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Original Article

Inflammatory cytokines, metabolites, and pre-eclampsia: a two-sample Mendelian randomization study

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Abstract: Objectives: Pre-eclampsia (PE) is a leading cause of maternal and fetal mortality, with inflammatory dysregulation implicated in its pathogenesis. This Mendelian randomization (MR) study aimed to investigate the causal effects of 91 inflammatory cytokines on PE and to identify potential mediating metabolites. Methods: We conducted a two-sample MR analysis using genome-wide association study data from European-ancestry populations: including 91 inflammatory cytokines (14,824 participants), 1,400 plasma metabolites (8,299 participants), and PE (2,355 cases; 264,887 controls). Instrumental variables were selected at $P < 1 \times 10^{-5}$. Causal estimates were assessed using inverse-variance weighted regression, with additional sensitivity analyses to evaluate MR assumptions. Mediation analysis was subsequently performed to identify relevant metabolite pathways. Results: We identified two novel risk factors and two protective factors for PE: genetically proxied elevations in fibroblast growth factor 5 (FGF-5) and Matrix metalloproteinase-1 (MMP-1) increased PE risk, whereas interleukin-10 (IL-10) and interleukin-20 (IL-20) were protective. Importantly, this is the first MR study to identify N-acetyl-L-alanine (ALA) as a significant mediator of cytokine effects in PE. ALA mediated 5.56% of the effect of FGF-5, revealing a pathway whereby elevated FGF-5 reduces ALA levels and consequently increases PE risk. Conclusions: This study establishes FGF-5 and MMP-1 as novel causal risk factors for PE, while IL-10 and IL-20 exert protective effects. The identification of ALA as a partial mediator of FGF-5 uncovers a new metabolic-inflammatory pathway in the pathogenesis of PE. These findings highlight potential biomarkers and therapeutic targets for the prevention and treatment of PE.

Keywords: Inflammatory factors, pre-eclampsia (PE), Mendelian randomization (MR), causality, metabolites

Introduction

Hypertensive disorders of pregnancy (HDP), including pre-eclampsia (PE), eclampsia, gestational hypertension, and chronic hypertension, are major contributors to maternal and fetal morbidity and mortality worldwide [1]. Among these conditions, PE is the most clinically significant, complicating 5-7% of pregnancies and accounting for more than 70,000 maternal and 500,000 fetal deaths annually [2]. PE is characterized by hypertension and proteinuria and, in severe cases, may progress to multi-organ dysfunction. Although delivery generally alleviates symptoms, PE can persist into the postpartum period or arise de novo after childbirth, contributing to substantial peripartum morbidity [3]. Furthermore, HDP - particularly preterm PE - is associated with increased long-term risks of cardiovascular and cerebrovascular disease [4].

The pathophysiology of PE involves a complex interplay of placental dysfunction, endothelial impairment, and systemic inflammation [5]. Placental-derived factors contribute to oxida-

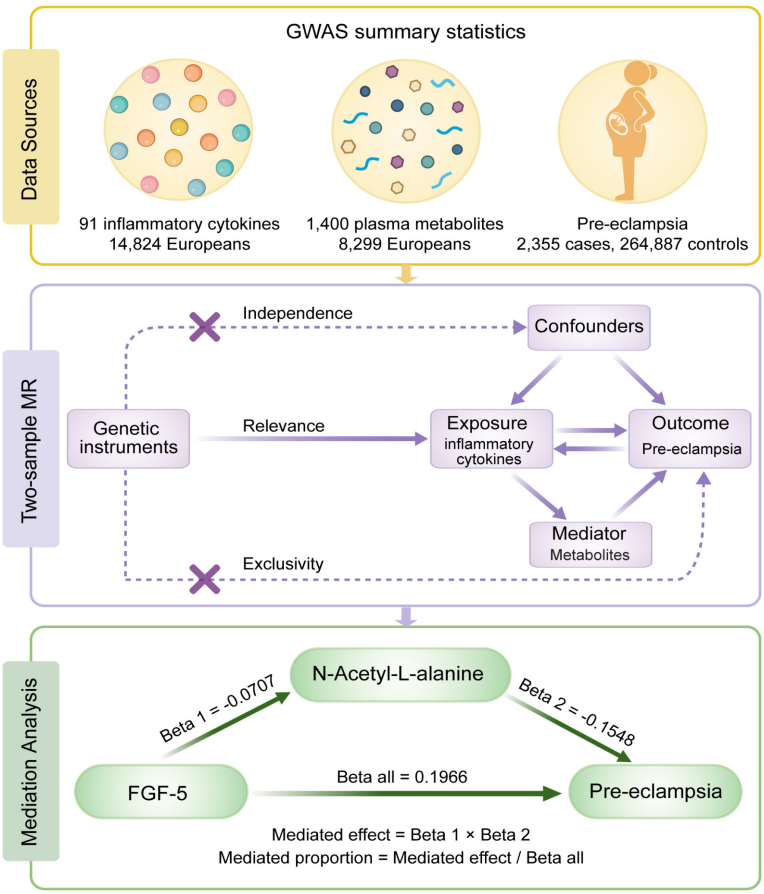


Figure 1. Flowchart of the Mendelian randomization (MR) analyses conducted in this study. Published genome-wide association study (GWAS) summary statistics were first obtained for 91 inflammatory cytokines, 1,400 plasma metabolites (including 1,091 metabolites and 309 metabolite ratios), and pre-eclampsia (PE). Two-sample MR analyses were then performed to evaluate the causal relationships between inflammatory cytokines, plasma metabolites, and PE. Finally, mediation analyses were concucted to quantify the proportion of the cytokine-to-PE causal effect mediated by plasma metabolites, thereby identifying potential biological pathways.

tive stress, stimulate the release of anti-angiogenic mediators such as sFlt-1, and amplify inflammatory signaling, collectively driving endothelial injury [6]. Dysregulated immune responses further worsen placental malperfusion and promote fetal growth restriction [7]. Although observational studies have reported associations between specific inflammatory cytokines - such as macrophage inflammatory protein-1β (MIP-1β) [8] and interleukin-18 (IL-18) [9] - and HDP, confounding variables and reverse causality limit the ability of such studies to establish definitive causal relationships.

