

Exploring the Shared Genetic Architecture Between Obstructive Sleep Apnea and Body Mass Index

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Purpose: The reciprocal comorbidity of obstructive sleep apnea (OSA) and body mass index (BMI) has been observed, yet the shared genetic architecture between them remains unclear. This study aimed to explore the genetic overlaps between them.

Methods: Summary statistics were acquired from the genome-wide association studies (GWASs) on OSA ($N_{\text{case}} = 41,704$; $N_{\text{control}} = 335,573$) and BMI ($N_{\text{overall}} = 461,460$). A comprehensive genome-wide cross-trait analysis was performed to quantify global and local genetic correlation, infer the bidirectional causal relationships, detect independent pleiotropic loci, and investigate potential comorbid genes.

Results: A positive significant global genetic correlation between OSA and BMI was observed ($r_g = 0.52$, $P = 2.85e-122$), which was supported by three local signal. The Mendelian randomization analysis confirmed bidirectional causal associations. In the meta-analysis of cross-traits GWAS, a total of 151 single-nucleotide polymorphisms were found to be pleiotropic between OSA and BMI. Additionally, we discovered that the genetic association between OSA and BMI is concentrated in 12 brain regions. Finally, a total 134 expression-tissue pairs were observed to have a significant impact on both OSA and BMI within the specified brain regions.

Conclusion: Our comprehensive genome-wide cross-trait analysis indicates a shared genetic architecture between OSA and BMI, offering new perspectives on the possible mechanisms involved.

Keywords: genome-wide cross-trait analysis, Mendelian randomization, genetic architecture

Introduction

Obstructive sleep apnea (OSA), which is characterized by recurrent blockages of the upper respiratory tract while sleeping, is a globally increasingly prevalent health issue impacting around 936 million adults in the general population.^{1,2} Body mass index (BMI) is the most frequently employed method to evaluate obesity, a condition characterized by the excessive accumulation of fat that detrimentally affects one's health.³ Numerous clinical studies have implied that OSA is comorbid with BMI.⁴⁻⁷ Approximately 50% of individuals diagnosed with OSA exhibit obesity, and OSA affects 40–90% people with moderate to severe obesity.⁷ The heritability of BMI, estimated at 40–70%,^{8,9} highlights a significant genetic basis for obesity. Similarly, OSA shows genetic predisposition, with heritability estimates of 0.06 to 0.17 in population-based studies^{10,11} and 0.33–0.37 in family-based studies,¹² emphasizing the genetic intersection between these conditions. Potential shared mechanistic factors, including oxidative stress,¹³ inflammation,¹⁴ metabolic dysregulation,^{15,16} gut microbiota,¹⁷ have been implicated in both OSA and obesity. The identification of shared genetic variants associated with both OSA and obesity has the potential to yield valuable insights into the underlying pathogenic mechanisms, and facilitate the development of novel targeted drugs and therapies.

Strausz et al have quantified a strong genetic correlation ($r_g = 0.72$) and proposed a potential causal relationship between OSA and BMI.¹⁰ However, these results should be interpreted cautiously because of the relatively limited

sample sizes and potential sample overlap. Additionally, no studies have uncovered the risk loci exhibiting pleiotropic effects that are shared between OSA and BMI.

In this study, we extended previous findings by conducting a comprehensive genome-wide cross-trait analysis, utilizing summary data from the largest available genome-wide association studies (GWASs) on both OSA and BMI. Firstly, we calculated the global and local genetic correlations between OSA and BMI, and subsequently assessed the causal relationship between them. Then, we utilized a genome-wide cross-trait meta-analysis to investigate the pleiotropic loci. Finally, we employed the Genotype-Tissue Expression (GTEx v8) database to identify SNP (single nucleotide polymorphism) -enriched tissues and potential functional genes associated with both OSA and BMI. This study design is illustrated in [Figure 1](#).

Methods

Datasets

GWAS summary statistics for OSA were provided by the FinnGen Consortium (<https://www.r9.finngen.fi/>),¹⁸ which contain 41,704 cases and 335,573 controls. Analysis adjusted for covariates such as sex, age, genotyping batch, and ten principal components (PCs) to account for population stratification. The diagnosis of OSA in FinnGen was defined according to ICD-10: G47.3. Diagnosis required patients to exhibit subjective symptoms, undergo clinical examinations, and have sleep registration findings of an apnea-hypopnea index (AHI) or respiratory event index (REI) >5/hour, thus confirming OSA. The GWAS data for BMI, comprising 461,460 individuals, was acquired from a meta-analysis of GWASs in the UK Biobank conducted by MRCIEU (ID: ukb-b-19953). The model used covariates such as genotype array, sex, and the first 10 out of 40 PCs.

The IEU Open GWAS Project (<https://gwas.mrcieu.ac.uk/>) made the statistical data available for public download. The study's analyses relied on publicly accessible summary-level GWAS datasets, which have obtained ethical approval from their respective institutional review boards and informed consent from participants. Considering our study's exclusive reliance on pre-approved, publicly accessible datasets and the absence of any further data collection or human participant analysis, it was deemed exempt from separate ethical approval requirements.

