Review Article

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Association of TCF7L2 Polymorphisms with Susceptibility to Gestational Diabetes Mellitus: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is a complex metabolic disorder of pregnancy with a strong genetic predisposition. GDM is associated with complications during pregnancy and increased risk of type 2 diabetes later in mothers and develops a vicious cycle of metabolic diseases for future generations. Evidence is accumulating that women with genetic variants at transcription factor 7-like 2 (TCF7L2) gene are more susceptible to GDM. The aim of the current meta-analysis was to assess the association of the TCF7L2 polymorphisms with GDM risk.

Methods: PubMed, Web of Science, Embase, SID and CNKI databases were searched to identify relevant studies up to November 01, 2020. Using the fixed-effect or random-effect model, the pooled odds ratio and its corresponding 95% confidence interval were computed.

Results: A total of 38 case-control studies including 24 studies with 6021 cases and 13289 controls on rs7903146, eight studies with 2404 cases and 2615 controls on rs12255372 and six studies with 1357 cases and 2858 controls on rs7901695 polymorphism were selected. Pooled data showed that there was a significant association between the TCF7L2 rs7903146, rs12255372 and rs7901695 polymorphisms and an increased risk of GDM in whole population. Stratified analysis showed that the TCF7L2 rs7903146 polymorphism was associated with GDM in Caucasian, mixed and Chinese women, but not in Asians. Moreover, the TCF7L2 rs12255372 polymorphism was associated with GDM in Asians and Caucasians women with GDM.

Conclusion: The combined data indicated that the TCF7L2 rs7903146, rs12255372 and rs7901695 polymorphisms were associated with a significant risk of GDM in whole population, especially in Caucasian women.

Introduction

Gestational diabetes mellitus (GDM) is described as abnormal glucose tolerance that is first identified or diagnosed during pregnancy.[1,2] The number of women diagnosed with GDM will continue to increase in the face of epidemic rates of obesity.[3,4] GDM causes adverse pregnancy outcomes, including long-term effects on the offspring through metabolic programming and epigenetic changes in utero.[5-7] It is estimated that almost 4% of all pregnancies could increase to as much as 18% if the new International Association of the Diabetes and Pregnancy Study Groups (IADPSG) guidelines are implemented.[8–11] It is estimated that GDM affected about 204 million women worldwide in 2017 and would be increased to 308 million by 2045.[12] Similar to type 2 diabetes mellitus (T2DM), GDM is also increasing alarmingly, attributed partly to increasing maternal age and body weight.[4,13,14] However, GDM is distinguished from diabetes mellitus (DM) as the onset of Type II-like, impaired musculoskeletal insulin sensitivity during pregnancy. There is not any internationally accepted method of screening for GDM with disparities in whom to screen, gestation of screening, dose and duration of glucose tolerance test (GTT), and the cut-off levels used.[15] In the United States, insulin is the only approved treatment for GDM.[16]

Women with GDM are more prone to have complications during the pregnancy with higher risk of polyhydramnios, hypertension and vaginal candidiasis, pre-eclampsia and primary caesarean section.[17-19] The most common and serious outcomes of GDM in pregnancy are fetal macrosomia (defined as birth weight > 4-4.5 kg) and large for gestational age (LGA) (defined as birth weight > 2 SD greater than mean or > 90 centile after controlling for age and sex), shoulder dystocia and birth injuries, neonatal hypoglycaemia and respiratory distress syndrome.[20-24] Moreover, women diagnosed with GDM and their offspring are at increased risk of developing of T2DM.[3,25]

