Dissecting shared genetic architecture between obesity and multiple sclerosis

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Summary

Background Observational studies have associated obesity with an increased risk of multiple sclerosis (MS). However, the role of genetic factors in their comorbidity remains largely unknown. Our study aimed to investigate the shared genetic architecture underlying obesity and MS.

Methods By leveraging data from genome-wide association studies, we investigated the genetic correlation of body mass index (BMI) and MS by linkage disequilibrium score regression and genetic covariance analyser. The casualty was identified by bidirectional Mendelian randomisation. Linkage disequilibrium score regression in specifically expressed genes and multimarker analysis of GenoMic annotation was utilised to explore single-nucleotide polymorphism (SNP) enrichment at the tissue and cell-type levels. Shared risk SNPs were derived using cross-trait meta-analyses and Heritability Estimation from Summary Statistics. We explored the potential functional genes using summary-data-based Mendelian randomization (SMR). The expression profiles of the risk gene in tissues were further examined.

Findings We found a significantly positive genetic correlation between BMI and MS, and the causal association of BMI with MS was supported ($\beta = 0.22$, $P = 8.03E\text{-}05$). Cross-trait analysis yielded 39 shared risk SNPs, and the risk gene *GGNBP2* was consistently identified in SMR. We observed tissue-specific level SNP heritability enrichment for BMI mainly in brain tissues for MS in immune-related tissues, and cell-type-specific level SNP heritability enrichment in 12 different immune cell types in brain, spleen, lung, and whole blood. The expressions of *GGNBP2* were significantly altered in the tissues of patients with obesity or MS compared to those of control subjects.

Interpretation Our study indicates the genetic correlation and shared risk genes between obesity and MS. These findings provide insights into the potential mechanisms behind their comorbidity and the future development of therapeutics.

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Keywords: Obesity; Multiple sclerosis; Body mass index; Shared genetic architecture

Research in context

Evidence before this study

Several observational studies have revealed that children with a higher body mass index (BMI) are associated with a higher risk of developing multiple sclerosis (MS) in later life. However, the role of genetic factors in their comorbidity remains largely unknown.

Added value of this study

In this study, by leveraging data from genome-wide association studies, we found significant genetic correlation and identified shared risk SNPs between BMI and MS. We further identified a putative functional gene shared between obesity and MS. These findings could provide insights into the shared genetic architecture between obesity and MS.

Implications of all the available evidence

Our study highlights the importance of early detection and prevention of neurodegenerative disorders, including MS, amongst overweight and obese people. New therapeutics for the two diseases could be explored, and it is promising to develop modalities targeting both diseases based on their shared genetic architecture. Moreover, our findings might provide new understandings for the pathogenesis of the two diseases, and inspire future research to keep digging into their comorbidity.

Introduction

Obesity is a growing health and economic issue.[1,2] It is often comorbid with a wide range of conditions, including neurodegenerative disorders.[3,4] In recent years, growing evidence from observational studies has illustrated the associations between obesity and multiple sclerosis (MS). MS is a debilitating chronic demyelinating and neurodegenerative disease of the central nervous system, and leads to an impaired quality of life and disability.[5]

Several observational studies have revealed that children with a higher body mass index (BMI) have a higher risk of developing MS later in life.[6–8] Amongst children with obesity, a 101% higher risk of developing MS compared to normal-weight children was revealed by a meta-analysis.[9] In addition, previous Mendelian randomisation (MR) studies have indicated the potential causal effect of BMI on MS.[10–13] These epidemiological studies provide hints of shared genetic risk components between obesity and MS. However, more updated data are needed to evaluate their causality, and the shared genetic architecture between obesity and MS remains largely unknown.

Understanding the causality and biology underlying this association is important for deciphering the aetiology of MS and can potentially provide therapeutic insights. Several mechanisms have been proposed. Studies suggest that obesity aggravates central inflammation and disability in multiple sclerosis.[14,15] Alterations in hormones and gut microbiota in patients with obesity might also account for the development of MS.[16–18] Clearly, it is still very challenging to obtain a full picture of this complex link. Studying the shared genetic risk components could potentially provide a unique perspective in this direction.

Here, using large-scale genome-wide association study (GWAS) summary statistics (Fig. 1), we aimed to investigate the genetic correlation, causal association, and shared risk loci with potential functions between obesity and MS, to provide insights into their comorbidity.

Methods

Datasets

GWAS summary statistics

Effect estimates for SNPs associated with BMI, which was calculated by weight and height information of included participants, were obtained from the GWAS meta-analysis by the Genetic Investigation of Anthropometric Traits (GIANT) consortium, which involved 2.4 million HapMap 2 SNPs from approximately 0.7 million participants.[19] GWAS summary results for MS were derived from the meta-analysis by the International MS Genetics Consortium (IMSGC), which included 15 datasets involving 26,703 controls and 14,802 MS cases of European ancestry, and the diagnostic criteria had been reported in each included studies.[20] The collection of samples, quality control, and imputation methods for each study have been previously described.[19,20]

Bulk-tissue RNA sequencing gene expression data

In the subsequent linkage disequilibrium score regression (LDSC)-specifically expressed genes (SEG) and

