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REVIEW

Identification of Biomarkers for Preeclampsia Based on Metabolomics

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Background: Preeclampsia (PE) is a significant cause of maternal and neonatal morbidity and mortality worldwide. However, the pathogenesis of PE is unclear and reliable early diagnostic methods are still lacking. The purpose of this review is to summarize potential metabolic biomarkers and pathways of PE, which might facilitate risk prediction and clinical diagnosis, and obtain a better understanding of specific metabolic mechanisms of PE.

Methods: This review included human metabolomics studies related to PE in the PubMed, Google Scholar, and Web of Science databases from January 2000 to November 2021. The reported metabolic biomarkers were systematically examined and compared. Pathway analysis was conducted through the online software MetaboAnalyst 5.0.

Results: Forty-one human studies were included in this systematic review. Several metabolites, such as creatinine, glycine, L-isoleucine, and glucose and biomarkers with consistent trends (decanoylcarnitine, 3-hydroxyisovaleric acid, and octenoylcarnitine), were frequently reported. In addition, eight amino acid metabolism-related, three carbohydrate metabolism-related, one translation-related and one lipid metabolism-related pathways were identified. These biomarkers and pathways, closely related to renal dysfunction, insulin resistance, lipid metabolism disorder, activated inflammation, and impaired nitric oxide production, were very likely to contribute to the progression of PE.

Conclusion: This study summarized several metabolites and metabolic pathways, which may be associated with PE. These high-frequency differential metabolites are promising to be biomarkers of PE for early diagnosis, and the prominent metabolic pathway may provide new insights for the understanding of the pathogenesis of PE.

Keywords: gestational hypertension, metabolite, biomarker, prediction

Introduction

Preeclampsia (PE), a disorder of pregnancy associated with new-onset hypertension after 20 gestational weeks, is a progressive and heterogeneous disease involving multiple organ systems. Different classifications of PE based on onset of clinical symptoms [early-onset PE (EO-PE)<34 weeks and late-onset PE (LO-PE) ≥34 weeks; preterm PE <37 weeks and term PE ≥37 weeks] or severity of disease (severe and mild) had been proposed.[1] PE complicates about 3–5% of all pregnancies and is one of the leading causes of maternal and perinatal morbidity and mortality.[2] In addition, the adverse impact of PE may persist even after delivery, as evidence suggests that women who suffered from PE and their corresponding children tend to have an increased risk of cardiovascular disease later in life.[3] Despite decades of research, the pathogenesis of this disease remains unclear. The only effective treatment for PE is timely termination of pregnancy, which often results in adverse neonatal outcomes (such as preterm birth), and the only helpful prevention comes from low-dose aspirin prophylaxis.[4] Therefore, identification of possible predictive markers for PE is necessary for early identification and prevention of women at risk.

Over the course of pregnancy, mothers face a unique physiological challenge that requires complex metabolic adaptations to support fetal growth and development.[5] Regarding the complexity and heterogeneity of PE, it is unlikely

to find a single biomarker that could predict all sorts of PE disorders. As an emerging high-throughput technique, metabolomics is dedicated to simultaneously and quantitatively assessing all small molecule metabolites within specific biological samples, enabling the delineation of the metabolic phenotype and phenotypic perturbations in various obstetric diseases, including PE.[6] Therefore, it has the potential to identify the metabolites and metabolic pathways related to PE, which may advance more comprehensive understanding of the pathophysiology of PE and facilitate its diagnosis and prevention.

In this study, we reviewed all metabolomics studies related to PE from January 2000 to November 2021 and comprehensively summarized and analyzed the information from these studies. The aim of this review was to identify metabolic biomarkers that may facilitate risk prediction, clinical diagnosis, and obtain an improved understanding of specific metabolic mechanisms of PE.

Methods
Literature Search
We obtained relevant publications by searching the PubMed, Google Scholar, and Web of Science databases from January 2000 to November 2021. The searching terms were ("metabolomics" or "metabonomics" or "metabolome" or "metabolic profiling" or "metabolic signature" or "metabolic biomarker" or "metabolic profile") AND ("pre-eclampsia" [MeSH]). Two researchers searched the articles independently and a third researcher made a final decision in cases of disagreement.

Inclusion and Exclusion Criteria
The inclusion criteria were as follows: 1) metabolomics studies on PE, 2) full text available in English, and 3) studies clearly recording the positive or negative relationship between metabolite markers and PE.

We included all the relevant metabolomics studies on PE except 1) animal studies, 2) review articles, 3) studies evaluating drug effects, 4) results reporting unidentified metabolites, and 5) studies only reporting insignificant metabolites.

Information Extraction
After reading the full articles and supplementary materials, the following information was extracted from the final retained studies: first author, title, publication date, publication journal, study subjects (sample sizes, singleton/twins), diagnostic criteria of PE, analytical platforms, biological specimen, study design, subtypes of PE, gestational age of sample collection, and potential metabolic biomarkers with directions of change (increase or decrease in concentration). In addition, studies by the same first or corresponding author were judged whether there were overlaps in content.

Statistical Analysis
Frequencies on biological samples, sampling time, subtypes of PE, and significant metabolites along with their changing trends were counted and graphed. All the metabolites were matched with their unique Human Metabolome Database (HMDB) IDs to unify the metabolites with different terminologies but with the same chemical structure in different literature. Pathway analysis, including enrichment analysis and topology analysis, was performed using the MetaboAnalyst 5.0 online software (https://www.metaboanalyst.ca).[7] The significant pathways were selected based on the criteria of the raw $P <0.05$.

Results
Study Characteristics
After literature searching and screening, a total of 41 studies[8–48] were included. Characteristics of the 41 studies are presented in Table 1. Blood (serum, plasma, and cord plasma) is the mostly used biospecimen (in 33 studies), followed by placenta (in 4 studies) and urine (in 1 study). Meanwhile, 2 studies simultaneously collected urine and serum, and 1 study used both placenta and plasma (Figure 1A). These included articles involving different etiological subtypes of PE,

Table 1 Characteristics of the 41 Included Studies

First Author (Year)	Country	S/Twin	Gestational Age	Outcome	Case	Control	Bio-Specimen	Analytic Platform	Targeted/ Untargeted	Up-Regulated	Down-Regulated
Kivelä (2021)[8]	Finland	S	Predo:13,20,28w Radiel:13,23,35w (pooled across the 3 measurement points)	PE	43 (Predo) 11 (Radiel)	254 (Predo) 292 (Radiel)	Serum	NMR	Targeted	Extremely large VLDL; very large VLDL; large VLDL; medium VLDL; small VLDL; triglycerides in VLDL; total triglycerides; monounsaturated fatty acids; L-isoleucine; L-leucine	None
Jääskeläinen (2021)[9]	Finland	S	10–15w	PE	46	53	Serum	LC-MS	Untargeted	Monoacylglyceride 18:1; urea; glycerophosphocholine	None
			23–41w	PE	57	14	Serum	LC-MS	Untargeted	None	None
Harville (2021)[10]	USA	S	6^{+1}–13^{+6}w	PE	18	109	Serum	LC-MS and NMR	Untargeted	Bolasterone; cerasinone	L-Asparagine; N-dimethylglycine; trimethylamine
Tan (2020)[11]	China	S	26.6±1.7w(case) 26.1±1.4w (control)	PE	29	29	Serum	UPLC-MS	Targeted	LysoPC(18:0); LysoPC(22:6); phytosphingosine; palmitic acid	Behenic acid; 14-methyl hexadecanoic acid; 1,25-dihydroxyvitamin D3-26,23-lactone
Sovio (2020)[12]	UK	S	36w	Term PE	165	323	Serum	UPLC-MS /MS	Untargeted	sFlt-1/PlGF; 4-hydroxyglutamate; C-glycosyltryptophan; 1-palmitoyl-2-linoleoyl-GPE (16:0/18:2)	None
Lee (2020)[13]	Korea	S	16–24w	PE	33	66	Plasma	GC-TOF MS and LC-Orbitrap MS	Untargeted	3-Phosphoglycerate; glutamate; palmitoleic acid; xanthine; LysoPE C16:1; LysoPE C17:0; LysoPE C20:0; PC C32:1; PC C32:2; PI C38:3; SM C30:1; SM C34:1	Lyxose; propane-1,3-diol; LysoPC C19:0; LysoPC C22:1; OxPC C38:4 + 1O; OxPI C38:4 + 1O; PE C23:1e; PE C24:1e; PE C34:3e; PI C36:2; SM C28:1
			Within 3 d of delivery	PE	13	21	Plasma	GC-TOF MS and LC-Orbitrap MS	Untargeted	3,6-Anhydro-d-galactose; erythritol; 2-deoxytetronic acid; isomaltose; myo-inositol; thymine; xylitol; FAHFA C18:0; OxPC C38:4 + 1O(1Cyc); OxPE C38:3 + 1O; OxPI C38:4 + 1O; PC C36:5e; PC C38:5; PC C40:7; PE C36:4; SM C30:1; SM C32:1; SM C33:2; SM C34:2; SM C38:1	None

Table 1 (Continued).

