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Evidence from Mendelian randomization: increased risk of miscarriage in patients with asthma

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Abstract. – OBJECTIVE: Several observational studies have revealed a possible association between asthma and miscarriage. However, inferring causal relationships from observational studies may be fraught with problems like bias, reverse causation, and residual confounding. Therefore, to assess the possible causal effect of asthma on miscarriage, we performed a two-sample Mendelian randomization (MR) analysis.

MATERIALS AND METHODS: Asthma (56,167 cases and 352,255 controls) and miscarriage (9,113 cases and 89,340 controls) data from two GWAS of European ancestry were evaluated. Single nucleotide polymorphisms (SNPs) were used as instrumental variables (IVs). The random effect inverse-variance weighted (IVW) Mendelian randomization approach was used as the primary method, and MR-Egger, weighted-median, and MR-PRESSO approaches were replenished as sensitivity analysis to test the robustness of the results.

RESULTS: In total, 70 SNPs were obtained using the SNP criteria. Additionally, the MR study found substantial evidence of the causality between asthma and miscarriage [IVW, OR=1.092; 95% CI=1.017-1.174; $p<0.05$]. The sensitivity analysis demonstrated the reliability of the MR findings [horizontal pleiotropy (MR-Egger, intercept=-0.0002; Standard error of mean, se=0.006; $p=0.975$)].

CONCLUSIONS: Asthma is a causal risk factor for miscarriage in European populations, according to MR evidence. Our results emphasize the significance of asthma management in reducing the risk of miscarriage in individuals with asthma.

Key Words:
Asthma, Miscarriage, Mendelian randomization.

Introduction

Bronchial asthma (asthma) is a chronic inflammatory disease that affects multiple cells and cellular components[1]. Changes in both the environment and people's lifestyles have contributed to a considerable rise in the number of people worldwide who suffer from asthma, making it a great concern in terms of public health[2]. It affects approximately 300 million people globally[3] and is responsible for over 1,000 deaths a day[4]. It is projected that 400 million individuals will be suffering from asthma worldwide by the year 2025[5], posing a huge burden on society and individuals. The burden and impact of asthma can be reduced through a better understanding of its relationship with other diseases or risk factors, enabling the development of disease-preventive measures. Existing research[6-8] suggests that asthma is associated with factors including being overweight, having a lower level of education, and suffering from allergic rhinitis, as well as having a history of high blood pressure and breathing high levels of Particulate Matter (PM) 2.5. Unfortunately, no modifiable risk factors have been established for asthma. Additional research into other possibly linked morbidities and modifiable risk factors is warranted to further alleviate the burden of asthma.

Accumulating evidence has shown that asthma is associated with immunity and inflammation[9,10], and altered maternal immunity and inflammation would impose additional effects on miscarriage[11,12]. As a result of these discoveries, researchers have been more interested in deter-

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mining whether or not asthma causes miscarriage. According to a series of studies[13], the risk of pregnancy losses (PL) for pregnant women who suffer from asthma is significantly greater. The odds ratios (ORs) of having one, two, or PLs were 1.05 [(95% confidence interval (CI)=1.03-1.07], 1.09 (95% CI=1.05-1.13), and 1.18 (95% CI=1.11-1.24), correspondingly, in a cohort study comprising 128,553 women with asthma and 1,297,233 without asthma[14]. Some literature showed no significant association between a history of asthma diagnosis and a higher risk of miscarriage; conversely, a study[15] illustrated that severe asthma (as measured by medication usage) was correlated with an elevated risk of miscarriage. It is uncertain if asthma and miscarriage have a causal link since evidence from human observational research is vulnerable to reverse causality and confounders, leading to inconsistent findings. The widespread contention on the causality between asthma and miscarriage provides more proof that well-designed research is essential for arriving at a conclusive finding.