Several lines of evidence support that GDM is a multigenic disease in which common variants in multiple genes interact with environmental factors to cause the disease.[26-29] It is suggested that GDM share common genetic polymorphisms with T2DM and with the advent of the sequencing technologies and genome-wide association studies (GWASs), the number of confirmed susceptible loci such as TCF7L2, CDKAL1, TCF2, and FTO for development of GDM increased dramatically.[28,30,31] Evidence is also accumulating that polymorphisms at transcription factor 7-like 2 (*TCF7L2*) gene might be associated with development of GDM.[31,32] The *TCF7L2* gene, also known as *TCF4*, is located on chromosome 10q25.2-q25.3 and encompass 19 exons.[33,34] Human *TCF7L2* gene encodes a high mobility group (HMG) box-containing transcription factor that plays an important role in the Wnt/β-catenin signaling pathway and negative regulation of adipogenesis.[33,35] This gene harbors several polymorphisms which among them rs7903146, rs12255372 and rs7901695 have been widely studied in GDM and T2DM risk.[36,37] To date, several epidemiological studies have evaluated the association between the *TCF7L2* polymorphisms with susceptibility to GDM in different populations [32,38,39]. However, those studies results are controversial or inconclusive. Therefore, we performed this meta-analysis to obtain a more precise estimation of the association of the *TCF7L2 rs7903146* polymorphism with susceptibility to GDM in whole population and by ethnicity.

Materials and Methods

Study Selection: The online databases including PubMed, Web of Knowledge, Web of Science, Embase, Scientific Information Database (SID), WanFang, VIP, Chinese Biomedical Database (CBD), Scientific Electronic Library Online (SciELO) and China National Knowledge Infrastructure (CNKI) database were used for the

publication search. Two authors independently carried out a comprehensive search up to November 01, 2020, with the following key terms: (''Gestational Diabetes'' OR ''gestational Diabetes Mellitus'' OR ''GDM'') AND (''Transcription factor 7-like 2'' OR ''TCF7L2'' OR ''TCF4'') AND (''Gene'' OR ''Genotype'' OR ''Allele'' OR ''Polymorphism'' OR ''Single nucleotide polymorphisms'' OR ''SNPs'' OR ''Variant'' OR ''Variation'' OR ''Mutation''). Moreover, the reference lists of the literature items were reviewed independently by two authors to find more potential relevant studies. The search was carried out in English, Chinese and Persian. If there was overlapping data on the same cases in more than one publication, only the one with the larger sample size was selected.

Selection criteria: The inclusion criteria for these studies were as follows: 1) studies evaluating the association between the *TCF7L2* polymorphisms and GDM risk; 2) the study design was a case-control study in humans; 3) studies reported universal allele and genotype frequency; 4) Studies written in English, Persian and Chinese; 5) detailed data for estimation of odds ratio (OR) and 95% confidence interval (CI), as well as available allele genotype frequencies for cases and controls. The exclusion criteria were as follows: 1) Studies that did not describe the association of *TCF7L2* polymorphisms with GDM; 2) studies focusing on animals or in vitro; 3) studies that did not provide sufficient data for meta-analysis; 4) case only studies or no controls; 5) linkage studies and family based studies (twins and sibling); 6) case reports, abstracts, comments, conference abstracts, editorials, reviews, meta-analysis; and 7) duplicated studies or data.

Data Extraction: Data extraction was done by two authors independently and third author verified the data. The data was compared, and any disagreement was discussed and resolved with consensus. First author name, year of publication, ethnicity (Asian, Caucasian, African and mixed populations), country of origin, genotyping methods, number of cases and controls for each genotype, frequencies of genotypes in cases and controls, minor allele frequency (MAF) in controls, and Hardy-Weinberg equilibrium (HWE) in controls were data extracted from each study. If selected articles had not reported the necessary data, the corresponding authors were contacted by email to request the missing data. Using excel-based Court lab-HW calculator software, Minor allele frequencies and Hardy-Weinberg equilibrium in control groups were calculated.

Assessment of study quality: The quality of the selected studies was verified by the Newcastle-Ottawa Scale (NOS). NOS is consisted of three parts including a selection of participants (four items), comparability of cases, and control groups (two items), and adequacy of outcome (three items). It evaluated studies with a star-rating system ranging from zero to nine stars, in which the score ≥ 7 were expressed high quality and <7 represent low or moderate quality (high or moderate risk of bias).

