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Genetic analysis of endometriosis and depression identifies shared loci and implicates causal links with gastric mucosa abnormality

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Conflicts of interest/Competing interests

All researchers had full independence from the funders. The authors report no biomedical financial interests or potential conflicts of interest.

Ethics approval

This study has been included in the 'genetic analysis and comorbid PSYCHIATRIC disorders using twin families' (P5890) project in the 'genetic epidemiology portfolio'. The Human Research Ethics Committee had earlier granted ethical approval for the project and approval for the addition of the present study was granted on the 3rd of November 2017.

Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material (data transparency)

The present study was based on a secondary analysis of GWAS data, and all data generated during the study are included in this published article [and its supplementary files]. The GWAS data analysed for depression and MDD are available and accessible online by contacting the PGC. The GWAS data for GERD and gastritis/duodenitis are freely accessible using the links provided within the articles. The endometriosis GWAS data were sourced from the International Endogen Consortium (IEC); for access to these, contact the consortium directly.

Code availability

Not applicable

Abstract

Evidence from observational studies indicates that endometriosis and depression often co-occur. However, conflicting evidence exists, and the etiology as well as biological mechanisms underlying their comorbidity remain unknown. Utilizing genome-wide association study (GWAS) data, we comprehensively assessed the relationship between endometriosis and depression. Single nucleotide polymorphism effect concordance analysis found a significant genetic overlap between endometriosis and depression ($P_{Fsig\text{-}permuted} = 9.99 \times 10^{-4}$). Linkage disequilibrium score regression analysis estimated a positive and highly significant genetic correlation between the two traits ($r_G = 0.27$, $P = 8.85 \times 10^{-27}$). A meta-analysis of endometriosis and depression GWAS (sample size = 709,111), identified 20 independent genome-wide significant loci ($P < 5 \times 10^{-8}$), of which eight are novel. Mendelian randomization analysis suggests a causal effect of depression on endometriosis. Combining gene-based association results across endometriosis and depression GWAS, we identified 22 genes with a genome-wide significant Fisher's combined *P* value ($FCP_{gene} < 2.75 \times 10^{-6}$). Genes with a nominal gene-based association ($P_{gene} < 0.05$) were significantly enriched across endometriosis and depression ($P_{binomial\text{-}test} = 2.90 \times 10^{-4}$). Also, genes overlapping the two traits at $P_{gene} < 0.1$ ($P_{binomial\text{-}test} = 1.31 \times 10^{-5}$) were significantly enriched for the biological pathways 'cell-cell adhesion', 'inositol phosphate metabolism', 'Hippo-Merlin signaling dysregulation' and 'gastric mucosa abnormality'. These results reveal a shared genetic etiology for endometriosis and depression. Indeed, additional analyses found evidence of a causal association between each of endometriosis and depression and at least one abnormal condition of gastric mucosa. Our study confirms the comorbidity of endometriosis and depression, implicates links with gastric mucosa abnormalities in their causal pathways and reveals potential therapeutic targets for further investigation.

Keywords: depression, endometriosis, genome-wide association study, molecular genetics, causal relationship, genetic overlap

Introduction

Endometriosis is one of the leading gynecological disorders defined by the presence of endometrial tissues in sites other than within the endometrial cavity (Adamson et al. 2010; Giudice 2010; Treloar et al. 1999). The disorder continues to be a subject of increasing global public health importance, affecting approximately 10% of reproductive-aged women, and, up to 50% of women with infertility or sub-fertility, worldwide (Giudice 2010; Zondervan et al. 2018). Menstrual irregularities, dysmenorrhea, and varying degrees of chronic pelvic pains are among the most common clinical signs of endometriosis (Laganà et al. 2015; Tripoli et al. 2011). Depression, on the other hand, is a chronic psychiatric illness characterized primarily by social dysfunction, feelings of guilt or low self-worth, cognitive impairment, loss of- and changes in sleep, appetite, and libido as well as a substantial deterioration in mood and behaviors (Lépine and Briley 2011; World Health Organization 2017). Similar to endometriosis, which is predominantly found in women, depression ranks as the leading cause of disease burden among women and is associated with increased risks of morbidity and mortality (Kuehner 2017; Lépine and Briley 2011; Mathers 2008; Rei et al. 2018).

Both endometriosis and depression carry considerable personal, social, as well as economic burdens on sufferers, their families, and indeed the larger society (Greenberg et al. 2015; Rush and Misajon 2018). A recent study (Rush and Misajon 2018), for example, reveals that the personal wellbeing index for women with endometriosis was lower than those reported for other chronic diseases including cancers and HIV/AIDS (Cummins et al. 2009; Hutton et al. 2013). Similarly, compared to the general population, depressed patients have over 20-fold increased risks of mortality from suicide (Bachmann 2018; Lépine and Briley 2011; Ösby et al. 2001). Despite the consistent evidence on the growing global burden of endometriosis and depression (Chisholm et al. 2016; Lépine and Briley 2011; Rush and Misajon 2018), their adverse impacts on patients' quality of life and consequences for higher risks of morbidity, infertility (endometriosis) and mortality (depression), the two disorders remain underdiagnosed, often misdiagnosed and undertreated, worldwide (Bedaiwy et al. 2017; Centers for Disease Control and Prevention 2010; Ghai et al. 2020; Lépine and Briley 2011; Ricky and O'Donnell Siobhan 2017). Also, while several theories have been proposed to explain the pathogenesis of endometriosis (Burney and Giudice 2012; Sampson 1925; Sourial et al. 2014) and depression (Gałecki and Talarowska 2018; Hasler 2010), the etiologies of the two disorders remain relatively obscure. There is currently no sufficient evidence on the effectiveness of laboratory diagnostic markers for endometriosis or depression just as no

known treatment offers curative assurance for any of them (Bedaiwy et al. 2017; Gupta et al. 2016; Marian and Hermanowicz-Szamatowicz 2020; Strawbridge et al. 2018).

Evidence from observational studies indicates that a significant association exists between endometriosis and depression (Cavaggioni et al. 2014; Lorencatto et al. 2006; Pope et al. 2015). For example, a study in the United States, found the prevalence of depression to be nearly two-fold higher among women with endometriosis than in the general population (6.8% vs 3.9%, $P < 0.001$) (Mirkin et al. 2007). Another study reported more than twice the prevalence of depression in endometriosis cases compared to controls (39.4% vs 18.6%, $P = 0.045$) in an Italian population (Cavaggioni et al. 2014). A longitudinal follow-up study similarly found elevated risks of major depression and any depression among endometriosis patients with estimated hazard ratios (HR) of 1.56 (95%CI: 1.24–1.97) and 1.44 (95%CI: 1.25–1.65), respectively (Chen et al. 2016). More recently, another longitudinal study reported bidirectional relationships between endometriosis and several psychiatric disorders including depressive disorders (endometriosis as the outcome variable [Adjusted HR = 1.89 (95%CI: 1.78–2.01)]; depressive disorder as the outcome variable [Adjusted HR = 1.81 (95%CI: 1.71–1.92)]) (Gao et al. 2020). These associations are supported also in animal models; female mice with induced endometriosis were found to be 'more depressed', and 'anxious compared to sham controls' with evidence for gene expression alterations in the brain (Li et al. 2018). Similar findings were reported in another recent animal study in rats models (Lima Filho et al. 2019). Comorbid depression in endometriosis patients may predispose to disease worsening, poor prognosis, lower quality of life and increased cost of treatments (Mirkin et al. 2007; Valderas et al. 2009).

Notwithstanding the number of studies reporting a significant association between endometriosis and depression, the biological mechanism(s) underlying their possible comorbid relationship remain(s) unknown. A recent systematic review and meta-analysis of cross-sectional studies concluded that the association between endometriosis and depressive symptoms is largely determined by chronic pain (Gambadauro et al. 2019). The study reported that i) endometriosis patients with pelvic pain had higher levels of depressive symptoms compared to endometriosis patients without pelvic pain (Gambadauro et al. 2019), and ii) women with pelvic pain and endometriosis do not have higher levels of depressive symptoms compared to women with pelvic pain and no endometriosis. These results are consistent with the previous finding of when pain is moderate to severe, it is associated with more depressive symptoms (Bair et al. 2003); and suggest that depressive symptoms are related to chronic pain

rather than endometriosis (Gambadauro et al. 2019). However, further interpretation of these results is limited due to their reliance on cross-sectional data (Gambadauro et al. 2019). Also, given that both endometriosis and depression are complex disorders, we hypothesize that pain does not seem plausible for a complete explanation of their potential comorbid relationship. Moreover, several other studies did not find a significant association between endometriosis and depressive symptoms (Cavaggioni et al. 2014; Gambadauro et al. 2019; Novais et al. 2018). Hence, clear, and convincing evidence on the comorbidity, as well as the possible biological mechanisms underlying endometriosis and depression association is lacking.

With a twin-based heritability (the proportion of variance in phenotypes explained by variance in genotype) estimate of about 0.50 and single nucleotide polymorphism (SNP)-based heritability of 0.26, there is strong evidence for a role of genetic factors in the risk of endometriosis (Kennedy 1999; Lee et al. 2012; Montgomery et al. 2008; Simpson and Bischoff 2002; Stefansson et al. 2002). Similarly, consistent evidence supports the contribution of genetics in the development of depression (Levinson 2006; Ripke et al. 2013), with a twin-based heritability estimate of 0.31–0.42 (Sullivan et al. 2000). Indeed, several genome-wide association studies (GWAS) have been conducted and an increasing number of SNPs, as well as susceptibility loci, are being identified for both endometriosis and depression (Howard et al. 2019; Sapkota et al. 2017; Wray et al. 2018). No study has, however, leveraged on the possible pleiotropy of genetic variants among the two disorders as a basis for the discovery of new susceptibility loci shared by both endometriosis and depression. Furthermore, studies with a specific focus on the mechanism of association between endometriosis and depression, using the molecular genetic study approach, are lacking.

Therefore, we comprehensively assessed the genetic relationship between endometriosis and depression by analyzing large population-based GWAS data. The approaches used in this study minimize the challenges often associated with the conventional observational studies such as small sample sizes, the bias of reverse causation and the confounding influence of environments or lifestyles. Moreover, analysis of such molecular genetic data offers a unique opportunity to assess not only the shared genetics but also the potential causal associations between the two traits. Hence, findings in the present study will improve our understanding of the genetic architecture of the two disorders, as well as provide insights into the mechanisms of their co-occurrence. This knowledge is expected to contribute to efforts aimed at identifying druggable targets and subsequently enhance better outcomes for both endometriosis and depression.

Materials and Methods

Our study comprises five broad components. First, we assessed the molecular genetic overlap and correlation between endometriosis and depression using SNP effect concordance analysis (SECA) and linkage disequilibrium score regression (LDSC) analysis methods, respectively. Second, leveraging on the power afforded by pooling GWAS data, we investigated SNPs and loci shared by the two traits using cross-disorder meta-analysis of GWAS. Third, utilizing Mendelian randomization (MR), we assessed potential causal relationships between endometriosis and depression. Fourth, to identify genes shared by endometriosis and depression as well as assess gene-level genetic overlap, we performed gene-based association studies and independent gene-based test. Lastly, to gain mechanistic insights into the biology of the two disorders, we investigated biological pathways shared by endometriosis and depression using pathway-based functional enrichment analysis method.

Data sources

GWAS summary statistics data sourced from large international consortia including the International Endogene Consortium (IEC, endometriosis GWAS data) (Sapkota et al. 2017) and the Psychiatric Genomics Consortium (PGC, PGC_UKB depression GWAS data) were utilized for analyses in the present study. There is no sample overlap between these two GWAS data; hence, limitations associated with overlap of samples do not apply in our study.

IEC Endometriosis GWAS data

The 'IEC endometriosis' GWAS summary statistics data analyzed in this study have been well described in previous studies (Adewuyi et al. 2020; Sapkota et al. 2017). In brief, the data consist of a total sample of 208,912 individuals (17,054 cases of endometriosis and 191,858 controls), and 6,979,035 SNPs (that passed quality control in at least 50% of the studies), representing the largest GWAS published to date in the genetic study of endometriosis (Sapkota et al. 2017). The 'IEC endometriosis' GWAS data combined 11 separate GWA case-control data sets as previously described in Sapkota et al. (2017). Similar quality control (QC) procedures were applied in each of the individual datasets and study participants were of European (93%) and Japanese (7%) ancestry from Australia, Iceland, Belgium, the UK, the USA, Denmark and Japan (Sapkota et al. 2017).