Statistical Analysis

Overall and Local Genetic Correlation Analysis

The genetic correlations between OSA and BMI were estimated through linkage disequilibrium score regression (LDSC, <https://github.com/bulik/ldsc>) and the high-definition likelihood (HDL, <https://github.com/zhenin/HDL>) methods,

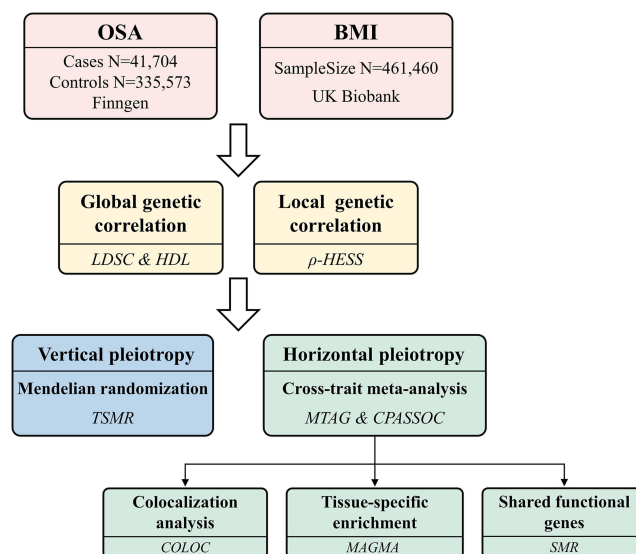


Figure 1 Overall study design of genome-wide cross-trait analysis.

Abbreviations: OSA, obstructive sleep apnea; BMI, body mass index; LDSC, linkage disequilibrium score regression; HDL, high-definition likelihood; ρ -HESS, rho-heritability estimation from summary statistics; TSMR, two sample Mendelian randomization; MTAG, Multi-Trait Analysis of GWAS; CPASSOC, Cross Phenotype Association; MAGMA, Multi-marker Analysis of GenoMic Annotation; SMR, Summary-data-based Mendelian randomization.

utilizing GWAS summary statistics.^{19,20} The LDSC method enables the quantification of the impact of polygenicity and confounding biases (cryptic relatedness and population stratification) through the analysis of the association between test statistics and linkage disequilibrium (LD). We excluded the SNP with a minor allele frequency (MAF) lower than 0.01 and estimated the single-trait SNP heritability for OSA and BMI using LDSC with the baseline-LD model. Next, we conducted bivariate LDSC analysis without imposing constraints on the intercept to estimate the r_g coefficient, which quantifies the genetic correlations between OSA and BMI. Since there was no sample overlap, we also performed a sensitivity analysis by constraining the single-trait heritability intercept. Compared with LDSC, the precision of genetic correlation estimation is enhanced by the HDL method by considering genome-wide LD. Thus, we performed HDL analysis to guarantee reliable results of the genetic association between OSA and BMI.

To evaluate the local genetic correlation between OSA and BMI, we employed the rho-heritability estimation from summary statistics (ρ -HESS; <https://github.com/huwenboshi/hess>) technique.²¹ The algorithm's analysis of 1703 independent LD regions, each averaging around 1.6 Mb, not only facilitates the identification of genomic areas with a disproportionate influence on genetic sharing across traits but also significantly enhances the precision of genetic association analyses. Utilizing the 1000 Genomes Project as the reference, we calculated the local SNP heritability for the two aforementioned traits across 1703 independent genomic blocks, as well as the local (at each LD-independent region in the genome) and genome-wide genetic correlation existing between them. For multiple testing, the Bonferroni correction (0.05/1703) was applied.

Bidirectional Mendelian Randomization

Based on the findings of genetic correlations, a two-sample Mendelian randomization (MR) analysis was employed to investigate the bidirectional causal association between OSA and BMI using the “TwoSampleMR” R package.²² The analysis was undertaken in both directions, (i) using OSA as exposure and BMI as outcome, and (ii) using BMI as exposure and OSA as outcome. We used SNPs as instrumental variables that were associated with exposure at a genome-wide significance level ($P < 5e-8$) and were not in LD with other SNPs ($r^2 < 0.001$ within a clumping window of 10,000 kb). When the instrumental variable SNPs were absent from the outcome GWAS, we selected proxy SNPs ($r^2 > 0.8$ with the original SNP) using the “LDLinkR” package.²³ For harmonizing the SNP effects on the exposure and the outcome, we corrected the strand for non-palindromic SNPs and dropped all palindromic SNPs.

The inverse variance weighted (IVW) regression under random or fixed effects was employed for the primary MR analysis. For sensitivity analyses, other methods such as MR-Egger, weighted median, and maximum likelihood were also used as supplements to IVW.²⁴⁻²⁶ To detect the horizontal pleiotropy, the MR-Egger regression intercept was employed. Furthermore, MR pleiotropy residual sum and outlier (MR-PRESSO) analysis was performed to identify any potential horizontal pleiotropy and outliers. In the case of outliers, we removed the outlier SNPs and repeated the MR analysis. Finally, a leave-one-out analysis was performed in order to examine the robustness of MR results for any outlier SNP.

