Genetic and non-genetic risk factors for pre-eclampsia: an umbrella review of systematic reviews and meta-analyses of observational studies

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Abstract

Objective: To summarize evidence from the literature on the risk factors associated with preeclampsia, assess the presence of statistical biases and identify associations with robust evidence.

Methods: We searched PubMed and ISI Web of Science from inception to October, 2016, to identify systematic reviews and meta-analyses of observational studies examining associations between genetic and non-genetic risk factors for preeclampsia. For each meta-analysis we estimated the summary effect size by random-effects and fixed-effects models, the 95% confidence interval and the 95% prediction interval. We estimated the between-study heterogeneity expressed by I^2 (considering above 75% as very large), evidence of small-study effects (large studies had significantly more conservative results than smaller studies and evidence of excess significance bias (too many studies with statistically significant results).

Results: Fifty-seven eligible papers were identified providing data on 130 associations including 1466 primary studies, covering a very wide range of risk factors: co-morbid diseases, genetic factors, exposure to environmental agents and a range of biomarkers. Sixty-five (50%) associations had nominally statistically significant findings at $P<0.05$, while sixteen (12%) were significant at $P<10^{-6}$. Sixty-four (49%) associations had large or very large heterogeneity. Evidence for small-study effects and excess significance bias was found in ten (8%) and twenty-six (20%) associations, respectively. Oocyte donation vs normal conception (OR 4.33, 95% CI: 3.11-6.03) had >1000 cases, 95% prediction intervals excluding the null, not suggestive of large heterogeneity ($I^2<50\%$), small-study effects (P for Egger's test>0.10), or excess of significance (P>0.05). Across the statistically significant genetic risk factors ($P<0.05$), only PAI-1 4G/5G (recessive

model) polymorphism was supported with strong evidence for a contribution to the pathogenesis of preeclampsia. Eleven factors (serum iron level, PAPP-A, chronic kidney disease, polycystic ovary syndrome, mental stress, bacterial & viral infections, cigarette smoking, oocyte donation vs assisted reproductive technology, obese vs normal weight women, severe obese vs normal weight women and primiparity) presented highly suggestive evidence for preeclampsia.

Conclusions: A large proportion of meta-analyses of genetic and non-genetic risk factors for preeclampsia have caveats, which threaten their validity. Oocyte donation vs normal conception and PAI-1 4G/5G polymorphism (recessive model) show the strongest consistent evidence.

Introduction

Preeclampsia (PE) is a severe pregnancy-associated disease, characterized by the occurrence of hypertension and proteinuria in previously healthy women after the 20th weeks of gestation. PE affects approximately 2-8% of all pregnancies and is associated with substantially higher maternal and fetal morbidity and mortality worldwide.[1-2] The clinical spectrum of PE varies, from mild, which is characterized by a moderate increase in blood pressure and proteinuria, to the most severe outcome of eclampsia, described by seizures as a sign of damage of the cerebral vessels, and HELLP syndrome (Hemolysis, Elevated Liver enzyme, Low platelets), which significantly threatens the lives of pregnant women and their fetuses.[3] The true etiology of PE remains an issue of debate, and generates uncertainty on prediction, prevention and treatment, occurring as interplay between genetic and non-genetic factors.[4-5]

Numerous meta-analyses and systematic reviews have claimed that several environmental, biological and genetic risk factors are associated with PE risk. If causal, these associations might be useful for the accurate prediction and diagnosis of this condition in early pregnancy, which would allow a timely allocation of screening resources and prevention of maternal and fetal complications.[6-8] In addition, preventive measures such as aspirin administration in high risk women appear more likely to be beneficial if started earlier in pregnancy during the first trimester or even preconception.[9-10] Nevertheless, there is a possibility that some observed associations in the literature do not reflect a genuine association but include different types of bias in favor of positive statistically significant associations.[11] The pursuit of positive results may be generated with several different mechanisms[12], such as selective analyses,

outcome bias and fabrication bias.[13] These biases can cause either false published findings[12] or inflated effects.[14]

To our knowledge, this is the first attempt to summarize the evidence from existing meta-analyses on genetic and non-genetic risk factors for PE. We aim to summarize evidence from meta-analyses on the risk factors that have been associated with PE, evaluate whether there are hints of biases in this literature and how they manifest, and finally identify which of the previously studied associations represent robust epidemiologic evidence.

Methods

The concept of umbrella review

We conducted an umbrella review, which is a systematic collection and evaluation of multiple systematic reviews and meta-analyses performed on a specific research topic.[15] An umbrella review brings together comparisons of a large number of existing systematic reviews and meta-analyses on risk factors into one accessible and usable document.[15-16] The methods of the umbrella review are standardized and in this work we follow state-of-the-art approaches as previously published umbrella reviews on risk factors and various outcomes.[17-20]

Literature search

Two researchers (KG and SP) independently searched PubMed and ISI Web of Science from inspection to October 8, 2016, to identify systematic reviews and meta-analyses of observational studies examining associations between risk factors and PE. The search strategy used the keywords ("pre-eclampsia" OR "preeclampsia") AND ("systematic review" OR "meta-analysis"). Initially, the title and abstract of each these articles were examined and then we retrieved potentially eligible articles for full text evaluation. We also systematically searched PubMed to identify genome-wide association studies (GWAS) examining genetic associations with PE. Any discrepancies were resolved with discussion.

Eligibility criteria and data extraction

Articles were eligible if the authors had performed a systematic search to identify pertinent studies that examined the association between various risk factors and PE. The

full text of potentially eligible articles was scrutinized independently by two investigators (KG, SP). Meta-analyses or systematic reviews were retained if they included at least three studies in which information was provided per included study on a measure of association and its standard error between the risk factor and PE and on the number of cases/population. We excluded studies in which risk factors were used for screening, diagnostic, or prognostic purposes or meta-analyses that examined PE as a risk factor for other medical conditions. We did not apply any language restrictions in the selection of eligible studies. When more than one meta-analysis on the same research question was eligible, the meta-analysis with the largest number of component studies with data on individual studies' effect sizes was retained for the main analysis.

Data extraction was performed independently by two investigators (KG, SP), and in case of discrepancies, the final decision was reached by discussion or a third investigator, when necessary (EE). From each eligible meta-analysis, we extracted information on the first author, year of publication, the examined risk factors, the number of studies included, the study-specific relative risk estimates (risk ratio, odds ratio) or standardized mean differences along with the corresponding confidence intervals (CI). Also we recorded the reported summary meta-analytic estimates using both fixed and random effect methods along with the corresponding confidence intervals and the number of cases and controls for each study. We noted whether the selected meta-analyses applied any criteria to evaluate the quality of the included observational studies.

Assessment of summary effect and heterogeneity

For each meta-analysis, we estimated the summary effects and its 95% confidence interval by using both fixed and random effect models.[21-22] Additionally, we calculated the 95% prediction intervals (PI) for the summary random effects estimates, which further account for between-study heterogeneity and indicates the uncertainty for the effect that would be expected in the new study observing the same association.[23-24] For the largest study of each meta-analysis, we calculated the standard error (SE) of the effect size, and we examined whether the standard error was less than 0.10 and whether the largest study presented a statistically significant effect. In a study with SE of less than 0.10, the difference between the effect estimate and the upper or lower 95% confidence interval is less than 0.20 (i.e. this uncertainty is less than what is considered a small effect size).

We assessed heterogeneity between studies, and we reported the P value of the χ^2-based Cochran Q test and the I^2 metric for inconsistency, which could reflect either diversity or bias. I^2 ranges between 0% and 100% and is the ratio of between-study variance over the sum of within and between-study variances.[25] Values exceeding 50% or 75% are usually considered to represent large or very large heterogeneity, respectively. Confidence intervals were calculated as per Ioannidis et al.[26]

Assessment of small study effects

We evaluated whether there is evidence for small study effect (i.e. if small studies tend to give higher risk estimates than large studies). Small study effects can indicate publication and other selective reporting biases, but they can also reflect genuine

heterogeneity, chance, or other reasons for differences between small and large studies.[27] We used the regression asymmetry test proposed by Egger for this assessment.[28] A P-value <0.10 accompanied by a more conservative effect in larger studies was considered evidence for the existence small-study effects.

