sources can be found in Table 1.

The genetic association of ED was obtained from one previous GWAS generated by Bovijn J and his colleagues [27]. This GWAS combined individuals from three cohorts: the UK biobank, Estonian Genome Center of the University of Tartu cohort, and hospital-recruited Partners HealthCare Biobank cohort. A total of 6175 cases and 217,630 controls of European descent were genotyped. The diagnosis of ED relied on the international classification of diseases-10 codes (F52.2 or N48.4), oral medications, surgical intervention for ED, or self-reports from the respondents.

2.2 Selection of genetic instruments

As shown in Fig. 1, the IVs were first selected as a genome-wide significance threshold of $p < 1 \times 10^{-5}$. Given the correlations of single nucleotide polymorphisms (SNPs), we further clumped the retrieved IVs at a window size of 1 Mb. The 1000G phase III reference genome was used as the reference genome and IVs with $r^2 \geq 0.001$ were filtered to ensure independence [24]. Generally, SNPs with minor allele frequencies <0.01 were considered rare SNPs and were excluded from our analyses. To satisfy the basic assumption of MR, the remaining IVs were subjected to weak IVs and pleiotropic outlier tests. The strength of the IVs was evaluated by F statistics (F statistics = $(\beta/\mathrm{Se})^2$) and weak IVs were defined as F statistics < 10, as in previous studies [24, 28]. In our study, no weak IVs were detected. In addition, pleiotropic outliers were investigated by the radial MR and MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) approaches [25]. If outliers were identified, these SNPs were excluded and not used as IVs. Finally, to reduce bias from reverse causality, the Steiger-MR test was adopted to confirm that SNPs explained

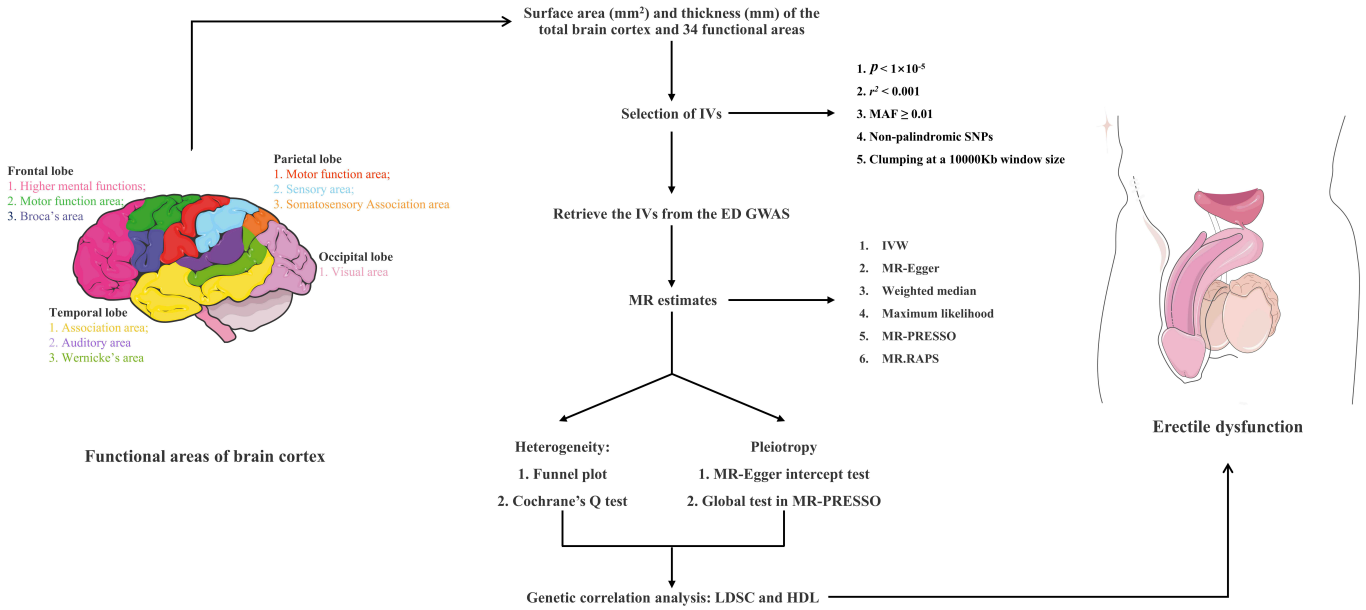

FIGURE 1. Schematic diagram of the study design and analysis strategy. ED: erectile dysfunction; GWAS: genome-wide association studies; IVW: inverse variance weighting; IV: instrumental variables; MR: Mendelian randomization; MR-PRESSO: MR Pleiotropy Residual Sum and Outlier; MAF: minor allele frequency; MR.RAPS: MR robust adjusted profile score; SNP: single nucleotide polymorphisms; LDSC: linkage disequilibrium score regression; HDL: High-Definition Likelihood.