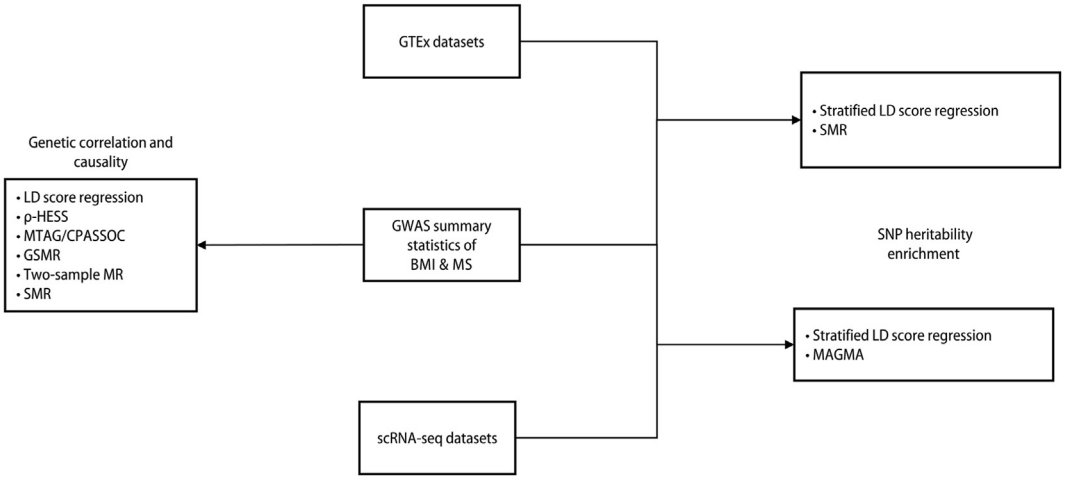

***Fig. 1:* Overview of statistical analyses performed in the study.** CPASSOC: Cross Phenotype Association; GNOVA: Genetic covariance analyser; GSMR: Generalised summary-data-based Mendelian randomisation; GWAS: Genome-wide Association Study; LD: linkage disequilibrium; MAGMA: Multi-marker Analysis of GenoMic Annotation; MTAG: Multi-Trait Analysis of GWAS; MR: Mendelian Randomisation; ρ-HESS: Heritability Estimation from Summary Statistics; scRNA-seq: single-cell RNA sequencing; SMR: Summary-databased Mendelian randomisation.

summary-data-based Mendelian randomisation (SMR) analysis, we obtained bulk-tissue RNA-seq gene expression data from the Genotype-Tissue Expression (GTEx) project, which is a public data resource of gene expression in 53 nondiseased human primary tissues.[21] We download the GTEx v6p dataset, which has been fixed.[22] We then chose the lite version of the GTEx V8 expression quantitative trait locus (eQTL) summary data ($P < 1 \times 10^{-5}$). cis-eQTL summary statistics for whole blood were downloaded for the downstream analysis from eQTLGen, a meta-analysis of 14,115 individuals.[23]

Single-cell RNA sequencing gene expression data

We obtained four single-cell RNA sequencing (scRNA-seq) resources from human lung (N = 57,020 cells), spleen (N = 94,257 cells), and whole blood from 10X Genomics Chromium and mouse brain (N = 133,509,876 cells).[24,25] The "EWCE" R package was utilised to process the scRNA-seq data and convert mouse genes to human gene symbols.[26]

Statistical analyses

Heritability and genetic correlation

LDSC is a useful method to estimate the genetic correlation for multiple traits or diseases.[27] Based on the precomputed LD scores of the 1000 Genomes projects, which were calculated for SNPs in the HapMap 3 SNP set, we removed SNPs that did not match the reference panel (MAF $\leq$ 0.01 or INFO score $\leq$ 0.9) and reformatted new GWAS summary statistics.[28] We estimated single-trait SNP heritability for BMI and MS using stratified linkage disequilibrium score regression (SLDSC) with the baseline-LD model. According to the recommendation, we set the population prevalence and observed sample prevalence as 0.0003 and 0.63, respectively, to convert observed scale heritability to the liability scale. Then we performed bivariate LDSC without constraining the intercept to estimate the r_g value, representing genetic correlations between MS and BMI, and selected the suggestive ($P < 0.05$) genetic associations as the significant correlation.[29,30] Sensitivity analyses were conducted based on LDSC with the single-trait heritability intercept constrained. Because there was no sample overlap in our two traits, we set all single-trait intercepts to 1 and all cross-trait intercepts to 0.