Depression GWAS data

The '2019 PGC_UKB Depression Genome-wide' summary data ('PGC_UKB depression' GWAS data) analyzed in our study were obtained from the PGC (https://www.med.unc.edu/pgc/). The 'PGC_UKB depression' GWAS combines two large depression data sourced from the PGC and the United Kingdom Biobank (UKB). The PGC components of the data comprise of a meta-analysis of 33 cohorts (excluding the 23andMe and the UKB data) and have been previously described (Wray et al. 2018). The second component of the 'PGC_UKB depression' GWAS data was obtained from the UKB broad depression phenotype described in (Howard et al. 2019). Together, the PGC_UKB depression' GWAS data consist of a total sample of 500,199 individuals (170,756 cases of depression and 329,443 controls), of European ancestry, and a total of 8,483,301 SNPs.

To test the reproducibility of our study, we utilized two additional depression datasets—the 2018 major depressive disorder (MDD) GWAS and the self-reported depression GWAS, sourced from the PGC and the UKB, respectively. The 2018 MDD GWAS comprised of 135,458 cases and 344,901 controls (Wray et al. 2018). Of these, 75,607 cases and 231,747 controls were obtained from 23andMe. The data utilized in the present study (the 'PGC 2018 MDD excl23andMe') excluded the 23andMe data (to avoid sample overlap with the IEC endometriosis GWAS) and consisted of 59,851 cases, 113,154 controls, and a total of 13,554,551 SNPs. A more comprehensive description of the data has previously been published (Wray et al. 2018). The self-reported depression UKB GWAS data (https://atlas.ctglab.nl/ukb2_sumstats/20002_1286_logistic.EUR.sumstats.MACfilt.txt.gz) consist of 289,307 individuals (cases = 22,055, control = 267,252) and 10,321,706 SNPs.

Assessing SNP-level genetic overlap

We assessed the SNP-level genetic overlap between endometriosis and depression using the standalone version of SECA (https://sites.google.com/site/qutsgel/software/seca-local-version) (Nyholt 2014). We used the default '*P* value informed' setting of SECA to extract the subset of independent SNPs overlapping the two GWAS datasets accounting for linkage disequilibrium (LD) $r^2 < 0.1$. We first assigned the 'IEC endometriosis' GWAS as dataset 1 and the 'PGC_UKB depression' GWAS as dataset 2 to extract the set of independent SNPs with the smallest endometriosis GWAS *P* values. We performed an analogous analysis in which the 'PGC_UKB depression' GWAS was assigned as dataset 1 and the 'IEC endometriosis' GWAS as dataset 2 to analyze the set of independent SNPs with the smallest

depression GWAS *P* values. This procedure enabled us to assess and allow for possible differences between the two GWAS to detect association at their overlapping SNPs or where one trait may be more predictive of the other (Adewuyi et al. 2020; Nyholt 2014). Last, we utilized the 'PGC 2018 MDD excl23andMe' and the 'self-reported depression UKB' GWAS in reproducibility testing for the SNP-level genetic overlap between endometriosis and depression. A more comprehensive description of our SNP-level genetic overlap assessment is presented in Supplemental Note 1.

Cross-disorder genetic correlation

We estimated the SNP-based heritability as well as examined the genetic correlation between the 'IEC endometriosis' GWAS and the 'PGC_UKB depression' GWAS, using the LDSC method (https://github.com/bulik/ldsc) (Bulik-Sullivan et al. 2015). We performed further analyses to test the reproducibility of the genetic correlation between endometriosis and depression using two additional GWAS datasets, the 'PGC 2018 MDD excl23andMe' and the 'self-reported depression UKB' GWAS. Supplemental Note 1 provides more comprehensive and specific details of this analysis.

Cross-disorder meta-analysis of endometriosis and depression GWAS

To identify SNPs and loci shared by both endometriosis and depression, we performed a cross-disorder meta-analysis of 'IEC endometriosis' and the 'PGC_UKB depression' GWAS data. Complementary models of meta-analysis methods including the inverse variance-weighted fixed effects (FE), the conventional random effects (RE) and the 'Han and Eskin's random effects' (RE2) models (Han and Eskin 2011) were utilized in the present study. The FE model is limited under heterogeneity while the RE is overly conservative. The RE2, a modified RE model, is optimized for detecting associations even where heterogeneity exists (Han and Eskin 2011). All these models were implemented in the METASOFT software (http://genetics.cs.ucla.edu/meta) (Han and Eskin 2011). We included a total of 709,111 participants and meta-analyzed 6,694,342 SNPs overlapping the two GWAS datasets. Identifying SNPs and loci reaching genome-wide *significant* association ($P < 5 \times 10^{-8}$) in the meta-analysis, and, associated with both endometriosis and depression GWAS at $5 \times 10^{-8} < P < 0.05$, was the major aim of the present analysis.

Using FUMA (Watanabe et al. 2017), we identified significant independent SNPs alongside SNPs in LD with them, defined lead SNPs as well as characterized the associated genomic loci ($r^2 < 0.1$). SNPs reaching genome-wide significant association ($P < 5 \times 10^{-8}$, $n = 625$) in the

cross-disorder meta-analysis but not in the individual endometriosis and depression GWAS ($5 \times 10^{-8} < P < 0.05$) were used for this analysis. We first identified genome-wide significant independent SNPs at $r^2 < 0.6$ (that is SNPs that are independent of one another at $r^2 < 0.6$). From these, lead SNPs, defined as a subset of significant independent SNPs in LD with each other at $r^2 < 0.1$, were determined. Genomic loci were thereafter characterized with respect to a physical distance of 250 kb from each lead SNP. In other words, lead SNPs within 250 kb from each other were merged into the same genomic locus. Hence, more than one independent or lead SNP may be present in a genomic locus.

Further, we performed gene mapping in which all the SNPs reaching genome-wide significance were mapped to genes using three gene mapping strategies, implemented in FUMA (Watanabe et al. 2017). Briefly, SNPs were first annotated with their biological functions and subsequently linked to genes using the three methods (positional, expression quantitative trait loci [eQTL], and chromatin interaction) in line with practice in previous studies (Nagel et al. 2018; Watanabe et al. 2017). Additionally, we performed a gene-based genome-wide association study (GBGWAS) on the same set of SNPs using MAGMA software (implemented in FUMA). A detailed description of our cross-disorder meta-analysis, genomic loci characterization, SNP annotation, and functional gene mapping is provided in Supplemental Note 1.

Association between significant independent SNPs and other traits

We assessed a possible SNP-phenotype association between our independent genome-wide significant SNPs and other previously published GWAS traits. Specifically, we assessed whether our independent SNPs were associated with traits previously reported to be associated with endometriosis or depression. This assessment was carried out using PhenoScanner (v2, accessed on 07/01/2020) at $P < 5 \times 10^{-8}$) (Staley et al. 2016).

Assessing causal relationships between endometriosis and depression

We assessed a causal relationship between endometriosis (exposure variable) and depression (outcome variable) utilizing the two-sample Mendelian randomization analysis ("TwoSampleMR") method (https://mrcieu.github.io/TwoSampleMR) (Hemani et al. 2018) implemented in the R statistical software. To estimate the weighted mean of depression risk per standard deviation increase in the risk of endometriosis, we utilized the inverse variance weighted (IVW) MR model in which the effects of the individual IVs were combined (Burgess et al. 2020). To test the validity of our IVW results, we conducted sensitivity analyses using the weighted median estimation, the MR-Egger regression, and the MR-PRESSO (Mendelian

randomization pleiotropy residual sum and outlier) methods (Verbanck et al. 2018). We also assessed the causal influence of depression on endometriosis in which depression was assessed as an exposure variable and endometriosis as an outcome variable. Additional details of these analyses are provided in Supplemental Note 1.

Gene-based association study

To complement our SNP-level genetic overlap analysis across endometriosis and depression GWAS, and identify genes shared by the two disorders, we performed gene-based association analyses for the two traits. Unlike the SNP-based study which can be limited by small effect sizes, allelic heterogeneity and correlation among SNPs, gene-level association analysis aggregates the effects of multiple SNPs and may provide greater power for identifying risk variants for a complex trait (Liu et al. 2010; Zhao and Nyholt 2017). The MAGMA software, implemented in FUMA, was used to perform this analysis (de Leeuw et al. 2015; Watanabe et al. 2017). A total of 6,694,342 SNPs overlapping the endometriosis and depression GWAS was used in computing gene-based *P* values for the respective traits. SNPs were mapped in MAGMA to a gene if they were located within the gene (i.e., a window of '+/- 0kb outside the gene') in our analysis. From the results of our MAGMA analysis, we extracted and assessed genes with *P* values at $P_{gene} < 0.1$ overlapping both traits. To identify shared genome-wide significant genes for both endometriosis and depression, we combined gene-based association *P* values for the two disorders using the Fisher's Combined *P* value (*FCP*) method.

Independent gene-based test

Using the genetic type 1 error calculator (GEC) (Li et al. 2012), we conducted independent gene-based tests, first to identify the effective number of independent genes, and second to generate data for assessing the gene-level genetic overlap between endometriosis and depression**.** GEC estimates independent markers while accounting for LD and adjusting for multiple testing corrections (Li et al. 2012). We first performed a gene-based test for endometriosis and depression using VEGAS2 software. We used 'ALL' chromosomes, restricted gene definition to '+/- 0kb outside gene' and selected sub-population from 'ALL EUROPEAN' in our VEGAS2 gene-based analysis (Adewuyi et al. 2020; Mishra and Macgregor 2015). Given our aim of performing an independent gene-based test, we specified the 'Best-SNP test' option in our VEGAS2 gene-based analysis (Adewuyi et al. 2020; Mishra and Macgregor 2015). We processed 'Best-SNPs' (index SNPs) obtained in our gene-based

analysis, for endometriosis and depression, respectively, as input files for GEC. See Supplemental Note 1 for further details of this analysis.

Assessing gene-level genetic overlap

We assessed whether the proportion of overlapping genes, between endometriosis and depression, at three nominal *P* values ($P_{gene} < 0.1$, $P_{gene} < 0.05$, and $P_{gene} < 0.01$) thresholds, were more than expected by chance. The independent gene-based analyses results were utilized for this analysis. First, we estimated the effective number of independent genes overlapping endometriosis and depression at the three-nominal *P* values. Second, we assigned endometriosis as the 'discovery' and depression as the 'target' set; and thereafter, calculated the proportion of expected as well as observed genes overlapping the two traits. Last, using the binomial test, we compared the proportion of observed and expected overlapping independent genes across the three *P* value thresholds to assess the statistical significance of their respective differences. In other words, we assessed whether the proportion of overlapping genes observed were significantly higher than by chance. The expected proportion of overlapping genes was defined as the effective number of independent genes with a *P* value less than the threshold in the target set divided by the total effective number of independent genes in the target set (Adewuyi et al. 2020; Zhao et al. 2016). The observed proportion of overlapping genes was calculated as the observed effective number of independent overlapping genes divided by the effective number of independent genes with a *P* value less than the threshold in the discovery set (Adewuyi et al. 2020; Zhao et al. 2016).

Gene-drug targets search

We searched for 'gene-drug interactions' and 'potential targets for drugs' using the drug-gene interaction database (DGIdb 3.0, www.dgidb.org, accessed on 24/12/2019) (Cotto et al. 2017; Griffith et al. 2013). Utilizing genes overlapping endometriosis and depression at $P_{gene} < 0.1$, we first searched 20 DGIdb drug-gene source databases to identify interactions with existing medicines based on 41 gene categories and 51 types of known interactions. We filtered drugs that interact with our input genes using the following terms or categories: antineoplastic, immunotherapies and the United States Food and Drug Administration (FDA) approved pharmaceutical molecules. Moreover, to identify genes for potential therapeutic targets (druggable targets), we conducted a further search in 10 source databases (implemented in the DGIdb tool), based on 41 gene categories. A list of overlapping genes having $P_{gene} < 0.1$ were similarly used as an input in the druggable targets search.

