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Systematic Review

Studies on the Association of *GCK* and *GCKR* Polymorphisms with Susceptibility to Gestational Diabetes Mellitus: A Meta-Analysis

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Abstract

Background: A prevalent condition during pregnancy, gestational diabetes mellitus (GDM) affects a significant proportion of pregnancies worldwide and poses substantial risks to maternal as well as fetal health. Polymorphisms in the *glucokinase* (*GCK*) and *glucokinase regulatory protein* (*GCKR*) genes, which are crucial for glucose homeostasis, may modulate susceptibility to GDM. Hence, this meta-analysis aimed to assess the relationship between GDM and polymorphisms in *GCK* (rs1799884, rs4607517) and *GCKR* (rs780094, rs1260326). **Methods**: In this systematic review, we retrieved data from PubMed, EMBASE, Medline, EBSCO, Cochrane Library, and Chinese National Knowledge Infrastructure (CNKI) databases. Studies were critically appraised using the Newcastle-Ottawa Scale, and meta-analyses were performed using STATA 12.0. The odds ratios (ORs) were calculated with 95% confidence intervals (CIs) and heterogeneity was assessed with Cochran's Q test as well as I^2 statistical tests, respectively. Moreover, Begg's test helped in evaluating publication bias. **Results**: We included 20 studies, comprising 9745 GDM women and 15,830 controls. All genetic models showed a strong correlation between the *GCK* rs1799884 polymorphism and GDM, with carriers of the A allele exhibiting an increased risk. Conversely, *GCK* rs4607517, *GCKR* rs780094, and rs1260326 were not significantly associated. However, heterogeneity was influenced by ethnicity and diagnostic criteria. **Conclusions**: The *GCK* rs1799884 polymorphism can be a potential predictive marker because it is significantly associated with an increased risk of GDM.

Keywords: gestational diabetes mellitus; *GCK* gene; *GCKR* gene; polymorphisms; meta-analysis

1. Introduction

A significant public health concern, gestational diabetes mellitus (GDM) affects approximately 7%–18% of pregnancies worldwide [1–3]. GDM is characterized by the development of pregnancy-related glucose intolerance [4] and is substantially risky for maternal and fetal health. GDM increases the risk of cesarean delivery, hypertensive disorders, and long-term metabolic complications for both the mother and child [5–7]. Increased obesity and sedentary lifestyles exacerbated the incidence of GDM [8,9], necessitating a comprehensive understanding of its pathophysiology and genetic underpinnings to enhance prevention and treatment strategies. The *glucokinase* (*GCK*) and *glucokinase regulatory protein* (*GCKR*) genes, essential for glucose metabolism and homeostasis, are linked to GDM [10,11]. Primarily expressed in pancreatic beta cells, *GCK* acts as a glucose sensor that regulates insulin secretion [12,13]. Conversely, *GCKR* modulates *GCK* activity, thereby influencing glucose metabolism and insulin sensitivity [14–16]. Thus, variations in these genes can disrupt glucose regulation and lead to GDM [17,18].

Several studies have implicated *GCK* and *GCKR* gene polymorphisms in GDM susceptibility [19,20]. These genetic variants may affect glucose metabolism and insulin response. She *et al*. [19] suggested that the *GCK* gene rs1799884 (–30G > A) polymorphism's AA genotype is a risk factor for GDM. Moreover, *GCK* rs4607517, and *GCKR* (rs780094 and rs1260326) polymorphisms were not significantly associated with GDM susceptibility. However, Zhu *et al*. [20] found that *GCKR* rs1260326 polymorphism was significantly correlated with elevated GDM risk. Varying results from different studies highlight the necessity of a meta-analysis to assemble data and provide a more definitive conclusion.

This meta-analysis aimed to systematically evaluate the association between *GCK* (rs1799884 and rs4607517) and *GCKR* (rs780094 and rs1260326) polymorphisms as well as GDM susceptibility. By integrating data from multiple studies, we sought to clarify the genetic components of GDM and provide relavant insights for future research and clinical practice.

2. Materials and Methods

2.1 Research Selection

We used databases like PubMed (https://pubmed.ncbi.nlm.nih.gov/), EMBASE (https://www.embase.com/), Medline (https://www.nlm.nih.gov/medline/medline_home.html), EBSCO (http://search.ebscohost.com/), Cochrane Library (https://www.cochranelibrary.com/), and the Chinese National Knowledge Infrastructure (CNKI) (https://www.cnki.net/) for literature search. Keywords like "*glucokinase*" or "*GCK*", "*glucokinase*