Statistical Analysis*:* The association of the *TCF7L2* polymorphisms with GDM risk was analyzed by calculating the odds ratio (OR) and 95% confidence interval (95% CI). The significance of the pooled OR was evaluated by the Z-test. The associations was performed under all five genetic models, i.e., allele (B vs. A), homozygote (BB vs. AA), heterozygote (BA vs. BB), dominant (BB+BA vs. AA) and recessive (BB vs. BA+AA). To evaluate the heterogeneity between these studies, a Chi-square-based Q-test was performed. Moreover, in order to evaluate the HWE of TCF7L2 genotypes frequency distribution in the control group, the Chi-square test was used. A Cochran's Q-test was carried out to examine the heterogeneity between studies and was considered significant when $P < 0.10$. Besides, I^2 value was used for heterogeneity validation as well. The test of heterogeneity using I^2 statistics was as follows: I^2 = 0-25%, no heterogeneity; I^2 = 25-50%, moderate

heterogeneity; I^2 = 50-75%, large heterogeneity; I^2 = 75-100%, extreme heterogeneity. The pooled data in the fixed effect model (Mantel-Haenszel method) were selected when no significance between-study heterogeneity existed; otherwise, the random-effects model (DerSimonian-Laird method) was used.[40] To assess the potential sources of heterogeneity across different studies, subgroup analysis based on ethnicity, genotyping methods and HWE was performed. Sensitivity analysis was performed by the leave-one-out method to assess the effects of individual studies on pooled results and the stability of the results. The funnel plot was applied to evaluate the publication bias. The asymmetry of the funnel plot was assessed by Egger's test. Using Fisher's exact test, the HWE was tested. All of the statistical calculations were performed using Comprehensive Meta-Analysis (CMA) software version 2.0 (Biostat, USA). Two-sided P < 0.05 were considered statistically significant.

Results

Figure 1 shows the flowchart of literature search and selection process in this meta-analysis. Four hundred thirty seven potentially relevant studies were retrieved from the initial literature searches in online databases.