TABLE 1. Characteristics of included GWASs.

Traits	Sample size	Authors	Descent	PMID	nSNP	F statistics	Unit
Entorhinal cortex	33,992	Grasby KL *et al.* [26]	European	32193296	30	23.71	mm^2 (surface area)
Superior frontal cortex	33,992	Grasby KL *et al.* [26]	European	32193296	30	23.98	mm^2 (surface area)
Inferior temporal cortex	33,992	Grasby KL *et al.* [26]	European	32193296	27	21.35	mm (thickness)
Paracentral cortex	33,992	Grasby KL *et al.* [26]	European	32193296	23	23.86	mm (thickness)
Erectile dysfunction	223,805 (6175 cases and 217,630 controls)	Bovijn J *et al.* [27]	European	30583798	-	-	logOR

SNP: Single nucleotide polymorphism; PMID: PubMed Identifier; OR: odds ratio.

more variance in exposures than in the outcome [29].

2.3 Statistical analyses

To infer the causal associations between the cerebral cortex and ED, an inverse variance weighting (IVW) estimator was used as the primary method to combine the effects of IVs. This method assumes that all IVs are valid IVs and thus has greater statistical power than other estimators. In addition to the IVW method, we also employed five other methods for sensitivity analyses, namely, MR-Egger, Weighted median, Maximum likelihood, MR.RAPS and MR-PRESSO. The MR-Egger [30] and Weighted median [31] methods have the ability to yield consistent causal estimations when invalid IVs exist. Additionally, the intercept of ME-Egger regression can be used to quantify horizontal pleiotropy. Given the relatively limited sample size of the exposures, we also adopted Maximum likelihood estimator as a supplement for its high statistical power in limited sample datasets. Furthermore, to mitigate bias from pleiotropic outliers, the MR-PRESSO [32] method was used. If pleiotropic outliers were identified, this method first excluded the outliers and then used the same technique as IVW to combine the effects of the IVs. Finally, the MR.RAPS estimator was supplemented due to its robustness when weak IVs and both systematic and idiosyncratic pleiotropy exist.

Given the tiny unit for the surface area of the cortex (mm^2), the effect size, namely the β value, seems to be very small. Thus, we scaled the effect size according to the standard deviation (SD). The odds ratios (ORs) for the entorhinal cortex and superior frontal cortex corresponded to a 1 SD alteration in surface area. For the thickness of the inferior temporal cortex and paracentral cortex, the effect size was not scaled. The ORs corresponded to a one-unit alteration (mm) in thickness. For exposures with significant associations with ED, we further evaluated the genetic correlation using the linkage disequilibrium score (LDSC) [33] regression and the High-Definition

Likelihood (HDL) [34] method.

All the analyses were performed with R 4.0.1 software (R Foundation for Statistical Computing, Vienna, Austria). In this study, $p < 0.05$ was used as a significance threshold for statistical inference.

3. Results

As summarized in Fig. 2, only the entorhinal cortex and superior frontal cortex were significantly associated with an increased risk of ED across the 35 phenotypes of surface area. For the 35 phenotypes of thickness, only the inferior temporal cortex and paracentral cortex were significantly associated with an increased risk of ED. The other areas of the cortex were not statistically associated with ED in our results.

3.1 Causal association between the surface area of the entorhinal cortex and ED

As shown in Table 2, there was a significant association between the surface area of the entorhinal cortex and ED. The IVW estimator showed that a 1 SD increment in the surface area of the entorhinal cortex corresponded to a 1.25-fold (95% CI = 1.03–1.53, $p = 0.026$) risk of ED, in line with the scatter plot in Fig. 3A. The ORs were 1.26 (95% CI = 1.04–1.52, $p = 0.016$) for the Maximum likelihood, 1.25 (95% CI = 1.03–1.53, $p = 0.034$) for the MR-PRESSO and 1.26 (95% CI = 1.04–1.53, $p = 0.020$) for the MR.RAPS estimators, respectively. The statistical inferences by the MR-Egger and Weighted median estimators were insignificant ($p = 0.187$ for MR-Egger and $p = 0.177$ for Weighted median). However, the effect size and direction remained consistent with those of the other four methods. No horizontal pleiotropy was detected by the MR-Egger intercept ($p > 0.05$) and Global test ($p > 0.05$). In Fig. 3B, Cochrane's Q test identified no heterogeneity ($p > 0.05$). Of note, LDSC regression found a significant genetic correlation between the surface area of the entorhinal cortex and ED ($rg = 0.093$, $p < 0.05$, Fig. 3C). The correlation coefficient was 0.216 as revealed by the HDL method.