Mendelian randomization (MR) is a new approach to statistical analysis that evaluates the causal effect of modifiable exposures on outcomes by using genetic variants as instrumental variables (IVs)[16]. Because of the randomization of genetic variant inheritance, MR analysis can reduce the possibility of being influenced by potential confounders and reverse causation bias, inferring the correlation between exposure and outcome genetically, thus providing more reliable results[17]. Such MR studies have been conducted within many fields, including asthma and miscarriage[18-21]. Nevertheless, no relevant research has used MR analysis to elucidate the causal relationship between asthma and miscarriage.

Herein, the causal relationship between asthma and miscarriage was explored using a two-sample MR analysis.

Materials and Methods

Study Design

A two-sample MR analysis was performed to evaluate the causal effect of asthma on miscarriage with single nucleotide polymorphisms (SNPs) serving as the IVs. The steps include the retrieval of genome-wide association studies (GWAS) data, selecting and assessing SNPs, statistical analysis, and sensitivity analysis. Three crucial assumptions must be fulfilled during the procedure to maximize the accuracy of the outcomes. (1) Relevance assumption: the chosen SNPs must be robustly related to asthma; (2) exclusivity assumption: the selected SNPs cannot be directly related to miscarriage; (3) independence assumption: the selected SNPs are independent of any potential confounding factors that impact asthma and miscarriage (Figure 1).

Due to such a re-analysis of previously collected and published data, no additional ethics approval was needed.

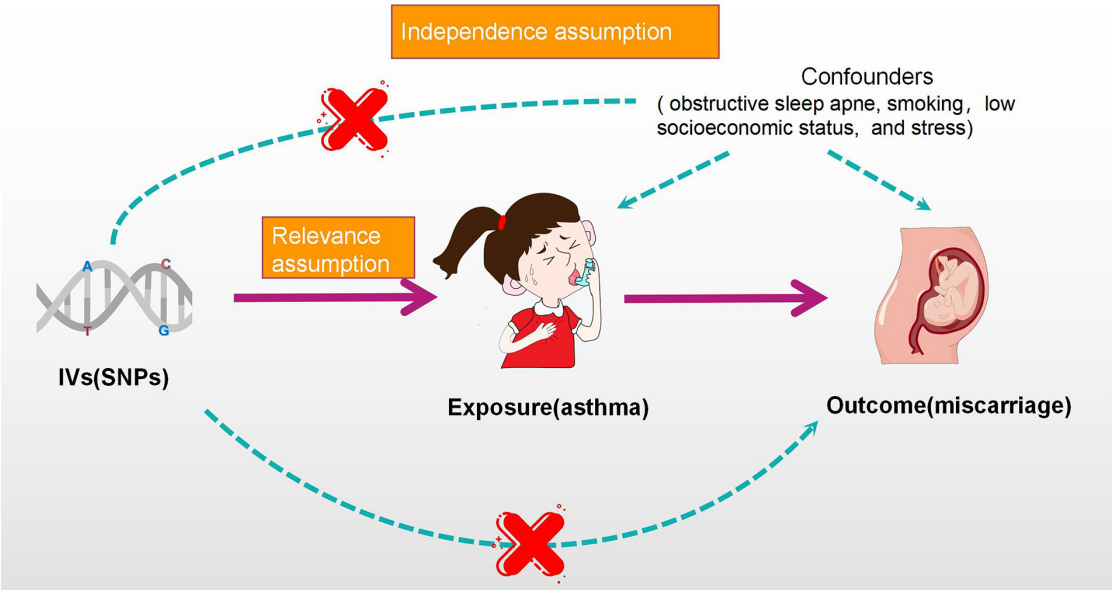

Figure 1. Overview of the MR design.

Table I. Information on data sources.

Traits	GWAS ID	N case	N control	Number of SNPs	Population	Year
Asthma	ebi-a-GCST90014325	56,167	352,255	34,551,291	European	2021
Spontaneous abortion	finn-b-O15_ABORT_SPONTAN	9,113	89,340	16,379,138	European	2021

Data Sources

The IEU Open Gaws Project (https://gwas.mrcieu.ac.uk/) was searched for retrieving summary data from published GWASs on asthma and miscarriage. All participants were of European descent, eliminating the possibility of pleiotropic bias in cross-lineage cases[22]. Summary data on miscarriage were retrieved from the FinnGen consortium to avoid including data from the same participant. Information on data sources is provided in Table I.