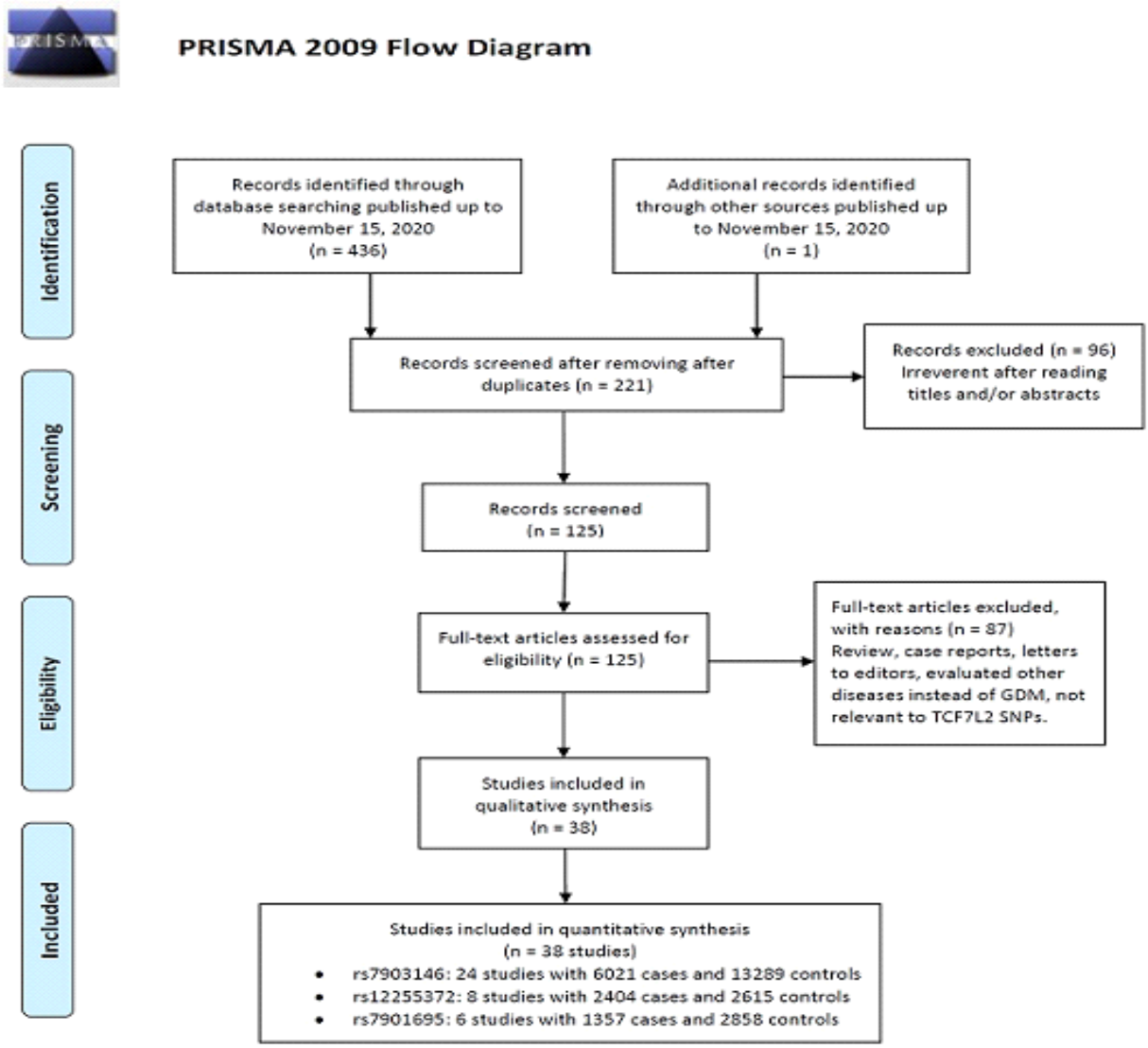

Figure 1. The Study Selection and Inclusion Process

Two authors independently screened all titles and abstracts of the identified studies. After the first screening, 216 irrelevant and duplicate articles were excluded. Among the remaining articles, 87 studies were excluded because evaluated other disease instead of GDM; had incomplete data or insufficient genotype frequencies, and were review or meta-analyses studies. Finally, a total of 38 case-control studies including 24 studies with 6021 cases and 13289 controls on rs7903146, eight studies with 2404 cases and 2615 control on rs12255372 and six studies with 1357 cases and 2858 controls on rs7901695 polymorphism were selected.[7,27,29,31,39,41-58] Characteristics of included studies are shown in tables 1. All the included studies were published between 2007 and 2019, sample size in GDM cases ranged from 40 to 868. All eligible studies were published in English and Chinese. Among them, 19 studies were based on Caucasians, 12 based on Asian women, six studies were based on mixed population and one on African-American women. Six GDM Criteria were applied in the included studies: OGTT, NDDG, IADPSG, ADA, WHO, and PGSC. The genotypes and minor allele frequency (MAF) distributions in the cases and controls are shown in table 1. Besides, the distribution of genotypes in the controls was in agreement with Hardy-Weinberg equilibrium (HWE) for all selected studies, except for four studies on rs7903146 and two studies on rs12255372 (Table 1).