3.2 Causal association between the surface area of the superior frontal cortex and ED

In Table 2, the IVW method found that one 1 SD increase in the surface area of the superior frontal cortex was associated with a 1.24-fold (95% CI = 1.02–1.50, $p = 0.031$) risk of ED, in line with the results of the Maximum likelihood (OR = 1.25, 95% CI = 1.02–1.52, $p = 0.030$), MR-PRESSO (OR = 1.24, 95% CI = 1.03–1.49, $p = 0.029$), and MR.RAPS (OR = 1.24, 95% CI = 1.01–1.53, $p = 0.041$). The scatter plot in Fig. 3D also revealed a positive correlation between the surface area of the superior frontal cortex and ED. Like for the entorhinal cortex, the MR-

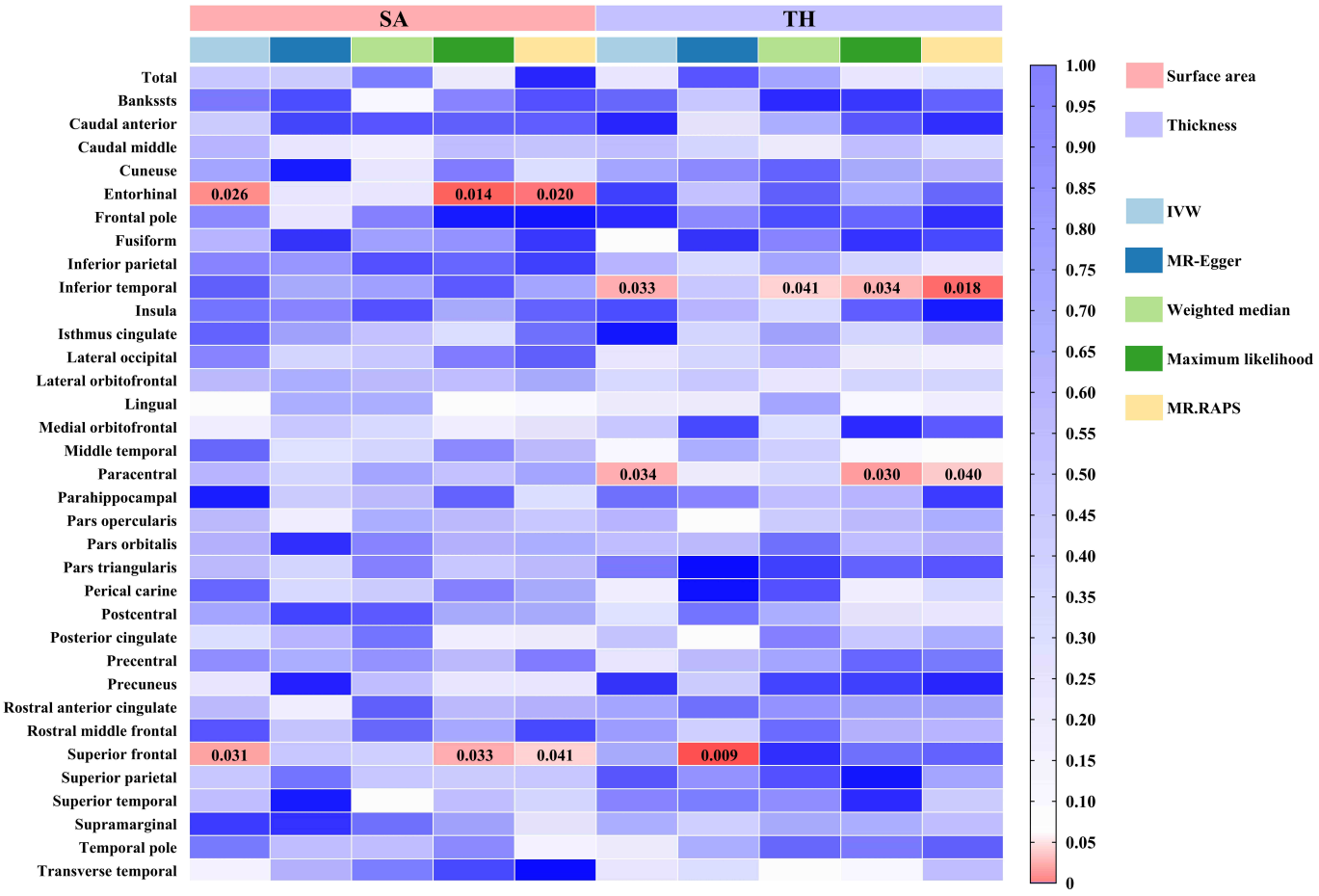

FIGURE 2. Summary of results on the impact of 70 cortical phenotypes on ED. The size of the p value is mapped to the depth of colors in the heatmap. SA: surface area; TH: thickness. IVW: inverse variance weighting; MR: Mendelian randomization; MR.RAPS: MR.robust adjusted profile score.