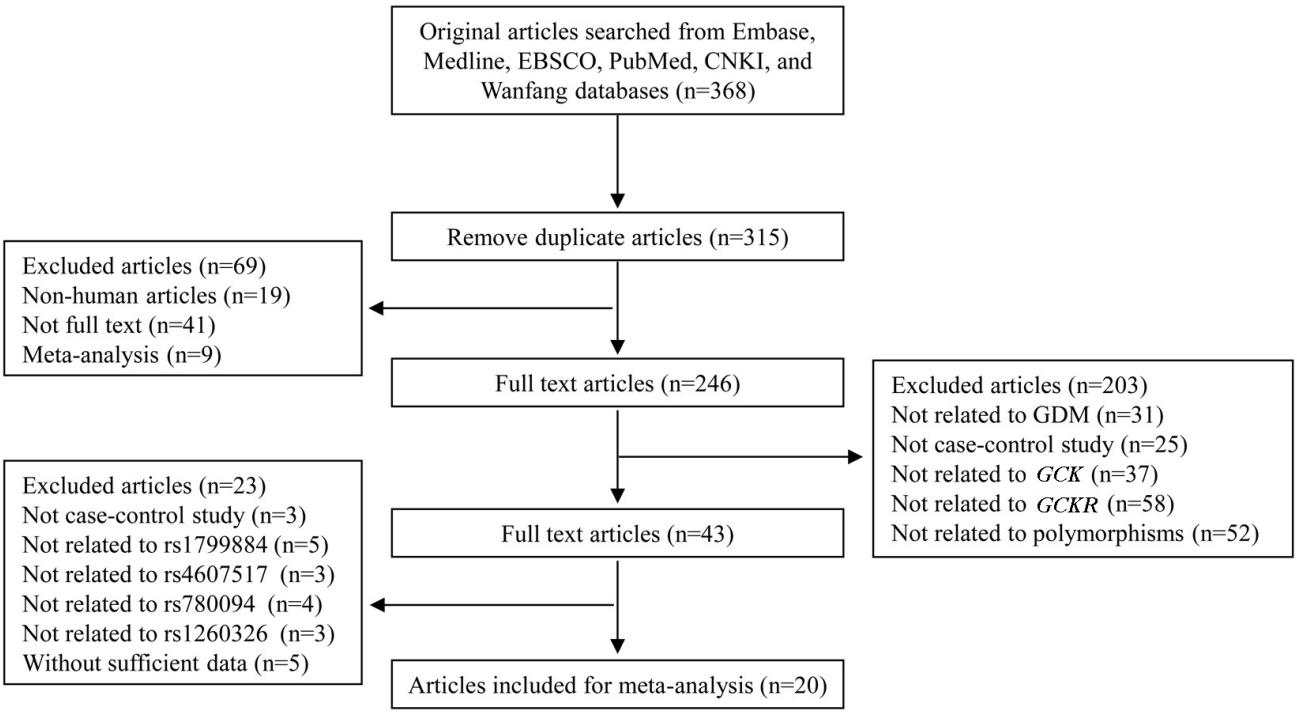

Fig. 1. Flow diagram for eligible article selection. CNKI, China National Knowledge Infrastructure; GDM, gestational diabetes mellitus; *GCK*, *glucokinase*; *GCKR*, *glucokinase regulatory protein*.

regulatory protein" or "*GCKR*", "gestational diabetes mellitus" or "gestational diabetes" or "GDM", along with terms for genetic variations such as "polymorphisms", "mutations", or "variants", as well as "risk" and "susceptibility" were used. Reference lists from identified articles were screened to ensure a comprehensive collection of relevant studies.

2.2 Inclusion and Exclusion Criteria

Our inclusion criteria were: (1) case-control studies comprising both a GDM group and a control group of pregnant women without GDM, and (2) those with adequate data on the genotypes of the *GCK* gene variants rs1799884 and rs4607517, as well as the *GCKR* gene variants rs780094 and rs1260326. Our exclusion criteria were: (1) studies lacking publication details; (2) case reports, reviews, abstracts, or meta-analyses; (3) those not on *GCK* or *GCK*R polymorphisms or GDM susceptibility; (4) research without case-control design; (5) those with incomplete odds ratio (OR) calculation data, and (6) those with genotype distributions that deviated from the control group's Hardy-Weinberg equilibrium (HWE).

2.3 Data Extraction

Using eligible publications, we meticulously extracted data like the first author's name, publication year, the participants' ethnicity, the genotype methodology, sample size, gestational age, and the number of genotypes as well as alleles in both study and control groups, respectively.

2.4 Statistical Analysis

Each study was rigorously assessed using the Newcastle-Ottawa Scale (NOS) score [21]. Our analysis only included studies that met the NOS score of $\geq$5. Meta-analysis was performed by STATA 12.0 software (StataCorp, College Station, TX, USA). Heterogeneity among studies was calculated by Cochran's Q and I^2 statistical tests, respectively [22]. We employed a random-effects model to calculate pooled effects in significant heterogeneity ($p < 0.05$ or $I^2 > 50\%$) [23]; otherwise, the fixed-effects model was used [24]. ORs with 95% confidence intervals (CIs) were calculated using the Z test to evaluate the association between the polymorphisms and GDM susceptibility. Subgroup analyses helped to explore potential heterogeneity sources. While publication bias was assessed by Begg's test [25]. GPower 3.1 (University of Duesseldorf, Duesseldorf, Germany) conducted power analysis for individual single nucleotide polymorphism (SNP).

3. Results

3.1 Characteristics of Enrolled Studies

Our literature search yielded 368 articles from Embase, Medline, EBSCO, PubMed, CNKI, and Wanfang databases. After removing 53 duplicates, we excluded 69 articles that did not fit our inclusion criteria, like being non-human studies, lacking full texts, or being meta-analyses. Additionally, 203 articles were disqualified because they were irrelevant to GDM, did not employ a case-control

Table 1. Characteristics of eligible studies.

