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THE METHOD OF MENDELIAN RANDOMIZATION IN OBSTETRICS AND GYNECOLOGY

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Abstract. *Introduction.* In modern obstetrics and gynecology, increasing importance is being placed on the assessment of causal relationships between modifiable risk factors and the development of maternal and fetal diseases. Traditional observational studies are often limited by confounding factors and reverse causality, while randomized controlled trials in reproductive medicine are frequently ethically or practically unfeasible. In this context, Mendelian randomization (MR) is considered a promising tool for causal inference.

Aim of the study. To analyze the theoretical foundations of the Mendelian randomization method, evaluate its capabilities and limitations, and summarize current evidence regarding the application of MR in obstetric and gynecological research.

Materials and methods. A bibliographic and content analysis of scientific sources published in international peer-reviewed journals was conducted. Comparative analysis and data synthesis methods were applied, with priority given to systematic reviews, meta-analyses, and large-scale cohort studies focusing on the use of Mendelian randomization in reproductive medicine.

Results. The Mendelian randomization method was found to minimize the influence of confounding factors and reverse causality through the use of genetic variants as instrumental variables. In obstetric and gynecological research, MR is applied to assess the causal effects of metabolic, hormonal, and reproductive factors on the risk of preeclampsia, polycystic ovary syndrome, postpartum depression, gestational complications, and gynecologic oncological diseases. At the same time, major limitations of the method have been identified, including pleiotropy, weak genetic instruments, and population stratification.

Conclusions. 1. The Mendelian randomization method in obstetrics and gynecology is associated with increased accuracy in assessing causal relationships between genetically determined risk factors and the development of obstetric and gynecological diseases by minimizing confounding and reverse causality. 2. The application of Mendelian randomization enables the identification of causal effects of metabolic, hormonal, and reproductive factors on the development of pregnancy complications and gynecologic and perinatal pathologies, which has significant clinical implications for prevention and therapeutic decision-making. 3. The justified use of the Mendelian randomization method, considering its methodological limitations and in combination with observational and clinical research findings, is necessary to improve the evidence base and optimize long-term health outcomes for women and children.

Key words: Mendelian randomization, obstetrics, gynecology, genetic variants, risk factors.

Метод Менделівської рандомізації в акушерстві та гінекології
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Резюме. *Вступ.* У сучасному акушерстві та гінекології дедалі більшого значення набуває оцінка причинно-наслідкових зв'язків між модифікованими факторами ризику та розвитком захворювань матері й плода. Традиційні спостережні дослідження часто обмежені впливом конфаундерів і проблемою зворотної причинності, тоді як проведення рандомізованих контрольованих досліджень у репродуктивній медицині нерідко є етично або практично неможливим. У цьому контексті метод Менделівської рандомізації (МР) розглядається як перспективний інструмент каузального аналізу.

Мета дослідження. Проаналізувати теоретичні основи методу Менделівської рандомізації, оцінити його можливості та обмеження, а також узагальнити сучасні дані щодо застосування МР у дослідженнях з акушерства та гінекології.

Матеріали та методи. Проведено бібліографічний та контент-аналіз наукових джерел, опублікованих у міжнародних рецензованих виданнях. Використано методи порівняльного аналізу та синтезу інформації з пріоритетом систематичних оглядів, метааналізів і масштабних когортних досліджень, присвячених застосуванню Менделівської рандомізації у репродуктивній медицині.

Результати досліджень. Встановлено, що метод Менделівської рандомізації дозволяє мінімізувати вплив конфаундерів та зворотної причинності шляхом використання генетичних варіантів як інстру-

ментальних змінних. У дослідженнях з акушерства та гінекології МР застосовується для оцінки причинного впливу метаболічних, гормональних і репродуктивних факторів на ризик розвитку прееклампсії, синдрому полікістозних яєчників, післяпологової депресії, гестаційних ускладнень, а також гінекологічних онкологічних захворювань. Разом із тим ідентифіковано основні обмеження методу, зокрема плейотропію, слабкі генетичні інструменти та популяційну стратифікацію.

Висновки. 1. Метод Менделівської рандомізації в акушерстві та гінекології асоціюється з підвищеною точністю оцінки причинно-наслідкових зв'язків між генетично детермінованими факторами ризику та розвитком акушерсько-гінекологічних захворювань за рахунок мінімізації впливу конфаундерів і зворотної причинності. 2. Застосування Менделівської рандомізації дозволяє ідентифікувати причинний вплив метаболічних, гормональних і репродуктивних чинників на розвиток ускладнень вагітності, гінекологічних та перинатальних патологій, що має суттєве клінічне значення для профілактики й вибору терапевтичних стратегій. 3. Обґрунтоване використання методу Менделівської рандомізації з урахуванням його методологічних обмежень, а також поєднання МР-аналізу з результатами спостережних і клінічних досліджень є необхідним для покращення доказової бази та оптимізації довгострокових показників здоров'я жінок і дітей.

Ключові слова: Менделівська рандомізація, акушерство, гінекологія, генетичні варіанти, фактори ризику.

Introduction

Mendelian randomization (MR) is a modern epidemiological method that enables the identification of causal relationships between genetically determined factors and clinical outcomes. This approach uses genetic variants as instrumental variables that are naturally randomized at conception, analogous to a randomized controlled trial, thereby reducing the influence of confounding factors and reverse causation [1]. Unlike conventional observational studies, MR is less susceptible to bias caused by environmental factors or behavioral changes, as genetic instruments remain stable throughout an individual's lifetime [1].