While randomized controlled trials (RCTs) remain the gold standard for establishing causal inference, their implementation in pregnancy is often limited by ethical and practical constraints. Mendelian randomization (MR) has therefore emerged as a powerful alternative, leveraing genetic variants as instrumental variables to infer causality while minimizing confounding [10].

In this study, we applied a two-sample MR framework to systematically evaluate the causal effects of 91 inflammatory cytokines on PE risk. The selection of these cytokines was derived from a recent large-scale proteomic genome-wide association study (GWAS) [11], providing unprecedented breadth of coverage and enabling the discovery of novel causal factors in PE. Furthermore, we integrated metabolomic data to investigate potential mediating pathways, thereby offering new insights into the mechanistic links between inflammation and PE. Collectively, our findings aim to identify novel biomarkers and therapeutic targets for the early detection and intervention of PE.

Materials and methods

Study design

The overall MR analysis framework is illustrated in **Figure 1**. We first obtained published GWAS summary statistics for 91 inflammatory cytokines, 1,400 plasma metabolites (including 1,091 metabolites and 309 metabolite ratios), and PE. We then performed two-sample MR analyses to evaluate the causal relationships between inflammatory cytokines, plasma metabolites, and PE. Finally, a two-step MR mediation analysis was conducted to quantify the proportion of the cytokine-PE causal effect mediated by plasma metabolites, thereby identifying potential biological pathways.

Data sources

Details of all GWAS summary statistics used in this study are summarized in **Table 1**. The GWAS dataset for 91 circulating inflammatory

Table 1. Summary of genome-wide association study (GWAS) datasets used in this study

Traits	Sample size	Ancestry	Accession codes
91 inflammatory cytokines	14,824 participants	European	GCST90274758 - GCST90274848
1091 plasma metabolites and 309 plasma metabolite ratios	8,299 participants	European	GCST90199621 - GCST90201020
Pre-eclampsia	267,242 participants (2,355 cases; 264,887 controls)	European	ebi-a-GCST90018906

cytokines was obtained from a comprehensive meta-analysis published by Zhao JH in 2023 [11], comprising 11 cohorts and a total of 14,824 participants of European ancestry (accession numbers GCST90274758 - GCST90274848). Summary statistics for 1091 plasma metabolites and 309 plasma metabolite ratios were retrieved from the GWAS catalog (https://www.ebi.ac.uk/gwas) under accession numbers GCST90199621 - GCST90201020, encompassing 8299 European participants [12]. The PE dataset was derived from ebi-a-GCST90018906, also based on a European population, inclusing 2,355 PE cases, 264,887 controls, and 24,165,538 SNPs. As this study relies solely on published GWAS summary statistics, no additional ethical approval or patient consent was required.

Selection of instrumental variables (IVs)

MR analyses rely on three key assumptions: (1) the relevance assumption, which requires that the genetic instrumental variables (IVs) are strongly associated with the exposure; (2) the independence assumption, which states that the IVs are not associated with any potential confounders; and (3) the exclusion restriction assumptions, which requires that the IVs influence the outcome exclusively through the specified exposure. Firstly, SNPs strongly associated with each exposure were selected as IVs using a threshold of $P < 1 \times 10^{-5}$. This threshold was chosen to ensure an adequate number of instruments while maintaining a strong genetic relevance to the exposure. To satisfy the independence assumption, linkage disequilibrium clumping was performed using threshold of kb > 10000 and $r^2 < 0.001$. In addition, the F statistic for each IV was calculated, and only strong instruments (F > 10) were retained for subsequent MR analysis.

Mendelian randomization (MR) analysis

Using two-sample MR analyses, we evaluated the causal effects of 91 inflammatory cytokines and 1,400 plasma metabolites on PE. Potential PE-associated inflammatory cytokines and plasma metabolites were initially screened using a significance threshold of $P < 0.05$.

Reverse Mendelian randomization (MR) analysis

To examine whether PE exerts a causal effect on the inflammatory cytokines identified in the initial analysis ($P < 0.05$), we conducted a reverse MR analysis. In this framework, PE-associated SNPs were treated as instrumental variables (IVs), PE served as the exposure, and the previously identified inflammatory cytokines were considered the outcomes. For the primary reverse MR analysis, we applied the same significance threshold for IV selection as in the forward MR ($P < 1 \times 10^{-5}$). In addition, a supplementary analysis was performed using a more lenient threshold ($P < 1 \times 10^{-4}$) to identify potential causal signals that might be overlooked under the stricter criterion.

