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META-ANALYSIS

Xu et al: PPARγ2 Pro12Ala and GDM risk

Association of *PPARγ2* Pro12Ala polymorphism with gestational diabetes mellitus risk: A systematic review and meta-analysis

Yuanting Xu[1#], Yi Du[1#], Tengfei Shan[1], Qingwen Xie[1], Hongli Zhu[2*]

[1]Department of Obstetrics and Gynecology, Hangzhou Linping District First People's Hospital, Hangzhou, China;

[2]Department of Obstetrics and Gynecology, Hangzhou First People's Hospital, Hangzhou, China.

*Correspondence to Hongli Zhu: zhuhlhfph@ph-edu.cn.

[#]Equally contributed to this work: Yuanting Xu and Yi Du.

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ABSTRACT

Gestational diabetes mellitus (GDM) is a prevalent pregnancy complication that poses significant risks to both mothers and their offspring, with genetic susceptibility believed to play a role in its pathogenesis. This study examined the association between the Pro12Ala (Pro [C]→Ala [G]) polymorphism in the peroxisome proliferator-activated receptor γ2 (*PPARγ2*) gene and the risk of developing GDM. A systematic literature search was conducted across databases including PubMed/Medline, Web of Science, Embase, and the Cochrane Library, identifying clinical studies that evaluated the relationship between the *PPARγ2* Pro12Ala variant and GDM. Strict inclusion criteria ensured that all case groups comprised exclusively women diagnosed with GDM. Data on study characteristics, sample sizes, and allele frequencies were extracted, and meta-analyses were performed using RevMan 5.3 and Stata with Hartung-Knapp random-effects models. Fifteen studies were included in the analysis. The Pro12Ala polymorphism showed no significant association with GDM risk across allelic (Ala [G] vs. Pro [C]), dominant (CG+GG vs. CC), and recessive (GG vs. CG+CC) models (allelic: OR=0.90, 95% CI=0.75–1.08, p=0.26; dominant: OR=0.92, 95% CI=0.74–1.13, p=0.42; recessive: OR=0.82, 95% CI=0.54–1.25, p=0.33; all p>0.05). Subgroup analyses by ethnicity indicated a potential protective association of the Ala (G) allele with GDM in East Asian populations, while no significant associations were found in European or Middle Eastern populations; ethnicity was identified as a significant effect modifier (p<0.05). There were no meaningful differences in subgroups categorized by study quality and sample size. Sensitivity analyses confirmed the robustness of the findings, and small-study effects detected by Egger's test did not substantially alter the pooled estimates. In conclusion, the *PPARγ2* Pro12Ala polymorphism was not significantly associated with GDM risk in the general population. The potentially protective trend observed in East Asian women warrants cautious interpretation due to concerns regarding multiple testing, allele-frequency variation, and limited statistical power.

Keywords: Gestational diabetes mellitus, PPARγ2, Pro12Ala polymorphism, genetic susceptibility, updated meta-analysis.

INTRODUCTION

Gestational diabetes mellitus (GDM), a common pregnancy complication, is defined as abnormal glucose metabolism during pregnancy in women with pre-pregnancy normal glucose metabolism or potential glucose intolerance, which usually resolves after delivery [1]. However, GDM poses serious health threats to both mothers and offspring. Poor glycemic control may result in maternal complications such as miscarriage, gestational hypertension and progression to type 2 diabetes, while higher maternal glucose concentrations can lead to adverse neonatal outcomes including macrosomia, respiratory distress, and hypoglycemia [2]. The prevalence of gestational diabetes mellitus is rapidly increasing worldwide. In Europe, the overall prevalence is estimated at 10.9%, with the highest rates in Eastern Europe (31.5%) and the lowest in Northern Europe (8.9%); in Poland it is 6.2%. In North America and the Caribbean, the prevalence is 7.1%, in South and Central America 10.4%, and in Asia it varies widely from 1.2% to 49.5% [3]. Besides established risk factors such as advanced maternal age and obesity, genetic susceptibility also contributes to the pathogenesis of GDM [4, 5].

Peroxisome proliferator-activated receptor (PPAR), a ligand-activated nuclear receptor, is involved in adipocyte differentiation, lipid metabolism, and insulin sensitivity [6]. Variants in the PPARγ gene may therefore influence glucose homeostasis and GDM risk. Among these, the Pro12Ala polymorphism (a C→G missense mutation in exon 2 causing a proline-to-alanine substitution) is the most widely studied [7, 8]. Functional studies suggest that the G (Ala) allele may enhance insulin sensitivity and reduce diabetes risk [9].

However, evidence linking the Pro12Ala (Pro [C]→Ala [G]) polymorphism to GDM risk remains inconsistent across studies and populations. A previous meta-analysis published in 2016 [8], suggested a possible protective effect of the Ala (G) allele but was limited by a small sample size, incomplete subgroup analyses, and lack of recent data. Since then, multiple studies with larger cohorts and broader ethnic representation have been reported, yet results remain contradictory. To address these gaps, we conducted an updated and comprehensive meta-analysis to reassess the association between the PPARγ2 Pro12Ala (Pro [C]→Ala [G]) polymorphism and GDM risk, aiming to better characterize its potential genetic role and provide more robust evidence for future research.

MATERIALS AND METHODS

Subjects

The diagnostic criteria for the case group met the standards for GDM. Specifically, the diagnosis was based on the criteria recommended by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) [10], using a 75 g oral glucose tolerance test (OGTT). Venous blood samples were collected at three time points: fasting (before glucose intake), 1 hour after ingestion, and 2 hours after ingestion. GDM was diagnosed when any of the following plasma glucose concentrations met or exceeded the specified thresholds: (1) Fasting glucose ≥5.1 mmol/L; (2) 1-hour post-load glucose ≥10.0 mmol/L; (3) 2-hour post-load glucose ≥8.5 mmol/L.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) studies reporting the association between PPARγ2 and risk of GDM, (2) case-control or cohort studies, (3) studies with subjects meeting the diagnostic criteria for GDM, and (4) studies with the odds ratio (OR) and corresponding 95% confidence interval (CI) calculated for number of cases and genotyping method in the case and control groups. Exclusion criteria included: (1) non-case-control studies, and (2) duplicate publications and studies that did not report necessary data. To avoid potential double counting, when multiple articles originated from the same research group or appeared to use overlapping cohorts, only the study with the largest or most complete dataset was included.