Author	Year	Country	Ethnicity	Diagnosis		GDM group			Control group			p_{HWE}	Genotype method	SNPs
				Procedure	Criteria	Size	Gestational age	Age (mean ± SD)	Size	Gestational age	Age (mean ± SD)			
Chiu *et al*. [26]	1994	USA	African	OGTT	WHO	174	/	28.2 ± 5.8	99	/	22.1 ± 4.6	0.286	PCR-SSCP	*GCK* rs1799884
Zaidi *et al*. [30]	1997	UK	Caucasian	75 g OGTT	WHO	92	28–32	31 ± 5.5	45	28–32	/	0.414	PCR-SSCP	*GCK* rs1799884
Shaat *et al*. [29]	2006	Sweden	Caucasian	75 g OGTT	DPSG-EASD	642	27–28	32.3 ± 0.2	1229	27–28	30.5 ± 0.1	0.504	PCR-RFLP	*GCK* rs1799884
Freathy *et al*. [27]	2010	UK, Australia, Thailand	Caucasian, Asian	75 g OGTT	IADPSG	998	24–32	/	5587	24–32	/	0.91	Illumina	*GCK* rs1799884
Santos *et al*. [28]	2010	Brazil	Caucasian	75 g OGTT	ADA	150	24–28, 32–36	31.9 ± 6.2	600	24–28, 32–36	25.2 ± 6.5	0.371	PCR-RFLP	*GCK* rs1799884
Li W [31]	2011	China	Asian	100 g OGTT	ADA	668	28.2 ± 2.2	32.5 ± 3.9	758	27.7 ± 2.6	31.2 ± 3.8	0.558	TaqMan	*GCK* rs1799884, *GCKR* rs780094
Han *et al*. [34]	2015	China	Asian	75 g OGTT	/	948	2–32	/	975	/	/	0.985	PCR-based invader assay	*GCK* rs1799884
Tarnowski *et al*. [36]	2017	Poland	Caucasian	75 g OGTT	IADPSG	207	24–28	31.7 ± 4.5	204	/	29.2 ± 5.0	0.875	TaqMan	*GCK* rs1799884, *GCKR* rs780094
Zhou [43]	2020	China	Asian	75 g OGTT	National	835	24–28	30.97 ± 4.56	870	/	28.84 ± 4.21	0.246	MassARRAY	*GCK* rs1799884 and rs4607517, *GCKR* rs780094 and rs1260326
Popova *et al*. [41]	2021	Russia	Caucasian	75 g OGTT	IADPSG	688	24–28	31.9 ± 4.5	454	24–28	29.5 ± 4.7	0.141	TaqMan	*GCK* rs1799884
She *et al*. [19]	2022	China	Asian	75 g OGTT	IADPSG	835	24–28	30.97 ± 4.56	870	/	28.84 ± 4.21	0.246	MassARRAY	*GCK* rs1799884 and rs4607517, *GCKR* rs780094 and rs1260326
Wang *et al*. [32]	2011	China	Asian	100 g OGTT	ADA	1701	/	30 (30, 35)	1023	/	32 (28, 33)	0.804	Taqman	*GCK* rs4607517
Stuebe *et al*. [33]	2014	USA	Caucasian, African–American	100 g OGTT	/	80	24–29	28.3 ± 6.1	1138	24–29	/	0.324	Sequenom iPLEX	*GCK* rs4607517, *GCKR* rs780094 and rs1260326
Ao *et al*. [40]	2021	China	Asian	75 g OGTT	National	562	/	30.18 ± 2.64	452	/	29.50 ± 2.68	0.28	MassARRAY	*GCK* rs4607517
Anghebem-Oliveira *et al*. [35]	2017	Brazil	Caucasian	/	/	127	/	31.9 ± 6.4	125	/	30.6 ± 4.7	0.094	RT-PCR	*GCKR* rs780094
Jamalpour *et al*. [37]	2018	Malaysia	Asian	OGTT	/	186	/	/	588	/	29.9 ± 4.4	0.512	Sequenom iPLEX	*GCKR* rs780094
Li *et al*. [42]	2018	China	Asian	75 g OGTT	ADA	127	24–32	31.9 ± 6.4	125	/	30.6 ± 4.7	0.094	RT-PCR	*GCKR* rs780094
Franzago *et al*. [38]	2017	Italy	Caucasian	75 g OGTT	IADPSG	102	24–28	34.6 ± 5.4	66	24–28	31.9 ± 5.1	0.46	High resolution melting	*GCKR* rs1260326
Franzago *et al*. [39]	2018	Italy	Caucasian	75 g OGTT	IADPSG	104	24–28	34.6 ± 5.4	124	24–28	32.5 ± 5.2	0.276	RT-PCR	*GCKR* rs1260326
Zhu *et al*. [20]	2023	China	Asian	75 g OGTT	IADPSG	519	24–28	31 (28–34)	498	24–28	29 (27–32)	0.737	Illumina	*GCKR* rs1260326

Notes: GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; WHO, World Health Organization; DPSG-EASD, Diabetic Pregnancy Study Group of the European Association for the Study of Diabetes; IADPSG, new International Association of Diabetes and Pregnancy Study Groups; ADA, American Diabetes Association; PCR-SSCP, polymerase chain reaction–single strand conformation polymorphism; PCR-RFLP, polymerase chain reaction restriction fragment-length polymorphism; RT-PCR, real time-polymerase chain reaction; SD, standard deviation; p_{HWE}, p value of Hardy-Weinberg Equilibrium in control group; SNPs, single nucleotide polymorphisms; GCK, glucokinase; GCKR, glucokinase regulatory protein; MassARRAY, Sequenom MassARRAY iPLEX system.

design, or did not investigate the specified *GCK* or *GCKR* polymorphisms. This resulted in 43 full-text articles for further analysis. Our final analysis included 20 articles [19,20,26–43] comprising 9745 GDM patients and 15,830 healthy controls after excluding those without investigations on polymorphisms of interest (rs1799884, rs4607517, rs780094, or rs1260326) or lacked sufficient data (Fig. 1; Table 1, Ref. [19,20,26–43]). All included trials had NOS scores >6 (**Supplementary Table 1**).

3.2 The Combined Analyses of GCK and GCKR Polymorphisms with GDM Susceptibility

Eleven articles (encompassing 12 studies) focused on the *GCK* rs1799884 polymorphism with a power of 1.0, while five articles on *GCK* rs4607517 had a power of 0.812. Eight articles (including 11 studies) and six articles (including 7 studies) concentrated on *GCKR* rs780094 with a power of 0.829 and *GCKR* rs1260326 with a power of 1.0, respectively. Table 2 (Ref. [19,20,26–43]) shows the genotype distributions for these SNPs.

