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Dissecting the genetic determinants and biological associations between body mass index and female reproductive disorders based on genome-wide association study

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Abstract

Background While the phenotypic link between body mass index (BMI) and some female reproductive disorders is well established, the genetic architecture and causal relationships have not been systematically studied. We aimed to create an atlas of the shared genetic associations of BMI and 16 female reproductive disorders and to identify their common risk loci, biological pathways, and potential mechanisms.

Methods We assessed the genetic correlations between BMI and 16 reproductive disorders using summary data from large-scale genome-wide association studies. Cross-trait pleiotropic analysis identified shared loci and genes, while functional annotation and tissue-specific analysis revealed relevant biological pathways and tissues. Multi-trait colocalization analysis examined the role of hormones and metabolites in these traits. Additionally, bidirectional Mendelian randomization (MR) analysis was employed to assess causal relationships between BMI and reproductive outcomes. We also conducted summary data-based MR (SMR) analysis to identify potential drug targets.

Results Our results revealed a significant genetic correlation between BMI and eight female reproductive diseases. Furthermore, we identified 50 shared pleiotropic loci between BMI and these traits, with 21 of them showing significant colocalization, suggesting a complex shared genetic architecture across the genome. In addition, the top biological pathways and tissues enriched with these pleiotropic loci were associated with RNA metabolism, macromolecule biosynthesis, type B pancreatic cell apoptosis, various brain regions, and the pituitary. Moreover, multi-trait colocalization indicated that insulin, lipid metabolites, glucose, glycine, and glutamine mediate shared mechanisms between BMI, gestational diabetes mellitus (GDM), and endometrial cancer. MR analysis suggested

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BMI may cause several reproductive diseases, with only GDM affecting BMI reversely. Finally, SMR analysis revealed *EIF2S2P3* and *MCM6*, which may have a causative effect on both BMI & GDM and BMI & gestational hypertension.

Conclusion Our results suggest a significant genetic link between BMI and eight female reproductive diseases, highlighting a shared and causal genetic basis. Reducing BMI in women may serve as an effective strategy to lower the risk of female reproductive disorders. The identified pleiotropic loci, genes, and shared pathways could provide new therapeutic targets for both obesity and reproductive diseases, along with their comorbidities.

Clinical trial number Not applicable.

Keywords Body mass index, Female reproductive disorders, Genetic architecture, Hormones, Metabolites

Introduction

The prevalence of obesity has been steadily increasing worldwide, with alarmingly high rates observed in both developed and developing nations [1]. This trend is particularly concerning for women of reproductive age, as observational epidemiological studies have revealed that excess body weight is associated with various adverse reproductive outcomes, including infertility, menstrual irregularities, pregnancy complications, and even gynecological cancers [2–6]. Moreover, underweight women also have an increased risk of infertility and recurrent miscarriages [7]. Body mass index (BMI), a common measure of adiposity, is widely used in epidemiological and clinical research as a key tool for assessing obesity and its related health risks [8, 9]. Numerous studies have demonstrated that BMI can serve as a predictor of risk for female reproductive disorders. In a multicenter prospective cohort study, researchers found that women with a BMI ≥ 25 kg/m² had nearly double the risk of developing gestational diabetes mellitus (GDM) during pregnancy compared to those with a BMI < 25 kg/m² [10]. Additionally, a case-control study revealed that women with a BMI > 30 kg/m² had a significantly increased risk of endometrial cancer (EC), with an odds ratio (OR) as high as 4.08 [11].

Obesity is significantly influenced by genetic factors, with heritability estimates ranging from 40 to 70% [12]. BMI, a key indicator of obesity and related health risks, has garnered increasing attention for its genetic basis. Over the past decade, genome-wide association studies (GWAS) have identified approximately 150 genetic loci associated with BMI, offering critical insights into the genetic mechanisms underlying obesity [13]. Female reproductive disorders have unclear heritability estimates, and their genetic underpinnings remain poorly understood due to the complexity of these diseases and the challenges in obtaining comprehensive genetic data. Nevertheless, recent advances have begun to uncover important genetic factors of these diseases. For instance, a large twin study of over 3,100 Dutch twins found 92 cases of polycystic ovary syndrome (PCOS) and reported that 72% of the variance in PCOS risk is attributable to genetic factors, with a monozygotic twin correlation of 0.72 (r^2) and a dizygotic twin correlation of 0.38 (r^2), highlighting the significant genetic contribution to this condition [14]. Moreover, the genetic associations between BMI and female reproductive diseases have garnered increasing attention and validation. Jiang et al. conducted a large-scale genomic analysis revealing significant genetic links between BMI and PCOS, identifying several shared genetic loci [15]. Similarly, genetic variations in BMI have been closely associated with the risk of EC. Hazelwood et al. demonstrated a significant causal relationship between BMI and the risk of EC, showing that each standard deviation increase in BMI corresponded to a 1.88-fold increase in risk [16]. In addition, Prescott et al. found that the genetic risk score of BMI is statistically associated with the risk of endometrial cancer, with each additional 10 BMI-related risk alleles increasing the risk of developing EC by 13% [17]. The genetic susceptibility to gestational hypertensive diseases and GDM is also linked to BMI variations. Specifically, the T allele (CT genotype) of the *AVP* rs3729965 polymorphism [18] and the A allele of the *AGTR2* C4599A polymorphism [19] were found to increase the risk of preeclampsia in pregnant women with a BMI ≥ 25 kg/m². Furthermore, several genetic studies have shown that higher genetically predicted BMI is significantly associated with an increased risk of GDM [20]. Finally, BMI-related genetic variations are also closely associated with the incidence of uterine fibroids (UFs). In Korean women with a BMI greater than 25 kg/m², the A allele and AA genotype of a polymorphism (G870A) in cyclin D1 significantly increased the risk of UFs (OR = 3.61) [21]. These observed epidemiological genetic studies provide valuable insights into the comorbidities of BMI and certain female reproductive disorders. However, the extent to which various female reproductive diseases and BMI share common genetic underpinnings remains uncertain.

In this study, we began by assessing the genetic correlation between BMI and 16 female reproductive diseases using large-scale GWAS summary data. Next, we performed a cross-trait pleiotropic analysis to identify shared loci that could serve as potential intervention targets for the simultaneous prevention or treatment of these conditions. Moreover, pathway enrichment, tissue

enrichment, and multi-trait colocalization analyses were conducted to explore the potential mechanism behind the genetic correlation of BMI and these female reproductive diseases. Finally, we performed bidirectional two-sample MR and summary data-based MR (SMR) analyses to investigate the causal association and shared functional genes between BMI and female reproductive diseases. Our study may provide new insights into the underlying genetic mechanisms and lay the foundation for effective interventions to protect women's reproductive health. The study flowchart is displayed in Fig. 1.