Database

The following databases were used: (1) PubMed/Medline, (2) Web of Science, (3) Cochrane Library, and (4) Embase.

Search strategy

A comprehensive literature search was conducted across PubMed/Medline, Web of Science, Embase, and Cochrane Library from inception to August 2025, using combinations of Medical Subject Headings (MeSH) and free-text terms related to gestational diabetes mellitus and PPARγ2 polymorphisms. The following search terms and their synonyms were used: (“gestational diabetes mellitus” OR “GDM”) AND (“peroxisome proliferator-activated receptor gamma” OR “PPARG” OR

"PPARγ" OR "PPARG2") AND ("Pro12Ala" OR "rs1801282" OR "Proline12Alanine" OR "polymorphism" OR "variant" OR "mutation"). Boolean operators (AND, OR) were applied to combine terms as appropriate. Filters were set to English language, human subjects, and case-control or cohort studies. Reference lists of relevant reviews and meta-analyses were also manually screened to identify additional eligible studies.

Study screening and data extraction

At least two investigators were independently responsible for study screening. By reading the title and abstract, significantly irrelevant studies were first excluded, and then the full text of the remaining studies was obtained for further evaluation. The following data were extracted: basic information of study (author, year of publication, study site, *etc*.), sample size, study population, genotype, *etc*. Disagreement was resolved by consultation with a third investigator. In addition, potential overlapping populations were carefully checked across publications from the same institutions or author groups. Sensitivity analyses were performed by sequentially excluding such studies to confirm that the pooled results were not driven by overlapping cohorts.

Quality evaluation

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS). This tool evaluates studies across three domains: (1) selection of study groups, (2) comparability of groups, and (3) ascertainment of outcome. Each study was awarded a maximum of nine stars, with higher scores indicating better methodological quality. Studies with NOS scores ≥7 were considered high-quality studies. Two independent reviewers performed the assessment, and any discrepancies were resolved by discussion.

Statistical analysis

Meta-analyses were conducted using RevMan 5.3, Stata 18.0, and R software (metafor and meta packages). Effect sizes were initially calculated as log odds ratios (log ORs) with corresponding standard errors, which were then exponentiated and presented as odds ratios (ORs) with 95% confidence intervals (CIs) for interpretation. Given the genetic association study design and the small number of included studies, we followed current methodological recommendations and applied a random-effects model with the Hartung-Knapp adjustment regardless of the magnitude of

heterogeneity. Prediction intervals (PIs) were estimated to quantify the expected range of true effects in future studies. Statistical heterogeneity was assessed using the Q-test, I^2, and τ^2 statistics. Publication bias was evaluated using funnel plots, Begg's test, Egger's regression, and trim-and-fill analysis. For the model with non-significant Egger tests (i.e., the recessive model), trim-and-fill imputed no studies ($k_0=0$) and the original pooled estimate was retained. Sensitivity analyses were performed by sequentially excluding individual studies. Meta-regression was not feasible because the number of studies per subgroup was <10, which would yield unstable estimates. As prespecified alternatives, we conducted influence diagnostics using Baujat plots and a leave-one-out (LOO) analysis. Study influence was quantified as the absolute change in the pooled OR after sequential omission of each study. Subgroup analyses were stratified by ethnicity, study quality, and sample size.

RESULTS

Search results and study selection

A total of 1,054 records were retrieved from PubMed/Medline, Embase, Web of Science, and the Cochrane Library. After removing 549 duplicates, 505 records remained for screening. Based on titles and abstracts, 184 irrelevant studies were excluded, and 321 full-text articles were assessed for eligibility. Of these, 306 articles were excluded due to non-case-control design, insufficient data, animal or in-vitro studies, conference abstracts, reviews, or overlapping cohorts. Finally, 15 studies met the inclusion criteria and were included in both qualitative and quantitative synthesis (Figure 1).

Basic characteristics of included studies

The included studies involved 12,760 subjects including 4,085 in the case group and 8,675 in the control group [7, 11-24]. They were all observational case-control studies, including five in the East Asia group, seven in the Europe group, one in the Middle East group, one in the Middle East/Europe group and one in the North East group. In addition to demographic characteristics, the diagnostic criteria for GDM and the timing of testing (gestational weeks) were extracted and are presented in Table 1 to standardize phenotyping across studies.

Quality assessment of included studies

The methodological quality of the included case-control studies was evaluated using the NOS. For the selection domain, three items were assessed: (1) Representativeness of the cases: whether the cases accurately represented individuals in the target population who developed the disease of interest; (2) Selection of controls: whether the controls were appropriately chosen (e.g., community-based or hospital-based); (3) Definition and representativeness of controls: whether the controls adequately represented the non-diseased population from which the cases arose. For the comparability domain, two items were considered: (4) Comparability of cases and controls with respect to key confounding factors (such as age and sex); (5) Comparability regarding other potential confounders beyond the main exposure of interest. For the exposure assessment domain, three items were evaluated: (6) Ascertainment of exposure among cases, (7) Ascertainment of exposure among controls, and (8) Accuracy and reliability of exposure measurement, including additional factors related to measurement precision, consistency, and methodological rigor in capturing true exposure levels. Most studies received high scores in terms of participant selection and outcome ascertainment. The comparability between groups, a core NOS criterion, was also well addressed in the majority of studies. Overall, the included studies were of satisfactory methodological quality, meeting the expected standards for inclusion in this meta-analysis (Table 2).

Hardy-Weinberg equilibrium test

The results of the Hardy-Weinberg equilibrium test indicated that the control groups in 14 studies conformed to Hardy-Weinberg equilibrium ($P>0.05$). However, in the study by Bhushan R (2024) involving a South Asian population, the control group data did not conform to Hardy-Weinberg equilibrium ($P<0.05$, Table 3).

Allelic model (Ala [G] vs. Pro [C])

A meta-analysis using the Hartung-Knapp random-effects model showed no significant association between the Ala allele and GDM risk. Pooled OR=0.90, 95% CI=0.75-1.08, P=0.26. The 95% PI was 0.63-1.29, suggesting that future studies are also unlikely to show a strong association. Heterogeneity was modest (I^2=33.2%, τ^2=0.0403). Overall, the results indicate no significant association between the Ala allele and GDM risk (Figure 2).