For these SNPs, 2 referes risk allele and 1 defiene as reference allele. The combined analyses for *GCK* (rs1799884 and rs4607517) and *GCKR* (rs780094 and rs1260326) polymorphisms indicated that these SNPs were significantly correlated with elevated GDM susceptibility under 22 *vs.* 11 (OR = 1.28, 95% CI = 1.08–1.51, Fig. 2A); decreased GDM susceptibility under 12 *vs.* 11 (OR = 0.65, 95% CI = 0.52–0.81, Fig. 2B) and 22 *vs.* 11 + 12 (OR = 0.80, 95% CI = 0.70–0.92, Fig. 2C) genetic models. However, no significant association was discovered in 22 + 12 *vs.* 11 (OR = 1.05, 95% CI = 0.91–1.21, Fig. 2D) and 2 *vs.* 1 (OR = 1.07, 95% CI = 0.96–1.20, Fig. 2E) genetic models, respectively.

3.3 Pooled Association of GCK rs1799884 and rs4607517 Polymorphisms with GDM Susceptibility

Regarding the rs1799884 polymorphism, significant heterogeneity was observed in the GA *vs.* GG model ($p < 0.05$, Fig. 2B), but not in the other four genetic models. Consequently, we used a random-effects model to assess the pooled association of rs1799884 with GDM susceptibility; however, a fixed-effects model was used for other models. Additionally, rs1799884 and GDM susceptibility were positively correlated in the AA *vs.* GG (OR = 1.55, 95% CI = 1.29–1.86, Fig. 3A) and AA + GA *vs.* GG (OR = 1.19, 95% CI = 1.11–1.27, Fig. 3B) genetic models, negatively correlated in the AA *vs.* GG + GA (OR = 0.67, 95% CI = 0.56–0.80, Fig. 3C) and A *vs.* G (OR = 1.19, 95% CI = 1.12–1.26, Fig. 3D) genetic models, respectively. No significant association was discovered between rs1799884 and GDM susceptibility uncer GA *vs.* GG model (Fig. 3E). The rs4607517 polymorphism showed significant heterogeneity across all five genetic models (**Supplementary Fig. 1**), and the random-effects model revealed a significant association with GDM susceptibility under AA + GA *vs.* GG model (OR = 0.66, 95% CI = 0.59–0.74) (**Supplementary Fig. 1C**), but not in other genetic models.

3.4 Pooled Associations of GCKR rs780094 and rs1260326 Polymorphisms with GDM Susceptibility

The rs780094 polymorphism showed significant heterogeneity in the TC *vs.* TT, CC *vs.* TT+TC, and C *vs.* T genetic models ($p < 0.05$), leading to the usage of a random-effects model. The results indicated a significant correlation between the rs780094 polymorphism and reduced GDM susceptibility in the TC *vs.* TT model (OR = 0.47, 95% CI = 0.30–0.73, Fig. 4A); however, no significant associations were found in the other models (Fig. 4B–D). For the rs1260326 polymorphism, the TC *vs.* TT model ($p < 0.05$) displayed significant heterogeneity. The random-effects model was used to analyze the association under this model, fixed-effects model analyzed for other genetic models. The pooled results revealed no significant association in any of the genetic models (**Supplementary Fig. 2**).

3.5 Subgroup Analysis

Stratified by ethnicity and diagnostic criteria, subgroup analyses were conducted to fine heterogeneity sources. The heterogeneity observed in the rs1799884 polymorphism's GA *vs.* GG model might have stemmed from variable ethnic and diagnostic criteria. Due to fewer studies for rs4607517, rs780094, and rs1260326 polymorphisms and multiple diagnostic criteria, diagnostic criteria-based subgroup analysis was not feasible. The heterogeneity in these polymorphisms was attributed to varying ethnicity.

In the ethnicity-based subgroup analysis, a positive association between rs1799884 polymorphism and GDM susceptibility was evident in the AA *vs.* GG model in both Asian (OR = 1.48, 95% CI = 1.16–1.90) and Caucasian (OR = 1.63, 95% CI = 1.24–2.15) subgroups, respectively (Fig. 3A). Analysis by diagnostic criteria revealed a positive association in the AA *vs.* GG model in subgroups following the Diabetic Pregnancy Study Group of the European Association for the Study of Diabetes (DPSG-EASD) (OR = 2.21, 95% CI = 1.26–3.90), International Association of Diabetes and Pregnancy Study Groups (IADPSG) (OR = 1.63, 95% CI = 1.25–2.13), and National criteria (OR = 1.91, 95% CI = 1.17–3.12) (**Supplementary Fig. 3A**). We also observed positive associations in the AA+GA *vs.* GG (Fig. 3B), AA *vs.* GG+GA (Fig. 3C), and A *vs.* G (Fig. 3D) models in the specified ethnic and diagnostic subgroups (**Supplementary Fig. 3B–D**). Conversely, the ethnicity-based subgroup analysis revealed a negative correlation between the rs780094 polymorphism and GDM susceptibility in the African-American subgroup under the TC *vs.* TT model (OR = 0.07, 95% CI = 0.02–0.20, Fig. 4A), but not in other for genetic models (Fig. 4B–D). Only one Caucasian study was conducted on the rs4607517 (**Supplementary Fig. 1**) and one African-American study was conducted on rs1260326 (**Supplementary Fig. 2**) polymorphism. Small

