

Systematic Review

IRS1 rs1801278 Polymorphism and Risk of Gestational Diabetes Mellitus: A System Review and Meta-Analysis

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Abstract

Background: The association between the insulin receptor substrate-1 (*IRS1*) rs1801278 polymorphism and the risk of gestational diabetes mellitus (GDM) remains controversial based on existing published data. A meta-analysis was conducted to evaluate the potential correlation between the *IRS1* rs1801278 polymorphism and GDM risk. **Methods:** Eligible studies were identified by conducting comprehensive searches in PubMed, Embase, Web of science, the China National Knowledge Infrastructure, and the Chinese Biomedicine databases. Pooled odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated using appropriate fixed-effects or random-effects models to evaluate the relationship between *IRS1* rs1801278 polymorphism and the risk of GDM. **Results:** A total of nine studies were included in this meta-analysis, and the pooled analysis indicated no significant association between *IRS1* rs1801278 and the risk of GDM. Heterogeneity among the studies was detected, and a Galbraith plot analysis was conducted to explore the source of heterogeneity. It was revealed that one study was responsible for the heterogeneity. After excluding this study, the heterogeneity decreased significantly. **Conclusions:** The present meta-analysis reveals that *IRS1* rs1801278 polymorphism may not be correlated with GDM risk. The study was registered on PROSPERO (<https://www.crd.york.ac.uk/prospero/>), registration number: CRD42023460095.

Keywords: gestational diabetes mellitus; *IRS1*; polymorphisms; meta-analysis

1. Introduction

Gestational Diabetes Mellitus (GDM), which is characterized by glucose intolerance and hyperglycemia during pregnancy [1,2], is estimated to affect approximately 10% to 25% of all pregnancies globally [3,4]. In addition to posing dangers to the pregnant woman, GDM is also associated with adverse outcomes for the baby, including a predisposition to chronic metabolic diseases in later life [5–7]. The etiology and mechanism of GDM have not been fully understood. GDM has been shown to be a multifactorial disorder influenced by both genetic and environmental factors [8–10]. Among these, genetic susceptibility has emerged as a major risk factor for GDM [11].

The insulin receptor substrate-1 (*IRS1*) gene, found on chromosome 2q36, encodes a protein substrate of the IRS family [12,13]. After the insulin receptor, *IRS1* is the main dock protein and is crucial to the insulin signaling pathways [14,15]. The abnormal expression and phosphorylation of the *IRS1* protein are the primary cause of selective insulin resistance [16,17]. Research has reported that *IRS1* Gly972Arg polymorphism (rs1801278) may be involved in the etiology of type 2 diabetes mellitus [18,19].

Over the past twenty years, several studies have examined the possible association between the *IRS1* rs1801278 variant and the risk of GDM. However, these studies have yielded conflicting and inconclusive results [13,20–24]. To address this ambiguity, a meta-analysis of published case-

control studies was conducted to investigate the potential relationship between the *IRS1* rs1801278 variant and the risk of GDM.

2. Methods

This study protocol was followed PRISMA guidelines and previously registered with PROSPERO (<https://www.crd.york.ac.uk/prospero/>) on 13th September 2023, registration number: CRD42023460095.

2.1 Publication Search

A comprehensive search was carried out for articles exploring the relationship between *IRS1* rs1801278 and the risk of GDM. The databases consulted included PubMed, Embase, Web of science, the China Biomedical Database, and CNKI (China National Knowledge Infrastructure). The keywords employed in the search were “*IRS1* rs1801278”, “variant”, “polymorphism”, and “gestational diabetes mellitus”. The most recent update to this search was made on October 10, 2022.

2.2 Inclusion and Exclusion Criteria

To be eligible for inclusion, all studies, irrespective of their sample sizes, had to meet the following criteria: (i) investigate the correlation between *IRS1* rs1801278 polymorphism and GDM risk; (ii) employ a case-control design; and (iii) provide enough data to calculate the odds ra-