Methods

Data source

We included 16 female reproductive disorders, with GWAS data for 13 of these sourced from the FinnGen

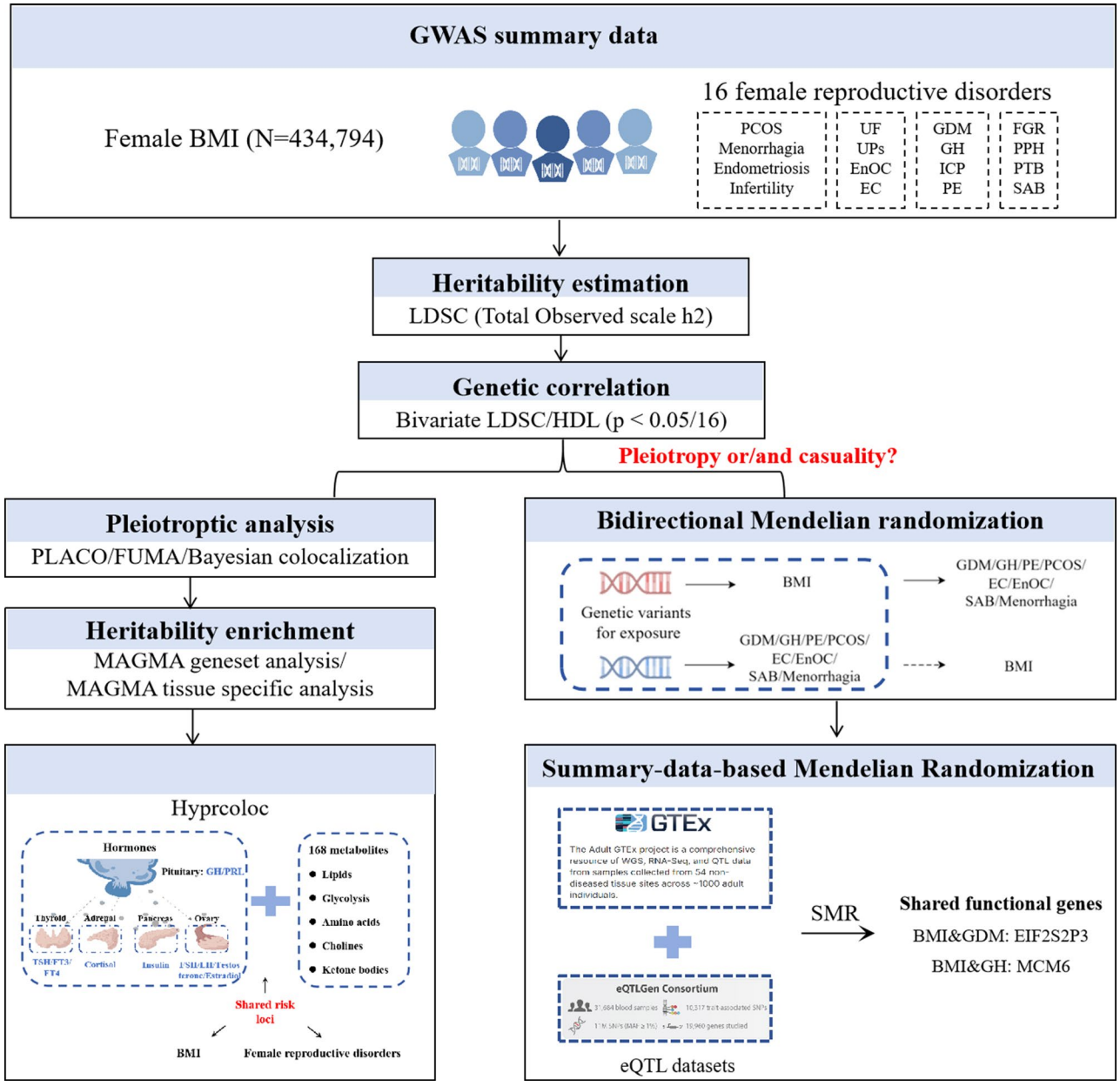

Fig. 1 The overall design followed in the study is shown. BMI, body mass index; PCOS, polycystic ovary syndrome; GDM, gestational diabetes mellitus; GH, gestational hypertension; PE, pre-eclampsia or eclampsia; EC, endometrial cancer; EnOC, endometrioid ovarian cancer; SAB, spontaneous abortion; UFs, uterine fibroids, UPs, uterine polyps; ICP, intrahepatic cholestasis of pregnancy; FGR, poor fetal growth, PPH, postpartum hemorrhage, PTB, preterm labor and delivery; LDSC, linkage disequilibrium score regression; HDL, high-definition likelihood; PLACO, pleiotropic analysis under composite null hypothesis; MAGMA, multimarker analysis of GenoMic annotation; COLOC, colocolization analysis; SMR, summary-data based Mendelian randomization; HyPrColoc, Hypothesis Prioritization Colocalization. TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; FSH, follicle-stimulating hormone; LH, luteinizing hormone; GH, growth hormone; and PRL, prolactin

R11 database (https://www.finngen.fi/en), including UFs, PCOS, GDM, endometriosis, female infertility, uterine polyps (UPs), spontaneous abortion (SAB), gestational hypertension (GH), intrahepatic cholestasis of pregnancy (ICP), poor fetal growth (FGR), postpartum hemorrhage (PPH), pre-eclampsia or eclampsia (PE), and preterm labor and delivery (PTB). For endometrial cancer (EC), we utilized GWAS data from the study by O'Mara et al. [22]; for endometrioid ovarian cancer (EnOC), data from the study by Phelan et al. [23]; and for menorrhagia, data from the study by Gallagher et al. [24]. All reproductive disorders were treated as binary traits. The detailed information of these datasets, including the source of the GWAS data, sample size, and case definitions, is summarized in Table S1.

We used the largest GWAS on female BMI to date, which is a meta-analyzed data from the UK Biobank and the GIANT consortium, involving approximately 700,000 individuals of European ancestry, including 434,794 females with BMI data. The procedures for sample collection, quality control, and imputation have been thoroughly outlined in earlier publications [25, 26].

To ensure the accuracy of the GWAS data, we applied strict quality control measures in this study. First, we excluded SNPs in the major histocompatibility complex (MHC) region (25–35 Mb on chromosome 6) due to its complex gene structure and high linkage disequilibrium, which can lead to false positives. Additionally, we filtered out rare variants by retaining only SNPs with a minor allele frequency (MAF) above 0.01, focusing on common variants to enhance statistical power and reduce false positives.

Cross-trait genetic correlation at the genome-wide level

Linkage Disequilibrium Score (LDSC) is a statistical method used to estimate heritability and genetic correlation from GWAS summary data. In the LDSC analysis, LD scores were computed using common SNPs from European ancestry samples in the 1000 Genomes Project [27]. We conducted the LDSC genetic correlation analysis to calculate the shared genetic factors between BMI and the 16 female reproductive disorders, by dividing the shared genetic variance by the square root of the product of the heritability estimates for both traits. Notably, there was no significant population overlap between the GWAS data on female reproductive diseases and BMI, enhancing the reliability of our findings. Moreover, we utilized a likelihood-based method known as high-definition likelihood (HDL) to estimate genetic associations using GWAS summary statistics. This method enabled a reduction in the variance of genetic association estimates by approximately 60% compared to LDSC [28]. To avoid false positives, Bonferroni correction was implemented on all p-values, with the significance threshold set at $p < 0.003 = 0.05/16$.

Identification of pleiotropic loci

Using GWAS summary statistics, pleiotropic analysis under the composite null hypothesis (PLACO) was applied to identify pleiotropic loci across phenotypes [29]. Variants were scored based on squared Z values, with those exceeding $Z^2 > 80$ excluded. To account for potential trait correlations, the Z correlation matrix was calculated and incorporated. The hypothesis of no pleiotropy was tested using the level-α cross-over-unit method, yielding the final pleiotropy P value. Significant pleiotropic variants were defined as those with $P < 5 \times 10^{-8}$ for single-nucleotide variants. Furthermore, to further validate the biological significance of these pleiotropic SNPs, we utilized the functional mapping and annotation tool (FUMA) to map these risk variants to specific genomic regions (i.e., risk loci), thereby providing an in-depth understanding of the potential functions of these variants [30]. Subsequently, to identify risk loci shared by BMI and major female reproductive diseases, we conducted a Bayesian colocalization analysis, assessing posterior probabilities across five hypotheses: the null hypothesis of no association with either trait; H1, association with trait 1 only; H2, association with trait 2 only; H3, independent associations with each trait; and H4, a shared association signal for both traits. Colocalization was determined if the posterior probability for H4 (PP.H4) exceeded 0.70 [31].