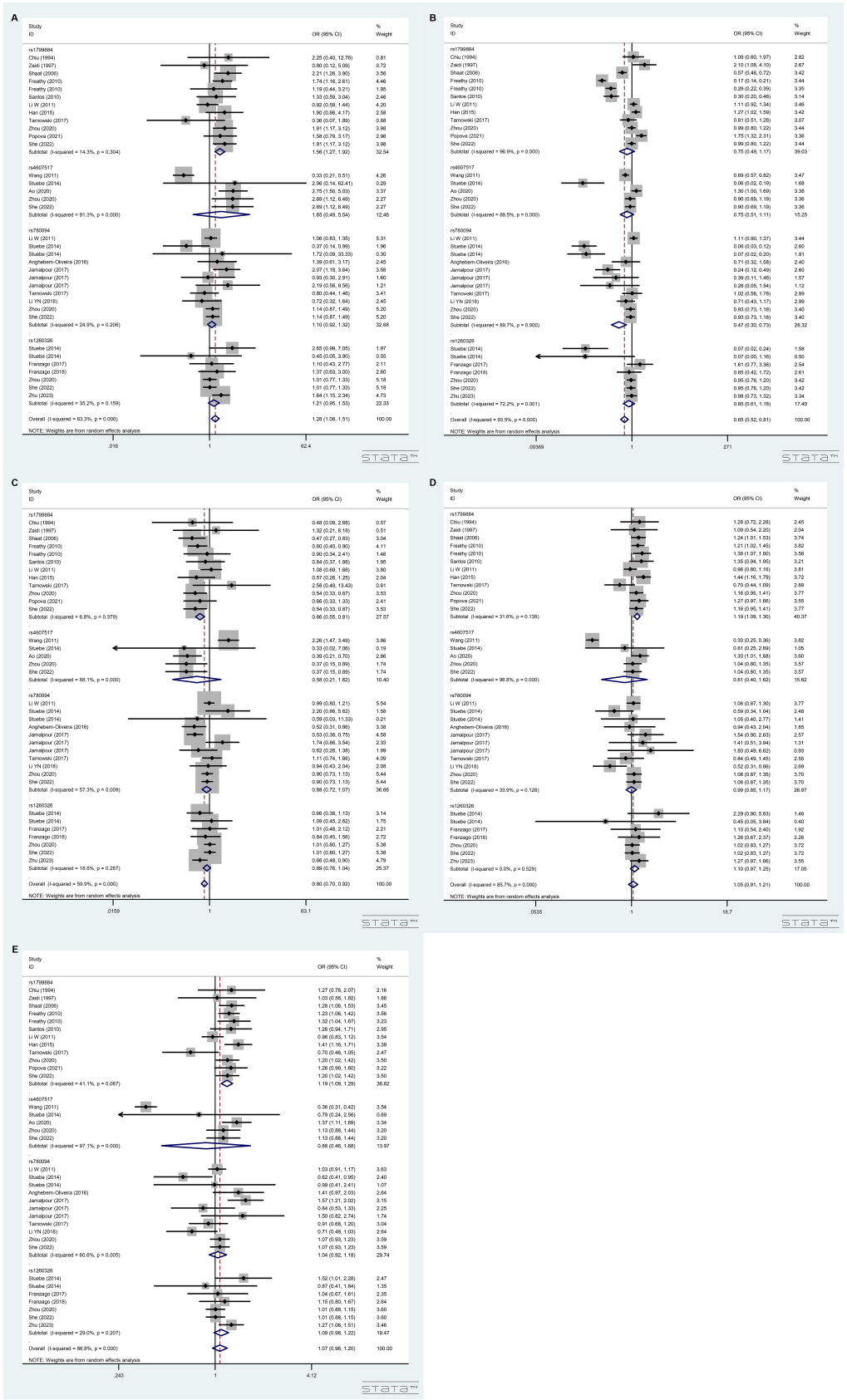

Fig. 2. Forest plot for merged odds ratios (ORs) with 95% confidence intervals (CIs) for *GCK* and *GCKR* polymorphisms. (A) Forest plot under 22 *vs.* 11 model. (B) Forest plot under 12 *vs.* 11 model. (C) Forest plot under 22 *vs.* 11 + 12 model. (D) Forest plot under 22 + 12 *vs.* 11 model. (E) Forest plot under 2 *vs.* 1 model.

Table 2. Genotype distributions of *GCK* and *GCKR* polymorphisms.

Author	Year	Country	Ethnicity	GDM group			Control group		
				11	12	22	11	12	22
rs1799884				GG	GA	AA	GG	GA	AA
Chiu *et al.* [26]	1994	USA	African	56	37	4	63	34	2
Zaidi *et al.* [30]	1997	UK	Caucasian	47	42	3	25	20	2
Shaat *et al.* [29]	2006	Sweden	Caucasian	435	181	26	889	316	24
Freathy *et al.* [27]	2010	UK, Australia	Caucasian	388	194	32	2575	1114	122
Freathy *et al.* [27]	2010	Thailand	Asian	288	91	5	1375	311	20
Santos *et al.* [28]	2010	Brazil	Caucasian	86	56	8	387	186	27
Li W [31]	2011	China	Asian	632	349	42	552	315	40
Han *et al.* [34]	2015	China	Asian	705	226	17	787	178	10
Tarnowski *et al.* [36]	2017	Poland	Caucasian	163	42	2	147	52	5
Zhou [43]	2020	China	Asian	506	277	47	556	280	27
Popova *et al.* [41]	2021	Russia	Caucasian	488	173	27	343	99	12
She *et al.* [19]	2022	China	Asian	506	277	47	556	280	27
rs4607517				GG	GA	AA	GG	GA	AA
Wang *et al.* [32]	2011	China	Asian	1420	244	37	618	356	49
Stuebe *et al.* [33]	2014	USA	Caucasian	49	3	0	731	53	2
Ao *et al.* [40]	2021	China	Asian	316	200	46	283	154	15
Zhou [43]	2020	China	Asian	702	112	18	735	124	7
She *et al.* [19]	2022	China	Asian	702	112	18	735	124	7
rs780094				TT	TC	CC	TT	TC	CC
Li W [31]	2011	China	Asian	275	502	247	265	453	225
Stuebe *et al.* [33]	2014	USA	Caucasian	24	23	5	266	376	150
Stuebe *et al.* [33]	2014	USA	African–American	16	6	0	255	87	4
Anghebem-Oliveira *et al.* [35]	2017	Brazil	Caucasian	15	48	64	14	68	43
Jamalpour *et al.* [37]	2018	Malaysia	Asian	18	69	95	84	284	214
Jamalpour *et al.* [37]	2018	Malaysia	Asian	5	30	13	23	76	64
Jamalpour *et al.* [37]	2018	Malaysia	Asian	3	13	16	16	47	39
Tarnowski *et al.* [36]	2017	Poland	Caucasian	33	101	73	28	99	77
Li *et al.* [42]	2018	China	Asian	64	48	15	43	68	14
Zhou [43]	2020	China	Asian	200	371	213	227	401	212
She *et al.* [19]	2022	China	Asian	200	371	213	227	401	212
rs1260326				TT	TC	CC	TT	TC	CC
Stuebe *et al.* [33]	2014	USA	Caucasian	5	26	25	154	395	291
Stuebe *et al.* [33]	2014	USA	African–American	1	7	16	7	107	248
Franzago *et al.* [38]	2017	Italy	Caucasian	21	58	23	15	36	15
Franzago *et al.* [39]	2018	Italy	Caucasian	21	58	25	30	68	26
Zhou [43]	2020	China	Asian	220	404	182	238	424	195
She *et al.* [19]	2022	China	Asian	220	404	182	238	424	195
Zhu *et al.* [20]	2023	China	Asian	142	241	122	164	245	86