Cross-Trait Meta-Analysis

Utilizing the genetic correlation and estimation error correlation across traits, Multi-Trait Analysis of GWAS (MTAG; <https://github.com/JonJala/mtag>) conducts multivariate analysis on genetically correlated traits to enhance the detection power for each input trait, offering trait-specific effect estimates and P values.²⁷ MTAG was employed to identify novel candidate SNPs associated to joint phenotypes of OSA and BMI. The “maxFDR”, an upper bound on the false discovery rate (FDR) for the GWAS, was computed according to the recommended methodology. Leveraging MTAG to generate trait-specific SNP effect estimates, we utilized MTAG summary statistics (MTAG_{OSA} and MTAG_{BMI}) in subsequent analyses. This approach capitalizes on MTAG's ability to serve as an effective substitute for individual trait GWAS summary data.

The Cross Phenotype Association (CPASSOC) is a method devised to incorporate multiple traits' association evidence from numerous GWASs, thereby facilitating the detection of cross-phenotype associations.²⁸ We executed CPASSOC analysis to identify shared loci between GWAS_{OSA} and GWAS_{BMI}, thus substantiating the findings derived

from MTAG. Two statistics, S_{Het} (heterogeneous effects between GWASs) and S_{hom} (homogeneous effects between GWASs), were calculated by CPASSOC. While S_{hom} serves as the foundation for S_{Het} , the latter's power can be strengthened when the genetic effect sizes demonstrate variations across different traits. The SNPs with $P_{\text{Shet}} < 5e-8$ and $P_{\text{MTAG}} < 5e-8$ were considered as candidate SNPs exhibiting effects on both traits. The PLINK “clumping” function was then utilized to identify the independent SNPs that exhibited the most significant association with both traits, which was achieved by applying the following parameters: $-\text{clump-p1 } 5e-8 -\text{clump-p2 } 1e-5 -\text{clump-r2 } 0.2 -\text{clump-kb } 500$. Novel loci were defined as independent SNPs that were not genome-wide significant ($P < 5e-8$) or in LD ($r^2 > 0.01$ within a clumping window 1000 kb) with any genome-wide significant SNPs in the GWAS_{OSA} and GWAS_{BMI}.

Colocalization Analysis and SNP Annotation

We utilized the “coloc” R package for colocalization analysis to estimate the probability that the independent SNPs associated with OSA and BMI represented shared genetic causal variants between the two traits.²⁹ We procured summary data from MTAG (MTAG_{OSA} and MTAG_{BMI}) for variants located within 1-Mb regions centered on each independent SNP. Subsequently, we calculated the PPH4, which stands for the posterior probability of H4, which represents the likelihood that both traits share a single causal variant. $\text{PPH4} > 0.95$ was considered colocalized. The colocalizing pleiotropic SNPs identified through colocalization analysis were mapped to genes using the Ensembl Variant Effect Predictor (VEP).³⁰

Tissue-Specific Enrichment Analysis

Multi-marker Analysis of GenoMic Annotation (MAGMA) was utilized to conduct a gene-based association and tissue-specific enrichment analysis.³¹ The estimation of the association between a specific gene and the trait was conducted by averaging P -values of the SNPs located near the target gene, utilizing the MTAG summary statistics (MTAG_{OSA} and MTAG_{BMI}). To determine which tissues are most strongly associated with the shared genes, we calculated the correlation between tissue-specific gene expression profiles and trait-gene associations using data from GTEx, which contains information from 54 different tissues. The Bonferroni correction (0.05/54) was applied for multiple testing.

Summary-Data-Based Mendelian Randomization

Summary-data-based Mendelian Randomization (SMR) utilizes Mendelian randomization for testing pleiotropic connections between gene expression and complex traits by utilizing expression quantitative trait loci (eQTL) and trait GWAS data.³² We performed SMR analysis using MTAG summary statistics (MTAG_{OSA} and MTAG_{BMI}) in conjunction with cis-eQTL summary data from 49 human tissues provided by the GTEx project, to identify potentially causal genes for OSA and BMI. A heterogeneity in dependent instruments (HEIDI) test was also conducted to examine the presence of heterogeneity. Genes that met the criteria of passing the Bonferroni correction for multiple comparisons test ($P < 0.05/\text{number of genes}$) and the HEIDI outlier test ($P_{\text{HEIDI}} > 0.05$) in each tissue were considered to be significant causal genes. The causal genes that co-occurred in the same tissue in both traits and overlapped with colocalizing SNP-associated genes were considered as shared functional genes.

Results

Genetic Corrections

Single-trait LDSC shows SNP heritability estimates of 0.0439 (SE = 0.0026) for GWAS_{OSA} and 0.2532 (SE = 0.0087) for GWAS_{BMI}. The LD Score regression intercept for GWAS_{OSA} and GWAS_{BMI} were 1.1116 (SE = 0.0104) and 1.0999 (SE = 0.022) respectively. The genetic correlation between OSA and BMI was estimated using bivariate LDSC. The genetic correlation between OSA and BMI ($r_g = 0.52$, $P = 2.85e-122$) was significant positive. By assuming no sample overlap, we constrained the LDSC intercept, resulting in a slightly weaker but still significant genetic correlation ([Supplementary Table S1](#)). HDL also shows a positive genome-wide correlation of OSA and BMI ($r_g = 0.486$, SE = 0.050, $P_{\text{HDL}} = 4.73E-22$) ([Supplementary Table S2](#)).