Quantitative Data Synthesis

rs7903146: The summary of association between the *TCF7L2 rs7903146* polymorphism with GDM risk is presented in table 2. The pooled data showed that the *TCF7L2 rs7903146* polymorphism was associated with an increased risk of GDM risk under all five genetic models, i.e., allele (T vs. C: OR = 0.539, 95% CI 0.713-0.713, P ≤ 0.001, Figure 2A), homozygote (TT vs. CC: OR = 1.572, 95% CI 1.227-2.015, P ≤ 0.001), heterozygote (TC vs. CC: OR = 1.407, 95% CI 1.173-1.687, P ≤ 0.001), dominant (TT+TC vs. CC: OR = 1.465, 95% CI 1.219-1.760, P ≤ 0.001) and recessive (TT vs. TC+CC: OR = 1.534, 95% CI 1.251-1.880, P ≤ 0.001, Figure 2B) in the whole population. When stratified by ethnicity, there was a significant association in Caucasians (T vs. C: OR = 0.377, 95% CI 0.289-0.491, P ≤ 0.001; TT vs. CC: OR = 1.601, 95% CI 1.224-2.095, P = 0.001; TC vs. CC: OR = 1.348, 95% CI 1.085-1.675, P = 0.007; TT+TC vs. CC: OR = 1.396, 95% CI 1.122-1.738, P = 0.003; and TT vs. TC+CC: OR = 1.420, 95% CI 1.228-1.641, P ≤ 0.001), Latinos (T vs. C: OR = 0.584, 95% CI 0.377-0.905, P = 0.016; TT vs. CC: OR = 1.744, 95% CI 1.366-2.227, P ≤ 0.001; TC vs. CC: OR = 1.798, 95% CI 1.099-2.942, P = 0.020; and TT+TC vs. CC: OR = 1.760, 95% CI 1.395-2.221, P ≤ 0.001) and Chinese (TT vs. CC: OR = 4.595, 95% CI 1.872-11.278, P = 0.001; TC vs. CC: OR = 1.979, 95% CI 1.236-3.169, P = 0.004; TT+TC vs. CC: OR = 2.388, 95% CI 1.528-3.731, P ≤ 0.001; and TT vs. TC+CC: OR = 4.098, 95% CI 1.731-9.704, P = 0.001), but not in Asian women.

rs12255372: The summary of association between the *TCF7L2 rs12255372* polymorphism with GDM risk is presented in Table 2. The pooled data showed that the *TCF7L2 rs12255372* polymorphism was significantly associated with an increased risk of GDM risk under all five genetic models, i.e., allele (T vs. G: OR = 1.433, 95% CI 1.104-1.860, p=0.007), homozygote (TT vs. GG: OR = 1.535, 95% CI 1.188-1.982, P = 0.001, Figure 3A), heterozygote (TG vs. GG: OR = 1.609, 95% CI 1.149-2.253, P = 0.006), dominant (TT+TC vs. GG: OR = 1.649, 95% CI 1.177-2.309, P = 0.004, Figure 3B) and recessive (TT vs. TG+GG: OR = 1.302, 95% CI 1.019-1.664, P = 0.035) in the whole population. Subgroup analysis by ethnicity indicated that the polymorphism was associated with GDM risk in Asians (TG vs. GG: OR = 2.903, 95% CI 1.239-6.832, P = 0.014; and TT+TC vs. GG: OR = 2.792, 95% CI 1.205-6.465, P = 0.017) and Caucasians (T vs. G: OR = 1.307, 95% CI