IVs Selection

First, to satisfy the relevance assumption, SNPs need to be associated with exposure at the genome-wide significance level ($p<5x10^{-8}$), and SNPs need to be removed with linkage disequilibrium (LD $r^2<0.001$, clumping distance within 10,000 kb)[23]. The F-statistic, which characterizes the exposure variance explained by the IVs, was then used to assess instrument strength[24]. The formula below was used to calculate the F-statistic:

$$F=[R^2/(1-R^2)]x[(N-K-1)/K]$$

where R^2 explains the extent of exposure[21], N denotes the total number of samples from the exposure GWAS, and K denotes the number of SNPs in the IV (the value of K is 1 when only a single SNP is being calculated). The instruments were strong (satisfactory strength) enough if F>10, which implies the estimated impacts of the IVs were sufficient for the subsequent MR analysis without any weak IV bias.

To satisfy the exclusivity assumption, before performing MR analysis, any SNPs with a $p<5x10^{-5}$ that were shown to be associated with miscarriage were eliminated from the IVs[25].

To satisfy the independence assumption, the PhenoScannerV2 website (http://www.phenoscanner.medschl.cam.ac.uk/) was used to rule out the possibility of any SNPs being associated with potential confounders, such as obstructive sleep apnea, low socioeconomic status, stress, and smoking[26-29].

Meanwhile, overlapping proxy SNPs (LD $r^2>0.8$) were used to replace SNPs that were missing from the miscarriage GWAS datasets. Then, palindromic SNPs with intermediate allele frequency (MAF>0.3) and incompatible SNPs were eliminated by harmonization procedures.

Statistical Analysis

In this research, the causal effects of asthma on miscarriage were evaluated utilizing four MR analytical approaches to address the potential pleiotropic effects of genetic variants. Inverse-variance weighted (IVW) estimates were applied for the main analysis, which combined the Wald ratio of each SNP on the outcome and obtained a pooled causal estimate. Additionally, the IVW was supplemented with other MR analyses, including MR-Egger regression, weighted median, and weighted mode. The randomized effects IVW served as the gold standard for MR results and the other methods were taken as auxilia[21]. The results were shown as ORs with their corresponding 95% CIs because asthma and miscarriage were both binary variables. $p<0.05$ was considered statistically significant[30]. Both the statistical analysis and the visualization of the results were carried out in R (4.2.2), using "Two Sample MR" and "MR-PRESSO" R packages.

Sensitivity Analysis

Sensitivity analyses were performed to evaluate the robustness of the MR estimates. Firstly, heterogeneity was examined using Cochran's Q. Secondly, the *p*-value from the MR-Egger regression intercept was used to test the pleiotropy. Third, leave-one-out sensitivity tests were conducted to calculate the MR result of the remaining SNPs after eliminating the SNPs one by one. $p<0.05$ was considered statistically significant[30].