Functional analysis for pleiotropic genes

To investigate the shared mechanisms of the identified loci, we utilized multi-marker analysis of genomic annotation (MAGMA) to map genes near lead SNPs within each locus and assess their biological functions [32]. Specifically, MAGMA gene analysis was conducted to identify pleiotropic genes by accounting for LD between markers and detecting multi-marker effects ($P < 2.730 \times 10^{-6} = 0.05/18{,}345$). We further performed MAGMA gene-set analysis to evaluate the biological functions of lead SNPs, testing 10,678 curated gene sets and Gene Ontology (GO) terms from the Molecular Signatures Database (MSigDB) ($P < 4.680 \times 10^{-6} = 0.05/10{,}678$ after Bonferroni correction) [33]. Additionally, genome-wide tissue-specific enrichment analysis was performed across 54 GTEx tissues using PLACO results to pinpoint tissues with significant heritability enrichment [34].

Multitrait colocalization analysis

Our pathway and tissue enrichment analyses reveal that pleiotropic loci are predominantly associated with biosynthetic and metabolic processes, exhibiting significant

enrichment in tissues such as the hypothalamus, pituitary gland, and ovaries. Therefore, we applied the Hypothesis Prioritization Colocalization (HyPrColoc) method [35] to conduct multi-trait colocalization analysis, identifying the roles of eleven hormone levels and 168 metabolites in the genetic correlation between BMI and female reproductive disorders. HyPrColoc, a computationally efficient alternative to moloc, facilitates the colocalization of numerous traits. Using data from 121,000 European ancestry participants provided by Nightingale Health, we included 168 metabolites whose absolute concentrations were measured by nuclear magnetic resonance for HyPrColoc analysis [36]. These metabolites primarily include lipids and lipoprotein sub-fractions (81%), along with amino acids, cholesterol (free and esterified), cholines, fatty acids, glycolysis-related metabolites, ketone bodies, phospholipids, lipoprotein particle sizes, apolipoproteins, and triglycerides. For hormones, we included fasting insulin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, testosterone, thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), cortisol, growth hormone (GH), and prolactin (PRL). Detailed information on the GWAS summary datasets for the eleven hormones and 168 metabolites has been added to Table S1. Colocalization was carried out using the hyprcoloc function's default settings, which included a prior probability of initial trait association of 0.0001 and a conditional probability of subsequent trait sharing association of 0.02.

Bidirectional Mendelian randomization analysis

MR analysis is commonly used to infer causal relationships between an exposure and an outcome, utilizing exposure-related SNPs as instrumental variables. In our MR analysis, we set the linkage disequilibrium (LD) threshold at 0.001 and the physical distance threshold at 10 Mb for selecting clusters. For BMI as the exposure variable, we applied a p-value threshold of 5×10^{-8}. Additionally, F statistics ($F = beta^2/se^2$) were calculated for each SNP to assess statistical power. In addition, to reduce the impact of horizontal pleiotropy, each SNP was individually analyzed in the LDtrait human genotype-phenotype databases [37] using the "EUR" population data, an R^2 threshold of 0.5, and a 500 kb base pair window. We mainly conducted inverse variance weighted (IVW) meta-analysis, MR Egger regression analysis, and weighted median to determine whether BMI has a causal impact on different adverse female reproductive outcomes. Sensitivity analyses were conducted to assess the robustness of the results. Cochran's Q test was used to examine heterogeneity among the SNPs in each analysis. The MR-Egger regression intercept test was also applied to detect horizontal pleiotropy. Additionally, bidirectional MR analysis was performed with female reproductive diseases as the exposure variable to exclude reverse causality.

Summary data-based Mendelian randomization (SMR)

The SMR method integrates summary-level GWAS data with expression quantitative trait loci (eQTL) data to identify genes whose expression is linked to complex traits through pleiotropy [38]. We conducted SMR and Heterogeneity of Causal Instruments (HEIDI) test using summary-level data from GWAS and eQTL studies to examine causal associations between gene expression levels and the complex traits of interest. The risk genes with causal effects were determined through our analysis, with validation from both the Benjamini-Hochberg test ($P < 0.05$) and the HEIDI-outlier test ($P > 0.05$).

Software and packages

The main statistical analysis was conducted in R (version 4.3.3). LDSC analysis was carried out using the "LDSC" software (v1.0.1), and PLACO analysis was performed with the "PLACO" package. Bayesian colocalization analysis was done using the "coloc" package (version 5.2.3), while multi-trait colocalization analysis was performed with the "hyprcoloc" package (https://github.com/jrs95/hyprcoloc). Functional analysis was carried out using the FUMA web tool. MAGMA gene and gene-set analysis were performed with MAGMA software. Bidirectional MR was conducted using the "TwoSampleMR" package (version 0.6.8).

Results

Genetic correlations between BMI and female reproductive disorders

We assessed the genetic correlation between BMI and 16 female reproductive disorders, finding highly consistent results from both the bivariate LDSC and HDL methods. Specifically, we identified seven traits genetically correlated with BMI using LDSC: GDM (r_g = 0.448, P = 5.876E-40), GH (r_g = 0.308, P = 1.721E-24), PE (r_g = 0.328, P = 1.566E-19), SAB (r_g = 0.209, P = 4.380E-04), PCOS (r_g = 0.323, P = 1.756E-13), Menorrhagia (r_g = 0.313, P = 7.939E-13), and EC (r_g = 0.488, P = 3.632E-25) (Table 1). The HDL method also revealed significant genetic correlations between BMI and various female reproductive diseases, including GDM (r_g = 0.554, P = 8.580E-18), GH (r_g = 0.353, P = 1.330E-23), PE (r_g = 0.377, P = 4.030E-17), PCOS (r_g = 0.669, P = 2.760E-3), Menorrhagia (r_g = 0.307, P = 5.790E-12), EC (r_g = 0.411, P = 2.520E-34), and EnOC (r_g = 0.134, P = 1.840E-02) (Table 1). Together, these two methods led to a final set of eight pairwise traits for further analysis. Additionally, it is worth noting that apart from EnOC, other reproductive traits remained significantly genetically correlated

Table 1 Genetic correlation between BMI and female reproductive disorders

Trait pairs	LDSC		HDL	
	r_g (SE)	*p* value	r_g (SE)	*p* value
BMI & GDM	0.448 (0.034)	5.876E-40*	0.554 (0.065)	8.580E-18*
BMI & GH	0.308 (0.030)	1.721E-24*	0.353 (0.035)	1.330E-23*
BMI & PE	0.328 (0.036)	1.566E-19*	0.377 (0.045)	4.030E-17*
BMI & ICP	0.003 (0.036)	9.350E-01	0.013 (0.034)	6.980E-01
BMI & FGR	-0.044 (0.054)	4.108E-01	-0.086 (0.069)	2.080E-01
BMI & SAB	0.209 (0.059)	4.380E-04*	0.427 (0.226)	5.870E-02
BMI & PTB	0.069 (0.038)	7.023E-02	0.089 (0.060)	1.380E-01
BMI & PPH	0.085 (0.056)	1.279E-01	0.083 (0.071)	2.440E-01
BMI & Infertility	0.027 (0.036)	4.539E-01	-0.007 (0.042)	8.690E-01
BMI & PCOS	0.323 (0.044)	1.756E-13*	0.669 (0.223)	2.760E-03
BMI & Menorrhagia	0.313 (0.044)	7.939E-13*	0.307 (0.045)	5.790E-12*
BMI & UPs	-0.076 (0.107)	4.753E-01	-Inf (NA)	NA
BMI & UF	0.023 (0.023)	3.001E-01	0.022 (0.023)	3.460E-01
BMI & Endometriosis	0.013 (0.025)	6.034E-01	-3e-04 (0.026)	9.900E-01
BMI & EC	0.488 (0.047)	3.632E-25*	0.411 (0.034)	2.520E-34*
BMI & EnOC	0.094 (0.073)	1.990E-01	0.134 (0.057)	1.840E-02

Abbreviations: BMI, body mass index; PCOS, polycystic ovary syndrome; GDM, gestational diabetes mellitus; GH, gestational hypertension; PE, pre-eclampsia or eclampsia; EC, endometrial cancer; EnOC, endometrioid ovarian cancer; SAB, spontaneous abortion. * represents traits that pass the Bonferroni correction ($p = 0.003 < 0.05/16$)

with BMI risk after applying the Bonferroni correction ($P < 0.003 = 0.05/16$).