To ascertain local genetic correlations between OSA and BMI, the ρ -HESS approach was utilized. Following the application of the Bonferroni correction, significant regional associations were observed in chromosome 3 (130244735–131836516),

chromosome 14 (78561945–80186579) and chromosome 16 (53382572–55903774) (Figure 2; Supplementary Tables S3–S5). Following this analysis, the genes located within the regions exhibiting significant local correlations were annotated. A total of 22 genes, such as FTO, MMP2, and NRXN3, were identified. Detailed information on these genes can be found in Supplementary Table S6. We calculated the local single-trait SNP heritability across 1703 independent genomic blocks for OSA ($h^2 = 0.0801$, $SE = 0.00322$) and BMI ($h^2 = 0.317$, $SE = 0.00233$). The genome-wide genetic correlation, calculated using ρ -HESS, between OSA and BMI ($r_g = 0.303$) showed substantial consistency when compared to bivariate LDSC.

Bidirectional Mendelian Randomization

To investigate the causal relationship between OSA and BMI, we performed a bidirectional two-sample MR analysis. In the forward MR analysis, a total of 10 SNPs from $GWAS_{OSA}$ were finally identified as instrumental variables after excluding outliers detected in the MR-PRESSO analysis (Supplementary Table S7). Using IVW method, genetically predicted OSA was associated with a 0.160 (kg/m^2) increase in BMI ($P = 7.25e-24$), which was further supported by MR-Egger, weighted median, and maximum likelihood methods (Figure 3). There was no detected pleiotropy in MR-Egger analyses ($P = 0.395$, Egger_intercept = -0.00629) (Supplementary Table S8).

The reverse MR analysis identified 43 SNPs as the final instrumental variables referring to BMI from $GWAS_{BMI}$ after excluding outlying SNPs from the MR-PRESSO analysis (Supplementary Table S9). With every 1-SD kg/m^2 increase in genetically predicted BMI, the MR IVW estimate revealed a higher likelihood of OSA ($OR = 2.32$, $P = 1.72e-20$). Sensitivity analyses (MR-Egger, weighted median, and maximum likelihood) yielded consistent findings (Figure 3). No evidence of imbalanced horizontal pleiotropy was found in the MR-Egger test ($P = 0.156$, Egger_intercept = -0.00923) (Supplementary Table S8). In both forward and reverse MR analyses, the results were robust to leave-one-out sensitivity analyses (Supplementary Figure S1).

Cross-Trait GWAS Meta-Analysis

The cross-trait GWAS meta-analyses were conducted to discover risk SNPs that underlie the joint phenotypes OSA-BMI, considering the substantial genetic correlations between OSA and BMI. We employed two different approaches, MTAG and CPASSOC, that complemented each other. MTAG identified a collective sum of 5539 genome-wide significant SNPs ($P < 5e-8$), all of which exhibited overlap with the 58,716 genome-wide significant SNPs revealed in CPASSOC (Supplementary Table S10), indicating the reliability of MTAG results. No inflation problems were indicated by the maxFDR values of 0.020 and $4.98e-06$ for OSA and BMI in the MTAG analyses, respectively. The $MTAG_{OSA}$ and $MTAG_{BMI}$ were then used for subsequent analysis. By LD analyses for the 5539 SNPs present in both MTAG and CPASSOC, a total of 151 shared independent SNPs were identified (Supplementary Table S11). After excluding independent SNPs that exhibited genome-wide significance ($P < 5e-8$) or were in LD with previously significant

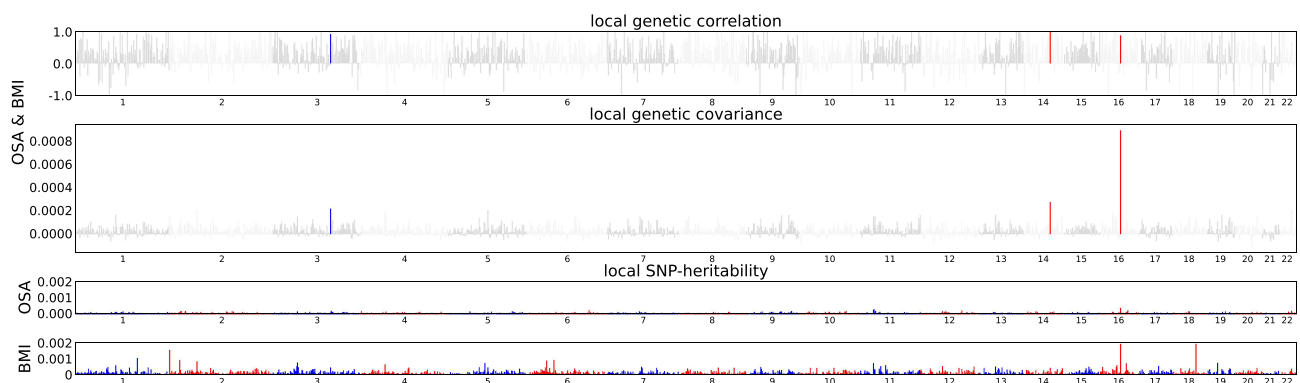
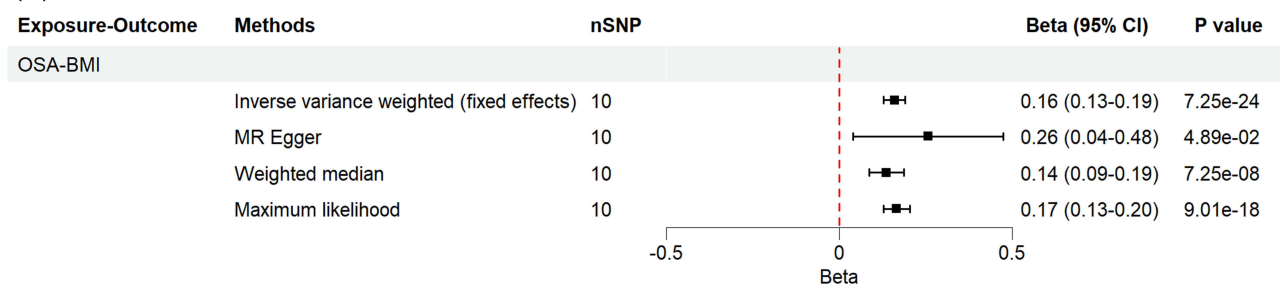