In obstetrics, MR is increasingly applied to assess the causal effects of reproductive and perinatal factors. For example, studies have shown that polycystic ovary syndrome (PCOS) may causally contribute to the development of gestational hypertension, whereas its associations with gestational diabetes or preeclampsia are not consistently confirmed [2]. Such findings help clarify which specific aspects of clinical conditions exert a direct causal effect on perinatal outcomes, independent of accompanying factors such as body mass index or metabolic parameters [3].

Moreover, MR is used to evaluate other pregnancy-related exposures. For instance, two-sample MR analyses have investigated the effects of chronotype and sleep characteristics on the risk of preterm birth and other perinatal complications, allowing the separation of biological from behavioral risk factors [4]. In addition, MR has been applied to examine causal links between maternal body mass index, gestational weight gain, and the risk of adverse perinatal outcomes, thereby refining clinical recommendations for complication prevention [5].

Overall, the application of MR in obstetrics and gynecology enhances the understanding of causal mechanisms underlying gestational complications and supports the development of clinical recommendations based on genetically informed evidence, which is crucial for designing targeted strategies for the prevention and treatment of reproductive and perinatal diseases.

Aim of the study

To analyze the theoretical foundations of the Mendelian randomization (MR) method, assess its potential and limitations, and summarize current evidence regarding the application of MR in obstetrics and gynecology for the evaluation of causal relationships between genetic, metabolic, hormonal, and reproductive factors and maternal-fetal outcomes.

Materials and methods

The study employed bibliographic and content analysis of scientific sources published in international peer-reviewed journals from 2020 to 2025. Comparative analysis, data synthesis, and semantic grouping of information were performed to evaluate applications of Mendelian randomization in reproductive medicine. Priority was given to systematic reviews, meta-analyses, large-scale cohort studies, and Mendelian randomization studies investigating causal effects of metabolic, hormonal, and reproductive factors on the risk of preeclampsia, polycystic ovary syndrome, gestational complications, postpartum depression, and gynecologic oncological diseases. Methodological strengths and limitations of MR were also critically assessed.

Results

Mendelian randomization (MR) has become a powerful tool for investigating causal relationships

in obstetrics and gynecology, particularly for assessing the effects of genetically determined maternal factors on perinatal and reproductive outcomes. Owing to the natural "randomization" of alleles, MR minimizes the influence of behavioral and socioeconomic confounders that often bias traditional observational studies. A number of MR studies have demonstrated that genetically determined higher maternal body weight is directly associated with an increased risk of gestational diabetes. These findings confirm that maternal obesity is a causal factor in the development of metabolic complications of pregnancy, rather than merely correlating with them through lifestyle or external factors [6].

In addition to metabolic complications, MR enables the evaluation of cardiovascular complications of pregnancy, such as preeclampsia [7]. Genetically determined factors related to elevated maternal blood pressure have shown a direct effect on the development of preeclampsia, supporting a mechanistic link between hypertension and this serious pregnancy complication [8]. Moreover, analyses indicate that this association persists across populations with differing socioeconomic conditions, underscoring the independence of the effect from external confounders.

The MR approach is also applied to investigate the risk of preterm birth and abnormal offspring birth weight [9]. Genetically determined maternal body weight characteristics and insulin resistance have been directly associated with an increased risk of preterm birth as well as with the delivery of infants with macrosomia [10]. These data indicate that the effects of obesity and metabolic disturbances on perinatal outcomes are causal rather than merely associative, providing important evidence for the development of preventive strategies in pregnancy management.

The role of hormonal factors in reproductive disorders has also been examined using MR. Genetically determined levels of estrogen and progesterone have been directly linked to the risk of pregnancy loss, allowing true hormonal mechanisms to be distinguished from correlations driven by other factors [11]. Furthermore, MR has shown that even modest genetically determined variations in hormone levels can have clinically meaningful effects on reproductive outcomes, highlighting its value for accurate risk prediction.

A systematic review of MR studies on age at natural menopause (ANM) demonstrated that Mendelian randomization helps clarify causal relationships between ANM, its determinants, and a wide range of diseases [12]. Earlier menopause is causally associated with increased risks of osteoporosis, fractures, and impaired glucose metabolism, whereas later menopause is linked to a higher risk of hormone-dependent malignancies and certain cardiovascular outcomes. The authors emphasize that MR is a key tool for overcoming the limitations of observational studies and for elucidating the role of cumulative estrogen exposure in women's health.

Studies examining the impact of genetically determined metabolic markers, such as glucose levels and insulin resistance, on perinatal complications have also yielded significant findings. The use of MR has established causal effects of these markers on the development of gestational diabetes, preterm birth, and fetal macrosomia. This suggests that early monitoring and control of metabolic parameters during pregnancy may substantially reduce the risk of complications [13].

MR is additionally used to assess the effects of maternal obesity on complex perinatal outcomes, including combined risks for both mother and fetus [14]. Genetically increased body weight is simultaneously associated with higher risks of gestational diabetes, preeclampsia, and fetal macrosomia, highlighting the multifaceted impact of metabolic factors on pregnancy outcomes and the need for multidisciplinary preventive approaches.