Shared loci between BMI and female reproductive disorders

Through PLACO analysis, we identified 422 potential polymorphic SNPs ($P < 5 \times 10^{-8}$) in the pairings between BMI and eight female reproductive traits (SAB, EC, EnOC, GDM, GH, Menorrhagia, PCOS, and PE) (Table S2). Based on these SNPs, the FUMA analysis uncovered 50 independent genomic risk loci with pleiotropic effects, comprising 23 novel loci and 27 previously reported loci (Table S3). According to the GWAS catalog, these known loci are primarily associated with traits such as BMI, metabolic syndrome, obesity, diabetes, and abnormal body fat distribution (Tables S4). Moreover, the 50 pleiotropic SNPs are located in 41 unique chromosomal regions (Table S3). Multiple pleiotropic regions exist among various trait pairs. For example, 16p11.2 was found in both BMI & EnOC and BMI & EC, 11p15.4 in BMI & GH and BMI & PE, 1p31.1 in BMI & GH and BMI & GDM, and 8p23.1 in BMI & GH, BMI & PE, and BMI & SAB (Table S5). Furthermore, Bayesian colocalization analysis finally identified 21 of 50 (42.0%) potential pleiotropic loci with PP.H4 greater than 0.7 (Table 2 and Table S3).

Pleiotropic gene enrichment analysis

MAGMA analysis identified 936 significant pleiotropic genes shared between BMI and female reproductive disorders (Table S6). Sixteen genes, including *ANKRD55*, *BLK*, *C11orf80*, *DNAJC5*, *FAM216A*, *GDN3*, *HCVN1*, *LTBP3*, *MSRA*, *NR1H3*, *PPTC7*, *SORT1*, *TCTN1*, *UBA7*, *VPS29*, *and WEE1*, were confirmed across multiple trait pairs (e.g., BMI with EnOC, GH, EC, SAB, GDM, and PE) (Table S6), demonstrating their pleiotropic effects. Pathway enrichment analysis suggested that the identified pleiotropic genes may participate in controlling the biosynthetic processes, RNA biosynthetic and metabolic processes, PTEN regulation pathway, gastrin signaling pathway, type B pancreatic cell apoptotic process, and various other processes (Fig. 2A and Table S7). In addition, tissue enrichment analysis found these pleiotropic loci were enriched in several tissues (e.g., different regions of the brain, hypothalamus, pituitary, and ovary) (Fig. 2B and Table S8).

Metabolite and hormone-related mechanisms shared between BMI and female reproductive diseases

The pathway and tissue enrichment analysis highlighted metabolic and biosynthetic pathways, along with key tissues such as the hypothalamus and pituitary, suggesting a critical role of endocrine and metabolic processes in the interplay between BMI and these diseases. Hence, we conducted the multi-trait colocalization analysis using HyPrColoc. The results highlighted seven pleiotropic SNPs (rs12602912, rs13083375, rs7713317, rs1899951, rs7550711, rs891387, and rs1801282), which are associated with 53 unique hormones and metabolites. These SNPs shared causal variants with posterior probability (PP) > 0.7 in both BMI & GDM and BMI & EC, supporting the role of these hormones and metabolites in the two relationships (Table 3 and Table S9). The 53 hormones and metabolites belong to 13 panels: hormones, glycolysis, amino acids, size & Apo-LP, cholesterol,

Table 2 21 Colocalized loci identified by colocalization analysis performed on 51 pleiotropic loci (PP.H4 > 0.7)

Trait pairs	LeadSNPs	Region	Locus boundary	SNP.PP.H4
BMI & EnOC	rs7204632	16p11.2	16:30591675–30,660,700	0.864
BMI & EC	rs11066188	12q24.13	12:111826477–112,906,415	0.707
BMI & EC	rs11865403	16p12.3	16:19706199–19,831,532	0.789
BMI & EC	rs3922668	16p11.2	16:28510393–29,008,079	0.766
BMI & EC	rs12602912	17q24.2	17:65822573–66,096,529	0.987
BMI & PCOS	rs2990997	1q31.1	1:190112653–190,163,532	0.842
BMI & PCOS	rs9819875	3p22.1	3:42303074–42,334,191	0.911
BMI & PCOS	rs12981256	19p13.3	19:1812682–1,920,342	0.988
BMI & GH	rs1013293	1p31.3	1:62488918–62,634,303	0.981
BMI & GH	rs4988235	2q21.3	2:135771974–136,823,866	0.828
BMI & GH	rs6985109	8p23.1	8:9735970–11,450,422	0.863
BMI & GH	rs11066188	12q24.13	12:111826477–112,906,415	0.925
BMI & PE	rs656980	11q13.1	11:65575263–65,663,547	0.943
BMI & PE	rs9955276	18p11.32	18:1811604–1,914,051	0.975
BMI & GDM	rs17024258	1p13.3	1:110078255–110,216,436	0.999
BMI & GDM	rs12713419	2p23.3	2:25074874–25,453,968	0.865
BMI & GDM	rs4684847	3p25.2	3:12329783–12,413,339	0.988
BMI & GDM	rs7717348	5q15	5:95388015–95,765,413	0.998
BMI & GDM	rs1579557	6p21.2	6:40348653–40,383,533	0.758
BMI & GDM	rs11663558	18q11.2	18:21075441–21,165,409	0.980
BMI & GDM	rs11671664	19q13.32	19:46148237–46,177,235	0.983

Abbreviations: BMI, body mass index; PCOS, polycystic ovary syndrome; GDM, gestational diabetes mellitus; GH, gestational hypertension; PE, pre-eclampsia or eclampsia; EC, endometrial cancer; EnOC, endometrioid ovarian cancer; PP.H4, posterior probability for H4

triglycerides, free cholesterol, phospholipids, lipoprotein particles, total lipids, fatty acids, compounds, and esterified cholesterol. Among them, 45 hormones and metabolites are associated with BMI and EC, all influenced by rs12602912; 21 hormones and metabolites are associated with BMI and GDM, mainly affected by rs13083375, rs7713317, rs1899951, rs7550711, rs891387, and rs1801282. Additionally, lipid metabolites constitute the largest proportion (49/53 = 92.5%) of the 53 unique hormones and metabolites. Insulin, with the highest posterior probability, was significantly colocalized with both BMI and GDM (PP = 0.932), as well as BMI and EC (PP = 0.906). Glucose also showed a significant genetic association between BMI and GDM (PP = 0.892), with rs7717348 affecting these associations. In addition, glycine and glutamine exhibited significant relationships with both BMI and GDM, which is influenced by the risk loci rs4684847 (Table 3).

