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ORIGINAL ARTICLE *Reproductive genetics*

Genetic overlap analysis of endometriosis and asthma identifies shared loci implicating sex hormones and thyroid signalling pathways

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STUDY QUESTION: Is there a shared genetic or causal association of endometriosis with asthma or what biological mechanisms may underlie their potential relationships?

SUMMARY ANSWER: Our results confirm a significant but non-causal association of endometriosis with asthma implicating shared genetic susceptibility and biological pathways in the mechanisms of the disorders, and potentially, their co-occurrence.

WHAT IS KNOWN ALREADY: Some observational studies have reported a pattern of co-occurring relationship between endometriosis and asthma; however, there is conflicting evidence and the aetiology, as well as the underlying mechanisms of the relationship, remain unclear.

STUDY DESIGN, SIZE, DURATION: We applied multiple statistical genetic approaches in the analysis of well-powered, genome-wide association study (GWAS) summary data to comprehensively assess the relationship of endometriosis with asthma. Endometriosis GWAS from the International Endogene Consortium (IEC, 17 054 cases and 191 858 controls) and asthma GWAS from the United Kingdom Biobank (UKB, 26 332 cases and 375 505 controls) were analysed. Additional asthma data from the Trans-National Asthma Genetic Consortium (TAGC, 19 954 cases and 107 715 controls) were utilized for replication testing.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We assessed single-nucleotide polymorphism (SNP)-level genetic overlap and correlation between endometriosis and asthma using SNP effect concordance analysis (SECA) and linkage disequilibrium score regression analysis (LDSC) methods, respectively. GWAS meta-analysis, colocalization (GWAS-PW), gene-based and pathway-based functional enrichment analysis methods were applied, respectively, to identify SNP loci, genomic regions, genes and biological pathways shared by endometriosis and asthma. Potential causal associations between endometriosis and asthma were assessed using Mendelian randomization (MR) methods.

MAIN RESULTS AND THE ROLE OF CHANCE: SECA revealed significant concordance of SNP risk effects across the IEC endometriosis and the UKB asthma GWAS. Also, LDSC analysis found a positive and significant genetic correlation ($r_G = 0.16$, $P = 2.01 \times 10^{-6}$) between the two traits. GWAS meta-analysis of the IEC endometriosis and UKB asthma GWAS identified 14 genome-wide significant ($P_{meta\text{-}analysis} < 5.0 \times 10^{-8}$) independent loci, five of which are putatively novel. Three of these loci were consistently replicated using TAGC asthma GWAS and reinforced in colocalization and gene-based analyses. Additional shared genomic regions were identified in the colocalization analysis. MR found no evidence of a significant causal association between endometriosis and asthma. However, combining gene-based association results across the GWAS for endometriosis and asthma, we identified 17 shared genes with a genome-wide significant Fisher's combined *P*-value (FCP_{gene}) $< 2.73 \times 10^{-6}$. Additional analyses (independent gene-based analysis) replicated evidence of gene-level genetic overlap between endometriosis and asthma. Biological mechanisms including 'thyroid hormone signalling', 'abnormality of immune system physiology', 'androgen biosynthetic process' and 'brain-derived neurotrophic factor signalling pathway', among others, were significantly enriched for endometriosis and asthma in a pathway-based analysis.

[†]Full lists of consortia members appear in the Appendix.

LARGE SCALE DATA: The GWAS for endometriosis data were sourced from the International Endogen Consortium (IEC) and can be accessed by contacting the consortium. The GWAS data for asthma are freely available online at Lee Lab (https://www.leelabsg.org/resources) and from the Trans-National Asthma Genetic Consortium (TAGC).

LIMITATIONS, REASONS FOR CAUTION: Given we analysed GWAS datasets from mainly European populations, our results may not be generalizable to other ancestries.

WIDER IMPLICATIONS OF THE FINDINGS: This study provides novel insights into mechanisms underpinning endometriosis and asthma, and potentially their observed relationship. Findings support a co-occurring relationship of endometriosis with asthma largely due to shared genetic components. Agents targeting 'selective androgen receptor modulators' may be therapeutically relevant in both disorders. Moreover, SNPs, loci, genes and biological pathways identified in our study provide potential targets for further investigation in endometriosis and asthma.

STUDY FUNDING/COMPETING INTEREST(S): National Health and Medical Research Council (NHMRC) of Australia (241,944, 339,462, 389,927, 389,875, 389,891, 389,892, 389,938, 443,036, 442,915, 442,981, 496,610, 496,739, 552,485, 552,498, 1,026,033 and 1,050,208), Wellcome Trust (awards 076113 and 085475) and the Lundbeck Foundation (R102-A9118 and R155-2014-1724). All researchers had full independence from the funders. Authors do not have any conflict of interest.

Key words: endometriosis / asthma / molecular genetics / GWAS / comorbidity / biological mechanisms / sex hormones

Introduction

Endometriosis and asthma rank among leading chronic disorders with consequences for a wide range of adverse outcomes on sufferers, their relationships, and the larger society (Culley *et al.*, 2013; Nunes *et al.*, 2017; Nurmagambetov *et al.*, 2018). Globally, endometriosis affects ~196 million women, while over 300 million people, worldwide, suffer from asthma (Adamson *et al.*, 2010; Zein and Erzurum, 2015; D'Amato *et al.*, 2016). Similar to endometriosis, which is found predominantly in women, post-pubertal women have a higher incidence and greater severity of asthma disease (Zein and Erzurum, 2015; Greenblatt *et al.*, 2017; Rei *et al.*, 2018). Both endometriosis and asthma differ anatomically and nosologically; however, a growing body of observational studies suggests a comorbid relationship between the two disorders (Sinaii *et al.*, 2002; Valderas *et al.*, 2009; Matalliotakis *et al.*, 2012; Kvaskoff *et al.*, 2015; Peng *et al.*, 2017). Comorbidity signifies a co-occurrence of two or more different conditions, in the same individual, with predisposing potentials for disease worsening, complicated management plans, poor prognosis and increased costs of treatments (Mirkin *et al.*, 2007; Valderas *et al.*, 2009).

Consistent with the hypothesis of endometriosis and asthma co-occurrence, a case report, published as far back as 1984, indicates that two patients on Danazol, a medication for managing endometriosis, had a remission from asthma (Pride and Yuen, 1984). Findings from several other studies support a co-occurring relationship between the two disorders. For example, a study in the USA found more than twice the prevalence of asthma in women with endometriosis (12%) compared to the general population (5%, $P < 0.001$) (Sinaii *et al.*, 2002). Another study similarly reported a significantly higher rate (9% in cases versus 4.3% in controls) and increased odds of endometriosis (odds ratio [OR] = 2.2, $P = 0.038$) among asthmatic patients compared to controls (Matalliotakis *et al.*, 2012). More recently, a population-based study (Peng *et al.*, 2017) revealed a 50% increased risk of endometriosis among asthmatic patients compared to their non-asthmatic counterparts (hazard ratio = 1.50, 95% CI = 1.33–1.70) (Peng *et al.*, 2017). Further findings from the study (Peng *et al.*, 2017) showed a substantially higher incidence rate of endometriosis among women with asthma compared to non-asthmatics (4.63 per 1000 person-years and 2.88 per 1000 person-years, respectively).

Despite the number of studies reporting the comorbidity of endometriosis and asthma, the biological mechanism(s) underpinning their relationship remains elusive. Furthermore, contrasting findings have been reported. For instance, two of the earliest USA studies found no statistically significant difference in the risk of endometriosis between asthma cases and controls (Lamb and Nichols, 1985; Nichols *et al.*, 1987). In another case–control study, the prevalence of asthma was similar with (4.9%) or without (5.3%) endometriosis ($P = 0.781$) (Ferrero *et al.*, 2005). Hence, inconclusive evidence exists for endometriosis and asthma comorbidity. Given they were based on conventional observational study designs, findings to date, on this subject, may have suffered a range of limitations including small sample sizes and non-adjustment for known or unknown confounders.

Endometriosis continues to be an enigmatic disorder whose aetiology and pathogenesis are poorly understood. However, with a twin and single-nucleotide polymorphism (SNP)-based estimated heritability of 50% and 26%, respectively, genetic factors contribute to the risk of endometriosis (Kennedy, 1999; Simpson and Bischoff, 2002; Stefansson *et al.*, 2002; Montgomery *et al.*, 2008; Lee *et al.*, 2012). Asthma is similarly phenotypically heterogeneous, with strong evidence implicating genetic factors in its pathogenesis (twin-based heritability of ~60% and SNP-based heritability of 21%) (Van Beijsterveldt and Boomsma, 2007; Willemsen *et al.*, 2008; Thomsen *et al.*, 2010; Johansson *et al.*, 2019). Several SNPs and susceptibility loci have been identified for both endometriosis and asthma (Almoguera *et al.*, 2017; Sapkota *et al.*, 2017; Demenais *et al.*, 2018; Adewuyi *et al.*, 2020, 2021). However, to our knowledge, studies focussing on the mechanism(s) of association underlying the two disorders, using a more reliable study design based on genetics, are lacking. Also, no study has leveraged the possible pleiotropy between endometriosis and asthma as a basis for discovering SNPs and loci shared by both traits.

Thus, using a suite of statistical genetic analysis methods, we comprehensively assess, for the first time, the relationship between endometriosis and asthma. Unlike previous traditional observational studies, the present study is based on the analysis of genome-wide association

studies (GWAS) data which are less susceptible to biases such as reverse causation and lifestyle or environmental confounders. Thus, findings from such post-GWAS analyses are expected to provide robust evidence on the potential relationships between endometriosis and asthma. These analyses, allowing investigation into susceptibility loci, genes and biological pathways shared by both disorders, will provide insights into the mechanisms of their association, improve our understanding of their underlying biology and characterize potential druggable targets for endometriosis and asthma.

Materials and methods

Figure 1 presents the workflow for this study. First, we assessed whether the independent genome-wide significant SNPs or loci in asthma GWAS (the sentinel SNPs and loci) were similarly associated with the endometriosis GWAS, and vice-versa. Also, we assessed SNP-level genetic overlap and correlation between endometriosis and asthma using the SNP effect concordance analysis (SECA) and the linkage disequilibrium score regression analysis (LDSC) methods, respectively. Additionally, we performed a cross-disorder GWAS meta-analysis, leveraging on the increased power from data pooling and pleiotropy of genetic variants, to identify SNPs and susceptibility loci shared by both disorders. Furthermore, we investigated the potential causal association between endometriosis and asthma using Mendelian randomization (MR) methods. To complement our SNP-level study, we carried out gene-based analyses, first, to investigate genome-wide significant genes shared by both endometriosis and asthma, and second, to assess gene-level genetic overlap between the two traits (using data generated from the independent gene-based analysis). Last, we conducted pathway-based functional enrichment analyses for insights into the biological mechanisms shared by endometriosis and asthma.

