SELECTED GENETIC POLYMORPHISMS AND THEIR ASSOCIATION WITH PRE-ECLAMPSIA: A META-ANALYSIS AND POWER ANALYSIS

Sharon Benita Stephen[1], Rozario Cyril[2*], Dapkupar Wankhar[3*], M.K Anbumozhi[4*], M. Muthuselvi[5*] and Gowtham Kumar Subbaraj[1#]

[1]*Faculty of Allied Health Science, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Tamil Nadu, India*
[2]*Department of Pharmacology, JKKN Dental College and Hospital (Affiliated Tamil Nadu Dr. MGR Medical University), Kumarapalayam, Namakkal District 638183, Tamil Nadu, India*
[3]*Faculty of Paramedical Sciences, Assam down town University, Sankar Madhab Path, Gandhi Nagar, Panikhaiti, Guwahati, cAssam, India*
[4] *Department of Pathology, Sree Balaji Medical College And Hospital, Chrompet, Chennai-600044,Tamilnadu, India*
**Equal Contributors*

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Corresponding author:

Gowtham Kumar Subbaraj

Faculty of Allied Health Science, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam, 603103, Tamil Nadu, India

E-mail: gowtham_phd@yahoo.com

ABSTRACT

This meta-analysis investigates the association between four gene polymorphisms - IL1A rs17561, IFN-γ rs2430561, STOX1 rs1341667, and PPAR-γ rs1801282 and the risk of preeclampsia (PE). Case-control studies published between 2005 and 2025 were retrieved from Scopus, PubMed, Web of Science and Google Scholar. The inclusion of newly available data enhances statistical power and offers an updated, reliable synthesis of evidence. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using MetaGenyo software across various genetic models. Power analysis validated statistical strength, and protein-protein interaction (PPI) networks were constructed using the database, STRING. A total of 14 research articles, including 3,151 PE cases and 6,101 controls data were analysed. The IL1A rs17561 polymorphism was significantly linked to preeclampsia (PE) susceptibility, demonstrating a protective effect under the recessive model (OR = 0.67) and an elevated risk for heterozygous carriers in the over-dominant model (OR = 1.49). Subgroup analyses were feasible for IFN-γ, STOX1, and PPAR-γ, but no significant associations were identified. Power analysis confirmed an adequate sample size, and PPI network analysis revealed interactions involving 8 nodes and 7 edges. The findings suggest that IL1A rs17561 has a variant-specific influence on preeclampsia risk, supporting the role of IL-1–mediated inflammation in its pathogenesis, while IFN-γ, STOX1, and PPAR-γ polymorphisms showed no significant associations.

Keywords: *Pre-eclampsia, Gene Polymorphism, IL1A, IFN-γ, STOX1, PPAR-γ.*

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INTRODUCTION

Preeclampsia (PE) is a hypertension-related condition that occurs during pregnancy and continues to be a major contributor to maternal and fatal complications and deaths worldwide. Contributing to over 50,000 maternal deaths annually, recent estimates indicate that PE complicates approximately 4.6% of pregnancies globally [1,2]. PE occurs after 20 weeks of pregnancy with symptoms of proteinuria and elevated blood pressure, presenting a major risk to the mother as well as the fetus, such as preterm birth, intrauterine growth retardation, and long-term cardiovascular complications [3]. Although preeclampsia's exact cause is unknown, an intricate interplay of environmental variables, immunological, and genetic factors is thought to be a reason. [4]. Furthermore, there is growing evidence that the pathophysiology of PE is profoundly influenced by both poor placental development and dysregulation of the maternal immune response. Gene polymorphisms about trophoblast function and immune response are now being studied as possible factors contributing to PE risk. Among the genetic factors under investigation, key polymorphisms in cytokines and transcription factors, including Interleukin-1 Alpha (IL1A rs17561), Interferon-gamma (IFN-γ rs2430561), Storkhead Box 1 [STOX1 rs1341667 (Y513H)], and Peroxisome Proliferator-Activated Receptor Gamma [PPAR-γ rs1801282 (Pro12Ala)], have been identified as potential contributors to PE risk. IL1A rs17561 is a strong pro-inflammatory cytokine that modulates placental growth and trophoblast invasion during pregnancy. However, high IL1A rs17561 activity causes endothelial damage and persistent inflammation, both essential for developing PE [5]. The IL1A rs17561 polymorphism, a missense variant resulting in an amino acid change, has been linked to increased PE risk and altered cytokine production. The protein's stability and function may be affected by this polymorphism, which could worsen the inflammatory response at the maternal-fetal interface and impair placentation. Like IL1A rs17561, IFN-γ rs2430561 is a pro-inflammatory cytokine that shows a dual role in pregnancy by regulating immune responses and placental development. However, dysregulated IFN-γ rs2430561 has been associated with impaired trophoblast function and increased inflammation, which are hallmarks of PE [6]. The IFN-γ rs2430561 polymorphism, which comprises a T to A substitution, is located in the gene's first intron. It is speculated that this alteration affects IFN-γ rs2430561 transcriptional activity, which could result in an imbalance between pro- and anti-inflammatory responses that aid in the pathophysiology of PE. STOX1 rs1341667 (Y513H), which is a transcription factor expressed in the placenta, has also been identified as a candidate gene for PE. It is involved in the regulation of trophoblast proliferation, invasion, and differentiation, which are essential for successful placentation. Dysregulation of STOX1 rs1341667 expression has been associated with defective spiral artery remodelling, which is a characteristic feature of PE [7]. The STOX1 rs1341667 polymorphism has been linked to altered trophoblast function and increased susceptibility to PE [8]. This polymorphism may disrupt the normal development of the placenta, leading to inadequate blood supply to the foetus and the subsequent development of PE. Similarly, PPAR-γ rs1801282 (Pro12Ala) is a nuclear receptor involved in lipid metabolism and inflammation and plays a key role in angiogenesis and immune tolerance. The PPAR-γ rs1801282 polymorphism, a missense variant, has been associated with altered receptor activity and increased PE risk [9]. This polymorphism can affect the transcriptional activity of PPAR-γ rs1801282, altering its ability to regulate genes involved in lipid metabolism and inflammation, which are critical for maintaining a healthy pregnancy. While individual studies have explored the associations between polymorphisms in these genes and the risk of preeclampsia, findings have often been inconsistent, likely due to variations in study design, population demographics, and sample sizes. A comprehensive meta-analysis is therefore essential to synthesize the available evidence and clarify the strength and consistency of these associations. Therefore, the current meta-analysis aims to assess the association between IL1A rs17561, IFN-γ rs2430561, STOX1 rs1341667, and PPAR-γ rs1801282 gene polymorphisms and PE in pregnant women.

RATIONALE OF THE STUDY

This meta-analysis aims to explore the genetic factors contributing to PE, focusing on IL1A, IFN-γ, STOX1, and PPAR-γ as key candidate genes. The year 2005 was chosen as the starting point for our search because large-scale, peer-reviewed genetic association studies on preeclampsia became available only after this time. Earlier publications often lacked standardized genotyping methods or uniform diagnostic criteria for preeclampsia, which could introduce methodological heterogeneity. Restricting inclusion from 2005 onward ensured the consistency and reliability of the data analysed. The development of PE is influenced by the roles of these genes in inflammation, placental function, and metabolic control. IFN-γ affects trophoblast activity and immune tolerance, while IL1A encodes IL-1α, a cytokine associated with the elevated inflammatory response in PE. Trophoblast development and spiral artery remodelling depend on STOX1, while PPAR-γ controls lipid metabolism and vascular health. This meta-analysis aims to expand the available data, evaluate ethnic differences, and elucidate the link among these polymorphisms and PE risk by combining data from several studies. The findings could advance our knowledge of the genetic foundation of PE, encourage tailored preventative strategies, and advance the integration of genetic screening into prenatal care, which can help to improve the health outcomes of both the mother and the fetus by identifying potential genetic risks early and enabling personalized interventions.

MATERIALS AND METHODOLOGY

The protocol for this review was registered with PROSPERO (ID NO: CRD420251130314). The review process was conducted in accordance with the PRISMA 2020

guidelines, and the search policy and study selection procedure are detailed in Figure 1.

Literature search

Related articles were obtained by widespread electronic searches conducted by using Web of Science, Scopus, PubMed, and Google Scholar from 22nd April 2005 till 15th February 2025. From the Scopus database, we have searched the articles using the keywords "IL1A and Pre-eclampsia", "IFN-γ and Pre-eclampsia", "STOX1 and Pre-eclampsia", "PPAR-γ and Pre-eclampsia, were identified; IL1A (rs17561) – 84 articles; IFN-γ (rs2430561) – 114 articles; STOX1 (rs1341667) – 43 articles; PPAR-γ (rs1801282) – 114 articles.