The causal relationship between BMI and female reproductive disorders

In addition to pleiotropy, we also aimed to determine whether the genetic correlation is related to causality. Therefore, we investigated the putative causal link between BMI and eight female reproductive disorders, which displayed a significant genetic correlation in LDSC and HDL analysis. To obtain more robust results, we used bidirectional MR estimation method. All genetic instruments used in the MR analysis are listed in Table S10 and were deemed robust instruments, with F-statistics greater than 10. Sensitivity analysis did not detect pleiotropy ($P_{MR-Egger} > 0.05$). For those with heterogeneity ($P_{Cochran's\ Q} < 0.05$), we used the weighted median method or inverse variance weighting (IVW). As a result, we found that BMI was causally associated with the risk of GDM (odds ratio [OR], 1.719; 95% CI, 1.480–1.996; $P < 0.001$), Menorrhagia (OR, 1.011; 95% CI, 1.004–1.019; $P = 0.004$), GH (OR, 1.581; 95% CI, 1.337–1.870; $P < 0.001$), PCOS (OR, 1.920; 95% CI, 1.282–2.874; $P = 0.002$), PE (OR, 1.436; 95% CI, 1.214–1.698; $P < 0.001$), EnOC (OR, 1.436; 95% CI, 1.014–1.980; $P = 0.027$), and EC (OR, 1.804; 95% CI, 1.513–2.151; $P < 0.001$) respectively, as shown in Fig. 3A and Table S11. Concurrently, reverse MR analysis was conducted. Under stringent selection criteria, we found no suitable instruments for SAB and EnOC. Thus, our analysis focuses on GDM, Menorrhagia, GH, PE, PCOS, and EC, providing preliminary insights into their potential causal effects on BMI. We only found a reverse causal relationship between GDM and BMI (OR, 1.021; 95% CI, 1.008–1.035; $P = 0.001$) (Fig. 3B and Table S11).

Identification of shared functional genes for BMI and female reproductive disorders

We combined GWAS summary data for BMI and female reproductive disorders with eQTL summary data of whole blood tissue in GTEx and eQTLGen. As a result, we identified 10 shared risk genes between BMI & GDM,

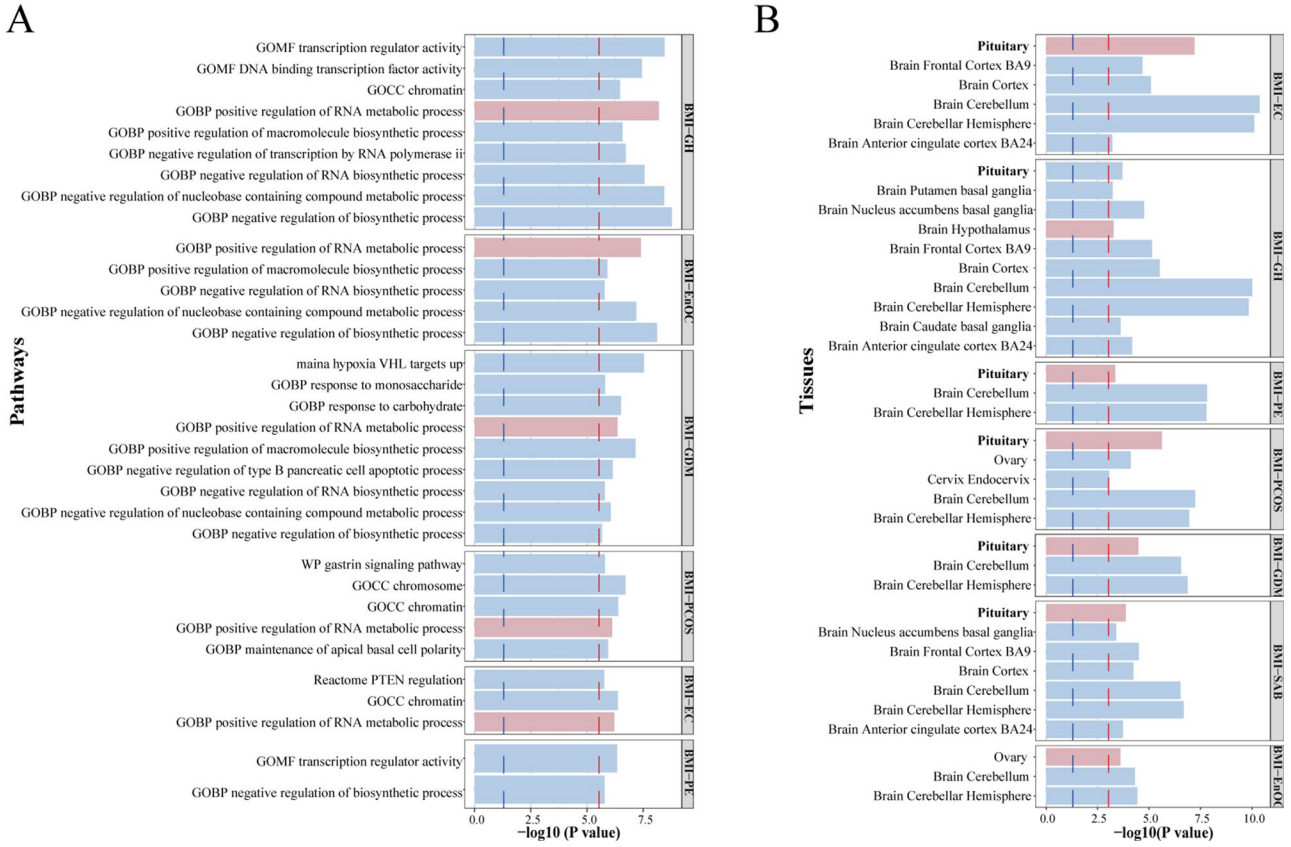

Fig. 2 Bar plots of genome-wide pleiotropic results. (**A**) MAGMA gene-set analysis; (**B**) MAGMA tissue-specific analysis. The red dotted line indicates a significance threshold of 0.05 after multiple corrections, while the blue line represents a threshold of 0.05. BMI, body mass index; PCOS, polycystic ovary syndrome; GDM, gestational diabetes mellitus; GH, gestational hypertension; PE, pre-eclampsia or eclampsia; EC, endometrial cancer; EnOC, endometrioid ovarian cancer; SAB, spontaneous abortion

BM I& GH, and BMI & EC in whole blood, including *EIF2S2P3*, *MCM6*, *EVI2A*, *MRPL34*, *DNAJC3-DT*, *LCT-AS1*, *MFHAS1*, *CSK*, *ULK3*, and *NF1*. Among them, only *EIF2S2P3* (BMI & GDM) and MCM6 (BMI & GH) passed the HEIDI-outlier test for cis_eQTL data (Table S12). Notably, *MCM6* was a pleiotropic gene between BMI and GH in the MAGMA analysis above (Table S6). Additionally, *MCM6* and *EVI2A* are potentially shared causal risk genes between BMI & GH and BMI & EC, further highlighting their pleiotropy in these traits (Table S12).

Discussion

In this study, we performed a comprehensive assessment of the shared genetic architecture and causal relationship between BMI and female reproductive diseases by analyzing large-scale GWAS summary data, aiming to elucidate their shared underlying molecular biological mechanisms. We revealed a significant genetic correlation between BMI and GDM, EC, GH, PE, PCOS, SAB, menorrhagia, and EnOC. Additionally, we investigated whether the correlation reflects pleiotropy or causality and found that, except for miscarriage, both pleiotropic loci and causal relationships exist between BMI and the other diseases. The genetic association between BMI and miscarriage is primarily driven by pleiotropy. Furthermore, we identified significant enrichment of metabolic processes, biosynthetic processes, and transcriptional regulation pathways in brain, pituitary, and ovarian tissues. Insulin, various lipid metabolites, glucose, and amino acids may be involved in mechanisms shared between BMI & GDM and BMI & EC. Finally, SMR analysis showed that *EIF2S2P3* and *MCM6* may serve as potential drug targets for obesity, GDM, GH, or their comorbidities. To the best of our knowledge, this is the first study to comprehensively explore the genetic relationships and potential mechanisms between BMI and these female reproductive diseases, which have significant implications for women's health.