Table 1. Characteristics of Studies Included in the Meta-analysis

First Author/Year	Country (Ethnicity)	GDM Criteria	Genotyping Technique	Case/Control	Cases					Controls					MAFs	HWE	NOS
					Genotypes			Allele		Genotypes			Allele				
rs7903146					CC	CT	TT	C	T	CC	CT	TT	C	T			
Shaat 2007	Sweden (Caucasian)	OGTT	TaqMan	585/1111	271	255	59	797	373	650	392	69	1692	530	0.239	0.338	8
Cho 2009	Korean (Asian)	NDDG	ADA	868/627	803	63	2	1669	67	596	31	0	1223	31	0.025	0.525	7
Lauenborg 2009	Denmark (Caucasian)	OGTT	TaqMan	276/2353	118	125	33	361	191	1292	863	198	3447	1259	0.268	0.001	7
Freathy 2010	UK (Caucasian)	IADPSG	IGGP	614/3811	293	246	75	832	396	1884	1557	370	5325	2297	0.301	0.066	7
Freathy 2010	UK (Caucasian)	IADPSG	IGGP	384/1332	338	46	0	722	46	1211	108	3	2530	114	0.043	0.717	7
Rizk 2011	Qatar (Asian)	ADA	TaqMan	40/74	16	18	6	50	30	29	37	8	95	53	0.358	0.451	7
Aris 2011	Malaysian (Asian)	ADA	IGGP	173/114	129	43	1	301	45	99	15	0	213	15	0.066	0.452	7
Papadbouolou 2011	Sweden (Caucasian)	IADPSG	TaqMan	803/1110	363	352	88	1078	528	644	384	82	1672	548	0.247	0.020	7
Pappa 2011	Greek (Caucasian)	WHO	PCR-RFLP	148/107	49	81	18	179	117	62	38	7	162	52	0.243	0.719	8
Vcelak 2012	Czech (Caucasian)	NA	TaqMan	261/376	142	102	17	386	136	156	185	35	497	255	0.339	0.058	8
Ekelund 2012	Sweden (Caucasian)	OGTT	MALDITFMS	125/476	49	56	20	154	96	239	194	42	672	278	0.293	0.769	7
Klein 2012	Australia (Caucasian)	IADPSG	AS-PCR	125/125	8	112	5	128	122	10	107	8	127	123	0.492	≤0.001	8
Pagan 2014	Spain (Caucasian)	NDDG	Sequencing	45/24	19	18	8	56	34	10	12	2	32	16	0.333	0.540	8
Reyes-Lopez 2014	Mexico (Mixed)	ADA	PCR	90/108	55	29	6	139	41	81	23	4	185	31	0.144	0.164	8
Thomas 2014	India (Asian)	NA	TaqMan	261/376	142	102	17	386	136	156	185	35	497	255	0.339	0.058	8
Kan 2014	China (Asian)	OGTT	ADA	100/100	84	15	1	183	17	95	5	0	195	5	0.025	0.797	8
Shi 2014	China (Asian)	IADPSG	AS-PCR	100/100	40	36	24	116	84	55	38	7	148	52	0.260	0.900	8
Zhang 2015	China (Asian)	OGTT	PCR-RFLP	113/115	96	17	0	209	17	110	5	0	225	5	0.022	0.811	7
de Melo 2015	Brazil (Mixed)	ADA	IGGP	200/200	76	104	20	256	144	98	86	16	282	118	0.295	0.632	7
Huerta-Chagoya 2015	Mexico (Mixed)	OGTT	NA	408/342	265	124	19	654	162	265	67	10	597	87	0.127	0.029	8
Michalak-Wojnowska 2016	Poland (Caucasian)	PGSC	TaqMan	50/26	19	29	2	67	33	10	15	1	35	17	0.327	0.112	7
Mashfiqul-Hasan 2016	Bangladesh (Asian)	WHO	PCR	50/50	28	20	2	76	24	35	13	2	83	17	0.170	0.578	8
Franzago 2016	Italy (Caucasian)	IADPSG	qRT-PCR	104/124	38	38	28	114	94	59	48	17	166	82	0.331	0.162	8
Chen 2019	China (Asian)	OGTT	PCR	98/119	38	31	29	107	89	64	47	8	113	63	0.265	0.873	8
rs12255372					GG	GT	TT	G	T	GG	GT	TT	G	T			
Cho 2009	Korean (Asian)	NDDG	ADA	867/630	860	7	0	1727	7	628	2	0	1258	2	0.002	0.968	7
Rizk 2011	Qatar (Asian)	ADA	TaqMan	40/74	6	28	6	40	40	25	38	11	88	60	0.405	0.575	7
Papadbouolou 2011	Sweden (Caucasian)	IADPSG	TaqMan	801/1102	387	333	81	1107	495	633	385	84	1651	553	0.251	0.019	8
Vcelak 2012	Czech (Caucasian)	NA	TaqMan	261/376	124	115	22	363	159	206	147	23	559	193	0.257	0.632	8
Pagan 2014	Spain (Caucasian)	NDDG	Sequencing	45/25	19	20	6	58	32	9	14	2	32	18	0.360	0.281	8
Reyes-Lopez 2014	Mexico (Mixed)	ADA	PCR	90/108	60	23	7	143	37	101	5	2	207	9	0.042	≤0.001	8
Shi 2014	China (Asian)	IADPSG	AS-PCR	100/100	100	0	0	200	0	100	0	0	200	0	NA	NA	8
de Melo 2015	Brazil (Mixed)	ADA	IGGP	200/200	92	88	20	272	128	102	75	23	279	121	0.303	0.115	7
rs7901695					TT	TC	CC	T	C	TT	TC	CC	T	C			
Papadbouolou 2011	Sweden (Caucasian)	IADPSG	TaqMan	794/1102	343	356	95	1042	546	607	405	90	1619	585	0.265	0.056	8
Vcelak 2012	Czech (Caucasian)	NA	TaqMan	261/376	106	130	25	342	180	205	147	24	557	195	0.259	0.730	8
Pagan 2014	Spain (Caucasian)	NDDG	Sequencing	45/25	17	20	8	54	36	10	13	2	33	17	0.340	0.427	8
Stuebe 2014	African-American	OGTT	iPLEX	80/1204	22	45	13	89	71	536	519	149	1591	817	0.339	0.181	8
Michalak-Wojnowska 2016	Poland (Caucasian)	PGSC	TaqMan	50/26	19	30	1	68	32	9	16	1	34	18	0.346	0.066	8
Anghebem-Oliveira 2017	Brazil (Mixed)	ABDA	qRT-PCR	127/125	44	67	16	155	99	52	62	11	166	84	0.336	0.212	7