Evaluation of Excess Statistical Significance

The excess of statistical significance test was performed to evaluate whether there is a relative excess of formally significant findings in published literature due to any reason. The number of expected positive studies is estimated and compared against the number of observed number of studies with statistically significant results (P<0.05).[13] A binomial test was used to evaluate whether the number of positive studies in a meta-analysis is too large according to the power that these studies have to detect plausible effects at α=0.05. A comparison between observed vs expected is performed separately for each meta-analysis and it is also extended to groups of many meta-analyses after summing the observed and expected from each meta-analysis. The power of each component study was estimated using the fixed effects summary, the random effects summary, or the effect size of the largest study (smallest SE) as the plausible effect size.[29] The power of each study was calculated with an algorithm using a non-central *t* distribution.[30] Excess statistical significance for single meta-analyses was claimed at P<0.10 (one-sided P<0.05, with observed > expected as previously proposed) given that the power to detect a specific excess will be low, especially with few positive studies.[13]

We classified risk factors into categories based on biological pathways or types of exposures involved: biomarkers, environmental factors, genetic markers, diseases and

disorders, supplementation, infections and other risk factors. We examined excess statistical of significance separately in each of these categories as selective reporting bias may arise in different domains of research. The excess of statistical significance test was conducted separately for meta-analyses with I^2 values less than or equal to 50% and greater than 50%, because values above 50% are typically reflected evidence of large heterogeneity beyond chance.[31]

Grading of non-genetic and genetic associations

We characterized as convincing the non-genetic associations fulfilling the following criteria: had significant effect under the random-effects model at $P<10^{-6}$, were based on evidence from more than 1000 cases, the between-study heterogeneity was not large ($I^2<50\%$), the 95% PI excludes the null value and had no evidence of small-study effects and excess of significance bias. Additionally, associations with more than 1000 cases, a significant effect at $P<10^{-6}$ and nominally statistically significant effect present at the largest study were characterized as highly suggestive. We considered as suggestive the associations with significant effect at $P<10^{-3}$ and more than 1000 cases. The rest of statistically significant associations at $P<0.05$ under random-effects model were graded as weak associations.

We used the Venice criteria to evaluate the epidemiological credibility of all significant genetic associations.[32] Credibility was defined based upon the grade (A=strong, B=moderate or C=weak) of three categories: amount of evidence, replication of the association, and protection from bias. Amount of evidence was graded by the sum of test alleles or genotypes among both cases and controls in the meta-analysis; ('A' for

over 1,000, 'B' for 100 to 1,000, and 'C' for less than 100). Replication of the association was graded as "A" if there was an extensively replicated study supported by at least 1 well conducted meta-analysis, "B" if it was a well-conducted meta-analysis with some methodological limitations and "C", if there was no independent replication, failed replication or flawed meta-analysis. Assessment of protection from bias included consideration of the magnitude of the association, heterogeneity statistic and findings from tests for selective reporting biases (test for small-study effects and excess statistical significance). According to these criteria, the credibility level of the cumulative evidence was defined as high (A grades only), low (one or more C grades) or intermediate (all other combinations).[32]

All authors had full access to all of the data in the study. Statistical analysis and the power calculations were performed in STATA version 14 (STATA Corp, College Station, TX).

Results

Description of Eligible Meta-analyses

The search identified 634 items, of which 535 were excluded after the title and abstract review. Of the remaining 99 articles that entered the full-text review, 8 articles did not report the appropriate information for the calculation of excess of statistical significance (either because the total sample size was missing or the study-specific relative risk estimates were missing), one article was a pooled analyses of cohort studies, two articles included only 2 component studies, and 18 articles excluded because a larger systematic review or meta-analysis investigating the same risk factor was available (Figure 1). Therefore, 57 articles were selected[5,33-89], including data on 130 meta-analyses (comparisons) in seven broad areas (biomarkers [n=27 comparisons], environmental factors [n=6 comparisons], genetic markers [n=66 comparisons], diseases and disorders [n=8 comparisons], supplementation [n=1 comparisons], infections [n=3] and other risk factors [n=19 comparisons]).

The characteristics of the included meta-analyses are shown in Table 1. Based on the study design of the synthesized studies that examined non-genetic associations, we had 7 (20%) meta-analyses synthesizing retrospective case-control data only, 3 (9%) meta-analyses that included prospective data (cohort studies) and 25 (71%) of studies including both types of data, noted as mixed. Regarding the genetic association studies, 15 (65%) meta-analyses synthesized case-control data, 7 (30%) of studies used both types of data (case-control and cohort data), and 1 (4%) meta-analysis that included only cohorts.

There were 3 to 51 studies per meta-analysis, with a median of eight studies. The median number of case and control subjects in each study was 96 and 161, respectively. The median number of case and control subjects in each meta-analysis was 1123 and 3598, respectively. The number of cases was greater than 1000 in 70 meta-analyses. Overall, 441 (30%) individual studies observed nominally statistically significant results. Twenty articles (35%) used Newcastle Ottawa Scale (NOS) to qualitatively assess the included primary studies. Two articles used assessment criteria for non-randomized observational studies adapted from Duckitt & Harrington, two articles used the Methodological Index for Non-Randomized Studies (MINORS) and nine articles used other assessment tools. Twenty-four papers (42%) did not perform any quality assessment. Supplementary Table S1 (available online) summarizes these 130 meta-analyses that included 1466 individual study estimates.

Systematic reviews with qualitative synthesis

We have also summarized the evidence of the published systematic reviews without any quantitative component. According to their findings, serum calprotectin and cardiac troponin I levels were elevated in women with PE compared to healthy controls, where cell-free fetal DNA quantification has been shown to be a promising marker for PE prediction, especially for the development of early-onset or severe PE.[90-92] PE was more prevalent in cold and humid seasons,[93] whereas long inter-pregnancy intervals, possibly longer than 5 years, are also independently associated with an increased risk of PE.[94] Psychotropic drugs such as lithium for the management of antenatal psychiatric disorders have been also associated with PE.[95] Pregnant women with systemic lupus erythematosus and Cushing's syndrome are at higher risk of developing PE in contrast

to healthy pregnancies.[96,97] Laparoscopic adjustable gastric band (LAGB) surgery seems to improve pregnancy outcomes such as PE in obese women compared to pregnancies in obese women without LAGB.[98,99] Little evidence was found whether shift work, HIV infection, or antiretroviral therapy and thrombophilic disorders are increase the risk of PE.[100-102]

Summary Effect Sizes and Significant Findings

Of the 130 meta-analyses, 65 (50%) had nominally statistically significant findings at $P<0.05$ using the random effects model, of which 53 reported increased risks and 12 showed decreased risks of PE. Out of these, a total of 28 (22%) associations presented statistically significant effect at $P<0.001$, while only 16 (12%) survived after the application of a more stringent p-value threshold of $P<10^{-6}$ (Table 1). The sixteen risk factors that presented a significant effect at $P<10^{-6}$ for an association with PE were; the serum iron level, PAPP-A, PP13, PlGF, F5 rs6025, F2 rs1799963, chronic kidney disease, polycystic ovary syndrome, mental stress, bacterial & viral infections, cigarette smoking, oocyte donation vs ART, oocyte donation vs normal conception, obese vs normal weight, severe obese vs normal weight and primiparity. Additional information on all 130 meta-analyses is available online (Supplementary Table S1).

Across the seven areas of risk factors there were differences in the proportion of associations that had nominally statistically significant summary effects. Based on the random effects calculations at $P<0.05$, 100%, 75%, 63% and 59% of the meta-analyses on infections, diseases and disorders, other risk factors and biomarkers respectively, found nominally statistically significant summary effects. On the contrary, this was seen

only in 39% and 33% of the meta-analyses on genetic markers and environmental factors, respectively.

Between-Study Heterogeneity and Prediction Intervals

33 (25%) meta-analyses had large heterogeneity estimates ($I^2 \geq 50\%$ and $I^2 \leq 75\%$) and 32 (25%) meta-analyses had very large heterogeneity estimates ($I^2 > 75\%$) (Table 1). The highest proportion (56%) of I^2 exceeding 75% was observed in meta-analyses of biomarkers. When we calculated the 95% prediction intervals, in only 14 (11%) meta-analyses the null value was excluded. This included two risk factors on biomarkers (PAPP-A and Vitamin D <50 mmol/l), five on genetic markers (G20210A SNP, PAI-1 4G/5G, F5 rs6025, F2 rs1799963, AGT/T704C-Met235Thr), two on diseases and disorders (chronic kidney disease and polycystic ovary syndrome), and five on other risk factors (oocyte donation vs ART, oocyte donation vs natural conception, early pregnancy PA high vs low activity, Obese vs normal weight and primiparity) (Table 1).

Small-Study Effects

Evidence for statistically significant small-study effects (Egger test P<0.10 and the random effects summary estimate was larger compared to the point estimate of the largest study in the meta-analysis) was identified in 10 of 130 (8%) meta-analyses (Supplementary Table S1, available online). These included two meta-analyses on biomarkers (PAPP-A, PlGF), one on environmental factors (NOx), four on genetic markers (NOS3 27 bp-VNTR in intron 4, F2 rs1799963, ACE rs4646994, ACE-I/D), two on diseases and disorders category (polycystic ovary syndrome and mental stress) and one on other risk factors (Pre-pregnancy physical activity per 1hr per day).