Description of GWAS datasets

GWAS summary data for endometriosis were sourced from the International Endogene Consortium (IEC). A total sample of 208 912 participants of European (93%) and Japanese ancestry, comprising 17 054 endometriosis cases and 191 858 controls, was included in the data—representing the largest published GWAS in the genetic study of endometriosis (Sapkota *et al.*, 2017). Association results for a total of 6 979 035 SNPs were available for analysis (Sapkota *et al.*, 2017). A comprehensive description of the IEC endometriosis data, including details of quality controls and meta-analysis, is available in the original publication (Sapkota *et al.*, 2017).

We used the full European subset of asthma GWAS in the United Kingdom Biobank (UKB) as our main asthma data in this study. The GWAS (Phecode 495) comprised 26 332 asthma cases and 375 505 controls, sourced from the Lee Lab (https://www.leelabsg.org/resources) (Zhou *et al.*, 2020) and can be freely accessed at ftp://share.sph.umich.edu:21/UKBB_SAIGE_HRC/PheCode_495_SAIGE_MACge20.txt.vcf.gz.tbi. For reproducibility testing, we also utilized asthma GWAS from the Trans-National Asthma Genetic Consortium (TAGC), described in Demenais *et al.* (2018). The TAGC asthma GWAS data contained association results for 2 001 281 SNPs from analysis of 19 954 asthma cases and 107 715 controls of European ancestry (Demenais *et al.*, 2018). Supplementary Table SI summarizes GWAS data analysed in this study.

Assessing SNP-level genetic overlap

We assessed the SNP-based genetic overlap of endometriosis with asthma, first, by examining the overlap of independent genome-wide significant SNPs or loci (sentinel SNPs) across the IEC endometriosis and each of UKB and TAGC asthma GWAS. In other words, we assessed whether any or all the independent genome-wide significant SNPs or loci, previously identified, in endometriosis were associated with asthma, and vice-versa. Second, using the standalone version of the SECA software pipeline (https://sites.google.com/site/qutsgel/software/seca-local-version), we carried out further SNP-level genetic overlap assessment and statistical tests between endometriosis and asthma. A detailed description of the SECA software and methods have been published (Nyholt, 2014).

We utilized the endometriosis GWAS as dataset 1 and UKB asthma GWAS as dataset 2. We carried out quality control in which all non-rsID(s) and duplicate variants were excluded, after which SECA aligns SNP effects to the same effect allele across the endometriosis and asthma GWAS. Furthermore, we performed a *P*-value informed linkage disequilibrium (LD) clumping following the procedures described in previous studies (Nyholt, 2014; Nyholt *et al.*, 2015; Adewuyi *et al.*, 2020, 2021) and in line with the scripts from the program developer: https://sites.google.com/site/qutsgel/software/seca-local-version/ld-clumping-tutorial.

Independent SNPs resulting from our LD clumping were partitioned by SECA into 12 subsets of SNPs, based on *the P-value* associated with dataset 1 (P1), as follows: $P1 \leq$ (0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0). SECA subsequently performs Fisher's exact tests ($_{FT}$) to assess the presence of excess SNPs in which the direction of effects is concordant across dataset 1 and dataset 2 (i.e. for the corresponding *P*-value derived 12 subsets of SNPs associated in dataset 2, P2). Hence, a total of 144 SNP subsets was assessed for SNP effect concordance. For nominally significant concordance ($OR > 1$ and $P_{Fisher's\text{-}exact} < 0.05$), effects for the proportion of concordant SNP subsets ($OR > 1$) and discordant subsets ($OR < 1$) alongside the adjusted *P*-value (adjustment made for the 144 SNP subsets tested) [$P_{FTsig\text{-}permuted}$] were estimated using permutation of 1000 replicates (Nyholt, 2014). Also, we performed an analogous SECA analysis in which endometriosis was assessed as dataset 2 and asthma as dataset 1.

Assessing genetic correlation

To complement our SECA-based genetic overlap assessment, we performed LDSC regression analysis (https://github.com/bulik/ldsc), to estimate SNP-level heritability for endometriosis and asthma and assess the genetic correlation between the two traits (bivariate LDSC). LDSC estimates and distinguishes the contributions of polygenicity, sample overlap and population stratification to the heritability and genetic correlation between traits (Bulik-Sullivan *et al.*, 2015). In the present study, we carried out LDSC analysis using the standalone version of the software (https://github.com/bulik/ldsc).

First, we estimated the SNP-based liability heritability (h^2_{SNP}) for the IEC endometriosis (sample prevalence = 8.2%, population prevalence = 8% (Sapkota *et al.*, 2017)), the UKB asthma (sample

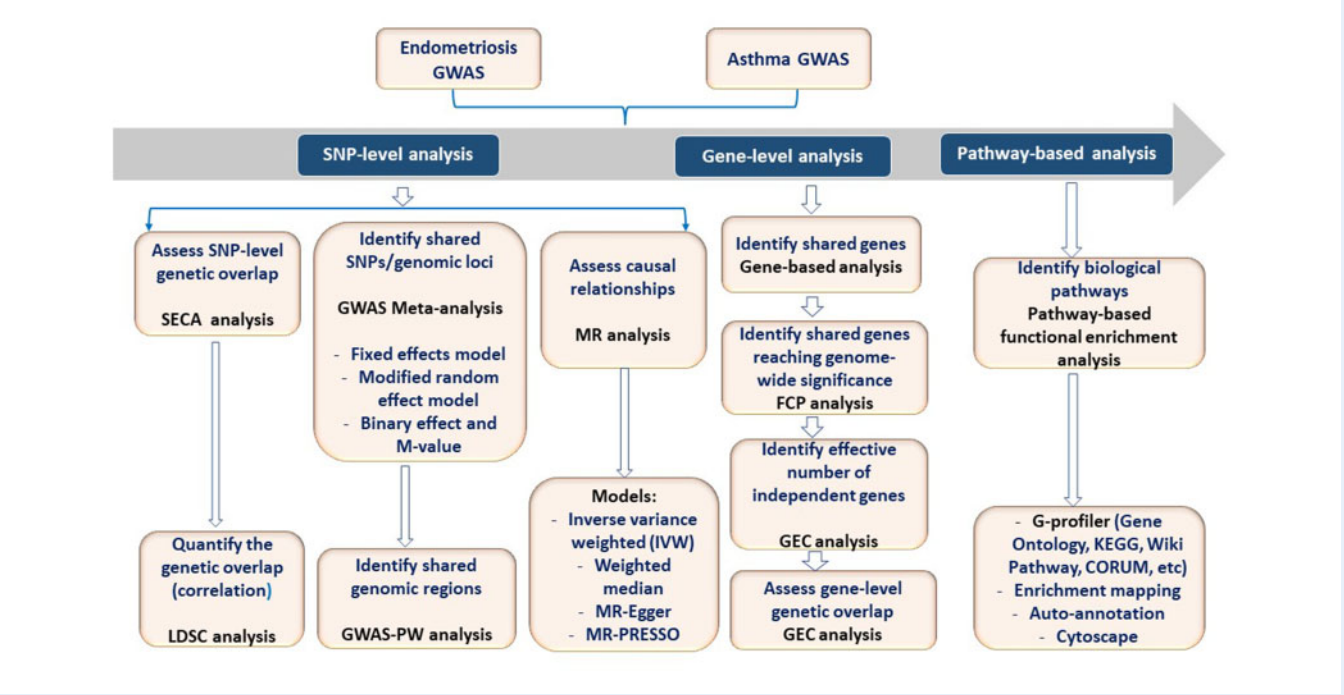

Figure 1. Workflow and study design: assessing shared genetic relationship between endometriosis and asthma. FCP, Fisher's combined *P*-value; GEC, genetic type 1 error calculator; GWAS, genome-wide association studies; KEGG, Kyoto Encyclopedia of Genes and Genomes; LCV, latent causal variable; LDSC, linkage disequilibrium score regression; MR, Mendelian randomization; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; SECA, SNP effect concordance analysis; SNP, single-nucleotide polymorphism.

prevalence = 14.72%, population prevalence = 4%) and the TAGC asthma (sample prevalence = 15.6%, population prevalence = 4% (To *et al.*, 2012)). Second, we assessed the cross-disorder genetic correlation (r_G) between the IEC endometriosis and UKB asthma GWAS using the bivariate LDSC analysis. Given the complex LD structure at the MHC region, we excluded the region from our analysis. Also, we constrained the h^2_{SNP} intercept for endometriosis GWAS since the estimated intercept (in the initial observed scale LDSC analysis) did not differ significantly from one. Also, there was no sample overlap between our GWAS data; hence we constrained the intercept for the genetic covariance estimates. For replication testing, we utilized the TAGC asthma GWAS.

Cross-disorder GWAS meta-analysis

We conducted a cross-disorder GWAS meta-analysis of the IEC endometriosis and UKB asthma GWAS to identify SNPs and susceptibility loci shared by both traits. Two models of meta-analysis—the Fixed Effect (FE) and the modified Random Effect (RE2) (Han and Eskin, 2011)—implemented in the METASOFT software (http://genetics.cs.ucla.edu/meta/) were used in the present study. The FE model assumes that the endometriosis and asthma GWAS are assessing the same (fixed) effect (FE) and estimates the FE *P*-value using the inverse variance weighted (IVW) estimator; hence, the model can be limited in the presence of SNP effect heterogeneity. Conversely, the RE2 model (Han and Eskin, 2011), allows for differences in SNP effects by estimating *P*-values using a modified random-effects model that is powerful in the presence of SNP effect heterogeneity. A total of 6 333 281 SNPs overlapping the IEC endometriosis and UKB asthma GWAS were meta-analysed in the combined sample of 610 749 individuals. SNPs and loci which were not genome-wide significant in any of the two GWAS data ($5 \times 10^{-8} < P_{GWAS\text{-}SNP} < 0.05$) but became significant after a meta-analysis ($P_{meta\text{-}analysis} < 5 \times 10^{-8}$) were of primary interest. Previously identified genome-wide significant SNPs and loci which showed evidence of involvement in both traits were similarly identified. We consider *P*-values at $P_{meta\text{-}analysis} < 5 \times 10^{-8}$ and $P_{meta\text{-}analysis} < 1 \times 10^{-5}$ as *genome-wide significant* and *genome-wide suggestive*, respectively.