Dominant model (Ala carriers [CG+GG] vs. Pro homozygotes [CC])

Using the Hartung-Knapp random-effects model, carriers of the Ala allele (CG+GG) did not show a significantly different risk of GDM compared with Pro homozygotes. Pooled OR=0.92 (95% CI: 0.74-1.13), 95% PI: 0.61-1.36, P=0.42, I^2=36%. These findings suggest no association between the PPARγ2 Pro12Ala variant and GDM under the dominant model (Figure 3).

Recessive model (Ala homozygotes [GG] vs. Pro carriers [CG+CC])

Using the Hartung-Knapp random-effects model, no significant association was observed under the recessive model. Pooled OR=0.82 (95% CI: 0.54-1.25), 95% PI: 0.37-1.81, P=0.33, I^2=0%. These findings indicate that homozygosity for the Ala (G) allele does not confer a significantly altered risk of GDM (Figure 4).

Publication bias

To assess potential publication bias, funnel plots and Egger's test were constructed for each genetic model (Figure 5). In the allelic model (Ala [G] vs. Pro [C]), most scatter points were concentrated on the left side of the funnel plot, suggesting possible publication bias. The Egger's test further confirmed this, with Z=-2.41, P=0.016, indicating a small-sample effect and the presence of publication bias. In the dominant model (Ala carriers [CG+GG] vs. Pro homozygotes [CC]), the majority of points were likewise clustered on the left side of the funnel plot, suggesting evident publication bias. The Egger's test yielded Z=-2.25, P=0.0246, confirming the presence of publication bias. In contrast, the recessive model (Ala homozygotes [GG] vs. Pro carriers [CG+CC]) showed a symmetrical distribution of scatter points, indicating a lower likelihood of publication bias. The Egger's test result (Z=-0.91, P=0.3611) suggested that no significant publication bias was present.

To further evaluate publication bias, Begg's rank correlation test was conducted. Begg's test did not detect significant publication bias in any model (allelic: P=0.15; dominant: P=0.15; recessive: P=0.66), although point estimates suggested weak negative correlation. Trim-and-fill procedures for the allelic and dominant models yielded similar pooled estimates, indicating robustness of results (supporting information, Figure S1). Trim-and-fill analysis imputed no missing studies (k_0=0), indicating no evidence of publication bias under the recessive model. Collectively, although Egger's test suggested small-study effects in the allelic and dominant models,

the absence of significance in Begg's test and the stability of trim-and-fill estimates support the overall conclusion of no material publication bias.

Sensitivity and influence analyses

Sensitivity analyses were performed by sequentially excluding each included study. For the allelic model (Ala [G] vs. Pro [C]), the I^2 values remained below 50% after the exclusion of any single study, indicating consistently low heterogeneity. The pooled ORs were consistently less than 1, with the lowest heterogeneity (I^2=8%) observed after removing Yan Y (2020). These findings suggest that the results of the meta-analysis were robust. For the dominant model (Ala carriers [CG+GG] vs. Pro homozygotes [CC]), sensitivity analysis likewise showed I^2<50% across all iterations, maintaining a low level of heterogeneity. The combined ORs remained below 1, and heterogeneity was minimal (I^2=1%) when Chon SJ (2013) was excluded. This further supports the stability of the meta-analytic findings. For the recessive model (Ala homozygotes [GG] vs. Pro carriers [CG+CC]), I^2 consistently equaled 0%, with pooled ORs<1 throughout the analysis, indicating that the meta-analysis results were highly stable and reliable.

Given that the number of studies per subgroup was <10, meta-regression was not feasible. As prespecified alternatives, we performed influence diagnostics (Baujat plot and delta-influence analysis) and LOO sensitivity analysis. For the allelic model, the Baujat plot identified Yan 2020 as contributing most to heterogeneity and exerting the largest influence on the pooled estimate, followed by Chon 2013 and Bhushan 2024. However, the magnitude of influence was small (all Δ-OR ≤0.03). LOO analysis showed that removal of any single study yielded stable estimates (pooled OR range 0.88-0.94), indicating robustness of the results (supporting information, Figure S2). Dominant and recessive models demonstrated similar stability, with no single study materially altering the pooled effect or heterogeneity (supporting information, Figure S3 and S4).

Subgroup analysis

Subgroup analyses were performed by ethnicity, study quality, and sample size (Table 4). By ethnicity: In the allelic (Ala [G] vs. Pro [C]) and dominant (Ala carriers [CG+GG] vs. Pro homozygotes [CC]) models, heterogeneity was low (I^2<50%), and only the East Asian subgroup showed a suggestive protective trend of the Ala (G)

allele against GDM, while European and Middle Eastern groups did not. Between-group differences were significant (P<0.05). In the recessive model (Ala homozygotes [GG] vs. Pro carriers [CG+CC]), heterogeneity was negligible (I^2=0%) with no significant subgroup differences. By study quality: Both high- and moderate-quality studies showed low to moderate heterogeneity and no significant associations across all genetic models. Between-group differences were non-significant (P>0.05). By sample size: All subgroups showed low or no heterogeneity and no significant associations in any model, with non-significant between-group differences (P>0.05). Overall, ethnicity appeared to be a key effect modifier, whereas study quality and sample size had minimal influence on the pooled results. After trim-and-fill adjustment for potential publication bias, the East Asian subgroup retained a similar protective direction and magnitude, with no material change in statistical significance, suggesting robustness of the observed trend.

DISCUSSION

This meta-analysis integrated data from 15 case-control studies to comprehensively examine the association between the PPARγ2 gene Pro12Ala (Pro [C]→Ala [G]) polymorphism and the risk of GDM. PPARγ2, a member of the nuclear hormone receptor superfamily, plays a central role in lipid metabolism, glucose homeostasis, and insulin sensitivity. The Pro12Ala missense mutation, a variant unique to the PPARγ2 isoform, has been widely reported to be associated with a reduced risk of type 2 diabetes. This mutation, caused by a C→G substitution at codon 12 in exon 2, results in the replacement of proline (Pro) with alanine (Ala), and represents one of the most common variants of the PPARγ gene [25]. Phosphorylation of insulin can enhance ligand-dependent activation of the N-terminal domain of PPARγ, indicating a close link between insulin signaling and PPARγ function [26]. The presence of the Pro12Ala polymorphism may alter this interaction, thereby influencing cellular insulin responsiveness and lipid metabolism. However, the role of this genetic variant in the specific physiological context of GDM remains controversial. The present pooled analysis found no significant association between the Pro12Ala polymorphism and GDM risk across any of the three genetic models. Subgroup analyses suggested possible ethnic differences, but these findings should be interpreted cautiously given multiple testing, allele-frequency variation, and limited power in some comparisons.