Test of Excess Statistical Significance

Twenty-six (20%) associations had hints for excess statistical significance bias with statistically significant (P<0.05) excess of positive studies under any of the three assumptions for the plausible effect size; the fixed effects summary, the random effects summary or the results of the largest study (Supplementary Table S1). Ten (38%) of them pertained to the biomarkers, nine (35%) pertained to genetic markers, three (12%) pertained to diseases and disorders, and four (15%) pertained to other risk factors. Also, the observed and expected number of positive studies shows that overall the excess of positive results was driven by meta-analyses with small estimates of heterogeneity ($I^2 \leq$ 50%). Table 2 shows the results of excess of statistical significance bias according to category of risk factor.

Risk factors with Strong Evidence of Association

After applying our credibility criteria, only one non-genetic risk factor, oocyte donation vs natural conception, presented convincing evidence for an association with PE, supported by more than 1000 cases, $P<10^{-6}$ under the random effect model, no hints for small-study effects and for excess statistical significance, not large heterogeneity (I^2<50%) and a 95% PI excluding the null value. This association had a summary OR of 4.33 (95% CI: 3.11-6.03; p=3.48 x 10^{-18}) with small heterogeneity (I^2=26%) and supported by 2712 cases. Eleven risk factors (serum iron level, PAPP-A, chronic kidney disease, polycystic ovary syndrome, mental stress, bacterial & viral infections, cigarette smoking, oocyte donation vs ART, obese vs normal weight women, severe obese vs normal weight women and primiparity) presented highly suggestive evidence for PE. Five risk factors were supported by suggestive evidence, and 22 associations presented

weak evidence. An overall assessment of statistically significant associations for PE is presented in Table 3.

Assessment of the cumulative epidemiologic evidence for genetic associations was also conducted and evidence was scored as strong, moderate, or weak based on grades of 'A', 'B', or 'C', as specified by the Venice criteria. Of the 26 variants with significant associations with PE risk with $P<0.05$ using the random effects model, only the PAI-1 4G/5G polymorphism (recessive model) was supported by strong evidence for a contribution to the pathogenesis of PE (Table 4).

Independent tool based quality assessment of the primary studies

We have also assessed the quality of the included studies of the meta-analysis of the non-genetic risk factor that presented convincing evidence for an association with PE using the Newcastle Ottawa Scale[103] in addition to the MINORS scale that the authors used in the original assessment. The methodological quality ranged from 3 points to 8 points maximally, with a median of 6 points, which implies a fair quality of the majority of studies. A quality assessment was also performed among the included studies of meta-analysis of the PAI-1 4G/5G polymorphism using the Q-Genie tool.[104] Among the reviewed studies, 8 (67%) studies were rated to have high quality (>45) and 4 (33%) were rated to have moderate quality (>35 and ≤45).

Discussion

Main Findings

Overall, 130 associations have been studied as risk factors for PE, including biomarkers, genetic markers, environmental factors, supplementation, diseases and disorders, infections and other risk factors. Of those, oocyte donation vs natural conception provided convincing evidence. PAI-1 4G/5G (recessive model) polymorphism had strong evidence for a contribution to the pathogenesis of PE, as specified by the Venice criteria. Eleven risk factors from various fields achieved highly suggestive evidence for an association with PE.

Interpretation

PE remains a disease of theories, as a large number of factors and a genetic component is likely to be involved, but none have been clearly established to date. From biological standpoint, oocyte donation can act as an independent risk factor for development of PE. During normal pregnancy, various immunosuppressive mechanisms maintain to diminished innate immune response in order to prevent fetal rejection as the fetal tissue is directly exposed to the maternal blood and hence, at risk of being attacked by components of both the innate and acquired immune system.[105-106] Because the fetus in pregnancy after oocyte donation is absolute allograft compared to the semi-allograft fetus in normal conception, in which both maternal and paternal genes are expressed,[107] this could lead to an altered or inadequate immune-protection of placentation and eventually resulting in PE.[107-110] This theory is further supported from the fact that oocyte donation versus other assisted reproduction techniques had highly suggestive evidence of epidemiological credibility. Moreover, immune dysregulation may interpret

the highly suggestive evidence in the risk of pre-eclampsia among primiparous women because the first successful (non-preeclamptic) pregnancy may induce adaptive changes in favor to immune tolerance in subsequent pregnancies.[89]

The genetic architecture behind PE is complex.[111] To date, most effort has been focused on candidate genes, primarily those for which a plausible role in the known underlying pathophysiology.[112] Only three genome-wide association studies were identified that include several genetic loci associated with PE.[113-115] One study,[114] identified two loci (rs7579169 and rs12711941) near the Inhibin beta B gene that satisfied the genome-wide significance threshold but they could not be replicated in two cohorts from Norway and Finland. Subsequent case-control studies in European and Chinese women have shown a significant association between the SNP rs7579169 and PE.[116-117]

Eleven factors (serum iron level, PAPP-A, chronic kidney disease, polycystic ovary syndrome, mental stress, bacterial & viral infections, cigarette smoking, oocyte donation vs ART, obese/severe vs normal weight women, primiparity*),* achieved highly suggestive evidence for an association with PE. There are several mechanisms that support these findings. Regarding biomarkers, iron is considered a significant etiologic factor in the endothelial cell damage in PE cases because of its effects on the formation of oxygen free radicals and subsequent lipid peroxidation.[118-120] Reduced PAPP-A, being an important regulator of IGF, can play a role in the development of PE in normal karyotype pregnancies.[121]

Renal insufficiency, maternal hypertension, proteinuria, and recurrent urinary tract infection which are often coexist in women with chronic kidney disease, may contribute individually and cumulatively to PE.[122-124] Insulin resistance and/or associated hyperglycemia that often exist in polycystic ovary syndrome (PCOS) and obese patients could be a possible explanation of a higher risk for PE, since it possibly directly predispose women to hypertension by increased renal sodium re-absorption and stimulation of the sympathetic nervous system and/or may impair endothelial function.[125] Increased levels of androgens in PCOS pregnancies have also been associated with the development of PE.[126]

Cigarette smoking during pregnancy seems protective against developing PE. Experimental studies have demonstrated that carbon monoxide decrease the levels of antiangiogenic factors such as sFlt1 and soluble endoglin, or increase the levels of angiogenic factors like VEGF,[127] which have been involved in the pathogenesis of PE.[128-130] Infection may be important in the pathogenesis of PE, either through initiation by increasing the risk of acute uteroplacental atherosclerosis and/or its enhancement by magnifying the maternal systemic inflammatory response[131] or through direct effect on trophoblast cells by destruction or impairment of trophoblast cells, resulting in shallow invasion of maternal spiral arteries.[132]

Strengths and limitations

Both Egger and excess of significance test offer hints of bias, not definitive proof thereof, while the Egger test is difficult to interpret when the between-study heterogeneity is large. The frequency of meta-analyses with small-study asymmetry

effects was not high (8%), and this rate is commensurate with chance. Nevertheless, our estimates are likely to be conservative as a negative test result does not exclude the potential for bias.

The majority of the included studies for non-genetic associations were retrospective which is indicative of a higher potential for bias inherent in the included studies. However, by performing a standardized methodological process for the assessment of the epidemiological credibility of the findings using a variety of test we accomplish to incorporate all these biases together and provide a complete picture of the totality of evidence as it stands today. The interpretation of excess of statistical significance test for the results of a single meta-analysis, especially one with few studies, should be cautious because a negative test does not exclude the potential for bias.[13] Furthermore, quality assessment of the primary studies was very heterogeneous, reflecting the lack of standardized quality assessment methodologies.

Conclusion

Oocyte donation vs natural conception was supported by convincing evidence for an association with PE. Eleven risk factors, achieved highly suggestive evidence for an association with PE. The use of standardized definitions and protocols for exposures, outcomes, and statistical analyses,[133-134] the adoption of reporting guidelines (e.g. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and STrengthening the REporting of Genetic Association Studies (STREGA))[135-136] and registration of hypothesis-testing observational studies,[137-138] may help improve the evidence in the future, diminish the threat of biases and improve the reliability of this important literature.