Abbreviations: GDM: gestational diabetes mellitus; OGTT; oral glucose tolerance test; ADA; American Diabetes Association; IADPSG: International Association of Diabetes and Pregnancy Study Group; NDDG: National Diabetes Data Group WHO: World Health Organization; PGSC: polish gynecological society criteria; ABDA: American and Brazilian Diabetes Association; NA: not available; ADA: allelic discrimination assay; IGGP: Illumina Golden Gate platform; PCR: polymerase chain reaction; AS-PCR: allele-specific polymerase chain reaction; MALDITFMS: matrix assisted laser desorption ionization time of flight mass spectrometry; RFLP: restriction fragment length polymorphism; MAF: minor allele frequency; HWE: Hardy-Weinberg equilibrium.

Table 2. Summary Risk Estimates for Association of TCF7L2 Polymorphisms with GDM Risk

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	T vs. C	Random	94.09	≤0.001	0.539	0.713-0.713	-4.323	≤0.001	0.756	0.542
	TT vs. CC	Random	50.70	0.004	1.572	1.227-2.015	3.575	≤0.001	0.545	0.894
	TC vs. CC	Random	75.20	≤0.001	1.407	1.173-1.687	3.687	≤0.001	0.843	0.421
	TT+TC vs. CC	Random	78.13	≤0.001	1.465	1.219-1.760	4.068	≤0.001	0.887	0.403
	TT vs. TC+CC	Fixed	40.98	0.022	1.534	1.251-1.880	4.120	≤0.001	0.903	0.801
Ethnicity										
Asians	T vs. C	Random	91.45	≤0.001	0.631	0.296-1.347	-1.189	0.234	1.000	0.048
	TT vs. CC	Random	62.14	0.015	1.654	0.647-4.229	1.050	0.294	0.548	0.303
	TC vs. CC	Random	77.43	≤0.001	1.533	0.952-2.467	1.758	0.079	0.173	0.022
	TT+TC vs. CC	Random	82.53	≤0.001	1538	0.826-2.866	1.356	0.175	0.132	0.049
	TT vs. TC+CC	Fixed	0.00	0.680	0.893	0.544-1.464	-0.450	0.653	0.707	0.028
Caucasians	T vs. C	Random	90.05	≤0.001	0.377	0.289-0.491	-7.215	≤0.001	0.212	0.523
	TT vs. CC	Random	51.55	0.019	1.601	1.224-2.095	3.434	0.001	0.372	0.819
	TC vs. CC	Random	76.83	≤0.001	1.348	1.085-1.675	2.701	0.007	0.243	0.930
	TT+TC vs. CC	Random	79.51	≤0.001	1.396	1.122-1.738	2.987	0.003	0.303	0.927
	TT vs. TC+CC	Fixed	11.19	0.335	1.420	1.228-1.641	4.732	≤0.001	0.631	0.661
Mixed	T vs. C	Random	74.46	0.020	0.584	0.377-0.905	-2.405	0.016	1.000	0.968
	TT vs. CC	Fixed	0.00	0.805	1.744	1.366-2.227	4.465	≤0.001	1.000	0.994
	TC vs. CC	Fixed	0.00	0.904	1.798	1.099-2.942	2.335	0.020	0.296	0.377