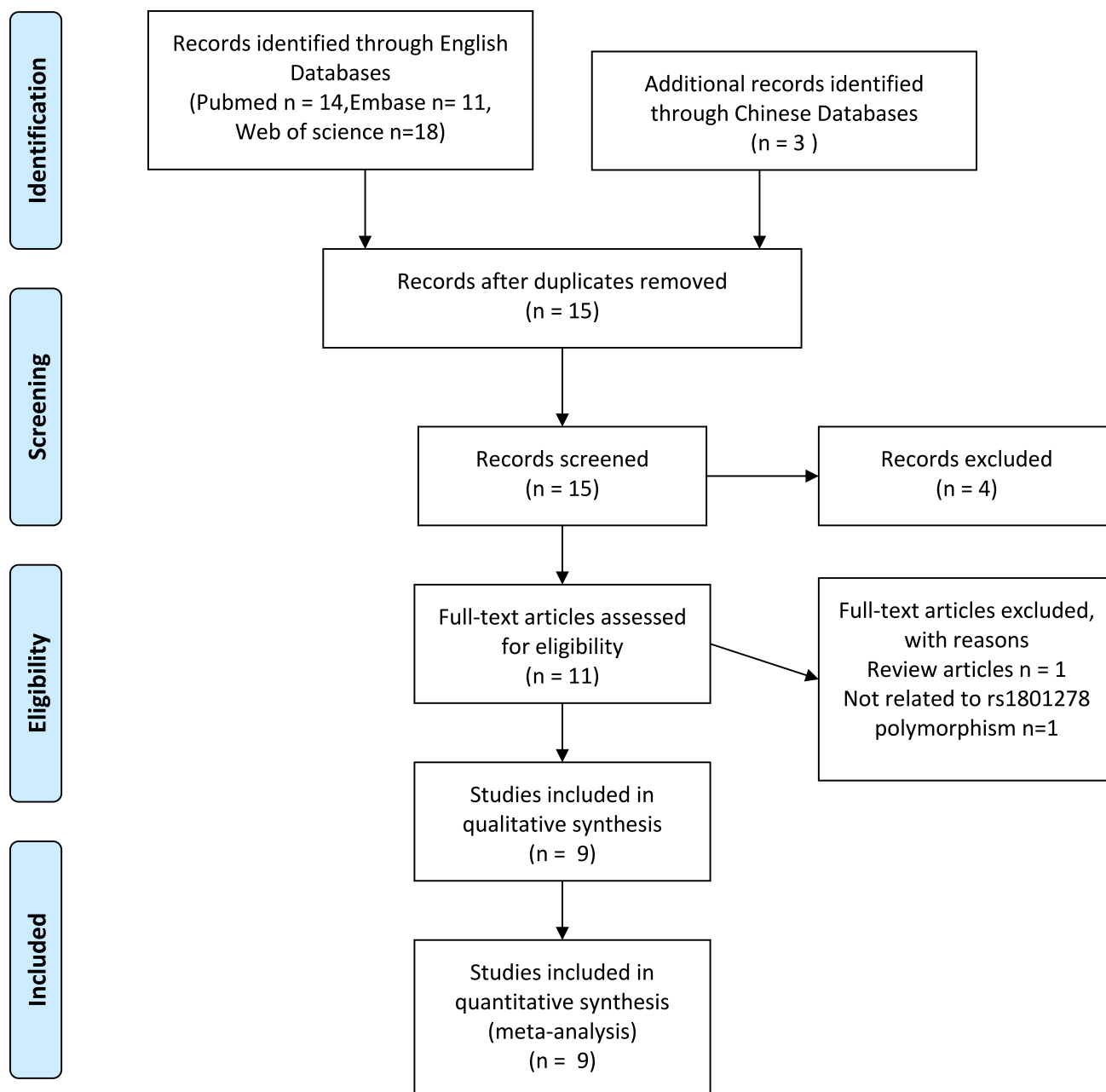


Fig. 1. Literature search and study selection procedures used for a meta-analysis of *IRS1* rs1801278 genetic polymorphism and GDM. *IRS1*, insulin receptor substrate-1; GDM, gestational diabetes mellitus.

tio (OR) with a 95% confidence interval (95% CI). Studies that fit into any of the following categories were excluded: (i) abstracts, reviews, overviews, or editorials; (ii) lacking sufficient data.

2.3 Data Extraction

In accordance with the aforementioned inclusion criteria, two authors (HS and AW) independently retrieved information from all eligible and qualified publications. Any discrepancies encountered were resolved by conferring with corresponding author (KY).

Data extracted from the eligible publications included the last name of the first author, publication date, country of participants, sample sizes of cases and controls, racial backgrounds, genotyping methods, and minor allele frequencies (MAF). Ethnic groups have been classified as either Asian or Caucasian.

2.4 Statistical Analysis

The strength of the association between the *IRS1* rs1801278 polymorphism and the risk of GDM was assessed using odds ratios (ORs) and the corresponding 95% confidence intervals (CIs). Furthermore, we performed