We applied the posterior probability (*m*-value) method (Han and Eskin, 2012) to further assess SNPs and loci shared by endometriosis and asthma. Briefly, the *m*-value was estimated, using cross-study information, to effectively predict whether an effect exists (for an SNP or locus) in each of the studies meta-analysed, especially, in the presence of heterogeneity (Han and Eskin, 2012). When *m*-value is >0.9, it indicates that effect exists, while *m*-values less than 0.1 predicts that there is no effect; values between 0.1 and 0.9 predict an ambiguous effect (Han and Eskin, 2012).

For replicability testing, we similarly meta-analysed a total of 1 960 896 SNPs overlapping the IEC endometriosis and TAGC asthma GWAS in a combined sample of 336 580 individuals. To be considered reproduced, meta-analysis' *P*-value ($P_{[FE]}$ or $P_{[RE2]}$) for a locus must be less than the respective *P*-values for each of endometriosis and asthma GWAS (that is, $P_{Endometriosis\text{-}GWAS} > P_{Meta\text{-}analysis} < P_{Asthma\text{-}GWAS}$).

Moreover, there must be evidence that the meta-analysis improved the results and that the association was not primarily driven by only one of the GWAS ($P_{\text{Endometriosis-GWAS}} < 0.05 > P_{\text{Asthma-GWAS}}$).

Genomic loci characterization

To identify and characterize independent SNPs and loci associated with both endometriosis and asthma GWAS (overlapping the two traits), we carried out further analysis, processing the results of our meta-analysis using the FUMA software (https://fuma.ctglab.nl) (Watanabe *et al.*, 2017). SNPs reaching genome-wide significance following a meta-analysis were processed as input to FUMA. These SNPs: (i) were associated with both endometriosis and asthma and were not genome-wide significant in any of the GWAS data but, at the least, were nominally significant ($5 \times 10^{-8} < P_{\text{GWAS}} < 0.05$); and (ii) reached genome-wide significance, after the meta-analysis ($P_{\text{meta-analysis}} < 5 \times 10^{-8}$), supporting evidence of potential involvement in endometriosis and asthma.

Briefly, FUMA performs LD clumping and identifies SNPs that are weakly correlated with each other at $r^2 < 0.6$, and independent lead SNPs that are not in LD with each other ($r^2 < 0.1$). Physical regions within 250 kb of a lead SNP were characterized as a genomic locus, and all lead SNPs (if multiple LD independent [$r^2 < 0.1$] lead SNPs are present) in this region were merged into the same locus. So, it is possible to have more than one lead SNP in a locus. The 1000 Genomes Phase 3 (EUR) data were used in estimating all LD information.

Lastly, independent SNPs reaching genome-wide significance were searched in PhenoScanner (v2) (Staley *et al.*, 2016) to investigate whether they (or SNPs in LD with them at $r^2 > 0.5$) were already genome-wide significant in published GWAS for endometriosis, asthma or other traits.

Pairwise GWAS analysis

To further examine and identify genomic regions shared by endometriosis and asthma, we utilized the Pairwise GWAS (GWAS-PW) method (Pickrell *et al.*, 2016) for a co-localization analysis. Briefly, GWAS-PW (https://github.com/joepickrell/gwas-pw) jointly analyses two GWAS and identifies genetic regions that influence both traits. The summary statistics for the IEC endometriosis and each of the UKB and the TAGC asthma GWAS were analysed by splitting the genome into approximately 1702 LD-independent regions. GWAS-PW estimates the posterior probability (PPA) by modelling the probabilities that (i) the locus is associated with either endometriosis [PPA1] or asthma [PPA2], (ii) the locus is shared by both traits [PPA3] and (iii) the locus is associated with both traits but through different causal variants [PPA4]. Using the output of GWAS-PW analysis, we selected the posterior probability >0.5 in the models that represent the shared SNPs and regions [PPA3 and PPA4].

Causal relationship assessment

We performed two-sample Mendelian randomization (2SMR) analyses (Hemani *et al.*, 2018) to investigate bidirectional causal relationships between endometriosis and asthma. We implemented the 2SMR analysis using the R statistical package (https://mrcieu.github.io/TwoSampleMR/). First, we assessed the IEC endometriosis GWAS as the exposure and the UKB asthma GWAS as the outcome variable. In an analogous 2SMR analysis, we assessed UKB asthma GWAS as the exposure and the endometriosis GWAS as the outcome variable by reversing the direction of the analysis. In all the analyses, independent (LD clumping at $r^2 < 0.001$) genome-wide significant SNPs were utilized as instrumental variables (IVs).

We examined the causal influence of endometriosis on asthma and vice versa using the IVW method. Additional MR methods, including the MR-Egger, the weighted median (Bowden *et al.*, 2015, 2016), and the 'Mendelian randomization pleiotropy residual sum and outlier' (MR-PRESSO) (Verbanck *et al.*, 2018) were conducted for sensitivity testing. We carried out a heterogeneity test (using Cochran's *Q* statistics), performed individual SNP MR analysis and used a 'leave-one-out' test to further assess the validity of our estimates. For replication testing, we utilized the TAGC asthma GWAS and followed the same procedure of the 2SMR analysis described here. We utilized proxy SNPs (Hartwig *et al.*, 2016) for endometriosis IVs missing in the TAGC asthma. Additional details of our MR analysis are provided in Supplementary Data File SI.

Gene-based association analysis

Moving beyond SNP-level studies, we performed gene-based association analyses to identify genome-wide significant genes shared by both endometriosis and asthma. Our gene-based analysis was conducted in MAGMA (implemented in the FUMA platform) (de Leeuw *et al.*, 2015; Watanabe *et al.*, 2017), separately for endometriosis and asthma, utilizing a total of 6 333 281 SNPs overlapping the IEC endometriosis and the UKB asthma GWAS. We defined boundaries of gene length within '±0 kb outside the gene'. From the results of gene-based analyses, we extracted genes overlapping both endometriosis and asthma, at a *P*-value threshold less than 0.1 ($P_{\text{gene}} < 0.1$) and combined their respective gene-based *P*-values using the Fisher's combined *P*-value method (*FCP*) (Zhao *et al.*, 2016; Zhao and Nyholt, 2017; Yang *et al.*, 2018; Adewuyi *et al.*, 2020, 2021). Thereafter, we assessed shared genes reaching a genome-wide level of significance for both endometriosis and asthma based on our *FCP* results. We carried out additional gene-based association analyses using the IEC endometriosis, and the TAGC asthma GWAS, to test the reproducibility of our findings.

Independent gene-based test

Gene-based analyses have the potential to provide readily interpretable insights into the biology of complex traits (Li *et al.*, 2012; de Leeuw *et al.*, 2015). However, the likely presence of LD between best SNPs (the most significant SNPs) assigned to each gene implies that gene-based association results may also be limited by the non-independence of SNPs (correlated SNPs) across neighbouring genes. To address this limitation and consolidate our assessment of gene-level genetic overlap, we conducted independent gene-based analyses to estimate the effective number of independent genes (Li *et al.*, 2012) associated with each of endometriosis and asthma. The 'genetic type 1 error calculator' (GEC) software (Li *et al.*, 2012) was utilized in carrying out this analysis as implemented in previous studies (Zhao *et al.*, 2016; Zhao and Nyholt, 2017; Yang *et al.*, 2018; Adewuyi *et al.*, 2020, 2021).

First, we performed gene-based association analyses in Vegas2 software (Mishra and Macgregor, 2015), for endometriosis and asthma,

using SNPs overlapping the two GWAS, respectively. In our Vegas2 analysis, we specified the 'best SNP test' option, which is suitable for our independent gene-based analysis. Also, we restricted gene definition to '± 0 kb outside gene', utilized all chromosomes and selected sub-population 'all Europeans'. Second, the best SNPs assigned to genes in our Vegas2 results for endometriosis and asthma GWAS, respectively, were processed as inputs for GEC analysis. GEC analysis accounts for possible LD across neighbouring genes in the gene-based association results, controls type I errors, adjusts for multiple testing, and, subsequently estimates the effective number of independent genes (i.e. independent gene-based tests) (Li *et al.*, 2012). Thus, we estimated the effective number of independent genes separately for endometriosis and asthma. The IEC endometriosis and the UKB asthma GWAS were used for this analysis. For replication, we used the IEC endometriosis and the TAGC asthma GWAS.

Test for gene-level genetic overlap

Using our independent gene association results for endometriosis and asthma, we assessed genes overlapping the two traits at three nominal *P*-value thresholds ($P_{gene} < 0.1$, $P_{gene} < 0.05$ and $P_{gene} < 0.01$). The number of genes overlapping both traits in each of these three nominal *P*-value thresholds was described as the raw number of genes. However, we require the effective number of independent genes overlapping both traits in each of the *P*-value thresholds, to enable us to assess whether the proportions of overlaps were more than expected by chance (Zhao *et al.*, 2016; Zhao and Nyholt, 2017; Yang *et al.*, 2018; Adewuyi *et al.*, 2020, 2021). Thus, with endometriosis assigned as the discovery set and asthma as the target set, we carried out another round of independent gene-based tests, utilizing genes overlapping both traits in each of the three nominal *P*-value thresholds for GEC analysis.

We estimated the expected proportion of genes overlapping endometriosis and asthma GWAS, 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 (Zhao *et al.*, 2016; Adewuyi *et al.*, 2020). We similarly estimated the observed proportion of genes overlapping the two traits, 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 (Zhao *et al.*, 2016; Adewuyi *et al.*, 2020). Using a one-sided exact binomial test, we compared the expected proportion of overlapping genes against the observed proportion of genes overlapping endometriosis and asthma, at each of the *P*-value thresholds. The results of these comparisons will determine whether the number of overlapping genes were more than expected by chance.

