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Research article

Asthma and risk of adverse pregnancy outcomes: A Mendelian randomization study

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ABSTRACT

Background: Multiple empirical investigations have indicated a connection between asthma and adverse pregnancy outcomes (APOs). Nevertheless, the effects of asthma on APOs remain uncertain.

Methods: We performed bi-directional Univariable Mendelian randomization (UVMR) analyses using combined information obtained from genome-wide association studies (GWAS) data that is publicly accessible. The principal approach used to analyze the causal association between asthma or age when diagnosed and APOs was the inverse variance weighted (IVW) method. The two types of data regarding exposure originate from the IEU Open GWAS project, which includes 56,167 and 47,222 European asthma patients, respectively. The data of four APOs were acquired via the GWAS dataset of the FinnGen collaboration. In addition, we implemented multivariable Mendelian randomization (MVMR), controlling for confounding factors such as smoking status, frequent drinking, body mass index (BMI), and live birth quantity. Furthermore, we executed several meticulous sensitivity studies to ascertain the reliability of our MR results.

Results: Following the implementation of the Bonferroni adjustment, the UVMR assessment revealed that in the IVW model, asthma was significantly linked to an elevated risk of spontaneous abortion (SA) (odds ratio [OR]: 1.115; 95 % confidence interval [CI]: 1.031–1.206; $P = 0.006$) and gestational diabetes mellitus (GDM) (OR: 1.125; 95 % CI: 1.037–1.220; $P = 0.005$). However, there was no causal correlation between asthma and preterm birth (PTB) (OR: 0.979; 95 % CI: 0.897–1.068; $P = 0.629$) or preeclampsia (PE) (OR: 1.059; 95 % CI: 0.951–1.179; $P = 0.297$). After adjusting for confounding factors, including smoking status, frequent drinking, BMI, and live birth quantity, the MVMR analysis shows a statistically significant causal relationship between asthma and SA or GDM. Furthermore, our investigation's findings did not reveal a substantial correlation between the age of asthma onset based on genetics and the likelihood of SA or GDM. The inverse MR outcomes indicate a lack of causal connection linking APOs to the incidence of asthma. The validity of these findings were verified by sensitivity analyses.

Conclusions: The evidence provided by this study proves that genetically determined asthma is linked to a higher likelihood of SA and GDM. Further research is required to examine potential pathways. However, no conclusive evidence has been found to support the increased risk of SA and GDM in early asthma diagnosis or the interaction between asthma and PTB or PE, indicating that confounding factors may affect the results of previous observational studies.

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1. Introduction

Asthma is a heterogeneous disease characterized by chronic inflammation and hyperresponsiveness of the respiratory tract, with reversible expiratory airflow restriction as the primary manifestation. Frequently, it is accompanied by symptoms including recurring wheezing, shortness of breath, chest tightness, and coughing [1]. Adverse pregnancy outcomes (APOs) encompass a range of conditions detrimental to the well-being of mothers, fetuses, or infants throughout pregnancy, childbirth, or the postpartum period. These complications include spontaneous abortion (SA), preterm birth (PTB), preeclampsia (PE), and gestational diabetes mellitus (GDM), among others. Due to their immediate and enduring adverse consequences, it is imperative to promptly identify and proactively prevent them [2].

Asthma affects 8 %–13 % of pregnant women globally [3]. Pregnancy-induced physiological changes may exacerbate asthma in pregnant women. These changes primarily encompass an increased metabolic rate, elevated oxygen consumption, reduced functional residual capacity, mechanical compression due to uterine enlargement, fluctuations in hormone secretion levels, and modifications in immune system function [4–6]. Previous studies have demonstrated that asthma can increase the risk of APOs in pregnant women [7, 8]. A retrospective cohort study conducted at 12 clinical centers in the United States found that women suffering asthma had a greater chance of experiencing APOs, including PE (OR: 1.14; 95 % CI: 1.06–1.22), GDM (OR: 1.11; 95 % CI: 1.03–1.19), and PTB (OR: 1.17; 95 % CI: 1.12–1.23), compared to women without asthma [7]. Additionally, research findings indicate that women diagnosed with asthma are prone to experience spontaneous abortion(adjusted relative risk [aRR]:1.21; 95 % CI:1.15–1.28) [8]. Nevertheless, a prospective study has shown no substantial link between a diagnosis of asthma before pregnancy and the occurrence of SA (hazard ratio [HR]:0.98; 95 % CI: 0.84, 1.14). Notably, only severe asthma grades 2–3 are connected to a greater chance of SA (HR:1.39; 95 % CI: 1.02, 1.89) [9]. Since the evidence for the correlation between asthma and APOs comes from observational studies, there are limitations in elucidating confounding factors and reverse causal bias. Hence, the causalities of these links remain uncertain, and further compelling evidence is needed to validate them.

Conceptually similar to randomized controlled trials, Mendelian randomization (MR) is a reliable analytical method for evaluating causal associations, utilizing genetic variations closely related to exposure as instrumental variables (IVs) to assess the impact of exposure on outcomes [10]. Given the random allocation of genetic variation during meiosis, MR results are more resistant to interference from confounding variables and reverse causality [11,12]. Multivariate Mendelian randomization (MVMR) represents an innovative technology that integrates genetic variations of multiple risk factors into a unified model. This approach enables the simultaneous assessment of relevant exposures, effectively mitigating the impact of confounding factors [13]. Consequently, we performed univariate Mendelian randomization (UVMR) and MVMR studies to identify the causal association between asthma and APOs.

2. Materials and methods

2.1. Study design

In MR studies, depicted in Fig. 1, the validity of causal estimates hinges on fulfilling three critical assumptions: first, the genetic variants must have a robust association with the exposure; second, they should not be associated with any potential confounders of the

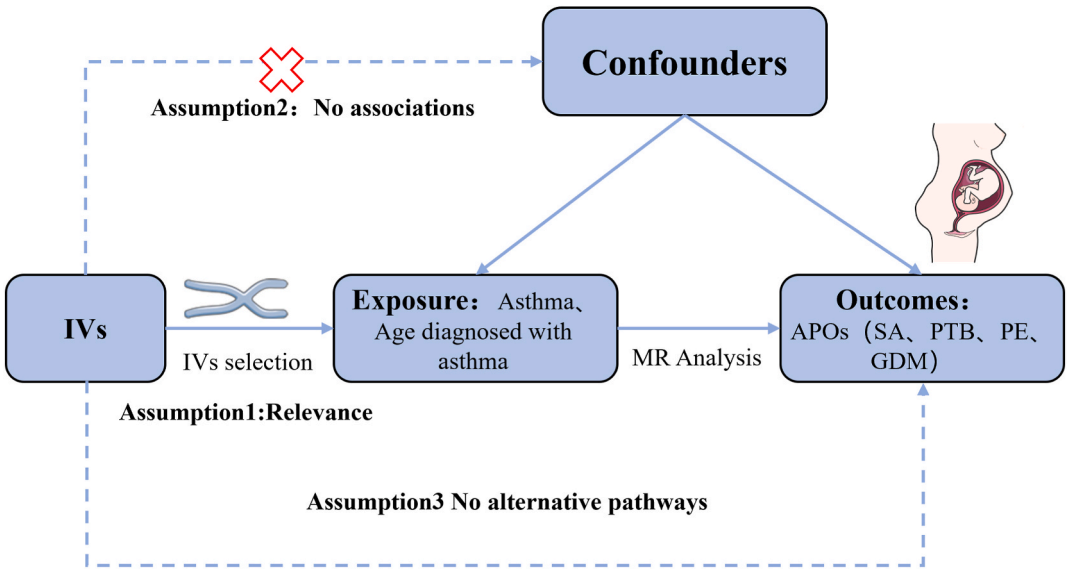

Fig. 1. Assumptions behind the MR study about asthma and the potential danger of APOs.

exposure-outcome relationship; and third, the variants should not have a separate impact on the outcome, apart from their correlation with the exposure. Previous studies have provided proof suggesting that smoking status, frequent drinking, body mass index (BMI), and live birth quantity are risk determinants associated with the onset of APOs [14–22]. Thus, we further estimated the direct influence of asthma on APOs utilizing MVMR analysis.

2.2. Data sources

The summary statistics for asthma were obtained from the UK Biobank, which included 56,167 asthma cases and 352,255 controls [23]. Asthma cases were identified by self-reported questionnaires, hospital records coded according to the International Classification of Diseases (ICD-9 and ICD-10), and primary care records. IVs of age at which asthma was diagnosed were sourced from the UK Biobank and included 47,222 European participants. To prevent inflated type 1 error caused by sample overlap, the summary-level data for specific APOs, including SA, PTB, PE and GDM were acquired from the FinnGen consortium [24]. In addition, data on smoking status, frequent drinking, BMI, and live birth quantity were collected from the MRC-IEU or Neale Lab consortium. Table 1 presents a concise overview of all the datasets incorporated.