From the PubMed database, we have searched the articles using the keywords "IL1A and Pre-eclampsia", "IFN-γ and Pre-eclampsia", "STOX1 and Pre-eclampsia", "PPAR-γ and Pre-eclampsia, were identified IL1A (rs17561) – 7 articles; IFN-γ (rs2430561) – 112 articles; STOX1 (rs1341667) – 42 articles; PPAR-γ (rs1801282) – 53 articles.

From the Web of Science database, we have searched the articles using the keywords "IL1A and Pre-eclampsia", "IFN-γ and Pre-eclampsia", "STOX1 and Pre-eclampsia", "PPAR-γ and Pre-eclampsia, were identified; IL1A (rs17561) – 102 articles; IFN-γ (rs2430561) – 144 articles; STOX1 (rs1341667) – 77 articles; PPAR-γ (rs1801282) – 117 articles.

From the Google Scholar, we have searched the articles using the keywords "IL1A and Pre-eclampsia", "IFN-γ and Pre-eclampsia", "STOX1 and Pre-eclampsia", "PPAR-γ and Pre-eclampsia, were identified IL1A (rs17561) – 1370 articles; IFN-γ (rs2430561) – 5520 articles; STOX1 (rs1341667) – 685 articles; PPAR-γ (rs1801282) – 848 articles.

The examination policy employed the Boolean operator "AND" to achieve precise results. English-language articles were used exclusively throughout the search. In addition to the above, all databases, Google Scholar was also used to identify the relevant case vs. control studies using the following keywords ("IL1A", "IFN-γ", "STOX1", "PPAR-γ, Pre-eclampsia) and the filters (22nd April 2005 till 15th February 2025). Rayyan software was employed as an automation tool to facilitate duplicate removal and initial screening of articles during the literature search. Additionally, we ensured data reliability by removing duplicates within the updated database, including reviews, and existing meta-analyses as well. The year 2005 was chosen as the starting point for our literature search because large-scale, peer-reviewed genetic association studies on preeclampsia became increasingly available only after this time. Earlier publications often lacked standardized genotyping methods, consistent diagnostic criteria for preeclampsia, or adequate sample sizes, which could introduce methodological heterogeneity and reduce comparability across studies. Restricting inclusion from 2005 onward, therefore, ensured that the studies analyzed were conducted with improved methodological rigor, enhancing the reliability and reproducibility of the meta-analysis findings. We have analysed and extracted data from the two authors (Sharon Benita Stephen and Rozario Cyril), independently selected the titles, abstracts, and full texts of all selected studies. Discrepancies regarding eligibility were resolved through discussion, and when consensus could not be reached, a third author (Gowtham Kumar Subbaraj) adjudicated.

Inclusion criteria

Articles are cautiously selected for the meta-analysis based on selection criteria. To fulfil the inclusion criteria, the article needed to examine the IL1A rs17561, IFN-γ rs2430561, STOX1 rs1341667, and PPAR-γ rs1801282 gene polymorphisms association with PE. The criteria were considered for the inclusion of the data: Full text in the English language is available; Case-control studies using gene polymorphism association studies on PE and variations in IL1A rs17561, IFN-γ rs2430561, STOX1 rs1341667, and PPAR-γ rs1801282. Study examines how allele and genotype data are distributed among cases and controls.

Exclusion criteria

The following articles were excluded: Reviews or prior meta-analyses about IL1A rs17561, IFN-γ rs2430561, STOX1 rs1341667, and PPAR-γ rs1801282 with PE; Investigations not associated between the genes IL1A rs17561, IFN-γ rs2430561, STOX1 rs1341667, and PPAR-γ rs1801282 and pre-eclampsia risk; Articles with duplicated data; Case studies and research on animals that overlapped with different areas of study. Studies in which ethnic subgroups were reported but genotype frequencies were not separable according to our predefined classification criteria were excluded from subgroup analyses to avoid misclassification bias.

Data extraction and Quality assessment

Extracting key data from each study, including name of the author, publication year, ethnicity of the study population, country, allele frequencies, and genotype of IL1A rs17561, IFN-γ rs2430561, STOX1 rs1341667, and PPAR-γ rs1801282. The individual characteristics like gender, age, and sample size were taken into consideration. The HWE p-value has also been determined. To assess the risk of studies, we assessed their methodological quality using the Newcastle–Ottawa Scale. Because all eligible studies were observational case-control genetic association studies, we assessed study quality using the Newcastle-Ottawa Scale (NOS; case-control version). Two authors independently evaluated each study across the NOS domains (Selection, Comparability, Exposure). Disagreements were resolved by consensus with a third reviewer. We categorized the overall risk as low (NOS 7–9), some concerns/moderate (NOS 5–6), or high (NOS ≤4).

Power analysis

The acquired metadata was subjected to power analysis with a 95% CI (0.05 α error). By using the GPower 3.1 software, the sample size power of each study (case and control) was aggregated and analysed individually for each selected gene.

Protein-to-protein interactions

To understand the gene variations linked to PE and the protein function of three genes, such as IL1A rs17561, STOX1 rs1341667, and PPAR-γ rs1801282, was analyzed. The IFN-γ rs2430561 gene couldn't be identified in the database. The STRING database (version 11.0) was utilized to predict functional changes and protein-protein interactions (PPIs) with a confidence score of ≥ 0.4.

Statistical analysis

Statistical analysis was done in analyzing the importance of IL1A rs17561, IFN-γ rs2430561, STOX1 rs1341667, and PPAR-γ rs1801282 gene polymorphism with PE susceptibility. The association between IL1A rs17561, IFN-γ rs2430561, STOX1 rs1341667, and PPAR-γ rs1801282 polymorphism and PE susceptibility was estimated, along with the 95% confidence interval (CI) range of values lying within the degree of confidence. A p-value of <0.05 was considered statistically significant. The Index of Inconsistency (I^2) was utilized to assess the consistency of findings across all studies. I^2 quantifies the percentage of the total variability in observed effect estimates that is attributable to true between-study heterogeneity rather than sampling error. I^2 value of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity. A heterogeneity value less than 50% led the study group for a fixed effect model, and a heterogeneity value above 50% led the study group to use a random effect model. A Chi-square test was conducted to determine the heterogeneity, using the Q statistic. A Z-test was used to calculate the odds ratios (ORs) for multiple comparisons. A combined Odds Ratio (OR) was calculated across all studies to evaluate the overall impact of genetic factors. When the Z-test p-value was less than 0.05, the combined effect was deemed statistically significant. MetaGenyo, a robust programme used to conduct statistical analysis.

RESULTS

Search results

The present research observed 14 studies [5, 9-21], out of which studies comprising four genes, namely IL1A rs17561, IFN-γ rs2430561, STOX1 rs1341667, and PPAR-γ rs1801282, with a sum of 3151 PE cases and 6101 normal controls, were selected for this meta-analysis. Figure 1 represented the data of the selected case vs. control studies.

Risk bias

Based on the NOS assessment, studies were assigned overall risk classifications (low, moderate, or high) according to the total NOS score. In line with our prespecified rule, the pooled evidence was considered to present a low overall risk of bias.

Quantitative data analysis of IL1A rs17561, IFN-γ rs2430561, STOX1 rs1341667, and PPAR-γ rs1801282 and PE

Across four candidate gene polymorphisms, significant associations with preeclampsia (PE) risk were only identified for the IL1A (rs17561) gene polymorphism, while IFN-gamma (rs2430561), STOX1 (rs1341667), and PPAR-gamma (rs1801282) showed no significant link in any tested genetic model. Exposure to IL1A rs17561 was significantly associated with preeclampsia risk across multiple genetic models. Specifically, the recessive model (AA vs. AC+CC, OR = 0.67, 95% CI 0.52-0.87, p = 0.002) indicated a significant protective effect, whereas the dominant model (AA+AC vs. CC, OR = 1.03, 95% CI 0.56-1.88, p = 0.92) suggested there is no significant association with PE. In contrast, the allelic model (A vs. C, OR =0.88, 95% CI 0.76-1.0, p = 0.07) suggested that there is no significance with PE and the over-dominant model (AC vs. AA+CC, OR = 1.49, 95% CI 1.16-1.91, p = 0.001) indicated that heterozygous carriers (AC) may have an increased risk. These findings highlight a complex genetic influence of IL1A rs17561, consistent with the variable roles of IL-1 signalling in inflammatory responses during pregnancy, as shown in Figure 2. The results of IFN-γ rs2430561 for the all the four models had no significant link with PE [the allelic model (T vs. A OR 1.05, 95% CI 0.59-1.86, p=0.8); the recessive model (TT vs. TA+AA OR 0.86, 95% CI 0.32-2.32, p=0.7); the dominant models (TT+TA vs. AA OR 1.18, 95% CI 0.66-2.11, p=0.5); and the over-dominant models (TA vs. TT+AA OR 1.26, 95% CI 0.98-1.61, p=0.06)] as shown in Figure 3.