Pathway-based functional enrichment analysis

To functionally interpret and make a biological sense of genes overlapping endometriosis and asthma GWAS, we performed pathway-based functional enrichment analysis using the online version of the g:GOst tool implemented in the G:profiler platform. The g:GOst performs statistical analysis using a cumulative hypergeometric test to identify biological pathways, mechanisms or processes overrepresented or significantly enriched for a list of user-inputted genes (Raudvere *et al.*, 2019). The software interrogates many databases including Gene Ontology, Human Phenotype Ontology, WikiPathway, Human Protein Atlas, CORUM, Reactome and Kyoto Encyclopedia of Genes (KEGG) and is updated regularly (Raudvere *et al.*, 2019). In the present study, we utilized genes overlapping the IEC endometriosis and each of the UKB and the TAGC asthma GWAS at $P_{gene} < 0.1$ (FCP < 0.05) in performing our pathway-based analysis. We applied the recommended 'g:SCS algorithm' for multiple testing correction and reported overrepresented pathways at the adjusted *P*-value (g:SCS P_{adj}) < 0.05 (Raudvere *et al.*, 2019) in our analysis.

Ethics approval

Relevant ethics approval was obtained for the collection of all samples underpinning the IEC endometriosis GWAS utilized in this study as previously published (Sapkota *et al.*, 2017). The present study which is based on a secondary analysis of existing data has been included in the 'Genetic analysis of migraine and comorbid psychiatric disorders using twin families' (P589) and 'Susceptibility of Migraine in the Endometriosis Cohort' (P1408) projects in the QIMR Berghofer Medical Research Institute '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 3 November 2017. The current research is approved under QUT Ethics Clearance Number (approval number) 1500000115 (Project title 'Genetic biomarkers and molecular pathways').

Results

Results for SNP-level genetic overlap

A total of 339 SNPs (at 12 independent loci) were genome-wide significant ($P < 5 \times 10^{-8}$) in the IEC endometriosis GWAS, 2750 SNPs (at 71 independent loci) were genome-wide significant in the UKB asthma GWAS, and 674 SNPs (at 16 independent loci) were genome-wide significant in the TAGC asthma GWAS. Nine genome-wide significant endometriosis SNPs (sentinel SNPs) overlapped at a nominal level ($P < 0.05$) with the UKB-asthma GWAS, of which six (at two independent loci) had risk effects in the same direction (Supplementary Table SII). Also, 22 UKB asthma sentinel ($P < 5 \times 10^{-8}$) SNPs (at three independent loci) overlapped with endometriosis SNPs at a nominal level ($P < 0.05$, Supplementary Table SII). A similar pattern of overlap was observed between the endometriosis and the TAGC asthma GWAS (Supplementary Table SII).

SECA genetic overlap results

SECA found a significant concordance of SNP risk effects across the IEC endometriosis (dataset 1) and the UKB asthma (dataset 2) GWAS. Of the 144 SNP subsets assessed, 120 produced evidence of nominally significant concordant effects (OR > 1 and $P < 0.05$). The empirical (permuted) *P*-value ($P_{Fsig\text{-}permuted}$) for observing 120 or more SNP subsets with nominally significant concordant effects = 9.99×10^{-4} (95% CI: 5.12×10^{-5}–5.64×10^{-3}). The number of SNP subsets with nominally significant concordant effects is

significantly more than expected by chance, indicating a significant concordance of genetic risk between the two traits. Supplementary Table SIII provides additional details for these findings.

In a reverse analysis in which the UKB asthma GWAS was assessed as dataset 1 and the IEC endometriosis GWAS as dataset 2, SECA confirms the presence of genetic overlap between the two disorders with a total of 132 SNP subsets producing evidence of nominally significant concordant effects (OR > 1 and $P < 0.05$). SNP subsets having smaller GWAS *P*-values demonstrated stronger concordance (Supplementary Table SIII). Utilizing an independent asthma GWAS (the TAGC asthma), SECA produced a similar pattern of results, replicating our finding of significant genetic overlap between endometriosis and asthma (Supplementary Table SIII).

Genetic correlation between endometriosis and asthma

Consolidating SECA results, we found a positive and significant genetic correlation between the IEC endometriosis and the UKB asthma GWAS using the LDSC method ($r_G = 0.16$, $P = 2.01 \times 10^{-6}$). We repeated this analysis using the TAGC asthma GWAS and found a similarly significant positive genetic correlation between endometriosis and asthma ($r_G = 0.19$, $P = 8.45 \times 10^{-6}$). Table I summarizes the results for our SNP-based genetic correlation and heritability estimates for endometriosis and asthma.

SNPs and loci shared by endometriosis and asthma

A total of 210 SNPs was genome-wide significant following a cross-disorder meta-analysis of the IEC endometriosis and the UKB asthma GWAS (Supplementary Table SIV). We performed LD clumping through which 26 of the identified SNPs ($r^2 < 0.6$), at 14 loci ($r^2 < 0.1$) were assessed as independent (Table II). Four of these 14 independent loci—rs72828033 (2q12.1), rs2894221 (6p21.33), rs72782675 (10p14), rs56062135 (15q23)—were already genome-wide significant ($P < 5 \times 10^{-8}$) in the UKB asthma GWAS. Our study indicates that the loci are similarly shared by endometriosis. The remaining nine loci were not genome-wide significant but were at the least nominally significant ($5 \times 10^{-8} < P_{GWAS\text{-}data} < 0.05$) in each of endometriosis and asthma GWAS. These reached genome-wide significance following the GWAS meta-analysis. A search in the PhenoScanner database (on 20 July 2021) indicates that five of these nine loci—rs4480415 (1q25.1), rs399123 and rs13250871 (8p23.1), rs12253527 (10p12.31), rs10893844 (11q24.3) and rs35653192 (17q21.31)—were not previously reported for endometriosis or asthma, at a genome-wide level of significance, indicating they are putative novel loci for the two traits. Notably, findings from the posterior probability (*m*-value) and the Binary Effect *P*-value methods (Han and Eskin, 2012) support the identified independent SNPs and loci in both the IEC endometriosis and the UKB asthma GWAS (Table II). Additional 44 SNPs at eight independent loci reached a genome-wide suggestive level of significance for endometriosis and asthma (Supplementary Table SV).

Replication of identified loci

A meta-analysis of the IEC endometriosis and TAGC asthma GWAS identified a total of 22 SNPs at four independent loci reaching a genome-wide level ($P_{meta\text{-}analysis} < 5 \times 10^{-8}$) of significance (Supplementary Table SVI and Table II). Two of the loci (10p12.31 and 10q23.31, Table II) are novel for the two traits, having not previously been reported for endometriosis or asthma at a genome-wide level of significance. One of the loci (at 9p21.3) has previously been reported in endometriosis (Uno *et al.*, 2010; Nyholt *et al.*, 2012) and our study indicates that it is associated with both endometriosis and asthma. The remaining locus (rs17293632 at 15q22.33) is well established for asthma but equally showed evidence of being shared by endometriosis following the IEC endometriosis and the TAGC asthma meta-analysis (Table II). An additional 38 independent SNPs at 28 loci produced evidence for genome-wide *suggestive* association ($P < 1 \times 10^{-5}$) in the IEC endometriosis and the TAGC asthma meta-analysis (Supplementary Table SVII).

Of the loci reaching genome-wide significance in the IEC endometriosis and the TAGC UKB asthma meta-analysis, two were replicated using the TAGC asthma data at a genome-wide significant level (rs10828264 on 10p12.31 and rs17293632 on 15q23); and one SNP replicated at a genome-wide suggestive level (rs1039916 on 8p23.1) (Table II and Supplementary Table SVI).

Regional association plots

We plotted regional association for the six putatively novel LD-independent SNPs (at five loci) identified in the meta-analysis of the IEC endometriosis and the UKB asthma GWAS, using the LocusZoom. The regional association plots were based on (i) the IEC endometriosis GWAS data, (ii) UKB asthma GWAS and (iii) meta-analysis GWAS data. Supplementary Figs S1–S6 provide details of these plots. A meta-analysis of the 'IEC endometriosis' and the 'TAGC asthma' GWAS identified two potentially new SNPs and loci, and we similarly plotted regional association for the SNPs (Supplementary Figs S7 and S8).

Pairwise GWAS co-localization results

Using the pairwise GWAS analysis method (GWAS-PW), we conducted co-localization analyses to assess whether the endometriosis and the asthma association represent the same signal. The relationship between the two traits was assessed using the posterior probabilities of association (PPA) with higher values indicating greater probability. First, we applied the GWAS-PW method to the association of IEC endometriosis with UKB asthma GWAS thereby identifying 216 genomic regions influencing both endometriosis and asthma (PPA4 > 0.5, Supplementary Table SVIII). Of these 216 genomic regions, a total of 38 had PPA4 > 0.9 providing strong evidence of the loci being shared by endometriosis and asthma (Supplementary Table SVIII). Given that Model 3 (PPA3) was less than 0.5 for these regions, the results suggest that the causal variants at the loci are different for the two disorders. We note, however, that GWAS-PW may be limited by its inability to reliably distinguish Model 3 from Model 4 in regions where there are strong LD between variants (Pickrell *et al.*, 2016) which may be the case in the present analysis.

Importantly, based on the PPA3 results, GWAS-PW identified an additional 37 genomic regions where the presence of a variant influencing both endometriosis and asthma can be inferred (PPA3 > 0.5, Supplementary Table SIX), indicating that the regions are shared by both traits and the causal variants are same. Interestingly,

Table I Heritability and genetic correlation analysis results.

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
Asthma	UKB	10.85% (10.01–11.69%)	1.04 (0.0092)
Asthma	TAGC	8.15% (6.03–10.27%)	1.06 (0.009)

SNP-based genetic correlation				
Phenotype 1 (data source)	**Phenotype 2 (data source)**	**r_G (se)**	***P*-value**	**Gencov intercept (se)**
Endometriosis (IEC)	Asthma (UKB)	0.155 (0.033)	2.01×10^{-6}	Constrained to 0
Endometriosis (IEC)	Asthma (TAGC)	0.193 (0.043)	8.45×10^{-6}	Constrained to 0

CI, confidence interval; Gencov, genetic covariance; h^2, heritability; h^2_{SNP}, SNP-based heritability; IEC, International Endogene Consortium; r_G, genetic correlation; se, standard error; SNP, single-nucleotide polymorphism; TAGC, Trans-National Asthma Genetic Consortium; UKB, United Kingdom BioBank.

the identified regions capture many of the genome-wide significant independent loci found in the meta-analysis of the IEC endometriosis and the UKB asthma GWAS, particularly, those on chromosomes 8, 10 and 15 (Supplementary Table SIX) supporting the involvement of these loci in both traits. GWAS-PW found additional genomic regions (PPA3 > 0.5) on chromosomes 8, 10, 14 and 20 which were not identified in our GWAS meta-analysis (Supplementary Table SIX). Moreover, of the 37 shared regions identified at PPA3 > 0.5, 11 had PPA3 > 0.90 (Supplementary Table SIX), providing strong evidence of their involvement in both endometriosis and asthma.