Genetic covariance analyser (GNOVA) was supplemented to estimate the SNP-based heritability and genetic correlation between BMI and MS.[31] GNOVA estimates genetic covariance based on all genetic variants shared between two GWAS summary statistics. Genetic correlations were then calculated based on variant heritability and genetic covariance. Calculations were based on the 1000 Genomes Project's European population-derived reference data using default parameters. In addition, sample overlap correction between two different sets of GWAS summary statistics was statistically calculated. Compared to LDSC, GNOVA provides higher estimation accuracy for genetic correlations and more powerful statistical inference.[31]

Cross-trait meta-analysis

To detect the shared risk SNPs in BMI and MS, we performed two cross-trait meta-analyses, including multi-trait analysis of GWAS (MTAG) and cross-phenotype association test (CPASSOC).[32–34] MTAG is a generalised meta-analysis method that enhances statistical power to estimate the genotypic and phenotypic

variance-covariance matrices to generate trait-specific estimates for each SNP. SNPs were restricted with a minor allele frequency (MAF) ≥ 0.01 and sample size $N \geq (2/3) \times 90^{th}$ percentile. MTAG adjusts for possible errors by using bivariate LD score regression when sample overlap is present. MTAG is suitable when all variants have the same effect sizes on traits and generate trait-specific association statistics. We calculated the upper bound for the false discovery rate ('maxFDR') to examine the assumptions on the equal variance-covariance. In addition, as a sensitivity analysis, CPASSOC integrates association evidence from multiple traits' GWAS summary statistics when the variant is correlated to at least one trait. We utilised the SHet version to assume heterogeneous effects across traits. The SNP set was obtained by applying pairwise LD pruning with $r^2 = 0.2$ using the software "PLINK". We prioritised independent SNPs that were genome-wide significant ($P < 5 \times 10^{-8}$) in the cross-trait meta-analyses using both MTAG and CPASSOC and were in significant regions identified by ρ-HESS.

Identification of local genetic correlations

Heritability Estimation from Summary Statistics (ρ-HESS) is a method to estimate local SNP-heritability and genetic correlation.[35] We estimated the local genetic correlations to examine whether BMI shared genetic correlation with MS at the local independent region in the genome using ρ-HESS. There were 1699 potential regions that were approximately LD-independent loci, with an average size of nearly 1.5 MB.[36] Then we calculated the local SNP heritability for two traits and the genetic correlation between two traits using the 1000 Genomes Project as the reference provided on the ρ-HESS webpage. The pairwise GWAS (GWAS-PW) method was also used to examine shared genomic regions by BMI and MS.[37] GWAS-PW can provide estimations of the posterior probability for the locus shared by both traits (PPA3), or the locus associated with both traits but by distinct causal variants (PPA4). The threshold of PPA3/4 > 0.8 was used in our models.

Mendelian randomisation

To explore putative causal relationships between BMI and MS, the R packages "TwoSampleMR" and "GSMR" were used for suggestive associations ($P < 0.05$). We undertook Mendelian randomisation analysis, mainly including five MR methods, MR-Egger, inverse variance weighting (IVW), weighted median, weighted mode, and generalised summary-data-based Mendelian randomisation (GSMR) with different assumptions about horizontal pleiotropy.[38–41] Briefly, when there is one single genetic variant, the Wald ratio is used to calculate the causative effect between the exposure and the outcome. Using the meta-analysis approach, IVW analysis can estimate the causal effects of two phenotypes. The MR-Egger method further added a weighted linear regression of the gene–outcome coefficients for non-measured horizontal pleiotropy, which allows for the presence of directional uncorrelated pleiotropy. The pleiotropy test and heterogeneity test were conducted by the MR-Egger intercept test and Cochran's Q statistic. We used single SNP effect analysis and MR-PRESSO analysis to detect pleiotropy and outliers.[42] The variants were mainly selected based on three assumptions: (1) they are correlated with the exposure; (2) they are not dependant on confounding factors; and (3) they do not directly generate effects on the outcome. For these five methods, we selected SNPs with genome-wide significance ($P \leq 5 \times 10^{-8}$) of the exposure trait as instrumental variables. F statistics for each instrument were estimated by $F = \beta^2/SE^2$, and an F statistic < 10 was regarded as insufficiently informative for further analysis.[43] The study power (at $\alpha = 0.05$) was calculated to illustrate a causal effect depending on the percentage of risk factor variance accounted for by instruments.[44] The heterogeneity Q statistics were calculated, and the leave-one-out method was used as the sensitivity analysis.

LDSC-SEG analysis

We performed LDSC-SEG to investigate whether SNP heritability for BMI and MS is evident for trait-tissue relevance inference.[45] The 1000 Genomes Phase 3 of European ancestry was utilised as a reference panel to calculate LD scores, and SNPs only in HapMap 3 with MAF > 0.05 were included as input. Based on the baseline model and all gene sets, we ranked genes from the GTEx project by computed t-statistics reflecting critical tissue types and their specific expression in 53 tissues. We obtained the top 10% of specifically expressed candidate genes with the highest t-statistic to estimate the significance of tissue type-specific SNP heritability enrichment. The coefficient *P* values were calculated based on the regression coefficient Z score, and the Benjamini-Hochberg FDR-corrected *P* value of $< 5 \times 10^{-3}$ was determined as significant for enrichment tissues across the two traits.