Pathway-based functional enrichment analysis

We conducted functional enrichment analysis using the 'g:GOSt' tool, implemented in the 'g-profiler' software (Raudvere et al. 2019; Reimand et al. 2016), to identify significantly enriched (overrepresented) biological processes and pathways underlying endometriosis and depression. We utilized the web version of the 'g:GOSt' tool (accessed on 15th December 2019) to analyze genes overlapping endometriosis and depression GWAS at $P_{gene} < 0.1$, in the present study. We applied the recommended 'g:SCS algorithm' in multiple testing correction and restricted term size (functional category) of the significantly enriched pathways to the recommended 5 and 350 values (Adewuyi et al. 2020; Raudvere et al. 2019). By default, the 'g:GOSt' software only reports overrepresented pathways at the adjusted enrichment *P* value (P_{adj}) < 0.05 (Raudvere et al. 2019). Given some of the significantly enriched pathways may be redundant, we carried out enrichment mapping, collapsing related pathways into similar biological themes, and subsequently enhancing the visualization of overrepresented pathways (Merico et al. 2010; Reimand et al. 2019). Lastly, to further enhance the interpretation of our results, we organized 'enrichment maps' (biological themes of pathways generated using the 'enrichment mapping' method) into clusters using the 'auto annotate' software (Reimand et al. 2019). The 'enrichmentmap' and 'auto-annotate' applications were implemented in the Cytoscape platform (version 3.7.1) (Reimand et al. 2019; Shannon et al. 2003).

Results

SNP-level genetic overlap between endometriosis and depression

The first aspect of this study assessed SNP-level genetic overlap between the endometriosis and depression GWAS utilizing SECA. Results indicate that a significant genetic overlap, more than expected by chance, exists between endometriosis and depression. In the primary test for concordance of effects, all 144 SNP subsets across 'IEC endometriosis' and 'PGC_UKB depression' GWAS produced nominally significant concordance of effects (Fisher's exact test OR > 1 and $P < 0.05$)—a result unlikely to have occurred by chance, with a permuted *P* value ($P_{Fsig\text{-}permuted}$) of 9.99×10^{-4} (95%CI: 5.12×10^{-5}–5.64×10^{-3}). The most statistically significant *P* value for effects concordance ($P = 1.04 \times 10^{-19}$, $OR_{FT} = 1.31$) was for SNP subsets with $P1 \leq 0.3$ (endometriosis) and $P2 \leq 0.4$ (depression). When the direction of the analysis was reversed (see methods), the total number of SNP subsets producing nominally significant concordance effects remained unchanged at 144, further supporting our findings of significant genetic overlap between the two traits.

Additional results from SECA reveal that of the total 50,413 independent SNPs (LD independent [$r^2 < 0.1$]) overlapping both the IEC Endometriosis and the PGC-UKB depression GWAS, 26,102 (51.8%) SNP effects were significantly concordant across the two traits (OR = 1.13, $P_{Fisher's\text{-}exact} = 1.36 \times 10^{-11}$). Notably, and in line with expectation (Table 1), SNP subsets with smaller *P* values (*P*1 and *P*2) exhibit even greater effect concordance (measured by OR). For instance, at $P < 0.05$ (SNP subsets with $P1 = P2 < 0.05$), 57.8% (1,065) of the 1,844 independent SNPs were concordant (OR = 1.86, $P_{Fisher's\text{-}exact} = 4.72 \times 10^{-11}$). The proportion of effect concordance increased to 66.7% for SNP subsets with $P1 = P2 < 0.01$ (OR = 3.98, $P_{Fisher's\text{-}exact} = 2.67 \times 10^{-7}$). Reproducibility testing using two separate depression GWAS (the MDD 2018 and the self-reported UKB depression GWAS) revealed a similar pattern of results (Supplementary Table S1 and S2). For example, at $P1 = P2 < 0.01$ (for the 'IEC endometriosis' and the 'PGC 2018 MDD excl23andMe' GWAS genetic overlap assessment), the OR was 3.95 ($P_{Fisher's\text{-}exact} = 3.28 \times 10^{-4}$). Similarly, OR was 3.27 ($P_{Fisher's\text{-}exact} = 2.14 \times 10^{-3}$) for the genetic overlap between the 'IEC endometriosis' and the 'self-reported UKB depression' at $P1 = P2 < 0.01$ (Supplementary Table S1 and S2).

Table 1 Genetic overlap between endometriosis and depression

***P*1**	***P*2**	[a]**Total SNPs**	**Concordant SNPs**	**Proportion of concordance**	**OR**	[b]$P_{Fishers\text{-}exact}$
≤1	≤1	50,413	26,102	0.52	1.13	1.36×10^{-11}
0.9	0.9	45,446	23,502	0.52	1.15	2.88×10^{-13}
0.8	0.8	40,343	20,939	0.52	1.17	2.20×10^{-14}
0.7	0.7	35,086	18,339	0.52	1.20	2.07×10^{-17}
0.6	0.6	29,807	15,656	0.52	1.22	3.27×10^{-18}
0.5	0.5	24,608	12,977	0.53	1.24	1.16×10^{-17}
0.4	0.4	19,416	10,313	0.53	1.28	4.81×10^{-18}
0.3	0.3	14,178	7,596	0.54	1.33	1.85×10^{-17}
0.2	0.2	9,022	4,877	0.54	1.38	1.47×10^{-14}
0.1	0.1	4,049	2,252	0.56	1.57	9.13×10^{-13}
0.05	0.05	1,844	1,065	0.58	1.86	4.72×10^{-11}
0.01	0.01	246	164	0.67	3.98	2.67×10^{-7}

*P*1: *P* value for the International Endogene Consortium (IEC) Endometriosis data; *P*2: *P* value for the PGC-UKB depression data; SNP: Single Nucleotide Polymorphism; OR: Odds ratio for the effect direction concordance association test for endometriosis and depression; $P_{Fishers\text{-}exact}$: Fisher's exact *P* value for the effect direction concordance association test between endometriosis and depression. [a]There was a total 50,413 independent SNPs (LD independent [$r^2 < 0.1$]) with smallest *P* values in the IEC Endometriosis GWAS.

Genetic correlation between endometriosis and depression

To further assess the SNP-level genetic overlap between endometriosis and depression GWAS, we examined the correlation between endometriosis and depression using the LDSC software. Univariate LDSC analysis estimated SNP-based heritability on the liability scale (h^2_{SNP}) of 11.44% (95%CI: 10.73–12.15%) for endometriosis and 8.02% (95%CI: 7.77–8.27%) for depression. Also, bivariate LDSC analysis found a positive and highly significant genetic correlation (r_G) between endometriosis and depression ($r_G = 0.27$, $P = 8.85 \times 10^{-27}$). LDSC results are provided in Table 2. Notably, we reproduced the significant genetic correlation between endometriosis and depression using two separate depression GWAS (Table 2).

Table 2 LD Score regression analysis summary

A. SNP-based Heritability			
Phenotype	**Dataset source**	**Liability scale h^2_{SNP} (95% CI)**	**h^2 Intercept (se)**
Endometriosis	IEC	11.44% (10.73–12.15%)	Constrained to 1
PGC-UKB depression	PGC-UKB 2019	8.02% (7.77–8.27%)	Constrained to 1
MDD	PGC 2018	6.93% (6.64–7.22%)	0.9945 (0.0087)
Depression	UKB	8.25% (7.08–9.41%)	Constrained to 1

B. SNP-based Genetic Correlation					
Phenotype 1 (data source)	**Phenotype 2 (data source)**	**rG (se) [*P* value]**	**Phenotype 1 h^2 Intercept**	**Phenotype 2 h^2 Intercept**	**Gencov Intercept**
Endometriosis (IEC)	Depression (PGC-UKB, 2019)	0.27 (0.0248) [8.85×10^{-27}]	Constrained to 1	Constrained to 1	Constrained to 0
Endometriosis (IEC)	MDD (PGC 2018)	0.28 (0.0321) [1.79×10^{-18}]	Constrained to 1	0.9945 (specified)	Constrained to 0
Endometriosis (IEC)	Depression (UKB)	0.21 (0.0476) [1.10×10^{-5}]	Constrained to 1	1.0123	Constrained to 0

IEC: International Endogene Consortium, PGC: Psychiatric Genomic Consortium, UKB: United Kingdom BioBank, SNP: Single Nucleotide Polymorphism, h2**:** heritability**,** $h2_{SNP}$: SNP-based heritability, CI: Confidence Interval, se: Standard error

GWAS meta-analysis results

We performed a cross-disorder meta-analysis of endometriosis and depression GWAS to identify genome-wide significant SNPs and loci shared by both traits. A total of 625 SNPs was significant ($P_{SNP} < 5\times10^{-8}$) in the FE model of our cross-disorder meta-analysis (Supplementary Table S3), all of which were at least nominally significant ($P < 0.05$), but not genome-wide significant in the individual endometriosis and depression GWAS (i.e., $5 \times 10^{-8} < P < 0.05$). From the 625 SNPs reaching genome-wide significant association, we identified 34 moderately independent (LD $r^2 < 0.6$) SNPs (Table 3A). Of these 34 SNPs, 22 were characterized as lead SNPs (genome-wide significant SNPs that are independent of one another

at LD $r^2 < 0.1$). A total of 20 independent genomic loci were characterized as having lead SNPs at least 250 kb from another lead SNP (i.e., lead SNPs within 250 kb from each other were merged into the same genomic locus). Thus, the 22 lead SNPs were in 20 genomic loci, with two loci containing two independent lead SNPs each. Eight of the 20 independent genomic loci have not previously been reported at a genome-wide level of significance for endometriosis or depression, thus, they represent novel loci for the two disorders (Table 3A).

Table 3 Summary of the independent genome-wide significant SNPs and loci for endometriosis and depression GWAS meta-analysis