Our genetic correlation analysis revealed significant positive associations between BMI and eight female reproductive diseases (SAB, EC, EnOC, GDM, GH, Menorrhagia, PCOS, and PE), suggesting that a higher BMI may increase the risk of these diseases through genetic synergistic effects. Currently, there is limited research on the genetic associations between BMI and female reproductive diseases. Liu et al. previously identified a

Table 3 Multi-trait colocalization analysis highlighted key role of metabolites and hormones (pp > 0 0.7)

Trait pairs	Panel	Trait	loci_SNP	PP	RP	Post_exp_snp
BMI & GDM	Hormone	Insulin	rs13083375	0.932	0.994	0.403
BMI & EC	Hormone	Insulin	rs12602912	0.906	0.938	0.971
BMI & GDM	Glycolysis	Glucose	rs7713317	0.892	1.000	0.257
BMI & GDM	Amino acids	Glycine	rs1801282	0.889	0.994	0.399
BMI & GDM	Amino acids	Glutamine	rs1801282	0.869	0.961	0.329
BMI & GDM	Size & Apo-LP	Average diameter for VLDL particles	rs1801282	0.841	0.993	0.336
BMI & GDM	Size & Apo-LP	Average diameter for LDL particles	rs1801282	0.839	0.973	0.243
BMI & EC	Cholesterol	Cholesterol in large VLDL	rs12602912	0.831	0.991	0.665
BMI & EC	Triglycerides	Triglycerides in very small VLDL	rs12602912	0.830	0.991	0.677
BMI & EC	Free cholesterol	Free cholesterol in large VLDL	rs12602912	0.829	0.991	0.666
BMI & EC	Triglycerides	Triglycerides in large LDL	rs12602912	0.828	0.990	0.669
BMI & EC	Phospholipids	Phospholipids in large VLDL	rs12602912	0.828	0.990	0.673
BMI & EC	Triglycerides	Triglycerides in LDL	rs12602912	0.828	0.991	0.671
BMI & EC	Cholesterol	Cholesterol in very large VLDL	rs12602912	0.827	0.990	0.652
BMI & EC	Triglycerides	Triglycerides in medium LDL	rs12602912	0.827	0.990	0.673
BMI & EC	Triglycerides	Triglycerides in IDL	rs12602912	0.827	0.991	0.666
BMI & EC	Triglycerides	Triglycerides in small HDL	rs12602912	0.826	0.990	0.686
BMI & EC	Triglycerides	Triglycerides in medium VLDL	rs12602912	0.826	0.990	0.684
BMI & EC	Lipoprotein particles	Concentration of small VLDL particles	rs12602912	0.826	0.991	0.668
BMI & EC	Total lipids	Total lipids in large VLDL	rs12602912	0.825	0.990	0.673
BMI & EC	Lipoprotein particles	Concentration of large VLDL particles	rs12602912	0.825	0.990	0.669
BMI & EC	Total lipids	Total lipids in VLDL	rs12602912	0.824	0.990	0.657
BMI & EC	Triglycerides	Triglycerides in small VLDL	rs12602912	0.824	0.990	0.682
BMI & GDM	Triglycerides	Triglycerides in very large VLDL	rs1801282	0.823	0.983	0.372
BMI & EC	Free cholesterol	Free cholesterol in very large VLDL	rs12602912	0.823	0.990	0.648
BMI & EC	Phospholipids	Phospholipids in very large VLDL	rs12602912	0.822	0.990	0.650
BMI & GDM	Triglycerides	Triglycerides in large VLDL	rs1801282	0.819	0.988	0.377
BMI & EC	Triglycerides	Triglycerides in large VLDL	rs12602912	0.818	0.990	0.672
BMI & EC	Fatty Acids	Monounsaturated fatty acids	rs12602912	0.818	0.990	0.654
BMI & EC	Triglycerides	Triglycerides in HDL	rs12602912	0.818	0.987	0.671
BMI & EC	Lipoprotein particles	Concentration of very large VLDL particles	rs12602912	0.817	0.990	0.654
BMI & EC	Total lipids	Total lipids in very large VLDL	rs12602912	0.817	0.990	0.654
BMI & EC	Triglycerides	Triglycerides in small LDL	rs12602912	0.816	0.990	0.655
BMI & EC	Compounds	Total triglycerides	rs12602912	0.815	0.990	0.662
BMI & GDM	Triglycerides	Triglycerides in chylomicrons and extremely large VLDL	rs1899951	0.815	0.991	0.287
BMI & GDM	Lipoprotein particles	Concentration of chylomicrons and extremely large VLDL particles	rs1801282	0.813	0.977	0.333
BMI & EC	Triglycerides	Triglycerides in medium HDL	rs12602912	0.813	0.983	0.670
BMI & EC	Triglycerides	Triglycerides in VLDL	rs12602912	0.812	0.990	0.657
BMI & EC	Triglycerides	Triglycerides in very large VLDL	rs12602912	0.808	0.990	0.652
BMI & EC	Total lipids	Total lipids in small VLDL	rs12602912	0.807	0.991	0.664
BMI & EC	Esterified cholesterol	Cholesteryl esters in chylomicrons and extremely large VLDL	rs12602912	0.806	0.979	0.624
BMI & EC	Cholesterol	Cholesterol in chylomicrons and extremely large VLDL	rs12602912	0.806	0.983	0.617
BMI & EC	Fatty Acids	Total fatty acids	rs12602912	0.806	0.979	0.644
BMI & EC	Phospholipids	Phospholipids in VLDL	rs12602912	0.805	0.991	0.653
BMI & EC	Size & Apo-LP	Average diameter for HDL particles	rs12602912	0.800	0.976	0.609
BMI & EC	Free cholesterol	Free cholesterol in chylomicrons and extremely large VLDL	rs12602912	0.799	0.979	0.611
BMI & EC	Lipoprotein particles	Concentration of chylomicrons and extremely large VLDL particles	rs12602912	0.798	0.980	0.613
BMI & GDM	Phospholipids	Phospholipids in chylomicrons and extremely large VLDL	rs1801282	0.798	0.962	0.346
BMI & EC	Phospholipids	Phospholipids in chylomicrons and extremely large VLDL	rs12602912	0.791	0.967	0.617
BMI & EC	Fatty Acids	Saturated fatty acids	rs12602912	0.788	0.960	0.638
BMI & GDM	Total lipids	Total lipids in chylomicrons and extremely large VLDL	rs1801282	0.786	0.969	0.311
BMI & GDM	Triglycerides	Triglycerides in VLDL	rs1801282	0.784	0.958	0.381
BMI & EC	Esterified cholesterol	Cholesteryl esters in very large VLDL	rs12602912	0.781	0.990	0.647

Table 3 (continued)

Trait pairs	Panel	Trait	loci_SNP	PP	RP	Post_exp_snp
BMI & EC	Total lipids	Total lipids in chylomicrons and extremely large VLDL	rs12602912	0.780	0.961	0.608
BMI & GDM	Compounds	Total concentration of lipoprotein particles	rs7550711	0.776	0.802	0.946
BMI & EC	Size & Apo-LP	Average diameter for VLDL particles	rs12602912	0.773	0.965	0.638
BMI & EC	Esterified cholesterol	Cholesteryl esters in large HDL	rs12602912	0.766	0.988	0.628
BMI & GDM	Lipoprotein particles	Concentration of HDL particles	rs7550711	0.766	0.793	0.949
BMI & EC	Cholesterol	Cholesterol in large HDL	rs12602912	0.762	0.986	0.626
BMI & GDM	Total lipids	Total lipids in very large VLDL	rs1801282	0.750	0.923	0.395
BMI & GDM	Lipoprotein particles	Concentration of very large VLDL particles	rs1801282	0.746	0.910	0.398
BMI & EC	Triglycerides	Triglycerides in chylomicrons and extremely large VLDL	rs12602912	0.745	0.922	0.607
BMI & GDM	Free cholesterol	Free cholesterol in chylomicrons and extremely large VLDL	rs1801282	0.741	0.905	0.359
BMI & GDM	Phospholipids	Phospholipids in very large HDL	rs891387	0.728	0.950	0.222
BMI & GDM	Compounds	Total triglycerides	rs1801282	0.727	0.893	0.400
BMI & GDM	Total lipids	Total lipids in very large HDL	rs891387	0.705	0.930	0.218