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Table 1. Quantitative synthesis and assessment of bias across the 130 associations of genetic and non-genetic risk factors and preeclampsia

Area	Author, year	Comparison	Study design	Studies	Cases/controls	Random effects*	Largest effect‡	P Random	Egger§	I^2 (P)‖	95% PI ≠
Biomarker	Fan Y, 2016	Copper level	Retrospective	12	442/463	1.86 (0.41-8.51)	1.22 (0.64-2.34)	.4217606	0.26	97 (<0.01)	0.00-835.6
Biomarker	Song QY, 2015	Serum iron level	Mixed	23	1023/889	9.97 (4.00-24.9)	38.02 (17.6-82.1)	8.22×10^{-7}	<0.01	96 (<0.01)	0.09-1101
Biomarker	Cohen MJ, 2015	Serum Vitamin E	Mixed	34	1578/1820	0.46 (0.27-0.79)	1.11 (0.61-2.04)	.46495506	<0.01	93 (<0.01)	0.02-10.3
Biomarker	Cohen MJ, 2015	Serum Vitamin C	Mixed	29	1362/1415	0.37 (0.22-0.61)	0.65 (0.48-0.87)	1.170×10^{-4}	0.08	91 (<0.01)	0.02-5.69
Biomarker	Liu HQ, 2015	β-hCG	Retrospective	12	702/8233	88.7 (4.31-1824)	NA	3.655×10^{-3}	0.75	100 (<0.01)	NA
Biomarker	Ma Y, 2015	Serum zinc level	Retrospective	14	541/550	0.35 (0.17-0.68)	0.10 (0.05-0.21)	2.230×10^{-3}	0.63	88 (<0.01)	0.02-5.43
Biomarker	Allen RE, 2014	PAPP-A	Mixed	9	1147/52208	2.05 (1.62-2.59)	1.52 (1.16-2.00)	2.53×10^{-9}	0.04	45 (0.07)	1.13-3.71
Biomarker	Allen RE, 2014	PLGF	Mixed	4	147/840	1.94 (0.81-4.66)	1.57 (0.81-3.05)	.13891351	0.08	83 (<0.01)	0.04-105
Biomarker	Allen RE, 2014	PP13	Mixed	4	210/3851	4.43 (2.86-6.85)	3.32 (1.77-6.22)	2.832×10^{-11}	0.48	49 (0.11)	0.85-23
Biomarker	Allen RE, 2014	betaHCG	Mixed	4	654/11669	1.09 (0.86-1.39)	1.58 (0.64-3.90)	.47136751	0.04	0 (0.45)	0.64-1.85
Biomarker	Allen RE, 2014	Inhibin A	Mixed	3	63/1152	3.57 (1.68-7.61)	8.94 (2.31-34.5)	9.516×10^{-4}	0.78	21 (0.28)	0.01-2184
Biomarker	Yang Y, 2014	IL-18	Mixed	10	351/421	1.13 (0.49-2.60)	1.02 (0.53-1.95)	.78202462	0.75	89 (<0.01)	0.05-24.3
Biomarker	Yang Y, 2014	IFN-γ	Mixed	12	567/701	5.42 (1.14-25.7)	45.6 (30.6-67.9)	.03330384	0.55	97 (<0.01)	0.01-2713
Biomarker	Lashley EE, 2013	HLA antibodies	Retrospective	3	64/273	0.93 (0.09-9.77)	1.40 (0.58-3.39)	.94851452	0.82	66 (0.05)	0-2.65
Biomarker	Dai B, 2013	Serum concentration of NO	Retrospective	9	297/303	0.17 (0.04-0.81)	2.56 (1.41-4.66)	.02535206	0.14	95 (<0.01)	0.00-50.9
Biomarker	Wei SQ, 2013	25 (OH) D <50 mmol/l	Mixed	6	209/1799	2.11 (1.52-2.94)	1.40 (0.69-2.85)	8.658×10^{-6}	0.66	0 (0.49)	1.32-3.37
Biomarker	Wei SQ, 2013	25 (OH) D <75 mmol/l	Mixed	5	177/1134	1.72 (1.11-2.69)	1.39 (0.27-7.24)	.01610334	0.48	27 (0.24)	0.57-5.21
Biomarker	Kleinrouweler CE 2012	PIGF	Mixed	26	787/3638	0.36 (0.25-0.54)	0.64 (0.33-1.23)	3.207×10^{-7}	0.01	84 (<0.01)	0.06-2.4
Biomarker	Kleinrouweler CE 2012	VEGF	Mixed	4	80/185	0.10 (0.01-1.53)	0.22 (0.08-0.57)	.09872404	0.19	96 (<0.01)	0-42370
Biomarker	Kleinrouweler CE 2012	sFlt-1	Mixed	32	1111/4119	2.38 (1.47-3.86)	1.24 (0.65-2.38)	4.517×10^{-4}	0.12	93 (<0.01)	0.15-37
Biomarker	Kleinrouweler CE 2012	sENG	Mixed	19	739/2402	2.66 (1.53-4.63)	1.20 (0.62-2.30)	5.063×10^{-4}	0.54	91 (<0.01)	0.22-32.3
Biomarker	Hausvater A, 2012	Arterial stiffness	Mixed	9	212/633	18.6 (3.72-93.0)	NA	3.697×10^{-4}	0.26	93 (<0.01)	0.05-6658
Biomarker	do Prado AD, 2010	Anticardiolipin antibodies	Mixed	12	1636/5111	2.85 (1.37-5.95)	1.88 (1.23-2.85)	5.208×10^{-3}	0.36	69 (<0.01)	0.29-28.1
Biomarker	Clark P, 2008	AB blood group	Mixed	13	5710/49069	1.02 (0.86-1.22)	0.82 (0.45-1.50)	.81449562	0.46	18 (0.26)	0.72-1.45
Biomarker	Clark P, 2008	A blood group	Mixed	14	5047/44743	0.96 (0.85-1.07)	1.00 (0.81-1.24)	.43608716	0.82	57 (<0.01)	0.68-1.35
Biomarker	Clark P, 2008	B blood group	Mixed	12	5324/48911	1.05 (0.94-1.18)	1.01 (0.72-1.42)	.40009776	0.71	23 (0.21)	0.82-1.35
Biomarker	Clark P, 2008	O blood group	Mixed	18	5945/54609	1.01 (0.91-1.12)	0.98 (0.80-1.21)	.85278952	0.52	49 (0.01)	0.73-1.39
Environmental	Hu H, 2014	NO_2	Mixed	5	3629/117497	1.10 (1.03-1.17)	1.06 (0.96-1.17)	4.565×10^{-3}	0.12	0 (0.73)	0.99-1.21
Environmental	Pedersen M, 2014	Air pollution	Mixed	4	4905/165789	1.05 (0.99-1.13)	1.13 (1.07-1.19)	.14465134	0.19	65 (0.03)	0.79-1.40
Environmental	Pedersen M, 2014	NOx	Mixed	3	1385/48725	1.03 (0.91-1.17)	1.00 (0.87-1.15)	.63256347	0.08	0 (0.54)	0.46-2.28
Environmental	Pedersen M, 2014	PM_{10}	Mixed	4	4656/201197	0.95 (0.86-1.05)	0.83 (0.77-0.89)	.31586644	0.73	83 (<0.01)	0.60-1.50
Environmental	Pedersen M, 2014	CO	Mixed	3	3583/112308	1.10 (0.99-1.22)	1.18 (1.03-1.35)	.09113282	0.94	24 (0.27)	0.44-2.76
Environmental	Pedersen M, 2014	O_3	Mixed	4	4943/164360	1.03 (1.00-1.06)	1.10 (0.94-1.30)	9.954×10^{-3}	0.07	0 (0.85)	0.98-1.09
Genetic markers	Zeng F, 2016	G894T	Retrospective	26	3241/6419	1.45 (1.09-1.94)	1.37 (0.92-2.04)	.01179173	0.65	41 (0.02)	0.55-3.86
Genetic markers	Zeng F, 2016	T-786C	Retrospective	15	2268/3100	1.25 (0.94-1.68)	2.57 (1.27-5.19)	.1302688	0.14	46 (0.02)	0.52-3.00
Genetic markers	Zhang G, 2016	rs4762 in AGT gene	Retrospective	3	790/2492	0.95 (0.66-1.38)	1.07 (0.62-1.84)	.78438216	0.20	26 (0.26)	0.04-23.9
Genetic markers	Zhang G, 2016	rs18001133 in MTHFR	Retrospective	49	13356/23082	1.17 (1.05-1.31)	1.26 (1.04-1.53)	5.889×10^{-3}	0.32	75 (<0.01)	0.60-2.29
Genetic markers	Zhang G, 2016	rs6025 in F5 gene	Retrospective	28	8210/9834	1.53 (1.06-2.21)	1.73 (0.78-3.83)	.02393371	0.61	74 (<0.01)	0.28-8.41
Genetic markers	Zhang G, 2016	rs1800896 in IL-10 gene	Retrospective	9	3020/3786	0.91 (0.75-1.11)	1.15 (0.98-1.35)	.36360487	0.04	70 (<0.01)	0.50-1.68
Genetic markers	Zhang G, 2016	rs1800871 in IL-10 gene	Retrospective	4	978/2074	0.79 (0.59-1.07)	0.84 (0.63-1.11)	.12511238	0.87	65 (0.04)	0.23-2.75
Genetic markers	Zhang G, 2016	rs1137101 in LEPR gene	Retrospective	28	8210/9834	1.53 (1.06-2.21)	1.73 (0.78-3.83)	.02393371	0.61	74 (<0.01)	0.28-8.41
Genetic markers	Zhang G, 2016	rs18001131 in MTHFR gene	Retrospective	9	2780/3636	1.15 (0.93-1.40)	0.91 (0.64-1.29)	.1917049	0.21	59 (0.01)	0.63-2.07
Genetic markers	Li Y, 2015	A1675G of AT2R	Retrospective	5	972/3072	1.58 (1.05-2.37)	1.25 (0.82-1.90)	.02686257	0.47	50 (0.09)	0.47-5.35
Genetic markers	Yang W, 2014	IL-10 -1082 A/G	Mixed	11	1741/3560	0.93 (0.77-1.13)	1.38 (0.62-3.09)	.48667154	0.30	63 (<0.01)	0.51-1.70
Genetic markers	Yang W, 2014	IL-10 -819 C/T	Mixed	5	729/1146	1.28 (1.03-1.59)	1.19 (0.88-1.62)	.02483578	0.86	41 (0.15)	0.70-2.35
Genetic markers	Yang W, 2014	IL-10 -592 C/A	Mixed	3	459/926	1.28 (1.03-1.59)	1.55 (1.04-2.30)	.02641458	0.39	0 (0.46)	0.31-5.26
Genetic markers	Wang X, 2014	G20210A SNP	Mixed	16	2296 /3262	1.79 (1.23-2.61)	1.84 (0.51-6.57)	2.545×10^{-3}	0.96	0 (0.92)	1.18-2.71