First Author (Year)	Country	S/Twin	Gestational Age	Outcome	Case	Control	Bio-Specimen	Analytic Platform	Targeted/ Untargeted	Up-Regulated	Down-Regulated
Kenny (2020)[14]	UK	S	15±1w	PE	97	335	Plasma	LC-MS /MS	Targeted	Dilinoleoyl-glycerol	1-Heptadecanoyl-2-hydroxy-sn-glycero-3 phosphocholine; PIGF
				Preterm PE	23	335	Plasma	LC-MS /MS	Targeted	Dilinoleoyl-glycerol; choline; 2-hydroxybutanoic acid; NG-monomethyl-l-arginine; decanoylcarnitine	PIGF
				Term PE	74	335	Plasma	LC-MS /MS	Targeted	L-Isoleucine; decanoylcarnitine	1-Heptadecanoyl-2-hydroxy-sn-glycero-3 phosphocholine
Hong (2020)[15]	USA	S	Within 1–3 d after delivery	Preterm PE	79	980	Plasma	LC-MS	Untargeted	Symmetric dimethylarginine; C2 carnitine; xanthosine; xanthine; C34:1 DAG; C34:2 DAG; C36:3 DAG; C38:4 DAG; C22:5 LPC; C38:6 PC; C40:9 PC; C50:2 TAG; C52:3 TAG; creatine; creatinine; cystine; glutamine; homocitrulline; N-acetyltryptophan; N-acetylputrescine; N6,N6,N6-trimethyllysine; pyroglutamic acid; C3 carnitine; C5-DC carnitine; octanoylcarnitine; 4-acetamidobutanoate; imidazole propionate; 6.8-dihydroxypurine; uric acid; L-carnitine; C16:0 ceramide; C34:1 DAG/TAG fragment; C36:2 DAG; C38:5 DAG; C22:6 LPC; C22:6 LPE; C40:6 PC; C52:2 TAG; methylguanidine	Anthranilic acid; bilirubin; cytosine; 1-methylguanine; 7-methylguanine; cortisol; C14:0 CE; C18:2 CE; C16:0 CE; C18:0 CE; C18:3 CE; cortisone
Sander (2019)[16]	UK	Mainly S	35.9±2.8w(case) 36.7±3.2w (control)	PE	32	35	Plasma	LC-MS	Untargeted	Taurodeoxycholic acid isomer; methionine sulfoxide; 3-hydroxyanthranilic acid; N1-methyl-pyridone-carboxamide; urocanic acid; phosphatidylinositol isomer (32:1); diacylglycerol isomer(32:2); diacylglycerol isomer(32:1)	Hydroxyhexacosanoic acid isomer

Liu (2019)[17]	China	S	34w	PE	10	10	Plasma	LC-MS/MS	Targeted	16-HDoHE; 8-HEPE; LTB4; 8-HETE	18-HEPE; maresin; 14,15-DiHETE; 8,9-EEQ; 17-HDoHE
Lee (2019)[18]	Korea	S	Prior to preterm delivery or at the time of cesarean delivery	PE	14	9	Plasma	GC-MS	Targeted	Cholesterol/desmosterol; cholesterol/7-dehydrocholesterol	Individual cholesterol esters/cholesterol; total cholesterol esters/cholesterol
Do Nascimento (2019)[19]	Brazil	Not mentioned	Not mentioned	PE	14	10	Plasma	LC-HRMS	Targeted	None	L-Leucine; γ-aminobutyric acid; L-serine; L-isoleucine; L-methionine; L-valine; glycine; L-betaine; L-histidine; L-lysine; L-arginine; L-alanine
Austdal (2019)[20]	Norway	S	Before delivery	PE	62	65	Serum	HR-MAS MRS	Targeted	Glycerophosphocholine; phosphocholine; aspartate; creatine	Ethanolamine; dihydroxyacetone; glutamate; taurine; L-isoleucine; L-valine; L-threonine; L-lysine; glucose; 3-hydroxybutyric acid; ascorbate; glycine
Yang (2018)[21]	China	Not mentioned	Immediately after delivery	PE	16	16	Placenta	GC-MS	Targeted	Octadecanoic acid; 5,8,11-cis-eicosatrienoic acid; cis-11,14-eicosadienoic acid; 11,14,17-cis-eicosatrienoic acid; 9,12,15-cis-octadecatrienoic acid; 8,11,14-cis-eicosatrienoic acid; hexadecanoic acid; 7,10,13,16,19-cis-docosapentaenoic acid	Heneicosanoic acid; 11,14-eicosadienoic acid; 11-trans-octadecenoic acid; tridecanoic acid; heptanoic acid; nonanoic acid; decanoic acid
Powell (2018)[22]	Australia	S	26–41w	PE	17	82	Serum	NMR	Untargeted	Creatinine; acetyl groups	Acetic acid; 3-methylhistidine

(*Continued*)

Table 1 (Continued).

First Author (Year)	Country	S/Twin	Gestational Age	Outcome	Case	Control	Bio-Specimen	Analytic Platform	Targeted/ Untargeted	Up-Regulated	Down-Regulated
Jääskeläinen (2018)[23]	Finland	S	After delivery	PE	42	53	Cord plasma	LC-MS	Untargeted	Urea; creatine; creatinine; homocitrulline; guanidinopropionate; L-carnitine; trimethyllysine; γ-butyrobetaine; butyrylcarnitine; octenoylcarnitine; choline; 5-aminovaleric acid betaine; N-methyl-2-pyridone-5-carboxamide; acetylputrescine; 4-acetamidobutanoate; indolecarboxylic acid; indolelactic acid; phosphatidylcholines (PCs)[PC (16:1/18:1)PC(16:0/16:0)PC(16:0/18:1)]	4-Pyridoxic acid
Zhou (2017)[24]	China	S	Immediately after the cesarean section	Severe PE	11	11	Placenta	GC-MS	Targeted	2-Phosphoenolpyruvate; β-citryl -L-glutamate; ornithine; L-threonine; glutamine; L-asparagine; L-tyrosine; L-lysine; methionine; cysteine; L-phenylalanine; L-leucine; L-isoleucine; glycine; palmitelaidate; DPA; adrenat; γ-linoleate; 9-heptadecenoate; DHA; dihomo-γ-linoleate; 11,14-eicosadienoate; arachidonate; cis-vaccenate; linoleate; trans-vaccenate; 11,14,17-eicosatrienoate; heptadecanoate; pentadecanoate; nonadecanoate; margarate; myristate; arachidate; behenate; stearate; 10,13-dimethyltetradecanoate; oxalate; cabamate	Citraconate; caprylate