Mediation analysis

Mediation analysis is used to evaluate whether the effect of an exposure on an outcome operates through an intermediate variable (mediator), thereby providing insights into the potential mechanisms by which the exposure influences the outcome [13]. In the two-sample MR framework, inflammatory cytokines and serum metabolites that showed significant associations with PE were included in the mediation analysis. We first assessed whether these metabolites were causally associated with the cytokines. When such an association was identified, mediation MR analysis was conducted to determine whether the cytokines exerted their effects on PE and through specific serum metabolites and to quantify the extent of mediation.

Sensitivity analysis

To ensure the robustness of the MR results, several sensitivity analyses were conducted,

including the MR-Egger intercept test, the MRPRESSO global test, the Cochran Q-test, and the leave-one-out analyses [14]. Potential horizontal pleiotropy was evaluated using both the MR-Egger regression intercept and the MRPRESSO global test [15, 16], with $P > 0.05$ indicating no evidence of horizontal pleiotropy. Leave-one-out analyses were performed to assess whether any single SNP disproportionately influenced the causal estimates. In addition, heterogeneity was assessed using the Cochran Q statistic, with $P > 0.05$ indicating no heterogeneity. When heterogeneity was detected ($P < 0.05$), SNPs with highly significant associations were considered for exclusion, or a random-effects model was applied to obtain more reliable mr estimates [17]. The symmetry of the funnel plots was also examinedas an additional assessment of heterogeneity. Finally, prior to all MR analyses, exposure and outcome datasets were harmonized, including allele alignment and appropriate handling of palindromic SNPs.

Statistical methods

All MR analyses were performed using the "TwoSampleMR" package (version 0.5.6) in R (version 4.3.1). The inverse-variance weighted (IVW) method with random effects was used as the primary analytical approach, accompanied by four supplementary methods - weighted median, MR-Egger, simple mode, and weighted mode - to assess the robustness of the causal estimates [18]. Because the accuracy of the IVW method depends on the assumption of no horizontal pleiotropy, MR-Egger regression was applied throughout the MR workflow to evaluate the intercept and test for directional pleiotropy. In addition, the MR-PRESSO global test was conducted using the "MRPRESSO" package (version 1.0) to detect and, if necessary, correct for horizontal pleiotropy [16]. Heterogeneity among the instrumental variables was assessed using Cochran's Q test under both the IVW and MR-Egger frameworks. Sensitivity analyses were further conducted using the leave-one-out method to determine whether the causal relationship between the exposure and outcome was driven by any single SNP. Mediation analysis was implemented using a two-step MR approach. The mediation effect was calculated using the product-of-coefficients method, specifically, the product of β_1 (the causal effect of the inflammatory cytokine on the plasma metabolite) and β_2 (the causal effect of the plasma metabolite on PE). The proportion of the mediated effect was estimated as $(\beta_1 \times \beta_2)/\beta\_total$, where β_total represents the total causal effect of the inflammatory cytokine on PE.

Results

Causal effects of inflammatory cytokines on pre-eclampsia

We evaluated the causal effects of 91 inflammatory cytokines on PE risk using inverse-variance weighted (IVW) regression as the primary analytical method. Four cytokines showed significant associations with PE (**Figure 2A**). Specifically, genetically predicted elevated levels of fibroblast growth factor 5 (FGF-5) and Matrix metalloproteinase-1 (MMP-1) were associated with increased risk of PE, while elevated levels of interleukin 10 (IL-10) and interleukin 20 (IL-20) were associated with decreased risk. Sensitivity analyses, including MR-Egger regression and heterogeneity tests, supported the robustness of these findings, with no evidence of horizontal pleiotropy (all $P > 0.05$, **Table 2**). Although heterogeneity was detected for FGF-5, this concern was mitigated by applying a random-effects IVW model. Leave-one-out analysis further confirmed that no single SNP disproportionately influenced the results.

Reverse causality analysis

To assess potential reverse causation, we performed reverse MR analyses for the four cytokines identified in the primary analysis. Using the strict IV seletion threshold ($P < 1 \times 10^{-5}$), no significant causal effects of PE on FGF-5, IL-10, or IL-20 were detected, although a marginal association was observed for MMP-1. When a more lenient threshold ($P < 1 \times 10^{-4}$) was applied, no reverse causal effects were found for any of the cytokines (**Figure 2B**), thereby supporting the directionality and robustness of our primary MR findings.

Identification of mediating metabolites

We next sought to identify plasma metabolites that might mediate the effects of the four cytokines on PE. Initial screening identified 70 metabolites associated with PE risk ($P < 0.05$, IVW method), including 40 risk metabolites and