Across all genetic models, the pooled ORs were close to 1, with confidence intervals crossing the null value, suggesting that Pro12Ala is unlikely to be a major GDM susceptibility locus. This "negative" finding may reflect the complex pathophysiology of GDM, characterized by insulin resistance and inadequate compensatory β-cell compensation. The mild insulin-sensitizing influence of the Ala (G) allele may not offset this physiological burden. Furthermore, pooling studies from populations with diverse genetic backgrounds may have masked subgroup-specific effects.

Previous studies have suggested possible ethnic differences in GDM prevalence [27]. In ethnicity-based analyses, the Ala (G) allele showed a suggestive protective trend in East Asian populations under allelic and dominant models, while no association was observed in European or Middle Eastern groups. Given the small number of studies and multiple comparisons, this observation should be viewed as exploratory. This pattern may reflect gene-environment interactions, as lifestyle, adiposity, and dietary factors differ between ethnicities. Variations in allele frequencies and linkage disequilibrium structures may also contribute.

Placing these findings in a broader academic context, the overall null association contrasts with earlier small-sample studies, highlighting the greater reliability of conclusions derived from pooled data. The ethnicity-related trend observed here is consistent with findings from studies on PPARγ2 and type 2 diabetes but remains hypothesis-generating given limited power, especially under the recessive model where the Ala/Ala genotype is rare.

Publication bias analyses using Egger's, Begg's, and trim-and-fill methods suggested minor small-study effects without materially altering pooled estimates. Sensitivity and influence diagnostics further confirmed the robustness of results, and Hardy-Weinberg equilibrium testing supported the genetic validity of controls. Collectively, these findings reinforce the stability and methodological rigor of the meta-analysis, while acknowledging that undetected negative studies could make the overall "no association" conclusion conservative.

Of course, this study has several limitations. First, as a meta-analysis based on aggregated literature data, individual-level information was unavailable, making it difficult to precisely adjust for pre-pregnancy BMI, a major confounding factor for

GDM. Second, the diagnostic criteria for GDM varied slightly across studies. Although most studies performed well in this regard according to quality assessments, such inconsistencies may still represent a potential source of heterogeneity. Third, the relatively small number of studies in certain strata, especially the recessive model, and the multiple subgroup comparisons may increase the likelihood of type I error.

CONCLUSION

In summary, this meta-analysis found no statistically significant association between the PPARγ2 Pro12Ala (Pro [C]→Ala [G]) polymorphism and the overall risk of GDM across all genetic models. Compared with earlier meta-analyses, this study incorporated more recent data, applied genetics-appropriate quality assessment, and conducted detailed subgroup and sensitivity analyses, leading to a more robust and reliable pooled estimate. A suggestive protective trend of the Ala (G) allele among East Asian populations was observed but remains inconclusive due to limited power and multiple testing. Overall, PPARγ2 Pro12Ala may have only a minor influence on GDM susceptibility, warranting confirmation through large, multicenter studies using standardized protocols and multivariate analyses.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Fundamental characteristics of included studies

First author (year)	Race	Sample size		Genotype CC/CG/GG		Allele C/G		Study design	Diagnostic criteria	Timing of diagnosis (GA, weeks)
		Case group	Control group	Case group	Control group	Case group	Control group			
Lauenborg et al., 2009	Europe	265	2383	201/60/4	1790/542/51	462/68	4122/644	case-control	WHO	at 24 to 28 weeks
	East Asia	55	173	52/3/0	157/16/0	107/3	330/16	case-control	WHO	at 24 to 28 weeks
Cheng et al., 2010										
Chon et al., 2013	East Asia	94	41	89/5/0	34/7/0	183/5	75/7	case-control	IWC	at 24 to 28 weeks
Heude et al., 2011	Europe	109	1587	92/17/0	1265/305/17	201/17	2835/339	case-control	IWC	undefined
Pappa et al., 2011	Europe	148	107	143/5/0	100/7/0	291/5	207/7	case-control	ADA	undefined

Shaat et al., 2004	Middle East/Europe	500	550	377/120/3	423/120/7	874/126	966/134	case-control	Other criteria	undefined
Shaat et al., 2007	Europe	637	1232	468/158/11	918/298/16	1094/180	2134/330	case-control	EASD	at 24 to 28 weeks
Tok et al., 2006	Middle East	62	100	50/12/0	84/16/0	112/12	184/16	case-control	NDDG	at 24 to 28 weeks
Cho et al., 2009	East Asia	865	632	793/71/1	567/63/2	1657/73	1197/67	case-control	IWC	at 24 to 28 weeks
Yan et al., 2020	East Asia	156	180	144/12/0	153/24/3	300/12	330/30	case-control	Other criteria	undefined
Kuzmicki et al., 2013	Europe	20	20	18/2/0	17/3/0	38/2	37/3	case-control	PDA	undefined
Rosta et al., 2017	Europe	217	670	168/46/3	507/152/11	382/55	1166/174	case-control	IADPSG	undefined
Franzago et al., 2018	Europe	104	124	79/25/0	101/23/0	183/25	225/231	case-control	IADPSG	at 24 to 28 weeks
	East Asia		676	676/77/0	589/81/2	1429/77		case-control	IADPSG	
Shen et al., 2020	South	75					259/85			at 24 to 28

Bhushan et al., 2024	Asia	3 10 0	200	75/25/0	171/25/4	175/25	367/33	case-control WHO	weeks at 24 to 28 weeks

Abbreviations: WHO: World Health Organization; IWC: International Workshop-Conference; ADA: American Diabetes Association; EASD: European Association for the Study of Diabetes; NDDG: U.S. National Diabetes Data Group; PDA: Polish Diabetes Association; IADPSG: International Association of Diabetes in Pregnancy Study Groups.