We similarly applied GWAS-PW analysis to the association between the EIC endometriosis and the TAGC asthma GWAS thereby identifying 19 genomic regions where the presence of a variant influencing both endometriosis and asthma were inferred (PPA3 > 0.5, Supplementary Table SX). Notably, three of the four genome-wide significant independent loci, identified in the meta-analysis of the IEC endometriosis and the TAGC asthma GWAS, were represented among the 19 genomic regions found in the GWAS-PW analysis—rs10828264 on 10p12.31 (PPA3 = 0.93), rs12412656 on 10q23.31 (PPA 3 = 0.97) and rs17293632 on 15q22.33 (PPA3 = 0.95). The results, thus, provide additional support for the involvement of these loci in both traits and identify additional shared loci and variants for the two disorders. For the remaining genome-wide significant independent locus, rs1333042 (at 9p21.3), GWAS-PW indicates that the region containing the locus is associated with both endometriosis and asthma, but the causal variants are different (PPA4 = 0.95). Supplementary Table SX provides further details of these results.

Causal association assessment between endometriosis and asthma

We performed a 2SMR analysis to assess the potential causal relationships between endometriosis and asthma. First, 11 independent genome-wide significant SNPs (see the detailed methods in Supplementary Data File SI) from the IEC endometriosis GWAS were utilized as IVs (Supplementary Table SXI). Based on this analysis, we found no evidence to support a causal effect of endometriosis liability on asthma risk (IVW OR = 1.01, 95% CI: 0.93–1.10, *P* = 0.86). The MR-Egger (OR = 1.32, 95% CI: 0.87–2.06, *P* = 0.21), weighted median (OR = 1.01, 95% CI: 0.92–1.11, *P* = 0.87) and MR-PRESSO (raw estimate OR = 1.01 *P* = 0.86) models were supportive of the IVW findings (Table III). There were no outliers corrected results for the MR-PRESSO analysis. The result for the MR-Egger intercept test of pleiotropy indicates there was no unbalanced pleiotropy as the intercept did not deviate significantly from zero (intercept = −0.029, *P* = 0.23).

Second, in a reverse analysis, we assessed the UKB asthma GWAS as the exposure variable and the IEC endometriosis GWAS as the outcome. A total of 29 independent genome-wide significant SNPs from the UKB asthma GWAS were used as IVs (Supplementary Table SXII). The results of this analysis similarly did not provide evidence of a causal influence of asthma on endometriosis (IVW OR = 0.98, 95% CI: 0.91–1.06, *P* = 0.87) (Table III). Sensitivity testing using the MR-Egger (OR = 0.95, 95% CI: 0.75–1.21, *P* = 0.66), the weighted median (OR = 0.98, 95% CI: 0.89–1.07, *P* = 0.69) and MR-PRESSO (raw estimate OR = 0.98, *P* = 0.87) were consistent, indicating no evidence of a causal effect of asthma liability on endometriosis risk. As the MR-Egger intercept did not deviate significantly from zero (intercept = 0.0041, *P* = 0.68), the test for pleiotropy indicates there is no unbalanced pleiotropy. Supplementary Figs S9 and S10 provide details of the various plots (a. scatter plot, b. leave-one-out plots, c. Forest plot and d. funnel plot) in these analyses.

Lastly, for replication of our findings, we conducted 2SMR using the IEC endometriosis and the TAGC asthma GWAS. Briefly, the results of this analysis found no evidence for a significant causal association between endometriosis and asthma irrespective of whether endometriosis was the exposure or outcome variable (Table III). Supplementary Date File SI and Supplementary Figs S11–S13 (a. scatter plot, b. leave-one-out plots, c. Forest plot and d. funnel plot) provide more elaborate results in respect of this analysis.

Gene-based association findings

We performed gene-based association analysis separately for endometriosis and asthma using SNPs overlapping the IEC endometriosis and the UKB asthma GWAS. This analysis identified a total of 18340 protein-coding genes for each of the traits. Using a Bonferroni

Table II SNPs and loci reaching genome-wide significance for endometriosis and asthma in the GWAS meta-analysis.

SNP	Locus	Lead SNPs	Chr	Position	EA	NEA	Endometriosis		Asthma		Meta-analysis (FE)		BE *P*-value	Cochran's Q test (*P* for Q test)	*M*-value		Near genes/ cytobands
							BETA	*P*	BETA	*P*	BETA	*P*			Endo	Asthma	
IEC endometriosis and UKB asthma GWAS																	
rs9438873	1	rs9438873	1	25220590	T	C	−0.06	1.40×10^{-3}	−0.07	3.30×10^{-7}	−0.07	1.64×10^{-9}	5.61×10^{-9}	0.101 (7.51×10^{-1})	1.00	1.00	RUNX3/1p36.11
*rs4480415	2	rs4480415	1	174800121	A	G	−0.07	5.12×10^{-6}	−0.04	4.33×10^{-4}	−0.05	4.81×10^{-8}	1.58×10^{-7}	3.379 (6.60×10^{-2})	1.00	0.99	CACYBP/1q25.1
rs72828033	3	rs72828033	2	103277862	C	G	−0.09	1.79×10^{-3}	−0.10	6.20×10^{-9}	−0.10	4.14×10^{-11}	1.38×10^{-10}	0.153 (6.95×10^{-1})	1.00	1.00	SLC9A2/2q12.1
rs13099273	4	rs13099273	3	188133518	A	T	0.04	1.90×10^{-2}	0.05	5.84×10^{-7}	0.04	4.51×10^{-8}	1.36×10^{-7}	0.474 (4.91×10^{-1})	0.95	1.00	LPP/3q27.3-q28
rs2534687	5	rs2894221	6	31461608	T	C	0.05	1.54×10^{-3}	0.05	2.95×10^{-6}	0.05	1.72×10^{-8}	5.96×10^{-8}	0.004 (9.51×10^{-1})	1.00	1.00	MICB/6p21.33
rs2894221			6	31461771	A	T	0.04	5.78×10^{-3}	0.06	1.05×10^{-10}	0.05	5.89×10^{-12}	1.56×10^{-11}	1.984 (1.59×10^{-1})	0.97	1.00	MICB/6p21.33
rs12700186	6	rs12700186	7	20416711	T	C	0.05	2.37×10^{-4}	0.04	1.86×10^{-5}	0.04	1.93×10^{-8}	6.44×10^{-8}	0.306 (5.80×10^{-1})	1.00	1.00	ITGB8/7p21.1
rs55852693	7	rs399123	8	8175136	A	C	0.04	6.13×10^{-3}	0.05	2.61×10^{-6}	0.05	5.50×10^{-8}	1.85×10^{-7}	0.131 (7.17×10^{-1})	0.99	1.00	PRAG1/8p23.1
rs6601697			8	8270294	T	G	−0.03	1.65×10^{-2}	−0.05	1.91×10^{-7}	−0.05	1.61×10^{-8}	4.54×10^{-8}	0.980 (3.22×10^{-1})	0.95	1.00	PRAG1/8p23.1
rs7829975			8	8548117	A	T	−0.04	6.18×10^{-3}	−0.05	3.75×10^{-7}	−0.04	1.01×10^{-8}	3.35×10^{-8}	0.454 (5.01×10^{-1})	0.98	1.00	CLDN23/8p23.1
rs2409088			8	8645725	C	G	0.04	1.63×10^{-3}	0.05	1.61×10^{-6}	0.05	9.52×10^{-9}	3.30×10^{-8}	0.020 (8.89×10^{-1})	1.00	1.00	CLDN23/8p23.1
*rs399123			8	8747537	T	C	−0.05	4.18×10^{-4}	−0.04	2.79×10^{-6}	−0.05	4.95×10^{-9}	1.69×10^{-8}	0.096 (7.57×10^{-1})	1.00	1.00	MFHAS1/8p23.1
rs17658270			8	9153619	C	G	0.04	7.21×10^{-3}	0.05	2.22×10^{-7}	0.05	6.38×10^{-9}	2.08×10^{-8}	0.306 (5.80×10^{-1})	0.98	1.00	PPP1R3B/8p23.1
rs10099122			8	9568003	T	C	−0.05	9.31×10^{-4}	−0.04	9.59×10^{-6}	−0.04	3.23×10^{-8}	1.09×10^{-7}	0.024 (8.78×10^{-1})	1.00	1.00	TNKS/8p23.1
rs7838378	8	rs13250871	8	10731066	A	T	−0.04	3.31×10^{-3}	−0.04	5.30×10^{-6}	−0.04	6.03×10^{-8}	2.07×10^{-7}	0.024 (8.77×10^{-1})	0.99	1.00	PINX1/8p23.1
rs10109025			8	10815571	C	G	0.05	5.06×10^{-4}	0.04	1.46×10^{-5}	0.04	3.09×10^{-8}	1.05×10^{-7}	0.268 (6.05×10^{-1})	1.00	1.00	PINX1/8p23.1
rs12156009			8	11285219	A	C	0.05	8.24×10^{-4}	0.04	1.38×10^{-5}	0.04	4.43×10^{-8}	1.55×10^{-7}	0.102 (7.49×10^{-1})	1.00	1.00	FAM167A/8p23.1
*rs13250871			8	11467763	A	G	−0.05	3.61×10^{-3}	−0.05	1.35×10^{-6}	−0.05	1.68×10^{-8}	5.59×10^{-8}	0.0 (9.87×10^{-1})	0.99	1.00	GATA4/8p23.1
rs72782675	9	rs72782675	10	9028946	T	C	−0.11	2.87×10^{-2}	−0.25	2.80×10^{-8}	−0.19	2.81×10^{-8}	9.34×10^{-9}	4.714 (2.99×10^{-2})	0.69	1.00	GATA3/10p14
*rs12253527	10	rs12253527	10	21819824	A	G	0.06	1.68×10^{-5}	0.05	8.31×10^{-7}	0.05	7.94×10^{-11}	2.69×10^{-10}	0.561 (4.54×10^{-1})	1.00	1.00	MLLT10/10p12.31
*rs10893844	11	rs10893844	11	128185850	C	G	0.03	1.71×10^{-2}	0.05	7.57×10^{-7}	0.04	5.57×10^{-8}	1.67×10^{-7}	0.727 (3.94×10^{-1})	0.95	1.00	ETS1/11q24.3
rs56062135	12	rs56062135	15	67455630	T	C	0.05	1.39×10^{-3}	0.11	3.41×10^{-21}	0.09	7.46×10^{-22}	2.69×10^{-22}	7.457 (6.32×10^{-3})	0.88	1.00	SMAD3/15q23
rs28360855			15	67458805	A	G	−0.03	3.07×10^{-2}	−0.05	2.26×10^{-8}	−0.05	6.21×10^{-9}	9.79×10^{-9}	2.129 (1.45×10^{-1})	0.86	1.00	IQCH/15q23
*rs35653192	13	rs35653192	17	42975703	A	G	−0.19	9.15×10^{-6}	−0.09	8.81×10^{-5}	−0.12	2.11×10^{-8}	6.96×10^{-8}	3.708 (5.41×10^{-2})	1.00	1.00	CCDC103/17q21.31
rs8129889	14	rs8133814	21	36480229	A	G	0.04	2.14×10^{-2}	0.07	5.63×10^{-8}	0.06	7.34×10^{-9}	1.81×10^{-8}	1.234 (2.67×10^{-1})	0.93	1.00	CLIC6/21q22.12
rs8133814			21	36692450	C	G	0.04	6.40×10^{-3}	0.05	1.11×10^{-7}	0.05	3.47×10^{-9}	1.10×10^{-8}	0.706 (4.01×10^{-1})	0.98	1.00	CLIC6/21q22.12
IEC endometriosis and TAGC asthma GWAS																	
*rs10828264	1	rs10828264	10	22017545	A	G	0.05	3.07×10^{-4}	0.06	1.49×10^{-5}	0.06	1.81×10^{-8}	6.47×10^{-8}	*0.09 (7.65 × 10^−1^)*	1.00	1.00	*MLLT10/10p12.31*
*rs12412656	2	rs12412656	10	89781890	A	G	0.05	2.90×10^{-4}	0.07	1.53×10^{-6}	0.06	2.10×10^{-9}	7.33×10^{-9}	*0.36 (5.50 × 10^−1^)*	1.00	1.00	*MED6P1/10q23.31*
rs1333042	3	rs1333042	9	22103813	A	G	0.07	5.10×10^{-7}	0.05	2.97×10^{-4}	0.06	1.20×10^{-9}	4.13×10^{-9}	*1.35 (2.46 × 10^−1^)*	1.00	1.00	*CDKN2B-AS1/9p21.3*
rs17293632	4	rs17293632	15	67442596	C	T	0.04	1.61×10^{-3}	0.12	5.10×10^{-14}	0.08	#7.41×10^{-15}	2.59×10^{-15}	*8.72 (3.15 × 10^−3^)*	0.74	1.00	*SMAD3/15q22.33*