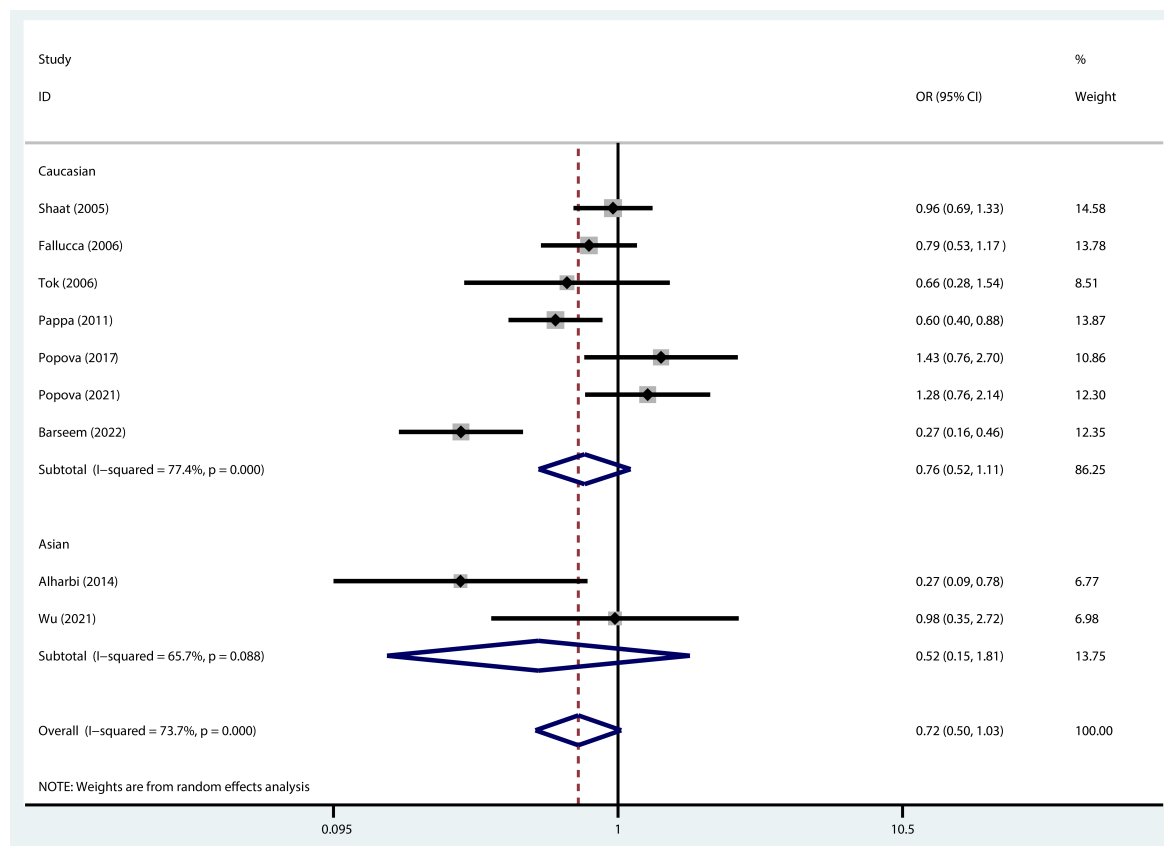


Fig. 2. Forest plots of ORs with 95% CIs for *IRS1* rs1801278 polymorphism and GDM risk stratified by ethnicity. OR, odds ratio; 95% CI, 95% confidence interval.

stratified analyses by ethnicity. To assess the heterogeneity among the studies, we utilized both the Cochran Q statistic and the I^2 index [25,26]. A p -value greater than 0.05 for the Q statistic indicates a significant lack of heterogeneity among the included studies [27]. In such cases, a fixed-effects model (utilizing the Mantel-Haenszel method) is appropriate [28]. Conversely, if there's evidence of heterogeneity, the random-effects model (employing the DerSimonian and Laird method) is employed [29].

To assess publication bias, we visually inspected funnel plots and utilized Egger's power-weighted regression approach and Begg's rank correlation method. Statistical significance was considered at $p < 0.05$ [30,31]. All statistical analyses were conducted using STATA software, version 13.0 (STATA Corp., College Station, TX, USA).

2.5 Trial Sequential Analysis

Trial Sequential Analysis (TSA) was conducted to determine the required information size (RIS) and to assess the reliability of the study findings [32]. The RIS was determined considering a 5% risk of type I error ($\alpha = 5\%$), a power of 80% ($\beta = 20\%$), and by applying a two-sided boundary [33]. The TSA software that the Copenhagen Trial Unit provided helped to facilitate the analysis.

3. Result

3.1 Characteristics of Studies

After the literature review, we shortlisted 15 publications deemed worthy of thorough examination. After evaluating the titles and abstracts, we eliminated the four papers that didn't meet our criteria. This led us to a detailed review of the full texts of the remaining 11 articles. We excluded one article as it primarily centered on a literature review [34], and one article because it is not related to *IRS1* rs1801278 polymorphism [35]. Finally, we compiled gathered nine case-control studies concerning the *IRS1* rs1801278 polymorphism and GDM [13,20–24,36–38], all of which adhered to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines [39]. The process of document retrieval and research selection is illustrated in Fig. 1.

The detailed characteristics of the chosen studies are presented in Table 1 (Ref. [13,20–24,36–38]). Seven of these studies focused on individuals of Caucasian descent, while two targeted those of Asian descent. The research was carried out across China, Egypt, Greece, Italy, Russia, Saudi Arabia, Sweden, and Turkey.