2.3. Selection and validation of SNPs

To meet the first assumption, genetic variants must exhibit a robust association with the exposure. We identified single nucleotide polymorphisms (SNPs) that had a significant relationship with asthma and the age asthma diagnosed, with a threshold of significance of $P < 5 \times 10^{-8}$. Due to the low amount of accessible SNPs, an acceptable threshold ($P < 5 \times 10^{-6}$) was selected in the reverse MR analysis. To achieve the criteria of hypothesis 2 in the MR framework, we implemented a strict standard ($r^2 < 0.001$ and a clumping distance of 10,000 kb) to minimize the influence of linkage disequilibrium (LD) within the SNPs [25]. Furthermore, to control potential pleiotropic effects, we obtained the secondary phenotype of every SNP through PhenoScanner V2 (http://www.phenoscanner.medschl.cam.ac.uk/) [26]. As it is widely recognized, factors such as BMI, low-density lipoprotein (LDL) cholesterol, smoking, and alcohol consumption are risk factors for APOs [14–17,20,22]. Consequently, we removed any IVs related to these factors or directly connected to the APOs. This methodology helps guarantee that the IVs utilized in our study are directly related to the specific exposure we are interested in and are not affected by other factors that could distort the results. This step was crucial to ensure that the independence and exclusiveness hypotheses—hypotheses 2 and 3 of our MR framework—are rigorously met.

To evaluate the robustness of the IVs, we assessed the variance explained (R^2) and the F-statistic, both crucial for minimizing the effects of weak instrument bias. The F-statistic is calculated using the equation: $F=R^2/(1-R^2) * [(N–K-1)/K]$, where N is the total sample size, K represents the quantity of SNPs chosen, and R^2 indicates the percentage of variance accounted for by the SNPs. This approach ensures the validity of the IVs, strengthening the reliability of our causal inferences [27]. To quantify the explained variance for each SNP, we employed the formula: $R^2 = 2*EAF*(1-EAF)*\beta^2$, where β denotes the effect size coefficient and EAF indicates the frequency of the effect allele [28]. This method facilitates a precise assessment of each SNP's contribution to the phenotypic variance within our MR framework, aligning with analytical standards in genomic research. An F-statistic exceeding ten indicates a lower probability of potential weak instrument bias [29]. The statistical power was calculated using the web resource available at

Table 1
Specifics of the research incorporated in the MR analyses.

Traits	Author	GWAS ID	Sample size (cases/controls)	Number of SNPs	Sex	Ancestry	Year	PMID
Exposure								
Asthma	Valette K	ebi-a-GCST90014325	56,167/352,255	34,551,291	Males and Females	European	2021	34103634
Age asthma diagnosed	Ben Elsworth	ukb-b-4575	47,222	9,851,867	Males and Females	European	2018	NA
BMI	Neale	ukb-a-248	336,107	10,894,596	Males and Females	European	2017	NA
Smoking status: Current	Neale	ukb-a-225	33,928/302,096	10,894,596	Males and Females	European	2017	NA
Alcohol intake frequency	Neale	ukb-a-25	336,965	10,894,596	Males and Females	European	2017	NA
Number of live births	Ben Elsworth	ukb-b-1209	250,782	9,851,867	Males and Females	European	2018	NA
Outcomes								
SA	NA	finn-b-O15_ABORT_SPONTAN	9113/89,340	16,379,138	Males and Females	European	2021	NA
PTB	NA	finn-b-O15_PRETERM	5480/98,626	16,379,340	Males and Females	European	2021	NA
PE	NA	finn-b-O15_PRE_OR_ECLAMPSIA	3903/114,735	16,379,723	Males and Females	European	2021	NA
GDM	NA	finn-b-GEST_DIABETES	5687/123,579	16,379,784	Males and Females	European	2021	NA

Body mass index (BMI); SA, spontaneous abortion; PTB, preterm birth; PE, preeclampsia; GDM, gestational diabetes mellitus.

https://shiny.cnsgenomics.com/mRnd/ [30]. We recommended achieving a sufficient power exceeding 80 % for robust results.

2.4. Statistical analyses

Various methodologies, including inverse variance weighted (IVW), MR-Egger, weighted median, weighted mode, simple mode, and Robust Adjusted Profile Score (RAPS), were implemented to assess the genetic causal effects. These approaches provided robust evidence across various conditions, with the IVW method as the principal technique for obtaining results [31]. The IVW method builds upon the Wald ratio estimations by applying the principles of meta-analysis. This technique aims to provide an unbiased estimate under optimal conditions, assuming that all included SNPs are valid IVs [32].

MR-Egger permits individual SNPs to influence outcomes through pathways that are not related to the exposure. Additionally, the MR-Egger intercept is capable of detecting and adjusting for pleiotropy [31,33]. The weighted median remains capable of dependable estimations of causality even though up to half of the data utilized by the analysis contains invalid IVs [34]. The weighted mode approach groups SNPs and computes estimations according to the group with the highest quantity of SNPs [33]. The

simple mode is not equally successful as IVW, it offers strength against pleiotropy [34]. The RAPS method is resistant to weak instruments. It maintains robustness even when systematic pleiotropy is present [35].

Building on the findings of previous studies [15–18], we incorporated BMI, smoking status, frequent drinking, and live birth quantity into our MVMR analysis. We employed methods such as IVW and MR-Lasso to conduct the MVMR analysis [36]. We conducted extensive sensitivity analyses in three key areas: heterogeneity, pleiotropy, and leave-one-out testing. Firstly, we calculated Cochran's Q statistic to assess the heterogeneity among individual SNPs. Subsequently, we evaluated pleiotropy in our effect estimates using the MR-Egger intercept method. Additionally, we employed MR-PRESSO analysis to uncover pleiotropic SNPs. Finally, we conducted a leave-one-out sensitivity analysis by sequentially removing different SNPs in each iteration to determine whether the excluded SNPs influenced the overall MR estimation.

A correlation between asthma and four APOs was considered of statistical significance if the dual-sided p-value was below 0.0125, calculated by dividing the alpha level of 0.05 by four outcomes to accommodate multiple assessments. A p-value less than 0.05 was regarded as indicative of a possible correlation.

The TwoSampleMR (version 0.5.6), MRPRESSO (version 1.0) and MVMR (version 0.3) packages in R (version 4.3.1) were used to conduct all MR analyses.

3. Result

3.1. SNPs selection and validation

In this study, we identified 42, 43, 41, and 45 SNPs as IVs for asthma to evaluate its associations with SA, PTB, PE, and GDM, respectively, as detailed in Supplementary Tables S1–4. Additionally, 17 and 19 SNPs were determined as IVs for the age of asthma diagnosis to assess its connections with SA and GDM, as presented in Supplementary Tables S5–6. The F-statistics for each SNP surpassed the critical threshold of ten, indicating a minimal risk of moderate instrumental bias. The statistical strength for SA and GDM exceeded 80 %, affirming the dependability of these findings, but it was below 80 % for other phenotypes, raising the possibility of false negatives. Table 2 comprehensively presents the strength and statistical power of the selected IVs. Furthermore, in the MR analysis of APOs on asthma, we chose 14, 8, 17, and 22 SNPs associated with SA, PTB, PE, and GDM, in that order (Supplementary Tables S7–10). The F-statistic provides adequate evidence to demonstrate that the probability of weak instrumental bias is extremely unlikely.

3.2. Causal associations of asthma on APOs

Upon applying the Bonferroni adjustment, we discovered a significant association between genetically predicted asthma and a greater likelihood of SA (OR: 1.115; 95 % CI: 1.031–1.206; $P = 0.006$) and GDM (OR: 1.125; 95 % CI: 1.037–1.220; $P = 0.005$) in the IVW model. These results aligned with those from the RAPS model. Conversely, the IVW model did not indicate a causal relationship of asthma on PE (OR: 1.059; 95 % CI: 0.951–1.179; $P = 0.297$) or PTB (OR: 0.979; 95 % CI: 0.897–1.068; $P = 0.629$). Consistent findings were reached using five other statistical models. Fig. 2 illustrates the causative relationship between asthma and the likelihood of

Table 2
The chosen IVs' potency and statistical efficacy.