TABLE 2. Causal estimates between cortical morphometry and ED.

Exposures	β (95% CI)	OR (95% CI)	p	p for Egger	p for Global test
Entorhinal cortex					
IVW	0.00369 (0.00044–0.00694)	1.25 (1.03–1.53)	0.026	0.523	0.208
MR-Egger	0.00671 (−0.00302–0.01643)	1.50 (0.83–2.72)	0.187		
Weighted median	0.00296 (−0.00120–0.00713)	1.20 (0.92–1.56)	0.177		
Maximum likelihood	0.00382 (0.00076–0.00688)	1.26 (1.04–1.52)	0.016		
MR-PRESSO	0.00369 (0.00044–0.00694)	1.25 (1.03–1.53)	0.034		
MR.RAPS	0.00380 (0.00059–0.00701)	1.26 (1.04–1.53)	0.020		
Superior frontal cortex					
IVW	0.00054 (0.00005–0.00104)	1.24 (1.02–1.50)	0.031	0.833	0.651
MR-Egger	0.00068 (−0.00068–0.00205)	1.31 (0.76–2.24)	0.336		
Weighted median	0.00038 (−0.00031–0.00106)	1.16 (0.88–1.53)	0.296		
Maximum likelihood	0.00055 (0.00005–0.00106)	1.25 (1.02–1.52)	0.030		
MR-PRESSO	0.00054 (0.00008–0.00101)	1.24 (1.03–1.49)	0.029		
MR.RAPS	0.00055 (0.00002–0.00108)	1.24 (1.01–1.53)	0.041		
Inferior temporal cortex					
IVW	1.88332 (0.15199–3.61465)	6.58 (1.16–37.14)	0.033	0.903	0.717
MR-Egger	2.11341 (−1.94472–6.17155)	8.28 (0.14–478.93)	0.317		
Weighted median	2.53569 (0.13113–4.94024)	12.63 (1.14–139.80)	0.039		
Maximum likelihood	1.91834 (0.14201–3.69466)	6.81 (1.15–40.23)	0.034		
MR-PRESSO	1.88332 (0.31218–3.45446)	6.58 (1.37–31.64)	0.027		
MR.RAPS	2.26860 (0.39534–4.14187)	9.67 (1.48–62.92)	0.018		
Paracentral cortex					
IVW	2.07854 (0.15897–3.99810)	7.99 (1.17–54.49)	0.034	0.657	0.894
MR-Egger	0.81288 (−5.01110–6.63686)	2.25 (0.01–762.70)	0.787		
Weighted median	1.51203 (−1.17314–4.19719)	4.54 (0.31–66.50)	0.270		
Maximum likelihood	2.16316 (0.20584–4.12049)	8.70 (1.23–61.59)	0.030		
MR-PRESSO	2.07854 (0.54078–3.61629)	7.99 (1.72–37.20)	0.015		
MR.RAPS	2.14370 (0.10090–4.18650)	8.53 (1.11–65.79)	0.040		

Given the tiny unit for the surface area of the cortex (mm^2), the effect size, namely the β value, seems to be very small. Thus, we scaled the effect size according to the standard deviation (SD). The ORs for the entorhinal cortex and superior frontal cortex corresponded to one SD alteration. For the thickness of the inferior temporal cortex and paracentral cortex, the effect size was not scaled. The ORs corresponded to a one-unit alteration (mm). F statistics = $(\beta/Se)^2$. IVW: inverse variance weighting; MR: Mendelian randomization; MR-PRESSO: MR Pleiotropy Residual Sum and Outlier; ME.RAPS: MR.robust adjusted profile score; CI: confidence interval; OR: odds ratio.

Egger and Weighted median estimators identified increased risks of ED (OR = 1.31 for MR-Egger and OR = 1.16 for Weighted median) with insignificant p values (both $p > 0.05$). This lack of significance may be attributed to the relatively lower statistical power relative to that of the IVW method. No horizontal pleiotropy was detected by the MR-Egger intercept ($p > 0.05$) and Global test ($p > 0.05$). In Fig. 3E, Cochrane's Q test identified no heterogeneity ($p > 0.05$). LDSC did not show a significant genetic correlation between the surface area of the superior frontal cortex and ED ($rg = -0.066$, $p > 0.05$), nor did HDL ($rg = 0.120$, $p > 0.05$, Fig. 3C).