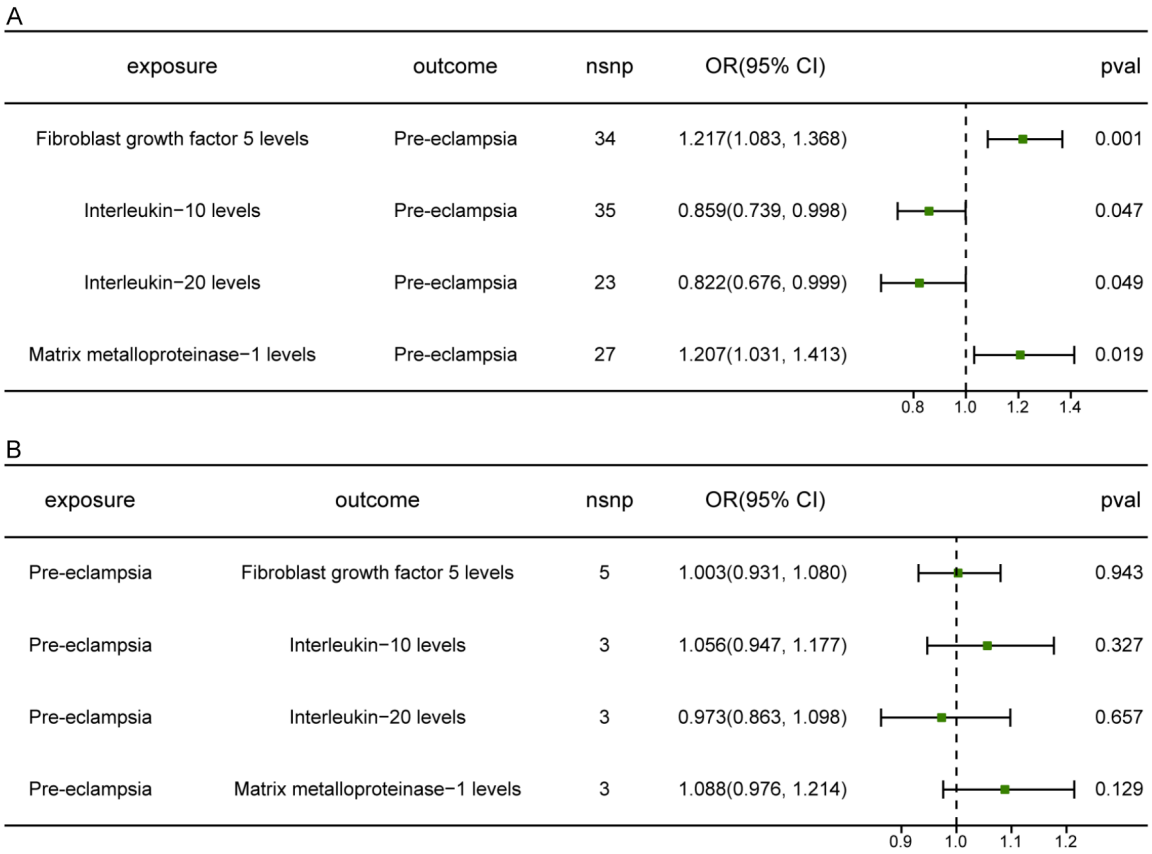


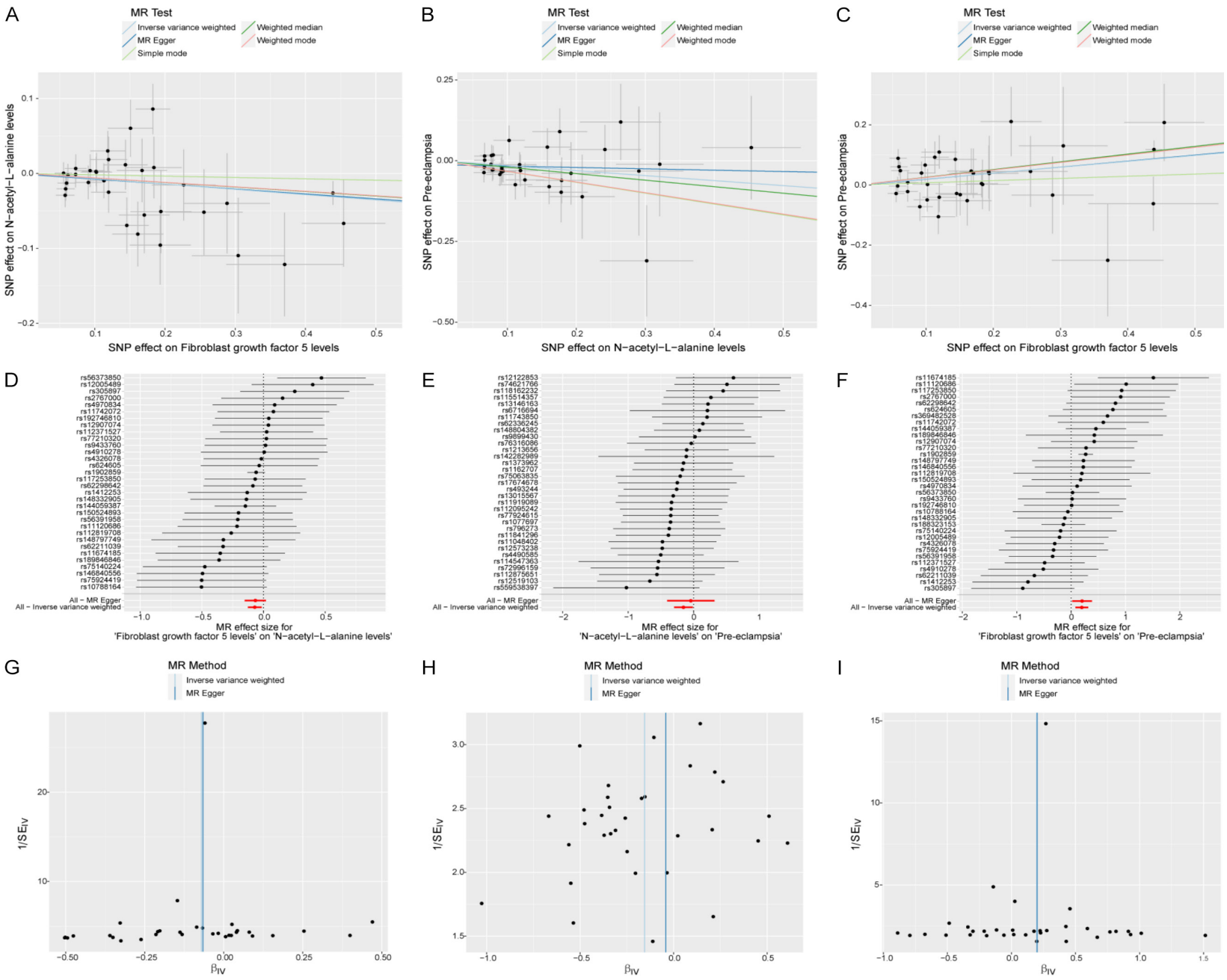
Figure 2. Causal associations between inflammatory cytokines and pre-eclampsia (PE). (A). Forest plot of forward MR analyses assessing the causal effects of inflammatory cytokines on PE. (B). Forest plot of reverse MR analyses evaluating the potential causal effects of PE on inflammatory cytokines.