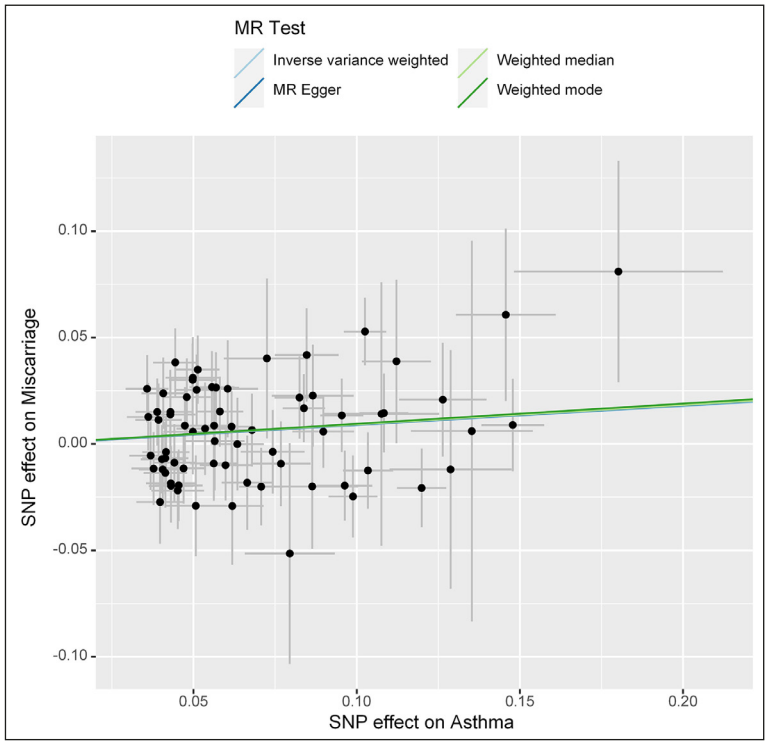

Figure 2. Scatter plot of MR analysis.

Results

Selection of IVs

A total of 70 SNPs were obtained in accordance with the SNP criteria. Both the independence assumption and the relevance assumption were satisfied for each SNP. The F-statistics computed for each SNP were used to rule out weak IVs (F<10), and no weak IVs were detected.

Statistical Analysis

The causal relationship between asthma and miscarriage was shown to be statistically significant in an IVW analysis [OR=1.092; 95% CI=1.017-1.174; p<0.05], while findings from the other three MR methods indicated a consistent but nonsignificant direction (Table II and Figure 2).

Sensitivity Analysis

IVs selected for asthma showed no evidence of heterogeneity (MR-Egger Q statistics=78.219; Q df=68; Q p=0.186; IVW Q statistics=78.221; Q df=69; Q p=0.209) or horizontal pleiotropy (intercept=-0.0002; se=0.006; p=0.975). The Wald ratio approach was utilized to evaluate the causal effect of each SNP on the risk of developing miscarriage, and the findings were visualized in a forest plot for interpretation (Figure 3). In the leave-one-out analysis test, no significant differences in the estimated causal effects were observed when removing individual SNPs and repeating the MR analysis (Figure 4). These results indicated that our findings were robust, and single IV leaving did not affect the overall causal estimation effect. Furthermore, MR-PRESSO did not identify any outlier SNPs in our sample, and the funnel plots

Table II. IMR results for the relationship between asthma and miscarriage.

Method	OR	95% CI	*p*-value	beta
Inverse variance weighted	1.092	1.017-1.174	0.016	0.088
MR Egger	1.096	0.906-1.324	0.349	0.091
Weighted median	1.096	0.984-1.220	0.097	0.091
Weighted mode	1.099	0.907-1.333	0.339	0.095

were symmetrical (Figure 5), proving no violation of the estimates.

Discussion

Using the two-sample MR analysis, the causal relationship between asthma and miscarriage was explored in this research. Our MR study supported that genetically determined asthma was positively related to the risk of developing miscarriage, which was in with findings from several other studies. Women with asthma are more likely to have a miscarriage, according to a population-based cohort study [adjusted RR (aRR)=1.21, 95% CI=1.15-1.28][31]. Similarly, a higher incidence of spontaneous abortion was observed in women with asthma during pregnancy, according to a cohort study [OR=1.41; 95% CI=1.33-1.49][32].

The mechanisms underlying the associations between asthma and miscarriage remain unclear, but two potential mechanisms may explain the positive association between them. Research has shown that inflammatory response is a factor in both asthma and miscarriage. One reasonable assumption is that the same inflammation and an elevated number of inflammatory cells and mediators are also present in asthmatic women, as in women with miscarriage, which might lead to a higher risk of miscarriage. The pathogenetic mechanism of asthma is persistent airway inflammation, typically referring, but not limited to, atopic response with Th2-predominant inflammation [related to the secretion of interleukin-(IL)-4, IL-5 and IL-13][33,34] and with elevated levels of inflammatory indicators like IL-6, tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP)[35]. Miscarriage is also greatly influenced by inflammatory processes. Increased levels of proinflammatory cytokines, such as IL-1β, TNF-α, and IL-6, play a crucial role in a healthy pregnancy[36]. However, excessive inflammation can trigger miscarriage[37]. A prospective study[38] found that the concentrations of IL-6, IL-1β, and TNF-α of the