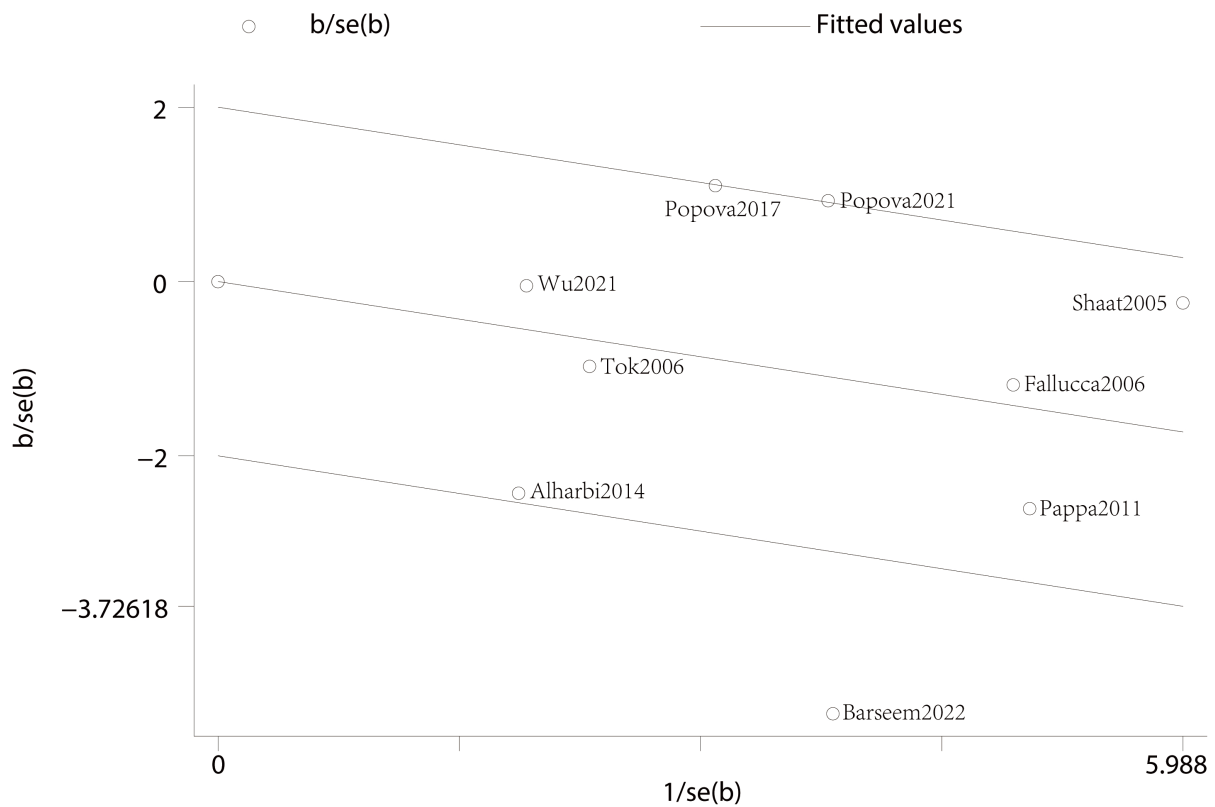


Fig. 3. Galbraith plots for heterogeneity analysis of *IRS1* rs1801278 polymorphism.

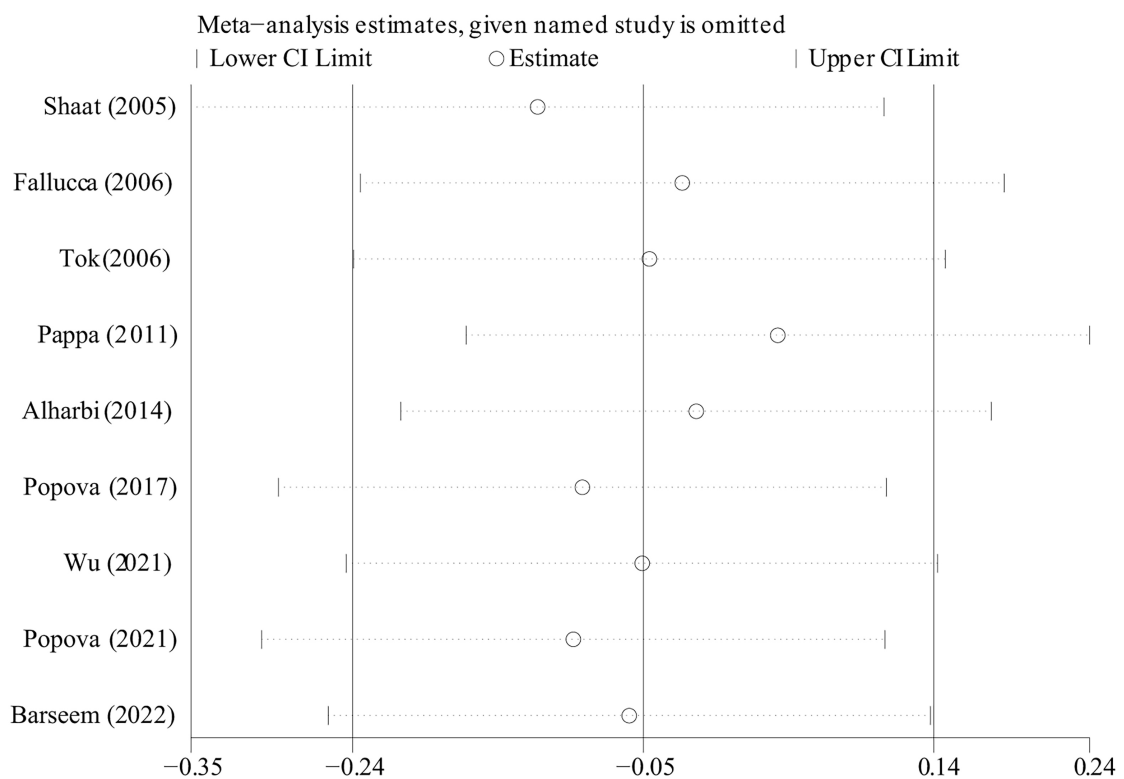


Fig. 4. Sensitivity analysis of associations between *IRS1* rs1801278 polymorphism and gestational diabetes mellitus.