Table 2. The heterogeneity and pleiotropy in Mendelian randomization (MR) analysis

Exposure	Outcome	Heterogeneity test				Pleiotropy test				
		IVW		MR Egger		MR Egger regression			MR PRESSO	
		Cochran Q	pval	Cochran Q	pval	Intercept	se	pval	RSSobs	pval
IL-10	Pre-eclampsia	31.834	0.574	31.661	0.534	0.007	0.016	0.680	33.671	0.600
IL-20	Pre-eclampsia	14.507	0.883	13.853	0.876	-0.022	0.027	0.428	15.731	0.886
Matrix metalloproteinase-1 (MMP1)	Pre-eclampsia	12.490	0.988	12.416	0.983	-0.004	0.016	0.788	13.421	0.989
Fibroblast growth factor 5 (FGF-5)	Pre-eclampsia	47.452	0.049	47.445	0.039	-0.001	0.015	0.949	53.232	0.090
FGF-5	N-acetyl-L-alanine (ALA)	34.287	0.313	34.262	0.270	-0.001	0.007	0.883	35.734	0.378
ALA	Pre-eclampsia	22.193	0.902	21.753	0.891	-0.013	0.019	0.512	23.613	0.925

30 protective metabolites (see Supplementary Table 1 for full list).

We then examined the causal effects of the four cytokines on these 70 metabolites. Notably, a significant negative causal relationship was observed between FGF-5 and N-acetyl-L-alanine (ALA) levels ($P < 0.05$). In addition, lower ALA levels were associated with increased PE risk ($P < 0.05$, **Figure 3**). Together, these findings indicate that FGF-5 may increase PE risk partly by reducing circulating ALA levels (**Figure 4**). The proportion of the total effect of FGF-5 on PE mediated by ALA was 5.56% (mediation effect = 0.0109, 95% CI: 0.00146-0.0204, $P = 0.024$, **Table 3**). Sensitivity analyses confirmed the absence of pleiotropy or heterogeneity in these relationships (all $P > 0.05$, **Table 2**). No significant mediating metabolites were identified for MMP-1, IL-10, or IL-20.


A
MR Test
Inverse variance weighted
MR Egger
Simple mode
Weighted median
Weighted mode
SNP effect on N−acetyl−L−alanine levels
SNP effect on Fibroblast growth factor 5 levels
B
MR Test
Inverse variance weighted
MR Egger
Simple mode
Weighted median
Weighted mode
SNP effect on Pre-eclampsia
SNP effect on N−acetyl−L−alanine levels
C
MR Test
Inverse variance weighted
MR Egger
Simple mode
Weighted median
Weighted mode
SNP effect on Pre-eclampsia
SNP effect on Fibroblast growth factor 5 levels
D
All − MR Egger
All − Inverse variance weighted
MR effect size for
'Fibroblast growth factor 5 levels' on 'N−acetyl−L−alanine levels'
E
All − MR Egger
All − Inverse variance weighted
MR effect size for
'N−acetyl−L−alanine levels' on 'Pre-eclampsia'
F
All − MR Egger
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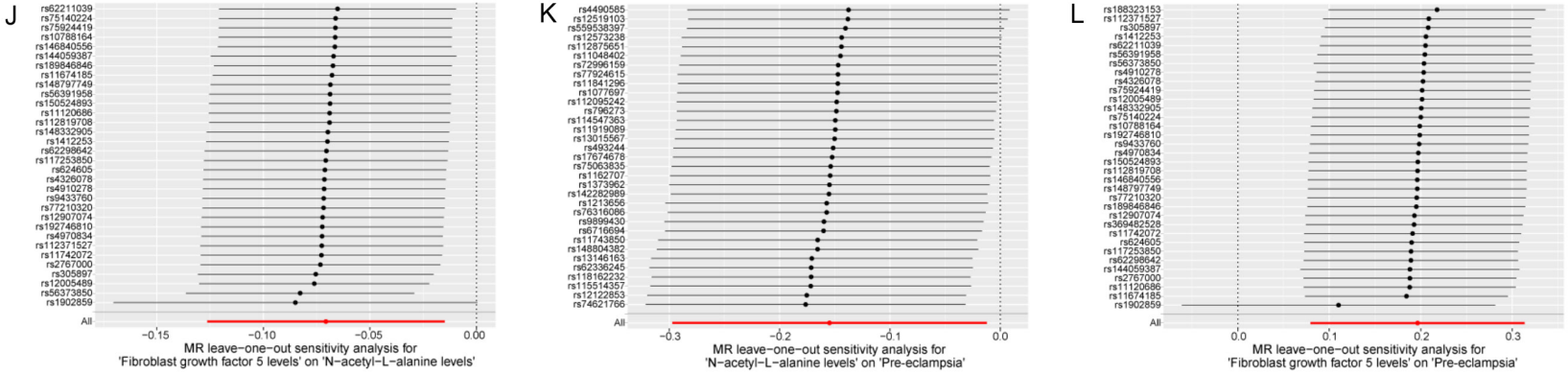