Abbreviations: BMI, body mass index; PCOS, polycystic ovary syndrome; GDM, gestational diabetes mellitus; GH, gestational hypertension; PE, pre-eclampsia or eclampsia; EC, endometrial cancer; EnOC, endometrioid ovarian cancer; SAB, spontaneous abortion; PP, posterior probability; RP, regional probability; post_exp_snp, osterior_explained_by_snp

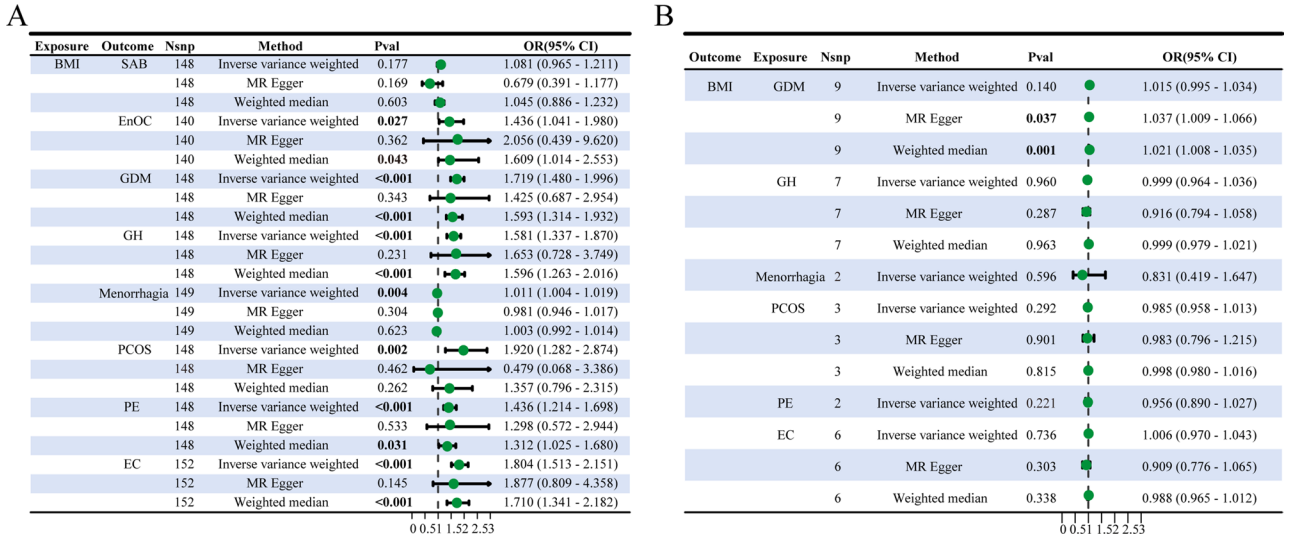

Fig. 3 Bidirectional Mendelian randomization analysis between BMI and multiple female reproductive disorders. (**A**) The causal effect of BMI on female reproductive disorders. (**B**) The causal effect of female reproductive disorders on BMI. BMI, body mass index; PCOS, polycystic ovary syndrome; GDM, gestational diabetes mellitus; GH, gestational hypertension; PE, pre-eclampsia or eclampsia; EC, endometrial cancer; EnOC, endometrioid ovarian cancer; SAB, spontaneous abortion

significant genetic correlation between BMI and PCOS through LDSC analysis [15], which aligns with our findings and further supports BMI as an important genetic factor in female reproductive health. Additionally, previous studies have shown a strong epidemiological link between BMI and the other seven reproductive disorders. Our study expands on this by identifying shared genetic backgrounds between BMI and these diseases, underscoring the importance of BMI management in reducing the risk of these female reproductive disorders in clinical practice. Furthermore, the bivariate LDSC and HDL methods are powerful and complementary approaches for genetic correlation analysis. While LDSC is widely used for estimating genetic correlations from GWAS data, HDL provides a significant advantage by fully accounting for genome-wide LD patterns, improving accuracy and robustness, especially for traits with complex polygenic architectures or smaller heritability. This study is the first to use both methods to evaluate the genetic links between BMI and 16 female reproductive disorders, offering a more comprehensive and precise understanding of their shared genetic architecture and setting a foundation for future research in this field.

Cross-trait PLACO analysis and FUMA analysis identified 50 pleiotropic genetic loci between the BMI and female reproductive diseases (SAB, EC, EnOC, GDM, GH, PCOS, and PE), including 23 novel loci and 27 previously reported loci. According to the existing

publications, the 27 known loci are mainly associated with BMI, obesity, T2D, metabolic syndrome, and lipid metabolism [39–42]. We also found that rs11066188, one of the 50 pleiotropic loci, is associated with blood pressure, cardiovascular, and neurological diseases [43], indicating that it may play a role in the BMI & GH and BMI & EC through vascular and neuroendocrine pathways. Additionally, these 50 loci are distributed across 42 gene regions, with the 8p23.1 region repeatedly appearing in multiple phenotypes (e.g., BMI & SAB, BMI & GH, BMI & PE), suggesting its pleiotropic role in these BMI and reproductive traits. The 8p23.1 region has been widely studied due to its involvement in neurodevelopment, cardiac development, and cancer [44, 45]. Moreover, previous research has suggested that inversions in the 8p23.1 region may interact with environmental factors to influence DNA methylation patterns during early life stages, which may play a critical role in obesity-related health outcomes [46]. The 12q24.13 locus also showed significant associations in the analysis of BMI & EC and BMI & GH. This region is notable for its association with several genes that play crucial roles in immune response and metabolic regulation. Previous studies have shown that this locus is closely related to metabolic traits such as high-density lipoprotein cholesterol and fasting glucose [47], which may support the hypothesis that BMI's impact on reproductive disease risk may be mediated through these metabolic elements.

Pathway enrichment analysis revealed that RNA metabolism and synthesis processes were enriched in multiple trait pairs, including BMI & GH, BMI & GDM, BMI & PCOS, and BMI & EnOC. This suggests that these processes may be involved in the genetic links between BMI and these traits. In BMI & GDM, pathways related to monosaccharide response, carbohydrate response, and β-cell apoptosis were enriched. GDM, a high blood glucose condition occurring during pregnancy, is strongly associated with maternal insulin resistance and β-cell dysfunction [48]. In BMI & PCOS, the gastrin signaling pathway was significantly enriched. Recent studies have suggested that gastrin, beyond its role in the digestive system, may be linked to endocrine disorders and metabolic diseases. For instance, through receptors such as the cholecystokinin B receptor, gastrin affects insulin secretion and sensitivity, potentially contributing to insulin resistance in PCOS patients [49]. Therefore, targeting the gastrin signaling pathway could offer new therapeutic options for obesity and PCOS. In BMI & EC, the PTEN regulation pathway was notably enriched. Research has shown that PTEN loss in obese patients leads to abnormal PI3K pathway activation, promoting uterine cancer [50]. Obesity may thus advance EC via the PTEN/PI3K/AKT pathway. Thereby, further investigation of the relationship between BMI and the PTEN pathway is essential for developing prevention and treatment strategies for EC. Furthermore, tissue enrichment analysis highlights the potential role of brain regions and the pituitary in the relationship between BMI and female reproductive diseases, which is consistent with previous studies. Snider et al. have found that obese women often experience ovulatory dysfunction due to disruptions in the hypothalamic-pituitary-ovarian axis, which is crucial for normal reproductive function [51]. Additionally, a meta-analysis from the GIANT Consortium (involving over 339,000 individuals) identified 97 BMI-associated genetic loci, with genes near these loci being enriched in the central nervous system, supporting the hypothesis that BMI is regulated by the hypothalamus [52]. In the trait pairs of BMI & PCOS and BMI & EnOC, ovarian involvement was notably enriched, which aligns with the strong link between PCOS, EnOC, and ovarian function. The study by Masao et al. also suggests that obesity, as a chronic inflammatory state, may promote macrophage infiltration in the ovaries via the MCP-1 pathway, thereby affecting ovarian function [53]. Therefore, improving ovarian health in obese women and developing strategies to address ovarian dysfunction are crucial for reducing the incidence of PCOS, EnOC, and related conditions.