The results of STOX1 rs1341667 for the all the four models had no significant link with PE [the allelic model (T vs. C OR 0.96, 95% CI 0.87-1.05, p=0.3); the recessive model (OR 0.86, 95% CI 0.62-1.20, p=0.3); the dominant model (TT+TC vs. CC OR 0.98, 0.86-1.12, p=0.7); the overdominant model (OR 1.08, 95% CI 0.83-1.39, p=0.5)] as shown in Figure 4.

The results of PPAR-γ rs1801282 for all the four models had no significant link with PE [the allelic model (C vs. G OR 1.03, 95% CI 0.74, 1.42, p=0.8); the recessive model (CC vs. CG+GG OR 1.00, 95% CI 0.69-1.44, p=0.9); the dominant model (CC+CG vs. GG OR 1.06, 95% CI 0.12-9.41, p=0.9); and the over-dominant model (CG vs. CC+GG OR 1.04, 95% CI 0.71-1.50, p=0.8) as shown in Figure 5.

Sensitivity analysis

To evaluate the robustness of our pooled estimates, the sensitivity analysis was done by sequentially omitting individual studies. The pooled ORs for several gene polymorphisms proved sensitive to the removal of single studies, suggesting a lack of complete robustness in these specific models (Figures 6–9). The combined effect size for the IL1A

(rs17561) gene polymorphism was found to be dependent on the inclusion of the study by Li et al. (2014). Omitting this study resulted in a loss of statistical significance for both the recessive model (OR = 0.75; 95% CI 0.52–1.07, becoming non-significant) and the over-dominant model (OR = 1.36; 95% CI 0.95–1.96, becoming non-significant). This sensitivity indicates that the statistical significance observed in the main analysis for these two models is not robust (Figure 6). Similarly, the results for the IFN-γ (rs2430561) polymorphism showed instability. The combined effect size for the recessive model was significantly altered by the removal of Pinheiro et al. (2015), which resulted in the combined effect size shifting from non-significant to significant (OR = 0.57; 95% CI 0.35–0.85). The dominant model was also sensitive: omitting Daher et al. (2006) resulted in a significant combined effect size (OR = 1.36; 95% CI 1.03–1.80) (Figure 7). For the STOX1 (rs1341667) gene polymorphism, the pooled estimate for the recessive model was likewise sensitive. Removal of the study by Fenstad et al. (2010) changed the result from non-significant to significant (OR = 0.77; 95% CI 0.61–0.98) (Figure 8). This sensitivity analysis suggests that the observed associations, including the significant IL1A findings and the non-significant findings for IFN-gamma and STOX1, are not entirely robust and must be interpreted with extreme caution. Therefore, we must downgrade the confidence in the significant associations found for the IL1A recessive and over-dominant models, as their significance was lost upon the removal of one study. Similarly, the non-significant findings for IFN-gamma and STOX1 cannot be definitively concluded, as removing other studies caused them to become significant. Future significant, well-designed studies are critically needed to independently validate the associations for the recessive and over-dominant models of IL1A (rs17561), and to confirm the true lack of association for IFN-gamma (rs2430561) and STOX1 (rs1341667). Until such replication occurs, these particular pooled findings should be considered preliminary and highly conditional.

Construction of PPI network and Power analysis

The STRING database was used to build and examine the Protein-Protein Interaction (PPI) network for polymorphic proteins, namely for PPAR-γ rs1801282, STOX1 rs1341667, and IL1A rs17561. The network consists of 8 nodes and 7 edges, where IL1A rs17561 and PPAR-γ rs1801282 exhibit a direct interaction, while STOX1 rs1341667 does not directly interact with any of the genes, as shown in Figure 10. Power analysis was used to further assess each study's significance level and validate the sample sizes within the necessary threshold (α error prob < 0.05). Table 5 provides specifics on the power analysis findings. Furthermore, the Circos plot, as shown in Figures 11(a), (b), (c) & (d), visually depicts the chromosomal locations of the genes under study, transcriptional regulators, and histone modifications, providing information about possible gene interactions and risk allele grouping.

Table 1. Characteristics of the studies for the association of IL1A rs17561, IFN-γ rs2430561, STOX1 rs1341667, and PPAR-γ rs1801282 gene polymorphism with PE

Gene	Study	Ethnicity	Country	PE Cases			Controls			HWE P-value	HWE adjusted P-value	NOS Score
				AC_Cases	CC_Cases	AA_Cases	AC_Controls	CC_Controls	AA_Controls			
IL1A rs (17561)	Li et al., 2014 [5]	Asian	China	53	344	5	111	436	7	0	0	8
	Andraweera et al., 2016 [10]	Asian	Sri Lanka	77	79	16	92	60	16	0.1865	0.1865	7
	Wu et al., 2017 [11]	Asian	China	15	76	0	39	192	1	0	0	7
				TT_Cases	TA_Cases	AA_Cases	TT_Controls	TA_Controls	AA_Controls			
IFN-γ (rs2430561)	Kamali-Sarvestani et al., 2006 [12]	Asian	Iran	21	66	42	30	78	53	0.8903	0.8903	6
	Daher et al., 2006 [13]	Mulatto	Brazil	6	25	24	22	38	29	0.1842	0.8776	7
	Daher et al., 2006_1 [13]	Black	Brazil	9	52	34	17	43	36	0.5075	0.8776	8
	de Lima et al., 2009 [14]	Caucasian	Brazil	7	46	32	18	45	33	0.7021	0.8776	8
	Pinheiro et al., 2015 [15]	Caucasian	Brazil	33	51	32	5	40	62	0.6497	0.8776	7
				TT_Cases	TC_Cases	CC_Cases	TT_Controls	TC_Controls	CC_Controls			
STOX1 (rs1341667)	Kim et al., 2009 [18]	Asian	Korea	155	42	5	150	53	1	0.1041	0.4164	7
	Fenstad et al., 2010 [19]	Caucasian	Norway	124	450	412	245	931	840	0.5981	0.9707	7
	Pinarbasi et al., 2020 [20]	Asian	Turkey	108	280	112	143	249	108	0.9839	0.9839	7
	Bildirici et al., 2023 [17]	Asian	Turkey	10	31	9	18	23	9	0.728	0.9707	8
				CC_Cases	CG_Cases	GG_Cases	CC_Controls	CG_Controls	GG_Controls			
PPAR-γ (rs1801282)	Laasanen et al., 2002 [16]	Caucasian	Finland	95	36	2	76	34	5	0.6334	0.6334	8
	Ghorbani et al., 2021 [21]	Asian	Iran	75	25	0	77	23	0	0.1938	0.5814	6
	Liu et al., 2021 [9]	Caucasian	France	26	8	1	1297	301	15	0.5922	0.6334	8

*HWE-Hardy-Weinberg equilibrium

Table 2. Subgroup analysis for the association of IFN-γ rs2430561 gene polymorphism with PE