Cell type enrichment analyses using scRNA-seq datasets

We conducted Multimarker Analysis of GenoMic Annotation (MAGMA) cell typing to evaluate the gene-level genetic correlation between BMI and MS GWAS traits and cell type expression specificity.[46] Cell types across the four tissues were considered significant in MAGMA with a *P* value < 0.05. The cell type specificity matrix for scRNA-seq used in MAGMA was calculated using Expression Weighted Cell Type Enrichment, "EWCE" and the "MAGMA_Celltyping" R package.[47]

Summary-data-based Mendelian randomization

We conducted SMR analysis to identify candidate risk genes with possible causal effects and SNPs significant in cross-trait meta-analyses of BMI and MS.[48] We used GWAS and eQTL data to detect the association between

trait-associated SNPs and gene expression. The heterogeneity in dependent instrument (HEIDI) test was applied to distinguish linkage in the causal association. Genomic expression data from GTEx V8 and cis-eQTL summary data from eQTLGen were used for the eQTL expression data of whole blood.[23,49] As a default, we removed SNPs in strong LD with an $r^2 > 0.9$ and with top associated eQTLs if MAF > 0.01. Expression probes with eQTL $P \leq 5 \times 10^{-8}$ were selected as the top associated variants. All SNPs were extracted by genome-wide complex trait analysis (GCTA) software, ensuring their independence.[50] SMR significant probes were selected using Bonferroni-corrected thresholds for SMR *P* values (0.05/number of probes) and HEIDI test *P* value thresholds >0.05 to indicate the lack of heterogeneity.

Validation of expressions of the risk gene

The expression profiles of adipose tissues, brain lesions, and peripheral blood mononuclear cells were evaluated for the risk gene by the datasets GSE9624, GSE38010, and GSE21942.[51–53] The GSE9624 dataset involved omental adipose tissues from obese and normal-weight children.[51] The GSE38010 dataset included histologically characterised MS brain lesions and control brain samples.[52] The GSE21942 dataset contained peripheral blood mononuclear cells from MS patients and controls.[53] The Mann–Whitney U test was used to evaluate the differences in gene expression between the diseased group and the control group. Analyses of the data were performed using R version 4.1.0 (R Project for Statistical Computing, Vienna, Austria), Python 2.7 (Python Software Foundation, Wilmington, US), or GraphPad Prism 8.0 (GraphPad Software, San Diego, US).

Ethics

Since the included studies had been approved by their independent review boards, additional ethical approval is not required in our study based on summary-level data.

Role of funders

Funders had no role in the in the study design, data collection, data formal analysis nor interpretation or writing of the report.

Results

Estimation of genetic correlations between obesity and MS

We used bivariate LDSC to estimate the genetic correlation (without constrained intercept) between BMI and MS ($r_g = 0.08$, $P = 3.45 \times 10^{-8}$, LDSC, Supplementary Fig. S1 and Table S1). The liability-scale SNP heritability estimates were 21.2% and 4.6% for the BMI and MS traits, respectively. The intercept of genetic covariance was calculated at approximately 0.01, indicating mild sample overlapping between BMI and MS. After constraining the LDSC intercept on the assumption of no sample overlap, the genetic correlation was slightly weaker but remained significant (Supplementary Fig. S1 and Table S1). Analyses by GNOVA also demonstrated a positive and consistent genetic association between BMI and MS (Supplementary Table S1).

Identification of genomic risk regions for BMI and MS

Given the strong genetic relationships between BMI and MS, we conducted MTAG to improve our power to identify genetic SNPs shared between traits. A total of 39 genome-wide significant SNPs ($P < 5 \times 10^{-8}$) were revealed in both MTAG and CPASSOC (Supplementary Table S2), including 18 newly identified shared SNPs (rs11647753, rs11649612, rs12716972, rs12716974, rs2289292, rs3809624, rs4407979, rs4609871, rs2306589, rs2306593, rs8070260, rs8882, rs9906189, rs1044821, rs11667487, rs2302299, rs4808762, rs8112975). The maxFDR values for MTAG analyses of BMI and MS were 1.4×10^{-6} and 1.8×10^{-2} respectively. Furthermore, the MTAG results were highly consistent with those generated by CPASSOC, indicating that the MTAG results are reliable and that bias in MTAG assumptions is likely to be negligible. Eventually, 13 risk SNPs were found to be consistently significant when examined by ρ-HESS, and the shared loci were verified by GWAS-PW (PPA4 > 0.8, Supplementary Table S3).

The local genetic correlation was estimated, and 57 suggestively significant regions were identified ($P < 0.05$, ρ-HESS, Supplementary Table S4). There was close agreement in the average local genetic correlation in regions harbouring BMI-specific loci or MS-specific loci (Fig. 2a and b and Supplementary Fig. S2). We estimated the local single-trait SNP heritability for BMI ($h^2 = 22.4\%$) and MS ($h^2 = 23.5\%$) (Table 1). Compared with bivariate LDSC, genome-wide local genetic correlations calculated by ρ-HESS between MS and BMI ($r_g = 0.0428$) were all largely consistent (Table 1).