Independent SNPs	Loci index	Lead SNP	Chr	Position (hg19)	EA	NEA	FE Meta-analysis		Endometriosis		Depression		Nearest coding gene/ cytoband
							OR	*P* value	OR	*P* value	OR	*P* value	
A. Summary of 'IEC endometriosis' and 'PGC-UKB depression' GWAS meta-analysis													
Loci linked with depression index SNPs													
rs1395455	1	rs1395455	1	37185190	A	G	1.025	4.09×10^{-8}	1.03	4.05×10^{-2}	1.024	2.92×10^{-7}	*CSF3R/ 1p34.3*
rs1620977	2	rs1620977	1	72729142	A	G	1.027	1.44×10^{-8}	1.037	2.19×10^{-2}	1.026	1.69×10^{-7}	*NEGR1/ 1p31.1*
rs12738134	3	rs12121863	1	197470756	A	T	0.971	1.17×10^{-8}	0.961	2.81×10^{-2}	0.972	1.01×10^{-7}	*CRB1/1q31.3*
rs1998711			1	197546093	A	T	0.976	1.87×10^{-9}	0.947	6.93×10^{-5}	0.979	4.96×10^{-7}	*DENND1B/1q31.3*
rs12121863			1	197785420	A	G	1.033	3.54×10^{-10}	1.065	2.22×10^{-4}	1.030	8.22×10^{-8}	*DENND1B/1q31.3*
rs1553172			1	197818233	A	G	1.023	4.62×10^{-8}	1.053	1.57×10^{-4}	1.020	6.47×10^{-6}	*C1orf53/1q31.3*
rs35207123			1	197827444	A	C	1.030	3.61×10^{-8}	1.063	5.12×10^{-4}	1.027	2.89×10^{-6}	*C1orf53/1q31.3*
rs11130182	4	rs9586	3	49206767	T	C	0.976	1.84×10^{-8}	0.952	5.87×10^{-4}	0.978	1.22×10^{-6}	*KLHDC8B/3p21.31*
rs9586			3	49213637	T	C	0.969	2.36×10^{-10}	0.939	1.24×10^{-4}	0.972	5.06×10^{-8}	*KLHDC8B/3p21.31*
rs9835157			3	49797769	A	G	1.034	3.80×10^{-10}	1.067	2.92×10^{-4}	1.031	6.58×10^{-8}	*IP6K1/3p21.31*
rs12512642	5	rs12512642	4	131209887	T	C	1.028	4.93×10^{-8}	1.044	2.71×10^{-2}	1.027	3.48×10^{-7}	*SCLT1/ 4q28.2*
rs13164188	6	rs13164188	5	103914523	T	C	1.025	9.21×10^{-9}	1.034	2.37×10^{-2}	1.024	1.32×10^{-7}	*NUDT12/ 5q21.2*
rs10085215	7	rs9885896, rs12206488	6	66559858	A	C	0.974	4.77×10^{-9}	0.968	2.46×10^{-2}	0.975	5.75×10^{-8}	*EYS/6q12*
rs9885896			6	66595931	A	G	0.976	3.53×10^{-9}	0.960	2.14×10^{-3}	0.978	2.00×10^{-7}	*EYS/6q12*
rs4710557			6	66623210	C	G	1.029	1.43×10^{-8}	1.040	1.92×10^{-2}	1.027	1.49×10^{-7}	*EYS/6q12*
rs767069			6	66646546	A	G	1.025	7.31×10^{-9}	1.030	3.50×10^{-2}	1.025	8.01×10^{-8}	*EYS/6q12*
rs12206488			6	66999917	T	G	1.031	2.23×10^{-9}	1.047	7.67×10^{-3}	1.029	5.12×10^{-8}	*EYS/6q12*
rs2328370	8	rs2328370	6	143006706	A	C	1.023	3.21×10^{-8}	1.031	2.55×10^{-2}	1.023	2.48×10^{-7}	*HIVEP2/6q24.2*
rs11561993	9	rs11561993	7	109102855	T	C	1.025	2.28×10^{-9}	1.036	9.25×10^{-3}	1.024	6.77×10^{-8}	*DNAJB9/7q31.1*
rs72694248	10	rs1931391, rs62553458	9	11120126	T	G	1.031	3.99×10^{-8}	1.039	4.19×10^{-2}	1.030	2.72×10^{-7}	*PTPRD/ 9p24.1-p23*
rs1931391			9	11213674	A	T	1.025	8.32×10^{-9}	1.027	4.92×10^{-2}	1.024	6.61×10^{-8}	*PTPRD/9p24.1-p23*
rs62553458			9	11695224	A	G	0.951	9.48×10^{-9}	0.934	4.65×10^{-2}	0.952	6.28×10^{-8}	*TYRP1/9p23*
rs13299293	11	rs13299293	9	31234705	A	T	0.976	2.03×10^{-9}	0.961	8.33×10^{-3}	0.977	5.31×10^{-7}	*ACO1/ 9p21.1*
rs5021654			11	88910589	C	G	1.024	7.96×10^{-9}	1.033	1.77×10^{-2}	1.024	1.10×10^{-7}	*TYR/11q14.3*

rs7933594	12	rs7933594	11	88973201	T	C	1.026	5.67×10^{-9}	1.031	3.60×10^{-2}	1.026	4.10×10^{-8}	*TYR/11q14.3*
rs1967203			11	89055293	A	G	0.977	3.73×10^{-8}	0.966	2.19×10^{-2}	0.978	5.56×10^{-7}	*TYR/11q14.3*
Novel Loci													
rs6680839	13	rs6680839	1	175902596	T	C	0.975	9.18×10^{-10}	0.952	5.24×10^{-4}	0.977	1.25×10^{-7}	*TNR/1q25.1*
rs72740410	14	rs72740410	1	191115099	T	C	1.048	1.25×10^{-8}	1.049	7.44×10^{-2}	1.048	6.65×10^{-8}	*BRINP3/1q31.1*
rs13118306	15	rs13118306	4	15477812	C	G	0.977	3.65×10^{-8}	0.960	3.76×10^{-3}	0.979	1.21×10^{-6}	*CC2D2A/4p15.32*
rs2134025	16	rs2134025	4	104932297	A	G	1.029	1.02×10^{-8}	1.057	4.12×10^{-4}	1.026	1.31×10^{-6}	*TACR3/4q24*
rs9347896	17	rs9347896	6	165077749	A	G	1.029	1.32×10^{-8}	1.033	4.56×10^{-2}	1.028	7.80×10^{-8}	*C6orf118/6q27*
rs11784932	18	rs11784932	8	130095478	A	C	1.026	2.82×10^{-8}	1.057	2.57×10^{-4}	1.023	3.25×10^{-6}	*GSDMC/ 8q24.21*
rs9538160	19	rs9538160	13	59254159	A	G	0.976	2.71×10^{-8}	0.964	8.96×10^{-3}	0.978	5.17×10^{-7}	*PCDH17/ 13q21.1*
rs35625885	20	rs35625885	15	96957969	A	G	0.965	1.33×10^{-8}	0.953	2.04×10^{-2}	0.966	2.10×10^{-7}	*NR2F2/15q26.2*
B. Summary of the meta-analysis of 'IEC endometriosis' and 'PGC 2018 MDD excluding 23andME' GWAS													
rs6808036	1	rs6808036	3	49236439	T	G	1.044	2.49×10^{-8}	1.065	4.31×10^{-5}	1.037	4.52×10^{-5}	*CCDC36/ 3p21.31*
rs323509	2	rs323509	5	104082179	A	C	1.042	2.15×10^{-8}	1.031	3.68×10^{-2}	1.046	1.45×10^{-7}	*NUDT12/ 5q21.2*
rs116810322	3	rs116810322	6	30223490	T	C	1.042	9.70×10^{-9}	1.064	4.79×10^{-5}	1.036	1.47×10^{-5}	*TRIM26/ 6p22.1*
rs1931388	4	rs1931388	9	11203149	A	G	1.039	4.44×10^{-8}	1.030	3.91×10^{-2}	1.042	3.01×10^{-7}	*PTPRD/ 9p24.1-p23*
C. Summary of the meta-analysis of 'IEC endometriosis' and 'UKB self-reported depression' GWAS													
rs6788293	1	rs6788293	3	13719848	T	C	0.952	$2.81 \times 10^{-8*}$	0.931	1.30×10^{-7}	0.972	4.75×10^{-3}	*LINC00620/ 3p25.1*

FE: Fixed effect; SNP: Single nucleotide polymorphism; Chr: Chromosome; EA: Effect allele; NEA: Non-effect allele; OR: Odds ratio. *RE2 model result reported (Table 3C) due to the substantial heterogeneity (I Square = 84.59). Of the 34 independent SNPs ($r^2 < 0.6$) reported in Table 3A, a total of 22 are independent from each other at $r^2 < 0.1$ (lead SNPs). Using physical regions in LD with lead SNPs that were >250 kb from each other, 20 genomic loci were characterized from the 34 independent SNPs. Lead SNPs within 250 kb of each other were merged into same locus; thus, the 22 lead SNPs were in 20 loci, with two genomic loci containing two lead SNPs each (Table 3A).

Our functional annotation analysis using FUMA (see methods), identified a total of 2,372 candidate SNPs (independent SNPs as well as those in LD with them at $r^2 \geq 0.6$), and 22 lead SNPs (genome-wide significant SNPs that are independent of one another at LD $r^2 < 0.1$). Most of the candidate SNPs were in the intergenic (66.30%), intronic (25.40%) and non-coding RNA (4.91%) regions (Supplementary **Fig. 1a**, and Supplementary Table S4). As evidenced by RegulomeDB scores having values less than two (Supplementary **Fig. 1b** and Supplementary Table S4), a total of 75 SNPs (3.20% of candidate SNPs) has a high likelihood of a regulatory function. Of the eleven exonic SNPs, six were synonymous while five were nonsynonymous (Supplementary **Fig.** 1**a**, and Supplementary Table S4 and S5). Several of the SNPs had a CADD score greater than 12.37 (Supplementary **Fig.** 1**c**) meaning they are potentially pathogenic. The nonsynonymous exonic SNP having the highest CADD score (an indication of strong deleterious effects) was rs1126809 (CADD score of 29.4). This SNP is located in exon 4 of *TYR* on chromosome 11 and it is in strong LD with a lead SNP (rs7933594, r^2 = 0.72), located at a genomic locus in LD with a depression index SNP (Table 3 and Supplementary Table S4).

Using three methods of gene mapping strategies, implemented in FUMA—positional, expression quantitative trait locus (eQTL), and chromatin interaction—we mapped the candidate SNPs to genes (see methods). Additionally, we carried out GBGWAS on the same set of SNPs using MAGMA software (implemented in FUMA). A total of 223 unique protein-coding genes was implicated, 20 of which were identified by all four methods (Supplementary **Fig.** 2, Supplementary Table S6, S7 and S8). A total of 49 genes were implicated by positional mapping, 73 by eQTL, and 217 by chromatin interaction mappings (Supplementary **Fig.** 2). GBGWAS analysis identified a total of 24 genome-wide significant genes (Supplementary **Fig.** 2 and Supplementary Table S7 and S8). Furthermore, we characterized a total of 90 independent loci reaching genome-wide *suggestive* association ($P < 1 \times 10^{-5}$) in the cross-disorder meta-analysis of the IEC endometriosis and the PGC-UKB depression GWAS (Supplementary Table S9).

Association between significant independent SNPs and other traits

Using PhenoScanner (v2), with an LD and significant threshold of $r^2 \geq 0.6$ and $P < 5 \times 10^{-8}$, respectively (Staley et al. 2016), we assessed whether the independent genome-wide significant SNPs identified in our meta-analysis were associated with other traits or conditions**.** Findings revealed a genome-wide significant ($P < 5 \times 10^{-8}$) association with several traits

(Supplementary Table S10). Notably, one of the independent significant SNPs, rs9835157 (hg19: chr3:49797769 A>G on chromosome 3p21.31) in *IP6K1* (encoding inositol hexakisphosphate kinase 1), was associated with several traits at a genome-wide significant level ($P < 5 \times 10^{-8}$), including qualifications (college or university degree), age at menarche, body mass index, pulse rate, impedance of the whole body, and overall health rating. One of these traits (age at menarche) is a risk factor for endometriosis (Nnoaham et al. 2012) and depression (Shen et al. 2019). Also, neuroticism (a possible risk factor for both endometriosis and depression) (Nyholt et al. 2009; Xia et al. 2011) was associated with one of the SNPs (rs62553458, hg19: chr9:11695224A>G). Lastly, rs13164188 (on chromosome*5q21.2)* was associated at a genome-wide significant level with waist circumference, hearing difficulty, as well as a doctor diagnosed 'bronchitis, emphysema, asthma, rhinitis, eczema or allergy'.

Replication of identified loci

To test whether the independent loci reaching genome-wide significance in our meta-analysis (for IEC endometriosis and PGC-UKB depression GWAS) can be replicated, we conducted additional meta-analyses using the 'PGC 2018 MDD excl23andMe' and the 'self-reported depression UKB' GWAS. Using the lead SNPs, we considered a locus reproduced when the *P* value obtained in a cross-disorder meta-analysis ($P_{[FE]}$ or $P_{[RE2]}$) is less than the respective *P* value for each of endometriosis and depression GWAS. The *P* value for each of endometriosis and depression GWAS must at the least be nominally significant ($P < 0.05$).

First, a meta-analysis of the 'IEC endometriosis' and the 'PGC 2018 MDD excl23andMe' reproduced 17 of the 20 independent loci at $P < 0.05$ (Supplementary Table S11). Although none of the loci reached genome-wide significant association, seven of them (rs9586 on chromosome 3p21.31, rs2134025 on 4q24, rs13164188 on 5q21.2, rs11561993 on 7q31.1, rs11784932 on 8q24.21, rs1931391 on 9p24.1-p23, and rs13299293 on 9p21.1) were genome-wide suggestive ($P < 1 \times 10^{-5}$, Supplementary Table S11). Also, additional four independent loci reached a genome-wide level of significance in the replication analysis (Table 3B), all (rs323509, rs1931388, rs116810322, rs1931388) of which have been identified in more powerful depression GWAS to be genome-wide significant (Howard et al. 2019; Nagel et al. 2018).