Figure 3. MR results of inflammatory cytokines, metabolic mediators, and PE. Scatter plots showing MR estimates for (A) Fibroblast growth factor 5 (FGF-5) on N-acetyl-L-alanine (ALA) levels, (B) ALA on PE, and (C) FGF-5 on PE. Forest plots showing MR estimates for (D) FGF-5 on ALA, (E) ALA on PE, and (F) FGF-5 on PE. Funnel plots assessing potential heterogeneity for (G) FGF-5 on ALA, (H) ALA on PE, and (I) FGF-5 on PE. Leave-one-out analyses evaluating the influence of individual SNPs for (J) FGF-5 on ALA, (K) ALA on PE, and (L) FGF-5 on PE.

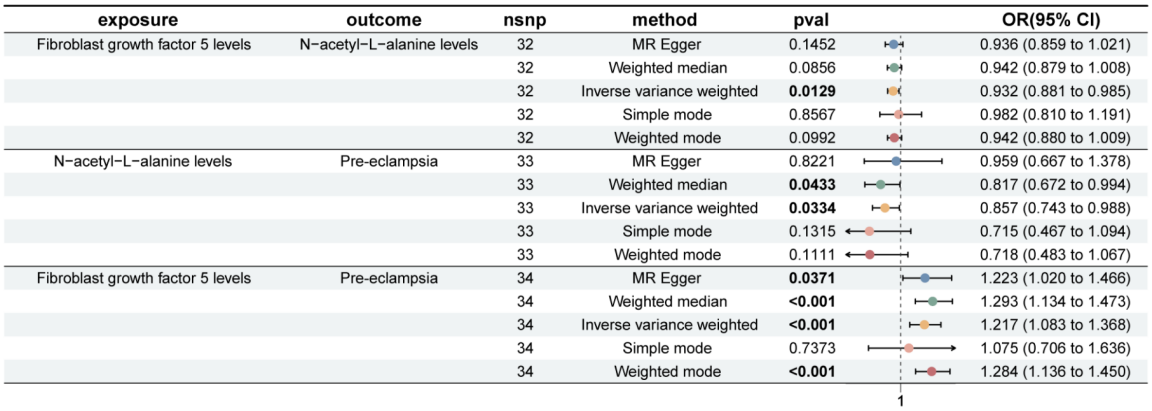

Figure 4. Forest plot illustrating the causal relationships among FGF-5, ALA, and PE. FGF-5 increases the risk of PE by recucing circulating ALA levels.

Table 3. The mediation effect of N-acetyl-L-alanine (ALA) levels on the causal effect of FGF-5 in PE

Inflammatory cytokines	Metabolites	Outcome	Beta all	Mediated effect	Mediated proportion	pval
FGF-5	ALA	Pre-eclampsia	0.1966	0.0109 (0.00146, 0.0204)	5.56%	0.024

Discussion

Our two-sample Mendelian randomization study provides novel genetic evidence supporting causal roles for specific inflammatory cytokines in PE and identifies, for the first time, a plasma metabolite that mediates one of these pathways. The key findings are as follows: (1) genetically proxied elevations in FGF-5 and MMP-1 increase the risk of PE, whereas IL-10 and IL-20 are protective effects; (2) reverse MR analyses largely ruled out reverse causation; and (3) ALA mediates approximately 5.56% of the causal effect of FGF-5 on PE risk, revealing a previously unrecognized metabolic-inflammatory pathway involved in PE pathogenesis.

FGF-5 has been implicated in hypertension and cancer progression, and recent studies have also suggested its involvement in PE susceptibility across diverse populations [19-21]. Our study expands on this evidence by demonstrating that its pathogenic effect is partially mediated through ALA. This metabolite may compete with L-alanine for nutrient receptors, potentially disrupting cellular metabolic pathways. Previous reports have associated elevated ALA with immunosuppressive states, such as reduced IFN-γ production in latent tuberculosis [22], and a recent MR study identified ALA as a mediator between T-cell markers and Guillain-Barré syndrome [23]. Take together, our findings suggest that FGF-5 - associated increases in ALA may reflect a state of metabolic dysregulation within placental or endothelial compartments during PE, contributing to impaired trophoblast function and vascular pathology.

MMP-1 plays a key role in extracellular matrix remodeling and vascular dysfunction. Elevated MMP-1 levels in PE may promote vascular collagen degradation, increase vascular sensitivity to vasoconstrictors such as angiotensin II, and facilitate neutrophil recruitment [24, 25]. The absence of an identified metabolite mediator for MMP-1 in our analysis suggests that its effects may act through direct tissue remodeling or through additional molecular pathways not captured by the available metabolomic data.

The protective roles of IL-10 and IL-20 underscore the complex immunoregulatory balance required for a successful pregnancy [26]. IL-10 supports placentation and suppress excessive inflammation [27], whereas IL-20, despite its reported anti-angiogenic properties [28], may contribute to modulating immune tolerance or preventing aberrant angiogenesis in the maternal-fetal interface. Our MR analysis provides robust genetic evidence supporting the protective functions of both cytokines in PE.