Genetic markers	Wang X, 2014	V G1691A SNP	Mixed	23	3131/4036	1.60 (1.25-2.06)	1.74 (0.78-3.89)	2.435×10^{-4}	<0.01	15 (0.25)	0.91-2.82
Genetic markers	Li X, 2014	MTHFR C677T	Mixed	47	6238/11771	1.12 (1.04-1.22)	1.28 (0.98-1.66)	5.188×10^{-3}	0.16	14 (0.21)	0.90-1.41
Genetic markers	Li X, 2014	TGF-β 1 869 T >C	Mixed	4	466/618	0.70 (0.57-0.86)	0.64 (0.39-1.03)	6.052×10^{-4}	0.93	0 (0.84)	0.45-1.09
Genetic markers	Gong LL, 2014	MMP9-1562C>T	Mixed	5	712/766	0.93 (0.61-1.42)	0.82 (0.53-1.27)	.7431311	0.34	72 (<0.01)	0.22-3.97
Genetic markers	Buurma AJ, 2013	AGT rs4762	Retrospective	5	497/1395	1.24 (0.67-2.30)	1.07 (0.62-1.84)	.4899227	0.31	80 (<0.01)	0.13-11.49
Genetic markers	Buurma AJ, 2013	APOE rs429358, rs7412	Retrospective	7	554/712	0.86 (0.65-1.13)	0.96 (0.60-1.55)	.27662924	0.04	4 (0.40)	0.57-1.29
Genetic markers	Buurma AJ, 2013	AT1R rs5186	Retrospective	9	886/1230	1.12 (0.95-1.33)	0.96 (0.69-1.34)	.18747175	0.33	0 0.78)	0.91-1.37
Genetic markers	Buurma AJ, 2013	CTLA4 rs231775	Retrospective	4	353/536	1.25 (1.01-1.56)	1.14 (0.80-1.61)	.04341501	0.82	1 (0.32)	0.68-2.29
Genetic markers	Buurma AJ, 2013	LPL rs1800590	Retrospective	3	395/579	2.27 (0.63-8.21)	0.81 (0.36-1.80)	.21122561	0.12	71 (0.03)	0-5626855
Genetic markers	Buurma AJ, 2013	LPL rs268	Retrospective	4	530/933	2.43 (1.26-4.68)	1.34 (0.51-3.50)	8.119×10^{-3}	0.66	20 (0.29)	0.35-17.1
Genetic markers	Buurma AJ, 2013	NOS3 27 bp-VNTR in intron 4	Retrospective	14	1593/2239	1.14 (0.90-1.43)	0.96 (0.71-1.30)	.2710968	0.03	63 (<0.01)	0.53-2.47
Genetic markers	Buurma AJ, 2013	NOS3 rs2070744	Retrospective	11	1571/2202	1.08 (0.95-1.23)	1.21 (0.96-1.52)	.25571731	0.10	28 (0.18)	0.80-1.46
Genetic markers	Buurma AJ, 2013	NOS3 rs1799983	Retrospective	24	2825/4048	1.19 (1.00-1.42)	1.79 (1.37-2.34)	.05650903	0.55	68 (<0.01)	0.56-2.52
Genetic markers	Buurma AJ, 2013	TLR4 rs4986790	Retrospective	4	723/614	1.07 (0.48-2.39)	3.03 (1.36-6.72)	.87139332	0.92	78 (<0.01)	0.03-38.2
Genetic markers	Buurma AJ, 2013	TLR4 rs4986791	Retrospective	3	614/461	1.20 (0.45-3.17)	2.92 (1.31-6.49)	.71483564	0.59	79 (<0.01)	0-123082
Genetic markers	Buurma AJ, 2013	TNF-alpha rs1800629	Retrospective	12	1592/1837	1.17 (0.91-1.49)	1.61 (1.17-2.22)	.21952434	0.48	54 (0.01)	0.56-2.41
Genetic markers	Buurma AJ, 2013	TNF-alpha rs1799724	Retrospective	3	390/385	0.66 (0.34-1.30)	1.18 (0.84-1.66)	.23144996	0.51	84 (<0.01)	0-2313
Genetic markers	Buurma AJ, 2013	VEGF rs3025039	Retrospective	3	377/514	1.36 (0.64-2.90)	0.73 (0.51-1.03)	.42048284	0.69	87(<0.01)	0-13603
Genetic markers	Cheng D, 2013	VEGF +936 C/T	Retrospective	8	805/1033	1.52 (1.09-2.12)	0.73 (0.51-1.03)	.0144147	0.58	69 (<0.01)	0.54-4.23
Genetic markers	Song GG, 2013	VEGF - 634 C/G	Retrospective	6	408/479	1.35 (1.09-1.67)	2.04 (1.33-3.13)	6.668×10^{-3}	0.86	12 (0.34)	0.90-2.01
Genetic markers	Song GG, 2013	VEGF -2578 A/ C	Retrospective	8	617/672	0.93 (0.78-1.10)	1.05 (0.78-1.41)	.39203909	0.99	13 (0.33)	0.68-1.26
Genetic markers	Song GG, 2013	VEGF -1154 A/G	Retrospective	3	159/161	1.14 (0.83-1.56)	1.06 (0.69-1.64)	.41612914	0.45	0 (0.89)	0.15-8.86
Genetic markers	Morgan JA, 2013	PAI-1 (4G/4G)	Mixed	12	1511/ 3492	1.28 (1.09-1.50)	1.19 (0.77-1.84)	2.646×10^{-3}	0.56	0 (0.63)	1.07-1.53
Genetic markers	Dai B, 2013	eNOS 4 b/a	Retrospective	10	1374/1376	1.43 (0.87-2.37)	1.77 (0.80-3.92)	.16052581	0.37	30 (0.17)	0.45-4.55
Genetic markers	Zhao L, 2013	SERPINE1 -675 4G/5G	Retrospective	11	1297/1791	1.37 (1.10-1.71)	1.66 (1.10-2.51)	5.112×10^{-3}	0.42	20 (0.25)	0.88-2.15
Genetic markers	Staines-Urias E, 2012	F5 rs6025	Mixed	41	4499/15188	1.74 (1.50-2.02)	1.67 (0.61-4.61)	2.902×10^{-13}	0.56	0 (0.53)	1.49-2.03
Genetic markers	Staines-Urias E, 2012	F2 rs1799963	Mixed	30	3546/11712	1.72 (1.40-2.12)	1.45 (0.67-3.14)	3.211×10^{-7}	0.03	0 (0.55)	1.38-2.14
Genetic markers	Staines-Urias E, 2012	ACE rs4646994	Mixed	30	3101/5134	1.17 (1.03-1.34)	1.03 (0.86-1.22)	.01714227	0.06	68 (<0.01)	0.65-2.13
Genetic markers	Staines-Urias E, 2012	AGT rs699	Mixed	27	2329/4896	1.26 (1.05-1.51)	1.31 (0.70-2.45)	.0110987	0.32	70 (<0.01)	0.57-2.79
Genetic markers	Staines-Urias E, 2012	MTHFR rs1801133	Mixed	51	5160/10151	1.06 (0.99-1.15)	1.21 (0.68-2.13)	.10516551	0.03	38 (<0.01)	0.79-1.49
Genetic markers	Staines-Urias E, 2012	SERPINE1 rs1799889	Mixed	12	1194/1757	0.89 (0.77-1.04)	0.90 (0.64-1.27)	.13240358	0.42	40 (0.76)	0.59-1.33
Genetic markers	Staines-Urias E, 2012	EPHX1 rs1051740	Mixed	4	562/462	0.85 (0.72-1.00)	0.94 (0.72-1.23)	.06194903	0.87	0 (0.51)	0.59-1.24
Genetic markers	Staines-Urias E, 2012	EPHX1 rs2234922	Mixed	3	425/427	1.28 (0.83-1.96)	1.87 (1.23-2.83)	.26470006	0.26	60 (0.08)	0.01-134
Genetic markers	Staines-Urias E, 2012	PPARG rs1801282	Mixed	3	390/449	0.80 (0.57-1.12)	0.81 (0.43-1.51)	.19441149	0.07	0 (0.90)	0.09-7.35
Genetic markers	Staines-Urias E, 2012	THBD C1418T	Mixed	3	260/268	0.71 (0.49-1.03)	0.78 (0.52-1.15)	.07266551	0.30	0 (0.50)	0.07-7.73
Genetic markers	Staines-Urias E, 2012	IL-6 rs1800795	Mixed	3	248/1575	0.91 (0.70-1.19)	0.91 (0.42-1.94)	.49809512	0.76	0 (0.90)	0.16-5.13
Genetic markers	Staines-Urias E, 2012	VEGFA rs699947	Mixed	3	225/269	0.88 (0.69-1.14)	0.92 (0.61-1.38)	.3352699	0.69	0 (0.90)	0.17-4.52
Genetic markers	Staines-Urias E, 2012	HLA-G -14 bp	Mixed	3	219/334	1.42 (0.68-2.98)	0.97 (0.68-1.38)	.35665444	0.90	85 (<0.01)	0-11540
Genetic markers	Staines-Urias E, 2012	LEP rs7799039	Mixed	3	198/326	1.51 (0.92-2.49)	1.20 (0.85-1.71)	.10567967	0.43	68 (0.05)	0.01-412
Genetic markers	Staines-Urias E, 2012	LEP TTTC	Mixed	3	141/227	0.86 (0.53-1.38)	1.01 (0.68-1.51)	.53082544	0.42	56 (0.10)	0.01-135
Genetic markers	Lin R, 2012	AGT M235T	Retrospective	29	5053/11578	1.61 (1.21-2.14)	1.40 (0.32-6.06)	9.986×10^{-4}	0.47	45 (<0.01)	0.57-4.52
Genetic markers	Lin R, 2012	AGT T174M	Retrospective	6	1362/4159	1.09 (0.76-1.57)	0.97 (0.54-1.74)	.63402843	0.35	48 (0.09)	0.40-2.95
Genetic markers	Zhao L, 2012	AGTR1 +1166A>C	Retrospective	10	845/1150	1.19 (0.96-1.47)	1.15 (0.67-1.99)	.11145683	0.42	27 (0.20)	0.74-1.91
Genetic markers	Zhong WG, 2012	ACE D/I	Retrospective	11	1600/1898	1.93 (1.19-3.12)	0.87 (0.59-1.28)	7.830×10^{-3}	0.26	91 (<0.01)	0.31-12.1
Genetic markers	Shaik AP, 2011	ACE (II genotype)	Retrospective	16	1620/2158	0.99 (0.70-1.40)	0.94 (0.57-1.54)	.93826151	0.79	73 (<0.01)	0.27-3.56
Genetic markers	Xie C, 2011	TNF-α 308 G/A	Retrospective	18	1888/2497	0.98 (0.76-1.25)	0.56 (0.36-0.87)	.85141826	0.56	52 (<0.01)	0.43-2.21
Genetic markers	Xie C, 2011	IL-6 -174 G/C	Retrospective	4	396/507	1.23 (0.93-1.61)	1.44 (0.89-2.33)	.14226516	0.44	0 (0.81)	0.67-2.24
Genetic markers	Rodger MA, 2010	FVL	Retrospective	9	1060/20773	1.26 (0.91-1.74)	1.27 (0.51-3.14)	.16965123	0.27	0 (0.99)	0.85-1.86
Genetic markers	Rodger MA, 2010	PGM	Prospective	6	549/13705	1.27 (0.80-2.03)	1.03 (0.41-2.56)	.31766677	0.30	0 (0.99)	0.65-2.46
Genetic markers	Medica I, 2007	AGT/T704C (Met235Thr)	Retrospective	15	1146/2276	1.66 (1.20-2.29)	0.29 (0.03-2.58)	2.242×10^{-3}	0.77	6 (0.38)	1.00-2.73
Genetic markers	Serrano NC, 2006	ACE-I/D	Mixed	22	2596/3828	1.23 (1.04-1.45)	0.90 (0.73-1.11)	.01737599	0.01	57 (<0.01)	0.66-2.26
Genetic markers	Lin J, 2005	FLV (1691 G-A)	Retrospective	11	1135/1471	2.25 (1.28-3.94)	2.21 (1.06-4.59)	4.609×10^{-3}	0.43	57 (<0.01)	0.42-12.2