Exposures	Outcomes	R^2 for TL(Total)	F for TL(Total)	Power
Asthma	SA	0.055	568.896	0.84
	PTB	0.069	701.513	0.08
	PE	0.062	662.727	0.19
	GDM	0.070	685.360	0.87
Age asthma diagnosed	SA	0.026	67.085	0.13
	GDM	0.019	55.110	0.06

SA, spontaneous abortion; PTB, preterm birth; PE, preeclampsia; GDM, gestational diabetes mellitus.

APOs. Cochran's Q test failed to detect heterogeneity, and the Egger intercept test and MR-PRESSO analysis detected no horizontal pleiotropy. Table 3 displays the results of the sensitivity analyses. The leave-one-out graphs in our study confirm the robustness of our findings, suggesting a negligible impact of any individual SNP on the causal estimates. Fig. 3 (A-D) and Fig. 4 (A-D) include scatter, funnel, forest, and leave-one-out images, demonstrating the relationships of asthma on SA and GDM, respectively. Supplementary Figs. S1–2 depict corresponding images for PTB and PE. According to the MVMR analysis, a robust causal association persisted of asthma on SA (OR: 1.120; 95 % CI: 1.044–1.202; $P = 0.002$) as well as GDM (OR: 1.115; 95 % CI: 1.012–1.229; $P = 0.028$) after adjusting for confounding variables such as smoking status, alcohol consumption, BMI, and the live birth number. The MR Lasso analysis outcomes remained consistent following the exclusion of heterogeneous SNPs. Fig. 5 provides a detailed summary of the MVMR results.

3.3. Causal associations of age asthma diagnosed on SA and GDM

The genetic predisposition to age asthma diagnosed was not found to have a causal relationship with SA (OR: 0.974; 95 % CI: 0.849–1.117, $P = 0.703$) and GDM (OR: 0.944; 95 % CI: 0.823–1.083; $P = 0.413$) in all six statistical models (Fig. 6).

Cochran's Q test failed to reveal heterogeneity, and the Egger intercept test and MR-PRESSO analysis detected no horizontal pleiotropy. Comprehensive findings from the sensitivity analyses are detailed in Table 4. The leave-one-out graphs in our investigation indicated that the specific SNPs were not likely to change the causality. Supplementary Figs. S3–4 illustrate the relationships between the age of asthma diagnosis and both SA and GDM via scatter, funnel, forest, and leave-one-out plots.

3.4. Causal associations of APOs on asthma

There was no link between genetic risk for SA (OR: 0.970; 95 % CI: 0.926–1.016, $P = 0.203$), PE (OR: 1.024; 95 % CI: 0.990–1.058, $P = 0.167$), PTB (OR: 0.957; 95 % CI: 0.896–1.023, $P = 0.196$), or GDM (OR: 0.979; 95 % CI: 0.945–1.014; $P = 0.238$) and asthma in any of the six statistical models (Fig. 7).

MR-Egger regression, MR-PRESSO analysis and Cochran's Q test indicated no directional pleiotropy and heterogeneity. The specifics of the sensitivity analysis can be found in Table 5. The leave-one-out analyses suggest that particular SNPs are improbable to have a substantial impact on the causal estimations. Scatter, funnel, forest, and leave-one-out charts illustrate these associations in Supplementary Figs. S5–8.

4. Discussion

In the present research, we investigated the underlying causality between asthma and four APOs employing MR techniques. We

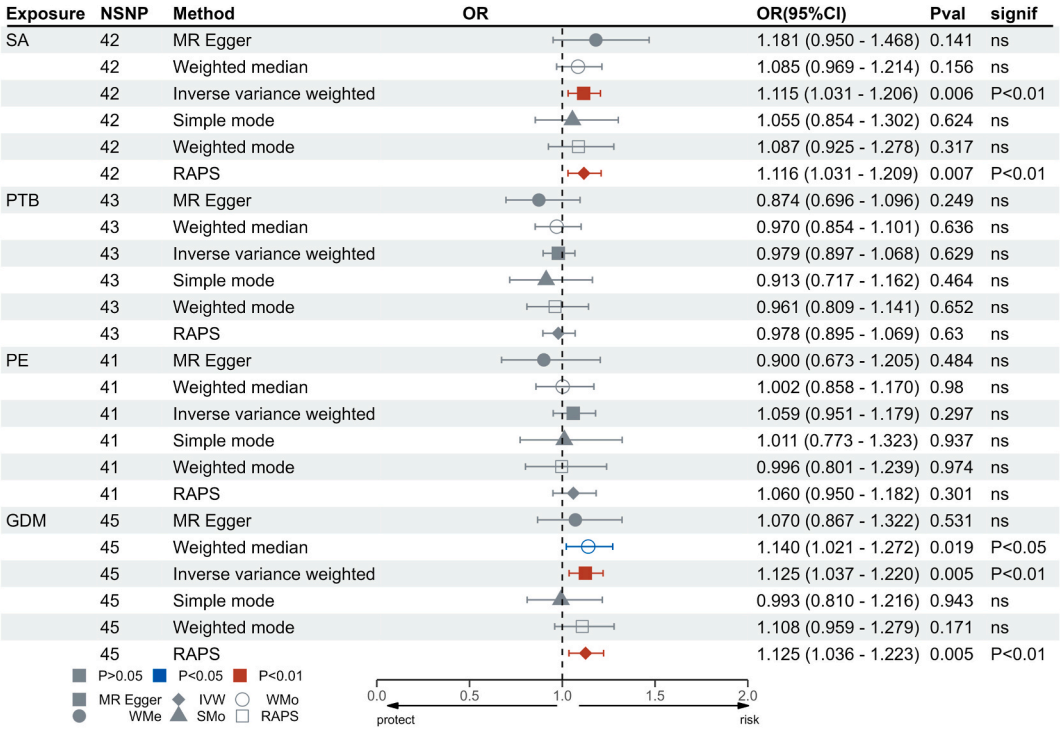

Fig. 2. Causal relationships of asthma on the danger of APOs.

Table 3
Heterogeneity, horizontal pleiotropy, and MR-PRESSO examinations of the relationships between Asthma and APOs.

Outcomes	Pleiotropy test			Heterogeneity test						MR-PRESSO
	MR-Egger			MR-Egger			Inverse-variance weighted			Global Test
	Intercept	SE	*P*	Q-value	Q-df	Q-pval	Q-value	Q-df	Q-pval	*P*value
SA	−0.004	0.007	0.582	26.959	40	0.943	27.267	41	0.951	0.428
PTB	0.008	0.008	0.293	34.988	41	0.734	36.122	42	0.726	0.221
PE	0.011	0.009	0.247	27.812	39	0.909	29.194	40	0.896	0.122
GDM	0.003	0.007	0.623	19.906	43	0.999	20.151	44	0.999	0.978

SA, spontaneous abortion; PTB, preterm birth; PE, preeclampsia; GDM, gestational diabetes mellitus; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; Q-value, the statistics of Cochran's Q test; SE, standard error.

concluded that genetically predicted asthma is correlated with a higher likelihood of experiencing APOs, such as SA and GDM. The causal association was still of statistical significance after controlling for smoking status, frequent drinking, BMI, and live birth quantity in the MVMR designs. However, our findings did not reveal a substantial correlation between the age of asthma diagnosed based on genetics and the likelihood of SA or GDM. The results from inverse MR analyses also indicate no causality of APOs on asthma.

Our analysis revealed a positive relationship between asthma and an elevated risk of both SA and GDM, aligning with previous studies [37–40]. For example, a 2019 study investigated reproductive decline in a cohort of 10,847 American women aged 15 to 44 with a medical history of asthma or hay fever. After controlling for confounding variables such as smoking, age, diabetes history, BMI, and other factors, the study showed that women with a medical history of asthma or hay fever had a higher rate of SA compared to those without asthma ($P = 0.001$) [37]. Another investigation demonstrated a notable rise in the occurrence of perinatal problems, such as SA and GDM, due to pre-existing moderate to severe asthma before pregnancy and the worsening of asthma symptoms during pregnancy ($P < 0.001$) [38]. A review of cohort data comprising 580 pregnant women discovered that the presence of maternal asthma (n = 274) considerably raised the likelihood of developing GDM in comparison to the group without asthma (n = 306) (OR = 2.64, $P < 0.05$) [39]. Another national cohort study undertaken in Denmark reported that asthma is linked with a greater probability of experiencing pregnancy loss (PL) (OR: 1.05; 95 % CI: 1.03–1.07) and recurrent PL (OR: 1.19; 95 % CI: 1.12–1.27) in women. Furthermore, the researchers observed that early-onset asthma (ages 6–15) had a stronger correlation with PL compared to asthma attacks in adulthood (ages 16–39) [40]. Research on the relationship between the age at which asthma begins and GDM is scarce. Recent data from a national registry study in Denmark indicate that childhood asthma may increase the risk of developing type 1 diabetes (T1DM) later in life [41]. Nevertheless, our investigation failed to establish a causal connection between the age of asthma diagnosed and the occurrence of SA and GDM. The disparity between the MR analysis and the observational study outcomes could be attributed to confounding variables such as BMI, waist-to-hip ratio, and cholesterol levels.