Kelly (2017)[25]	USA	S	10–18w	PE	47	62	Plasma	LC-MS	Untargeted	16-α-hydroxypregnenolone; ins-1-P-Cer(d18:1/22:0); C38:3 PC; 13'-carboxy-γ-tocopherol; C40:0 PC plasmalogen; dimethamine; quinoline; montecristin; terpinolene oxide; C34:2 PI; C50:1 TAG; C40:6 PC; C50:1 TAG; 1-(10-methylhexadecanyl)-2-(8-[3]-ladderane-octanyl)-sn-glycerophosphocholine; C16:3 CE; TAG source fragment; C54:1 TAG; C50:1 TAG; C37:3 PS; 13'-carboxy-γ-tocopherol; C32:1 PC; C18:0 LysoPE; C50:2 TAG; C38:5 DAG; C54:2 TAG; TAG source fragment; saccharin; cohibin A; chlormezanone; C32:1 PC; mabioside D; C36:4 DAG; artemoin A; quinoline; C16:0 LysoPC	Lutein; 3-hydroxy-10-apo-b, y-carotenal; GABA; N-phenylacetylphenylalanine; C40:1 PS; methylthioadenosine_isomer; C18:0 MAG
Chen (2017)[26]	China	Not mentioned	21.7–27.9w (case) 18.6–27.4w (control)	PE	20	20	Serum	LC-Q-TOF-MS	Untargeted	Phytosphingosine; phenylethylamine; sphinganine; phosphocholine; indole; ubiquinone-1; L-phenylalanine; PI (22:0/22:0); PI(20:4(5Z,8Z,11Z,14Z)/0:0); PE(P-16:0/0:0); PE(18:1(9Z)/0:0); PC(14:0/0:0); PC(13:0/0:0); palmitoylcarnitine; palmitic amide; MG(0:0/18:2(9Z,12Z)/0:0); MG(0:0/16:0/0:0); linoleyl-L-carnitine; Cer (d18:1/26:1(17Z)); C17 sphinganine; C16 sphinganine	Palmitic acid; ribose; PS(18:2 (9Z,12Z)/0:0); PS(20:2(11Z,14Z)/0:0)
Bahado-Singh (2017)[27]	UK	S	Within 3 d of assessment	LO-PE	59	115	Serum	NMR	Untargeted	L-Carnitine; 2-hydroxybutyric acid; citric acid; glucose; L-leucine; lactate; L-valine; 3-hydroxybutyric acid; 3-hydroxyisovaleric acid; pyruvate; methylhistidine	Dimethylamine

(*Continued*)

Table 1 (Continued).

First Author (Year)	Country	S/Twin	Gestational Age	Outcome	Case	Control	Bio-Specimen	Analytic Platform	Targeted/ Untargeted	Up-Regulated	Down-Regulated
Bahado-Singh (2017)[28]	UK	S	11–14w	Term PE	35	63	Serum	DI-LC-MS /MS	Targeted	PC aa C40:6	Glucose; putrescine
			11–14w	Term PE	35	63	Serum	^{1}H NMR	Targeted	None	Urea; dimethyl sulfone
			30–34w	Term PE	35	63	Serum	DI-LC-MS /MS	Targeted	None	Serotonin; t4-OH-pro; hexose
			30–34w	Term PE	35	63	Serum	^{1}H NMR	Targeted	Acetic acid; dimethyl sulfone	None
Koster (2015)[29]	Netherlands	S	8^{+0}–13^{+6}w	EO-PE	68	500	Serum	UPLC-MS /MS	Targeted	Hexanoylcarnitine; octenoylcarnitine; L-octanoylcarnitine; decenoylcarnitine; decanoylcarnitine; dodecenoylcarnitine; lauroylcarnitine; tetradecenoylcarnitine; hexadecenoylcarnitine	Isobutyrylcarnitine; linoleylcarnitine; stearoylcarnitine
				LO-PE	99	500	Serum	UPLC-MS /MS	Targeted	Octenoylcarnitine; L-octanoylcarnitine; decenoylcarnitine; decanoylcarnitine; dodecenoylcarnitine	Linoleylcarnitine; palmitoylcarnitine; oleylcarnitine; stearoylcarnitine
Bahado-Singh (2015)[30]	UK	S	Within 3 d of assessment	EO-PE	50	108	Serum	NMR	Untargeted	3-Hydroxyisovaleric acid; betaine; glucose; propylene glycol	Acetic acid; acetone; choline; formate; glycerol; glycine; isopropanol; L-phenylalanine; succinate
Austdal (2015)[31]	Norway	S	After delivery	PE	19	15	Placenta	HR-MAS MRS	Untargeted	None	Glutamine; glutamate; taurine; L-valine; 3-hydroxybutyrate; ascorbate
Austdal (2015)[32]	Norway	S	11^{+0}–13^{+6}w	PE	26	561	Urine	^{1}H NMR	Untargeted	Creatinine; glycine; α-hydroxyisobutyrate; L-histidine; dimethylamine; 4-deoxythreonic acid	Hippurate; L-threonine; proline betaine; creatine; lactate
				PE			Serum	^{1}H NMR	Untargeted	Signals from triglycerides; 3-hydroxybutyric acid	Pyruvate; phosphatidylcholine; lactate

Moon (2014)[33]	Korea	Not mentioned	22.2–40.5w (case) 24.1–37.6w (control)	PE	30	30	Serum	GC-MS	Targeted	Androsterone; etiocholanolone; 6β-OH-androstenedione; 11β-OH-androstenedione; pregnenolone; progesterone; 17α-hydroxypregnenolone; 17α-hydroxyprogesterone; 6β-hydroxycortisol; 7α-hydroxycholesterol; 7β-hydroxycholesterol; 4β-hydroxycholesterol; 20α-hydroxycholesterol; 24S-hydroxycholesterol; 27-hydroxycholesterol	16α-OH-dehydroepiandrosterone; 16α-OH-androstendione; cholesterol
Kuc (2014)[34]	Netherlands	S	8^{+0}–13^{+6}w	EO-PE	68	500	Serum	UPLC-MS/MS	Targeted	None	Taurine; L-asparagine
				LO-PE	99	500	Serum	UPLC-MS/MS	Targeted	None	Glycylglycine
Korkes (2014)[35]	Brazil	Not mentioned	Immediately after cesarean delivery	PE	10	10	Placenta	MALDI-MS	Untargeted	Glycerophosphoserines [GP03]-(PS); macrolide lactone polyketide [PK04]	Glycerophosphoethanolamines [GP02]-(PEt); glycerophosphoglycerols [GP04]-(PG); glycerophosphoinositols [GP06]-(PI); glycerophosphoinositol monophosphates [GP07]; diradylglycerols [GL02]-(DG); triradylglycerols [GL03]; acidic glycosphingolipids [SP06]- (GM3); steroid conjugates [ST05]; other acyl sugars [SL05]; flavonoids [PK12]
			At the time of delivery	PE	10	10	Plasma	MALDI-MS	Untargeted	Glycerophosphocholines [GP01]-(PC); glycerophosphoserines [GP03]-(PS); glycerophosphates [GP10]-(PAc); phosphosphingolipids [SP03]-(SM); neutral glycosphingolipids [SP05]; steroid conjugates [ST05]; flavonoids [PK12]	Glycerophosphoglycerols [GP04]-(PG); sterols [ST01]; other acyl sugars [SL05]; glycerophosphoethanolamines [GP02]-(PEt)

(*Continued*)

Table 1 (Continued).