Multi-trait colocalization analysis identified insulin with the highest posterior probability, colocalizing with BMI & GDM and BMI & EC. The role of insulin is a key focus in the research of GDM. Studies have shown that during pregnancy, insulin demand increases to support fetal growth and development. However, some women may be unable to produce sufficient insulin, leading to elevated blood glucose levels and the development of GDM [54]. Our study provides the first genetic evidence of this mechanism and highlights rs13083375 as a potential contributor to this association. Regarding the relationship between insulin and BMI & EC, prior studies have explored how insulin resistance and related metabolic abnormalities influence the risk of EC, particularly in overweight or obese women [55]. A large case-control study by Zhang et al. revealed a significant association between metabolic syndrome and the risk of EC [56]. Additionally, a MR analysis demonstrated insulin's mediating role in the BMI & EC risk relationship. Rs12602912, which mediated the colocalization of various lipid metabolites and BMI & EC, was previously reported to be associated with BMI, metabolic syndrome, triglyceride levels, and psoriasis [57–60]. Lipid metabolism is increasingly recognized in the pathogenesis of EC, with reprogrammed lipid metabolism driving tumorigenesis, invasion, and metastasis. Fatty acid uptake and metabolism are also proven crucial for cell proliferation and survival in the development of EC [61]. These findings suggest rs12602912 as a potential biomarker and therapeutic target for early EC diagnosis and treatment. Lastly,

we found that glycine and glutamine play important roles in the BMI & GDM relationship. Intake of these amino acids may improve insulin sensitivity, reduce blood glucose, and potentially lower the risk of GDM.

To distinguish between pleiotropy and causal relationships, we used MR analysis, which controls for confounding and reverse causality. Our bidirectional MR analysis showed that BMI may cause several female reproductive diseases (GH, Menorrhagia, PCOS, PE, GDM, EnOC, and EC), while only GDM had a causal effect on BMI. This underscores BMI's key role and the importance of weight management, particularly in GDM. In addition, SMR analysis revealed that EIF2S2P3 and MCM6 could be potential drug targets for obesity, GDM, and GH. MCM6, a key component of the mini-chromosome maintenance complex involved in DNA replication [62], has been shown to increase in the placenta under obesity, potentially impairing placental function and fetal health through enhanced insulin resistance [63]. *EIF2S2P3*, a pseudogene with limited research, has been suggested to play a role in metabolic regulation [64, 65]. Our study is the first to demonstrate that *EIF2S2P3* expression may directly influence the relationship between BMI and GDM. These findings highlight the potential of both genes as drug targets for addressing GDM and GH and warrant further investigation.

With the increasing global prevalence of overweight and obesity, it is crucial to better understand the molecular mechanisms through which obesity elevates the risk of female reproductive disorders. Our study is the first to systematically elucidate the genetic correlation and mechanisms between BMI and women's reproductive health through comprehensive genetic analysis. These findings suggest that increased BMI may elevate the risk of reproductive diseases through mechanisms such as metabolic dysregulation and insulin resistance, emphasizing the critical role of BMI management in the prevention and treatment of these conditions. In clinical practice, improving diet, increasing physical activity, and implementing effective weight management strategies, particularly for high-risk populations, can help reduce the incidence of these diseases. In addition to weight management strategies, our findings on the genetic molecular mechanisms between BMI and female reproductive disorders can aid in the development of drug targets for high-risk populations with these traits, thus providing a supplementary approach to preventing specific female reproductive diseases. However, our study also has some limitations. Firstly, we used summary-level data, lacking individual-level datasets, so we couldn't explore the impact across different reproductive stages or specific disease subgroups. Secondly, to minimize population stratification bias, the genetic data in this study were limited to individuals of European ancestry, which may limit the applicability of the results to other populations. Thirdly, the inferred causal relationship is based on GWAS summary statistics and is therefore speculative. Larger and more robust GWAS on BMI and female reproductive disorders are needed to establish (or rule out) potential causal links. Lastly, we were unable to obtain GWAS data for placental tissues in tissue enrichment analysis, which are crucial in pregnancy-related diseases, limiting our understanding of these pregnancy-related disorders. Future research could benefit from including diverse ethnic groups, particularly Asian and African populations, to further explore and validate the genetic associations between BMI and female reproductive diseases across different populations. Additionally, individual-level data analysis should be utilized to explore BMI's role at various reproductive stages and its impact on specific disease subgroups. Finally, further functional studies are also needed to investigate how pleiotropic loci and functional genes influence female reproductive diseases and to develop targeted therapies.

Conclusion

In summary, our study highlights the shared genetic and molecular mechanisms underlying BMI and various female reproductive diseases, emphasizing the critical role of metabolic and biosynthetic processes in their pathophysiology. The impact of BMI is characterized by its involvement in insulin regulation, lipid metabolism, glucose utilization, and amino acid pathways, which influence the development and progression of conditions such as GDM and EC. These mechanisms are mediated through pleiotropy and causal pathways. Exploring therapeutic targets based on shared pleiotropic loci, functional genes, or genetic pathways between BMI and female reproductive diseases holds great promise, particularly for developing interventions to improve reproductive health in women with high BMI.

Abbreviations

BMI	Body mass index
PCOS	Polycystic ovary syndrome
GDM	Gestational diabetes mellitus
GH	Gestational hypertension
PE	Pre-eclampsia or eclampsia
EC	Endometrial cancer
EnOC	Endometrioid ovarian cancer
SAB	Spontaneous abortion
UFs	Uterine fibroids, UPs, uterine polyps
ICP	Intrahepatic cholestasis of pregnancy
FGR	Poor fetal growth, PPH, postpartum hemorrhage, PTB, preterm labor and delivery
LDSC	Linkage disequilibrium score regression
HDL	High-definition likelihood
PLACO	Pleiotropic analysis under composite null hypothesis
MAGMA	Multimarker analysis of GenoMic annotation
SMR	Summary-data based Mendelian randomization
HyPrColoc	Hypothesis Prioritization Colocalization. TSH, thyroid stimulating hormone
FT3	Free triiodothyronine

FT4	Free thyroxine
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
GH	Growth hormone
PRL	Prolactin

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12958-025-01406-y.

Supplementary Material 1

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Summary-level data used in this study was downloaded from the GWAS Catalog (https://www.ebi.ac.uk/gwas/), IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/), FINNGEN database (https://www.finngen.fi/en/access_results), and The Genetic Investigation of ANthropometric Traits (GIANT) consortium database. The authors thank all investigators for sharing these data.

Author contributions

"B.X. and R.G. conceived and designed the study; H.S., C.X. and H.W. conducted the analysis and finished the original paper writing; H.S. and C.X. analyzed the data and discussed the results; N.L., H.G., and C.Z. conducted original figures and tables design; L.L. and Q.S. reviewed the figures and tables; R.G. and B.X. reviewed the article and provide suggestions and modifications for article writing. All authors read and approved the final version of the manuscript."

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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