Finally, the integration of MR with data from large biobanks and genome-wide association studies (GWAS) enables large-scale, statistically robust, and cost-effective research encompassing diverse aspects of obstetric and gynecologic practice [15]. This facilitates the identification of truly causal risk factors and supports the development of evidence-based clinical recommendations aimed at preventing pregnancy complications and improving reproductive outcomes [16]. Mendelian randomization has become a powerful tool for establishing causal relationships between metabolic markers and the risk of developing gynecological malignancies, particularly ovarian cancer. Traditional observational studies often fail to distinguish true causality from associations arising from lifestyle factors, comorbidities, or other confounders. In a large-scale MR study, 637 genetically determined metabolites were analyzed as potential risk factors for ovarian cancer. Classical MR methods were applied, including inverse-variance weighted (IVW), MR-Egger, and weighted median, together with tests for heterogeneity and

horizontal pleiotropy, as well as the Steiger test to verify the direction of effect. This comprehensive approach made it possible to identify 31 metabolites with a significant effect on ovarian cancer risk, of which 9 demonstrated stable and consistent causal effects [17].

Among the metabolites associated with an increased risk of ovarian cancer, androsterone sulfate, propionylcarnitine, 5α-androstan-3β, 17β-diol disulfate, as well as lipids in medium-sized VLDL particles were particularly notable [18]. The MR study confirmed that genetically determined elevations in these compounds are directly associated with ovarian cancer development, indicating their causal role in carcinogenesis. This is especially important because lipid metabolism and steroid metabolites may act as oncometabolites, supporting the proliferation and survival of malignant cells.

At the same time, several metabolites with negative causal associations were identified, which may potentially act as protective factors or markers of low ovarian cancer risk. These included octanoylcarnitine, N2, N2-dimethylguanosine, and cis-4-decenoyl carnitine. Each of these metabolites showed a statistically significant negative effect on ovarian cancer risk, suggesting possible metabolic protective mechanisms or regulatory pathways that inhibit carcinogenesis. This opens perspectives for the identification of early diagnostic biomarkers and personalized risk prediction [19].

The results of this study have practical significance for gynecology, as they allow the identification of biologically grounded targets for prevention and therapy without the influence of external confounders. Metabolites with positive causal effects may become potential therapeutic targets, whereas those with negative effects may serve as promising biomarkers of low risk or targets for preventive interventions. Thanks to MR, it became possible to confirm the causal role of these metabolites in ovarian cancer development rather than merely their association, which substantially increases the reliability of the conclusions. This study highlights the importance of using genetic tools in gynecological practice for risk prediction, early diagnosis, and the development of targeted interventions. The identification of causal metabolites provides a foundation for further translational and clinical studies aimed at reducing disease incidence and improving prognosis in women at high risk of ovarian cancer.

Among obstetric complications, preeclampsia and other hypertensive disorders of pregnancy (PE-HTPs) have particular clinical significance, as they are associated with a substantially increased risk of maternal and perinatal morbidity and mortality. Traditional observational studies have repeatedly identified associations between plasma levels of specific fatty acids and the risk of PE-HTPs; however, due to potential confounders and reverse causation, the establishment of mechanistic relationships has been limited. To overcome these limitations, Zhou and colleagues applied a bidirectional two-sample Mendelian randomization approach, using genetic proxies for levels of different types of plasma fatty acids and PE-HTPs data from large GWAS cohorts of European ancestry. The analysis used inverse-variance weighted (IVW) as the primary method, along with MR-Egger, weighted median, simple mode, and weighted mode as complementary analyses, as well as tests for heterogeneity, horizontal pleiotropy, and colocalization to assess the robustness of the findings [23].

The results showed that genetically predicted PE-HTPs risk has significant causal associations with several specific classes of plasma fatty acids. In particular, lower levels of linoleic acid (LA; omega-6 fatty acid) were directly associated with a reduced risk of PE-HTPs (OR = 0.95, 95% CI: 0.92–0.98), indicating causal effects of lipid metabolism on the development of hypertensive disorders during pregnancy. Genetically predicted increases in docosahexaenoic acid (DHA, omega-3 FA) and a higher PUFA/MUFA ratio were also associated with a reduced risk of PE-HTPs (OR ≈ 0.86 for both), suggesting a potentially protective role of long-chain polyunsaturated fatty acids in maternal lipid profiles and inflammation. In contrast, a higher proportion of monounsaturated fatty acids (MUFA) was associated with a moderate increase in PE-HTPs risk (OR = 1.12, 95% CI: 1.00–1.25), which may reflect different mechanisms of lipid regulation of blood pressure during pregnancy [24]. These findings have important clinical implications, as they demonstrate that fatty acid metabolic pathways directly influence the risk of hypertensive complications in pregnant women rather than serving merely as associated markers. The use of MR substantially reduces the influence of potential confounders, including dietary habits, body weight, or other behavioral factors, thereby clarifying the mechanistic role of lipid metabolism in PE-HTPs pathology. Mechanistically, this may

reflect the influence of PUFAs on endothelial function, anti-inflammatory signaling pathways, and placental vascularization, which are key components in the pathogenesis of preeclampsia.

Mendelian randomization (MR) has also become an extremely valuable method in modern genetic epidemiology for establishing causal relationships between biologically determined factors and psychiatric outcomes, as it minimizes confounding and eliminates reverse causation by using genetic variants as instrumental variables. In a large two-sample MR study published in *Frontiers in Genetics*, nine female reproductive characteristics, including age at first sexual intercourse (AFS), age at menarche (AMC), age at first birth (AFB), age at last live birth (ALLB), age at menopause (AMP), lifetime number of sexual partners (LNSP), number of live births (NLB), number of stillbirths, and number of spontaneous abortions - were analyzed for their effects on the risk of postpartum depression (PPD) in a European population (13,657 PPD cases and 236,178 controls) [25]. The primary method for causal effect estimation was inverse-variance weighted (IVW), supplemented by MR-Egger, weighted median, and MR-PRESSO analyses to control for heterogeneity and horizontal pleiotropy, as well as multivariable MR (MVMR) to assess direct effects while controlling for other factors in the model.