Notes: GDM, gestational diabetes mellitus; GCK, glucokinase; GCKR, glucokinase regulatory protein.

number of studies, especially only one study in the subgroup, usually lead to unreliable estimation of heterogeneity, such as false positive result. Therefore, the ethnicity-based subgroup analysis was not performed in five genetic models of rs4607517 and rs1260326.

Hence, these findings suggest a significant association between the rs1799884 as well as rs780094 polymorphisms and GDM susceptibility. However, the rs4607517 and rs1260326 polymorphisms were not be significantly associated with the overall population.

3.6 Publication Bias

Begg's test helped to assess publication bias across the combined analysis of *GCK* and *GCKR* genetic polymorphisms. None of the publications showed any significant publication bias (Begg's test: $p = 0.063$ for 22 *vs.* 11, Fig. 5A; $p = 0.386$ for 12 *vs.* 11; $p = 0.806$ for 22 *vs.* 11+12, Fig. 5B; $p = 0.088$ for 22+12 *vs.* 11; $p = 0.629$ for 2 *vs.* 1).

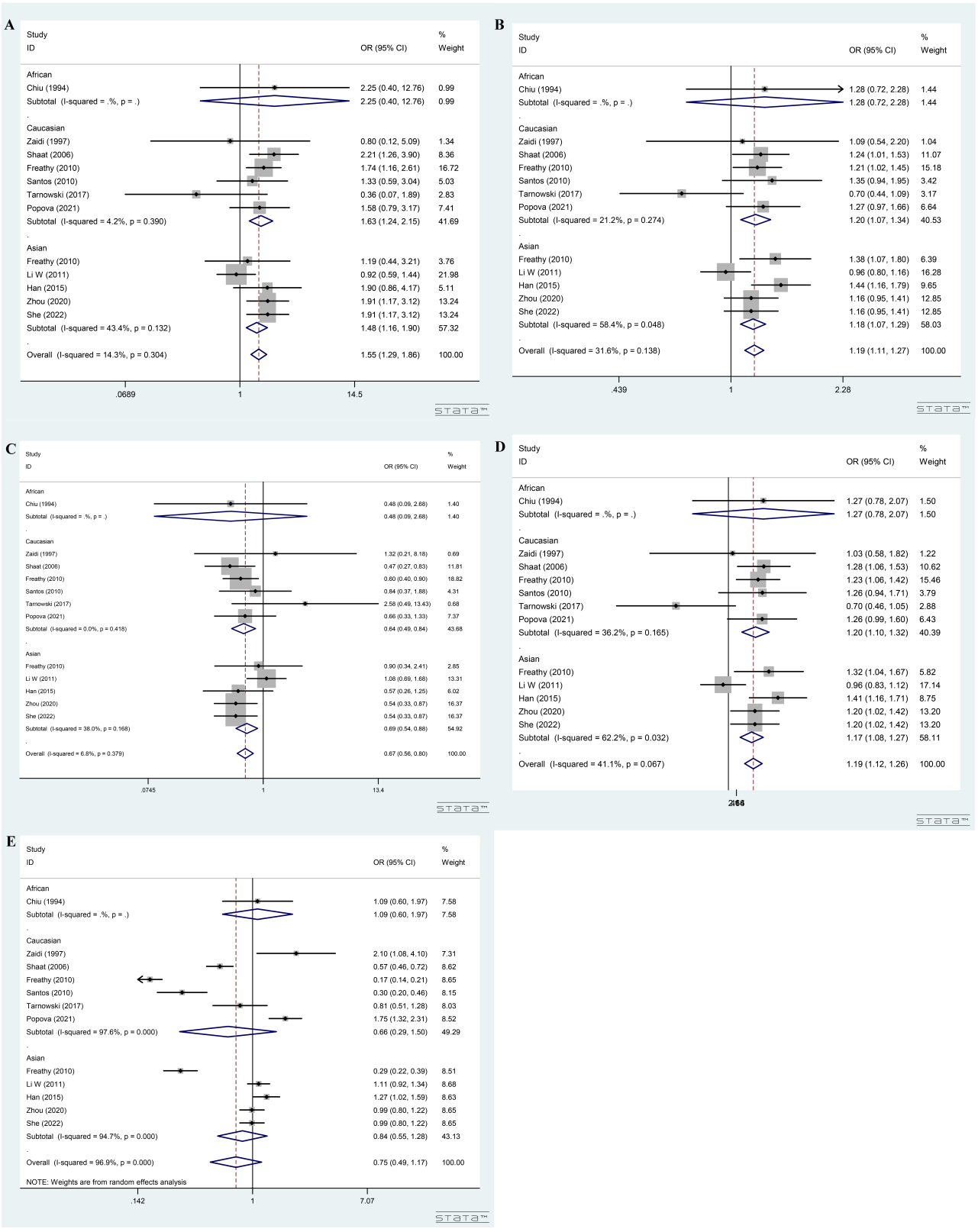

Fig. 3. Forest plot for merged odds ratios (ORs) with 95% confidence intervals (CIs) for *GCK* rs1799884 polymorphism. (A) Forest plot for subgroup analysis based on ethnicity under AA *vs.* GG model. (B) Forest plot for subgroup analysis based on ethnicity under AA + GA *vs.* GG model. (C) Forest plot for subgroup analysis based on ethnicity under AA *vs.* GG + GA model. (D) Forest plot for subgroup analysis based on ethnicity under A *vs.* G model. (E) Forest plot for subgroup analysis based on ethnicity under AG *vs.* GG model.