The identification of FGF-5, MMP-1, IL-10, and IL-20 as causal contributors to PE, together with the mediating role of ALA, opens new avenues for PE risk stratification and intervention. These molecules represent promising biomarkers for early detection. Therapeutic strategies aimed at targeting the FGF-5 - ALA axis, or modulating IL-10/IL-20 signaling, may offer novel approaches for the prevention or management of PE, particularly amng individuals with high-risk pregnancies.

However, this study has several limitations. First, all datasets were derived from individuals of European ancestry, which may limit the generalizability of the findings to other populations. Second, the metabolomic dataset provides only partial coverage of the human metabolome, and additional mediators may therefore remain undetected. Finally, MR cannot capture pregnancy-specific dynamic changes or delineate the precise tissue contexts in which these causal pathways operate.

Conclusions

In conclusion, this MR study provides robust genetic evidence for causal effects of specific inflammatory cytokines (FGF-5, MMP-1, IL-10, and IL-20) on pre-eclampsia risk and identifies N-acetyl-L-alanine (ALA) as a partial mediator of the FGF-5 pathway. These findings advance our understanding of the inflammatory mechanisms underlying PE pathogenesis and highlight promising avenues for developing novel biomarkers for early detection, as well as potential therapeutic strategies targeting these cytokine pathways or their downstream metabolic effects. Future research should aim to validate these findings in diverse populations, elucidate the precise biological mechanisms involved, and translate these insights into clinical applications to help reduce the burden of pre-eclampsia.

Acknowledgements

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Disclosure of conflict of interest

None.

Abbreviations

HDP, Hypertensive disorders of pregnancy; PE, Pre-eclampsia; MIP-1β, Macrophage inflammatory protein-1β; IL-18, Interleukin-18; RCTs, Randomized controlled trials; MR, Mendelian randomization; SNPs, Single-nucleotide polymorphisms; GWAS, Genome-wide association study; IVs, Instrumental variables; IVW, Inverse variance weighted method; FGF-5, Fibroblast growth factor 5; MMP-1, Matrix metalloproteinase-1; ALA, N-acetyl-L-alanine.

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Supplementary Table 1. The causal link between metabolites and pre-eclampsia (PE)

Exposure	Outcome	nsnp	OR (95% CI)	pval
Carnitine levels	Pre-eclampsia	26	1.200 (1.073, 1.342)	0.001
Imidazole lactate levels	Pre-eclampsia	28	1.116 (1.012, 1.231)	0.028
1-stearoyl-2-oleoyl-GPS (18:0/18:1) levels	Pre-eclampsia	21	0.704 (0.595, 0.833)	0.000
3-indoxyl sulfate levels	Pre-eclampsia	23	1.202 (1.020, 1.417)	0.028
1-arachidonylglycerol (20:4) levels	Pre-eclampsia	24	0.863 (0.754, 0.989)	0.034
Glutamine degradant levels	Pre-eclampsia	27	1.155 (1.000, 1.332)	0.049
Beta-hydroxyisovaleroylcarnitine levels	Pre-eclampsia	36	1.138 (1.009, 1.284)	0.035
Tetradecanedioate (C14-DC) levels	Pre-eclampsia	19	1.140 (1.036, 1.254)	0.007
Hexadecanedioate (C16-DC) levels	Pre-eclampsia	23	1.156 (1.044, 1.280)	0.005
Gamma-glutamylalanine levels	Pre-eclampsia	17	1.263 (1.056, 1.511)	0.011
21-hydroxypregnenolone disulfate levels	Pre-eclampsia	38	1.128 (1.009, 1.262)	0.034
1-lignoceroyl-GPC (24:0) levels	Pre-eclampsia	16	0.799 (0.640, 0.997)	0.047
1-(1-enyl-stearoyl)-GPE (p-18:0) levels	Pre-eclampsia	23	0.840 (0.706, 1.000)	0.050
N-oleoyltaurine levels	Pre-eclampsia	20	1.153 (1.006, 1.321)	0.041
Imidazole propionate levels	Pre-eclampsia	25	1.227 (1.039, 1.450)	0.016
Alliin levels	Pre-eclampsia	20	0.825 (0.724, 0.941)	0.004
Margaroylcarnitine (C17) levels	Pre-eclampsia	26	0.816 (0.704, 0.947)	0.007
(R)-3-hydroxybutyrylcarnitine levels	Pre-eclampsia	24	1.244 (1.040, 1.487)	0.017
2-hydroxydecanoate levels	Pre-eclampsia	18	0.788 (0.652, 0.953)	0.014
2-aminoheptanoate levels	Pre-eclampsia	27	0.833 (0.718, 0.966)	0.016
17alpha-hydroxypregnanolone glucuronide levels	Pre-eclampsia	33	1.137 (1.019, 1.269)	0.022
Octadecenedioylcarnitine (C18:1-DC) levels	Pre-eclampsia	17	1.135 (1.022, 1.260)	0.018
Sphingomyelin (d18:2/14:0, d18:1/14:1) levels	Pre-eclampsia	22	0.710 (0.589, 0.856)	0.000
Carnitine C14:1 levels	Pre-eclampsia	34	0.851 (0.733, 0.987)	0.033
Sphingomyelin (d18:1/20:1, d18:2/20:0) levels	Pre-eclampsia	29	0.867 (0.764, 0.983)	0.026
Glycodeoxycholate 3-sulfate levels	Pre-eclampsia	31	1.121 (1.033, 1.216)	0.006
1-linoleoyl-GPG (18:2) levels	Pre-eclampsia	25	1.163 (1.038, 1.302)	0.009
1-palmitoyl-2-oleoyl-GPI (16:0/18:1) levels	Pre-eclampsia	26	1.202 (1.055, 1.371)	0.006
1-palmitoleoyl-2-linolenoyl-GPC (16:1/18:3) levels	Pre-eclampsia	20	1.185 (1.035, 1.357)	0.014
Linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2] levels	Pre-eclampsia	35	0.891 (0.808, 0.983)	0.021
Hexadecenedioate (C16:1-DC) levels	Pre-eclampsia	31	1.151 (1.054, 1.257)	0.002
Perfluorooctanoate (PFOA) levels	Pre-eclampsia	23	0.821 (0.683, 0.987)	0.036
N-acetyl-isoputreanine levels	Pre-eclampsia	38	1.134 (1.024, 1.256)	0.016
N-lactoyl isoleucine levels	Pre-eclampsia	17	0.800 (0.653, 0.980)	0.031
Glucuronide of piperine metabolite C17H21NO3 (4) levels	Pre-eclampsia	21	1.172 (1.060, 1.296)	0.002
3-hydroxy-2-methylpyridine sulfate levels	Pre-eclampsia	21	0.813 (0.677, 0.976)	0.026
Cis 3,4-methyleneheptanoate levels	Pre-eclampsia	26	1.199 (1.048, 1.371)	0.008
Metabolonic lactone sulfate levels	Pre-eclampsia	31	1.097 (1.025, 1.173)	0.008
S-carboxyethylcysteine levels	Pre-eclampsia	23	1.282 (1.080, 1.521)	0.005
5-oxoproline levels	Pre-eclampsia	25	0.893 (0.802, 0.994)	0.039
N-acetyl-L-alanine levels	Pre-eclampsia	33	0.857 (0.743, 0.988)	0.033
Creatine levels	Pre-eclampsia	25	0.889 (0.792, 0.998)	0.046
4-acetaminophen sulfate levels	Pre-eclampsia	26	1.180 (1.029, 1.354)	0.018
Linoleate (18:2n6) levels	Pre-eclampsia	22	1.244 (1.011, 1.530)	0.039
Phenylalanine levels	Pre-eclampsia	21	1.186 (1.004, 1.402)	0.045
Mannose levels	Pre-eclampsia	26	0.863 (0.751, 0.993)	0.039
X-07765 levels	Pre-eclampsia	25	1.169 (1.011, 1.352)	0.035