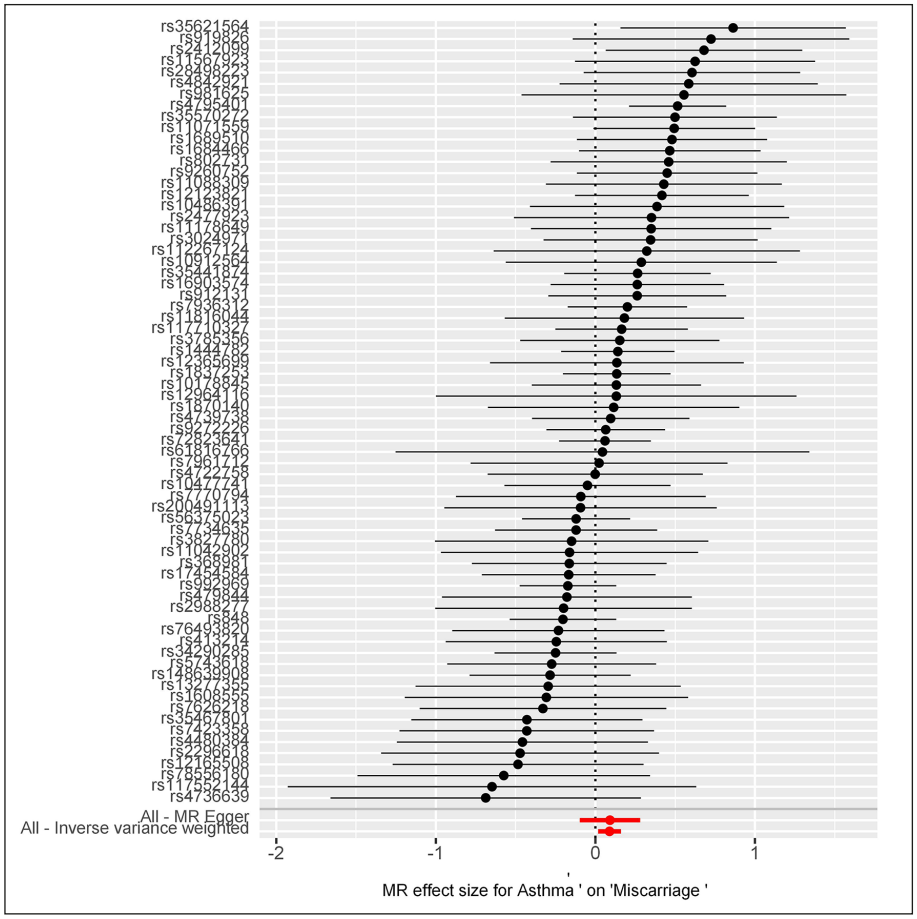

Figure 3. Forest plots depicting the causal effect of each SNP on the probability of a miscarriage.