Diseases/disorders	Saccone G, 2015	Celiac disease	Mixed	5	14618/507559	2.05 (0.89-4.74)	1.19 (0.79-1.78)	.09218346	0.66	90 (<0.01)	0.11-40.1
Diseases/disorders	Zhang JJ, 2015	Chronic kidney disease	Mixed	9	14993/504700	10.4 (6.28-17.1)	22.3 (15.6-31.9)	5.179×10^{-20}	0.71	77 (<0.01)	2.12-50.7
Diseases/disorders	Hu R, 2015	Depression	Mixed	5	1104/2874	1.66 (1.29-2.13)	1.12 (0.64-1.96)	6.521×10^{-5}	0.34	16 (0.32)	0.96-2.86
Diseases/disorders	Qin JZ, 2013	Polycystic ovary syndrome	Mixed	15	1866/1194098	3.26 (2.06-5.16)	2.04 (1.78-2.34)	4.327×10^{-7}	<0.01	41 (0.05)	1.02-10.43
Diseases/disorders	Zhang S, 2013	Mental stress	Mixed	12	16705/649188	1.49 (1.27-1.74)	1.14 (1.05-1.24)	5.169×10^{-7}	0.02	68 (<0.01)	0.97-2.29
Diseases/disorders	Zhang S, 2013	Work stress	Mixed	4	496/8246	1.50 (1.15-1.97)	1.51 (0.99-2.31)	3.197×10^{-3}	0.98	0 (0.75)	0.83-2.72
Diseases/disorders	Zhang S, 2013	Depression and anxiety	Mixed	5	753/7489	1.88 (1.08-3.25)	0.93 (0.55-1.59)	.0250717	0.44	73 (<0.01)	0.28-12.65
Diseases/disorders	Grigoriadis S, 2013	Maternal depression	Prospective	4	227/8843	1.35 (0.95-1.92)	1.24 (0.77-2.00)	.08895785	0.46	7 (0.36)	0.56-3.26
Supplementation	Schoenaker DA, 2014	Calcium intake	Mixed	3	387/1100	0.88 (0.60-1.29)	0.89 (0.53-1.52)	.51002502	0.87	0 (0.99)	0.07-10.82
Infections	Huang QT, 2016	Chronic hepatitis B infection	Retrospective	11	14298/423216	0.79 (0.63-1.00)	1.13 (0.78-1.63)	.04574222	0.90	20 (0.25)	0.51-1.25
Infections	Sgolastra F, 2013	Periodontal disease	Mixed	15	1040/3983	2.17 (1.38-3.41)	2.05 (1.47-2.86)	8.433×10^{-4}	0.50	78 (<0.01)	0.42-11.29
Infections	Rustveld LO, 2008	Bacterial & viral infections	Mixed	21	2390/11556	2.08 (1.63-2.66)	1.78 (1.18-2.67)	4.143×10^{-9}	0.65	56 (<0.01)	0.92-4.72
Other	Xu Y, 2016	Isolated single umbilical artery	Mixed	3	783/64443	0.82 (0.56-1.21)	0.84 (0.56-1.26)	.32120883	0.50	0 (0.85)	0.07-9.96
Other	Basaran A, 2016	CVS vs no invasive	Mixed	6	1189/46410	0.83 (0.42-1.66)	0.83 (0.61-1.13)	.60295188	0.29	92 (<0.01)	0.07-9.29
Other	Basaran A, 2016	CVS vs no invasive & amniocentesis	Mixed	7	1320/56266	1.00 (0.46-2.17)	0.83 (0.61-1.13)	.99506932	0.49	96 (<0.01)	0.06-16
Other	Wei J, 2015	Cigarette smoking	Prospective	17	62089/1784382	0.67 (0.60-0.75)	0.87 (0.83-0.91)	2.122×10^{-12}	0.36	92 (<0.01)	0.43-1.05
Other	Masoudian P, 2015	Oocyte donation vs ART	Retrospective	13	1499/25299	2.54 (1.98-3.24)	3.15 (2.27-4.37)	1.095×10^{-13}	0.90	14 (0.31)	1.61-4.00
Other	Masoudian P, 2015	Oocyte donation vs NC	Retrospective	4	2712/54816	4.33 (3.11-6.03)	3.35 (2.42-4.63)	3.477×10^{-18}	0.26	26 (0.26)	1.52-12.4
Other	Aune D, 2014	Pre-pregnancy PA high vs low activity	Mixed	5	621/9696	0.65 (0.45-0.94)	0.60 (0.30-1.20)	.02352111	0.63	0 (0.91)	0.36-1.19
Other	Aune D, 2014	Pre-pregnancy PA per 1hr per day	Mixed	3	479/6002	0.73 (0.53-0.99)	0.36 (0.07-1.88)	.04374593	0.09	0 (0.69)	0.10-5.42
Other	Aune D, 2014	Early pregnancy PA high vs low activity	Mixed	11	5702/162900	0.79 (0.70-0.91)	1.03 (0.74-1.44)	6.099×10^{-4}	0.90	0 (0.55)	0.68-0.92
Other	Aune D, 2014	Early pregnancy PA per 20 MET hrs/week	Mixed	3	2576/85388	0.86 (0.70-1.07)	0.98 (0.89-1.09)	.16690052	0.30	68 (0.04)	0.07-9.95
Other	Aune D, 2014	Early pregnancy PA per 1hr per day	Mixed	7	5293/151083	0.83 (0.73-0.95)	0.95 (0.80-1.14)	6.473×10^{-3}	0.66	20 (0.28)	0.63-1.09
Other	Aune D, 2014	Early pregnancy walking	Mixed	4	535/9674	0.68 (0.51-0.89)	1.00 (0.43-2.33)	5.549×10^{-3}	0.09	0 (0.75)	0.37-1.24
Other	Aune D, 2014	Early pregnancy occupational PA	Mixed	6	620/18119	0.82 (0.66-1.03)	0.75 (0.52-1.07)	.08838791	0.78	0 (0.68)	0.60-1.13
Other	González CM, 2014	Donor insemination	Mixed	7	2342/8556	1.57 (1.01-2.42)	1.69 (1.38-2.08)	.04326553	0.82	49 (0.07)	0.52-4.70
Other	Wang Z, 2013	Obese vs normal weight women (adjusted)	Prospective	10	34340/1685991	2.93 (2.58-3.33)	3.64 (2.54-5.21)	0	0.11	67 (<0.01)	2.07-4.15
Other	Wang Z, 2013	Severe obese vs normal weight women	Prospective	6	19976/877162	3.12 (2.24-4.37)	2.53 (2.32-2.76)	2.581×10^{-11}	0.60	97 (<0.01)	0.96-10.2
Other	Kasawara KT, 2012	Physical activity (case-control)	Mixed	6	923/8481	0.77 (0.53-1.11)	1.16 (0.72-1.86)	.15938804	0.93	76 (<0.01)	0.23-2.60
Other	Kasawara KT, 2012	Physical activity (cohort studies)	Mixed	10	5547/178680	0.94 (0.83-1.07)	1.10 (1.01-1.19)	.33829233	0.17	60 (<0.01)	0.67-1.32
Other	Luo ZC, 2007	Primiparity	Mixed	23	54462/1966490	2.42 (2.16-2.71)	2.27 (2.22-2.32)	0	0.58	92 (0)	1.47-3.97