Evidence for causality between BMI and MS

We conducted bidirectional MR to explore the potential causal effect and whether the shared genetic background between BMI and MS was consistent with pleiotropy. The IVs were selected after evaluation based on the three assumptions (Supplementary Table S5). The F statistics for the instrumental variables ranged from 28.6 to 1360.3, indicating that the probability of weak instrument bias was low. We conducted various bi-directional MR methods to test the stability of relationships for a more stable result. We found evidence to support the causality of BMI on MS in five methods (IVW β = 0.22, SE = 0.06, *P* = 8.03E-05; GSMR β = 0.32, SE = 0.05, *P* = 6.15E-13; Fig. 3 and Supplementary Fig. S3 and Table S6) with no significant evidence of heterogeneity (IVW Q = 356.49, *P* = 0.99, Supplementary Table S6). The leave-one-out analysis indicated the effect was not driven by any

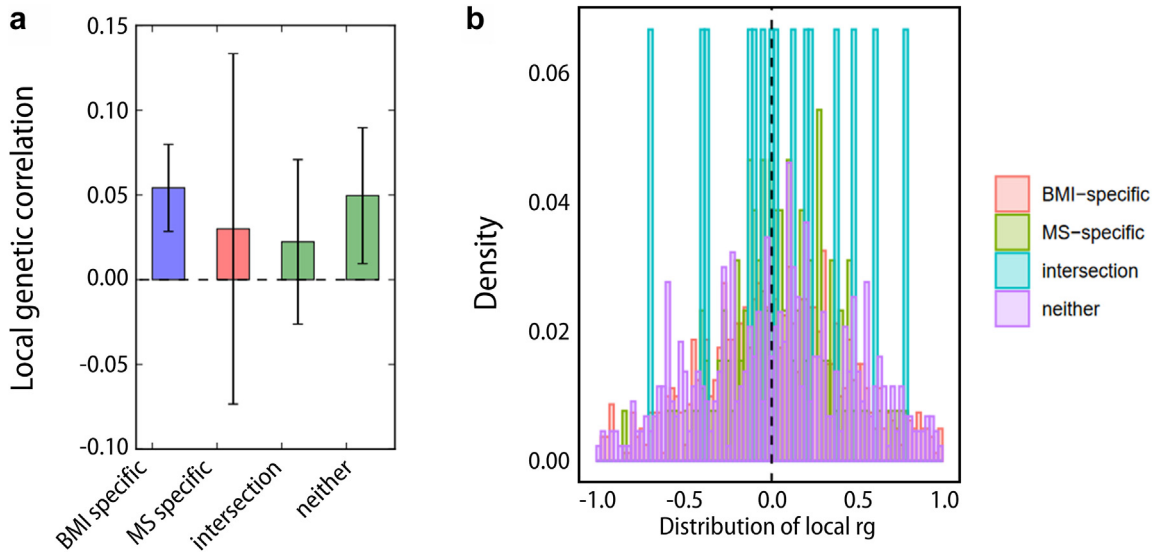

Fig. 2: **Local genetic correlations (r_g) between BMI and MS.** (a) Average local r_g estimates for two traits in regions harbouring disease-specific risk variants, regions harbouring shared risk variants ("intersection"), and all other regions ("neither"). Local genetic correlations with estimates less than −1 or greater than 1 were forced to −1 or 1, respectively. Error bars represent the 95% confidence intervals (CIs), which were calculated using a jackknife method. (b) Density distribution of local r_g estimates for two traits in disease-specific regions (red, green), intersection regions (blue) and other (purple) regions. BMI, body mass index; MS, multiple sclerosis.

single SNP (Supplementary Fig. S4a). The estimated power to detect a causal effect for BMI on MS was 100.0%. In the reverse analyses, all these methods except GSMR identified a nonsignificant causal effect of MS on BMI (IVW β = 4.47E-03, SE = 4.23E-03, P = 0.29; GSMR β = 0.04, SE = 0.01, P = 1.32E-3; Supplementary Table S6). The leave-one-out analysis was shown in Supplementary Fig. S4b.

Tissue-level SNP heritability enrichment in BMI and MS

To identify in which tissue these shared SNPs take effect, we used the LDSC-SEG method to identify specific tissues in which genes with increased expression were enriched in SNPs, using publicly available GWAS data and genotype tissue expression data from GTEx. After adjusting for the baseline model, we identified FDR-significant ($P < 5 \times 10^{-3}$, LDSC-SEG) SNP heritability enrichment for BMI across 9 tissues (Fig. 4a and Supplementary Table S7), particularly for central nervous system (CNS)-related tissues, including the frontal cortex, anterior cingulate cortex, nucleus accumbens, putamen, caudate, hypothalamus, cerebellar hemisphere, cerebellum, and cortex. For MS, a total of 4 tissues were significantly enriched, particularly for blood and immune-related tissues, including the spleen and Epstein–Barr virus (EBV)-transformed lymphoblastoid cell lines (LCLs) (Fig. 4b and Supplementary Table S7).

	Method	Body mass index	Multiple sclerosis
Heritability h^2	LDSC	0.2119	0.0457
Heritability h^2	GNOVA	0.1885	0.1385
Heritability h^2	ρ-HESS	0.2240	0.2350
Genetic correlation r_g	LDSC	0.0796	
Genetic correlation r_g	GNOVA	0.0647	
Genetic correlation r_g	ρ-HESS	0.0428	

LD: linkage disequilibrium. GNOVA: Genetic covariance analyser; ρ-HESS: Heritability Estimation from Summary Statistics.