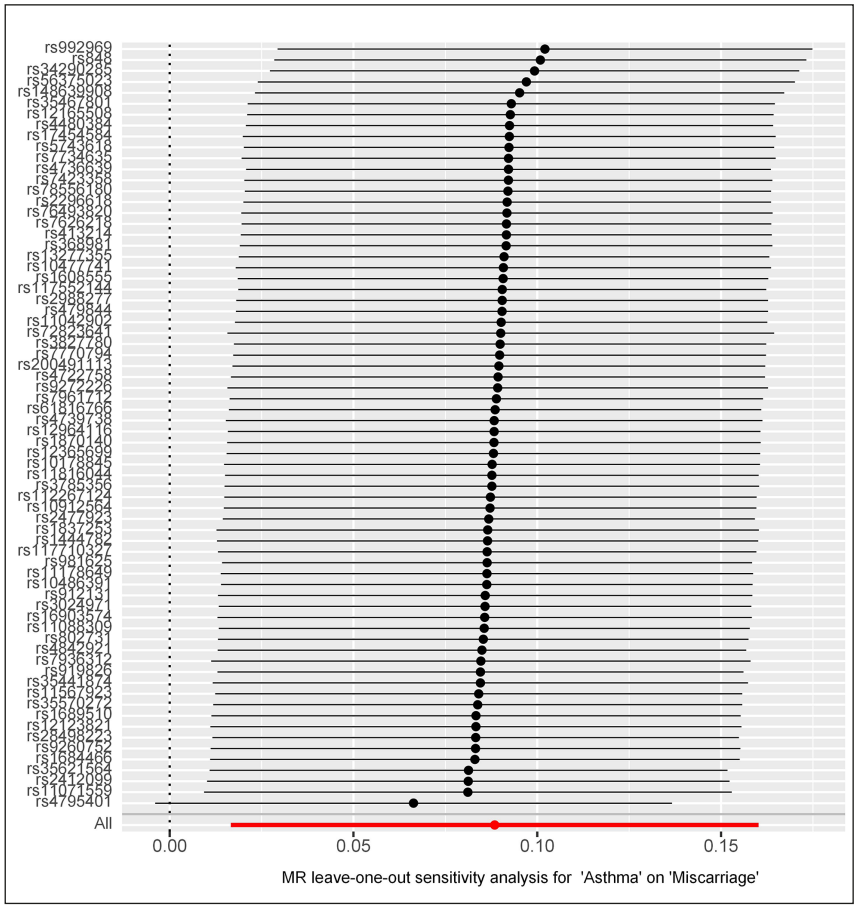

Figure 4. The impact of asthma on miscarriage was examined using a leave-one-out analysis.

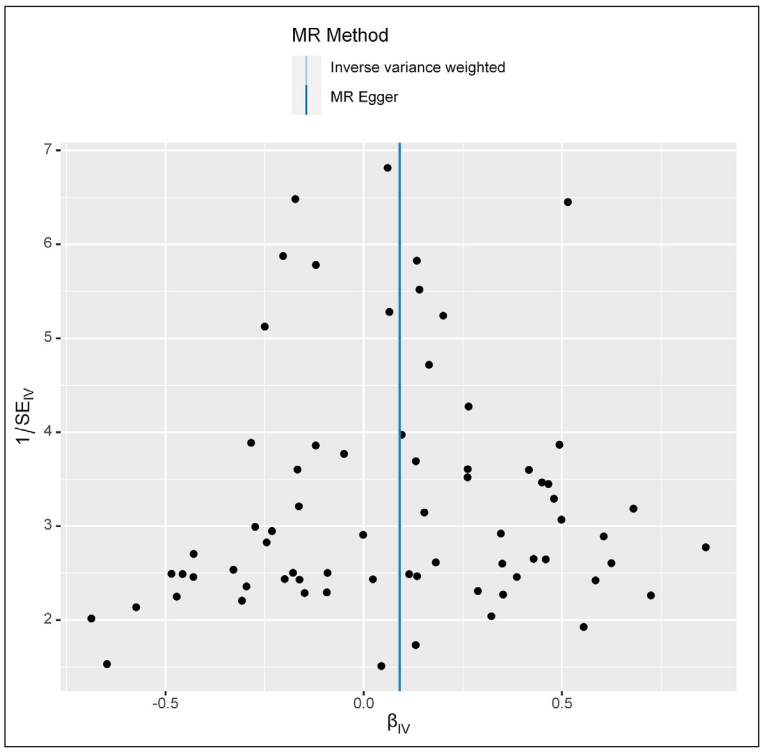

Figure 5. Overall heterogeneity in the impact of asthma on miscarriage is shown by a funnel plot.

serum samples persistently increased throughout pregnancy in the miscarriage group in comparison to the live birth cohort, supporting the pro-inflammatory and pro-abortive role of these cytokines in early pregnancy. In addition, treatment with TNF-α blocks has been shown to elevate live birth rates in women with recurrent spontaneous pregnancy loss[39]. Therefore, it is reasonably assumed that asthma might increase the risk of miscarriage by affecting reproductive function through systemic inflammatory pathways.