Figure 2 Local genetic correlation between OSA and BMI. Manhattan plot displayed the calculations of the local genetic correlation and local genetic covariance between OSA and BMI, along with their respective local SNP heritability. The presence of red and blue bars in “local genetic correlation” and “local genetic covariance” indicate significant regions sharing SNP heritability. These regions meet the criteria ($P < 5e-08$ in local SNP heritability test, and $P < 0.05/1703$ in local genetic covariance test).

(A) Forward-direction MR



(B) Reverse-direction MR

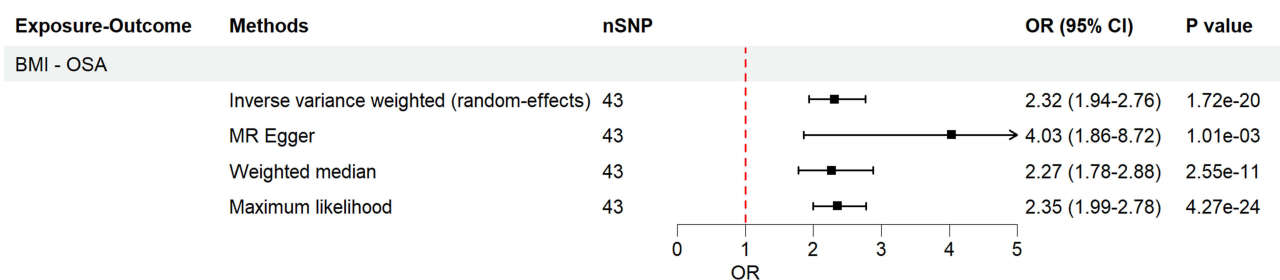


Figure 3 Forest plots of bidirectional MR analysis between OSA and BMI. **(A)** forward MR analysis; **(B)** reverse MR analysis. **Abbreviations:** MR, Mendelian randomization; OSA, obstructive sleep apnea; BMI, body mass index.

SNPs in the $GWAS_{OSA}$ and $GWAS_{BMI}$, we discovered 3 novel pleiotropic SNP (rs11782826, rs6730157, rs7701723) linked to the joint phenotype of OSA-BMI ([Supplementary Table S11](#)).

Colocalization and Annotation

To ascertain whether the genetic variants responsible for the association in both traits were identical or distinct, a colocalization analysis was then conducted. The majority of shared loci between $MTAG_{OSA}$ and $MTAG_{BMI}$ exhibited colocalization at identical candidate SNPs ($PPH4 > 0.95$) (117/151) ([Supplementary Table S12](#)). Two of the three novel pleiotropic loci (rs11782826 and rs7701723) displayed evidence of colocalization ($PPH4 > 0.95$). The most significant novel shared SNP, rs11782826 ($P_{CPASSOC}=1.51e-10$), is at an intron region of *ERII*. SNP rs7701723 is located in an intron of *COMMD10* ([Supplementary Table S13](#)).

Tissue Specific Enrichment Analysis

Utilizing $MTAG_{OSA}$ and $MTAG_{BMI}$ summary data, we employed MAGMA for tissue expression analysis to identify tissues enriched with SNPs associated with OSA and BMI. This analysis aimed to examine the associations between genes linked to OSA and BMI and tissue-specific gene expression profiles across 54 tissue types sourced from GTEx. SNPs associated with OSA and BMI were specifically enriched in the same 12 central nervous system (CNS) related tissues, leading by brain cerebellum, cerebellar hemisphere, frontal cortex Brodmann area 9 and cortex. ([Figure 4](#)).

Summary-Data-Based Mendelian Randomization

Utilizing GTEx eQTL summary data, SMR was adopted to identify functional genes implicated in both OSA and BMI. At the tissue-specific Bonferroni-corrected threshold, a total of 602 expression-tissue pairs were shared between OSA and BMI, covering all tissues except for the cervical C-1 region of the brain and spinal cord ([Supplementary Table S14](#)). Within these pairs, 98 are coincident with colocalizing pleiotropic SNP-associated genes, implicating 15 genes (C18orf8, PMS2P11, UPK3BP1, DTX2P1, ERI1, CPNE4, NPC1, SOX7, TRAF3, POC5, GRID1, MSRA, BDNF-AS, XKR6, MACF1) across 38 tissues. Among these genes, six (C18orf8, NPC1, PMS2P11, POC5, SOX7, TRAF3) were present in