First Author (Year)	Country	S/Twin	Gestational Age	Outcome	Case	Control	Bio-Specimen	Analytic Platform	Targeted/ Untargeted	Up-Regulated	Down-Regulated
Austdal (2014)[36]	Norway	Not mentioned	35.9(21.7–37.9) w (case) 35.2(18.6–37.4) w(control)	PE	10	10	Urine	NMR	Untargeted	Isobutyrate; dimethylamine	Glycine; p-cresol sulfate; hippurate; L-histidine; L-asparagine; trigonelline; glucose
							Serum	NMR	Untargeted	L-Histidine	None
Senyavina (2013)[37]	Russia	Not mentioned	Not mentioned	PE	6	25	Serum	HPLC	Targeted	Xanthine; uric acid	Hypoxanthine
Diaz (2013)[38]	Portugal	Not mentioned	14–26w	Preterm PE	9	84	Urine	^{1}H NMR	Untargeted	N-methyl-2-pyridone-5-carboxamide; 3-methylhistidine; 4-deoxyerythronic acid; cis-aconitate; citric acid; glutamine; hippurate; indoxyl sulphate; N-methylnicotinamide; sucrose; U35	2-Ketoglutarate; 4-OH-hippurate; acetic acid; L-carnitine; creatinine; formate; fumarate; galactose; L-isoleucine; lactose; phenylacetyl-glutamine; p-cresol sulphate; scyllo-ino; succinate; trigonelline; L-tyrosine; U14; U4; correlates to trigonelline
Bahado-Singh (2013)[39]	UK	S	11^{+0}–13^{+6}w	LO-PE	30	59	Serum	NMR	Targeted	Glycerol; 1-methylhistidine; L-valine; L-carnitine; acetone; isopropanol; pyruvate; 3-hydroxyisovaleric acid; glucose; 2-hydroxybutyric acid; creatinine; creatine; citrate; 3-hydroxybutyric acid	Trimethylamine; acetamide; dimethylamine
Bahado-Singh (2012)[40]	UK	S	11^{+0}–13^{+6}w	EO-PE	30	60	Serum	NMR	Untargeted	3-Hydroxyisovaleric acid; glucose; glutamine; propylene_glycol; pyruvate; trimethylamine	Acetic acid; L-alanine; choline; formate; glycerol; glycine; L-isoleucine; isopropanol; L-leucine; methionine; L-phenylalanine; serine; succinate; L-threonine
Odibo (2011)[41]	USA	S	11–14w	PE	41	41	Serum	LC-MS /MS	Targeted	C6OH (hydroxyhexanoylcarnitine); L-phenylalanine; glutamate; L-alanine	None

| Kenny (2010)[42]	Ireland	S	15±1w	PE	60	60	Plasma	UPLC-MS	Untargeted	Monosaccharide(s); decanoylcarnitine; oleic acid; docosahexaenoic acid and/or docosatriynoic acid; γ-butyrolactone and/or axolan-3-one; 2-oxovaleric acid and/or axo-methylbutanoic acid; acetoacetic acid; hexadecenoyl-eicosatetraenoyl-sn-glycerol; di-(octadecadienoyl)-sn-glycerol; sphingosine 1-phosphate; sphinganine 1-phosphate; vitamin D3 derivatives	5-Hydroxytryptophan; methylglutaric acid and/or adipic acid
Turner (2010)[43]	UK	Not mentioned	Not mentioned	PE	11	11	Plasma	¹H NMR	Targeted	L-Histidine; L-tyrosine; L-phenylalanine	None
Kenny (2008)[44]	UK	Not mentioned	245(186–272) d(case) 243(186–282) d(control)	PE	20	20	Plasma	UPLC-MS	Targeted	L-Alanine; 2-hydroxy-3-methyl-butanoic acid; 2-ethyl-3-hydroxypropionic acid; 2-oxoglutaric acid; glutamic acid; xylitol or ribitol; uric acid; creatinine	None
Turner (2007)[45]	UK	Not mentioned	Not mentioned	PE	11	11	Plasma	¹H NMR	Untargeted	None	VLDL lipids; lactate; fucose; L-threonine; glycoprotein; L-proline; 3-hydroxybutyric acid
Jain (2014)[46]	USA	Not mentioned	Immediately after delivery	PE	3	5	Placenta	ESI/MS	Untargeted	Free fatty acids	Plasmenyl phosphatidylethanolamine
McBride (2021)[47]	UK	S	26–28w	PE	74	1454	Plasma	NMR	Untargeted	None	None
He (2021)[48]	USA	S	Not mentioned	Severe PE	44	20	Plasma	LC-MS /MS	Untargeted	None	LPC 15:0; LPC 20:5; PC35:1e; LPE 18:2; LPE 20:4; cholesterol ester 22:5; ceramide d30:1; LPC 16:0/PC 16:0e; LPC 16:1/PC 16:1e; LPC 18:2e/PC18:2e

Abbreviation: S, singleton.
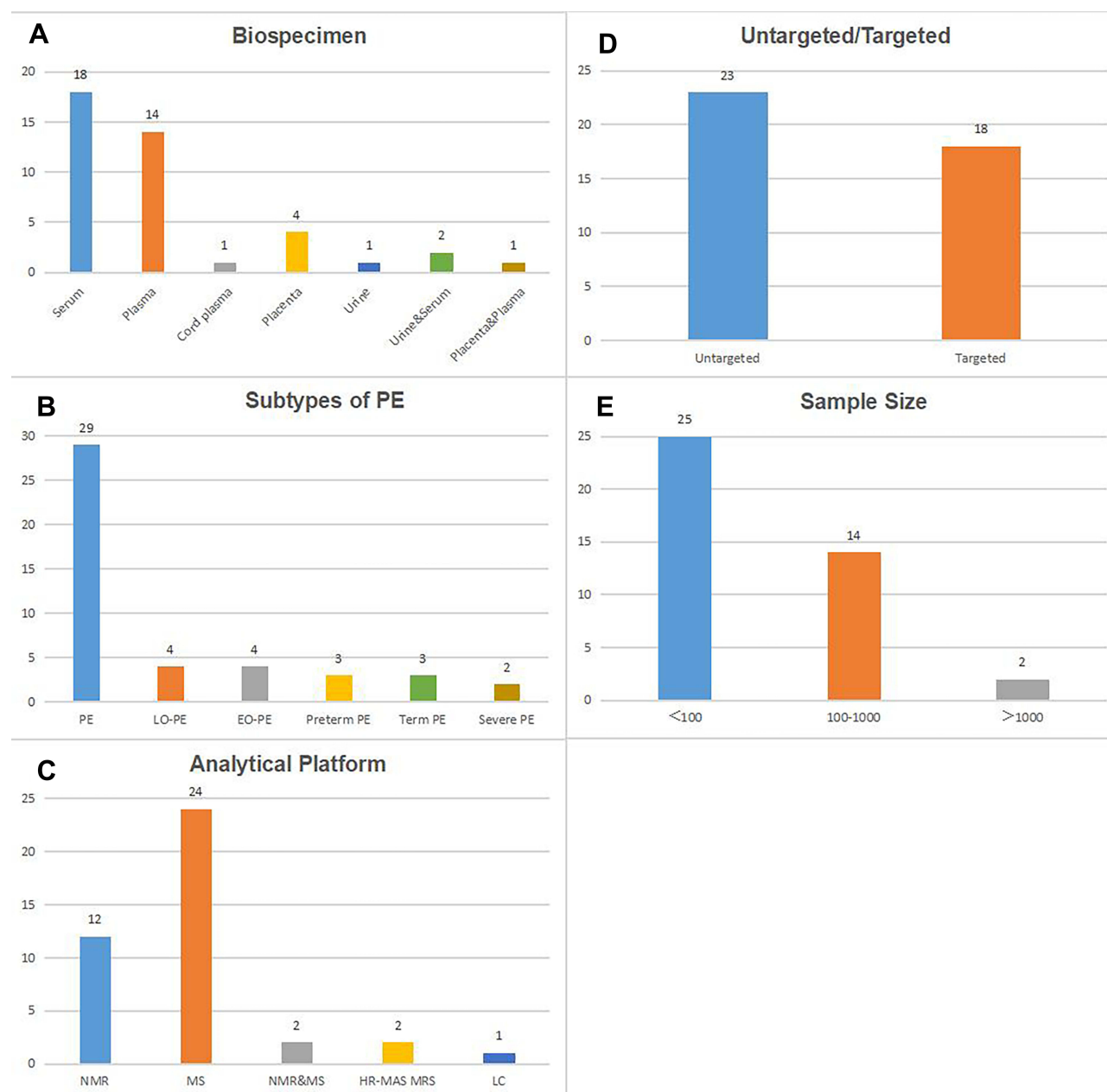
Figure 1 Numbers of the included studies according to biospecimen (**A**), subtypes of PE (**B**), analytical platform (**C**), untargeted/targeted (**D**) and sample size (**E**).

including PE (in 29 studies), LO-PE (in 4 studies), EO-PE (in 4 studies), preterm PE (in 3 studies), term PE (in 3 studies) and severe PE (in 2 studies) (Figure 1B). Regarding the analytic platform, 12 studies used nuclear magnetic resonance (NMR), 24 used mass spectrometry (MS), 2 used both NMR and MS, 2 used high resolution magic angle spinning magnetic resonance spectroscopy (HR-MAS MRS), the remaining 1 used liquid chromatography (LC) (Figure 1C). Besides, 23 studies were untargeted and the remaining 18 studies were targeted (Figure 1D). The total sample sizes ranged from 8 to 1528, with 16 studies including more than 100 subjects (Figure 1E). The majority of the studies were performed among singleton pregnancies.