Model	Ethnicity	Number of studies	Test of association			Test of heterogeneity		
			OR	95% CI	p-value	Model	p-value	$I^{\wedge 2}$
Allele contrast (A vs. a)	Overall	5	1.0490	[0.5910; 1.8618]	0.870201	Random	0	0.8985
	Asian	1	0.96	[0.6891; 1.3373]	0.80928	Fixed	NA	NA
	Black	1	0.8712	[0.5767; 1.3161]	0.512451	Fixed	NA	NA
	Caucasian	2	1.5813	[0.3650; 6.8515]	0.540133	Random	0	0.9596
	Mulatto	1	0.5934	[0.3623; 0.9718]	0.038098	Fixed	NA	NA
Recessive model (AA vs. Aa+aa)	Overall	5	0.8575	[0.3165; 2.3233]	0.76239	Random	0	0.8531
	Asian	1	0.8491	[0.4599; 1.5675]	0.600945	Fixed	NA	NA
	Black	1	0.4863	[0.2050; 1.1536]	0.101889	Fixed	NA	NA
	Caucasian	2	1.7678	[0.0901; 34.6947]	0.70757	Random	0	0.9484
	Mulatto	1	0.3729	[0.1407; 0.9886]	0.047374	Fixed	NA	NA
Dominant model (AA+Aa vs. aa)	Overall	5	1.1796	[0.6586; 2.1129]	0.578522	Random	0.0005	0.7998
	Asian	1	1.0165	[0.6205; 1.6653]	0.948084	Fixed	NA	NA
	Black	1	1.0765	[0.5974; 1.9396]	0.806235	Fixed	NA	NA
	Caucasian	2	1.7805	[0.4395; 7.2133]	0.418949	Random	0.0007	0.9128
	Mulatto	1	0.6243	[0.3121; 1.2486]	0.182821	Fixed	NA	NA
Overdominant (Aa vs. AA + aa)	Overall	5	1.2604	[0.9840; 1.6146]	0.066959	Fixed	0.9406	0
	Asian	1	1.1148	[0.7014; 1.7718]	0.645821	Fixed	NA	NA
	Black	1	1.4903	[0.8429; 2.6366]	0.17081	Fixed	NA	NA
	Caucasian	2	1.3245	[0.5918; 1.9670]	0.163787	Fixed	0.9665	0
	Mulatto	1	1.1184	[0.5684; 2.2007]	0.745874	Fixed	NA	NA
pairw1 (AA vs. aa)	Overall	5	0.9602	[0.2962; 3.1128]	0.945989	Random	0	0.8763
	Asian	1	0.8333	[0.4434; 1.7596]	0.724229	Fixed	NA	NA
	Black	1	0.5606	[0.2203; 1.4265]	0.224535	Fixed	NA	NA
	Caucasian	2	2.2588	[0.0759; 67.2004]	0.63785	Random	0	0.9551
	Mulatto	1	0.3295	[0.1151; 0.9429]	0.03869	Fixed	NA	NA
pairw2 (AA vs. Aa)	Overall	5	0.7764	[0.3299; 1.8271]	0.562168	Random	0.0011	0.78
	Asian	1	0.8273	[0.4332; 1.5797]	0.5656	Fixed	NA	NA
	Black	1	0.4378	[0.1774; 1.0804]	0.073098	Fixed	NA	NA
	Caucasian	2	1.2946	[0.1080; 15.5093]	0.798861	Random	0.0003	0.9241
	Mulatto	1	0.4143	[0.1474; 1.1661]	0.095159	Fixed	NA	NA
pairw3 (Aa vs. aa)	Overall	5	1.2652	[0.9630; 1.6623]	0.091184	Fixed	0.1302	0.4372
	Asian	1	1.0678	[0.6342; 1.7977]	0.805154	Fixed	NA	NA
	Black	1	1.2804	[0.6896; 2.3774]	0.433623	Fixed	NA	NA
	Caucasian	2	1.6266	[0.7062; 3.7468]	0.253147	Random	0.0553	0.7227
	Mulatto	1	0.795	[0.3794; 1.6658]	0.54432	Fixed	NA	NA

*OR- Odds Ratio, *I – Heterogeneity, *CI – Confidence Interval.

Table 3. Subgroup analysis for the association of STOX1 rs1341667 gene polymorphism with PE.

Model	Ethnicity	Number of studies	Test of association			Test of heterogeneity		
			OR	95% CI	p-value	Model	p-value	$I^{\wedge 2}$
Allele contrast (A vs. a)	Overall	4	0.9573	[0.8739;1.0486]	0.347607	Fixed	0.3168	0.1503
	Asian	3	0.8704	[0.7456;1.0162]	0.079072	Fixed	0.5181	0
	Caucasian	1	1.0067	[0.8994;1.1268]	0.907561	Fixed	NA	NA
Recessive model (AA vs. Aa+aa)	Overall	4	0.8644	[0.6250;1.1955]	0.378488	Random	0.0343	0.6532
	Asian	3	0.7751	[0.4843;1.2405]	0.288338	Random	0.0621	0.6401
	Caucasian	1	1.0398	[0.8255;1.3098]	0.740104	Fixed	NA	NA
Dominant model (AA+Aa vs. aa)	Overall	4	0.9803	[0.8559;1.1229]	0.774395	Fixed	0.5249	0
	Asian	3	0.9317	[0.7009;1.2385]	0.626105	Fixed	0.354	0.0371
	Caucasian	1	0.9951	[0.8527;1.1614]	0.950762	Fixed	NA	NA
Overdominant (Aa vs. AA + aa)	Overall	4	1.0762	[0.8331;1.3902]	0.574082	Random	0.0561	0.603
	Asian	3	1.1554	[0.7391;1.8061]	0.526314	Random	0.0609	0.6426
	Caucasian	1	0.9784	[0.8397;1.1400]	0.779761	Fixed	NA	NA
pairw1 (AA vs. aa)	Overall	4	0.9004	[0.7371;1.0998]	0.303905	Fixed	0.1801	0.3863
	Asian	3	0.69	[0.4893;0.9731]	0.034376	Fixed	0.4948	0
	Caucasian	1	1.0319	[0.8068;1.3198]	0.802505	Fixed	NA	NA
pairw2 (AA vs. Aa)	Overall	4	0.8681	[0.6008;1.2544]	0.451454	Random	0.0171	0.7051
	Asian	3	0.7741	[0.4391;1.3646]	0.376068	Random	0.0244	0.7308
	Caucasian	1	1.0471	[0.8208;1.3359]	0.711047	Fixed	NA	NA
pairw3 (Aa vs. aa)	Overall	4	1.0029	[0.8692;1.1572]	0.968297	Fixed	0.3458	0.0946
	Asian	3	1.0639	[0.7889;1.4347]	0.684766	Fixed	0.2102	0.3588
	Caucasian	1	0.9855	[0.8373;1.1599]	0.860306	Fixed	NA	NA

*OR- Odds Ratio, *I^2 – Heterogeneity, *CI – Confidence Interval.

Table 4. Subgroup analysis for association of PPAR-γ rs1801282 gene polymorphism with PE.

Model	Ethnicity	Number of studies	Test of association			Test of heterogeneity		
			OR	95% CI	p-value	Model	p-value	I^2
Allele contrast (A vs. a)	Overall	3	1.0252	[0.7404; 1.4197]	0.880652	Fixed	0.2569	0.2642
	Asian	1	0.9096	[0.4974; 1.6634]	0.758349	Fixed	NA	NA
	Caucasian	2	1.0768	[0.7316; 1.5849]	0.707445	Fixed	0.1135	0.6008
Recessive model (AA vs. Aa+aa)	Overall	3	1.0002	[0.6944; 1.4408]	0.999026	Fixed	0.4203	0
	Asian	1	0.8961	[0.4681; 1.7156]	0.740601	Fixed	NA	NA
	Caucasian	2	1.0523	[0.6769; 1.6358]	0.820909	Fixed	0.2098	0.3641
Dominant model (AA+Aa vs. aa)	Overall	2	1.0613	[0.1197; 9.4081]	0.957354	Random	0.0973	0.6364
	Asian	0	NA			Fixed	NA	NA
	Caucasian	2	1.0613	[0.1197; 9.4081]	0.957354	Random	0.0973	0.6364
Overdominant (Aa vs. AA + aa)	Overall	3	1.0367	[0.7141; 1.5050]	0.849601	Fixed	0.7199	0
	Asian	1	1.1159	[0.5829; 2.1365]	0.740601	Fixed	NA	NA
	Caucasian	2	0.9999	[0.6343; 1.5762]	0.999641	Fixed	0.4449	0
pairw1 (AA vs. aa)	Overall	2	1.0518	[0.1067;10.3726]	0.965492	Random	0.0835	0.6662
	Asian	0	NA			Fixed	NA	NA
	Caucasian	2	1.0518	[0.1067;10.3726]	0.965492	Random	0.0835	0.6662
pairw2 (AA vs. Aa)	Overall	3	0.9773	[0.6723; 1.4208]	0.904274	Fixed	0.6343	0
	Asian	1	0.8961	[0.4681; 1.7156]	0.740601	Fixed	NA	NA
	Caucasian	2	1.0203	[0.6456; 1.6127]	0.931304	Fixed	0.3687	0
pairw3 (Aa vs. aa)	Overall	2	1.2702	[0.3345; 4.8237]	0.725342	Fixed	0.1755	0.4553
	Asian	0	NA			Fixed	NA	NA
	Caucasian	2	1.2702	[0.3345; 4.8237]	0.725342	Fixed	0.1755	0.4553

*OR- Odds Ratio, *I^2 – Heterogeneity, *CI – Confidence Interval.