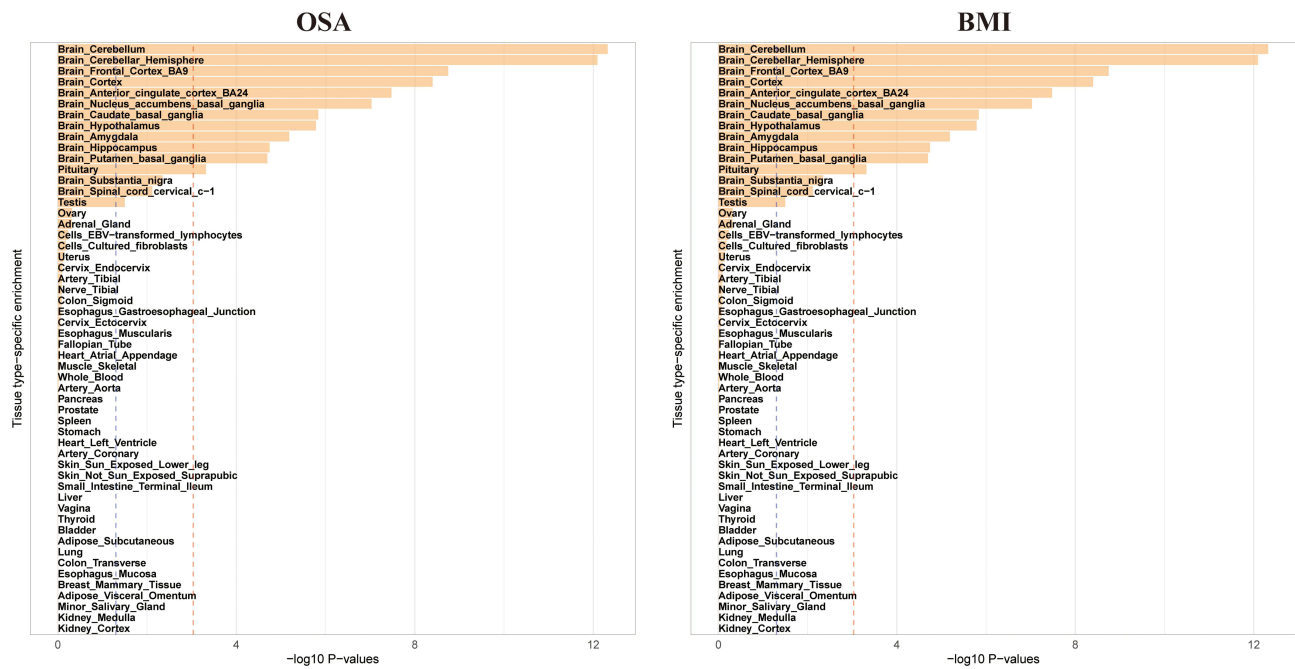


Figure 4 Tissue specific enrichment of SNP heritability for OSA and BMI. A total of 12 tissues were shared in enrichment of SNP heritability for OSA and BMI after adjustment ($P < 0.005/54$). Blue line indicates threshold 0.05 for P value, and red line indicates 0.05/54.

Abbreviations: OSA, obstructive sleep apnea; BMI, body mass index.

seven of the twelve central nervous system (CNS)-related tissues identified by the MAGMA analysis, suggesting their role as shared functional genes between OSA and BMI, as shown in Table 1.

Discussion

The objective of this research was to examine the shared genetic architecture between OSA and BMI by conducting a comprehensive genome-wide cross-trait analysis. Significant positive genetic correlations between OSA and BMI were observed at both the global and local levels, indicating an inherent association between these complex traits. The genetic

Table 1 Six Genes Obtained from the Intersection of Genes Identified by SMR and Those Associated with Colocalized SNPs

Ensembl	Gene	CHR	Colocalizing_SNP	Tissue	Annotation
ENSG00000131323	TRAF3	14	rs3803286	Brain_Cortex	TNF receptor associated factor (TRAF) protein family
ENSG00000141452	C18orf8	18	rs1788808	Brain_Cerebellar_Hemisphere	Regulator of MON1-CCZ1
ENSG00000141452	C18orf8	18	rs1788808	Brain_Cerebellum	
ENSG00000141452	C18orf8	18	rs1788808	Brain_Cortex	
ENSG00000141452	C18orf8	18	rs1788808	Brain_Frontal_Cortex_BA9	
ENSG00000141458	NPC1	18	rs1788808	Brain_Caudate_basal_ganglia	Intracellular cholesterol transporter
ENSG00000141458	NPC1	18	rs1788808	Brain_Cerebellar_Hemisphere	
ENSG00000141458	NPC1	18	rs1788808	Brain_Cerebellum	
ENSG00000141458	NPC1	18	rs1788808	Brain_Cortex	
ENSG00000141458	NPC1	18	rs1788808	Brain_Frontal_Cortex_BA9	
ENSG00000141458	NPC1	18	rs1788808	Brain_Nucleus_accumbens_basal_ganglia	
ENSG00000152359	POC5	5	rs2307111	Brain_Cortex	Assembly of the distal half of centrioles

(Continued)

Table 1 (Continued).