Table 1: **Heritability and genetic correlation between body mass index and multiple sclerosis.**

Cell-level SNP heritability enrichment in BMI and MS

We utilised publicly available scRNA-seq datasets of four tissues enriched in LDSC-SEG, including brain, spleen, lung, and whole blood, to evaluate the gene-level genetic association with cell type expression specificity for BMI and MS. In the lung dataset, we found significant enrichment at $P < 0.05$ (MAGMA) for both BMI and MS in mature B cells, naive B cells, mast cells, natural killer (NK) cells, dividing NK cells, $CD4^+$ T cells, $CD8^+$ cytotoxic T lymphocytes, dividing T cells, regulatory T cells, activated dendritic (DC) cells, plasmacytoid DC cells, and monocytes. We observed a significant enrichment across NK_FCGR3Apos in spleen tissue. Cells in the brain and in peripheral blood mononuclear cell (PBMC) tissues were not coenriched in BMI and MS traits. The

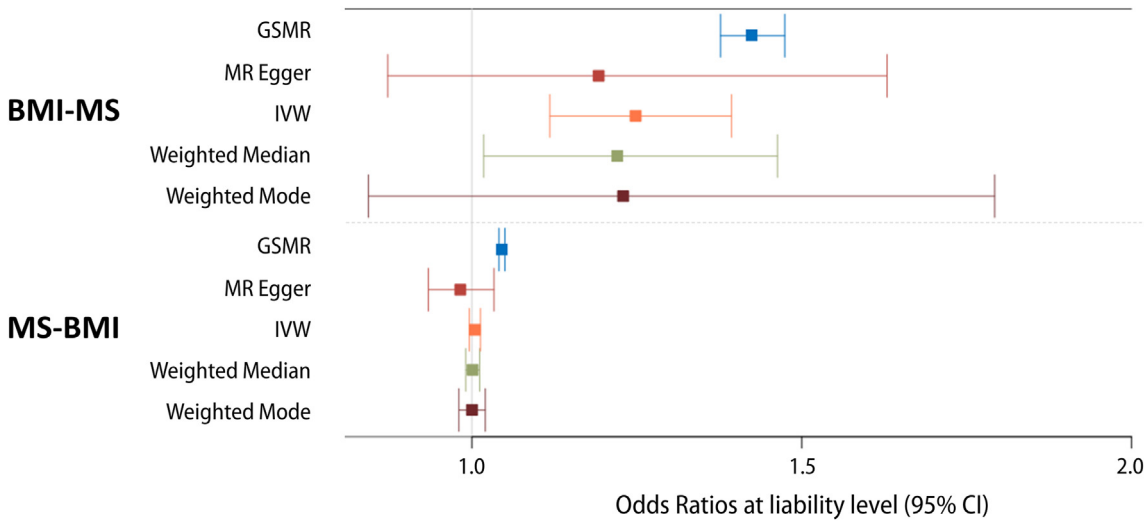

***Fig. 3:* Summary of bi-directional MR analyses between BMI and MS.** BMI, body mass index; GSMR: Generalised summary-data-based Mendelian randomisation; IVW: inverse variance weighting; MS, multiple sclerosis. Error bars represent the 95% confidence intervals for the associated MR estimates.

enriched cells in four tissues for BMI and MS are listed separately (Supplementary Figs. S5–S8).

Identification of shared functional genes for BMI and MS

We applied SMR to infer causality and identify the putative functional genes for BMI and MS, by jointly analysing GWAS summary data and whole blood eQTL summary data from eQTLGen and GTEx. We identified 12 shared risk genes, including *FAM213B*, *GGNBP2*, *HLA-B*, *HLA-C*, *MAST3*, *MICB*, *MYO19*, *PRXL2B*, *TBX6*, *TNFRSF14*, *TRAF3*, and *ZNHIT3*, of which only one gene, *GGNBP2*, was shared between BMI ($P_{SMR} = 3.69 \times 10^{-19}$, $P_{HEIDI} = 0.11$, topSNP: rs11263770) and MS ($P_{SMR} = 2.41 \times 10^{-7}$, $P_{HEIDI} = 0.98$, topSNP: rs11650008) and passed the HEIDI-outlier test in cis_eQTL data (Supplementary Table S8). More importantly, *GGNBP2* was also identified as one of the genetically shared variants in previous cross-trait meta-analysis phenotypes between BMI and MS.

Differential expressions of GGNBP2

The mRNA expressions of *GGNBP2* in tissues of patients with obesity or MS, and control subjects were