3.3 Causal association between the thickness of the inferior temporal cortex and ED

A greater thickness of the inferior temporal cortex is linked to a greater risk of ED (Table 2). Genetically proxied a one mm increase in the thickness of the inferior temporal cortex led to a 6.58-fold (95% CI = 1.16–37.14, $p = 0.033$) risk of ED, in line with the scatter plot in Fig. 4A. The result was further verified by the Weighted median (OR = 12.63, $p = 0.039$), Maximum likelihood (OR = 6.81, $p = 0.034$), MR-PRESSO (OR = 6.58, $p = 0.027$), and MR.RAPS (OR = 9.67, $p = 0.018$) estimators. The funnel plot in Fig. 4B showed a symmetric distribution of IVs, revealing no heterogeneity. There was no pleiotropy as

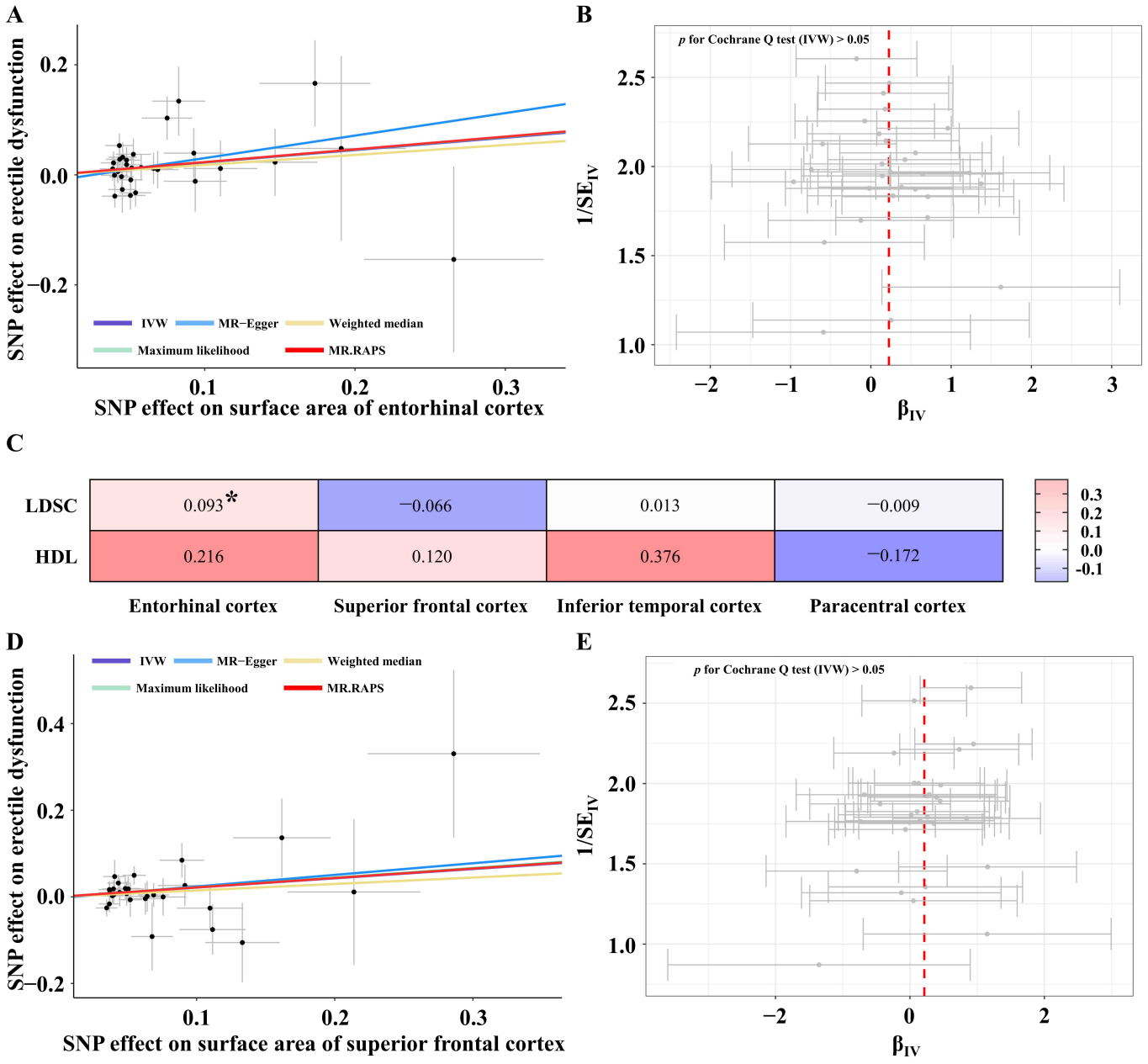

FIGURE 3. Scatter and funnel plots of the surface area of cortical morphometry with ED. (A,B): scatter and funnel plots visualizing the SNP effect on the surface area of the entorhinal cortex and erectile dysfunction, and the heterogeneity in the instrumental variables. (C) genetic correlation between cortical morphometry and ED. (D,E): scatter and funnel plots visualizing the SNP effect on the surface area of the superior frontal cortex and erectile dysfunction, and the heterogeneity in the instrumental variables. In Fig. 3C, the size of the correlation coefficient (*rg*) is mapped to the depth of colors in the heatmap. *: $p < 0.05$. IVW: inverse variance weighting; MR: Mendelian randomization; MR.RAPS: MR.robust adjusted profile score; IV: instrumental variables; SNP: Single nucleotide polymorphism. LDSC: linkage disequilibrium score regression; HDL: High-Definition Likelihood.