One proposed mechanism to explain the increased risk of miscarriage in women with asthma is hypoxia, which focuses on the role of hypoxia-inducible factor-1α (HIF-1α). As a cellular transcription factor, HIF-1α interacts with HIF-1β to form a heterodimer that may influence the expression of over a hundred target genes and performs a crucial function in the regulatory processes of apoptosis, autophagy, placental and embryonic development, and angiogenesis[40]. HIF-1α can be detected in human placentas; the production of HIF-1α protein is gestational age-dependent, with the highest expression in early pregnancy (~5 weeks). As pregnancy advances, HIF-1α protein levels gradually decrease and, by week 12, are almost undetectable[41]. Airway edema, inflammatory reactions, fibrosis, airway obstruction, decreased ventilation, and alveolar-capillary injury are among the consequences of asthma. These disorders have the potential to produce pulmonary ventilation problems, which may lead to inadequate delivery of oxygen to the lung tissues[42], thereby activating the HIF-1α signaling pathway[43]. As one of the most important downstream target genes of HIF-1α, vascular endothelial growth factor (VEGF) is a vascular permeability factor that is particularly important in endothelial cells[44]. Endothelial dysfunction and miscarriage may result from an overproduction of VEGF caused by a poorly hypoxic placenta throughout early gestation[45]. Hence, it is reasonable to suppose that abnormal activation of HIF-1α during gestation could represent a mechanism for miscarriage that has not been discovered. Overall, miscarriage risk may be elevated by the interaction of asthma-related inflammation with hypoxia. To clarify this issue, research is needed with a larger number of patients with asthma and miscarriage aimed at clarifying the endometrial changes caused by asthma.

Limitations

Nonetheless, it is important to note the limitations of our research. First, the European population was the only source for GWAS datasets. The generalizability of our results to other populations is unknown. Thus, more research involving different populations is needed to establish whether the results are generalizable. Second, this MR analysis used SNPs in the human genome to establish exposures, which failed to provide a thorough representation of the exposure factors. Future research is necessary to validate the causal relationship and examine possible processes due to the constraints of the GWAS datasets, which is essential for producing feasible treatment recommendations. Third, the possible sample overlap between the GWAS datasets of asthma and miscarriage could not be properly accounted for, which may contribute to bias in the overall estimates since individual data were not publicly accessible. Fourth, the data on outcomes were gathered from the population with asthma, but the severity of the condition was not specified. Further research is needed to determine the association between the severity of asthma and the risk of miscarriage.

Conclusions

This study is the first to suggest a positive association between asthma and miscarriage risk, using a two-sample MR analysis. Our findings highlight the importance of paying more attention to individuals with asthma to prevent potential miscarriage risks. Women with asthma require optimal asthma/medical management prenatally and throughout pregnancy. Preconception counseling and evaluation are particularly important for women with asthma. Moreover, further studies are needed to explore the potential mechanism mediating the causal effect of asthma on miscarriage.

Conflict of Interest

The authors declare that they have no conflict of interests.

Ethics Approval

Ethical approval was not required because all data used in this study were obtained from publicly available.

Informed Consent

Not applicable.

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Availability of Data and Materials
The datasets used in the study are GWAS summary-level statistics and were accessed through the IEU Open Gaws Project (https://gwas.mrcieu.ac.uk/) and the FinnGen study (https://fnngen.gitbook.io/docu mentation/data-download) web browsers. Individual-level data were not provided.

Authors' Contributions
Yin-song Xu: analyzed the data and wrote the manuscript; Ren-yan Liao and Dan Huang: assisted in analyzing the data; Dan Wang and Lan Zhang: assisted in revising the manuscript; Yuan-zhi Li: designed the study,critically read and edited the manuscript. All authors read and approved the final manuscript.

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