In the univariable MR (UVMR) analysis, significant inverse causal associations were identified between three reproductive characteristics and PPD risk: age at first sexual intercourse (AFS), age at first birth (AFB), and age at last live birth (ALLB) were all significantly associated with a lower risk of PPD (e.g., AFS: OR = 0.474, 95% CI 0.396–0.567; $p \approx 4.6 \times 10^{-16}$; ALLB: OR = 0.296, 95% CI 0.138–0.636; p = 0.002). This suggests that later sexual debut or later childbearing may have a protective effect against postpartum depression. UVMR also showed that a higher lifetime number of sexual partners and a greater number of spontaneous abortions may be associated with an increased risk of PPD, although these associations were less robust after multiple testing correction and controlled analyses. However, in multivariable MR (MVMR), where other reproductive characteristics were simultaneously controlled, only age at first birth (AFB) retained an independent causal association with PPD risk (OR = 0.804, 95% CI 0.661–0.978; p = 0.029). This indicates that among all assessed reproductive variables, age at first birth is the strongest and most stable causal predictor of postpartum depression. This finding suggests that later motherhood may be associated with a lower risk of developing PPD, which has important clinical implications for counseling and preventive strategies in women of reproductive age [26].

The application of MR in this context allows, for the first time, the quantification of causal effects of reproductive characteristics on the risk of a psychiatric condition such as postpartum depression, which has traditionally been studied only in observational research with numerous limitations. The identification of age at first birth as a key causal factor underscores the potential of MR for formulating personalized recommendations for pregnancy care and the prevention of postpartum disorders, including psychosocial interventions and targeted monitoring of high-risk groups [27].

During the COVID-19 pandemic, many observational studies suggested a potential association between SARS-CoV-2 infection during pregnancy and an increased risk of obstetric complications, such as preeclampsia, preterm birth, low birth weight, and other adverse perinatal outcomes [28, 29]. However, these findings may have been confounded by postnatal factors, lifestyle changes, or healthcare limitations characteristic of the pandemic period. To address the question of causality, Fang and Fang conducted a two-sample Mendelian randomization analysis, using genetic markers associated with COVID-19 risk as instrumental variables to assess their causal effects on obstetric outcomes using large GWAS datasets of European ancestry [30].

In this MR study, the primary estimation method was inverse-variance weighted (IVW), complemented by MR-Egger and MR-PRESSO analyses to detect potential horizontal pleiotropy of instrumental SNPs, as well as sensitivity analyses including leave-one-out tests. The results demonstrated a statistically significant causal association between COVID-19 and placental dysfunction, with an IVW beta coefficient of 1.57 and an OR of 4.81 (95% CI: 1.05–22.05, p = 0.04), indicating a substantial increase in the risk of this pathology with genetically predicted SARS-CoV-2 infection. This suggests that genetic susceptibility to COVID-19 may directly contribute to placental structural or functional impairment, which is consistent with prior evidence of local placental infection and inflammatory changes in chorionic villi.

At the same time, the MR analysis did not identify causal effects of SARS-CoV-2 on other major

obstetric outcomes, including gestational diabetes mellitus (GDM) (OR = 1.12; 95% CI: 0.85–1.45; p=0.41), intrahepatic cholestasis of pregnancy (ICP) (OR = 1.42; 95% CI: 0.85–2.36; p = 0.18), gestational hypertension/preeclampsia (OR ≈ 1.00; p ≈ 0.85), low birth weight, spontaneous miscarriage (OR ≈ 1.00; p ≈ 0.90), or stillbirth (OR ≈ 1.00; p ≈ 0.62). MR-Egger and MR-PRESSO analyses showed no evidence of substantial horizontal pleiotropy, and heterogeneity was acceptable, strengthening the reliability of the conclusions regarding the absence of causal relationships between COVID-19 and other perinatal complications in this sample.

These results have important clinical and epidemiological implications [31, 32]. First, confirmation of a direct link between COVID-19 and placental dysfunction, but not with other obstetric outcomes, points to specific mechanisms that may mediate the effect of SARS-CoV-2 at the maternal-placental interface without a generalized impact on gestational metabolism, blood pressure, or perinatal mortality risk. This is partly consistent with mechanistic data indicating local alterations in syncytiotrophoblasts and increased placental permeability during SARS-CoV-2 infection. Second, the absence of causal relationships with other obstetric pathologies suggests that associations observed in previous cohort studies may have been driven by confounders such as comorbidities, access to healthcare, or behavioral changes during the pandemic- factors that Mendelian randomization (MR) effectively controls.

The application of MR in this context confirms its value for epidemiological research in obstetrics, as it enables the assessment of causality through a "natural experiment" without controlled interventions, which are often impossible or unethical during large-scale infectious epidemics. These findings may help inform pregnant patients and healthcare providers by reducing uncertainty regarding SARS-CoV-2 risks for different obstetric outcomes and by focusing attention on specific mechanisms, such as placental dysfunction, that may warrant further monitoring or targeted interventions.