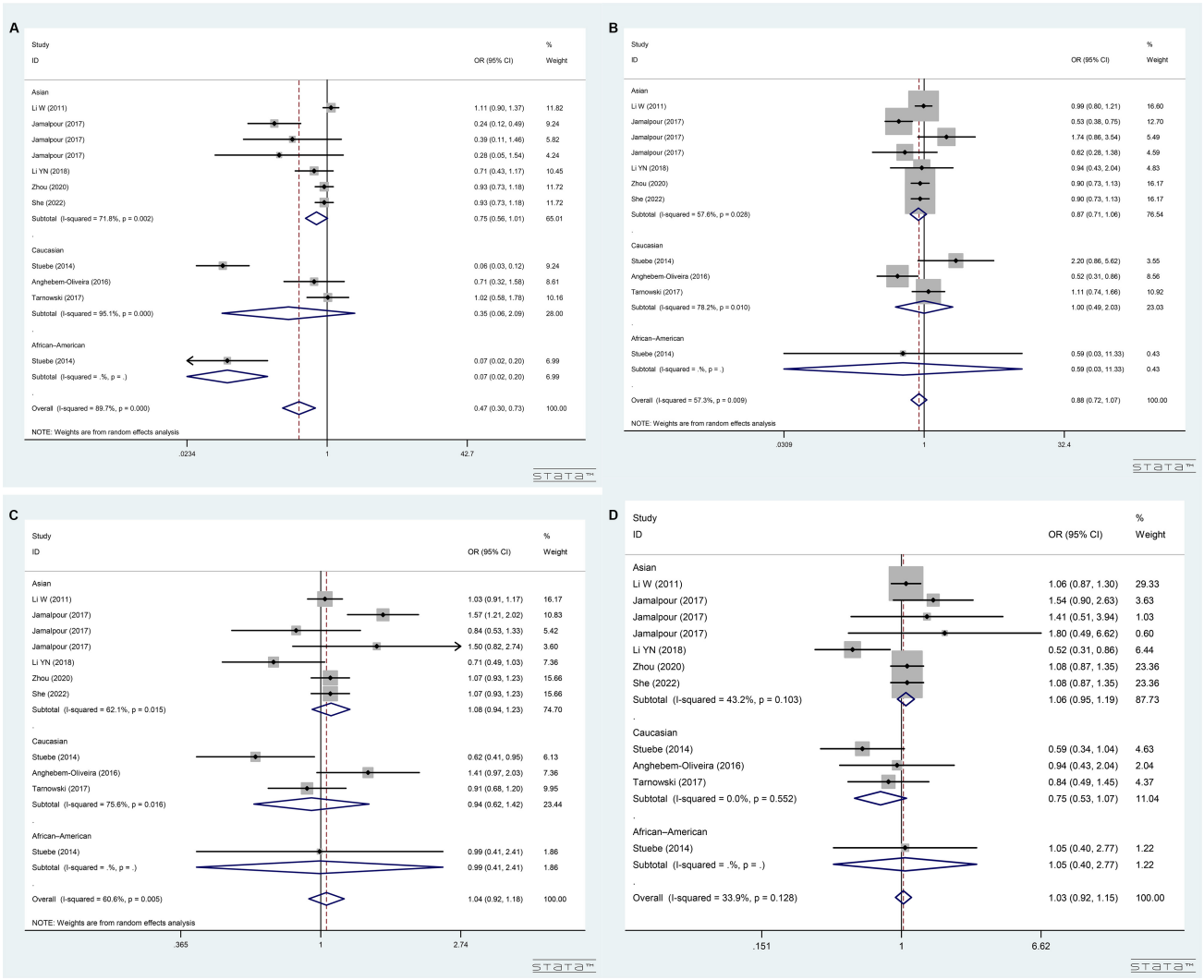

Fig. 4. Forest plot for merged odds ratios (ORs) with 95% confidence intervals (CIs) for *GCKR* rs780094 polymorphism. (A) Forest plot for subgroup analysis based on ethnicity under TC *vs.* TT model. (B) Forest plot for subgroup analysis based on ethnicity under CC *vs.* TT + TC model. (C) Forest plot for subgroup analysis based on ethnicity under C *vs.* T model. (D) Forest plot for subgroup analysis based on ethnicity under CC + TC *vs.* TT model.