Abbreviations: Random effects, summary odds ratio (95% CI) using random effects model; Largest effect, odds ratio (95% CI) of the largest study in the meta-analysis; Egger, p-value from Egger's regression asymmetry test for evaluation of publication bias; P, p-value; β-hCG, Human chorionic gonadotropin; PAPP-A, pregnancy-associated plasma protein A; PLGF, Placental growth factor; PP13, Placental Protein 13; sFlt-1, Soluble fms-like tyrosine kinase-1; HLA, Human leukocyte antigen; PIGF, placental growth factor; VEGF, vascular endothelial growth factor; sENG, soluble endoglin; NO_2, Nitrogen dioxide; NOx, Mono-nitrogen oxides; PM_{10}, Particulate matter 10 micrometers; CO, Carbon Monoxide; O_3, Ozone; IL-6, Interleukin 6; LEPR, leptin receptor; IL-18, Interleukin-18; IFN-γ, Interferon gamma; AT2R, Angiotensin type 2 receptor; IL-10, Interleukin 10; SNP, Single-nucleotide polymorphisms; MTHFR, Methylene tetrahydrofolate reductase; MMP-9, Matrix metallopeptidase 9; PAI-1, Plasminogen activator inhibitor-1; AGT, Angiotensinogen; AGTR1, Angiotensin II Receptor Type 1; ACE, Angiotensin; eNOS, Endothelial nitric oxide synthase; TNF, Tumor necrosis factor; FVL, Factor V Leiden; PGM, Prothrombin Gene Mutation; CVS, chorionic villus sampling; ART, assisted reproductive technology; NC, natural conception; PA, physical activity; NP, not pertinent, because the estimated is larger than the observed, and there is no evidence of excess of statistical significance based on the assumption made for the plausible effect size.

* Summary random effects odds ratio (95% CI) of each meta-analysis, except for two meta-analyses (Wei J 2015 and Aune D, 2014) where the RR was used.
‡ Odds ratio (95% CI) of the largest study in each meta-analysis, except for two meta-analyses (Wei J 2015 and Aune D, 2014) where the RR was used.
§ P-value from the Egger regression asymmetry test for evaluation of publication bias
|| I^2 metric of inconsistency and P-value of the Cochran Q test for evaluation of heterogeneity
≠ 95% Prediction Interval

Table 2. Observed and expected number of positive studies by type of risk factor*

Area	No. of studies	Observed positive	Expected positive (fixed) †	P‡ (fixed)	Expected positive (random)§	P‡ (random)	Expected positive (largest)‖	P‡ (largest)	Expected positive (composite) ¶	P‡ (composite)
All	1466	479	560.3	0.00	605.9	0.00	601.3	0.00	560.3	0.00
Biomarkers	353	178	166	0.20	200	0.02	133	0.00	133	0.00
Environmental	23	4	4.9	0.80	4.4	NP	10.5	0.01	4.4	NP
Genetic markers	830	162	229.6	0.00	235.5	0.00	323.4	0.00	229.6	0.00
Diseases & disorders	59	29	37.6	0.03	45	0.00	27.4	0.70	27.4	0.70
Supplementation	3	0	0.32	NP	0.32	NP	0.3	NP	0.3	NP
Infections	47	21	27.3	0.08	28.9	0.02	23	0.66	23	0.66
Other	151	85	95	0.09	92.2	0.24	84	0.93	84	0.93

* NP, not pertinent, because the estimated is larger than the observed, and there is no evidence of excess of statistical significance based on the assumption made for the plausible effect size.

† Expected number of statistically significant studies using the summary fixed effects estimate of each meta-analysis as the plausible effect size.

‡ P value of the excess of statistically significant test. All statistical tests were two-sided.

§ Expected number of statistically significant studies using the summary random effects estimate of each meta-analysis as the plausible effect size.

‖ Expected number of statistically significant studies using the effect of the largest study of each meta-analysis as the plausible effect size.

¶ Expected number of statistically significant studies using the most conservative of the three estimates (fixed effects summary, random effects summary, largest study) of each meta-analysis as the plausible effect size.