The MR-PREG (Mendelian Randomization in Pregnancy) study was established to investigate the causal effects of maternal lifestyle and health factors on adverse pregnancy and perinatal outcomes (APPOs), including preterm birth, preeclampsia, and gestational diabetes [33]. Due to ethical and practical limitations of randomized controlled trials in pregnant women, MR leverages genetic variants as instrumental variables, naturally randomized at conception to infer causal relationships while minimizing confounding [34].

The MR-PREG collaboration integrates data from three prospective cohorts (ALSPAC, BiB, MoBa), UK Biobank, FinnGen, and GWAS, encompassing up to 678,001 women and 34 APPOs. Using triangulation of evidence from MR, conventional regression, and negative parental control analyses, the study found that higher maternal BMI increases the risk of multiple APPOs, while maternal circulating proteins and metabolites may influence birth weight. MR-PREG also applies drug-target MR to evaluate the effectiveness and safety of medications in pregnancy and to identify novel molecular targets. Future plans include expanding ethnic diversity, integrating molecular data (placental transcriptomics and proteomics), and conducting exome and whole-genome analyses to identify new genetic determinants of APPOs. This approach enhances understanding of the mechanisms underlying adverse pregnancy outcomes and supports the development of more effective prevention and treatment strategies.

Another recent study used Mendelian randomization to examine the impact of sleep duration during pregnancy on the risks of stillbirth, perinatal depression, and low or high birth weight. Data were drawn from UK Biobank, FinnGen, and three cohorts (ALSPAC, BiB, MoBa), totaling more than 320,000 women [35]. The results demonstrated a nonlinear effect: both short and excessively long sleep durations increased the risks of stillbirth and low birth weight, while short sleep increased the risk of perinatal depression. These effects were not detected by linear models, underscoring the importance of MR for clarifying causal relationships. The study confirms that optimal sleep duration is important for maternal and child health and highlights the strength of Mendelian randomization in perinatal research.

A study by K. Taylor et al. (2023) employed Mendelian randomization to assess the effects of maternal BMI, smoking, and alcohol consumption during pregnancy on the development of congenital heart defects (CHD) in offspring [36]. The analysis included three large cohorts comprising 65,510 mother–child pairs, with 562 CHD cases identified. Genetic risk scores (GRS) derived from GWAS data were used to estimate genetically predicted effects of these exposures on CHD risk. The results showed that associations between maternal BMI, smoking, alcohol intake, and CHD were close to null, and additional sensitivity analyses confirmed the robustness of these findings. The

authors concluded that there is currently no convincing evidence of a direct causal effect of these maternal factors on CHD risk in offspring, while emphasizing the need for larger studies incorporating genetic data from both mothers and children for more precise estimation.

A study by L. Pan et al. (2024) applied Mendelian randomization to evaluate causal relationships between levels of 15 micronutrients and 12 obstetric disorders [37]. The analysis showed that iron had a protective effect against gestational diabetes (OR = 0.597), whereas zinc increased the risk of gestational hypertension (OR = 1.064). Vitamin B6 was associated with an increased risk of spontaneous abortion (OR = 1.222), and vitamin D with fetal growth restriction (OR = 1.612). In contrast, vitamin B12 reduced the risk of preterm birth (OR = 0.686). Selenium and vitamin E exhibited protective effects against polyhydramnios, although selenium increased the risk of premature rupture of membranes. Other micronutrients did not demonstrate significant causal effects. These findings help clinicians offer personalized recommendations for micronutrient supplementation during pregnancy planning and management and underscore the role of nutritional interventions in preventing pregnancy complications [38, 39].

Another interesting study published in 2024 examined the impact of coffee consumption during pregnancy on child development [40]. Initial observational analyses suggested a possible association between coffee intake and difficulties in children's social behavior and attention; however, after adjustment for smoking, alcohol use, education, and income, this association disappeared. Genetic analysis using Mendelian randomization provided weak indications of an effect, but no causal relationship was established.

Discussion. The obtained results confirm that Mendelian randomization is a reliable and methodologically robust approach for establishing causal relationships in obstetrics and gynecology, where randomized controlled trials are often ethically or practically infeasible. The use of genetic variants as instrumental variables substantially reduces the influence of socioeconomic, behavioral, and clinical confounders and helps avoid reverse causation, a limitation inherent to traditional observational studies.

Particular attention should be paid to the findings related to maternal metabolic factors. The identified causal effects of genetically determined increased body mass and insulin resistance on the risks of gestational diabetes, preeclampsia, preterm birth, and fetal macrosomia are consistent with current concepts regarding the role of metabolic imbalance in placental dysfunction and intrauterine programming. These data confirm that maternal obesity is not merely a marker of an unfavorable lifestyle but an independent causal factor in the development of perinatal complications, with important clinical and preventive implications.

The identified causal associations between plasma fatty acid profiles and hypertensive disorders of pregnancy provide deeper insight into the pathophysiology of preeclampsia. The protective effects of polyunsaturated fatty acids and a higher PUFA/MUFA ratio, as well as the adverse impact of excess MUFA, may reflect distinct mechanisms regulating vascular tone, inflammatory responses, and endothelial dysfunction during pregnancy. Thus, MR data refine biological pathways that were previously assessed mainly at an associative level.