Table 5. Emphasizing the importance of determining an appropriate sample size is crucial for accurately evaluating statistical significance and ensuring the reliability of findings in genetic association studies, especially when investigating specific polymorphisms. The estimation of sample size plays a pivotal role in determining the statistical power of these studies

Gene	SNP	No. of Studies	Cases	Control	α err prob	Power (1-β err prob)
IL1A	*rs17561*	3	665	954	0.02303	0.9
IFN-γ	*rs2430561*	5	480	549	0.05343	0.9
STOX1	*rs1341667*	4	1738	2770	0.000495	0.9
PPAR-γ	*rs1801282*	3	268	1828	0.06146	0.9

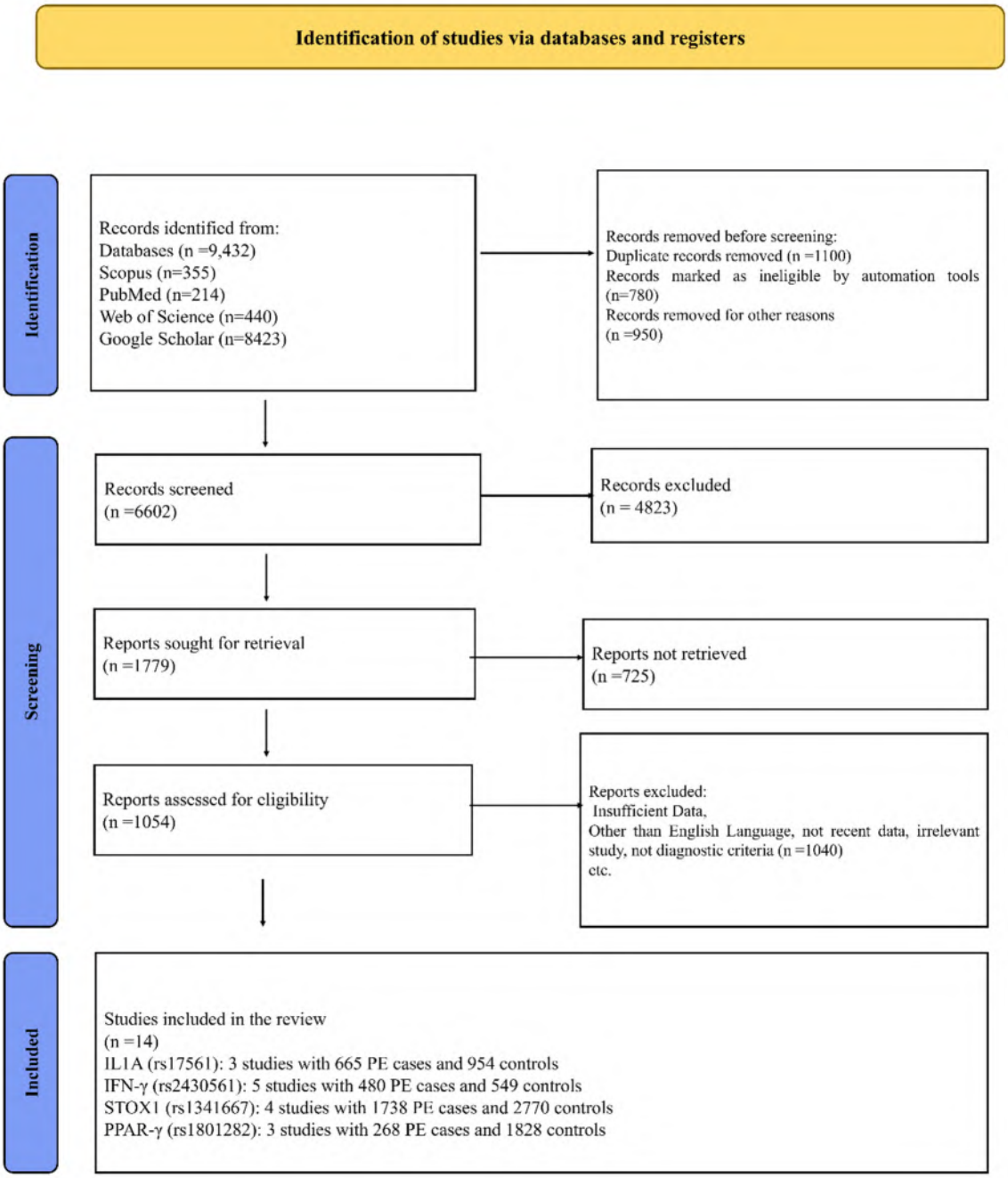

Figure 1. PRISMA

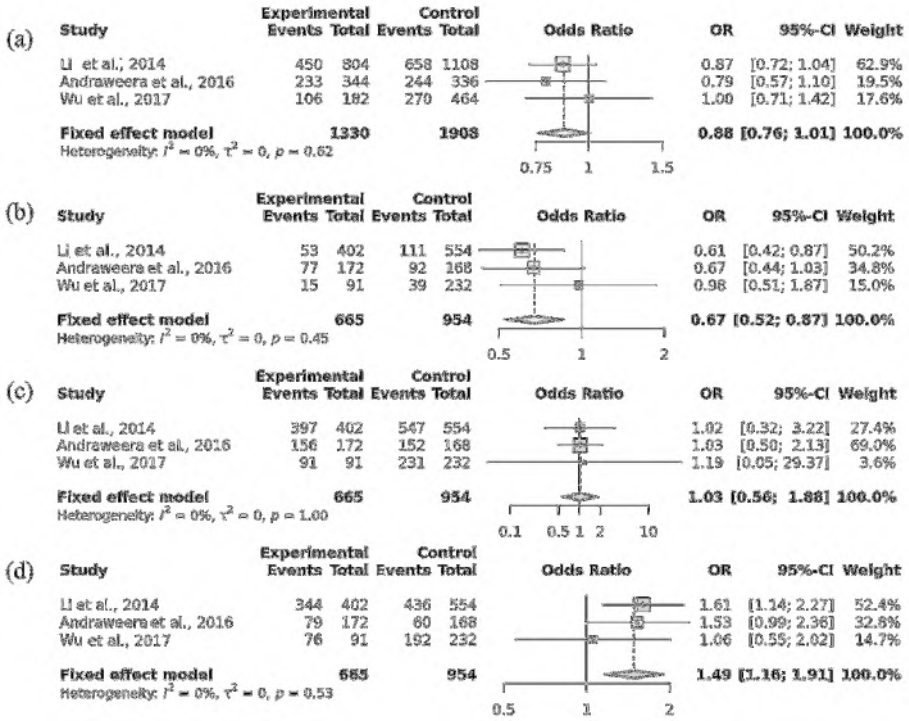

Figure 2. Forest plot for the association of IL1A (rs17561) gene polymorphism with PE risk (a) allelic, (b) recessive, (c) dominant, and (d) over-dominant model.

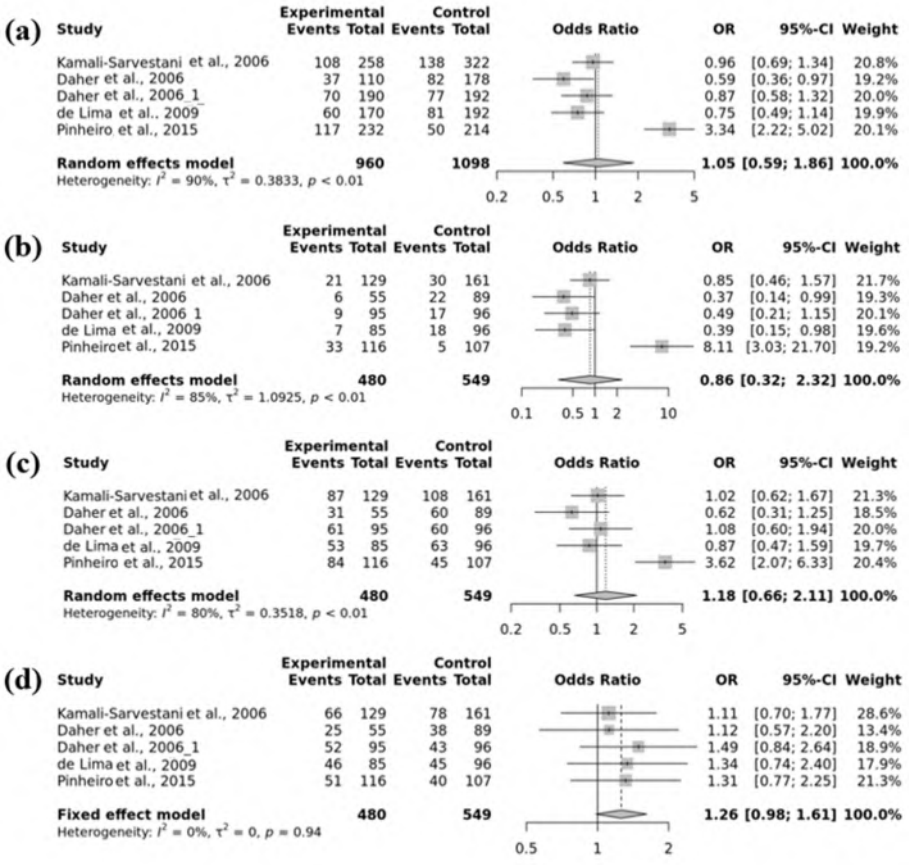

Figure 3. Forest plot for the association of IFN-γ (rs2430561) gene polymorphism with PE risk (a) allelic, (b) recessive, (c) dominant, and (d) over-dominant model.