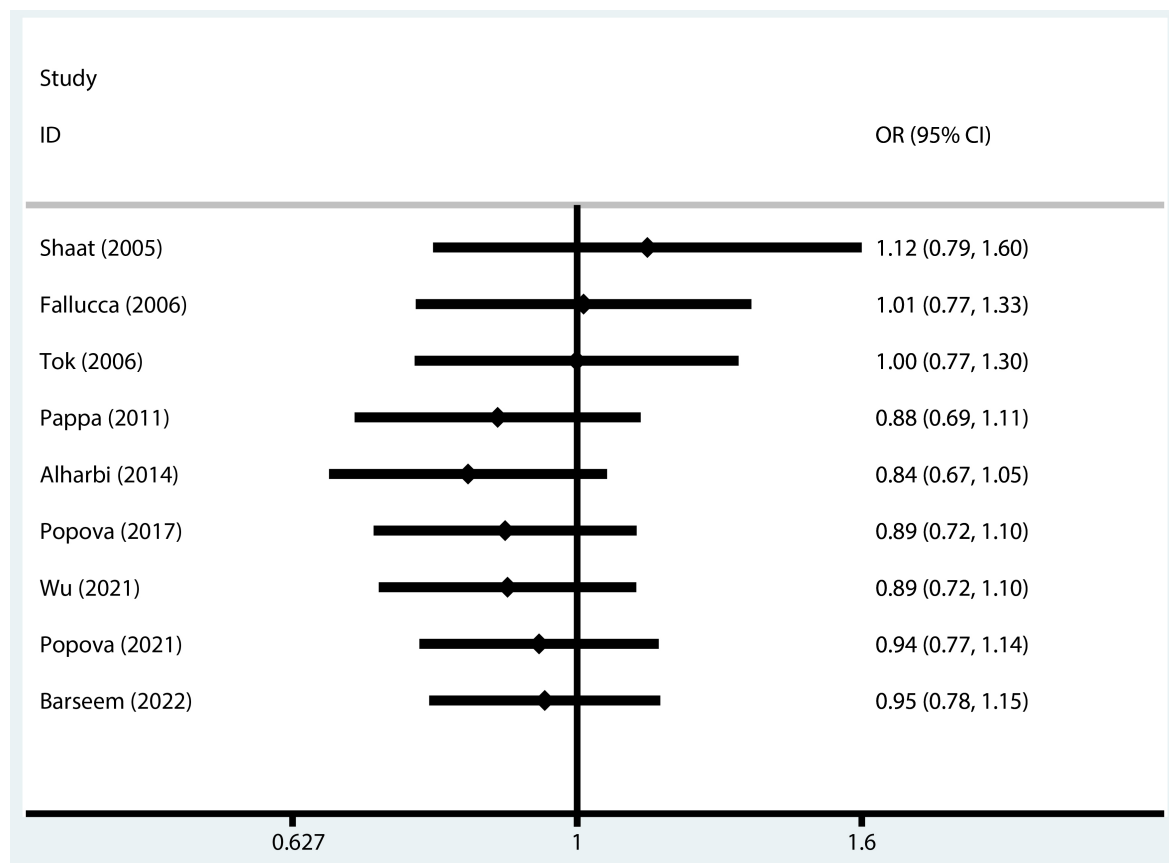


Fig. 5. Cumulative meta-analysis of associations between *IRS1* rs1801278 polymorphism and GDM.