revealed by the MR-Egger intercept ($p = 0.903$) and Global test ($p = 0.717$). In Fig. 3C, the correlation coefficients of LDSC and HDL were 0.013 and 0.376, respectively (both $p > 0.05$).

3.4 Causal association between the thickness of the paracentral cortex and ED

In Table 2, the IVW model found that a genetically predicted one mm increase in the thickness of the paracentral cortex was associated with a 7.99-fold risk of ED (95% CI = 1.17–54.49, $p = 0.034$). The scatter plot showed that with the increase of the SNP effect on the thickness of paracentral cortex, the SNP effect on ED also ascended (Fig. 4C). The ORs were 2.25 (95% CI = 0.01–762.70, $p = 0.787$) for the MR-Egger, 4.54 (95% CI = 0.31–66.50, $p = 0.270$) for the Weighted median, 8.70 (95% CI = 1.23–61.59, $p = 0.030$) for the Maximum likelihood, 7.99 (95% CI = 1.72–37.20, $p = 0.015$) for the MR-PRESSO, and 8.53 (95% CI = 1.11–65.79, $p = 0.040$) for the MR.RAPS, respectively. Although the results from the MR-Egger and Weighted median were not statistically significant (both $p >$

0.05), the directions were consistent with those of the IVW estimator, reinforcing the causal link between the paracentral cortex and ED. No pleiotropy or heterogeneity was detected (all $p > 0.05$, Table 2, and Fig. 4D). In Fig. 3C, neither LDSC nor HDL identified genetic correlation between the thickness of the paracentral cortex and ED ($p > 0.05$).

4. Discussion

This MR study utilized extensive population-based genetic data concerning cerebral cortical structure alongside MR techniques to delineate directional and biological links between human cortical morphometry and ED. Our study's substantial sample size enhanced the statistical power compared to that of prior investigations into brain structure and ED. Our findings suggest that genetically mediated increases in surface areas of the entorhinal and superior frontal cortex are associated with a heightened risk of ED, with a notable genetic correlation detected between the entorhinal cortex surface area and ED. Furthermore, genetically predicted greater thickness of the inferior temporal and paracentral cortex is implicated in an elevated risk of ED. These results carry significance, as a deeper comprehension of the underlying neuroanatomical associations is likely to enhance both the diagnosis and treatment strategies for ED.

Research exploring the link between cortical morphometry and male sexual dysfunction remains limited. Guo *et al.* [35] discovered cortical thickening in various brain regions in premature ejaculation patients, with stronger associations found in specific areas such as the right medial OFC, right precentral gyrus, and left superior frontal cortex. However, inconsistent with our research findings, Zhao *et al.* [10] investigated cortical thickness abnormalities using structural MRI in 40 patients with psychogenic ED and 39 healthy controls. Their findings revealed significantly reduced cortical thickness in multiple regions associated with male SA dynamics, including the medial prefrontal, orbitofrontal, cingulate, inferotemporal, and insular cortices, which were associated with a decline in male sexual function. The discrepancy in results may stem from variations in sample size and demographic characteris-