Second, meta-analyzing the 'IEC endometriosis' and the 'self-reported depression UKB' GWAS, we similarly reproduced 6 of the 20 loci at $P < 0.05$. Of these, two loci (rs12121863 on chromosome 1q31.3, and rs9586 on 3p21.31) were at least genome-wide suggestive

(Supplementary Table S12). Also, we identified an additional independent SNP locus shared by both endometriosis and depression (Table 3C).

Results of causal associations assessment

Table 4 summarizes the results of our MR analyses assessing the causal association between endometriosis and depression. Based on the IVW MR model (OR = 1.003, 95%CI: 0.967–1.041, P = 0.866), MR did not find evidence of a significant causal relationship between endometriosis (exposure variable) and depression (outcome variable). The results of our sensitivity analysis using the weighted median (OR = 1.018, 95%CI: 0.979–1.059, P = 0.371) and the MR Egger (OR = 1.134, 95%CI: 0.925–1.390, P = 0.258) models were consistent with that of the IVW in this respect (Table 4). The MR-Egger intercept was -0.0123 (SE: 0.0104), P = 0.262, which did not deviate significantly from zero, showing that there was no significant directional or unbalanced pleiotropy. Also, given the Cochran's Q statistics for IVW (Q = 17.23, degree of freedom, df = 10, P = 0.069) and MR-Egger (Q' = 14.87, df = 9, P = 0.095), there was no evidence for a significant heterogeneity. One of the SNPs (rs74485684) was associated with menstruation-related traits ('length of menstrual cycle' and 'excessive, frequent and irregular menstruation'). However, a leave-one-out analysis indicates that individual influential SNPs did not drive the observed results. A further assessment using the MR-PRESSO method supports the IVW model. For instance, MR-PRESSO's raw estimate was similar to that of the IVW (Table 4). Also, the 'global test' found no significant horizontal pleiotropy (global test P value = 0.0758) just as the 'outlier test' found no outlier SNPs.

In contrast, analysis for a causal influence of depression (exposure variable) on endometriosis (outcome variable) using the IVW model provided evidence of a causal association between the two traits (OR = 1.26, 95%CI: 1.046–1.51, P = 0.0149). A sensitivity assessment using the weighted median model supports this finding (OR = 1.24, 95%CI: 1.012–1.55, P = 0.0447); however, the MR-Egger method did not (OR = 1.069, 95%CI: 0.39–2.96, P = 0.8985). Given the Egger intercept did not deviate significantly from zero (intercept = 0.0050, SE = 0.0157, P = 0.7521), there was no evidence for unbalanced pleiotropy which would suggest that the IVW estimates were unbiased. Also, the difference between Q and Q' (Q - Q' = 0.16) is not sufficiently extreme under a χ_1^2 distribution, meaning, that the MR-Egger model was not a better fit for our data compared to the IVW model. Nonetheless, there was evidence for a significant heterogeneity (Q = 70.98, df = 46, P = 0.0105; and Q' = 70.82, df = 45, P = 0.0083). Hence, we performed MR-PRESSO test to detect pleiotropy (global test P value = 0.011) and

exclude outlier variants. Our findings remain consistent with the IVW's results even after correcting outlier SNPs (Table 4). The 'distortion test` *P* value was 0.60 which indicates that there was no difference between causal estimates before and after outlier removal. Also, we conducted a 'leave-one-out' MR analysis and the results remain consistent, showing that the finding in the model was not driven by individual influential SNPs.

Importantly, we replicated the results for the significant causal effect of depression on endometriosis using independent endometriosis and depression GWAS through the online platform (MR-Base). The GWAS data 'seen doctor (GP) for nerves anxiety tension or depression' (id: UKB-a:246) were utilized as the exposure variable and the 'self-reported: endometriosis' (id: UKB-b:10903) as the outcome variable. The results on the IVW (Beta = 0.0209, SE, = 0.0060, *P* =0.000622), the IVW Radial (Beta = 0.0208, SE = 0.0058, *P* = 0.000394), and the weighted median (Beta = 0.0191, SE = 0.00875, *P* = 0.0291) models, were consistent with our previous findings. Notably, the test for heterogeneity was not significant (MR Egger Q' = 16.58, df = 17, *P* = 0.483; and the IVW Q = 16.79, df = 18, *P* = 0.537). Also, the MR-Egger intercept was -0.0001161 (SE = 0.000252, *P* = 0.651), which rules out significant directional pleiotropy and lends further support for a causal influence of depression on endometriosis.

Table 4 MR results for endometriosis and depression association

MR results of endometriosis (exposure) and depression (outcome)					
S/N	**Methods**	**No of SNPs**	**OR**	**95%CI**	*P* value
1	IVW	11	1.003	0.967–1.041	8.66×10^{-1}
2	MR Egger	11	1.134	0.925–1.390	2.58×10^{-1}
3	Weighted median	11	1.018	0.979–1.059	3.71×10^{-1}
MR-PRESSO					
Method	Causal estimates (Beta)	OR	Sd	T-stat	*P* value
Raw	0.0032	1.003	0.019	0.168	8.70×10^{-1}
[a]Outlier corrected	-	-	-	-	-
Global test *P* value = 0.0758					
MR results of depression (exposure) and endometriosis (outcome)					
1	IVW	47	1.26	1.046–1.510	1.49×10^{-2}
2	MR Egger	47	1.07	0.390–2.960	8.99×10^{-1}
3	Weighted median	47	1.24	1.012–1.550	4.47×10^{-2}
MR-PRESSO					
Method	Causal estimates (Beta)	OR	Sd	T-stat	*P* value

Raw	0.229	1.257	0.094	2.436	1.88×10^{-2}
Outlier corrected	0.193	1.213	0.087	2.211	3.21×10^{-2}
Global test *P* value = 0.0112					

No: Number, CI: Confidence interval, OR: Odds ratio, MR: Mendelian Randomization, IVW: inverse-variance weighted model, MR-PRESSO: Mendelian randomization pleiotropy residual sum and outlier, [a]: no outlier SNPs, hence no results for outlier corrected analysis.

Gene-based association analyses results

MAGMA gene-based association analysis of the endometriosis and depression GWA data produced results for 18,188 genes. Using a gene-based genome-wide significant threshold of $P < 2.75 \times 10^{-6}$ (Bonferroni adjustment for testing 18,188 genes [0.05/18,188]), we identified eight genes associated with endometriosis and 116 for depression (Supplementary Table S13). We assessed genes overlapping the two traits at $P_{gene} < 0.1$, resulting in a total of 768 genes (Supplementary Table S14). Using *FCP* (see method), we estimated the combined *P* values for the overlapping endometriosis and depression genes (Supplementary Table S14). *FCP* results reveal a total of 22 genes overlapping endometriosis and depression that reached a gene-based genome-wide significant threshold of $P < 2.75 \times 10^{-6}$ (Table 5A). To replicate these 22 genes, we utilized additional depression GWAS in performing *FCP* analysis. To be considered replicated, a gene must at least be nominally significant for endometriosis ($P_{\text{gene (endometriosis)}} < 0.05$) and depression ($P_{\text{gene (depression)}} < 0.05$), and the *FCP* must be less than the respective gene association *P* values for the two traits (i.e., [$P_{\text{gene (endometriosis)}} < 0.05$] > *FCP* < [$P_{\text{gene (depression)}} < 0.05$]).

Using the PGC MDD GWAS we reproduced 17 of the 22 genes (Supplementary Table S15) three of which reached genome-wide significance (*RP11-3B7.1*, *RHOA* and *CCDC71)* for the PGC MDD (Table 5B). Also, we identified three additional genome-wide significant genes (*C3orf84, BSN, LAMB2*) in the replication analysis using the PGC MDD (Table 5B). Using the self-reported UKB depression GWAS, we replicated seven of the 22 genes (*CABP1, FOXP1, UBA7, TRAIP, RNF123, RP11-3B7.1, and RHOA* [borderline significance for the self-reported UKB depression GWAS]), as summarized in Supplementary Table S16, none of which reached genome-wide significance. However, two additional genes (*NRG1,* and *KLHL18*) reached genome-wide significance (Table 5C).

Table 5 Genome-wide significant genes for endometriosis and depression

Genes	Chr	Start position (hg19)	Stop position (hg19)	Endometriosis *P* value	Depression *P* value	*FCP* value

A. IEC endometriosis and PGC-UKB Depression						
RFWD2	1	175913967	176176629	3.73×10^{-3}	6.92×10^{-6}	4.77×10^{-7}
CCDC71	3	49199968	49203754	3.57×10^{-4}	2.50×10^{-5}	1.74×10^{-7}
CCDC36	3	49235861	49295537	4.14×10^{-4}	1.56×10^{-5}	1.28×10^{-7}
RP11-3B7.1	3	49297518	49298744	1.22×10^{-4}	6.02×10^{-6}	1.62×10^{-8}
RHOA	3	49396578	49450431	1.68×10^{-4}	1.84×10^{-5}	6.36×10^{-8}
NICN1	3	49460379	49466759	8.49×10^{-4}	4.33×10^{-6}	7.51×10^{-8}
DAG1	3	49506146	49573048	9.20×10^{-4}	1.13×10^{-4}	1.78×10^{-6}
MST1	3	49721380	49726934	5.10×10^{-4}	2.04×10^{-4}	1.78×10^{-6}
RNF123	3	49726932	49758962	2.62×10^{-3}	2.65×10^{-5}	1.21×10^{-6}
AMIGO3	3	49754267	49761349	1.47×10^{-2}	7.69×10^{-6}	1.92×10^{-6}
GMPPB	3	49754277	49761384	1.47×10^{-2}	7.69×10^{-6}	1.92×10^{-6}
UBA7	3	49842640	49851379	4.06×10^{-3}	1.02×10^{-5}	7.45×10^{-7}
TRAIP	3	49866034	49894007	2.46×10^{-3}	1.94×10^{-5}	8.52×10^{-7}
FOXP1	3	71003844	71633140	2.13×10^{-4}	1.54×10^{-4}	5.99×10^{-7}
FNIP2	4	159690290	159829201	4.17×10^{-2}	3.26×10^{-6}	2.28×10^{-6}
GABRA1	5	161274197	161326975	6.58×10^{-3}	2.45×10^{-5}	2.68×10^{-6}
ESR1	6	151977826	152450754	3.15×10^{-5}	3.66×10^{-3}	1.96×10^{-6}
ARL14EP	11	30344598	30359774	6.80×10^{-6}	3.38×10^{-3}	4.27×10^{-7}
UBE4A	11	118230300	118269926	1.31×10^{-2}	3.77×10^{-6}	8.83×10^{-7}
ATP5L	11	118271869	118302211	2.67×10^{-2}	3.98×10^{-6}	1.81×10^{-6}
CABP1	12	121078355	121105127	1.46×10^{-2}	2.75×10^{-6}	7.22×10^{-7}
WIPI1	17	66417089	66453654	1.13×10^{-3}	4.51×10^{-5}	9.03×10^{-7}
B. IEC endometriosis and PGC-MDD						
C3orf84	3	49215065	49229291	8.41×10^{-5}	1.02×10^{-4}	1.68×10^{-7}
BSN	3	49591922	49708978	1.69×10^{-4}	1.63×10^{-4}	5.07×10^{-7}
RP11-3B7.1	3	49297518	49298744	1.22×10^{-4}	2.89×10^{-4}	6.41×10^{-7}
RHOA	3	49396578	49450431	1.68×10^{-4}	3.80×10^{-4}	1.12×10^{-6}
LAMB2	3	49158547	49170551	3.16×10^{-4}	3.12×10^{-4}	1.69×10^{-6}
CCDC71	3	49199968	49203754	3.57×10^{-4}	3.82×10^{-4}	2.29×10^{-6}
C. IEC endometriosis and UKB self-reported depression						
NRG1	8	31496902	32622548	1.55×10^{-4}	4.11×10^{-4}	1.12×10^{-6}
KLHL18	3	47324407	47388306	2.71×10^{-2}	3.41×10^{-6}	1.59×10^{-6}

Chr: Chromosome, IEC: International Endogene Consortium, PGC: Psychiatric Genomic Consortium, UKB: United Kingdom Biobank, MDD: Major Depressive Disorder, *FCP*: Fishers Combined *P* value

Lastly, our independent gene-based analysis and binomial test confirmed that a significant gene-level genetic overlap exists between endometriosis and depression (Table 6). For example, the observed proportion (18.3%) of genes overlapping the two traits at $P_{gene} < 0.05$ was significantly higher ($P_{binomial\text{-}test} = 2.90 \times 10^{-4}$) than the expected proportion (15.0%) (Table 6). A similar pattern of results was obtained for overlapping genes at $P_{gene} < 0.01$ ($P_{binomial\text{-}test} = 1.32 \times 10^{-4}$) and $P_{gene} < 0.1$ ($P_{binomial\text{-}test} = 1.31 \times 10^{-5}$), providing further support for a highly significant molecular genetic overlap between the two disorders (Table 6).