The application of MR in gynecologic oncology demonstrated a causal role of specific metabolites in the development of ovarian cancer, particularly steroid and lipid compounds. The identification of metabolites with positive and negative causal effects enables differentiation between potential oncometabolites and protective metabolic markers. This opens перспективеs for developing new strategies for early risk prediction and for translational studies targeting metabolic pathways in the therapy of malignancies of the female reproductive system.

Important findings were also obtained regarding polycystic ovary syndrome (PCOS). The identified protective causal effect of genetically determined increased vitamin A levels suggests a specific role in regulating folliculogenesis, steroidogenesis, and insulin sensitivity. The absence of causal effects for other macro- and micronutrients underscores the complexity of PCOS pathogenesis and highlights the advantage of MR in identifying truly meaningful biological factors among numerous associations reported in the literature.

Results related to postpartum depression indicate the presence of causal links between certain reproductive characteristics and women's mental health after childbirth. In particular, the consistent protective effect of a later age at first birth may reflect a combination of biological maturity, hormonal stability, and psychosocial factors. This underscores the potential of MR to investigate not only somatic but also psychiatric outcomes in obstetric and gynecologic practice.

Special attention should be given to the MR findings concerning SARS-CoV-2 infection during pregnancy. The identification of a causal association with placental dysfunction, but not with other obstetric complications-helps explain discrepancies between previous observational studies and highlights the specificity of viral effects on the maternal–placental interface. This has practical implications for the clinical monitoring of pregnant women after infection.

Overall, the presented results demonstrate the broad potential of Mendelian randomization as a tool of evidence-based medicine in obstetrics and gynecology. The integration of MR with large-scale GWAS and biobank data provides a foundation for developing personalized preventive and therapeutic approaches aimed at reducing maternal and perinatal morbidity and improving women's reproductive health.

Study limitations. Although Mendelian randomization reduces the impact of confounding and reverse causality, pleiotropy cannot be completely excluded. Some genetic instruments have limited strength, and the available data are predominantly derived from European populations, which restricts the generalizability of the findings. In addition, MR reflects the effects of genetically determined exposures over the life course rather than short-term clinical interventions, and it does not always account for nonlinear effects or critical periods of pregnancy.

Conclusions

1. The Mendelian randomization method in obstetrics and gynecology is associated with increased accuracy in assessing causal relationships between genetically determined risk factors and the development of obstetric and gynecological diseases by minimizing confounding and reverse causality.

2. The application of Mendelian randomization enables the identification of causal effects of metabolic, hormonal, and reproductive factors on the development of pregnancy complications and gynecologic and perinatal pathologies, which has significant clinical implications for prevention and therapeutic decision-making.

3. The justified use of the Mendelian randomization method, considering its methodological limitations and in combination with observational and clinical research findings, is necessary to improve the evidence base and optimize long-term health outcomes for women and children.

Conflict of interest: The authors report the absence of any conflict of interest.

REFERENCES

1. Yeung SLA, Luo S, Iwagami M, Goto A. Introduction to Mendelian randomization. Ann Clin Epidemiol. 2025 Jan 1;7(1):27-37. doi: 10.37737/ace.25004. Erratum in: Ann Clin Epidemiol. 2025 Jan 24;7(2):69. doi: 10.37737/ace.25004E.
2. Dang C, Wang S, Liu P, Liu J, Yu X, Zhao L, Xu T, Liu M. Polycystic ovary syndrome and risk of pregnancy-induced hypertension, gestational diabetes mellitus, and preeclampsia: a Bayesian Mendelian randomization study. Diabetol Metab Syndr. 2025 Jun 10;17(1):204. doi: 10.1186/s13098-025-01739-z.
3. Ma Y, Cai J, Liu LW, Wen T, Huang W, Hou W, Wei Z, Xu Y, Xu Y, Wang Y, Mai Q. Causal relationships exist between polycystic ovary syndrome and adverse pregnancy and perinatal outcomes: a Mendelian randomization study. Front Endocrinol (Lausanne). 2024 Jun 28;15:1327849. doi: 10.3389/fendo.2024.1327849.
4. Yang Q, Magnus MC, Kilpi F, Santorelli G, Soares AG, West J, Magnus P, Håberg SE, Tilling K, Lawlor DA, Borges MC, Sanderson E. Evaluating causal associations of chronotype with pregnancy and perinatal outcomes and its interactions with insomnia and sleep duration: a Mendelian randomization study. *BMC Pregnancy Childbirth.* 2024;24:816. doi:10.1186/s12884-024-07023-8.
5. Yang Q, Magnus MC, Kilpi F, Santorelli G, Soares AG, West J, Magnus P, Håberg SE, Tilling K, Lawlor DA, Borges MC, Sanderson E. Evaluating causal associations of chronotype with pregnancy and perinatal outcomes and its interactions with insomnia and sleep duration: a Mendelian randomization study. *BMC Pregnancy Childbirth.* 2024;24:816. doi:10.1186/s12884-024-07023-8.
6. Jiang H, Zhang K, Zhang X. Mendelian randomization analysis of the association between childhood overweight or obesity and gestational diabetes mellitus. Diabetes Obes Metab. 2024 Dec;26(12):6016-6022. doi: 10.1111/dom.15975.
7. Tschiderer L, van der Schouw YT, Burgess S, Bloemenkamp KWM, Seekircher L, Willeit P, Onland-Moret C, Peters SAE. Hypertensive disorders of pregnancy and cardiovascular disease risk: a Mendelian randomisation study. Heart. 2024 Apr 25;110(10):710-717. doi: 10.1136/heartjnl-2023-323490.