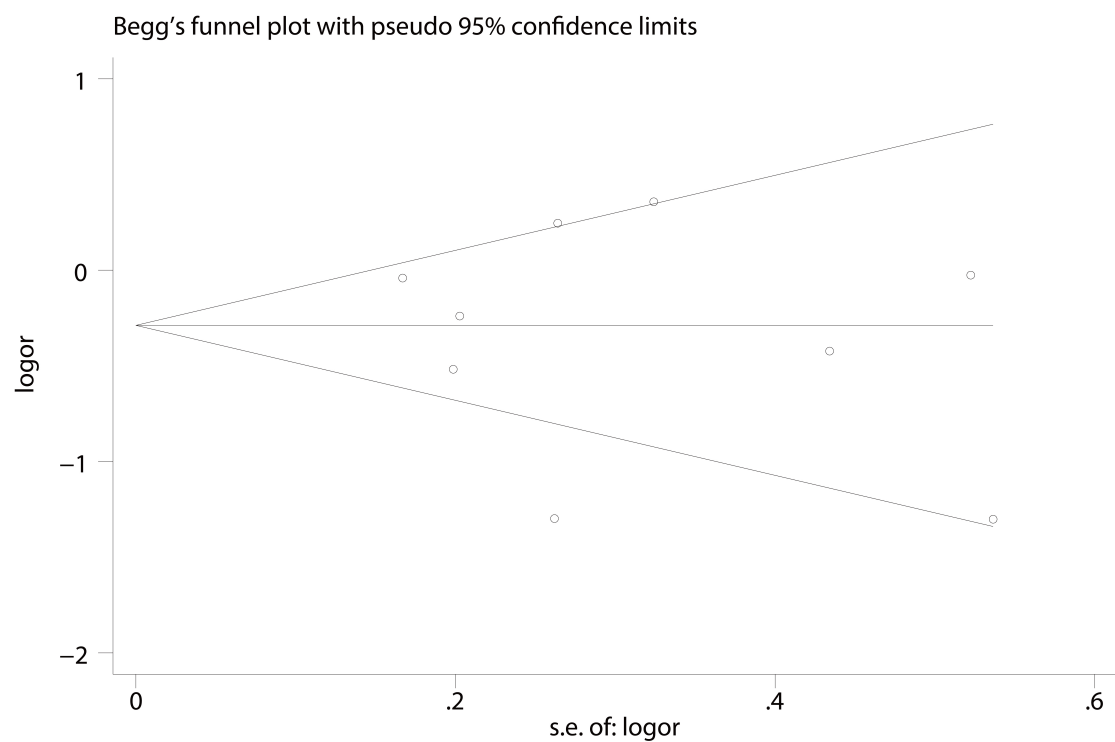


Fig. 6. Begg's funnel plot for publication bias test. s.e., standard error.

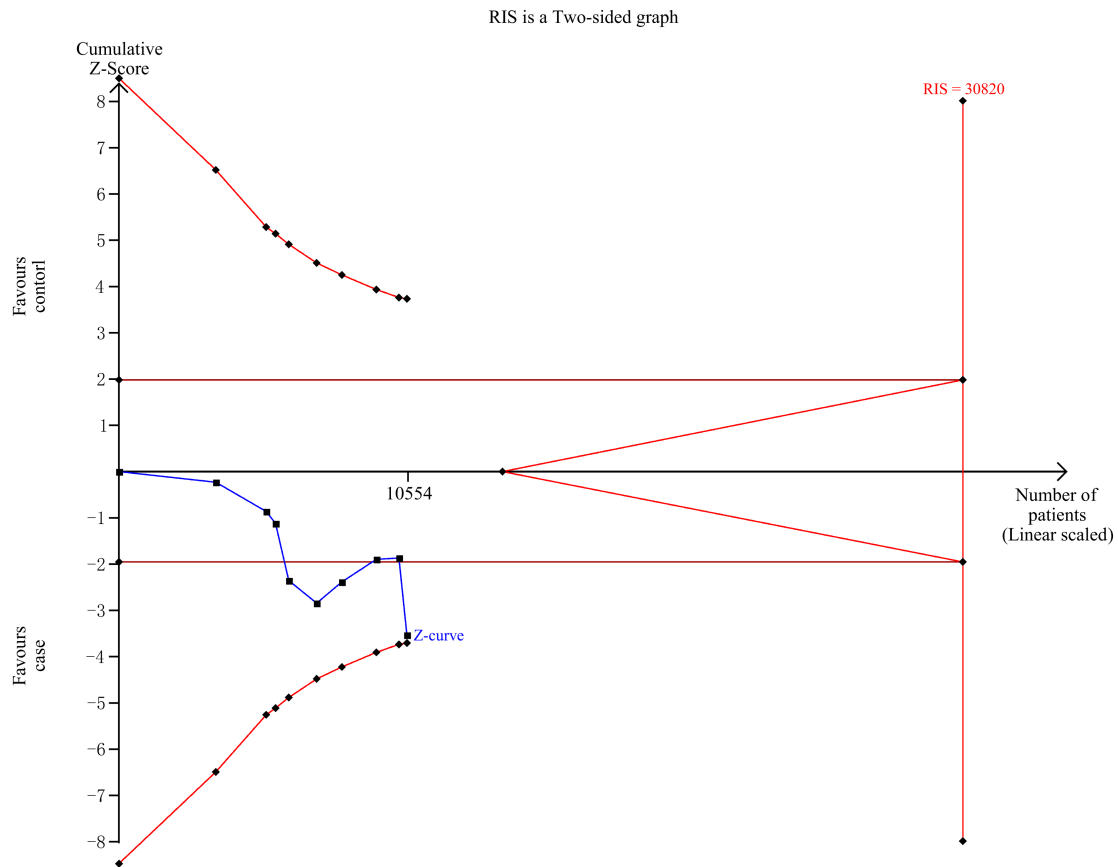


Fig. 7. Trial sequential analyses for *IRS1* rs1801278 polymorphism and GDM. RIS, required information size.

Table 1. Characteristics of studies included in this meta-analysis.