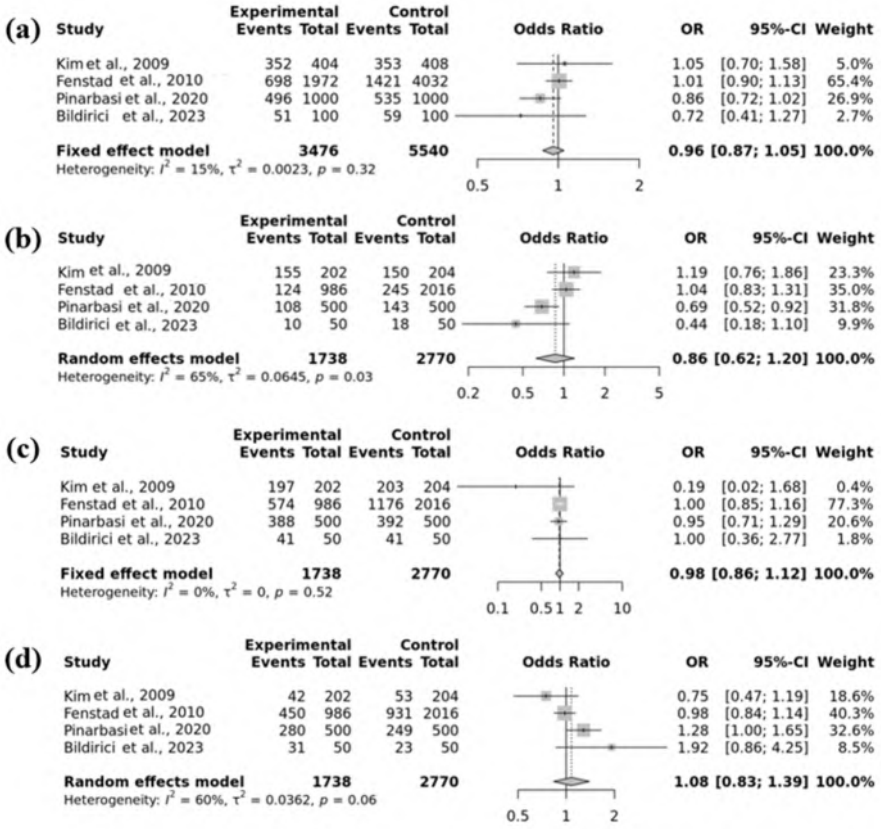

Figure 4. Forest plot for the association of STOX1 (rs1341667) gene polymorphism with PE risk (a) allelic, (b) recessive, (c) dominant, and (d) over-dominant model.

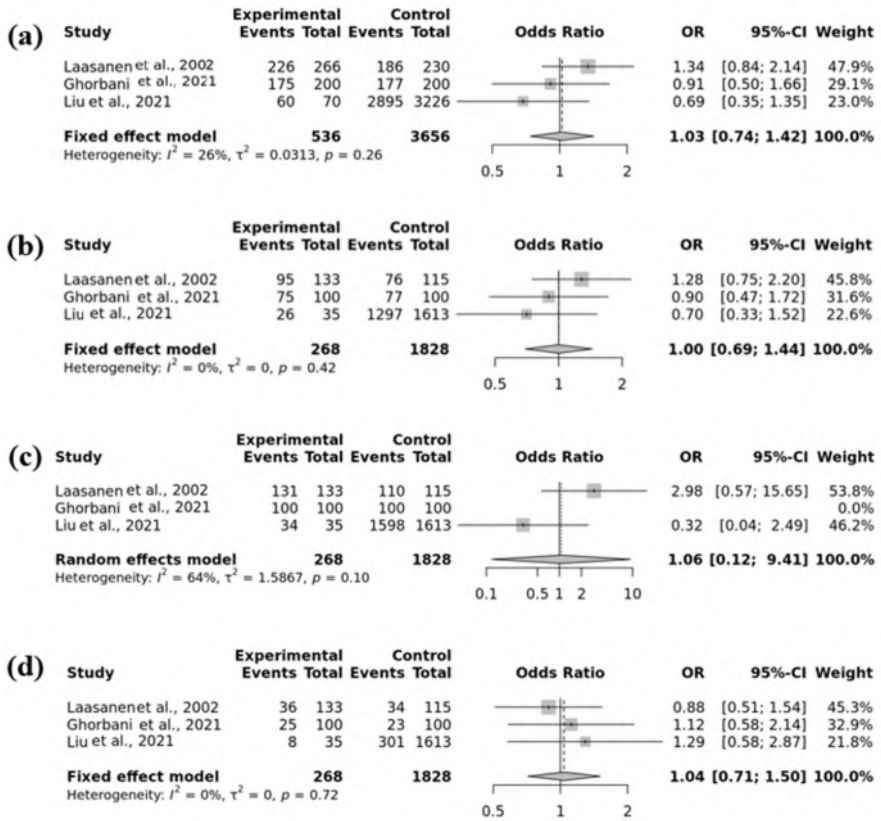

Figure 5. Forest plot for the association of PPAR-γ (rs1801282) gene polymorphism with PE risk (a) allelic, (b) recessive, (c) dominant, and (d) over-dominant model.

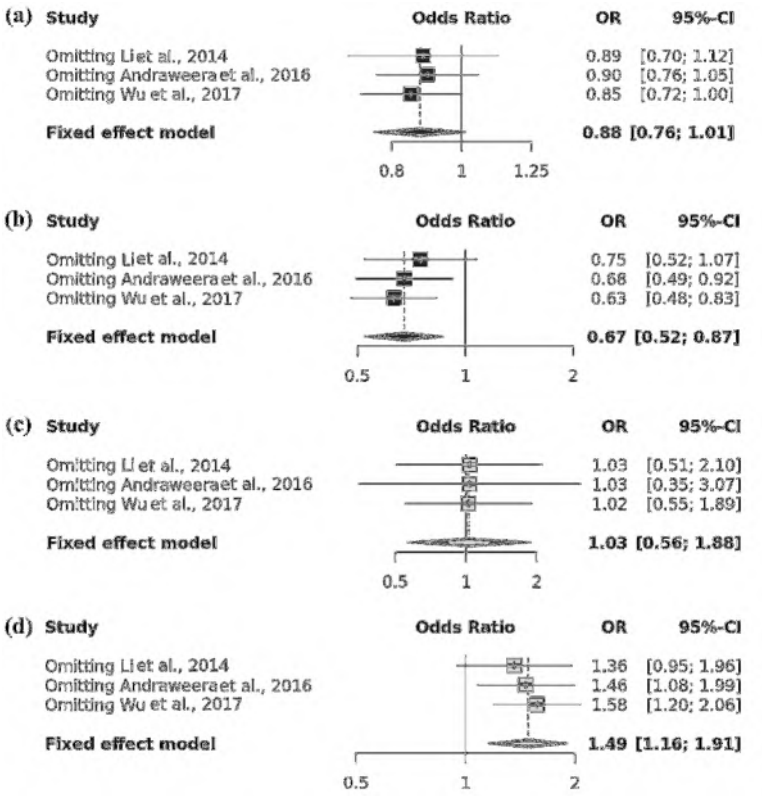

Figure 6. Sensitivity analysis for IL1A (rs17561) among PE cases and controls in all genetic models.

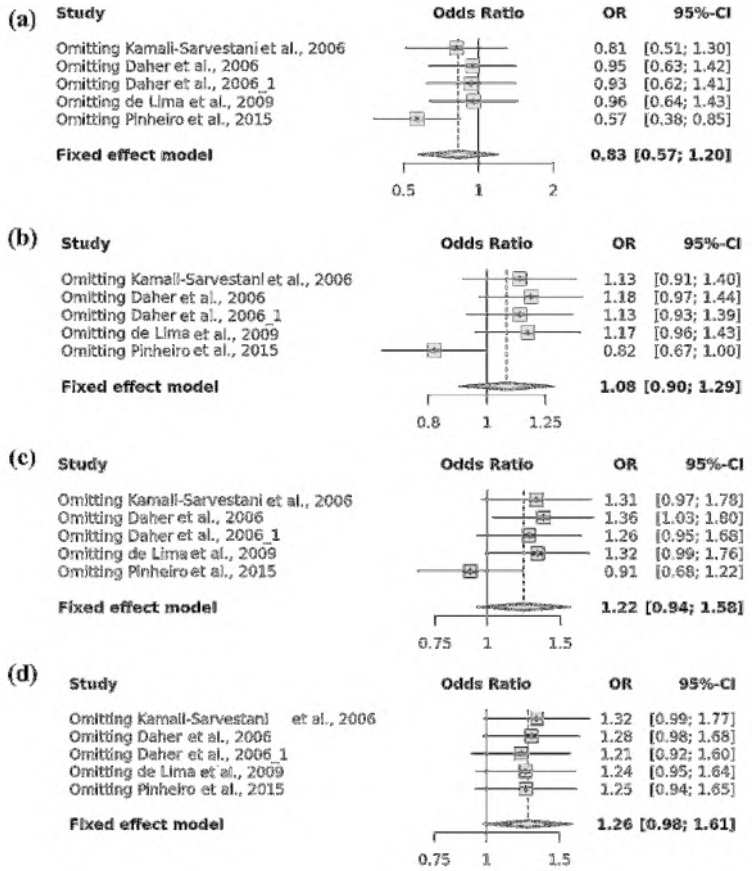

Figure 7. Sensitivity analysis for IFN-γ (rs2430561) among PE cases and controls in all genetic models.