High-Frequency Metabolic Biomarkers of PE

A total of 415 metabolic biomarkers were reported in the 41 included articles. Amino acids (eg, creatinine, glycine, L-isoleucine, creatine, L-phenylalanine, L-histidine, L-leucine, L-valine, and L-glutamine) are among the most frequently reported altered

metabolites that were related with PE. Meanwhile, lipids[8,18] and related metabolites, such as phosphatidylcholines,[13,15,23,25,26,28,32,48] lysophosphatidylcholine,[11,13,15,23,25,48] glycerophosphocholine,[9,20,25,35] acylcarnitines,[15] and sphingolipids[13] were generally detected. Thirty-three metabolites were reported in ≥ 3 studies (Table 2). Creatinine, glycine, L-isoleucine, and glucose were the most reported metabolites (appeared in 7 articles). Decanoylcarnitine, 3-hydroxyisovaleric acid, xanthine, and octenoylcarnitine showed a consistent upward trend in PE patients versus controls, while succinate, formate, and taurine were consistently reported to be down-regulated in patients with PE across different biospecimens.

Among the 33 high-frequency metabolites, 12 metabolites were just identified by single type of technology. For instance, decanoylcarnitine and octenoylcarnitine were identified by LC-MS, and other ten metabolites (acetic acid, 3-hydroxyisovaleric acid, pyruvate, dimethylamine, lactate, glycerol, hippurate, isopropanol, succinate, and formate) were found by NMR.

Potential of Metabolic Marker Panels to Predict and Classify PE

Several studies have assessed the potential of metabolic biomarker panels to predict and diagnose PE (Table 3). Lee et al[13] used a panel of five metabolites (SM C28:1, SM C30:1, LysoPC C19:0, LysoPE C20:0, and propane-1,3-diol) to

Table 2 High-Frequency Metabolic Biomarkers of PE

No.	Metabolites	Hits	Up	Down
1	Creatinine	7	6 plasma[15c 44] serum[22 39b] cord plasma[23] urine[32]	1 urine[38c]
2	Glucose	7	4 serum[27b 30a 39b 40a]	3 serum[20 28b] urine[36]
3	L-Isoleucine	7	3 serum[8] plasma[14d] placenta[24e]	4 plasma[19] serum[20 40a] urine[38c]
4	Glycine	7	2 placenta[24e] urine[32]	5 plasma[19] serum[20 30a 40a] urine[36]
5	L-Phenylalanine	6	4 placenta[24e] serum[26 41] plasma[43]	2 serum[30a 40a]
6	Decanoylcarnitine*	5	5 plasma[14cd] serum[29ab 42]	
7	L-Carnitine	5	4 plasma[15c] cord-plasma[23] serum[27b 39b]	1 urine[38c]
8	Creatine	5	4 plasma[15c] serum[20 39b] cord-plasma[23]	1 urine[32]
9	L-Histidine	5	3 urine[32] serum[36] plasma[43]	2 plasma[19] urine[36]
10	L-Leucine	5	3 serum[8 27b] placenta[24e]	2 plasma[19] serum[40a]
11	3-Hydroxybutyric acid	5	3 serum[27b 32 39b]	2 serum[20] plasma[45]
12	L-Valine	5	2 serum[27b 39b]	3 serum[20] plasma[19] placenta[31]
13	L-Threonine	5	1 placenta[24e]	4 serum[20 40a] urine[32] plasma[45]
14	Acetic acid**	5	1 serum[28b]	4 serum[22 30a 40a] urine[38c]
15	3-Hydroxyisovaleric acid**	4	4 serum[27b 30a 39b 40a]	
16	Pyruvate**	4	3 serum[27b 39b 40a]	1 serum[32]
17	Glutamine	4	3 plasma[15c] placenta[24e] serum[40a]	1 placenta[31]
18	Dimethylamine**	4	2 urine[32 36]	2 serum[27b 39b]
19	Choline	4	2 plasma[14d] cord-plasma[23]	2 serum[30a 40a]
20	Alanine	4	2 serum[41] plasma[44]	2 plasma[19] serum[40a]
21	Glutamate	4	2 plasma[13] serum[41]	2 serum[20] placenta[31]
22	Lactate**	4	1 serum[27b]	1 serum[32] urine[32] plasma[45]
23	Asparagine	4	1 placenta[24e]	1 serum[10 34a] urine[36]
24	Xanthine	3	3 plasma[13 15c] serum[37]	
25	Octenoylcarnitine*	3	3 cord-plasma[23] serum[29ab]	
26	Urea	3	2 serum[9] cord-plasma[23]	1 serum[28b]
27	Trimethylamine	3	1 serum[40a]	2 serum[10 39b]
28	Glycerol**	3	1 serum[39b]	2 serum[30a 40a]
29	Hippurate**	3	1 urine[38c]	2 urine[32 36]
30	Isopropanol**	3	1 serum[39b]	2 serum[30a 40a]
31	Succinate**	3		3 serum[30a 40a] urine[38c]
32	Formate**	3		3 serum[30a 40a] urine[38c]
33	Taurine	3		3 serum[20 34a] placenta[31]

Notes: *Identified by LC-MS only; **Identified by NMR only; [a]EO-PE; [b]LO-PE; [c]Preterm PE; [d]Term PE; [e]Severe PE.

Table 3 The Potential of Metabolic Markers for the Prediction of PE

Author	Comparison Groups	Bio-Specimen	Sensitivity	Specificity	AUC	Potential Biomarkers
Sovio[12]	Preterm PE	12w	-	-	0.887	PGAPE, PAPPA, PlGF, 4-hydroxyglutamate
	Preterm PE	20w	-	-	0.911	PGAPE, sFlt1/PlGF, 4-hydroxyglutamate
	Preterm PE	28w	-	-	0.926	PGAPE, sFlt1/PlGF, 4-hydroxyglutamate, C-glycosyltryptophan
Lee[13]	PE	Mid-trimester cohort	0.751	0.830	0.868	SM C28:1, SM C30:1, LysoPC C19:0, LysoPE C20:0, propane-1,3-diol
	PE	At-delivery cohort	0.693	0.846	0.858	SM C28:1, SM C30:1, LysoPC C19:0, LysoPE C20:0, propane-1,3-diol
			0.786	0.714	0.844	SM C30:1
			0.838	0.799	0.904	SM C30:1, oxidized PE C38:3
			0.923	0.857	0.972	SM C30:1, oxidized PE C38:3, isomaltose
Kenny[14]	Preterm PE	15±1w	0.650	0.830	0.780	PlGF, dilinoleoyl-glycerol, 1-heptadecanoyl-2-hydroxy-sn-glycero-3 phosphocholine
Liu[17]	PE	34w	-	-	0.895	14,15-DiHETE
			-	-	0.830	16-HDoHE
			-	-	0.820	LTB4
			-	-	0.795	8,9-EEQ
Powell[22]	PE	26–41w	0.870	0.917	0.938(discovery)	3-Methylhistidine, creatinine, acetyl groups, acetate
			0.600	0.955	0.936(validation)	
Zhou[24]	Severe PE	Immediately after the cesarean section	0.870	0.830	0.930	Arachidonate
			0.930	0.830	0.930	Docosapentaenoate
			0.860	0.890	0.920	γ-Linoleate
			0.930	0.890	0.930	Myristate
			0.860	0.830	0.920	Dihomo-γ-linoleate
Chen[26]	PE	21.7–27.9w(PE) 18.6–27.4w (control)	-	-	0.935	PC(14:0/00)
			-	-	0.928	Proline betaine
			-	-	0.923	Proline
Bahado-Singh[27]	LO-PE	Within 3 d of assessment	0.304	0.804	0.629(validation)	Carnitine, pyruvate, acetone
			0.391	0.804	0.722(validation)	UtPI, pyruvate, carnitine, glycerol
			0.348	0.826	0.734(validation)	Maternal weight, UtPI, pyruvate, carnitine