Prior research has yielded conflicting findings about the association between asthma and PTB or PE. Retrospective cohort studies have indicated that the prevalence of PTB is higher in individuals with asthma than in those without asthma (OR: 1.41; 95 % CI: 1.07–1.86; $P = 0.01$), even after adjusting for maternal smoking using logistic regression analysis. Additionally, asthmatic women were found to have a significantly increased risk of PE (OR: 1.71; 95 % CI: 1.09–2.67; $P = 0.02$) [42]. Multiple studies have arrived at consistent results [38,39,43]. However, meta-analyses have shown no significant statistical link between severe asthma episodes during pregnancy and the likelihood of PTB (RR: 1.57, 95 % CI: 0.80–3.1) or PE (RR: 1.37, 95 % CI: 0.65–2.92) [44]. Our research supports this assumption, as our UVMR analyses did not identify any statistically significant causal link between asthma and the occurrence of PTB and PE. The distinction between MR analysis and observational research conclusions can be attributed to the impact of confounding variables, including BMI, smoking status, frequent drinking, and reproductive factors like live births.

The precise mechanism behind the causal relationship of asthma on SA or GDM remains uncertain. However, based on current data, the specific way asthma heightens the risk of these two forms of APOs can be elucidated through the following factors: First and foremost is an exaggerated immunological inflammatory response. Persistent airway inflammation is a hallmark of asthma, characterized by two distinct pathways: Th2-dependent inflammation, triggered by interleukins such as IL-5 and IL-13, and Th2-low asthma, which is driven by IL-17 and tumor necrosis factor-α (TNF-α) [45]. However, the inflammatory response in asthma extends beyond the respiratory tract. Research indicates that individuals with asthma often suffer from chronic, low-grade systemic inflammation, which intensifies during episodes of uncontrolled asthma exacerbations [46]. This systemic inflammation can also impact reproductive organs [47]. A prospective cohort study discovered that the concentration of pro-inflammatory factors IL-6 and IL-1 in serum samples of patients with SA was notably higher on days 23 and 30 after embryo transfer compared to the group of patients who had a live birth [48].

Conversely, the anti-inflammatory factor TGF-β1 level was significantly lower in the miscarriage group than in women with live births. This suggests that the excessive immune inflammatory response resulting from the imbalance in the expression of pro-inflammatory and anti-inflammatory cytokines hampers the successful implantation of embryos and is closely related to PL [48]. Furthermore, research indicates a detrimental relationship between high-sensitivity C-reactive protein levels in the blood of women with asthma and the amount of vascular endothelial growth factor (VEGF) in their endometrial secretions [49]. Asthma-induced inflammation can decrease the ability of the endometrium to receive embryos by altering the production of VEGF [49].

Similarly, research has determined that, during 24–28 weeks of pregnancy, women experiencing GDM (n = 96 cases) exhibit considerably more serum amounts of high-sensitivity C-reactive protein (hs-CRP) and IL-6 in comparison with healthy pregnant controls (n = 95 instances). These levels were positively correlated with HbA1c levels [50]. Disrupted regulation of glucose levels

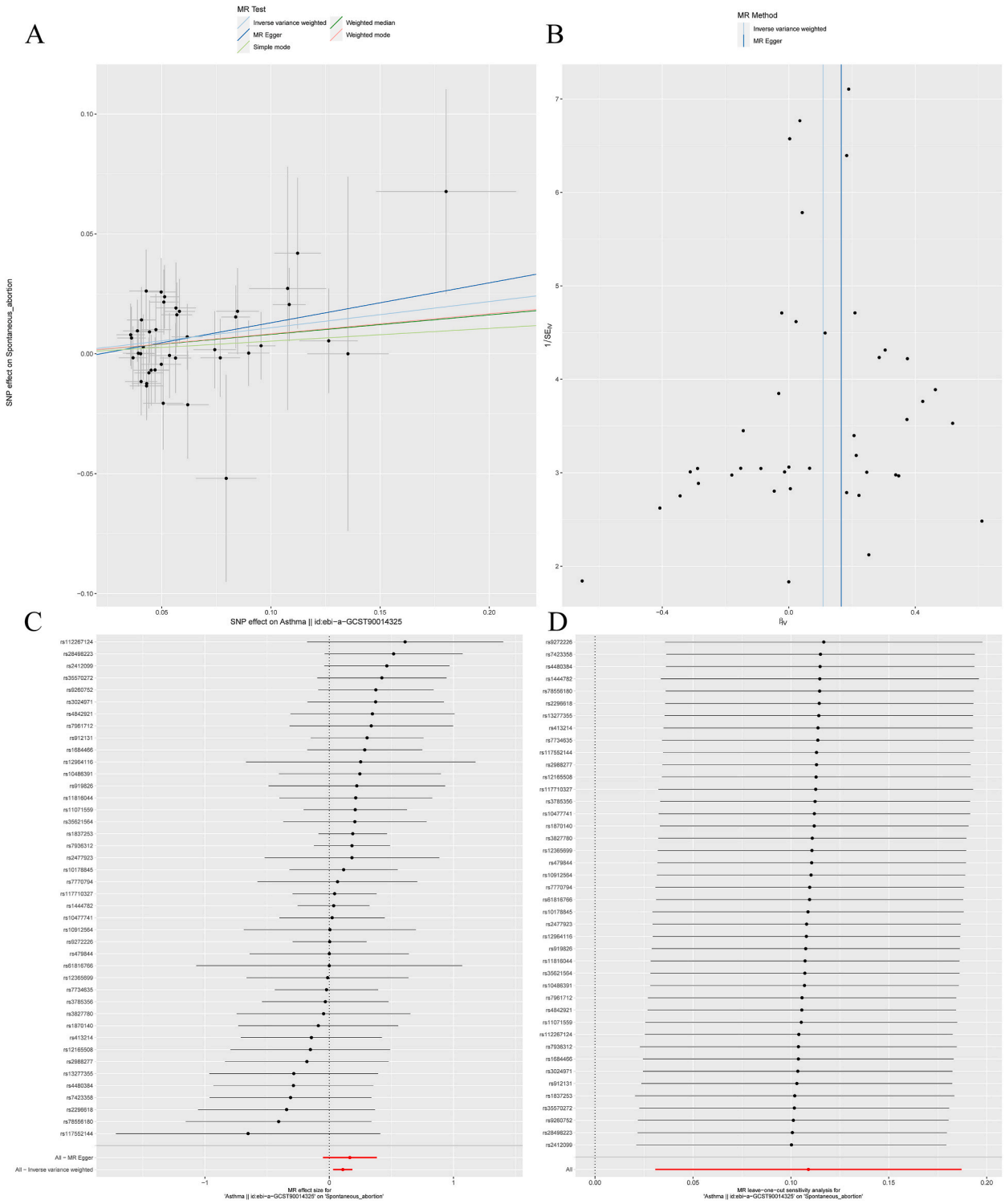

Fig. 3. Scatter, funnel, forest, and leave-one-out plots for MR investigations of the link of asthma on SA. (A) scatter plot; (B) funnel plot; (C) forest plot; (D) leave-one-out plot.

during pregnancy also leads to an imbalance of pro-inflammatory and anti-inflammatory biomarkers [51]. Consequently, it is plausible to suggest that asthma may influence the balance of maternal-fetal immune tolerance and glucose homeostasis through systemic inflammatory pathways, thereby elevating the risks of SA and GDM.