Author	Year	Country	Ethnicity	Sample	Genotyping Methods	MAF in Controls	HWE
Shaat, <i>et al.</i> [23]	2005	Sweden	Caucasian	588/1189	Taqman	0.05	0.09
Fallucca, <i>et al.</i> [13]	2006	Italy	Caucasian	309/627	PCR-RFLP	0.05	0.09
Tok, <i>et al.</i> [24]	2006	Turkey	Caucasian	62/100	PCR-RFLP	0.06	0.25
Pappa, <i>et al.</i> [21]	2011	Greece	Caucasian	148/107	PCR-RFLP	0.25	0.92
Alharbi, <i>et al.</i> [20]	2014	Saudi	Asian	200/300	PCR-RFLP	0.01	0.88
Popova, <i>et al.</i> [22]	2017	Russia	Caucasian	278/179	PCR-RFLP	0.05	0.45
Wu, <i>et al.</i> [37]	2021	China	Asian	213/191	PCR-RFLP	0.02	0.79
Popova, <i>et al.</i> [36]	2021	Russia	Caucasian	319/318	PCR-RFLP	0.05	0.31
Barseem, <i>et al.</i> [38]	2022	Egypt	Caucasian	80/80	PCR-RFLP	0.17	0.13

Abbreviations: PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; MAF, minor allele frequency; HWE, hardy-weinberg equilibrium.

3.2 Quantitative Synthesis

Eight case-control studies consisting of 2197 cases and 3091 controls were included in this analysis. The findings of the meta-analysis are presented in Table 2. The forest plots evaluating the association between the *IRS1* rs1801278 polymorphism and GDM risk are depicted in Fig. 2.

No significant association was found between the *IRS1* rs1801278 polymorphism and the risk of GDM in all models, with the exception of the homozygote comparison

(allele: CC vs. TT): OR, 0.24; 95% CI, 0.10–0.60. When stratified based on ethnicity, a significantly higher risk of GDM was detected in homozygous comparison between Caucasian descent OR, 0.22; 95% CI, 0.08–0.65.

The Newcastle-Ottawa Scale (NOS) scores for the selected studies can be found in Table 3 (Ref. [13,20–24,36–38]). The quality scores for the included studies ranged from 7 to 8 points. Studies with quality assessment scores below six stars are considered to be of low quality [40].

Table 2. Quantitative analyses of the *IRS1* rs1801278 polymorphism on the GDM risk.

Genetic model	Allele contrast				Homozygote		Heterozygote		Dominant Model		Recessive Model	
Variables	Sample size		C vs. T		CC vs. TT		CT vs. TT		CC + CT vs. TT		CC vs. CT + TT	
	N ^a	Case/control	OR (95% CI)	<i>p</i> _{value} ^b	OR (95% CI)	<i>p</i> _{value} ^b	OR (95% CI)	<i>p</i> _{value} ^b	OR (95% CI)	<i>p</i> _{value} ^b	OR (95% CI)	<i>p</i> _{value} ^b
Total	9	2197/3091	0.72 (0.50, 1.03)	<0.001	0.24 (0.10, 0.60)	0.235	0.95 (0.78, 1.15)	0.121	0.61 (0.38, 1.01)	0.201	0.83 (0.69, 1.00)	0.018
Ethnicity												
Caucasian	7	1784/2600	0.76 (0.52, 1.11)	<0.001	0.22 (0.08, 0.65)	0.148	0.98 (0.81, 1.20)	0.186	0.65 (0.47, 1.06)	0.436	0.86 (0.71, 1.04)	0.023
Asia	2	413/491	0.52 (0.15, 1.81)	0.088	0.21 (0.01, 1.27)	0.321	0.57 (0.27, 1.91)	0.146	0.48 (0.12, 1.65)	0.237	0.54 (0.26, 1.11)	0.112

^a Number of comparisons.

^b *p* value of Q-test for heterogeneity test. A random-effects model was utilized when the *p* value for the heterogeneity test <0.05; otherwise, the fixed-effects model was used.

C, allele; T, allele; GDM, gestational diabetes mellitus; OR, odds ratio; CI, confidence interval.

Table 3. Assessment of case-control study quality in the meta-analysis^a.

Study	Adequate definition of cases	Representativeness of cases	Selection of control	Definition of control	Control for important factors or additional factor ^b	Exposure assessment	The same method of ascertainment for cases and controls	Nonresponse rate ^c	Total Quality scores ^d
Shaat, <i>et al.</i> [23]	★	★	-	★	★★	-	★	★	7
Fallucca, <i>et al.</i> [13]	★	★	-	★	★★	-	★	★	7
Tok, <i>et al.</i> [24]	★	★	★	★	★★	-	★	★	8
Pappa, <i>et al.</i> [21]	★	★	★	★	★★	-	★	★	8
Alharbi, <i>et al.</i> [20]	★	★	★	★	★★	-	★	★	8
Popova, <i>et al.</i> [22]	★	★	★	★	★★	-	★	★	8
Wu, <i>et al.</i> [37]	★	★	★	★	★★	-	★	★	8
Popova, <i>et al.</i> [36]	★	★	★	★	★★	-	★	★	8
Barseem, <i>et al.</i> [38]	★	★	★	★	★★	-	★	★	8

^a In the assessment, each numbered item can receive a maximum of one star with the exception of the item Control for most important factor or second important factor.