Table 2. Assessment of quality in included studies

Studies	1	2	3	4	5	6	7	8	9	Score	Overall of quality	Reasons
Lauenborg J. et al. 2009	1	1	0	1	0	1	0	1	1	6	Moderate	Insufficient matching of exposure background; incomplete quality control records; inadequate control of confounding factors
Cheng Y et al. 2010	1	1	1	0	1	1	0	1	1	7	High	Age difference not statistically tested; key GDM-related features unreported; potential confounding bias due to lack of adjustment
Chon SJ et al. 2013	1	1	1	0	1	1	0	0	1	6	Moderate	Limited comparability of key traits; unadjusted confounders; lack of blinding in genotyping may introduce bias
Heude B et al. 2011	1	1	1	1	1	1	0	1	1	8	High	Unadjusted inter-center threshold differences and incomplete center effect control.

Pappa KI et al. 2011	1	1	1	0	1	1	0	0	1	6	Moderate	Limited comparability of key features, unadjusted core confounders, and lack of blinding in exposure assessment
Shaat N et al. 2004	1	1	1	1	1	1	0	1	1	8	High	Incomplete confounding control
Shaat N et al. 2007	1	1	1	1	1	1	1	1	0	8	High	HWE P-values not reported; insufficient detail on population representativeness
Tok EC et al. 2006	1	1	1	1	0	1	1	1	1	8	High	Incomplete quality control measures, limiting confirmation of genotyping reliability
Cho YM et al. 2009	1	1	1	1	1	1	0	1	1	7	High	Possible prior GDM history in controls not excluded; confounding control incomplete
Yan Y et al. 2020	1	1	1	0	1	1	1	1	1	7	High	Age data missing; incomplete baseline traits and unverified group comparability
Kuzmicki M et al. 2013	1	1	1	0	1	1	1	1	1	8	High	Lack of QC details limits assay reliability verification

Rosta K et al. 2017	1	1	1	1	1	1	1	1	0	8	High	No comprehensive correction provided for multiple testing of 77 SNPs
Franzago M et al. 2018	1	1	1	1	0	0	1	1	1	6	Moderate	Age/BMI imbalance unaddressed; genotyping QC data insufficient
Shen Y et al. 2020	1	1	1	1	1	1	0	1	1	8	High	Hospital source differences unadjusted; potential assay or procedural variations may introduce residual confounding
Bhushan R et al. 2024	1	1	1	1	1	1	0	1	1	8	High	No multivariable adjustment reported; confounding control uncertain

Abbreviations: GDM: Gestational diabetes mellitus; BMI: Body mass index; SNP: Single nucleotide polymorphism; HWE: Hardy–Weinberg equilibrium.

Table 3. Hardy-Weinberg equilibrium test: Expected genotype counts under HWE

Studies	Allele C frequency (P)	Allele G frequency (P)	Genotype CC/CG/GG frequency (P)	χ^2	*p*	HWE conformity
Lauenborg J et al. 2009	0.865	0.135	1784.6/555.0/43.4	2.03	0.154	Yes
Cheng Y et al. 2010	0.954	0.046	157.5/15.0/0.4	0.05	0.829	Yes
Chon SJ et al. 2013	0.915	0.085	34.3/6.3/0.3	0.19	0.665	Yes
Heude B et al. 2011	0.893	0.107	1265.6/303.9/17.5	0.02	0.888	Yes
Pappa KI et al. 2011	0.967	0.033	100.1/6.8/0.1	0.01	0.907	Yes
Shaat N et al. 2004	0.878	0.122	423.9/120.2/5.9	0.28	0.599	Yes
Shaat N et al. 2007	0.866	0.134	924.6/295.9/11.5	2.66	0.103	Yes
Tok EC et al. 2006	0.920	0.080	84.6/14.7/0.6	0.38	0.536	Yes
Cho YM et al. 2009	0.947	0.053	567.0/63.1/1.8	0.02	0.900	Yes
Yan Y et al. 2020	0.917	0.083	151.4/27.3/1.2	3.20	0.074	Yes
Kuzmicki M et al.	0.925	0.075	17.1/2.8/0.1	0.04	0.835	Yes

2013						
Rosta K et al. 2017	0.870	0.130	507.7/151.8/11.1	0.00	0.982	Yes
Franzago M et al. 2018	0.907	0.093	102.0/21.4/0.6	0.43	0.512	Yes
Shen Y et al. 2020	0.931	0.069	586.0/86.1/3.2	1.54	0.215	Yes
Bhushan R et al. 2024	0.918	0.083	168.4/30.5/1.4	4.27	0.039	No

Abbreviation: HWE: Hardy–Weinberg equilibrium.

Table 4. Subgroup analysis

Grouping methods	Genetic model	Groups	Number of studies	I^2(%)	Log OR	OR	95% CI	*p*
Subgroup by ethnicity	G vs. C	East Asia	5	19.98	-0.34	0.71	-0.55, -0.12	0.001
		Europe	8	0.00	0.00	1.00	-0.12, 0.12	0.98
		Middle East	2	24.84	-0.12	0.89	-0.68, 0.45	0.68
		Overall	15	25.13	-0.08	0.92	-0.18, 0.02	0.12
		Test of group difference: Q=7.42, *p*=0.02						
	CG+GG vs. CC	East Asia	5	14.34	-0.32	0.73	-0.54, -0.10	0.001
		Europe	8	0.00	0.00	1.00	-0.13, 0.14	0.95
		Middle East	2	13.10	-0.09	0.91	-0.68, 0.50	0.77
		Overall	15	18.63	-0.08	0.92	-0.19, 0.03	0.15
		Test of group difference: Q=6.25, *p*=0.04						
	GG vs. CG+CC	East Asia	5	0.00	-1.15	0.32	-2.47, 0.17	0.09
		Europe	8	0.00	-0.13	0.88	-0.62, 0.36	0.60