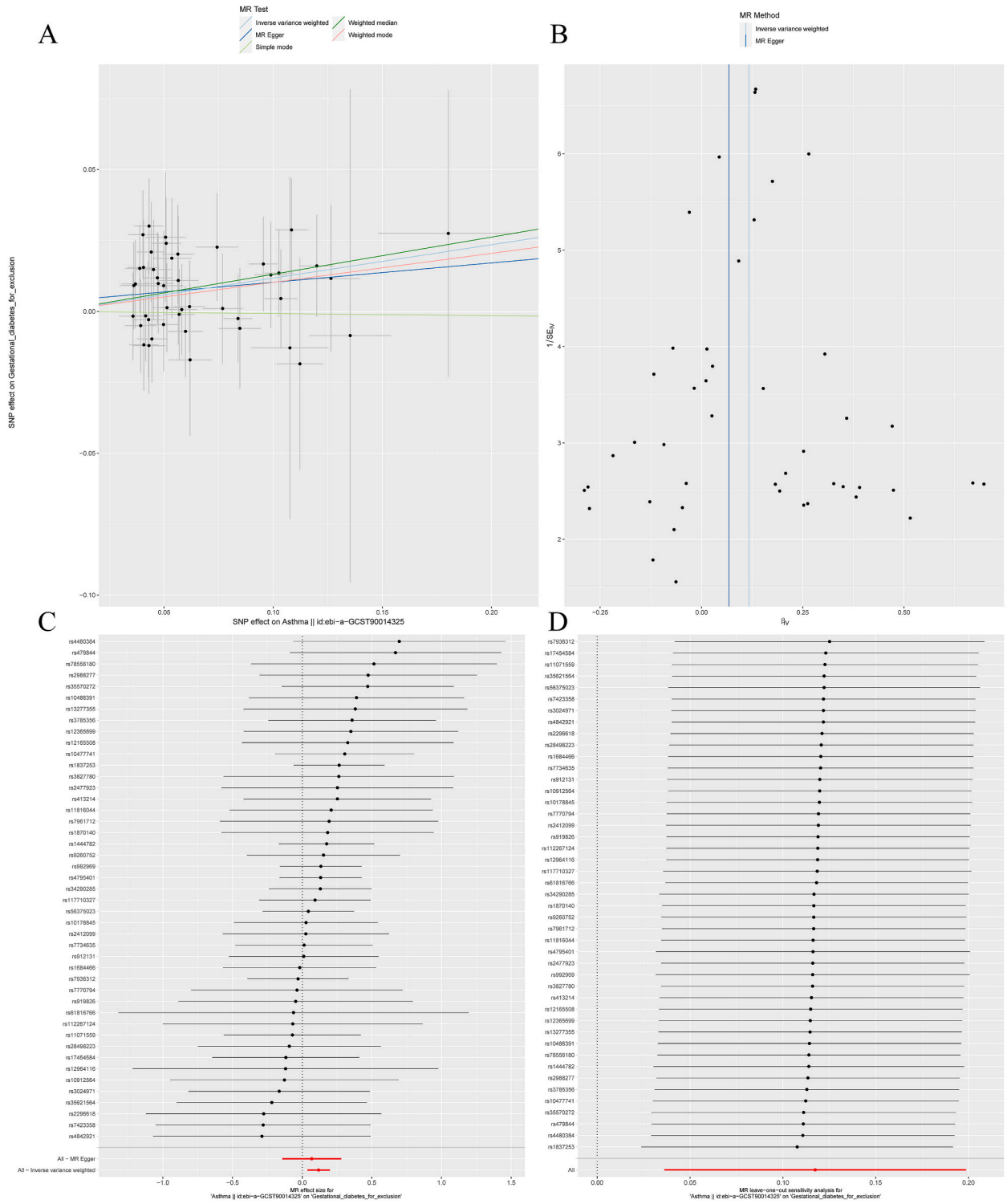

Fig. 4. Scatter, funnel, forest, and leave-one-out plots for MR investigations of the link of asthma on GDM. (A) scatter plot; (B) funnel plot; (C) forest plot; (D) leave-one-out plot.

A second potential mechanism involves hypoxia and oxidative stress (OS). Asthma can also be characterized by oxidative stress, which is linked to inflammation both in the lungs and systemically [52]. Hypoxia-inducible factor 1 (HIF-1) comprises α and β heterodimeric subunits. It performs a function in the immune system's response, induces neovascularization, and can contribute to airway

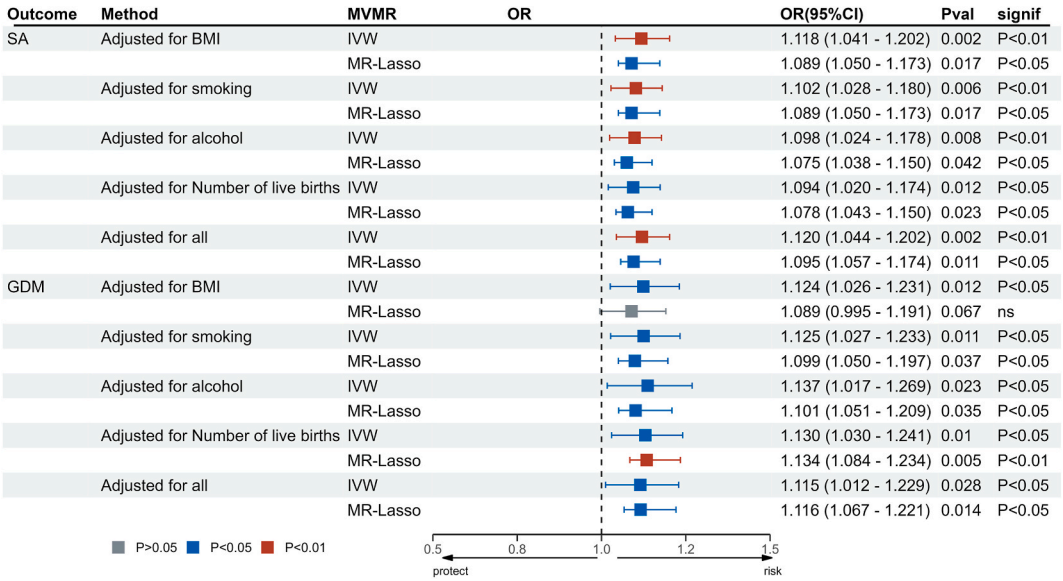

Fig. 5. A causal relationship between Asthma and SA or GDM in MVMR.

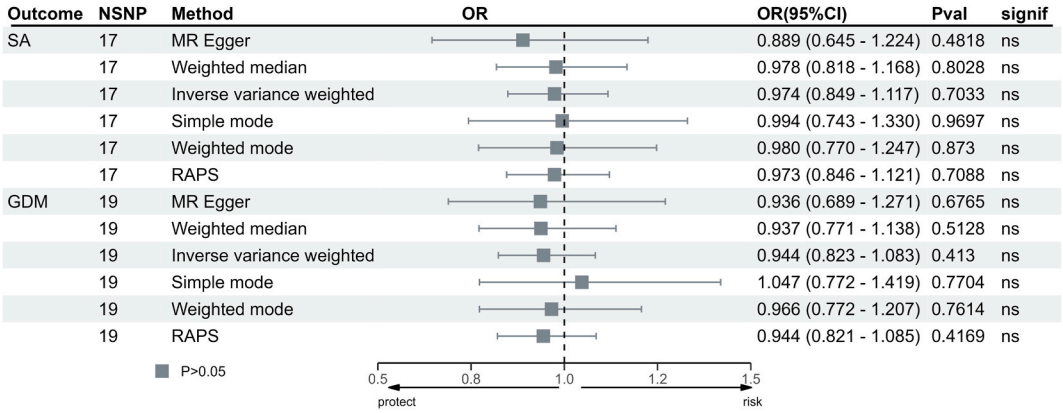

Fig. 6. The causal relationship between the genetically predicted age at which asthma was diagnosed and SA or GDM.

Table 4
Heterogeneity, horizontal pleiotropy, and MR-PRESSO tests of the relationships between age asthma diagnosed and APOs.

Outcomes	Pleiotropy test			Heterogeneity test						MR-PRESSO
	MR-Egger			MR-Egger			Inverse-variance weighted			Global Test
	Intercept	SE	*P*	Q-value	Q-df	Q-pval	Q-value	Q-df	Q-pval	*P*value
SA	0.006	0.009	0.546	5.676	15	0.985	6.057	16	0.987	0.261
GDM	0.0006	0.009	0.949	12.259	17	0.784	12.263	18	0.833	0.864

SA, spontaneous abortion; PTB, preterm birth; PE, preeclampsia; GDM, gestational diabetes mellitus; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; Q-value, the statistics of Cochran's Q test; SE, standard error.

inflammation in bronchial asthma through various pathways [53]. OS can impact the implantation of the gestational sac, embryo development, and placental angiogenesis, leading to SA [54]. Several studies have observed increased expression of HIF-1α in the endometrial cell line, endometrial epithelium, and stroma of women suffering recurrent pregnancy loss (RPL) in contrast to healthy controls.