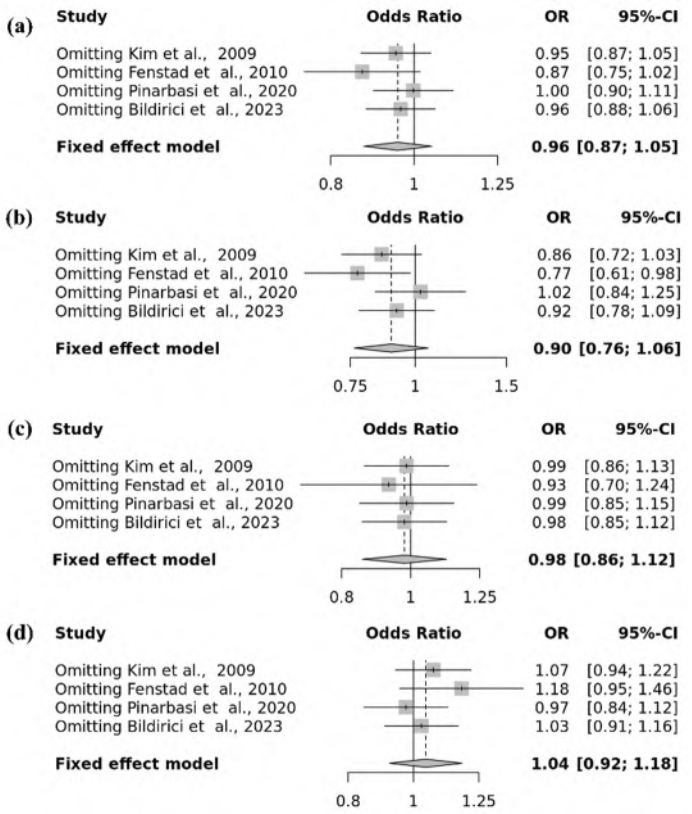

Figure 8. Sensitivity analysis for STOX1 (rs1341667) among PE cases and controls in all genetic models.

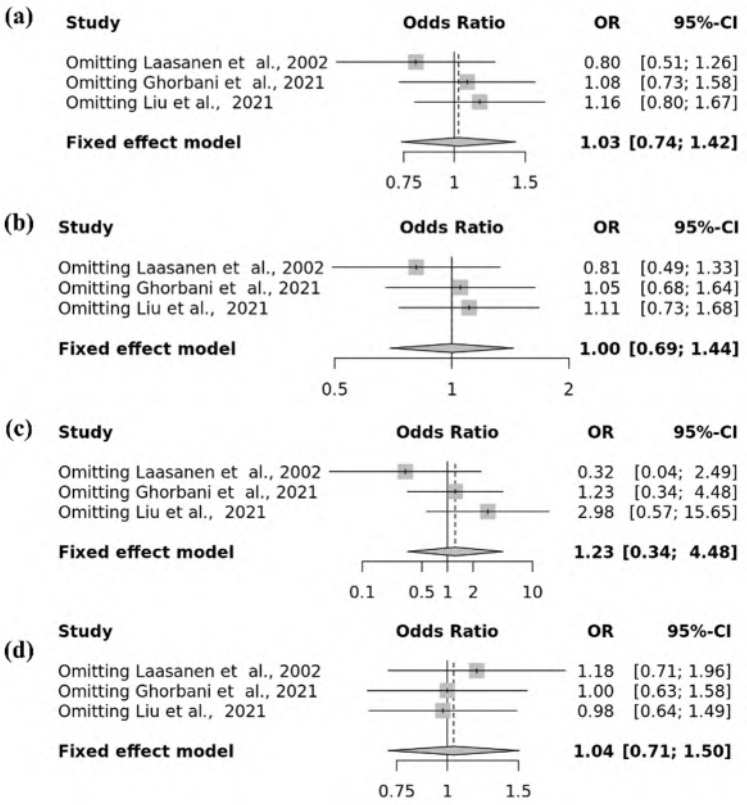

Figure 9. Sensitivity analysis for PPAR-γ (rs1801282) among PE cases and controls in all genetic models.

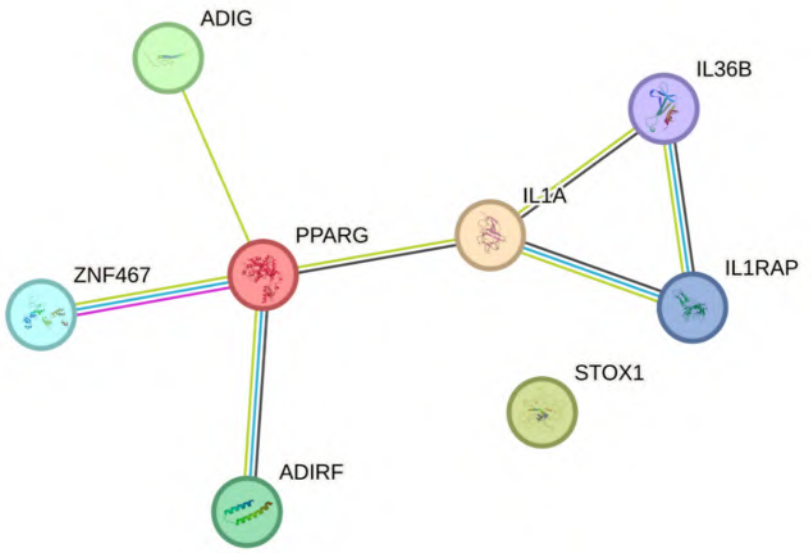

Figure 10. The Protein-Protein Interaction (PPI) network of differentially expressed genes (DEGs) among the selected genes associated with PE. We present the total clusters of the PPI network, f eaturing 8 nodes and 7 edges.

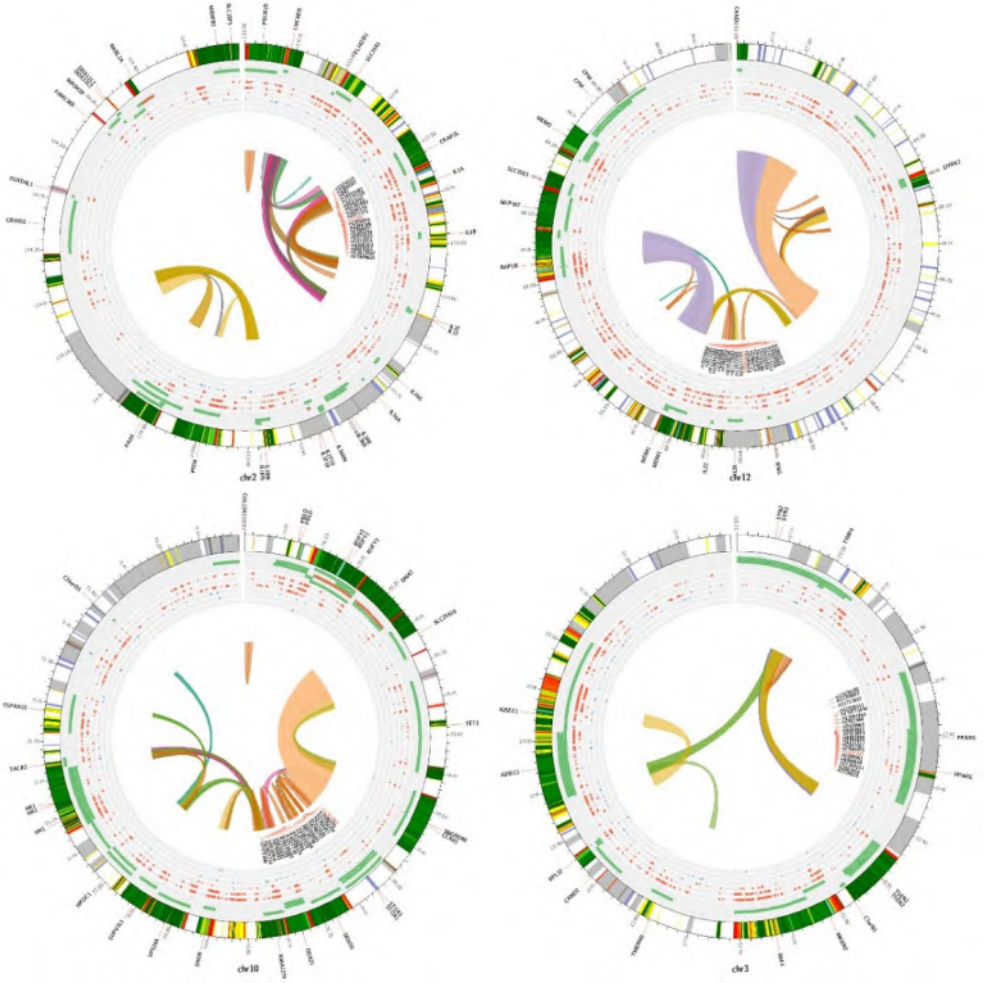

Figure 11. Circos plot visually represents the chromosomal relationships among the selected SNPs, focusing on IL1A (rs17561).