X-13723 levels	Pre-eclampsia	14	0.750 (0.626, 0.898)	0.002
X-15728 levels	Pre-eclampsia	32	0.859 (0.743, 0.992)	0.039
X-21471 levels	Pre-eclampsia	28	1.148 (1.029, 1.282)	0.014
X-21733 levels	Pre-eclampsia	29	0.782 (0.661, 0.924)	0.004
X-21470 levels	Pre-eclampsia	18	1.187 (1.051, 1.341)	0.006
X-23659 levels	Pre-eclampsia	28	1.123 (1.011, 1.248)	0.031
X-24243 levels	Pre-eclampsia	20	1.253 (1.057, 1.485)	0.009
X-24546 levels	Pre-eclampsia	28	1.172 (1.050, 1.308)	0.005
Adenosine 5’-diphosphate (ADP) to creatine ratio	Pre-eclampsia	22	1.141 (1.014, 1.284)	0.029
N-acetylputrescine to (N(1) + N(8))-acetylspermidine ratio	Pre-eclampsia	32	1.117 (1.018, 1.225)	0.019
Arachidonate (20:4n6) to oleate to vaccenate (18:1) ratio	Pre-eclampsia	20	0.886 (0.791, 0.993)	0.038
Arachidonate (20:4n6) to pyruvate ratio	Pre-eclampsia	16	0.852 (0.733, 0.991)	0.037
Serine to pyruvate ratio	Pre-eclampsia	19	0.834 (0.703, 0.989)	0.037
5-oxoproline to citrate ratio	Pre-eclampsia	16	0.863 (0.766, 0.972)	0.015
Oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [2] ratio	Pre-eclampsia	28	1.128 (1.012, 1.256)	0.029
Spermidine to N-acetylputrescine ratio	Pre-eclampsia	22	0.874 (0.773, 0.989)	0.033
Adenosine 5’-monophosphate (AMP) to valine ratio	Pre-eclampsia	19	0.808 (0.664, 0.984)	0.034
Adenosine 5’-monophosphate (AMP) to glutamate ratio	Pre-eclampsia	23	0.777 (0.641, 0.943)	0.010
Salicylate to caprylate (8:0) ratio	Pre-eclampsia	24	1.191 (1.029, 1.380)	0.019
Inosine to theophylline ratio	Pre-eclampsia	22	0.851 (0.744, 0.975)	0.020
Glucose-to-mannose ratio	Pre-eclampsia	25	1.176 (1.038, 1.332)	0.011
Phosphate to 5-oxoproline ratio	Pre-eclampsia	25	1.170 (1.037, 1.319)	0.011
Fructose to maltose ratio	Pre-eclampsia	23	1.158 (1.005, 1.335)	0.043