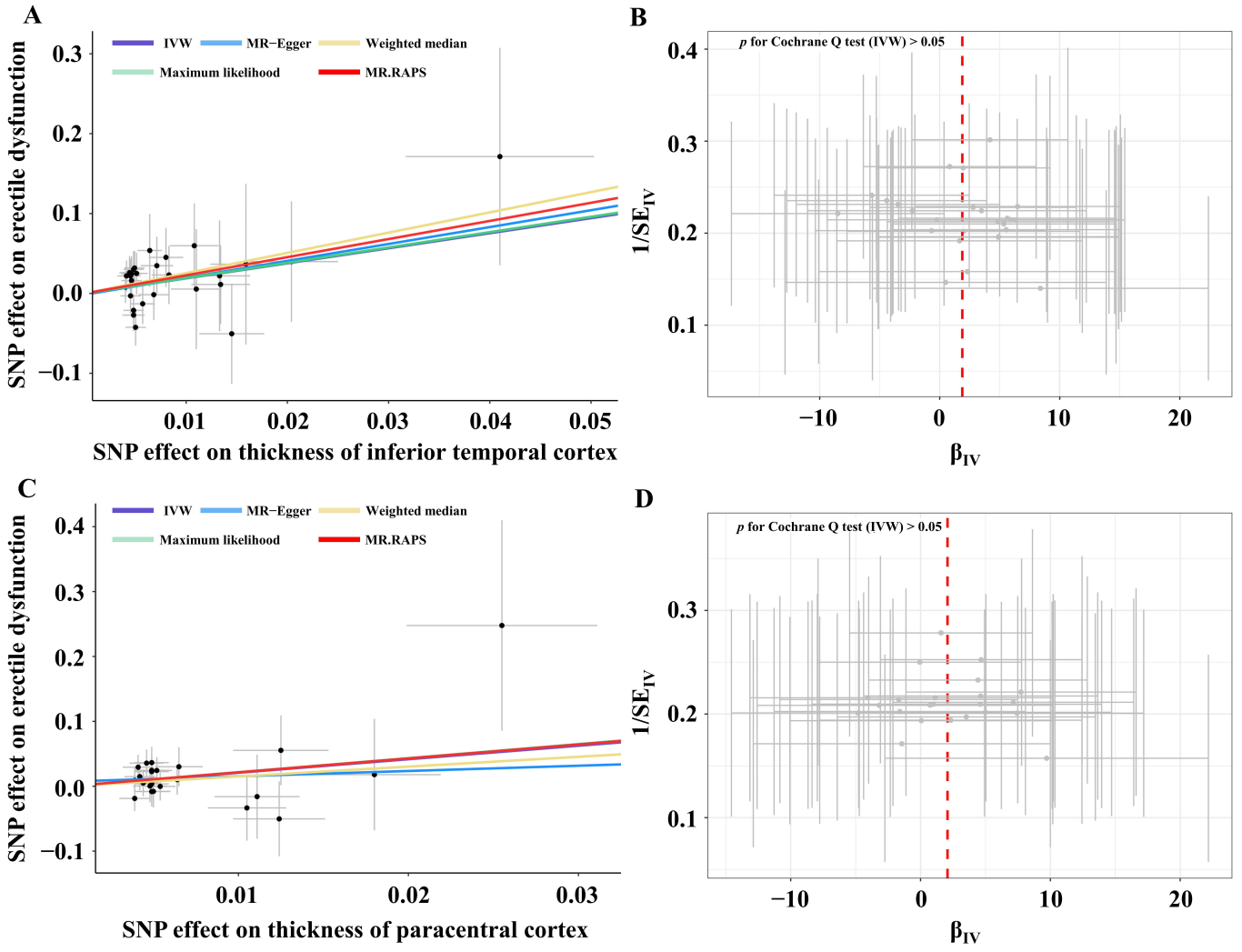

FIGURE 4. Scatter and funnel plots of the thickness of the cortical morphometry with ED. (A,B): scatter and funnel plots visualizing the SNP effect on the thickness of the inferior temporal cortex and erectile dysfunction, and the heterogeneity in the instrumental variables. (C,D): scatter and funnel plots visualizing the SNP effect on the surface area of the paracentral cortex and erectile dysfunction, and the heterogeneity in the instrumental variables. IVW: inverse variance weighting; MR: Mendelian randomization; MR.RAPS: MR.robust adjusted profile score; IV: instrumental variables; SNP: Single nucleotide polymorphism.

tics among the study populations, consequently impacting the statistical power and applicability of the findings. This emphasizes the complexity of ED as a multifaceted pathological process involving extensive alterations in the cerebral cortex.

To the best of our knowledge, this study represents the first to uncover a genetic association between increased surface area of the entorhinal cortex and superior frontal cortex and elevated risk of ED. As individuals age, cortical volume, thickness, and surface area across various regions of the frontal lobe notably decline [36]. Specifically, the volume, thickness, and surface area of the entorhinal cortex exhibit an upward trend with advancing age, peaking around 32, 40 and 50 years, respectively, before declining thereafter [37]. The entorhinal cortex serves as a crucial link between the temporal neocortex and hippocampus and is closely tied to cognitive functions [38]. Few investigations have explored the associations between regional cortical thickness and surface area and brain function [39]. The scarcity of studies employing various imaging modalities can be ascribed in part to the intricacies involved in aligning or registering datasets containing structural (thickness) and functional (activation) data among and between participants [39]. Indeed, as far as we are aware, no studies have directly associated fMRI signals with the underlying anatomical features acquired from structural MRI. Research on the connection between the entorhinal cortex and sexual function is scarce. In a neuroimaging study conducted on women, women with no history of sexual dysfunction exhibited markedly greater activation in the bilateral entorhinal cortex than did those with hypoactive sexual desire disorder when viewing erotic video materials [40]. Consistently, the superior frontal cortex exhibited the most substantial decline associated with age in terms of volume, thickness, and surface area [41]. This region is believed to play a significant role in higher cognitive functions, with a particular emphasis on working memory [42]. Regarding the association between the superior frontal cortex and ED, previous research by Yin *et al*. [43] found that the incidence of psychogenic ED was linked to irregular functional connectivity (FC) between the left dorsolateral superior frontal cortex and angular gyrus, along with FC between the posterior cingulate cortex and precuneus. A recent study discovered reduced fractional amplitude of low-frequency fluctuation (fALFF) and FC values in the dorsolateral superior frontal cortex of psychogenic ED patients, suggesting that dysfunction in this brain region might lead to difficulties in attentional focus during sexual activities and a diminished capacity to focus on pleasure and sensations, contributing to lower sexual satisfaction among patients [44]. However, the underlying mechanisms behind the variability in the surface area of the superior frontal cortex observed in ED patients require further investigation.