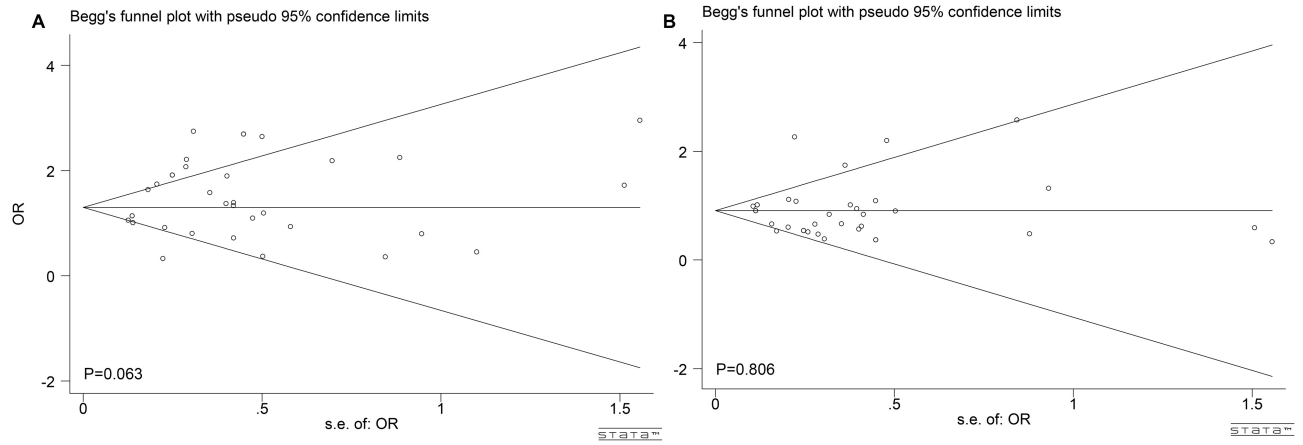

Fig. 5. Publication bias for eligible studies of *GCK* and *GCKR* polymorphisms. (A) Publication bias under 22 *vs.* 11 model. (B) Publication bias under 22 *vs.* 11 + 12 model. 22 is risk genotype, 12 is heterozygote genotype and 11 is the reference genotype.

4. Discussion

We systematically reviewed 20 eligible studies in this extensive meta-analysis that examined the relationship between GDM susceptibility and *GCK* (rs1799884 and rs4607517) and *GCKR* genes (rs780094 and rs1260326). Our results indicated that these SNPs were significantly correlated with GDM susceptibility. Meanwhile, *GCK* rs1799884 polymorphism was significantly associated with GDM susceptibility in five genetic models; the A allele carriers displayed a higher risk for GDM. This is consistent with previous meta-analytical results that identified a positive association between the rs1799884 polymorphism and GDM susceptibility [20,34,44]. Moreover, a positive association between rs1799884 polymorphism and GDM susceptibility was also noted. We found that *GCK* rs4607517 was a risk factor for GDM susceptibility in the AA *vs.* GG genetic model. Mao *et al*. [45] also reported a positive correlation between the *GCK* rs4607517 A allele and GDM risk, suggesting that *GCK* polymorphisms might lead to GDM.

However, we could not find a significant association between GDM risk and the *GCKR* genes rs780094 as well as rs1260326. This was in contrast with a few meta-analyses that suggested a high risk of GDM for rs780094 G allele carriers [37,46,47]. This discrepancy may be attributed to variable ethnicities among the study populations.

Enhanced heterogeneity was discovered in the rs1799884 polymorphism's GA *vs.* GG genetic model. We examined the rs1799884 polymorphism's heterogeneity origin across different ethnicities and diagnostic criteria. The possible causes of heterogeneity include various ethnicities and diagnostic criteria. Due to limited studies on rs4607517, rs780094, and rs1260326 polymorphisms, we discussed their heterogeneities in different ethnic groups. Subsequently, we found that the *GCK* rs4607517 heterogeneities in five genetic models stemmed from different ethnicities. Heterogeneities were also discovered in the TC *vs.* TT model of *GCKR* rs780094 as well as the TC *vs.* TT model of rs1260326 polymorphism and were derived from different ethnicities. However, no significant heterogeneity was discovered in previous meta-analyses [45–48]. Different diagnosis standards and ethnicities might be the cause of this discrepancy.

Ethnicity-based subgroup analysis revealed a positive correlation between rs1799884 polymorphism and GDM susceptibility in Asian and Caucasian populations. This is in line with the findings of Yang and Du [44] that A allele of rs1799884 is a risk factor for GDM in White and African populations. Notably, we also observed a negative correlation between the rs780094 polymorphism and GDM susceptibility in the African-American subgroup's TC *vs.* TT genetic model. Conversely, Jamalpour *et al*. [37] observed that the C allele of rs780094 was positively correlated with GDM susceptibility in the Asian population. The rs1260326 polymorphism's subgroup analysis was consistent with previous meta-analyses, indicating no significant association with GDM susceptibility across different populations [46,47].

Furthermore, diagnostic criteria-based subgroup analysis confirmed their influence on the association between the rs1799884 polymorphism and GDM susceptibility. The DPSG-EASD and IADPSG subgroups were positively correlated. Yang and Du [44] demonstrated that the A allele of rs1799884 was not significantly associated with GDM susceptibility under World Health Organization (WHO) and American Diabetes Association (ADA) subgroups. This underscores the importance of standardized criteria for future studies and the possible effects of varying GDM diagnostic criteria on research outcomes.

Begg's test revealed no significant publication bias, suggesting the reliability of observed associations. However, selection and information biases could potentially affect our results' generalizability and statistical power. Our findings highlight the importance of targeted screening guidelines for Asian and Caucasian populations as well as focusing on nutritional and lifestyle interventions for pregnant women. Additional research with larger sample sizes and multicenter studies should be conducted to validate our findings and explore the biological mechanisms influencing the associations between *GCK* and *GCKR* polymorphisms as well as GDM susceptibility.

5. Conclusions

According to our meta-analysis, the *GCK* rs1799884 polymorphism's A allele is associated with an increased risk of GDM. Although certain individuals with *GCK* rs4607517 and *GCKR* rs780094 polymorphisms may also be at higher risk for GDM, the overall association is less clear and warrants further investigation. These insights can help in identifying high-risk pregnant women early as well as emphasizing the necessity of genetic counseling and interdisciplinary collaboration for preventing and managing GDM.

Availability of Data and Materials

Corresponding authors may provide data and materials.

Author Contributions

HXT and MYW designed the research study. YYZ performed the research. HXT, YYZ and MYW analyzed the data. HXT and MYW wrote the manuscript. 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/CEOG26710.

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