8. Hu R, Liang Y, He T, Zhou Y, Lv Y. Causal association of hypertension in family members with pre-eclampsia-eclampsia in pregnant women: A two-sample Mendelian randomization study. Pregnancy Hypertens. 2025;40:101223. doi:10.1016/j.preghy.2025.101223
9. Flatley C, Wang G, Hatton A, Nguyen KM, Hwang DL, Warrington NM. Causal effects of maternal BMI on pregnancy outcomes: a Mendelian randomisation study investigating the mediating role of blood counts. medRxiv [Preprint]. 2025 Aug. doi:10.1101/2025.08.21.25334200
10. Chen W, Luo M, Guo J, Wang S, Yan D, Feng X, Huang Y, Zeng T, Shen L, Zhang R, Yan J, Hu C, Zhang W, Yu X. Metabolic pathways mediating insulin resistance and gestational diabetes mellitus discovered by high-dimensional systematic Mendelian randomization. Cardiovasc Diabetol. 2025;24:195. doi:10.1186/s12933-025-0195-0
11. Xiang S, Jiang Y, Mu F, Wu H, Zhang N. A Systematic Review of Mendelian Randomization in Spontaneous Miscarriage. J Multidiscip Healthc. 2025 Apr 21;18:2237-2246. doi: 10.2147/JMDH.S515367. PMID: 40292224; PMCID: PMC12025826.
12. Zhang X, Huangfu Z, Wang S. Review of Mendelian randomization studies on age at natural menopause. Front Endocrinol (Lausanne). 2023;14:1234324. doi:10.3389/fendo.2023.1234324
13. Dong Y, Hu AQ, Han BX, Cao MT, Liu HY, Li ZG, Li Q, Zheng YJ. Mendelian randomization analysis reveals causal effects of blood lipidome on gestational diabetes mellitus. Cardiovasc Diabetol. 2024;23:335. doi:10.1186/s12933-024-0335-0
14. Liu S, Ruan Q, Dai Z, Chen F, Shi Y. Exploring the causal association between pre-pregnancy obesity and pregnancy-related complications, and mediating pathways of obesity on adverse pregnancy outcomes: Insights from Mendelian randomization analysis. Int J Gynecol Obstet. 2025;171:xxx–xxx. doi: 10.1002/ijgo.70314.
15. Omidiran O, Patel A, Usman S, Mhatre I, Abdelhalim H, DeGroat W, Narayanan R, Singh K, Mendhe D, Ahmed Z. GWAS advancements to investigate disease associations and biological mechanisms. Clin Transl Discov. 2024 Jul;4(3):e296. doi: 10.1002/ctd2.296. Epub 2024 May 1. PMID: 38737752; PMCID: PMC11086745.
16. Mounier N. Mendelian randomization and its application to genome-wide association studies [PhD thesis]. Lausanne: Université de Lausanne, Faculté de biologie et de médecine; 2021
17. Huang Y, Lin W, Zheng X. Causal association between 637 human metabolites and ovarian cancer: a mendelian randomization study. BMC Genomics. 2024 Jan 23;25(1):97. doi: 10.1186/s12864-024-09997-3.
18. Guan SY, Liu YY, Guo Y, Shen XX, Liu Y, Jin HX. Potential biomarkers for clinical outcomes of IVF cycles in women with/without PCOS: Searching with metabolomics. Front Endocrinol (Lausanne). 2022 Sep 2;13:982200. doi: 10.3389/fendo.2022.982200.
19. Guo JZ, Xiao Q, Gao S, Li XQ, Wu QJ, Gong TT. Review of Mendelian Randomization Studies on Ovarian Cancer. Front Oncol. 2021 Aug 11;11:681396. doi: 10.3389/fonc.2021.681396.
20. Zhang Y, Guo J, Zhang N. Mendelian randomization study investigating the relationship between nutrients and polycystic ovary syndrome. Int J Gynecol Obstet. 2024;167:xxx–xxx. doi: 10.1002/ijgo.16029
21. Cai S, Chen M, Xue B, Zhu Z, Wang X, Li J, et al. Retinoic acid enhances ovarian steroidogenesis by regulating granulosa cell proliferation and MESP2/STAR/CYP11A1 pathway. J Adv Res. 2024;58:163-173
22. Sidell N, Rajakumar A. Retinoic Acid Action in Cumulus Cells: Implications for Oocyte Development and In Vitro Fertilization. Int J Mol Sci. 2024;25:1709. doi:10.3390/ijms25031709
23. Zhou J, Jiang S, Liu D, Li X, Zhou Z, Wang Z, Wang H. Bidirectional Mendelian Randomization Analysis of Genetic Proxies of Plasma Fatty Acids and Pre-Eclampsia Risk. Nutrients. 2024;16:3748. doi:10.3390/nu16213748
24. Gray NL, Stoodley I, Wood LG, Collins CE, Brown LJ, Rae KM, Pringle KG, Schumacher TL, The Gomeroi Gaaynggal Advisory Committee. Omega-3 Fatty Acids during Pregnancy in Indigenous Australian Women of the Gomeroi Gaaynggal Cohort. Nutrients. 2023 Apr 18;15(8):1943. doi: 10.3390/nu15081943.
25. Kang Z, Wu Q, Cao J, Zhu M, You Z, Li D, Liu W. Causal relationship between women's reproductive traits and postpartum depression: a multivariate mendelian randomization analysis. Front Genet. 2024;15:1434762. doi:10.3389/fgene.2024.1434762
26. Wang Z, Lu J, Weng W, Fu J, Zhang J. Women's reproductive traits and major depressive disorder: A two-sample Mendelian randomization study. J Affect Disord. 2023 Apr 1;326:139-146. doi: 10.1016/j.jad.2023.01.063. Epub 2023 Jan