Additionally, these studies noted a pathological rise in both the quantity and volume of microvessels [55,56]. These findings imply that a hypoxic environment during pregnancy may activate HIF-1α expression and subsequently affect endometrial angiogenesis, leading to the development of PL. Simultaneously, OS can adversely impact pancreatic islet β-cell function, resulting in the onset of

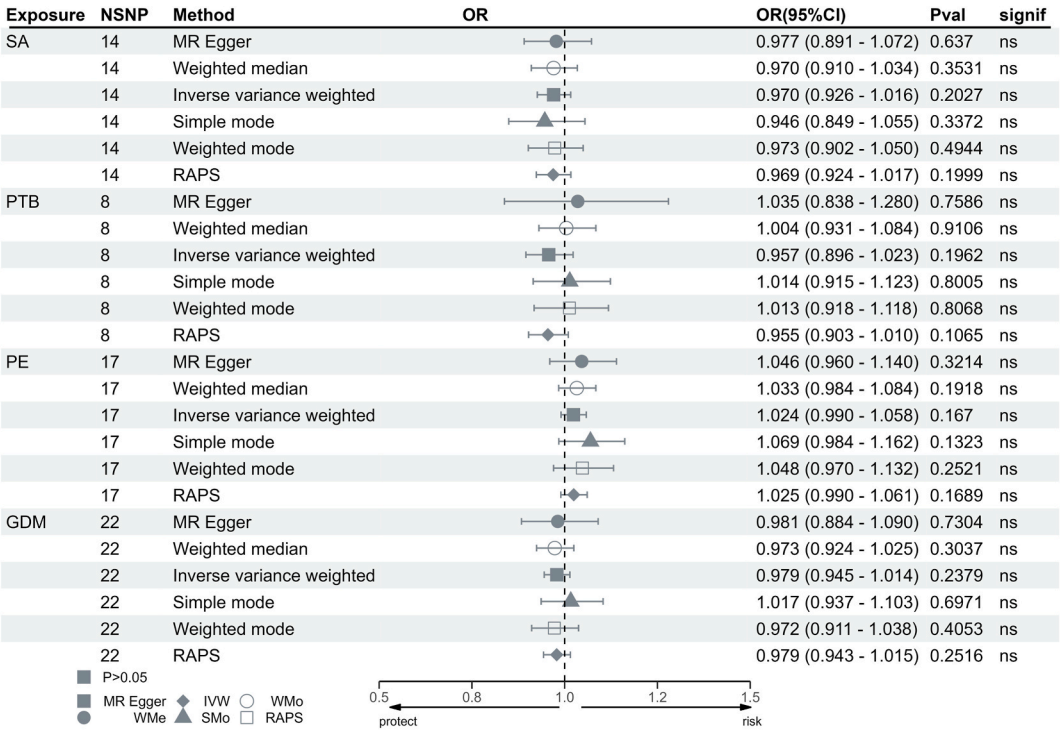

Fig. 7. The causality of genetically predicted APOs on asthma.

Table 5
Heterogeneity, horizontal pleiotropy, and MR-PRESSO tests of the relationships between APOs and Asthma.

Exposures	Pleiotropy test			Heterogeneity test						MR-PRESSO
	MR-Egger			MR-Egger			Inverse-variance weighted			Global Test
	Intercept	SE	*P*	Q-value	Q-df	Q-pval	Q-value	Q-df	Q-pval	*P*value
SA	−0.001	0.007	0.860	13.471	12	0.336	13.507	13	0.409	0.449
PTB	−0.011	0.009	0.302	4.855	5	0.434	6.181	6	0.403	0.237
PE	−0.003	0.006	0.601	15.903	15	0.389	16.206	16	0.439	0.457
GDM	−0.002	0.005	0.960	10.982	20	0.947	10.985	21	0.963	0.883

SA, spontaneous abortion; PTB, preterm birth; PE, preeclampsia; GDM, gestational diabetes mellitus; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; Q-value, the statistics of Cochran's Q test; SE, standard error.

GDM [57]. Numerous studies have identified elevated OS markers and HIF-1α levels in the maternal blood and placenta of women with GDM compared to those with standard glucose tolerance [58–60]. This phenomenon highlights the role of hypoxia and its associated HIF-1α overactivation in disrupting glucose metabolism in GDM. Hence, we hypothesize that the link between asthma and both SA and GDM may be attributable to hypoxic and oxidative stress responses.

Numerous studies have established asthma as a polygenic disease influenced by both genetic and environmental factors [61,62]. Recent research indicates that abnormal gene expression of SMAD3 and Interleukin 33 (IL-33) is strongly correlated with the onset of asthma [63,64]. Research has demonstrated that SNPs at the Smad3 gene locus are associated with RPL. Abnormal expression of the Smad3 gene can disrupt steroid hormone regulation and embryo implantation processes by impacting the Smad3-dependent signaling pathway, ultimately resulting in PL [65]. Likewise, bioinformatics investigation reveals that SMAD 3 is one of the central genes implicated in the onset of GDM [66]. IL-33, is pivotal in regulating angiogenesis and inflammatory immune responses. Recent studies indicate considerably greater serum concentrations of IL-33 ($P < 0.05$) and its receptor ST-2 ($P < 0.01$) in patients with RPL compared to healthy controls [67].

Moreover, research has found elevated plasma levels of IL-33 and soluble ST2 (sST2) in patients with GDM relative to pregnant women with normal glucose tolerance (NGT). These levels positively correlate with the Homeostatic Model Assessment (HOMA) index [68]. The SNPs adopted as IVs include rs56375023 and rs992969 in our research, which correspondingly relate to the SMAD3 and IL33 genes. Hence, we propose that inflammatory and immunological factors play an instrumental part in the link between asthma and SA or GDM by affecting these shared genetic pathways.

This study represents the first application of an MR framework to estimate the genetic causal relationship of asthma on APOs. Our

MR study boasts several strengths. First, it excluded genetic variations associated with potential confounding factors observed in epidemiological studies, focusing instead on SNPs closely related to asthma or the age at which asthma was diagnosed. Second, the substantial sample size enhances the statistical robustness of our analysis, providing strong evidence for the identified relationships. Third, we conducted thorough sensitivity examinations to verify the accuracy and reliability of our findings. Sufficient F-statistics and statistical power ensure the effectiveness of our study. Finally, using MVMR, including IVW and MR-Lasso, we explored the direct impact of asthma on APOs, accounting for factors such as smoking, drinking frequency, BMI, and the quantity of live births.

Nevertheless, there are restrictions. First, owing to the use of aggregate-level data from the GWAS database, it was not allowed to evaluate the non-linear connection between asthma and APOs. Second, A portion of the asthma cases in our study were identified through self-reported questionnaires. While self-reporting is valuable for large-scale and extensive data collection, it is susceptible to recall and other forms of bias. Participants may not accurately remember or report their medical history, and the precision of self-reported data can significantly vary based on participants' understanding, memory, and willingness to disclose personal information accurately. These factors can contribute to reporting bias, potentially impacting the reliability of our findings. Additionally, the predominance of participants of European ancestry minimizes demographic stratification bias but limits the applicability of our findings to diverse ethnic groups. Lastly, while the F-statistic indicates strong IVs, some phenotypes exhibited lower statistical power (below 80 %), potentially leading to false negatives.

5. Conclusion

This study presents evidence suggesting that genetically determined asthma is linked to a higher likelihood of SA and GDM. Additional investigation is needed to explore the underlying pathways. However, we found no definitive evidence that an earlier diagnosis of asthma elevates the risk of SA and GDM, nor did we see a clear interaction between asthma and either PTB or PE. These findings imply that the conclusions of prior research using observations might be subject to confounding factors.

Data availability statement

The datasets utilized in this investigation are sourced from IEU OpenGWAS (https://gwas.mrcieu.ac.uk/) and can be downloaded at no cost. Additional inquiries should be made to the respective authors.

Ethics statement

No extra ethical declarations or consents were needed for this analysis.

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CRediT authorship contribution statement

Xinyu Han: Writing – original draft, Methodology, Investigation, Conceptualization. **Tian qiang Wu:** Writing – original draft, Validation. **Yuanyuan Bian:** Writing – review & editing, Visualization. **Lu Chen:** Supervision, Funding acquisition. **Xiaoling Feng:** Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

[1] E.D. Bateman, S.S. Hurd, P.J. Barnes, et al., Global strategy for asthma management and prevention: GINA executive summary, Eur. Respir. J. 31 (2008) 143–178, https://doi.org/10.1183/09031936.00138707.

[2] F. Ap, Advanced maternal age and adverse pregnancy outcomes, Best Practice & Research, Clin. Obstet. Gynaecol. 70 (2021) 92–100, https://doi.org/10.1016/j.bpobgyn.2020.07.005.