		Middle East	2	0.00	-0.40	0.67	-2.79, 1.99	0.74
		Overall	15	0.00	-0.27	0.76	-0.72, 0.17	0.23
					Test of group difference: Q=2.02, *p*=0.36			
	G vs. C	High	10	20.04	-0.08	0.92	-0.19, 0.03	0.18
		Moderate	4	51.22	-0.08	0.92	-0.31, 0.16	0.52
		Overall	14	25.31	-0.08	0.92	-0.18, 0.02	0.13
					Test of group difference: Q=0.00, *p*=0.99			
Subgroup by quality of research	CG+GG vs. CC	High	10	5.24	-0.08	0.92	-0.20, 0.04	0.19
		Moderate	4	54.28	-0.07	0.93	-0.32, 0.19	0.61
		Overall	14	19.07	-0.08	0.92	-0.19, 0.03	0.16
					Test of group difference: Q=0.01, *p*=0.92			
	GG vs. CG+CC	High	10	0.00	-0.26	0.77	-0.77, 0.26	0.33
		Moderate	4	0.00	-0.35	0.71	-1.28, 0.59	0.46
		Overall	14	0.00	-0.28	0.76	-0.73, 0.17	0.23
					Test of group difference: Q=0.03, *p*=0.86			

		Large	3	13.79	-0.11	0.90	-0.28, 0.06	0.21
		Medium	7	38.48	-0.05	0.95	-0.18, 0.08	0.49
	G vs. C	Small	4	28.02	-0.31	0.73	-0.86, 0.23	0.26
		Overall	14	25.31	-0.08	0.92	-0.18, 0.02	0.13
					Test of group difference: Q=1.09, *p*=0.58			
		Large	3	22.85	-0.09	0.91	-0.28, 0.09	0.31
		Medium	7	26.10	-0.05	0.95	-0.19, 0.09	0.47
Subgroup by sample size	CG+GG vs. CC	Small	4	31.38	-0.34	0.71	-0.90, 0.23	0.24
		Overall	14	19.07	-0.08	0.92	-0.19, 0.03	0.16
					Test of group difference: Q=0.95, *p*=0.62			
		Large	3	0.00	-0.96	0.38	-2.06, 0.13	0.08
		Medium	7	0.00	-0.14	0.87	-0.66, 0.37	0.58
	GG vs. CG+CC	Small	4	0.00	0.18	1.20	-1.79, 2.15	0.86
		Overall	14	0.00	-0.28	0.76	-0.73, 0.17	0.23
					Test of group difference: Q=1.98, *p*=0.37			