Cochran's Q test is the traditional test for heterogeneity in meta-analyses.

BE, binary effects; Chr, chromosomes; EA, effect alleles; FE, fixed effect model of GWAS meta-analysis; GWAS, genome-wide association studies; IEC, International Endogene Consortium; NEA, non-effect alleles; *P*, *P*-value; SNP, single-nucleotide polymorphism; TAGC, Trans-National Asthma Genetic Consortium; UKB, United Kingdom Biobank.

*Putative novel SNPs and loci identified in this study.

#RE2 (modified random effect) model reported because of substantial heterogeneity ($I^2 > 78$).

Table III MR results for endometriosis and asthma.

Exposure (nSNPs)	Outcome	IVW		Weighted median		MR-Egger		MR-PRESSO					MR-Egger intercept	
		OR	P	OR	P	OR	P	Global test P	Raw OR	P	C-OR	P	Intercept	P
IEC endometriosis (11)	UKB asthma	1.01	0.86	1.01	0.87	1.32	0.21	0.042	1.01	0.86	–	–	−0.029	0.23
UKB asthma (29)	IEC endometriosis	0.98	0.87	0.98	0.69	0.95	0.66	0.22	0.98	0.87	–	–	0.0041	0.68
IEC endometriosis (8)	TAGC asthma	1.05	0.25	1.07	0.26	1.25	0.52	0.56	1.05	0.24	–	–	−0.021	0.58
TAGC asthma (13)	IEC endometriosis	1.08	0.12	1.08	0.16	1.04	0.88	0.051	1.08	0.16	–	–	0.0047	0.86
IEC endometriosis (11)*	TAGC asthma	0.99	0.97	1.01	0.86	1.11	0.71	0.26	0.99	0.97	–	–	−0.012	0.70

C-OR, corrected odds ratio; IEC, International Endogene Consortium; IVW, inverse variance weighted; MR, Mendelian randomization; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier; nSNP, number of SNPs utilized as instrumental variables; OR, odds ratio; *P*, *P*-value; SNP, single-nucleotide polymorphism; TAGC, Trans-National Asthma Genetic Consortium; UKB, United Kingdom Biobank.
*Proxy SNPS were utilized as a part of the instrumental variables. Note spaces marked with a dash indicate that there were no outlier SNPs and hence there was no outlier corrected results in the MR-PRESSO analysis.

correction for multiple testing (0.05/18 340), we considered a gene to be genome-wide significant at $P_{gene} < 2.73 \times 10^{-6}$. At this threshold, we found a total of six genome-wide significant genes for endometriosis and 108 for asthma (Supplementary Table SXIII). Supplementary Table SXIV presents all genes overlapping both the IEC endometriosis and the UKB asthma GWAS.

A total of 17 genome-wide significant genes showed evidence of being shared by both endometriosis and asthma following the FCP analysis (Table IV). Of these, seven genes (*SMAD3*, *PSORS1C2*, *RIN3*, *CLEC16A*, *AAGAB*, *SUOX* and *CASC10*) were already genome-wide significant in the UKB asthma GWAS and two (WNT4 and SKAP1) in the IEC endometriosis GWAS (Table IV). A search in PhenoScanner (on 09 September 2021) indicated that four genes—*IQCH*, *MRPS14*, *KRT222* and *XKR6*—were previously reported, at a genome-wide significant level, for asthma. The remaining four genes (*MLLT10*, *RABGAP1L*, *TNKS* and *MFHAS1*) are putatively novel for endometriosis and asthma as we found no evidence of their previous association with either of the traits, at a genome-wide level of significance.

Moreover, of the 17 shared genes, 10 were at genomic loci identified in our GWAS meta-analysis: 10p12.31 (*MLLT10* and *CASC10*), 15q23 (*AAGAB*, *IQCH* and *SMAD3*), 8p23.1 (*TNKS* and *MFHAS1*), 1q25.1 (*MRPS14* and *RABGAP1L*) and 6p21.33 (*PSORS1C2*). Lastly, using the TAGC asthma GWAS we reproduced four of these genes (*MLLT10*, *SMAD3*, *WNT4* and *CLEC16A*) at a genome-wide level (Table IV) and one gene (*MFHAS1*) at a nominal level ($FCP = 1.43 \times 10^{-4}$, Supplementary Table SXV). Supplementary Table SXVI presents the results of genome-wide significant genes identified for IEC endometriosis and TAGC asthma using SNPs overlapping the two GWAS. A more comprehensive description of the replication analysis results is provided in Supplementary Data File SII.

Gene-level genetic overlap between endometriosis and asthma

We performed independent gene-based analyses, and using the binomial test, assessed whether the proportion of genes overlapping the two traits was more than expected by chance. Our findings, using the IEC endometriosis and the UKB asthma GWAS, support the results of SNP-level studies revealing the presence of significant gene-based genetic overlap between endometriosis and asthma, at $P_{gene} < 0.1$, $P_{gene} < 0.05$ and $P_{gene} < 0.01$ (Table V). For example, the proportion of the observed effective number of independent genes overlapping the two traits (0.159) at $P_{gene} < 0.05$ was significantly higher than the expected proportion of 0.121 ($P_{binomial\text{-}test} = 1.32 \times 10^{-5}$). This result supports evidence of significant gene-level genetic overlap between endometriosis and asthma (Table V).

We repeated the gene-level genetic overlap assessment using the IEC endometriosis and the TAGC asthma GWAS, and the results were reproduced at $P_{gene} < 0.1$ and $P_{gene} < 0.05$ levels, supporting evidence of significant gene-level genetic overlap between endometriosis and asthma (Supplementary Table SXVII).

Biological pathways shared by endometriosis and asthma

We performed a pathway-based analysis of genes overlapping the IEC endometriosis and the UKB asthma GWAS at $P_{gene} < 0.1$ and $FCP < 0.05$ using the g:GOst tool of g-profiler software (Supplementary Table SXIV presents the lists of these overlapping genes). This analysis identified 15 biological pathways or processes, the majority of which cluster in the broad theme (following enrichment mapping and auto-annotation) of 'positive adhesion regulation' and 'nuclear receptor binding' (Fig. 2 and Supplementary Table SXVIII). We repeated this analysis using genes overlapping the IEC endometriosis and TAGC asthma GWAS at $P_{gene} < 0.1$ and $FCP < 0.05$, Supplementary Table SXV, thereby identifying seven more informative biological pathways significantly enriched for both endometriosis and asthma. These pathways include thyroid hormone signalling pathway ($P_{(adjusted)} = 0.026$), androgen biosynthetic process ($P_{(adjusted)} = 0.035$), mammary gland development ($P_{(adjusted)} = 0.023$) and male sex differentiation ($P_{(adjusted)} = 0.020$). Other pathways significantly enriched include abnormal oral physiology ($P_{(adjusted)} = 0.007$), abnormal respiratory system morphology ($P_{(adjusted)} = 0.003$) and brain-derived neurotrophic factor (BDNF) signalling pathway ($P_{(adjusted)} = 0.036$). Figure 3 and Table VI summarize the result of the analysis.

Table IV Genome-wide significant genes associated with endometriosis and asthma.