[3] K. McLaughlin, M. Foureur, M.E. Jensen, Review and appraisal of guidelines for the management of asthma during pregnancy, Women Birth 31 (2018) e349–e357, https://doi.org/10.1016/j.wombi.2018.01.008.

[4] H. Wang, N. Li, H. Huang, Asthma in pregnancy: pathophysiology, diagnosis, whole-course management, and medication safety, Cancer Res. J. 2020 (2020) 9046842, https://doi.org/10.1155/2020/9046842.

[5] C.A. Bonham, K.C. Patterson, M.E. Strek, Asthma outcomes and management during pregnancy, Chest 153 (2018) 515–527, https://doi.org/10.1016/j.chest.2017.08.029.

[6] M. Ve, J. Me, Longitudinal changes in upper and lower airway function in pregnancy, Immunol. Allergy Clin. 43 (2023) 17–26, https://doi.org/10.1016/j.iac.2022.07.005.

[7] P. Mendola, S.K. Laughon, T.I. Männistö, et al., Obstetric complications among US women with asthma, Am. J. Obstet. Gynecol. 208 (2013) 127.e1–127.e8, https://doi.org/10.1016/j.ajog.2012.11.007.

[8] A. Jöud, E. Nilsson-Condori, L. Schmidt, et al., Infertility, pregnancy loss and assisted reproduction in women with asthma: a population-based cohort study, Hum. Reprod. 37 (2022) 2932–2941, https://doi.org/10.1093/humrep/deac216.

[9] J.J. Yland, H.M. Crowe, E.E. Hatch, et al., A prospective study of preconception asthma and spontaneous abortion, Ann. Epidemiol. 69 (2022) 27–33, https://doi.org/10.1016/j.annepidem.2022.02.006.

[10] G. Davey Smith, G. Hemani, Mendelian randomization: genetic anchors for causal inference in epidemiological studies, Hum. Mol. Genet. 23 (2014) R89–R98, https://doi.org/10.1093/hmg/ddu328.

[11] J. Zheng, D. Baird, M.-C. Borges, et al., Recent developments in mendelian randomization studies, Curr Epidemiol Rep 4 (2017) 330–345, https://doi.org/10.1007/s40471-017-0128-6.

[12] J. Sheng, J. Liu, K.H.K. Chan, Evaluating the causal effects of gestational diabetes mellitus, heart disease, and high body mass index on maternal alzheimer's disease and dementia: multivariable mendelian randomization, Front. Genet. 13 (2022) 833734, https://doi.org/10.3389/fgene.2022.833734.

[13] E. Sanderson, Multivariable mendelian randomization and mediation, Cold Spring Harb Perspect Med 11 (2021) a038984, https://doi.org/10.1101/cshperspect.a038984.

[14] C.-X. Ye, S.-B. Chen, T.-T. Wang, et al., Risk factors for preterm birth: a prospective cohort study, Zhong Guo Dang Dai Er Ke Za Zhi 23 (2021) 1242–1249, https://doi.org/10.7499/j.issn.1008-8830.2108015.

[15] S. Yuan, J. Liu, S.C. Larsson, Smoking, alcohol and coffee consumption and pregnancy loss: a Mendelian randomization investigation, Fertil. Steril. 116 (2021) 1061–1067, https://doi.org/10.1016/j.fertnstert.2021.05.103.

[16] Y. Bar-Zeev, Z.T. Haile, I.A. Chertok, Association between prenatal smoking and gestational diabetes mellitus, Obstet. Gynecol. 135 (2020) 91–99, https://doi.org/10.1097/AOG.0000000000003602.

[17] S. Y, S. Z, Z. Y, et al., Effects of pre-pregnancy body mass index and gestational weight gain on maternal and infant complications, BMC Pregnancy Childbirth 20 (2020), https://doi.org/10.1186/s12884-020-03071-y.

[18] J. Qiu, T. Du, W. Li, et al., Impact of recurrent pregnancy loss history on reproductive outcomes in women undergoing fertility treatment, Am. J. Obstet. Gynecol. 228 (2023) 66.e1–66.e9, https://doi.org/10.1016/j.ajog.2022.08.014.

[19] J.S. Brown, T. Adera, S.W. Masho, Previous abortion and the risk of low birth weight and preterm births, J. Epidemiol. Community Health 62 (2008) 16–22, https://doi.org/10.1136/jech.2006.050369.

[20] R.J. Selvaratnam, U. Sovio, E. Cook, et al., Objective measures of smoking and caffeine intake and the risk of adverse pregnancy outcomes, Int. J. Epidemiol. 52 (2023) 1756–1765, https://doi.org/10.1093/ije/dyad123.

[21] L. Zc, A. N, X. Hr, et al., The effects and mechanisms of primiparity on the risk of pre-eclampsia: a systematic review, Paediatr. Perinat. Epidemiol. 21 (Suppl 1) (2007), https://doi.org/10.1111/j.1365-3016.2007.00836.x.

[22] E. Lendoye, E.B. Ngoungou, O.M. Komba, et al., Prevalence and factors associated to gestational diabetes mellitus among pregnant women in Libreville: a cross-sectional study, Pan Afr Med J 41 (2022) 129, https://doi.org/10.11604/pamj.2022.41.129.28710.

[23] K. Valette, Z. Li, V. Bon-Baret, et al., Prioritization of candidate causal genes for asthma in susceptibility loci derived from UK Biobank, Commun. Biol. 4 (2021) 700, https://doi.org/10.1038/s42003-021-02227-6.

[24] M.I. Kurki, J. Karjalainen, P. Palta, et al., FinnGen provides genetic insights from a well-phenotyped isolated population, Nature 613 (2023) 508–518, https://doi.org/10.1038/s41586-022-05473-8.

[25] L. Clarke, X. Zheng-Bradley, R. Smith, et al., The 1000 Genomes Project: data management and community access, Nat. Methods 9 (2012) 459–462, https://doi.org/10.1038/nmeth.1974.

[26] M.A. Kamat, J.A. Blackshaw, R. Young, et al., PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations, Bioinformatics 35 (2019) 4851–4853, https://doi.org/10.1093/bioinformatics/btz469.

[27] N. Papadimitriou, N. Dimou, K.K. Tsilidis, et al., Physical activity and risks of breast and colorectal cancer: a Mendelian randomisation analysis, Nat. Commun. 11 (2020) 597, https://doi.org/10.1038/s41467-020-14389-8.

[28] V. Codd, C.P. Nelson, E. Albrecht, et al., Identification of seven loci affecting mean telomere length and their association with disease, Nat. Genet. 45 (2013) 422–427, https://doi.org/10.1038/ng.2528.

[29] N.M. Davies, M.V. Holmes, G. Davey Smith, Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians, BMJ 362 (2018) k601, https://doi.org/10.1136/bmj.k601.

[30] M.-J.A. Brion, K. Shakhbazov, P.M. Visscher, Calculating statistical power in Mendelian randomization studies, Int. J. Epidemiol. 42 (2013) 1497–1501, https://doi.org/10.1093/ije/dyt179.

[31] S. Burgess, D.S. Small, S.G. Thompson, et al., A review of instrumental variable estimators for Mendelian randomization, Stat. Methods Med. Res. 26 (2017) 2333–2355, https://doi.org/10.1177/0962280215597579.

[32] P. Pagoni, N.L. Dimou, N. Murphy, et al., Using Mendelian randomisation to assess causality in observational studies, Evid. Base Ment. Health 22 (2019) 67–71, https://doi.org/10.1136/ebmental-2019-300085.

[33] G. Hemani, J. Bowden, G. Davey Smith, Evaluating the potential role of pleiotropy in Mendelian randomization studies, Hum. Mol. Genet. 27 (2018) R195–R208, https://doi.org/10.1093/hmg/ddy163.

[34] F.P. Hartwig, G. Davey Smith, J. Bowden, Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption, Int. J. Epidemiol. 46 (2017) 1985–1998, https://doi.org/10.1093/ije/dyx102.

[35] Q. Zhao, Y. Chen, J. Wang, et al., Powerful three-sample genome-wide design and robust statistical inference in summary-data Mendelian randomization, Int. J. Epidemiol. 48 (2019) 1478–1492, https://doi.org/10.1093/ije/dyz142.

[36] G. Hemani, J. Zheng, B. Elsworth, et al., The MR-Base platform supports systematic causal inference across the human phenome, Elife 7 (2018) e34408, https://doi.org/10.7554/eLife.34408.