Bahado-Singh[28]	Term PE	First trimester	0.727	0.574	0.701	Putrescine, urea, carnitine
	Term PE	Third trimester	0.742	0.723	0.761	Methylhistidine, serotonin, citrate, hexose, propylene glycol
	Term PE	Integrated first and third trimester	0.816	0.710	0.817	Urea (1st), SM C18:1 (1st), citrate (3rd), hexose (3rd)
Koster[29]	EO-PE	8⁺⁰–13⁺⁶w	-	-	0.878(training) 0.784(validation)	MC, MAP, PAPPA, PlGF, taurine, stearoylcarnitine
	LO-PE	8⁺⁰–13⁺⁶w	-	-	0.833(training) 0.700(validation)	MC, MAP, PAPPA, PlGF, stearoylcarnitine
Bahado-Singh[30]	EO-PE	Within 3 d of assessment	0.825 0.750 0.908 0.900	0.823 0.744 0.908 0.884	0.896(discovery) 0.835(validation) 0.956(discovery) 0.916(validation)	2-Hydroxybutyrate,3-hydroxyisovalerate, acetone, citrate, glycerol 3-Hydroxyisovalerate, arginine, glycerol, UtPI
Austdal[32]	PE	11⁺⁰–13⁺⁶w	0.192 0.423 0.538	- - -	0.694 0.778 0.807	Hippurate/creatinine Hippurate/creatinine, MAP, maternal age Hippurate/creatinine, MAP, UtPI, maternal age
Bahado-Singh[39]	LO-PE	11⁺⁰–13⁺⁶w	0.600	0.966	0.885(primary dataset)	Methylhistidine, glycerol, maternal weight, maternal race, acetoacetate
			0.767	1.000	0.960(primary dataset)	Valine, maternal weight, maternal race, pyruvate, 3-hydroxybutyrate, 1-methylhistidine, glycerol, trimethylamine, maternal medical disorder
			0.400	0.941	0.790(expanded dataset)	Glycerol
			0.400	0.950	0.796(expanded dataset)	Glycerol, maternal weight
			0.567	0.950	0.783(expanded dataset)	Glycerol, 1-methylhistidine
Bahado-Singh[40]	EO-PE	11–13w	0.759	0.951	0.904	Citrate, glycerol, hydroxyisovalerate, methionine
			0.826	0.984	0.980	Acetate, glycerol, hydroxyisovalerate, UtPI, fetal CRL
			0.500	0.950	0.840	Glutamine, pyruvate, propylene glycol, trimethylamine, hydroxy butyrate, maternal weight, maternal medical disorders
			0.600	0.970	0.940	Pyruvate, propylene glycol, trimethylamine, 3-hydroxisovalerate, UtPI
Odibo[41]	PE	11–14w	-	-	0.824	Hydroxyhexanoylcarnitine, phenylalanine, glutamate, alanine
	EO-PE		-	-	0.846	Hydroxyhexanoylcarnitine, phenylalanine, glutamate, alanine
	PE		-	-	0.818	Phenylalanine, glutamate, alanine

(*Continued*)

Table 3 (Continued).

Author	Comparison Groups	Bio-Specimen	Sensitivity	Specificity	AUC	Potential Biomarkers
Kenny[42]	PE	15±1w	-	-	0.940(discover) 0.920(validation)	5-Hydroxytryptophan, monosaccharide(s), decanoylcarnitine, methylglutaric acid and/or adipic acid, oleic acid, docosahexaenoic acid and/or docosatriynoic acid, γ-butyrolactone and/or oxolan-3-one, 2-oxovaleric acid and/or oxo-methylbutanoic acid, acetoacetic acid, hexadecenoyl-eicosatetraenoyl-sn-glycerol, di-(octadecadienoyl)-sn-glycerol, sphingosine 1-phosphate, sphinganine 1-phosphate, vitamin D3 derivatives
McBride[47]	PE	22–28w	-	-	0.620(training and testing) 0.620(validation) 0.710(training and testing) 0.630(validation) 0.680(training and testing) 0.660(validation)	Risk factor (BMI, age, parity, smoking) Risk factor (BMI, age, parity, smoking) Metabolite (154 metabolites) Metabolite (154 metabolites) Combined (BMI, parity, 26 metabolites) Combined (BMI, parity, 26 metabolites)

Abbreviations: AUC, area under the curve; PGAPE, the predicted gestational age of pre-eclampsia; PAPPA, pregnancy-associated plasma protein A; PLGF, placenta growth factor; sFlt1, soluble fms-like tyrosine kinase 1; UtPI, uterine artery pulsatility index; MC, maternal characteristics; MAP, mean arterial pressure; fetal CRL, fetal crown-rump length; BMI, body mass index.

predict PE, which exhibited an area under the receiver operating curve (AUC) of 0.868 in a mid-trimester cohort and 0.858 in an at-delivery cohort; the authors also evaluated a panel of another three metabolites (SM C30:1, oxidized PE C38:3, and isomaltose), yielding an AUC of 0.972 in the at-delivery cohort. Powell et al[22] identified a panel of four metabolite parameters (3-methylhistidine, creatinine, acetyl groups, and acetate) that could predict PE, which resulted in an AUC of 0.938 and 0.936 in discovery and validation sets, respectively. Odibo et al[41] used four significant metabolites (hydroxyhexanoylcarnitine, phenylalanine, glutamate, and alanine), achieving an AUC value of 0.824 to predict PE and 0.846 to predict EO-PE; they also assessed the predictive ability of three significant amino acids (phenylalanine, glutamate, and alanine), which got an AUC of 0.818. Kenny et al[42] used a panel of 14 metabolites to predict PE, reporting an AUC value of 0.940 in discovery group. Liu et al,[17] Zhou et al,[24] and Chen et al[26] all calculated AUC of single metabolites, resulting AUC values ranging from 0.795 to 0.935.

As several studies[27,29,30,32,39,40,47] reported, the distinguish performance had been remarkably improved after incorporating metabolites into maternal characteristics (eg, weight, age, and race), medical parameters (eg, mean arterial pressure and uterine artery plasticity index) or previously established biomarkers (eg, pregnancy-associated plasma protein A and placenta growth factor). In addition, Sovio et al[12] and Kenny et al[14] tried to build models for prediction of preterm-PE. Both of them found that metabolite markers are effectively complemented to existing biomarkers, for example, soluble fms-like tyrosine kinase receptor 1 or placenta growth factor. Besides, Bahado-Singh and coworkers[28] combined first and third trimester metabolites with maternal characteristics to predict term-PE.

Metabolic Pathways for PE

To figure out the potential metabolic pathways involved in the development of PE, 415 potential metabolite markers were imported to MetaboAnalyst for enrichment analysis and topological analysis. Figure 2 shows the results of the analysis. In comparison of patients with PE and normal controls, thirteen metabolic pathways were significantly enriched (Raw *P*<0.05, Supplementary Table S1). There are eight amino acid metabolism-related pathways, including arginine biosynthesis; alanine, aspartate and glutamate metabolism; arginine and proline metabolism; glycine, serine and threonine metabolism; valine, leucine and isoleucine biosynthesis; phenylalanine metabolism; D-glutamine and D-glutamate metabolism and histidine metabolism. Besides, three carbohydrate metabolism-related pathways were reported: butanoate metabolism; citrate cycle; and glyoxylate and dicarboxylate metabolism. Aminoacyl-tRNA biosynthesis was a translation-related pathway and sphingolipid metabolism was a lipid metabolism-related pathway (Figure 3).

Discussion

In this study, 41 metabolomics studies on PE were comprehensively reviewed and analyzed to identify valuable metabolic biomarkers and pathways involved in the pathologies of PE. Thirty-three high-frequency metabolites (reported in ≥3 studies) were found. In addition, several metabolic pathways involved with PE were identified, particularly alanine, aspartate and glutamate metabolism with a high impact.