Ensembl	Gene	CHR	Colocalizing_SNP	Tissue	Annotation
ENSG00000171056	SOX7	8	rs7009586	Brain_Cerebellar_Hemisphere	A member of the SOX (SRY-related HMG-box) family of transcription factors
ENSG00000241350	PMS2P11	7	rs4727295	Brain_Cortex	Pseudogene
ENSG00000241350	PMS2P11	7	rs4727295	Pituitary	

correlation could be categorized as vertical and horizontal pleiotropy, supported by validated bidirectional causal associations through MR analysis, the identification of shared independent pleiotropic loci in cross-trait meta-analysis, and the recognition of shared expression-trait pairs using MAGMA and SMR.

The significant result of global genome-wide genetic correlation between OSA and BMI calculated by LDSC ($r_g = 0.52$, $P = 2.85E-122$) and HDL ($r_g = 0.486$, $P_{HDL} = 4.73E-22$) was in line with the estimate of 0.72 reported by Strausz et al.¹⁰ In contrast to the study conducted by Strausz utilizing FinnGen dataset for both OSA (16,761 cases/ 201,194 controls) and BMI (159,731 individuals), we enhanced the reliability and accuracy of our findings by increasing the sample sizes and avoiding sample overlap. We achieved this by utilizing summary statistics of OSA (41,704 cases and 335,573 controls) from the latest FinnGen dataset (R9) and summary statistics of BMI (461,460 individuals) from the UK Biobank. The global correlation between OSA and BMI was supported by the local genetic correlation analysis, which identified three genomic regions at chr3: 130244735–131836516, chr14: 78561945–80186579, and chr16: 53382572–55903774, indicating significant local genetic correlations between the two traits. Within these genomic regions, a total of 22 genes were annotated. Notably, FTO^{10,33} and MMP2^{34,35} have been reported to have a strong association with both OSA and obesity. The majority of the remaining genes, such as AKTIP,³⁶ IRX3,³⁷ RBL2,³⁸ RPGRIP1L,³⁹ and SLC6A2,⁴⁰ are closely related to the pathogenesis of obesity. This genetic evidence highlights the intricate relationship between genetic factors and the development of obesity and OSA.

Our MR analysis not only supported previous findings but also extended them. Strausz reported that an elevated BMI correlated with a greater incidence of OSA ($\beta = 0.67$, OR = 1.95), aligning with our own findings, which demonstrated a BMI-related rise in OSA incidence (OR = 2.32).¹⁰ Furthermore, we identified a reverse causal relationship, namely, OSA was associated with a 0.160 (kg/m²) increase in BMI. The above results substantiated the tight relationship between OSA and BMI as indicated by previous observational studies.^{41–43}

Notably, existing research underscores a significant association between OSA and dyslipidemia. Evidence from twin studies indicates that the co-occurrence of OSA and hypertriglyceridemia is influenced by genetic factors.⁴⁴ Furthermore, a study conducted by Tang et al reveals that genetically increased triglyceride levels contributes to the risk of sleep apnea.⁴⁵ Additional research suggests that obesity leads to insulin resistance through the impaired production of adipokines and chronic low-grade inflammation in adipose tissue, which serves as the main driving force in the development of metabolic dyslipidemia.⁴⁶ These findings indicate a multifaceted relationship among OSA, BMI, and dyslipidemia. BMI may influence the development of OSA through dyslipidemic pathways, while OSA, in turn, might affect dyslipidemia through mechanisms related to BMI. Elucidating the precise mechanisms underpinning these associations necessitates comprehensive future research.

Through our cross-trait meta-analyses, we have identified multiple pleiotropic loci, suggesting a shared genetic basis between OSA and BMI. Notably, two of the three novel pleiotropic loci (rs11782826 and rs7701723) were co-localized for both traits. SNP rs12951387 is located within *ERII*, which encodes an evolutionary conserved 3'-to-5' exonuclease that plays a crucial role in various RNA metabolic pathways, such as the processing of 5.8S rRNA and the degradation of histone mRNAs.^{47–49} The *ERII* gene might affect OSA and BMI through effects on growth and development, as well as cardiac functioning and disease.^{50–52} A homozygous nonsense variant in *ERII* has been linked with developmental delay and distal limb abnormalities.⁵⁰ Choucair found that the homozygous microdeletion of *ERII* was correlated with the presence of intellectual disability, limb abnormalities, and cardiac malformation.⁵¹ Chai et al

discovered that SNPs in *ERII* were both associated with blood pressure and spontaneous coronary artery dissection.⁵² SNP rs7701723 is located within *COMMD10*, which encodes a protein (COMMD10) belonging to the copper metabolism MURR1 domain (COMMD) protein family.⁵³ COMMD10 has been reported to be important in immune cells function.^{54–56} The presence of COMMD10 plays a critical role in Kupffer cell survival⁵⁴ and phagolysosomal biogenesis and maturation,⁵⁵ as well as regulates the differentiation of monocytes in liver.⁵⁴ Yang discovered that COMMD10 exerts a suppressive effect on cell proliferation and facilitates apoptosis through the inhibition of NF- κ B signaling in hepatocellular carcinoma. Inflammation has been found to promote the development of OSA,^{57,58} and also lead to obesity and obesity-related metabolic diseases.^{59,60}