Table 6 Summary of independent gene-based association analysis and gene-level genetic overlap between endometriosis and depression

The effective number of independent genes in endometriosis and depression											
Disorder	**Total genes**		***P* value < 0.1**			***P* value < 0.05**			***P* value < 0.01**		
	Raw[c]	**Effective[d]**	**Raw[c]**	**Effective[d]**	**Proportion[e]**	**Raw[c]**	**Effective[d]**	**Proportion[e]**	**Raw[c]**	**Effective[d]**	**Proportion[e]**
Endometriosis[a]	20,225	17,331	2,954	2,494	0.144	1,729	1,450	0.084	473	393	0.023
Depression[b]	20,225	17,223	4,769	3,909	0.227	3,194	2,576	0.150	1,428	1,109	0.064

Number of overlapping genes and binomial test results for gene-level genetic overlap						
Discovery	**Targets**	**Overlapping genes**		**Proportion of overlap**		**Binomial test p value**
		Raw	**Effective**	**Expected**	**Observed**	
***P* value < 0.01**						
Endometriosis	Depression	62	45	1,109/17,223 = 0.064	45/393 = 0.115	1.32×10^{-4}
***P value* < 0.05**						
Endometriosis	Depression	322	266	2,576/17,223 = 0.150	266/1450 = 0.183	2.90×10^{-4}
***P* value < 0.1**						
Endometriosis	Depression	771	656	3,909/17,223 = 0.227	656/2494 = 0.263	1.31×10^{-5}

[a] Endometriosis data from International Endogene Consortium, [b] Depression data from Psychiatric Genomics Consortium and United Kingdom Biobank (PGC-UKB), [c] Raw number of genes (total number of genes obtained in the gene-based association analysis using VEGAS2 software), [d] Effective number of independent genes (the total number of independent genes obtained in the independent gene-based test using the 'genetic type 1 error calculator' method), [e] Proportion of total effective number of independent genes

Gene-drug targets results

Our gene-drug interaction testing indicates that several of our input genes interact uniquely with a range of different drugs (Supplementary Table S17). The types of interactions were known for eight of the genes—*ERBB4*, *CD3D*, *BLK*, *RARG*, *AURKB*, *POLE*, *FGFR1*, *HCK* (Supplementary Table S17). Notably, *CD3D* interacts with BLINATUMOMAB as an 'activator', while *RARG* interacts with 'TRETINOIN' as an agonist (Supplementary Table S17 and S18). Further, our search for potential druggable targets identified 11 genes with different druggable characteristics (Supplementary Table S19). These include tumor suppressor (*RHOA*, *CCDC36*), DNA repair (*UBA7*), serine-threonine kinase (*RHOA*, *MST1*), transporter and ABC transporter (*ATP5L*, *GABRA1*) and ion channel (*GABRA1*), among others (Supplementary Table S19).

Results of pathway-based functional enrichment analysis

Table 7 presents our findings for pathway-based functional enrichment analysis for genes overlapping both endometriosis and depression at $P_{gene} < 0.1$ ($P_{\text{binomial-test}} = 1.31 \times 10^{-5}$). A total of seven genetically influenced biological pathways were significantly enriched including, 'calcium-dependent cell-cell adhesion' ($P_{(\text{adjusted})} = 1.25 \times 10^{-2}$), and 'inositol phosphate metabolism' ($P_{(\text{adjusted})} = 5.65 \times 10^{-3}$). Others include 'Hippo-Merlin Signaling Dysregulation' ($P_{(\text{adjusted})} = 2.75 \times 10^{-2}$), 'peptic ulcer' ($P_{(\text{adjusted})} = 1.61 \times 10^{-3}$), and 'hypoplastic toenails' ($P_{(\text{adjusted})} = 3.65 \times 10^{-2}$). Further details about these pathways including genes implicated are presented in Table 7. Notably, 'pathways regulating Hippo Signaling' ($P_{(\text{adjusted})} = 2.52 \times 10^{-5}$), and 'abnormality of the gastric mucosa' ($P_{(\text{adjusted})} = 1.23 \times 10^{-4}$) produced the most statistically significant enrichment. Given that several related or overlapping pathways may be significantly enriched, we organized the overrepresented pathways found in the present study into clusters based on their biological themes. This practice eliminates redundancy and enhances both the visualization as well as the interpretation of significantly enriched pathways. We utilized the 'auto-annotate' software for this analysis, thereby identifying three clusters of pathways implicated in the biology of both disorders (**Fig. 1**).

Table 7 Significantly enriched pathways for endometriosis and depression

Pathway name	Pathway term Id	Adjusted *P* value	Genes
Gene Ontology: Biological Process			
Calcium-dependent cell-cell adhesion via plasma membrane cell adhesion molecules	GO: 0016339	1.25×10^{-2}	*CDH13, CDH9, CDH22, PCDHB5, PCDHB4, CDH8, PCDHGC3, PCDHB3, AJUBA, CDH12*
Reactome			
Inositol phosphate metabolism	REAC: R-HSA-1483249	5.65×10^{-3}	*IP6K1, PLCB3, INPP5A, IMPA1, PLCH1, INPP5B, ISYNA1, PLCH2, MTMR9, INPPL1*
Biological Pathways: WikiPathways			
Pathways Regulating Hippo Signaling	WP: WP4540	2.52×10^{-5}	*CDH13, RHOA, MST1, CDH9, CDH22, PRKCD, PLCB3, NTRK2, PRKAR2A, LATS1, FGFR1, TCF7L1, CDH8, GNAI2, LATS2, PRKAA2, CDH12*
Hippo-Merlin Signaling Dysregulation	WP: WP4541	2.75×10^{-2}	*CDH13, MST1, LIN28B, CDH9, CDH22, NTRK2, PRKAR2A, ITGB8, LATS1, FGFR1, CDH8, LATS2, AJUBA, CDH12*
Biological Pathways: Human Phenotype Ontology			
Abnormality of the gastric mucosa	HP: 0004295	1.23×10^{-4}	*ABCC2, PRKCD, GTF2I, ARID1B, CISD2, CLIP2, ERGIC1, RASGRP1, LIMK1, WFS1*
Peptic ulcer	HP: 0004398	1.61×10^{-3}	*GTF2I, ARID1B, CISD2, CLIP2, ERGIC1, LIMK1, WFS1, CDKN2C*
Hypoplastic toenails	HP: 0001800	3.65×10^{-2}	*SMARCE1, GTF2I, ARID1B, CLIP2, FGFR1, EZH2, COL11A1, SHOC2, LIMK1, INPPL1*

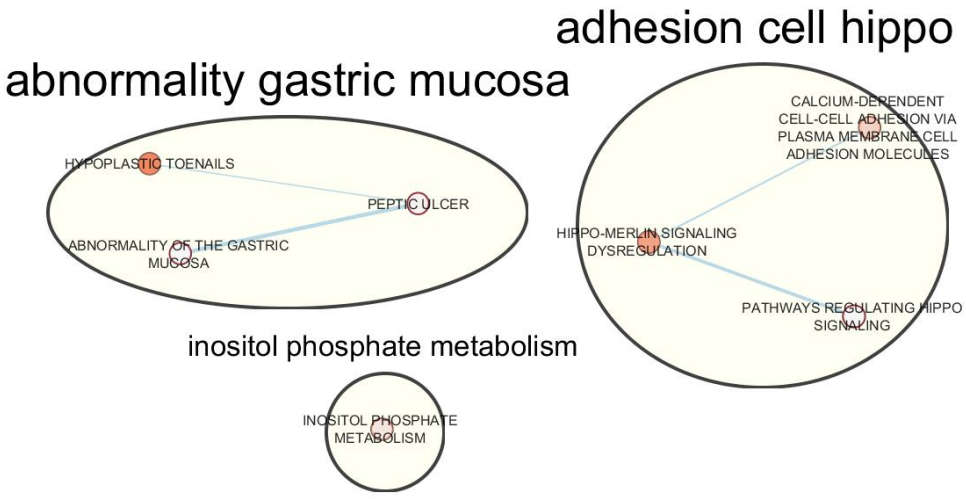

Fig. 1 Significantly enriched pathways for endometriosis and depression

Clustered biological themes of significantly enriched biological pathways for overlapping endometriosis-depression genes

'Abnormality of gastric mucosa' implicated in the biological mechanisms of both endometriosis and depression, and, likely in their comorbidity, in the present study, came

across as a noteworthy finding. Hence, using GWAS summary data, readily available in the public domain, we carried out a follow-up analysis to examine the relationship between each of endometriosis and depression and two of gastric mucosa-related disorders—gastroesophageal reflux disease (GERD) and gastritis/duodenitis, respectively (see Supplemental Note 2 for a comprehensive description of this assessment).

Our findings are summarized in **Fig. 2**. Briefly, LDSC regression analysis reveals a positive and highly significant genetic correlation between endometriosis and GERD ($r_G = 0.24$, $P = 1.17 \times 10^{-20}$) [**Fig. 2**]. There was also evidence for a positive and significant genetic correlation between endometriosis and gastritis/duodenitis ($r_G = 0.18$, $P = 1.5 \times 10^{-3}$) [**Fig. 2**]. Furthermore, we found a strong, positive and highly significant genetic correlation between depression and GERD ($r_G = 0.52$, $P = 1.96 \times 10^{-145}$), as well as between depression and gastritis/duodenitis ($r_G = 0.51$, $P = 3.21 \times 10^{-14}$) [**Fig. 2**].

A further assessment using the IVW model in a "TwoSampleMR" analysis indicates no evidence for a causal association when endometriosis was assessed as an exposure variable against GERD as an outcome (Supplemental Note 2). Conversely, when we assessed GERD as exposure and endometriosis as an outcome variable, we found a significant causal association between the two traits (IVW OR = 1.30, $P = 0.00653$) [**Fig. 2**, and Supplementary Table S20]. There was no evidence for significant heterogeneity (MR Egger Q' = 30.75, df = 22, $P = 0.102$; and the IVW Q = 30.85, df = 23, $P = 0.125$). Also, the test for directional pleiotropy was not significant (Egger intercept = 0.0078, SE = 0.0270, $P = 0.773$). Sensitivity analyses using the 'weighted median' model (close to border-line significance) and MR Egger models did not support findings for IVW model in this instance (Supplemental Note 2 and Supplementary Table S20). However, as indicated by the difference between Q and Q', the MR-Egger model was not a better fit for our data compared to the IVW (Supplementary Table S20). Importantly, the MR-PRESSO results were consistent with those of the IVW model (global test P value = 0.137 [supporting evidence of no horizontal pleiotropy]; outlier test = no outlier variants; and raw causal OR = 1.301, $P = 0.0122$). The leave-one-out analysis was similarly consistent indicating that the association was not driven by individual influential SNPs.