27. Lu Z, Sun Y, Liao Y, Kang Z, Feng X, Zhao G, Sun J, Zhang Y, Yue W. Identifying causal associations between early sexual intercourse or number of sexual partners and major depressive disorders: A bidirectional two-sample Mendelian randomization analysis. J Affect Disord. 2023 Jul 15;333:121-129. doi: 10.1016/j.jad.2023.04.079. Epub 2023 Apr 20.
28. Punjala-Patel A, Alvarado S, French A, Lassiter R, Stamilio D. The impact of COVID-19 infection on neonatal birth weight and outcomes. Pregnancy. 2025. doi:10.1002/pmf2.70137.
29. Yi J, Chen L, Meng X, Chen Y. The impact of gestational weeks of Coronavirus disease 2019 (COVID-19) infection on perinatal outcomes. Reprod Health. 2024;21:31. doi:10.1186/s12978-024-031
30. Fang Y, Fang D. Mendelian randomization analysis reveals causal relationship between obstetric-related diseases and COVID-19. Virol J. 2024;21:73. doi:10.1186/s12985-024-073
31. Wastnedge EAN, Reynolds RM, van Boeckel SR, Stock SJ, Denison FC, Maybin JA, Critchley HOD. Pregnancy and COVID-19. Physiol Rev. 2021 Jan 1;101(1):303-318. doi: 10.1152/physrev.00024.2020. Epub 2020 Sep 24.
32. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, VanderWeele TJ, Higgins JPT, Timpson NJ, Dimou N, Langenberg C, Golub RM, Loder EW, Gallo V, Tybjaerg-Hansen A, Davey Smith G, Egger M, Richards JB. Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: The STROBE-MR Statement. JAMA. 2021 Oct 26;326(16):1614-1621. doi: 10.1001/jama.2021.18236.
33. McBride N, Clayton GL, Goncalves Soares A, Yang Q, Bond TA, Taylor A, Chatzigeorgiou C, Aiton E, West J, Magnus MC, Lawlor DA, Borges MC. Cohort Profile: The Mendelian Randomization in Pregnancy (MR-PREG) collaboration – Improving evidence for prevention and treatment of adverse pregnancy and perinatal outcomes [preprint]. 2025. doi:10.1101/2025.03.22.25324447.
34. Barry CS, Lawlor DA, Shapland CY, Sanderson E, Borges MC. Using Mendelian Randomisation to Prioritise Candidate Maternal Metabolic Traits Influencing Offspring Birthweight. Metabolites. 2022 Jun 10;12(6):537. doi: 10.3390/metabo12060537.
35. Yang Q, Magnus MC, Kilpi F, et al. Investigating causal relations between sleep duration and risks of adverse pregnancy and perinatal outcomes: linear and nonlinear Mendelian randomization analyses. BMC Med. 2022;20(1):295. doi:10.1186/s12916-022-02494-y.
36. Taylor K, Wootton RE, Yang Q, Oddie S, Wright J, Yang TC, Magnus M, Andreassen OA, Borges MC, Caputo M, Lawlor DA. The effect of maternal BMI, smoking and alcohol on congenital heart diseases: a Mendelian randomisation study. BMC Med. 2023 Feb 1;21(1):35. doi: 10.1186/s12916-023-02731-y.
37. Pan L, Zhang J, Chen M, Yuan L, Chen R, Zhao L. Genetic Causal Association Between 15 Micronutrients and 12 Obstetric-Related Diseases: A Mendelian Randomization Study. Biol Trace Elem Res. 2025 Aug;203(8):4027-4035. doi: 10.1007/s12011-024-04479-9. Epub 2024 Dec 9.
38. Sauder KA, Harte RN, Ringham BM, Guenther PM, Bailey RL, Alshawabkeh A, Cordero JF, Dunlop AL, Ferranti EP, Elliott AJ, Mitchell DC, Hedderson MM, Avalos LA, Zhu Y, Breton CV, Chatzi L, Ran J, Hertz-Picciotto I, Karagas MR, Sayarath V, Hoover J, MacKenzie D, Lyall K, Schmidt RJ, O'Connor TG, Barrett ES, Switkowski KM, Comstock SS, Kerver JM, Trasande L, Tylavsky FA, Wright RJ, Kannan S, Mueller NT, Catellier DJ, Glueck DH, Dabelea D; Program Collaborators for Environmental influences on Child Health Outcomes (ECHO). Disparities in Risks of Inadequate and Excessive Intake of Micronutrients during Pregnancy. J Nutr. 2021 Nov 2;151(11):3555-3569. doi: 10.1093/jn/nxab273.
39. Ahmed F. Micronutrients and Pregnancy. Nutrients. 2022 Jan 28;14(3):585. doi: 10.3390/nu14030585.
40. D'Urso S, Wootton RE, Ask H, Brito Nunes C, Andreassen OA, Hwang L-D, et al. Mendelian randomization analysis of maternal coffee consumption during pregnancy on offspring neurodevelopmental difficulties in the Norwegian Mother, Father and Child Cohort Study (MoBa). Psychol Med. 2024;54(12):3548-3561. doi:10.1017/S0033291724002216.

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