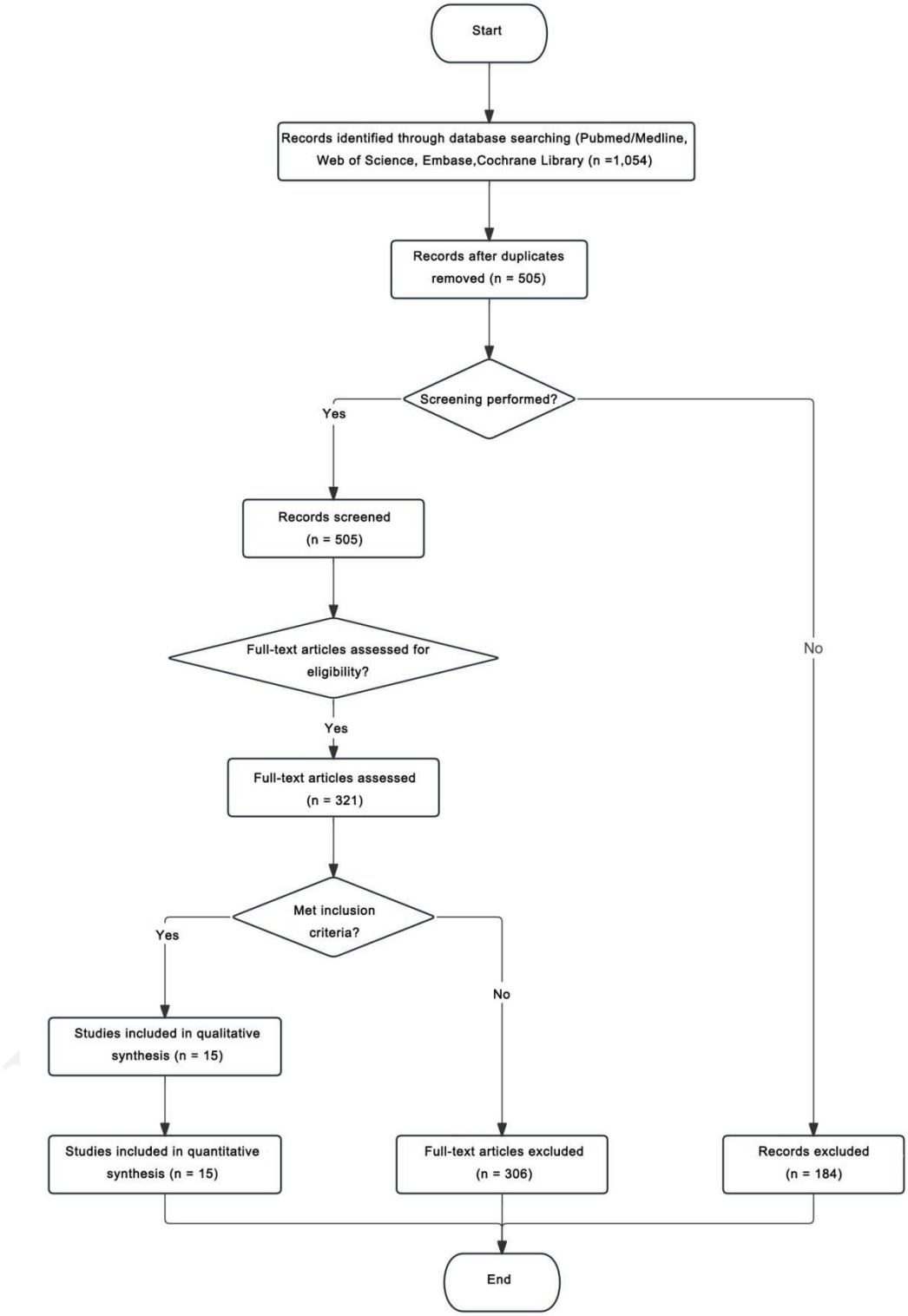

Figure 1. **PRISMA flow diagram of study selection process.**

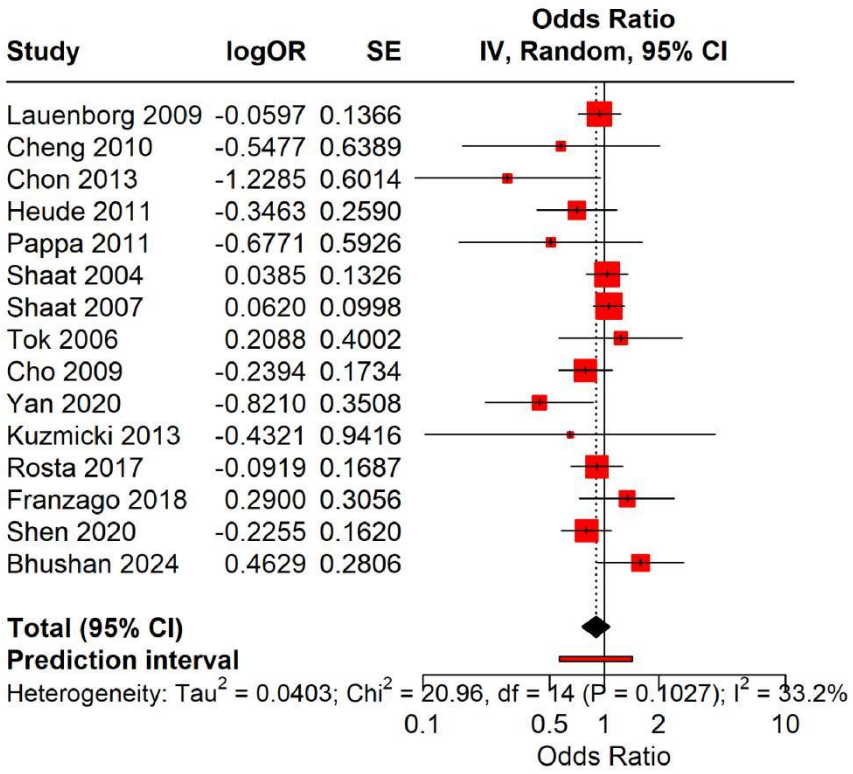

Figure 2. Forest plot illustrating the allelic model (Ala [G] vs. Pro [C]). Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated to assess the association between the Ala (G) allele and the risk of gestational diabetes mellitus (GDM), utilizing the Hartung–Knapp random-effects model. The summary odds ratio was 0.90 (95% CI: 0.75–1.08, p=0.26), accompanied by a 95% prediction interval of 0.63–1.29 and a modest degree of heterogeneity (I^2=33.2%, τ^2=0.0403), indicating no significant association.

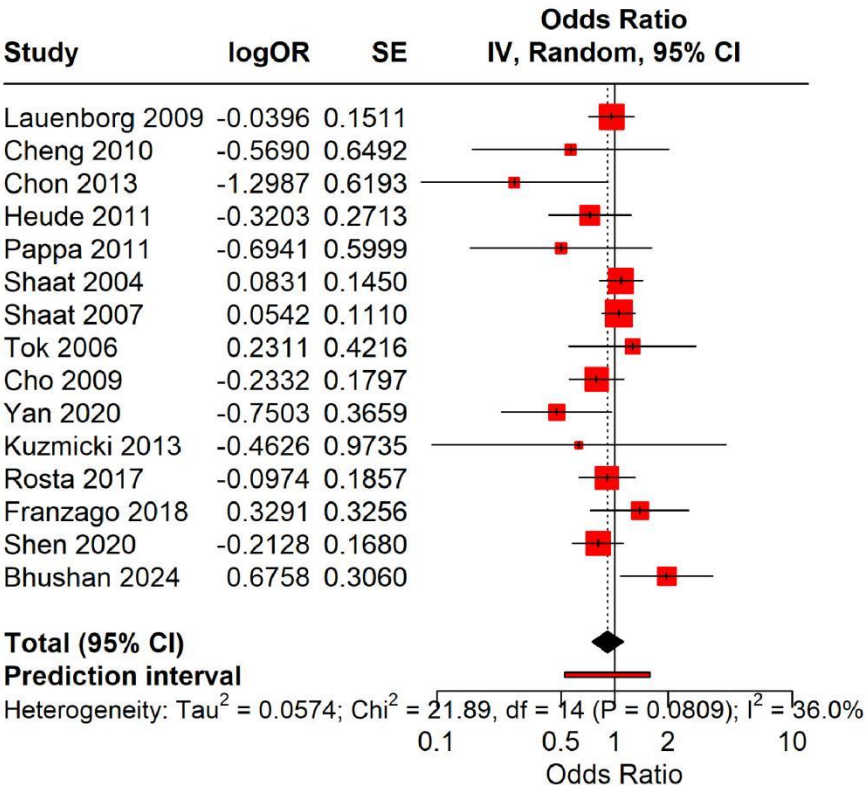

Figure 3. Forest plot for the dominant model (combined homozygous and heterozygous carriers of Ala [CG+GG] versus homozygous Pro [CC]). This figure presents study-specific and pooled odds ratios (OR) with 95% confidence intervals (CI) for gestational diabetes mellitus (GDM) risk among Ala allele carriers (CG+GG) in comparison to Pro homozygotes (CC). Estimates were derived using the Hartung–Knapp random-effects model. The pooled OR was 0.92 (95% CI: 0.74–1.13; p=0.42), with a 95% prediction interval of 0.61–1.36 and moderate heterogeneity (I^2=36%). These results indicate no significant association between the PPARγ2 Pro12Ala variant and GDM risk under the dominant model.