In a related assessment, we found a highly significant bidirectional causal association between depression and GERD (depression as an exposure variable versus GERD as an outcome variable: OR = 1.56, $P = 2.39 \times 10^{-23}$; GERD as an exposure variable versus depression as an outcome variable: OR =1.30, $P = 3.66 \times 10^{-9}$) [**Fig. 2** and Supplementary Table S21]. Also, MR

provides evidence for a causal association between depression and gastritis/duodenitis (depression as an exposure variable versus gastritis/duodenitis as an outcome variable OR = 1.29, $P = 0.000567$) [**Fig. 2** and Supplementary Table S22]. Sensitivity tests using the 'weighted median' model support all results for the IVW model. Although the MR Egger model supports IVW only in respect of depression (exposure variable) vs GERD (outcome variable), the MR-PRESSO was consistent with the IVW model in all analyses (see Supplemental Note 2 and Supplementary Table S22 for details).

Last, we did not find a significant causal association between endometriosis (as exposure variable) and gastritis/duodenitis (as outcome variable) [IVW OR = 1.039, $P = 0.35$] [Supplemental Note 2 and Supplementary Table S20]. No genome-wide significant SNP was associated in gastritis/duodenitis GWAS summary data (violation of the first MR assumption), hence further analysis—gastritis/duodenitis vs endometriosis and gastritis/duodenitis vs depression—were not conducted. Taken together, our study implicates abnormal conditions of gastric mucosa in the causal pathways of endometriosis and depression as summarized in **Fig.** 2.

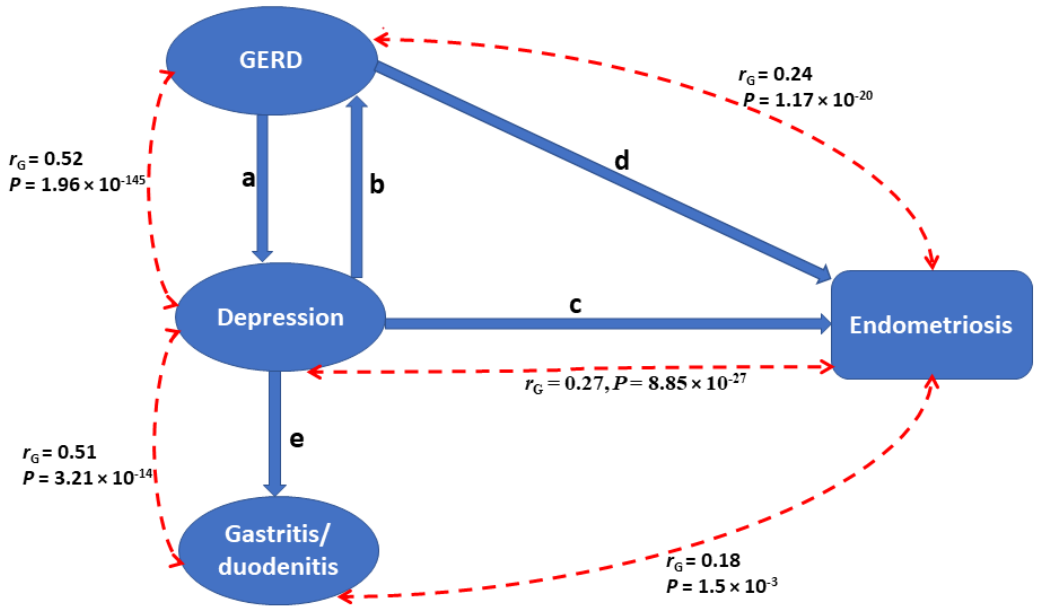

Fig. 2 Associations between endometriosis, depression, GERD and gastritis/duodenitis

Path diagram summarizing the relationship (correlation and causal association) between endometriosis, depression and two abnormal conditions of gastric mucosa (GERD and gastritis/duodenitis) found in our study. GERD: gastroesophageal reflux disease. The dashed bidirectional arrowhead line describes correlation relationships based on linkage disequilibrium score regression analyses (LDSC) results. $\mathbf{r_G}$: genetic correlation obtained for the pairs of traits in the LDSC. *P*: *P* value. a: causal relationship between GERD (as the exposure) and depression (as the outcome), odds ratio (OR) = 1.30, $P = 3.66 \times 10^{-9}$. b: causal relationship between depression (as exposure) and GERD (as outcome), OR = 1.56, $P = 2.39 \times 10^{-23}$. c: causal relationship between depression (as exposure) and endometriosis (as outcome), OR = 1.26, $P = 1.49 \times 10^{-2}$. d: causal relationship between GERD

(exposure) and endometriosis (outcome), OR = 1.30, $P = 6.53 \times 10^{-3}$. e: causal relationship between depression (exposure) and gastritis/duodenitis (outcome), OR = 1.29, $P = 5.67 \times 10^{-4}$.

Discussion

We assessed the comorbidity of endometriosis and depression using several statistical methods and performing both SNP- and gene-level analyses. Well-powered GWAS summary data from large research consortia were utilized for analysis. To our knowledge, this is the first study to comprehensively assess the relationship between endometriosis and depression by analyzing GWAS data. Findings from SECA and LDSC regression analyses indicate that a highly significant SNP-level genetic overlap and correlation exist between endometriosis and depression. For example, of the 1,844 independent SNPs associated with both endometriosis and depression at $P < 0.05$ (SNP subset having $P1$ and $P2 < 0.05$, see methods), a total of 1,065 (57.8%) showed evidence of significant concordance effects (OR = 1.86, $P_{Fisher's\text{-}exact} = 4.72 \times 10^{-11}$) in SECA. Consolidating the findings for SECA, bivariate LDSC regression analysis estimates a positive and highly significant genetic correlation between the two traits.

Traditional observational studies have reported conflicting findings for the co-occurrence of endometriosis and depression (Cavaggioni et al. 2014; Chen et al. 2016; Gambadauro et al. 2019; Novais et al. 2018). However, the significant genetic overlap and correlation between the two disorders found in our study confirm their comorbidity and indicate that, at the least, a proportion of endometriosis and depression patients share similar genetic etiology. Supporting this position, the independent gene-based test reveals the presence of a highly significant gene-level genetic overlap between endometriosis and depression. Our study was based on the analysis of genotype data; hence, findings are reliable and are not likely to suffer from methodological complications such as the bias of reverse causation or the confounding effects of lifestyles and/or environments, unlike the traditional observational studies.

Leveraging on the power afforded by data pooling and our finding of highly significant genetic overlap between endometriosis and depression, we meta-analyzed the respective GWAS summary statistics to discover susceptibility loci shared by both traits. Notably, our cross-disorder GWAS meta-analysis identified 20 independent genomic loci reaching genome-wide significance. Eight of the loci have not previously been reported for either endometriosis or depression at a genome-wide significant level, indicating them to be novel risk loci. The remaining twelve loci were either at or near a previously identified depression locus, and our

study reveals their potential involvement in both disorders, and perhaps their comorbid state. The identified novel SNPs and loci mapped to several genes including *TNR, BRINP3, CC2D2A, TACR3, C6orf118, GSDMC, PCDH17,* and *NR2F2*. The *TNR* gene is predominantly expressed in the brain and is involved in the focal adhesion pathway and microglia activation in neuroinflammation (Anlar and Gunel-Ozcan 2012; Roll and Faissner 2019) which may support the roles of the pathways (focal adhesion and neuroinflammation) in the pathogenesis of endometriosis and depression. Indeed, the genomic region harboring this gene has been implicated in some brain disorders like Alzheimer's disease, schizophrenia, neurological sleep disorder and narcolepsy (Zuo et al. 2012). *NR2F2* is similarly expressed in the brain, but more broadly in the ovary, endometrium, spleen as well as in several other tissues including the heart, kidney and gastrointestinal organs like the stomach, colon, duodenum, and esophagus (Lin et al. 2011). Pathogenic mutation in this gene has been implicated in cardiovascular disorders including congenital heart defects (Al Turki et al. 2014; Wang et al. 2019).

We replicated many of the loci (identified in our meta-analysis) using separate depression GWAS data, with some reaching genome-wide suggestive association—supporting evidence of their involvement in both traits. We note that the 'PGC_UKB depression' (n = 500,199) GWAS data, utilized in the initial meta-analysis, were better powered. Hence, it is not surprising that the replication analyses, using the less powerful 'PGC 2018 MDD excl23andMe' (n = 173,005) and 'self-reported depression UKB' (n = 289,307) GWAS, did not replicate loci reaching a genome-wide significance unlike in the primary cross-disease meta-analysis (for IEC endometriosis and the PGC_UKB depression GWAS). One of the more noteworthy findings in our replication analyses is the potential for identifying robust SNPs and loci, for endometriosis and depression, by meta-analyzing their respective GWAS data. For example, the SNPs (rs116810322, rs6808036, rs1931388 and rs323509) we identified, were genome-wide significant for depression in previous GWAS studies (Howard et al. 2019; Nagel et al. 2018) but not in the 'PGC 2018 MDD' used for replication testing in the present study. Following the meta-analysis of the 'IEC endometriosis' and the 'PGC 2018 MDD' GWAS, the named SNPs attained genome-wide significance, supporting our premise, and confirming evidence of shared genetics between endometriosis and depression.

We conducted MR analyses and our findings provided evidence of a causal association between depression (as the exposure variable) and endometriosis (as the outcome variable). We compared the results of the IVW model with three other MR methods (the weighted median, the MR-Egger and the MR-PRESSO) since consistent estimates across the four models may

strengthen evidence of a causal association. The MR-Egger method did not support the causal effects of depression on endometriosis which may indicate sampling variations or a possible violation of MR assumptions (Bowden and Holmes 2019). However, the weighted median model was consistent with that of the IVW. In instances where most IVs are valid, the weighted median method is known to be more precise than the MR-Egger model (Burgess and Thompson 2017), which may be the case in our study given the wide confidence interval of the MR-Egger's result. Other assessments carried out indicate that MR assumptions were not violated. For example, the Egger intercept was not significantly different from zero indicating that there was no unbalanced pleiotropy. While there was evidence for heterogeneity, the MR-PRESSO test excluded outlier SNPs and the results before and after outlier correction were consistent with those of the IVW model. Notably, using independent GWAS data for the respective traits, we replicated the causal effect of depression on endometriosis, in the online platform of MR analysis (the MR-Base), with no evidence for directional pleiotropy or heterogeneity.

The biological mechanism underpinning the causal influence of depression on endometriosis is, however, unclear; and to our knowledge, this is the first study to suggest this causal relationship. The finding is, nonetheless, consistent with a recent longitudinal study which found bidirectional associations between endometriosis and depressive disorders (Gao et al. 2020). A potential explanation for the relationship would be the likely roles of the immune system and inflammatory pathways which have been implicated in depression. For example, immune system dysregulation, in the central nervous system, may activate inflammatory responses, and in a prolonged state, inhibits apoptosis, as well as alters DNA repairs (Chida et al. 2008; Fedeles et al. 2015). These processes have been suggested in the relationship between depression and cancer (Chida et al. 2008; Fedeles et al. 2015) and may be relevant in the present findings given that inflammatory and immune system dysfunction have similarly been implicated in endometriosis (Adewuyi et al. 2020; Ahn et al. 2015; Miller et al. 2017). Moreover, higher levels of inflammatory and pro-inflammatory biomarkers including C-reactive protein, tumor necrosis factor and interleukins have been associated with both depression and endometriosis (Adewuyi et al. 2020; Kim et al. 2016), providing further support for our findings.

Reversing the direction of our analysis, MR found no evidence for a causal relationship between endometriosis (as an exposure variable) and depression (as an outcome variable). This non-significant finding may be because of the fewer number of endometriosis SNPs available as IVs which may have resulted in limited power to detect a causal association in MR. Hence,

we cannot completely rule out the possibility of a causal effect of endometriosis on depression. A re-assessment of this finding, when more genome-wide significant SNPs for endometriosis are available, should clarify these results.

To complement our SNP-level analyses, we further assessed the relationship between endometriosis and depression using gene-based association analyses. Gene-based analyses have the potential to be more powerful over SNP-based analyses and may provide mechanistic insights into the biology of complex diseases. Our analysis identified 22 genes with a combined gene-based genome-wide significant *P* value for endometriosis and depression. A gene-drug targets search revealed that some of these significant genes are known for crucial biological roles including tumor suppression (*RHOA*, *CCDC36*), DNA repair (*UBA7*), transcription factor binding (*ESR1*), transport activities (*ATP5L*, *GABRA1*) and ion channel functions (*GABRA1*). Also, one of the genes, *ARL14EP* at the *11p14.1* locus, previously implicated in endometriosis, and several female hormone-related traits (Adewuyi et al. 2020; Mbarek et al. 2016; Ruth et al. 2016a; Ruth et al. 2016b; Sapkota et al. 2017), was associated with both endometriosis and depression in the present study.