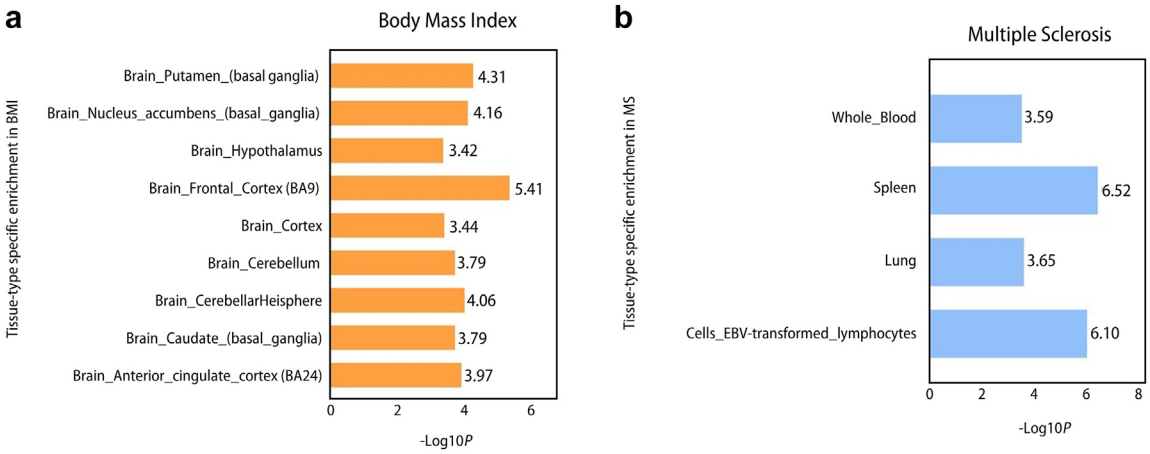

***Fig. 4:* Tissue type-specific enrichment of SNP heritability for BMI and MS estimated using LDSC-SEG.** (a) The heritability enrichment of tissues for BMI; (b) The heritability enrichment of tissues for MS. The x axis displays negative $\log_{10}$ *P*-values of coefficient Z-scores for each individual test. BMI, body mass index; MS, multiple sclerosis; SNP, single nucleotide polymorphism; LDSC-SEG: linkage disequilibrium score regression applied to specifically expressed genes.

further evaluated. The expression of *GGNBP2* was significantly increased in the adipose tissue of obese individuals compared to control subjects (Supplementary Fig. S9a, $P < 0.05$, unpaired t-test). In addition, *GGNBP2* expression was also enhanced in peripheral blood nuclear cells of MS patients compared to that in healthy controls (Supplementary Fig. S9b, $P < 0.0001$, unpaired t-test). In MS brain lesions, the expression of *GGNBP2* was generally raised compared to normal brain tissue, while studies involving more participants are warranted to increase the statistical power (Supplementary Fig. S9c, $P = 0.09$, unpaired t-test).

Discussion

In this study, we present evidence of causality and overlapping genetic architecture of BMI with MS. Our results provide new insights into their comorbidity, and might contribute to the prediction, diagnosis, and treatment of diseases.

We found a significant genetic correlation between BMI and MS, which supported the hypothesis that genetic factors play an important role in the comorbidity of obesity and MS. From the cross-trait meta-analysis, 39 SNPs were identified in both MTAG and CPASSOC analysis, in which 13 suggestively significant SNPs were located in the ρ-HESS-estimated significant genomic regions. We used two different statistical analysis methods, MTAG and CPASSOC, to reduce possible bias caused by potential sample overlap and further explored the risk SNPs obtained from MTAG with CPASSOC. Our results showed that the SNPs identified by MTAG were all consistently significant in the CPASSOC analysis, which improved the reliability of our findings. The causality of BMI on MS was consistent with previous studies,[10,54] and the sensitivity analyses confirmed the robustness of the findings.

In addition to the IVW methods, different statistical methods for Mendelian randomisation analysis were used to evaluate the robustness of our results. The MR-Egger regression yields less biased estimates and lower power than the IVW method.[55] The weighted-median method is able to provide effect estimates with lower bias than the IVW method, whereas a high type 1 error rate has been observed.[56] The weighted-mode method generally has a decreased bias and a type 1 error rate, whereas its power to detect a causal effect is low.[56] The GSMR method utilises the generalised least-squares approach to generate estimates, compared to the variance–covariance matrix used by the IVW method.[57] Since three of the five methods for the causal estimates of BMI on MS were statistically significant, the effect was considered robust in this study.

Functional enrichment for gene expression in multiple tissues and cells was also investigated using the GTEx datasets. We identified 9 tissues, mainly the brain, with significant SNP heritability enrichment for the BMI trait. Growing evidence also suggests that susceptibility to obesity is distributed across multiple brain regions and is strongly associated with structural abnormalities.[58–60] The enrichment results of the MS trait were mainly reflected in immune tissues, including the spleen and LCLs, which suggests the involvement of local immune responses in the development of MS. This is consistent with previous literature demonstrating a strong relationship between MS and immune dysregulation.[61] EBV-infected B cells and plasma cells that accumulate in meningeal immune cell collections may contribute to the progressive development of MS.[62] The lung could contribute to the activation and transformation of autoreactive T cells to a migratory mode, which allows them to enter the CNS and induce autoimmune conditions, including MS.[63] Our findings provide evidence to support the involvement of immune responses in MS, and further experimental validation of the enriched tissues and cells is warranted.

Notably, we identified SNP heritability enrichments in different immune cells in the lung and spleen for both BMI and MS. MS is an immunologically heterogeneous disorder, and $CD8^+$ T cells predominate in MS lesions.[64] B-cell depletion may reduce the proinflammatory cytokines produced by B cells, $CD4^+$ and $CD8^+$ T cells, which can effectively reduce MS relapses.[65,66] B cells interact with T helper cells to create a feedforward loop, and the highly pathogenic subsets enter the blood-CNS barriers, which can lead to MS pathological changes.[67] NK and DC cells control T-cell activation in CNS autoimmunity, and reduce the risk of MS.[68,69] Mast cells participate in the pathogenesis of MS by promoting angiogenesis.[70] Our results may provide insights into the pathogenesis of obesity and MS, and the development of therapeutics targeting specific tissues and cell types.