Tissue specific enrichment analysis revealed that central nervous system (CNS)-related tissues might play a pivotal role in the pathogenesis of both OSA and BMI, which was consistent with existing studies. Multiple neural mechanisms, including a lowered respiratory arousal threshold,^{61,62} heightened loop gain,^{63,64} and impaired sympathetic neural activity,^{65,66} have been linked to the pathogenesis of OSA. Variability in the structure and function of the frontal cortex across individuals influences variations in appetite and food preferences, thereby contributing to the diverse risk of obesity.⁶⁷ Inflammation and gliosis in the hypothalamic could impact the regulation of neuroendocrine circuits and contribute to the onset and persistence of obesity.^{68,69} And further research is warranted to investigate the shared neuropathogenesis underlying OSA and BMI. It is noteworthy that adipose tissue did not show significant enrichment in OSA or BMI. The constraints inherent in the GTEx eQTL reference data could potentially explain this outcome. The sample size for adipose tissue is around 500 samples, which may not adequately capture the complexity and variability inherent to this tissue. Additionally, the eQTL data for adipose tissue may lack specific gene expression information, further contributing to the non-significant findings. Larger-scale eQTL datasets in the future might provide new insights into tissue enrichment for shared SNPs between BMI and OSA.

Through SMR analysis across various tissues, a total of 602 expression-tissue pairs were identified, excluding the cervical C-1 region of the brain and spinal cord. Among these, 134 pairs were found within the 12 CNS-related brain tissues identified through the MAGMA analysis. Within this subset of 134 pairs, six genes (*TRAF3*, *RMCI*, *NPC1*, *PMS2P11*, *POC5*, *SOX7*) were overlapped with the colocalizing pleiotropic SNP-associated genes. These genes are implicated in diverse biological processes. TRAF3 has been reported as a regulator of neuroinflammation.^{70–72} RMC1 is a subunit of the CCZ1-MON1 RAB7A guanine exchange factor (GEF), and is essential for the proper functioning of endosomal/autophagic flux.⁷³ The NPC1 protein mediates intracellular cholesterol trafficking, and defects in *NPC1* result in a neurodegenerative disorder known as Niemann-Pick type C disease.⁷⁴ The POC5 protein, a crucial centriolar protein involved in both cell cycle progression and centriole elongation, has been identified as a potential causative gene for adolescent idiopathic scoliosis.⁷⁵ SOX7 has been recognized as a member of the SOX (SRY-related HMG-box) family of transcription factors, mainly involving in tumorigenesis and development,^{76,77} as well as muscle satellite cell development.⁷⁸ The *PMS2P11* gene is a pseudogene with unknown functions. Further investigation is necessary to determine the influence of these genes' expression in brain tissues on the occurrence and development of OSA and BMI.

Notably, in tissues associated with OSA and BMI—including adipose, heart, and lung tissues, which were not highlighted in MAGMA analysis—numerous expression-tissue pairs exhibited concurrent significance for both conditions. Among these genes, examples like *SULT1A1*,⁷⁹ *LIN7C*,⁸⁰ *SH2B1*,⁸¹ and *C1QTNF4*⁸² have established associations with obesity, yet their roles in OSA remain underexplored. The genes identified within these tissues may unveil potential shared pathophysiological mechanisms between OSA and BMI, meriting further detailed research.

It is necessary to acknowledge several study limitations. First, the GWAS summary statistics for both OSA and BMI in this study were derived from individuals of European ancestry, limiting the generalizability of our results to populations of non-European ancestry. Second, OSA prevalence in women is significantly lower than in men.⁸³ However, sex-specific analysis was precluded due to the unavailability of data. Third, the potential pleiotropic SNPs, genes and tissues identified in our study were based on computer algorithms, which should be interpreted with caution. Therefore, more animal and clinical studies are needed to investigate the potential mechanisms underlying OSA and BMI.

Conclusion

In summary, our study has uncovered an inherent genetic link underlying OSA and BMI, as evidenced by genetic correlation, causal relationship, and pleiotropic SNPs-associated gene and tissues. The results of our study enhance comprehension regarding the shared genetic basis between OSA and BMI. Future investigation is necessary to authenticate our discoveries and explore innovative pharmacological interventions targeting on the central nervous system for managing OSA and obesity.

Abbreviations

OSA, obstructive sleep apnea; BMI, body mass index; GWAS, genome-wide association study; GTEx, Genotype-Tissue Expression database; LDSC, linkage disequilibrium score regression; HDL, high-definition likelihood; LD, linkage disequilibrium; MAF, minor allele frequency; ρ -HESS, rho-heritability estimation from summary statistics; MR, Mendelian randomization; SNP, single nucleotide polymorphism; IVW, inverse variance weighted; MR-PRESSO, MR pleiotropy residual sum and outlier analysis; MTAG, Multi-Trait Analysis of GWAS; FDR, false discovery rate; CPASSOC, Cross Phenotype Association; VEP, Ensembl Variant Effect Predictor; MAGMA, Multi-marker Analysis of GenoMic Annotation; SMR, Summary-data-based Mendelian Randomization; eQTL, expression quantitative trait loci; HEIDI, heterogeneity in dependent instruments.

Data Sharing Statement

The GWAS summary statistics for OSA and BMI are publicly available from <https://r9.finngen.fi/>, and <https://gwas.mrcieu.ac.uk/>, respectively.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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