Drawing on the strength of a systematic literature review and meta-analysis of cross-sectional studies, a recent study has suggested that chronic pain largely explains endometriosis and depression association (Gambadauro et al. 2019). Evidence that pain is often associated with both endometriosis and depression (Bair et al. 2003; Demyttenaere et al. 2007; Facchin et al. 2015; Holmes et al. 2013; Sheng et al. 2017) may support its potential role in the two disorders, and possibly in their co-occurrence. Also, our study, implicating genes involved in inflammatory or neuroinflammatory processes (e.g., *TNR* and *NF2*) (Anlar and Gunel-Ozcan 2012; Omoigui 2007; Roll and Faissner 2019), in both endometriosis and depression, potentially suggests a role for pain, since inflammation and inflammatory response underlie the origin of pain (Omoigui 2007). Moreover, inflammatory mediators including interferon-gamma (IFN-γ), interleukin, and tumor necrosis factor-alpha (TNF-α) are parts of the mechanisms represented by the hippo signalling pathways (Zhou et al. 2018) identified in our study.

We note, however, that our study does not support pain (or chronic pain) as the determinant of the association between endometriosis and depression, in the classic or suggested way of pain in endometriosis leading to depression (i.e., depressed due to being in pain). While Gambadauro and colleagues' meta-analysis suggested that 'chronic pain, rather than

endometriosis itself, is the main determinant of depressive symptoms' (Gambadauro et al. 2019, pp238), the present study indicates that both endometriosis and depression share similar genetic etiology. First, genetic overlap assessment supports evidence of shared genetic susceptibility for both disorders. Indeed, we identify SNPs, genes and loci shared by both disorders. Second, our MR analysis suggests a causal relationship between endometriosis and depression and the direction of causation indicates endometriosis as the outcome. Last, the use of genotype data (as done in the present study) means the inheritance of shared genetic variants for the two traits preceded lifestyle and environmental exposures which would negate the suggestion that endometriosis-induced pain explains comorbid depression.

For further insight into the underlying biology of endometriosis and depression, we performed pathway-based functional enrichment analysis and identified seven genetically influenced biological pathways and processes shared by the two traits. For ease of visualization or interpretation, the identified pathways were grouped into three broad themes and clusters: 'cell adhesion hippo signaling', 'inositol phosphate metabolism' and 'abnormality of gastric mucosa' significantly enriched for endometriosis and depression. The first cluster, cell adhesion hippo signaling, comprises three pathways: 'hippo-merlin signaling dysregulation', 'pathways regulating hippo signaling' and 'calcium-dependent cell-cell adhesion'. Merlin is a multifunctional protein that integrates as well as regulates both extra- and intracellular signaling pathways maintaining cell size, motility, shape and survival (Stamenkovic and Yu 2010). The protein is encoded by the *NF2* gene and known to be a tumor suppressor (Stamenkovic and Yu 2010).

Hippo signaling pathway, also known to be a tumor suppressor, ensures a balance between apoptosis and cell proliferation, and it is activated and regulated by merlin (Li et al. 2015; Stamenkovic and Yu 2010). Dysregulation of this pathway is believed to contribute to decreased apoptosis and increased cell proliferation. Evidence similarly indicates that merlin regulates cell-cell and cell-matrix adhesion (Stamenkovic and Yu 2010). Furthermore, inositol phosphate metabolism pathway is critical to several physiological activities including apoptosis, endocytosis, cell migration or proliferation, vesicle trafficking, PI3K/Akt and insulin signalling (Tan et al. 2015). The dysregulation of this pathway has been noted in cancers (Tan et al. 2015). The recognition that endometriosis sometimes behaves as a tumor (Guo 2018) may, thus, be consistent with the dysregulation of the hippo-merlin as well as the inositol phosphate metabolism pathways. In support of our findings, hippo signaling pathways have been implicated in endometriosis (Song et al. 2016). In the case of depression, we do not have

previous evidence implicating the 'hippo-merlin-cell-adhesion' signaling pathways; however, mechanisms represented by those, for example, apoptosis, inflammation and cell proliferation have been reported in depression (McKernan et al. 2009; Shelton et al. 2011; Zhou et al. 2018).

'Gastric mucosa abnormality' emerged as one of the most significantly enriched findings in our pathway-based analysis. A follow-up study indicates the presence of a strong and highly significant genetic correlation between each of endometriosis and depression, and the respective 'gastric mucosa abnormality' traits, GERD and gastritis/duodenitis, assessed in the follow-up analysis. These findings are not only consistent with previous observational evidence (Choi et al. 2018; Haug et al. 2002; Kvaskoff et al. 2015; Parazzini et al. 2017; Roman et al. 2012), they confirm a comorbid relationship between the respective pairs of the disorders—endometriosis and GERD, endometriosis and gastritis/duodenitis, depression and GERD, and depression and gastritis/duodenitis. This would mean that both endometriosis and depression share some genetic predisposition with GERD, gastritis/duodenitis and by extension, peptic ulcer disease, implicating shared genetically determined mechanisms underlying their association.

The exact biological mechanism(s) underlying the roles of gastric mucosa in the pathobiology of endometriosis and depression, remains unclear. However, the effects of certain immune system and inflammatory mediators—interferon-gamma (*IFN-γ*), interleukin, and tumor necrosis factor-alpha [*TNF-α*] (Altomare et al. 2013; Kim et al. 2018)—may be a likely explanation. These mediators are highly concentrated in the gastric or esophageal mucosa of patients suffering an associated disorder, and are believed to up-regulate inflammatory responses in the central nervous system which may predispose to depression (Altomare et al. 2013; Berk et al. 2013; Lampa et al. 2012). In the same vein, a comorbid relationship has been reported between endometriosis and gastrointestinal symptoms (Parazzini et al. 2017). Given that inflammation has long been associated with both endometriosis and depression (Berk et al. 2013), this position supports current findings. Moreover, abnormal conditions of gastric mucosa (GERD, gastritis, peptic ulcer disease), implicated in our study, have inflammatory components. Thus, 'gastric mucosa abnormality' may represent an important link in the causal pathways of endometriosis and depression and probably in the comorbid state of the two disorders.

A further assessment using the MR analysis suggests causal associations of both endometriosis and depression with at least one of GERD and/or gastritis/duodenitis. We found a causal effect

of GERD on endometriosis as well as a bidirectional causal relationship between depression and GERD. The finding for depression and GERD agrees not only with a previous observational study (Kim et al. 2018) but also a recent GWAS analysis (Wu et al. 2019). Hence, causality may indeed explain the comorbidity of depression with GERD. On the other hand, while no previous study has reported a causal influence of GERD on endometriosis, observational evidence supports a comorbid relationship between endometriosis and several gastrointestinal disorders (Parazzini et al. 2017). Thus, gastric mucosa disorders may be a basis for the co-occurrence of endometriosis and depression. It is logical to suggest that the relationship between endometriosis and gastric mucosa traits could be due to the ulcerogenic tendencies of non-steroidal anti-inflammatory drugs commonly used in the treatment of endometriosis-associated pain. However, given the use of genotype data and the direction of causality (endometriosis as the outcome) found in our study, such a suggestion will not be consistent with the present study.

Taken together, we hypothesize that, abnormal conditions of gastric mucosa (e.g., GERD, gastritis and peptic ulcer) are causal risk factors for endometriosis. The role(s) of these risk factors may be through the direct causal effect or a link with depression or by mediating the relationship between comorbid endometriosis and depression. Further, we propose that effective treatment of underlying GERD (and other gastric mucosal abnormality traits including peptic ulcer disease) may be of therapeutic relevance in comorbid endometriosis. Recent observational studies suggest improved outcomes for endometriosis and gastrointestinal symptoms following dietary considerations (Borghini et al. 2020; Moore et al. 2017). At the end of a three-month administration of a low nickel diet, there was a significant improvement for endometriosis and gastrointestinal-like symptoms (Borghini et al. 2020). A similar finding has been reported for a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet (Moore et al. 2017). Thus, dietary approaches may be potentially beneficial in comorbid endometriosis and depression. Further investigation of the approach, for example, using randomized control trials, may be warranted in the context of the present study.

Conversely, non-steroidal anti-inflammatory drugs are first-line pharmacological agents for endometriosis-associated pain (Giudice 2010; Schwartz et al. 2020). These medications are contra-indicated (or at the least should be used with caution) in GERD, gastritis, peptic ulcer and indeed all conditions involving a compromised state of the gastric mucosa (Drini 2017). Also, certain proton pump inhibitors (medications for managing GERD, gastritis, and peptic

ulcer) have been associated with depression risk (Huang et al. 2018; Laudisio et al. 2018). Hence, as a matter of diagnostic and treatment practices, there is a need for thorough symptom investigations to rule out comorbid gastric mucosa abnormal conditions and depression before initiating these medications.

Strengths and Limitations

The use of multiple statistical methods means a comprehensive, complementary, and balanced assessment of the subject matter and represents a major strength of the present study. Unlike the conventional observational studies, which are prone to the bias of reverse causation and confounding effects of environments or lifestyles, our study is generally not susceptible to these limitations given it was based on the analysis of genotype data. Accordingly, our findings provide current and robust evidence on the co-occurrence of endometriosis and depression by analyzing GWAS data. Nonetheless, it is important to consider some limitations in interpreting findings in the present study.

First, the bias of sample overlap is likely between depression and GERD in our follow-up study since the depression and GERD GWAS data were both partly sourced from the UK Biobank. Such sample overlap is, however, unlikely to have affected our LDSC regression findings since we did not constrain any of the intercepts involving depression GWAS (in the follow-up analysis). Also, our MR analysis is not likely to have produced a biased conclusion given the consistency of its findings with previous observational studies and a recent GWAS-based analysis (Kim et al. 2018; Wu et al. 2019). Second, our study was based on the analysis of data from mainly European ancestry, hence, readers need to exercise caution in generalizing findings to other ancestries. Last, some of the significantly enriched pathways/mechanisms in the pathway-based functional enrichment study could be redundant, thus, we collapsed related pathways into simplified themes/clusters using enrichment mapping and auto-annotation methods thereby enhancing the interpretation and visualization of our results.

Conclusions

Our study provides strong evidence for the co-occurrence of endometriosis and depression, indicating that the two traits share similar genetic etiology. We identified 20 genome-wide significant independent genomic loci, eight of which are novel, and 22 genome-wide significant genes shared by both disorders. Also, we demonstrated a causal influence of depression on endometriosis and identified three clusters of biological pathways for the two traits (‘cell adhesion hippo signaling’, ‘abnormality of gastric mucosa’ and ‘inositol phosphate

metabolism'). These pathways potentially implicate biological processes such as cell proliferation, apoptosis, cell adhesion, as well as the possible roles of the immune system and inflammatory mediators including interferon-gamma (IFN-γ), interleukin, and tumor necrosis factor-alpha (*TNF-α*). Notably, gastric mucosa disorder traits were implicated in the causal pathways of both endometriosis and depression. Our study, thus, highlights the importance of screening for endometriosis among women presenting with depression and gastric mucosa abnormality traits including GERD, gastritis, duodenitis, and peptic ulcer disease and vice versa. Genes and pathways identified in our study could serve as potential druggable targets for endometriosis and depression and especially the comorbid state of the two disorders. We propose, given the novelty of our findings, that effective treatments for gastric mucosa diseases or depression may find relevant therapeutic benefits for improved outcomes in comorbid endometriosis. Also, we suggest possible benefits of dietary approaches in comorbid endometriosis and depression given their association with gastric mucosal abnormalities. Future studies using prospective follow-up or randomized control trial designs will need to assess these proposals.

Supplementary Materials:

1. Supplementary Table S1 to S22
2. Supplemental Note 1
3. Supplemental Note 2
4. Supplementary Fig1 and Fig2

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