Chr	Start position	Stop position	Gene	P_{gene} endometriosis	P_{gene} asthma	*FCP*
IEC endometriosis and UKB asthma GWAS						
15	67356101	67487533	*SMAD3*	8.49×10^{-4}	1.91×10^{-15}	6.80×10^{-17}
6	31105313	31107127	*PSORS1C2*	1.11×10^{-2}	5.04×10^{-11}	1.63×10^{-11}
14	92980118	93155339	*RIN3*	1.65×10^{-4}	3.99×10^{-8}	1.76×10^{-10}
16	11038345	11276046	*CLEC16A*	3.13×10^{-2}	1.70×10^{-9}	1.31×10^{-9}
15	67493371	67547533	*AAGAB*	1.92×10^{-3}	5.36×10^{-8}	2.47×10^{-9}
10	21823094	22032559	**MLLT10*	5.65×10^{-5}	3.37×10^{-6}	4.46×10^{-9}
12	56390964	56400425	*SUOX*	3.87×10^{-2}	1.10×10^{-8}	9.61×10^{-9}
10	21781587	21786191	*CASC10*	2.65×10^{-4}	2.07×10^{-6}	1.22×10^{-8}
1	22443798	22470462	*WNT4*	8.30×10^{-8}	1.81×10^{-2}	3.21×10^{-8}
15	67547138	67794598	*IQCH*	2.61×10^{-4}	1.46×10^{-5}	7.78×10^{-8}
17	46210802	46507637	*SKAP1*	8.09×10^{-7}	1.87×10^{-2}	2.87×10^{-7}
1	174128548	174964445	**RABGAP1L*	6.09×10^{-5}	8.07×10^{-4}	8.76×10^{-7}
8	9413424	9639856	**TNKS*	3.51×10^{-4}	2.12×10^{-4}	1.30×10^{-6}
1	174979925	174992561	*MRPS14*	1.26×10^{-4}	6.25×10^{-4}	1.37×10^{-6}
17	38785049	38821393	*KRT222*	1.40×10^{-3}	5.76×10^{-5}	1.40×10^{-6}
8	8640864	8751155	**MFHAS1*	3.89×10^{-3}	2.30×10^{-5}	1.54×10^{-6}
8	10753555	11058875	*XKR6*	2.97×10^{-3}	3.68×10^{-5}	1.86×10^{-6}
17	38810917	38821433	*KRT222*	1.33×10^{-3}	8.85×10^{-5}	2.00×10^{-6}
IEC endometriosis and TAGC asthma GWAS						
10	21823094	22032559	**MLLT10*	1.74×10^{-6}	3.66×10^{-4}	1.27×10^{-7}
12	102789645	102874423	*IGF1*	1.89×10^{-6}	9.54×10^{-3}	3.39×10^{-7}
19	46367247	46377055	*FOXA3*	2.69×10^{-4}	2.30×10^{-5}	1.23×10^{-7}
15	67356101	67487533	SMAD3	1.93×10^{-3}	3.08×10^{-9}	1.60×10^{-10}
1	22443798	22470462	WNT4	1.61×10^{-8}	3.63×10^{-2}	1.30×10^{-8}
16	11038345	11276046	CLEC16A	2.25×10^{-2}	4.55×10^{-8}	2.22×10^{-8}

Chr, chromosomes; FCP, Fisher's combined *P*-value; P_{gene}, gene-based *P*-value, genome-wide significant $P < 2.73 \times 10^{-6}$.
*Putatively novel genes for endometriosis and asthma.

Discussion

We present the first comprehensive study assessing the relationship between endometriosis and asthma based on the analysis of large-scale GWAS data. Briefly, we found a significant genetic overlap and correlation relationship between endometriosis and asthma as well as identifying genes, susceptibility loci and biological pathways shared by both traits. Although we found no evidence for a causal association, this study provides novel insights into the potential mechanisms underpinning the observed co-occurrence of endometriosis with asthma, revealing some noteworthy findings.

First, SNP-level assessment using SECA and LDSC methods provide evidence for significant genetic overlap between endometriosis and asthma. This finding confirms a relationship between the two disorders indicating that a proportion of endometriosis and asthma patients share genetic predisposition. Supportive of this result, the independent gene-based analyses revealed the presence of significant gene-level genetic overlap between endometriosis and asthma. Whereas previous conventional observational studies have reported conflicting results (Lamb and Nichols, 1985; Nichols *et al.*, 1987; Sinaii *et al.*, 2002; Ferrero *et al.*, 2005; Peng *et al.*, 2017), the present genetic-based findings agree with studies that have suggested an increased co-occurrence of endometriosis with asthma. Using the TAGC asthma GWAS, we replicated the significant genetic overlap and correlation—both at SNP and gene-level—between the disorders, further confirming the shared genetic aetiology of endometriosis with asthma.

Second, a meta-analysis of the IEC endometriosis and the UKB asthma GWAS identified 14 genomic loci reaching genome-wide significance for both disorders, five of which are putatively novel. Three of these loci—*MLLT10* (10p12.31), *SMAD3* (15q23) and *MFHAS1* (8p23.1)—were replicated in an independent TAGC asthma GWAS and reinforced in both the GWAS-PW and gene-based analyses. The MFHAS1 gene is well expressed in the lungs, spleen and several other tissues, including the endometrium, and has been associated with systemic lupus erythematosus, an autoimmune disorder (Wang *et al.*, 2018). Similarly, the MLLT10 gene encodes a transcription factor and is expressed in several tissues, including the testis, ovary, thyroid, endometrium, and lungs (Linder *et al.*, 2000; Ogoh *et al.*, 2017); hence, they are plausible biological candidate genes for endometriosis and asthma.

Third, MR analyses provided no evidence for a causal relationship between endometriosis and asthma suggesting that the association

Table V Independent gene-based and gene-level genetic overlap results for IEC endometriosis and UKB asthma GWAS.

The effective number of independent genes in endometriosis and asthma

Disorder	Total genes		Genes with *P*-value < 0.1			Genes with *P*-value < 0.05			Genes with *P*-value < 0.01		
	Raw[c]	Effective[d]	Raw[c]	Effective[d]	Proportion[e]	Rawc	Effective[d]	Proportion[e]	Raw[c]	Effective[d]	Proportion[e]
Endometriosis[a]	20 306	17 407	2949	2488	0.143	1733	1449	0.083	482	400	0.023
Asthma[b]	20 306	17 314	4114	3336	0.193	2634	2099	0.121	1069	830	0.048

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	Asthma	41	34	0.048	34/400 = 0.085	1.07×10^{-3}
***P*-value < 0.05**						
Endometriosis	Asthma	269	230	0.121	230/1449 = 0.159	1.32×10^{-5}
***P*-value < 0.1**						
Endometriosis	Asthma	625	540	0.193	540/2488 = 0.217	1.47×10^{-3}

IEC, International Endogene Consortium; UKB, United Kingdom Biobank.
[a]Endometriosis data from IEC.
[b]Asthma data from the UKB.
[c]Raw number of genes.
[d]Effective number of independent genes.
[e]Proportion of total effective number of independent genes.

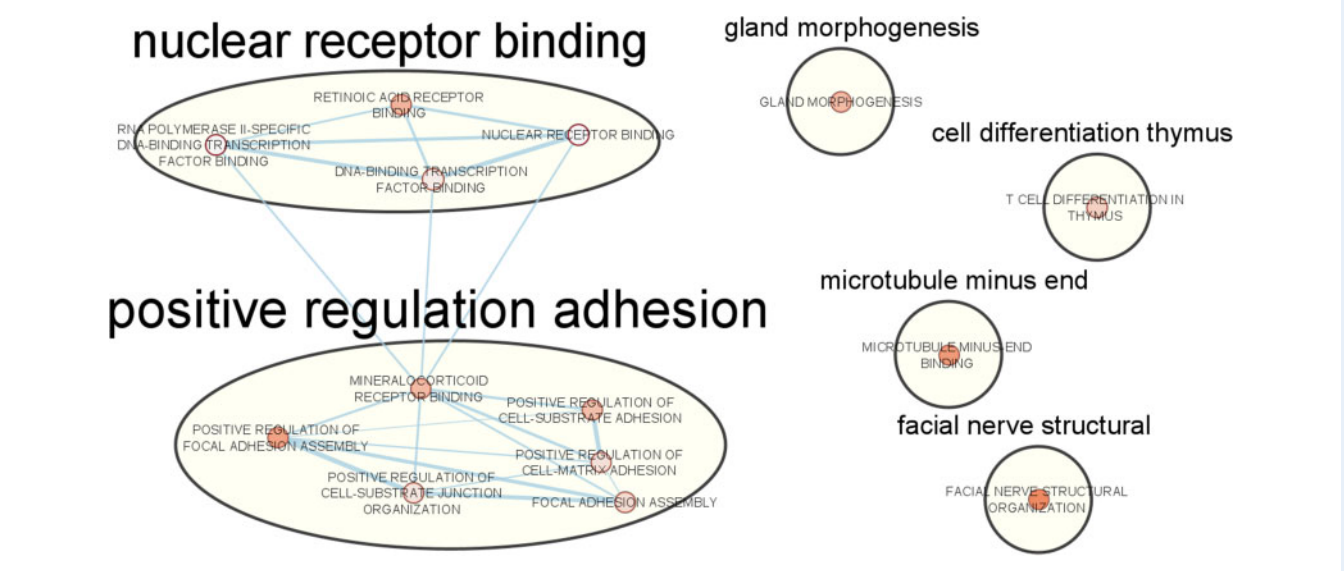

Figure 2. Significantly enriched biological pathways for genes overlapping IEC endometriosis and UKB asthma GWAS. GWAS, genome-wide association studies; IEC, Internation Endogene Consortium; UKB, United Kingdom Biobank.