Reliability of Metabolic Biomarkers/Metabolite Panels and Their Clinical Implications

Metabolomics studies have identified more than 30 metabolic biomarkers related to PE. Several metabolic biomarkers were repeatedly identified across these studies. Notably, the levels of some metabolic biomarkers, eg, decanoylcarnitine, 3-hydroxyisovaleric acid, xanthine, octenoylcarnitine, succinate, formate, and taurine, were consistently increased or decreased across these studies. The consistency increased the reliability of these metabolites as PE biomarkers. However, several metabolites were inconsistent across studies, for instance, creatinine, glycine, L-isoleucine, and glucose. The disparities may partly be explained by study differences in gestational age when biospecimens were collected, maternal characteristics (such as age, obesity, ethnic origin, and sort and severity of diseases), analytical platforms, and bioinformatics and biostatistical tools.

Seventeen metabolomics studies[12–14,17,22,24,26–30,32,39–42,47] used metabolic biomarker panels to discriminate patients with PE or subtypes of PE, yielding AUC values of 0.620–0.980 (Table 2). Also, more effective clinical models were achieved by incorporating metabolic biomarkers with traditional predictive biomarkers or clinical parameters. The results
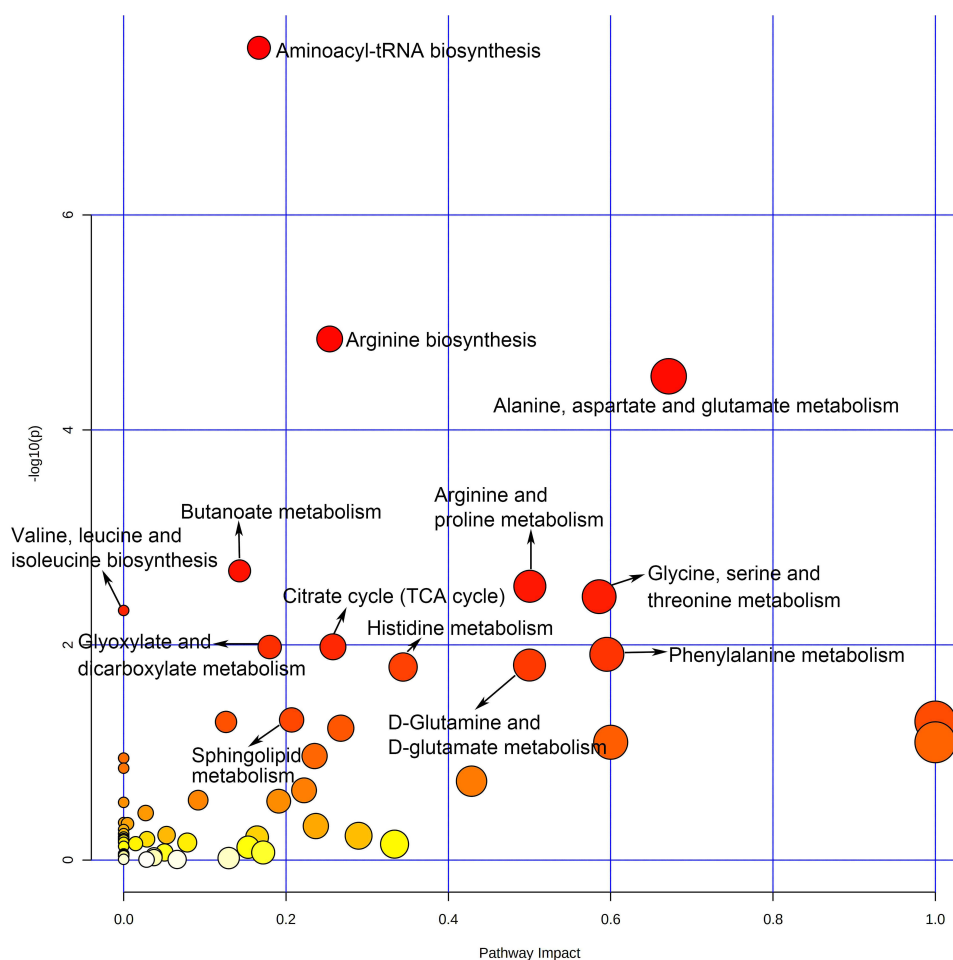
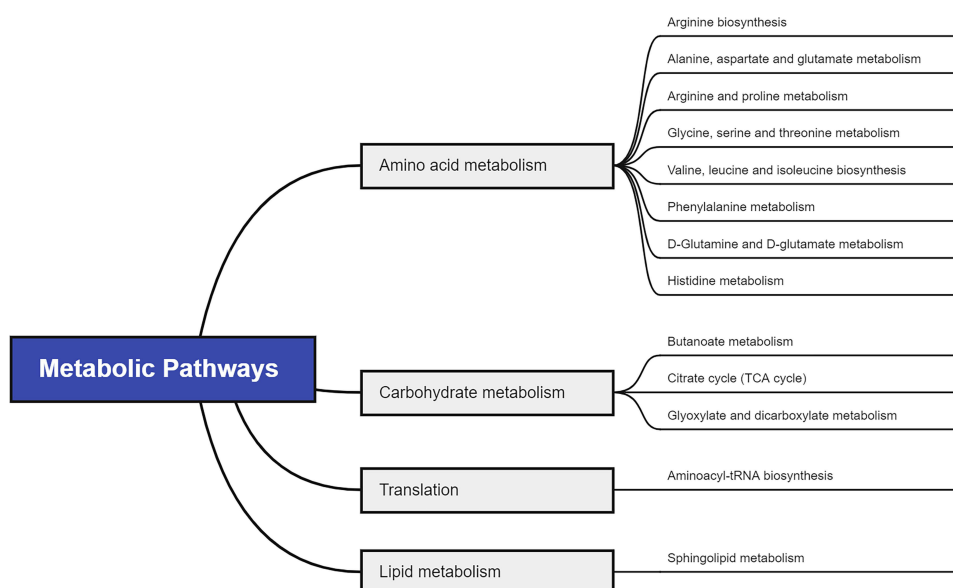**Figure 2** Overview of pathway analysis of PE.

Figure 3 Pathway analysis for significant metabolites of PE.

appeared promising. However, the related studies generally had small sample size and limited validation. Also, untargeted metabolomics only acquired semiquantitative metabolite concentrations. Further studies, such as independent external cohorts with large sample size, are needed for obtaining reliable conclusions. Moreover, before metabolite panels are applied to clinical practice, additional robust quantitative analyses of these metabolite panels are necessary.

Metabolic Dysregulations Implicated in PE Pathogenic Mechanisms

The pathological process of PE involves a series of biological changes and is incompletely elucidated.[49] Until now the diagnosis of PE has been focused on blood pressure and urinary protein levels with low specificity or sensitivity. Therefore, it is necessary to identify novel biomarkers to improve diagnosis and deepen the understanding of the pathogenesis of PE. Herein, we describe some important metabolites that may play a role in the etiology and early identification of PE patients. Amino acids (for example, creatinine, glycine, L-isoleucine, creatine, L-phenylalanine, L-histidine, L-leucine, L-valine, and L-glutamine) are the most frequently reported altered metabolites related with PE. According to our analysis, renal dysfunction, insulin resistance, lipid metabolism disorder, inflammatory activation and impaired NO production were interestingly concerned with the pathophysiology of PE.

Renal Dysfunction

Renal dysfunction is seen in asymptomatic women in whom PE will eventually develop, and proteinuria and decreased renal function are classic hallmarks of PE.[50] The levels of related low molecular weight substances, such as creatinine,[15,22,32,38,39,44] lactate,[27,32,45] urea,[9,23,28] and creatine,[15,20,23,32,39] could be used to monitor renal function and to assist the diagnosis of PE.

Insulin Resistance

Insulin resistance is a clear risk factor for PE.[51] Elevated insulin derived from insulin resistant may cause increases in sympathetic nervous system activity and renal sodium retention, which could increase blood pressure.[52] Glucose and several metabolites (eg, L-valine, and L-leucine) that can influence or reflect insulin release or insulin sensitivity were frequently reported in the included studies.