[37] P.C. Turkeltaub, R.F. Lockey, K. Holmes, et al., Asthma and/or hay fever as predictors of fertility/impaired fecundity in U.S. women: national Survey of Family Growth, Sci. Rep. 9 (2019) 18711, https://doi.org/10.1038/s41598-019-55259-8.

[38] A. Tanacan, E. Fadiloglu, E.D. Celebioglu, et al., The effect of asthma severity on perinatal outcomes: a tertiary hospital experience, Z. Geburtshilfe Neonatol. 225 (2021) 333–340, https://doi.org/10.1055/a-1264-8207.

[39] A. Vaezi, L. Haghighi, F. Beigmohammadi, et al., Maternal asthma, pregnancy, delivery and birth outcomes: a retrospective cohort study, Iran, J Allergy Asthma Immunol 16 (2017) 92–98.
[40] C. Tidemandsen, P. Egerup, C.S. Ulrik, et al., Asthma is associated with pregnancy loss and recurrent pregnancy loss: a nationwide cohort study, J. Allergy Clin. Immunol. Pract. 10 (2022) 2326–2332.e3, https://doi.org/10.1016/j.jaip.2022.04.044.
[41] M.S. Liljendahl, A. Sevelsted, B.L. Chawes, et al., Childhood asthma is associated with development of type 1 diabetes and inflammatory bowel diseases: a Danish nationwide registry study, Sci. Rep. 12 (2022) 21728, https://doi.org/10.1038/s41598-022-26067-4.
[42] S. Johnston, J. Said, Perinatal complications associated with maternal asthma during pregnancy, Obstet. Med. 5 (2012) 14–18, https://doi.org/10.1258/om.2011.110062.
[43] H. Baghlaf, A.R. Spence, N. Czuzoj-Shulman, et al., Pregnancy outcomes among women with asthma, J. Matern. Fetal Neonatal Med. 32 (2019) 1325–1331, https://doi.org/10.1080/14767058.2017.1404982.
[44] V.E. Murphy, V.L. Clifton, P.G. Gibson, Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes, Thorax 61 (2006) 169–176, https://doi.org/10.1136/thx.2005.049718.
[45] N. Habib, M.A. Pasha, D.D. Tang, Current understanding of asthma pathogenesis and biomarkers, Cells 11 (2022) 2764, https://doi.org/10.3390/cells11172764.
[46] M.C. Peters, K.W. McGrath, G.A. Hawkins, et al., Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts, Lancet Respir. Med. 4 (2016) 574–584, https://doi.org/10.1016/S2213-2600(16)30048-0.
[47] E. Juul Gade, S.F. Thomsen, S. Lindenberg, et al., Female asthma has a negative effect on fertility: what is the connection? ISRN Allergy (2014) 131092 https://doi.org/10.1155/2014/131092. Published 2014 Mar 27.
[48] Y. Zhao, G.C.W. Man, R. Zhang, et al., A prospective study comparing the inflammation-related cytokine and chemokine profile from the day of blastocyst transfer to 7 weeks of gestation between pregnancies that did or did not result in a miscarriage, J. Reprod. Immunol. 154 (2022) 103755, https://doi.org/10.1016/j.jri.2022.103755.
[49] E.J. Gade, S.F. Thomsen, S. Lindenberg, et al., Lower values of VEGF in endometrial secretion are a possible cause of subfertility in non-atopic asthmatic patients, J. Asthma 52 (2015) 336–342, https://doi.org/10.3109/02770903.2014.966915.
[50] L.L. Xiang, C. Chen, Q.Y. Wang, et al., Impact of inflammatory factors, hemoglobin A1c, and platelet parameters in gestational diabetes mellitus, Arch. Gynecol. Obstet. 307 (2023) 439–446, https://doi.org/10.1007/s00404-022-06528-x.
[51] N.P. Joshi, S.D. Madiwale, D.P. Sundrani, et al., Fatty acids, inflammation and angiogenesis in women with gestational diabetes mellitus, Biochimie 212 (2023) 31–40, https://doi.org/10.1016/j.biochi.2023.04.005.
[52] C. Michaeloudes, H. Abubakar-Waziri, R. Lakhdar, et al., Molecular mechanisms of oxidative stress in asthma, Mol Aspects Med 85 (2022) 101026, https://doi.org/10.1016/j.mam.2021.101026.
[53] C. Huang, M. Peng, J. Tong, et al., Vitamin D ameliorates asthma-induced lung injury by regulating HIF-1α/Notch1 signaling during autophagy, Food Sci. Nutr. 10 (2022) 2773–2785, https://doi.org/10.1002/fsn3.2880. (Accessed 19 April 2022).
[54] K. Ramandeep, G. Kapil, K. Harkiran, Correlation of enhanced oxidative stress with altered thyroid profile: probable role in spontaneous abortion, Int J Appl Basic Med Res 7 (2017) 20–25, https://doi.org/10.4103/2229-516X.198514.
[55] A. Joswig, H.-D. Gabriel, M. Kibschull, et al., Apoptosis in uterine epithelium and decidua in response to implantation: evidence for two different pathways, Reprod. Biol. Endocrinol. 1 (2003) 44, https://doi.org/10.1186/1477-7827-1-44.
[56] X. Chen, L. Jiang, C.C. Wang, et al., Hypoxia inducible factor and microvessels in peri-implantation endometrium of women with recurrent miscarriage, Fertil. Steril. 105 (2016) 1496–1502.e4, https://doi.org/10.1016/j.fertnstert.2016.02.032.
[57] E.H. Joo, Y.R. Kim, N. Kim, et al., Effect of endogenic and exogenic oxidative stress triggers on adverse pregnancy outcomes: preeclampsia, fetal growth restriction, gestational diabetes mellitus and preterm birth, Int. J. Mol. Sci. 22 (2021) 10122, https://doi.org/10.3390/ijms221810122.
[58] F. Rodrigues, L. de Lucca, W.S. Neme, et al., Influence of gestational diabetes on the activity of δ-aminolevulinate dehydratase and oxidative stress biomarkers, Redox Rep. 23 (2018) 63–67, https://doi.org/10.1080/13510002.2017.1402981.
[59] L. de Lucca, L.B. Jantsch, S.A. Vendrame, et al., Variation of the oxidative profile in pregnant women with and without gestational complications, Matern. Child Health J. 26 (2022) 2155–2168, https://doi.org/10.1007/s10995-022-03475-6.
[60] I. Baryla, E. Pluciennik, K. Kośla, et al., Identification of a novel association for the WWOX/HIF1A axis with gestational diabetes mellitus (GDM), PeerJ 9 (2021) e10604, https://doi.org/10.7717/peerj.10604.
[61] P. Ntontsi, A. Photiades, E. Zervas, et al., Genetics and epigenetics in asthma, Int. J. Mol. Sci. 22 (2021) 2412, https://doi.org/10.3390/ijms22052412.
[62] Y. Iv, L. Ca, S. Da, The environment, epigenome, and asthma, J. Allergy Clin. Immunol. 140 (2017), https://doi.org/10.1016/j.jaci.2017.05.011.
[63] H. Lin, J. Yi, CTRP3 regulates NF-κB and TGFβ1/Smad3 pathways to alleviate airway inflammation and remodeling in asthmatic mice induced by OVA, Allergol. Immunopathol. 51 (2023) 31–39, https://doi.org/10.15586/aei.v51i4.867.
[64] R. Pandey, V. Prakash, Expression of FOXP3 and GATA3 transcription factors among bronchial asthmatics in northern population, Indian J. Clin. Biochem. 36 (2021) 88–93, https://doi.org/10.1007/s12291-019-00853-w.
[65] J. Matheus Bremm, M. Michels, Rengel B. Duarte, et al., Genetic and in silico analysis show a role of SMAD3 on recurrent pregnancy loss, Hum. Fertil. 25 (2022) 754–763, https://doi.org/10.1080/14647273.2021.1922764.
[66] V. Alur, V. Raju, B. Vastrad, et al., Integrated bioinformatics analysis reveals novel key biomarkers and potential candidate small molecule drugs in gestational diabetes mellitus, Biosci. Rep. 41 (2021) BSR20210617, https://doi.org/10.1042/BSR20210617.
[67] L. Zhao, J. Fu, F. Ding, et al., IL-33 and soluble ST2 are associated with recurrent spontaneous abortion in early pregnancy, Front. Physiol. 12 (2022) 789829, https://doi.org/10.3389/fphys.2021.789829.
[68] W. Fan, W. Kang, T. Li, et al., Interleukin-33 and its receptor soluble suppression of tumorigenicity 2 in the diagnosis of gestational diabetes mellitus, Int. J. Clin. Pract. 75 (2021) e14944, https://doi.org/10.1111/ijcp.14944.