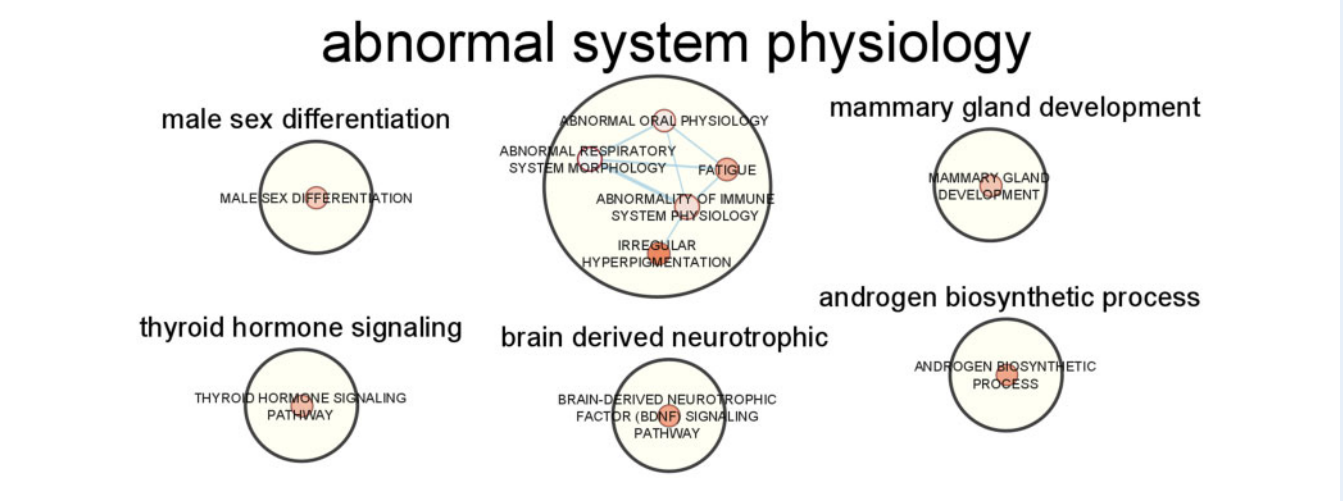

Figure 3. Significantly enriched biological pathways for genes overlapping IEC endometriosis and TAGC asthma GWAS. GWAS, genome-wide association studies; IEC, Internation Endogene Consortium; TAGC: Trans-National Asthma Genetic Consortium.

Table VI Summary of pathways associated with endometriosis and asthma.

Pathways	Term ID	Adjusted *P*-value	Genes
Male sex differentiation	GO:0046661	0.020	*WNT4, GATA3, GATA4, FGF10, BCL2, NCOA1, HOXA11, CBL, MGST1, AGO4, CSDE1, STAT5B*
Mammary gland development	GO:0030879	0.023	*WNT4, MED1, GATA3, CREB1, ERBB4, FGF10, ARHGAP35, LATS1, NCOA1, DEAF1, STAT5B*
Androgen biosynthetic process	GO:0006702	0.035	*WNT4, MED1, HSD17B6, SCARB1*
Thyroid hormone signalling pathway	KEGG:04919	0.026	*WNT4, MED1, ATP2A3, GATA4, ATP1B1, NCOA1, NRAS, MED12L, TSC2*
Brain-derived neurotrophic factor (BDNF) signalling pathway	WP:WP2380	0.036	*VAV3, CREB1, MAP3K1, ALPL, MEF2A, RHOG, TSC2, NCK1, CDK5R1, STAT5B*
Abnormal respiratory system morphology	HP:0012252	0.0042	*SMAD3, WNT4, FIP1L1, TBK1, FOXP1, GATA4, IRF5, FANCG, ERBB4, HPGD, MST1R, FGF10, BCL2, MLX, CD28, DNMT3B, IDUA, TRAIP, CD3G, CBL, ALPL, NRAS, HPS6, LBR, CRELD1, CTC1, VCP, KMT2E, LMNB1, TSC2, MGP, HAAO, F5, ITGA3, VPS13B, PRRX1, FLII, LAMTOR2, DEAF1, STAT5B*
Abnormal oral physiology	HP:0031815	0.0082	*FIP1L1, C12ORF65, TBK1, FOXP1, IRF5, ERBB4, FGF10, TH, CBL, ALS2, LBR, VCP, F5, DEAF1, STAT5B*
Abnormality of immune system physiology	HP:0010978	0.013	*SMAD3, WNT4, GATA3, FIP1L1, TBK1, FOXP1, GATA4, IRF5, FANCG, HPGD, FGF10, BCL2, MLX, TNPO3, CD28, DNMT3B, CTSB, CD70, IDUA, TRAIP, CD3G, CBL, ALPL, NRAS, HPS6, LBR, TOP3A, CRELD1, REV3L, CTC1, LMNB1, KDSR, TSC2, SHOC2, MGP, F5, ITGA3, WDR4, FLII, LAMTOR2, DEAF1, STAT5B, ATN1*
Fatigue	HP:0012378	0.028	*SMAD3, FIP1L1, TBK1, IYD, FOXP1, GATA4, IRF5, ERBB4, BCL2, MLX, TNPO3, ABCC2, CBL, LBR, VCP, TSC2, AGK, STAT5B*
Irregular hyperpigmentation	HP:0007400	0.048	*IGF1, SPRED1, FANCG, CD28, CBL, NRAS, LBR, TOP3A, CDKN2B, REV3L, CTC1, KMT2E, KDSR, TSC2*

Analysis was conducted in the g-profiler using genes overlapping IEC endometriosis and the TAGC asthma GWAS.
GWAS, genome-wide association studies; IEC, International Endogene Consortium; TAGC, Trans-National Asthma Genetic Consortium.

between the two disorders may be explained by shared molecular genetic mechanisms, a position informed by our genetic overlap assessments (both SNP-level and gene-based association) and reinforced by findings in the cross-disorder GWAS meta-analysis. Lastly, pathway-based functional enrichment analysis, using genes overlapping the IEC endometriosis and TAGC asthma GWAS, identified informative biological pathways, including sex-hormone related and oral pathology, shared by the disorders. Abnormal morphology of the respiratory

system, thyroid hormone and BDNF signalling pathways were similarly identified in the biological mechanisms of both endometriosis and asthma, and, potentially, the comorbidity of the two disorders.

Supportive of these findings, previous observational studies have suggested the roles of sex hormones in endometriosis and asthma (Parazzini *et al.*, 2017; DeBoer *et al.*, 2018). For example, frequent exposure or high oestrogen level increases the risks for both disorders (Missmer *et al.*, 2004; Matalliotakis *et al.*, 2008; Vercellini *et al.*, 2014; Keselman and Heller, 2015; Fuseini and Newcomb, 2017), which may also be consistent with the oestrogenic driven 'mammary gland development' pathway found in the present study. Early menarche, short and more frequent menstrual cycles, driven by oestrogen, are known risks for endometriosis (Vercellini *et al.*, 2014). In the same vein, female sex hormones are believed to modulate pulmonary inflammatory processes and smooth muscle functions in ways that may precipitate asthma (Haggerty *et al.*, 2003; McCleary *et al.*, 2018).

Additionally, while androgens are generally classified as male sex steroids, the hormones are also important in endometrial physiology, indicated by the detection of androgen receptors in the endometrium (Simitsidellis *et al.*, 2018). Dysregulation of androgen biosynthesis, for example, has been linked with endometrial pathologies, including endometrial cancer and endometriosis (Simitsidellis *et al.*, 2018). Changes in androgen levels have similarly been associated with asthma prevalence and severity. For example, sex differences in asthma prevalence (post-pubertal females having higher prevalence and more severe form of the disease) may be explained by the surge in circulating androgens in post-pubertal males (DeBoer *et al.*, 2018). This position may also be consistent with the 'male sex differentiation' pathway found in the present study.

Indeed, a synthetic androgen, Danazol, has been utilized, for decades, in the management of endometriosis-associated pain (Ferrero *et al.*, 2018). While, the medicine is no longer the first line for endometriosis, due to its virilizing adverse effects, newer molecules such as the 'selective androgen receptor modulators (SARMs)' (Burris *et al.*, 2013), may be a promising therapeutic avenue for endometriosis, and by extension, asthma. Thyroid hormone signalling pathway was significantly enriched in our study. There is evidence implicating the dysfunction of the hormone in endometriosis and asthma (Michalakis *et al.*, 2011; Bingyan and Dong, 2019; Peyneau *et al.*, 2019); however, the mechanisms are still not well-understood. Targeted functional studies are warranted to elucidate the roles of these genes and pathways in endometriosis and asthma.

The use of multiple and complementary statistical methods, which enabled a comprehensive assessment of endometriosis and asthma relationships, is a major strength of our study. Unlike previous traditional observational studies which may be limited by small sample sizes, possible reverse causality or confounding influence of lifestyles or environment, our findings are reliable since they were based on the use of genetic data. However, when interpreting our results, because we analysed GWAS datasets from mainly European populations, they may not be generalizable to other ancestries. Also, 7% of participants in our endometriosis GWAS were of Japanese ancestry. This observation may affect some of our analyses that are sensitive to LD patterns and differ with ancestries. However, we do not expect it will alter the conclusions of this study, especially, given the significant genetic overlap (polygenic prediction) found across the European and Japanese GWAS datasets (Nyholt *et al.*, 2012). Lastly, due to data limitation (i.e. lack of genome-wide significant SNPs or small sample size/case number) for the UKB endometriosis GWAS, we were only able to perform replication analysis for asthma and not for endometriosis.

Conclusion

Our study provides evidence for endometriosis and asthma comorbidity. Based on the present results, we recommend a concurrent screening for asthma in endometriosis patients and vice versa, although, we note that our findings do not necessarily indicate that the two disorders will always co-occur. Also, given our findings and previous evidence associating oral contraceptive use with increased risk of asthma, clinicians may need to be on the lookout for potential worsening of asthma symptoms in endometriosis patients prescribed with the medications. Notably, we identified loci and genes shared by both disorders, and further analyses implicate the roles of sex hormone-related and thyroid hormone signalling biological pathways in endometriosis and asthma and perhaps the comorbid state of the disorders. Agents targeting androgen receptors, for example, the 'selective androgen receptor modulators' may be therapeutically relevant in both endometriosis and asthma. SNPs, loci, genes and biological pathways identified in this study are potential targets for further investigations in both endometriosis and asthma.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The present study was based on a secondary analysis of GWAS summary statistics and all data generated are included in this published article (and its supplementary information files). The GWAS data analysed for asthma are available online through the links and references provided in the subsection describing GWAS data. The GWAS data for endometriosis data were sourced from the International Endogen Consortium and can be accessed by contacting the consortium directly.

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Authors' roles

E.O.A. and D.R.N. conceived and designed the study; E.O.A. carried out data analysis and interpreted the results with assistance from D.R.N.; D.M. provided advice on study design and result interpretation; IEC and 23andMe provided and curated data; E.O.A. wrote the first draft of the manuscript; D.R.N. supervised the project; E.O.A., D.M., IEC, 23andMe and D.R.N. reviewed, revised and agreed on the final draft of the manuscript.

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Conflict of interest

All researchers had full independence from the funders. We have no conflicts of interest to declare.

Appendix

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