In addition to cross-trait meta-analysis, we also used blood and tissue eQTL data to evaluate whether the BMI-MS association can be mediated by shared risk genes. Amongst the shared risk genes we identified, human leukocyte antigen (HLA) class genes have been identified to recruit macrophages into adipose tissues.[71] In addition, the primary function of HLA class genes is antigen presentation to T cells, which is involved in CNS-directed autoimmunity and MS development.[72] Striking interactions of BMI and HLA genotype with the risk of MS have been observed, which confirms our findings.[73] Using SMR and HEIDI, we discovered that *GGNBP2* might serve as another potential link between the two traits, and transcriptomic analyses using patient samples verified our findings. Prior studies have documented the biological relationship between *GGNBP2* and BMI. *GGNBP2* is a tumour suppressor gene involved in several types of cancer, such as glioma,[74] breast cancer,[75] and prostate cancer.[76] *GGNBP2* is also a shared gene for ALS and obesity-related traits.[77] Further investigations into the mechanisms of *GGNBP2* on obesity and MS pathogenesis are needed.

Numerous attempts have been made to evaluate the association between obesity and MS. Several MR studies have revealed the causal effect of BMI on MS.[10–13] However, the summary statistics used in previous studies were relatively outdated or smaller-scale, and previous evidence on their shared genetic basis is scarce. The prevalence of obesity is still rising globally, which is a great threat to public health.[78] To date, no curative treatment is available for multiple sclerosis.[79] Therefore, our study highlights the importance of early detection and prevention of neurodegenerative disorders, including MS, amongst overweight and obese people. New therapeutics for the two diseases could be explored, and it is promising to develop modalities targeting both diseases based on their shared genetic architecture. Moreover, our findings might provide a new understanding for the pathogenesis of the two diseases and inspire future research to continues to investigate their comorbidity. Our study could contribute to the improvement of disease management for patients with obesity or MS.

Caveats and limitations

Our study also has several limitations. Potential sample overlap might exist between the GWAS datasets from GIANT and IMSGC, both of which used samples from the Wellcome Trust Case Control Consortium (WTCCC) cohorts. However, this effect would be small since the samples from the WTCCC comprised ~2.5% of the samples from the GIANT consortium. In addition, the results of this study were based on individuals of European ancestry, and therefore our findings have limited generalisability to other ancestral populations. The initially identified shared regions did not strictly pass the threshold after Bonferroni correction (0.05/1699), while it was exploratory and part of the regions could be validated by other methods, which were considered more reliable. Moreover, based on the information from our study, further *in vitro* and *in vivo* studies could be conducted to evaluate the function and mechanisms of *GGNBP2* in obesity and MS.

Conclusion

In summary, we found a significant genetic correlation and identified shared risk SNPs between BMI and MS. We further identified a putative functional gene, *GGNBP2*, shared between obesity and MS. These findings could provide insights into the shared genetic architecture between obesity and MS, and contribute to a better understanding of their pathogenesis as well as the development of therapeutics.

Contributors

Conceptualisation and design: FWL, WHS, and HC; Funding acquisition: WHS and HC; Collection and assembly of data: JR, WTH, and JXW; Data analysis and interpretation: JR, WTH, JXW, RJZ, LJZ, YYM, YJW, MJM, HL, and QZL; Manuscript writing: RJZ, RJ, WTH and HC. RJ, WTH, and HC have directly accessed and verified the underlying data reported in the manuscript. All authors reviewed and approved the final manuscript.

Data sharing statement

Data source

GWAS summary statistics for MS are available by application from: https://imsgc.net/?page_id=31.

GWAS summary statistics for BMI are available by application from: http://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files.

The gene expression data are available from: https://www.ncbi.nlm.nih.gov/geo/.

The eQTL summary data for eQTLGen and GTEx are available from: https://www.eqtlgen.org/cis-eqtls.html; http://yanglab.westlake.edu.cn/software/smr/#eQTLsummarydata.

scRNA-seq data are available from: Whole blood: https://www.10xgenomics.com/resources/datasets; Lung and Spleen: https://doi.org/10.1186/s13059-019-1906-x; Brain: https://doi.org/10.1016/j.cell.2018.06.021; Small Intestinal Epithelium: https://singlecell.broadinstitute.org/single_cell/study/SCP44/small-intestinal-epithelium.

Code availability

The codes used in this study can be found at:

LDSC: https://github.com/bulik/ldsc.

PLINK: https://www.cog-genomics.org/plink/1.9.

MTAG: https://github.com/JonJala/mtag.

CPASSOC: http://hal.case.edu/~xxz10/zhuweb/.

GSMR: http://cnsgenomics.com/software/gsmr/.

TwoSampleMR: https://mrcieu.github.io/TwoSampleMR/.

SMR: https://cnsgenomics.com/software/smr/#Overview.

LDSC-SEG: https://github.com/bulik/ldsc/wiki/Cell-type-specific-analyses.

MAGMA Celltyping: https://neurogenomics.github.io/MAGMA_Celltyping.

Declaration of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2023.104647.

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