Metabolomics studies showed an upward trend in glucose in PE.[27,30,39,40] Insulin is a hypoglycemic hormone, promoting blood sugar into cells for use as energy.[53] Insulin resistance refers to impaired insulin sensitivity, and therefore a high blood glucose level could be explained.

L-isoleucine, L-leucine, and L-valine are essential branched chain amino acids (BCAAs). High levels of BCAAs can activate the mammalian target of rapamycin complex 1 that phosphorylates insulin receptor substrate 1, leading to insulin resistance.[54] In addition, a BCAA dysmetabolism model proposed that the accumulation of mitotoxic metabolites promotes pancreatic β-cell mitochondrial dysfunction.[55] Hence, the BCAAs are particularly sensitive to insulin resistant conditions and/or insulin deficiency.[56] Moreover, as a typical partial-degradation product of BCAAs, 3-hydroxybutyric acid is synthesized in the liver from acetyl-CoA and can be used as an energy source when blood glucose is low. Blood level of 3-hydroxybutyric acid can serve as a biomarker of insulin resistance and impaired glucose tolerance.[57]

Glutamate, glutamine, L-asparagine, L-alanine, and D-alanine are derived from intermediates of central metabolism, mostly the citric acid cycle, in one or two steps. A recent study performed high-throughput metabolite profiling in two large and well characterized community-based cohorts, observed a significant association of insulin resistance with glutamine and glutamate and found that administration of glutamine leads to both impaired glucose tolerance and decreased blood pressure.[58]

Lipid Metabolism Disorder

Excessive lipid in maternal serum may induce endothelial dysfunction secondary to oxidative stress. Lipid dysfunction may start early in pregnancies destined for PE development,[59] suggesting that related metabolomics may be used to predict the onset of PE. It was found that dietary acetic acid could reduce serum total cholesterol and triacylglycerol by inhibition of lipogenesis in liver and increment in faecal bile acid excretion in rats fed with cholesterol-rich diet.[60] Meanwhile, acetic acid was suggested to exhibit anti-hypertension effects via reducing the activity of renin-angiotensin system.[61]

Furthermore, fatty acids are necessary for proper pregnancy progression and fetal growth and development.[62] Carnitine, acylcarnitines (ie, decanoylcarnitine and octenoylcarnitine) play key role in transporting acyl-groups (including fatty acids) from the cytoplasm into the mitochondria so that they can be broken down to produce energy, which is known as β-oxidation.[63] It was also concluded that incomplete muscle fatty acid β-oxidation causes acylcarnitine accumulation and associated oxidative stress, raising the possibility that these metabolites play a role in muscle insulin resistance.[64]

Glycerol is a three-carbon alcohol metabolite that constitutes the backbone to which fatty acids and lipids are bound to form triglycerides and phospholipids. The metabolism of stored fats leads to the release of glycerol and fatty acids into the bloodstream. The glycerol component can be converted into glucose by the liver and provides energy for cellular metabolism. Pyruvate is a key intermediate in several metabolic pathways throughout the cell. Particularly, pyruvate can be made from glucose through glycolysis, converted back to carbohydrates (such as glucose) via gluconeogenesis, or to fatty acids through a reaction with acetyl-CoA. Therefore, altered glucose, pyruvate and glycerol levels are accompanied by perturbations of lipid metabolism.

Activated Inflammation

Inflammation and related oxidative stress can induce endothelial dysfunction, which are the features of PE.[65] Taurine is a vaso-protective and anti-hypertensive agent.[66] It can be synthesized by the body from cysteine when vitamin B6 is present. Decreases in placental taurine levels could impair trophoblastic invasion and spiral artery remodeling[67,68] and produce relative fetal intrauterine hypoxia, which may contribute to PE.[69]

Women with PE also showed altered choline and glycine, and hippurate, which may be related to increased oxidative stress. Choline and glycine are connected through the metabolic pathway of homocysteine, which increase the risk of PE.[70] Glycine is a precursor to glutathione, a tripeptide important for protection against oxidative stress.[71] Histidine is a precursor for histamine. L-histidine has anti-oxidant, anti-inflammatory and anti-secretory properties, mainly due to its singlet oxygen and hydroxyl radical scavenging characteristics. In many recent nonclinical studies, L-histidine has been shown to have significant potential as an anti-inflammatory therapeutic agent in a range of diseases.[72]

Impaired NO Production

Nitric oxide (NO) plays an important role in regulating various cardiovascular function. NO stimulates soluble guanylate cyclase to produce cGMP, which activates cGMP dependent Protein Kinase G (PKG) and subsequently results in smooth muscle cell relaxation, reduction of vascular resistance and eventually increase of blood perfusion in tissues.[73] Metabolomics studies on PE found changed levels of dimethylamine and L-phenylalanine. These metabolites were suggested to affect NO production in many ways.

Dimethylamine may have dietary origins, but is also derived from asymmetric dimethylarginine, a biomarker of increased renal disorder[74] and cardiovascular risk.[75,76] Asymmetric dimethylarginine is an endogenous inhibitor of NO synthases that attenuates NO production by inhibition of nitric oxide synthase (NOS) activity. Asymmetric dimethylarginine also enhances NOS uncoupling to produce reactive oxygen species such as superoxide anion and peroxynitrite, which could further reduce the cardiovascular NO bioavailability.[75] Besides, tetrahydrobiopterin (BH4) has been reported to be a powerful oxidant of oxygen.[77] L-phenylalanine, as the essential amino acid, may increase BH4-dependent NO production, thus helps restore vascular function and decrease blood pressure in rats.[78]

Methodological Considerations of Metabolomics Studies on PE

In metabolomics research, NMR and MS are common analytical techniques, and many high-frequent reported metabolites were identified by either NMR or MS. Different methods have their strengths and weaknesses. NMR is quantitative and requires minimal sample preparation making it more reproducible among different studies, while MS can offer a combined sensitivity and selectivity platform for metabolomics study.[79] The chosen method may influence the reporting of results to an extent. Unfortunately, only two included articles in this review employed both methods. More studies combining the two may provide the greatest opportunity to identify accurate and sensitive metabolic biomarkers of PE.

Limitations of Current Metabolomics Studies on PE

Several limitations of the existing metabolomics studies on PE should be noted. First, the biological samples are limited to blood samples in the majority of studies. Other types of samples (eg, urine and placenta) should be analyzed to allow researchers to obtain a more comprehensive understanding of metabolic signatures. Second, many studies had relatively small sample sizes, limiting statistical power and the generalizability of their research results. Third, the identification and analysis of metabolites are mostly based on public databases (eg, Human Metabolome Database), therefore some unidentified metabolites may be ignored. Fourth, when researchers used blood or other biofluids, profiling of metabolites may be greatly dynamic and influenced by diet, immune status, lifestyle, and environmental factors.[80] Unfortunately, the effect of sample collection on results is often overlooked in metabolomics studies. Finally, insufficient validations exist for many studies. Multiple independent validations, including external cohorts and animal and cell experiments, are necessary before translating the results into clinical practice. Future studies addressing these limitations may be performed to complement, validate, and expand current findings. In addition, the integration of metabolomics with other omics platforms (eg, genomics, transcriptomics, and proteomics) will enable researchers to obtain a global perspective of the complexity of PE.

Conclusion

In summary, this study presents a systematic review and analysis of metabolomics research into different aspects of PE. A series of small-molecule metabolites, including various amino acids, have been reported to be associated with PE. Those metabolites consistently reported to be associated with PE, including decanoylcarnitine, 3-hydroxyisovaleric acid, and taurine, warrant particular attention. Metabolic pathways, such as alanine, aspartate and glutamate metabolism, are suggested to be involved in the development and progression of PE. In the future, the construction of diagnostic or predictive models for PE may be achieved by combining these potential metabolite markers themselves or combining these metabolite markers with clinical parameters. Furthermore, the identification of interventional or therapeutic targets based on the underlying metabolic mechanisms is worthy of exploration.

Disclosure

The authors report no conflicts of interest in this work.

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