DISCUSSION

Pre-eclampsia (PE) remains a major obstetric complication with a multifactorial etiology involving complex interactions among genetic, environmental, and behavioural determinants [22]. Despite decades of research, the precise mechanisms underlying susceptibility remain elusive. While numerous studies have evaluated individual gene variants, the strength and direction of their associations with PE risk have varied considerably, underscoring the challenges of disentangling the genetic contribution to this condition [23]. The current meta-analysis explored the association of four gene polymorphisms-IL1A rs17561, IFN-γ rs2430561, STOX1 rs1341667, and PPAR-γ rs1801282-with the risk of PE by integrating evidence from 14 independent studies encompassing 3151 PE cases and 6101 healthy controls.

In this meta-analysis, a significant association was observed for the IL1A rs17561 polymorphism, which showed divergent effects across genetic models. The recessive model suggested a protective effect, while the over-dominant model indicated an increased risk of PE. In contrast, the dominant and allelic models showed no significant associations. This pattern suggests a context-dependent role of IL1A in inflammatory regulation during pregnancy, where different genotypic backgrounds may yield contrasting outcomes.IL1A encodes interleukin-1α, a key proinflammatory cytokine that contributes to trophoblast invasion, vascular remodeling, and immune modulation at the maternal–fetal interface [24,25]. The absence of a strong association may reflect the multifactorial contribution of IL-1 signaling, influenced by gene–environment interactions and compensatory mechanisms within the IL-1 family, including IL1B and IL1RN polymorphisms [26,27]. Moreover, population heterogeneity and differences in gestational age at disease onset may obscure genotype–phenotype correlations.

Similarly, no significant correlation was observed for IFN-γ rs2430561 polymorphism with PE risk in any genetic model. IFN-γ is a Th1 cytokine pivotal in immune activation, and elevated IFN-γ levels have been linked to defective placentation and exaggerated inflammation in PE [28,29]. The rs2430561 variant, located in the first intron, influences IFN-γ expression levels by modulating transcriptional activity [30]. However, our findings suggest that the variant alone may not confer a measurable risk, supporting the hypothesis that immune dysregulation in PE arises from polygenic effects and epigenetic regulation rather than single-locus polymorphisms [31].

The results of STOX1 rs1341667 for the all the four models had no significant link with PE. STOX1, a transcription factor expressed in trophoblasts, regulates placental growth and differentiation, and its dysregulation has been reported in familial and sporadic cases of PE [32,33]. Functional studies have shown that STOX1 interacts with the ENG and FLT1 gene pathways involved in endothelial dysfunction and anti-angiogenic signaling, key mechanisms underlying PE [34]. The genetic association observed in our analysis does not support these mechanistic insights and does not confirm STOX1 as a plausible genetic determinant of PE. Further functional validation is warranted to elucidate the biological significance of STOX1 gene polymorphism.

For the PPAR-γ rs1801282 polymorphism, no significant relationship was detected with PE across all genetic models, consistent with several prior meta-analyses [35,36]. PPAR-γ, a nuclear receptor involved in lipid metabolism and placental trophoblast differentiation, modulates vascular tone and anti-inflammatory responses. The rs1801282 (Pro12Ala) variant has been associated with improved insulin sensitivity and metabolic outcomes, which could theoretically influence PE pathogenesis [37]. However, the lack of association in this study may be attributed to ethnic variability in allele frequency, differences in diagnostic criteria, or gene–nutrient interactions affecting PPAR-γ activity during pregnancy.

The protein-protein interaction (PPI) network analysis further revealed that IL1A and PPAR-γ exhibit direct interactions, suggesting potential crosstalk between inflammatory and metabolic pathways in PE pathogenesis. The lack of a direct connection for STOX1 within this network supports the notion that STOX1-related effects might occur through transcriptional regulation rather than direct protein interactions. These findings emphasize the multifactorial and polygenic architecture of PE, wherein cumulative minor genetic effects and pathway-level interactions contribute more significantly to disease susceptibility than single variants [38,39].

The pooled ORs for several gene polymorphisms were sensitive to the removal of individual studies, indicating that some results lack complete robustness. Moreover, the power analysis verified that the included sample sizes were sufficient to detect moderate genetic effects, ensuring the reliability of the conclusions. The Circos plot provided additional insight into the genomic organization and potential epigenetic regulation of the studied genes, suggesting that histone modifications and transcriptional co-regulators might modulate their expression in placental tissue.

Moreover, population-specific allele frequency differences, as observed in prior studies [40,41], further complicate interpretation and suggest that the effect of IL1A variants may vary across ethnic backgrounds. The apparently opposite effects of IL1A rs17561 under different genetic models may also reflect epigenetic and environmental modulation. Dietary influences, obesity, and maternal metabolic status can shape the inflammatory and vascular responses in pregnancy, potentially amplifying or attenuating the genetic effects [42]. Likewise, epigenetic regulation of cytokine genes has been shown to impact PE risk, indicating that IL1A-related genetic susceptibility likely operates within a broader regulatory framework. Our findings reinforce the importance of IL1A as a candidate gene in PE but also underscore the multifactorial nature of disease susceptibility, where

protective and risk effects may co-exist depending on genetic model, ethnicity, and environmental context. This complexity highlights the need for integrative approaches that combine genetic, epigenetic, and clinical risk factors. Future research incorporating systems biology and multi-omics analyses may provide deeper insights into how IL1A polymorphisms interact with other determinants to influence PE outcomes. Ultimately, these advances could contribute to individualized risk prediction, early screening, and targeted interventions for women at risk of developing PE.

LIMITATIONS OF THE STUDY

First, although this meta-analysis focused on four key polymorphisms, numerous other candidate genes, as well as non-genetic environmental factors, may also contribute to PE susceptibility but were not considered here. Second, variations in study design, population characteristics, and sample size likely contributed to heterogeneity across the included studies. While this was partly mitigated using a random-effects model, residual heterogeneity may still have influenced the results. Third, reliance on published studies and the exclusion of non-English articles may have introduced selection bias. Fourth, publication bias could not be formally assessed, as fewer than 10 studies were available for each polymorphism. According to the Cochrane Handbook, statistical tests for funnel plot asymmetry (e.g., Egger's test) are underpowered with small sample sets; therefore, the potential influence of publication bias cannot be entirely ruled out. Finally, the statistical power of some findings may have been limited by the relatively small number of eligible studies included for each gene.

CONCLUSION

The present meta-analysis significantly identifies the IL1A rs17561 polymorphism as a crucial genetic susceptibility factor for preeclampsia, however its impact is highly depending upon the underlying genetic model. Collectively, these findings demonstrate a complex, model-dependent association between the IL1A rs17561 polymorphism and the risk of preeclampsia (PE) except dominant model. In contrast, the IFN-γ, STOX1, and PPAR-γ polymorphisms showed no significant link with preeclampsia across any of the four tested genetic models (allelic, recessive, dominant, or over-dominant), suggesting that its influence on PE risk may be negligible in this cohort.

Abbreviation

PE	Pre-eclampsia
IL1A	Interleukin-1 Alpha
INF-γ	Interferon-gamma
STOX1	Storkhead Box 1
PPAR-γ	Peroxisome Proliferator-Activated Receptor Gamma
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
HWE	Hardy-Weinberg equilibrium
CI	Confidential interval
OR	Odds Ratio
NOS	Newcastle-Ottawa scale
ROB	Risk of Bias
PPI	Protein-protein interaction
RPL	Recurrent Pregnancy Loss

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This study did not receive funding in any form.

ETHICAL APPROVAL

No ethical approval was required because this study was obtained from already published case vs. control studies. Since the present study was categorized as a meta-analysis, patient consent forms are not required.

CONFLICT OF INTEREST

The authors declare that there is no competing interest regarding the publication of this article.

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