Our study also revealed that higher thickness in the inferior temporal cortex and paracentral cortex was associated with an increased risk of ED. Stoléru *et al*. [9] found that the inferior temporal cortex region responds to visual sexual stimuli through deactivation, which is believed to aid in the cognitive processes of SA. Functional neuroimaging investigations focusing on normal male SA have suggested that the activation pattern of the inferior temporal cortex may be associated with distinguishing stimuli as either sexual or non-sexual, and the degree of inferior temporal cortex activation appears to correlate with the intensity of erection [16, 45]. However, contrary to our findings, Zhao *et al*. [10] discovered cortical thickness loss in both inferior temporal cortex regions among patients with psychogenic ED. Further research and replication studies are needed to clarify these discrepancies and establish more robust conclusions. The paracentral cortex governs both motor and sensory functions of the contralateral lower extremity, as well as cortical regulation of micturition and defecation [46]. Allen *et al*. [47] demonstrated that activation in a specific area of the paracentral cortex was observed following mild self-stimulation of the penile shaft. A resting-state fMRI study conducted in healthy subjects demonstrated functional connectivity between the paracentral cortex and other frontal and parietal regions, supporting motor function and spatial attention [48]. While our study suggested that altered paracentral cortex thickness is a potential indicator of ED, further investigations into specific motor dysfunctions and disturbances in attentional subdomains are warranted to determine its predictive value for ED.

This study has several limitations. Firstly, the data utilized were aggregated GWAS statistics data in public databases, lacking detailed information at the individual outcome level. This deficiency could introduce an unavoidable bias into our findings, and there is an inherent challenge in avoiding sample overlap. Due to the polygenic or omnigenic nature of intricate diseases and characteristics, widespread pleiotropy exists in the human genome, making it possible to pinpoint and take into account all conceivable confounding variables. Secondly, our study only conducted a unidirectional MR analysis. We did not explore the causality between ED and cortical morphometry. Thirdly, our study solely established a correlation between alterations in brain cortical structure and ED. Although we have offered potential interpretations for certain observed cortical structural changes associated with ED in the discussion section, further exploration is needed to uncover the underlying mechanisms. Fourthly, in this study, both the groups exposed to the factor and those experiencing the outcome were limited to individuals of European descent, with no examination of other racial or ethnic groups. This omission results in ongoing uncertainties when extending conclusions about the relationship between cortical morphometry and ED risk to non-European populations. Acknowledging this, more endeavors verifying the association between cortical morphometry and ED in other races are beneficial to provide more robust conclusions.

5. Conclusions

Based on genetic data from the cerebral cortex, this study provides evidence that genetically proxied higher surface areas of the entorhinal and superior frontal cortex are associated with an elevated risk of ED. There is a significant genetic correlation between the surface area of the entorhinal cortex and ED. In addition, genetically predicted higher thickness of the inferior temporal and paracentral cortex is associated with an increased risk of ED. This study investigates the influence of the central cerebral cortex on ED and provides a better understanding of the etiology of ED.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

CF and XFO—Conceptualization; writing-review & editing. CF and THW—Data curation. THW—Formal analysis. CF, JCJ and QHW—writing-original draft.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical review and approval were waived for this study, all the data from Mendelian randomization is publicly accessible. Informed consent was obtained from all subjects in the original genome-wide association studies.

ACKNOWLEDGMENT

The authors sincerely thank Tao Lin in statistical assistance.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Chen Fu, Tianhong Wang, Qihai Wan, Jiacheng Jiang, Xiaofeng Ou. Structural insights into cortical morphometry and erectile dysfunction: a Mendelian randomization and genetic correlation study. Journal of Men's Health. 2024; 20(11): 78-87. doi: 10.22514/jomh.2024.187.