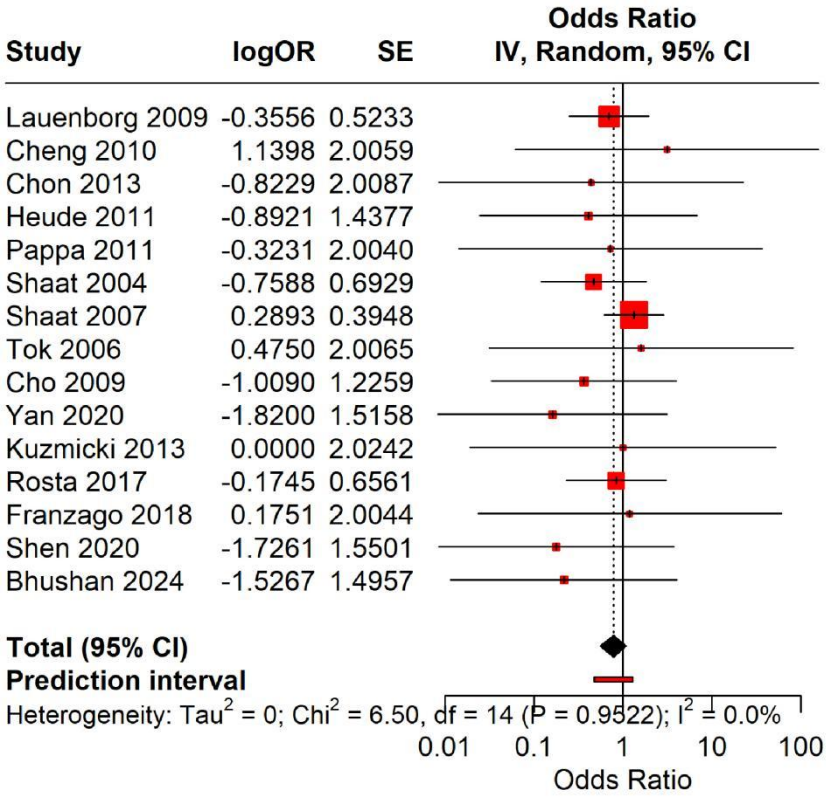

Figure 4. Forest plot for the recessive model (GG vs. CG+CC). Utilizing the Hartung–Knapp random-effects model, no significant association was identified under the recessive model. The pooled odds ratio (OR) was 0.82 (95% confidence interval [CI]: 0.54–1.25; p=0.33), with a 95% prediction interval of 0.37–1.81 and I^2=0%. These results indicate that homozygosity for the Ala (G) allele does not significantly alter the risk of gestational diabetes mellitus (GDM).

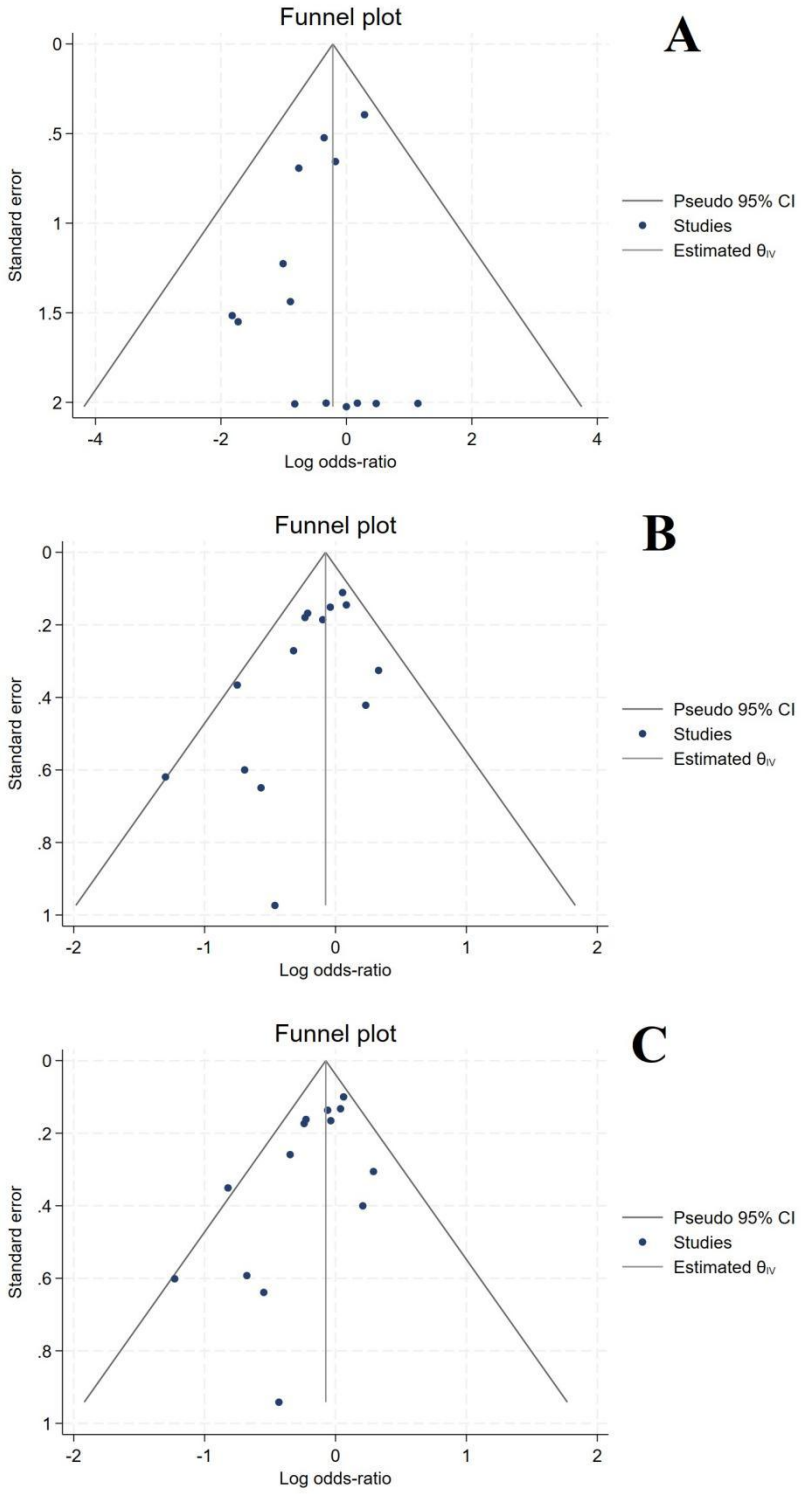

Figure 5. Funnel plots illustrating the assessment of publication bias across studies. (A) Funnel plot for the allelic model (Ala [G] vs. Pro [C]). (B) Funnel plot for the dominant model (combined homozygous and heterozygous carriers, Ala [CG+GG] vs. Pro homozygotes [CC]). (C) Funnel plot for the recessive model (GG vs. CG+CC).

SUPPLEMENTAL DATA

Supplemental data are available at the following link:

https://www.bjbms.org/ojs/index.php/bjbms/article/view/13079/4049