Table 3. Assessment across the statistically significant non-genetic associations for preeclampsia

Level of evidence	Criteria
Convincing	>1000 cases, [a] $P<10^{-6}$, not large heterogeneity (I^2 <50%), 95% prediction interval excluding the null value, no evidence for small-study effects [b] and excess significance bias [c]
Risk factors supported by convincing evidence	Oocyte donation vs normal conception
Highly suggestive	>1000 cases, [a] $P<10^{-6}$ and nominally statistically significant effect present at the largest study
Risk factors supported by highly suggestive evidence	Serum iron level, PAPP-A, Chronic kidney disease, Polycystic ovary syndrome, Mental stress, Bacterial & viral infections, Cigarette smoking*, Oocyte donation vs ART, Obese vs normal weight women, Severe obese vs normal weight women, Primiparity
Suggestive	>1000 cases, [a] $P<10^{-3}$
Risk factors supported by suggestive evidence	Serum Vitamin C*, sFLT1, Depression, Periodontal disease, Early pregnancy PA high vs low activity*
Weak	The rest associations with [a] $P < 0.05$
Risk factors supported by weak evidence	β-hCG, Serum zinc level*, PP13, Inhibin A, IFN-γ, Serum concentration of NO*, PlGF*, sENG, Arterial stiffness, Anticardiolipin antibodies, NO_2, O_3, Work stress, Depression and anxiety, 25 (OH) D <75 mmol/l, 25 (OH) D <50 mmol/l, Chronic hepatitis B infection*, Pre-pregnancy PA high vs low activity*, Pre-pregnancy PA per 1hr per day*, Early pregnancy PA per 1hr per day*, Early pregnancy walking*, Donor insemination

Abbreviations: β-hCG, Human chorionic gonadotropin; PAPP-A, pregnancy-associated plasma protein A; IFN-γ, Interferon gamma; PP13, Placental Protein 13; sFlt-1, Soluble fms-like tyrosine kinase-1; PlGF, placental growth factor; sENG, soluble endoglin; NO_2, Nitrogen dioxide; O_3, Ozone; ART, assisted reproductive technology; PA, physical activity

[a] P indicates the P-values of the meta-analysis random effects model.

[b] Small study effect is based on the P-value from the Egger's regression asymmetry test (P< 0.10).

[c] Based on the P-value (P<0.05) of the excess significance test using the largest study (smallest standard error) in a meta-analysis as the plausible effect size.

* Factors that show a protective effect against developing pre-eclampsia.

Table 4. Assessment of cumulative evidence on 26 significant (P<0.05) genetic associations with preeclampsia risk

Author, year	Gene or variant	Comparison	Studies	Cases/controls	Random effects*	P Random	Egger§	I^2 (P)‖	Excess statistical significance ≠	Venice Criteria†	Cumulative Evidence of Association ¥
Zeng F, 2016	G894T	TT vs GT + GG	26	3241/6419	1.45 (1.09-1.94)	.0118	0.65	41 (0.02)	No	BAA	++
Zhang G, 2016	rs18001133 in MTHFR	Carriers vs non-carriers	49	13356/23082	1.17 (1.05-1.31)	5.89×10^{-3}	0.32	75 (<0.01)	No	AAB	++
Zhang G, 2016	rs6025 in F5 gene	Carriers vs non-carriers	28	8210/9834	1.53 (1.06-2.21)	.0239	0.61	74 (<0.01)	No	BAB	++
Zhang G, 2016	rs1137101 in LEPR	Carriers vs non-carriers	28	8210/9834	1.53 (1.06-2.21)	.0239	0.61	74 (<0.01)	No	BAB	++
Li Y, 2015	A1675G of AT2R	GG vs AG + AA	5	972/3072	1.58 (1.05-2.37)	.0269	0.47	50 (0.09)	No	BAB	++
Yang W, 2014	IL-10 -819 C/T	C vs T	5	729/1146	1.28 (1.03-1.51)	.0248	0.86	41 (0.15)	No	AAB	++
Yang W, 2014	IL-10 -592 C/A	C vs A	3	459/926	1.28 (1.03-1.59)	.0264	0.39	0 (0.46)	No	BAA	++
Wang X, 2014	G20210A SNP	GG vs GA/AA	16	2296 /3262	1.79 (1.23-2.61)	2.55×10^{-3}	0.96	0 (0.92)	No	AAB	++
Wang X, 2014	V G1691A SNP	GG vs GA/AA	23	3131/4036	1.60 (1.25-2.06)	2.44×10^{-4}	<0.01	15 (0.25)	No	AAB	++
Li X, 2014	MTHFR C677T	CT + TT vs CC	47	6238/11771	1.12 (1.04-1.22)	5.19×10^{-3}	0.16	14 (0.21)	Yes	AAB	++
Li X, 2014	TGF-β 1 869 T >C	TT vs TC + CC	4	466/618	0.70 (0.57-0.86)	6.05×10^{-4}	0.93	0 (0.84)	No	BAA	++
Buurma AJ, 2013	CTLA4 rs231775	Carriers vs non-carriers	4	353/536	1.25 (1.01-1.56)	.0434	0.82	14 (0.32)	No	BAA	++
Buurma AJ, 2013	LPL rs268	Carriers vs non-carriers	4	530/933	2.43 (1.26-4.68)	.0081	0.66	20 (0.29)	No	BAA	++
Cheng D, 2013	VEGF +936 C/T	T vs C	8	805/1033	1.52 (1.09-2.12)	.0144	0.58	69 (<0.01)	No	BAC	+
Song GG, 2013	VEGF - 634 C/G	C vs G	6	408/479	1.35 (1.09-1.67)	6.67×10^{-3}	0.86	12 (0.34)	No	BAB	++
Morgan JA, 2013	PAI-1	4G/4G	12	1511/ 3492	1.28 (1.09-1.50)	2.65×10^{-3}	0.56	0 (0.63)	No	AAA	+++
Zhao L, 2013	SERPINE1 -675	4G/4G vs 4G/5G + 5G/5G	11	1297/1791	1.37 (1.10-1.71)	5.11×10^{-3}	0.42	20 (0.25)	No	BAB	++
Staines-Urias E, 2012	F5 rs6025	Carriers vs non-carriers	41	4499/15188	1.74 (1.50-2.02)	2.90×10^{-13}	0.56	0 (0.53)	Yes	AAB	++
Staines-Urias E, 2012	F2 rs1799963	Carriers vs non-carriers	30	3546/11712	1.72 (1.40-2.12)	3.21×10^{-7}	0.03	0 (0.55)	Yes	BAB	++
Staines-Urias E, 2012	ACE rs4646994	Carriers vs non-carriers	30	3101/5134	1.17 (1.03-1.34)	.0171	0.06	68 (<0.01)	Yes	AAC	+
Staines-Urias E, 2012	AGT rs699	Carriers vs non-carriers	27	2329/4896	1.26 (1.05-1.51)	.0111	0.32	70 (<0.01)	No	AAB	++
Lin R, 2012	AGT M235T	TT vs MM	29	5053/11578	1.61 (1.21-2.14)	9.99×10^{-4}	0.47	45 (<0.01)	Yes	AAC	+
Zhong WG, 2012	ACE D/I	D vs I	11	1600/1898	1.93 (1.19-3.12)	7.83×10^{-3}	0.26	91 (<0.01)	Yes	AAC	+
Medica I, 2007	AGT/T704C (Met235Thr)	CC + TT vs TT	15	1146/2276	1.66 (1.20-2.29)	2.24×10^{-3}	0.77	6 (0.38)	No	BAB	++
Serrano NC, 2006	ACE-I/D	Carriers vs non-carriers	22	2596/3828	1.23 (1.04-1.45)	.0174	0.01	57 (<0.01)	No	AAC	+
Lin J, 2005	FLV (1691 G-A)	Carriers vs non-carriers	11	1135/1471	2.25 (1.28-3.94)	4.61×10^{-3}	0.43	57 (<0.01)	No	BAA	++

Abbreviations: Random effects, summary odds ratio (95% CI) using random effects model; Largest effect, odds ratio (95% CI) of the largest study in the meta-analysis; Egger, p-value from Egger's regression asymmetry test for evaluation of publication bias; P, p-value; PIGF, placental growth factor; VEGF, vascular endothelial growth factor; IL-6, Interleukin 6; LEPR, leptin receptor; AT2R, Angiotensin type 2 receptor; IL-10, Interleukin 10; SNP, Single-nucleotide polymorphisms; MTHFR, Methylene tetrahydrofolate reductase; MMP-9, Matrix metallopeptidase 9; PAI-1, Plasminogen activator inhibitor-1; AGT, Angiotensinogen; AGTR1, Angiotensin II Receptor Type 1; ACE, Angiotensin; eNOS, Endothelial nitric oxide synthase; TNF, Tumor necrosis factor; FVL, Factor V Leiden; PGM, Prothrombin Gene Mutation.

* Summary random effects odds ratio (95% CI) of each meta-analysis.
‡ Odds ratio (95% CI) of the largest study in each meta-analysis
§ P-value from the Egger regression asymmetry test for evaluation of publication bias
‖ I^2 metric of inconsistency and P-value of the Cochran Q test for evaluation of heterogeneity
≠ Based on the P-value (P<0.05) of the excess significance test using the largest study (smallest standard error) in a meta-analysis as the plausible effect size.
†Venice Criteria grades are in the order of amount of evidence, replication of the association and protection from bias
¥ Cumulative epidemiological evidence as graded by the Venice criteria as strong (+++), moderate (++), or weak (+) for association with preeclampsia risk

Figure Legends

Figure 1. Flowchart of the included studies