^b The item “Control for the most important factor or the second important factor” can receive a maximum of two stars. One star is awarded to studies that controlled for maternal age, while an additional star can be given to studies that also controlled for high-risk factors such as diabetes, pre-pregnancy body mass index, or family history of hypertension.

^c One star was given if there was no significant difference observed in the chi-square test ($p > 0.05$).

^d Studies with quality assessment scores below six stars are categorized as low quality.

3.3 Heterogeneity Analysis

Significant heterogeneity was observed across multiple studies ($p_{\text{heterogeneity}} < 0.001$). For the purpose of identifying the sources of this heterogeneity, we utilized the Galbraith plot analysis. Our observations pinpointed a single study as the primary contributor to the heterogeneity linked to the *IRS1* rs1801278 polymorphism (Fig. 3) [38]. When this outlier research was removed, heterogeneity decreased dramatically ($p_{\text{heterogeneity}} = 0.115$).

3.4 Sensitivity Analysis and Cumulative Analysis

The sensitivity analyses, as exhibited in Fig. 4, and the cumulative meta-analysis, as depicted in Fig. 5, demonstrated the robustness as well as the stability of the results.

3.5 Publication Bias

We conducted Begg's and Egger's [30,31] tests to evaluate potential publication bias in the literature. As illustrated in Fig. 6, no significant asymmetry was observed in the Begg's [30] unnel plot. Furthermore, the statistical results indicated an absence of publication bias. Findings of Begg's and Egger's [30,31] test were [allele contrast 0.75 and 0.66, homozygote 0.31 and 0.28, heterozygote 0.57 and 0.50, dominant model 0.27 and 0.19, recessive model 0.49 and 0.38].

3.6 Trial Sequential Analysis

To learn more about the connection between *IRS1* rs1801278 and GDM risk, TSA was employed. The findings suggested that the cumulative Z value (Z-curve) did not cross the TSA boundary, pointing out that the cumulative amount of information did not reach the required information size (Fig. 7). This indicates that the meta-analysis may provide a false negative conclusion, necessitating further trials to confirm the association.

4. Discussion

The meta-analysis, based on nine case-controlled studies, revealed that the *IRS1* rs1801278 polymorphism was not considerably linked to GDM in allele contrast, heterozygote comparison, dominant model, and recessive model. Nonetheless, a significant association was seen between GDM and the homozygous comparison. Despite the fact that the reasons for this variation remain elusive, different patterns of linkage disequilibrium (LD) might play a role. While one ethnic group might not exhibit this polymorphism in LD with a proximate causative variation, it might be present in another ethnic group. Variations in genetic attributes may also be a contributing factor, given the variation of the *IRS1* rs1801278 polymorphism across different ethnicities. To evaluate ethnic differences, we conducted a subgroup analysis based on ethnicity. The findings showed that there was a significantly heightened risk of GDM in the homozygous comparison among those of Caucasian descent, but this was not observed in individuals of Asian descent.

The findings related to the *IRS1* rs1801278 polymorphism differ from an earlier study. In their meta-analysis based on five studies, Zhang *et al.* [34] determined a strong association between *IRS1* rs1801278 and GDM risk across various genetic models, which involve homozygote, heterozygote, dominant, and recessive. A potential reason for the observed discrepancy could be the limited sample size in the prior study, encompassing 1306 cases and 1973 controls, which may have compromised the reliability of its results. In contrast, our current meta-analysis comprises eight case-controlled studies, with 2197 patients and 3091 controls.

The degree of heterogeneity is a crucial concern in meta-analyses, as studies with significant inconsistencies can produce skewed results. In our meta-analysis, we employed the I^2 statistics and the Q-test so as to gauge heterogeneity. Significant heterogeneity was observed in both the allele contrast and recessive model. Galbraith plots were utilized to identify the sources of heterogeneity, and one study was found to be the primary contributor to the observed inconsistencies. By excluding this study, the heterogeneity markedly decreased, yet the overall conclusion remained consistent.

Publication bias, arising from selective reporting of studies, is an important consideration in meta-analysis. To address this concern in our study, we employed both Egger's and Begg's tests [30,31]. The statistical outcomes and the symmetry of the funnel plot indicate no apparent publication bias.

The current study has a number of limitations: (i) Due to the limited sample size in the studies and the small number of researches included in the meta-analysis, the results may not accurately reflect the true associations; (ii) Unadjusted OR estimates were utilized in our analysis as not all studies provided adjusted ORs. Moreover, where adjusted ORs were reported, the adjustments could differ based on factors such as ethnicity, age, or smoking habits; (iii) Significant heterogeneity was observed among studies, particularly in the allele contrast and the recessive model.

5. Conclusion

In summary, our meta-analysis findings indicate that there may be no significant association between the *IRS1* rs1801278 polymorphism and the risk of GDM. However, given the limited number of participants as well as the narrow racial group representation in this study, a comprehensive, large-scale multicenter case-control study is essential to validate and further strengthen these conclusions.

Availability of Data and Materials

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Author Contributions

KY conceived and designed the meta-analysis. HS and AW performed the literature search. AW analyzed the data. HS wrote the paper. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/j.ceog5101010>.

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