	TT+TC vs. CC	Fixed	0.00	0.779	1.760	1.395-2.221	4.762	≤0.001	1.000	0.960
	TT vs. TC+CC	Fixed	0.00	0.842	1.472	0.911-2.377	1.579	0.114	0.296	0.419
Chinese	T vs. C	Random	58.70	0.089	0.902	0.604-1.348	-0.501	0.616	1.000	0.008
	TT vs. CC	Random	0.00	0.847	4.595	1.872-11.278	3.328	0.001	NA	NA
	TC vs. CC	Random	55.00	0.108	1.979	1.236-3.169	2.842	0.004	1.000	0.074
	TT+TC vs. CC	Random	13.74	0.314	2.388	1.528-3.731	3.822	≤0.001	1.000	0.052
	TT vs. TC+CC	Fixed	0.00	0.848	4.098	1.731-9.704	3.207	0.001	NA	NA
GDM Criteria										
OGTT	T vs. C	Random	68.91	0.012	0.548	0.437-0.686	-4.072	≤0.001	0.259	0.058
	TT vs. CC	Fixed	0.00	0.968	2.001	1.573-2.545	5.654	≤0.001	0.806	0.413
	TC vs. CC	Fixed	0.00	0.553	1.617	1.406-1.859	6.743	≤0.001	0.462	0.211
	TT+TC vs. CC	Fixed	0.00	0.615	1.682	1.472-1.921	7.691	≤0.001	0.220	0.105
	TT vs. TC+CC	Fixed	0.00	0.936	1.654	1.314-2.081	4.284	≤0.001	0.806	0.373
IADPSG	T vs. C	Random	92.47	≤0.001	0.393	0.251-0.614	-4.100	≤0.001	0.806	0.932
	TT vs. CC	Random	59.21	0.044	1.711	1.097-2.668	2.370	0.018	0.806	0.899
	TC vs. CC	Random	69.00	0.012	1.335	1.021-1.747	2.109	0.035	1.000	0.806
	TT+TC vs. CC	Random	71.05	0.008	1.421	1.090-1.853	2.599	0.009	1.000	0.677
	TT vs. TC+CC	Fixed	55.34	0.062	1.425	1.173-1.731	3.572	≤0.001	1.000	0.995
ADA	T vs. C	Random	76.67	0.005	0.509	0.293-0.883	-2.403	0.016	1.000	0.718
	TT vs. CC	Fixed	0.00	0.954	1.664	0.957-2.894	1.804	0.071	0.734	0.564
	TC vs. CC	Fixed	4.255	0.372	1.615	1.211-2.153	3.268	0.001	0.734	0.749
	TT+TC vs. CC	Fixed	0.00	0.398	1.645	1.247-2.169	3.526	≤0.001	1.000	0.858
	TT vs. TC+CC	Fixed	0.00	0.960	1.416	0.834-2.403	1.288	0.198	0.308	0.201
By Genotyping										
TaqMan	T vs. C	Random	93.34	≤0.001	0.307	0.210-0.450	-6.074	≤0.001	0.176	0.151
	TT vs. CC	Random	77.65	≤0.001	1.231	0.778-1.947	0.887	0.375	0.176	0.255
	TC vs. CC	Random	88.40	≤0.001	1.071	0.748-1.535	0.375	0.707	0.176	0.253
	TT+TC vs. CC	Random	90.41	≤0.001	1.089	0.749-1.585	0.448	0.654	0.176	0.261
	TT vs. TC+CC	Fixed	51.86	0.052	1.345	1.122-1.611	3.211	0.001	0.176	0.294
IGGP	T vs. C	Random	88.51	≤0.001	0.505	0.315-0.812	-2.824	0.005	0.308	0.088
	TT vs. CC	Fixed	0.00	0.849	1.334	1.032-1.725	2.201	0.028	1.000	0.962
	TC vs. CC	Random	69.41	0.020	1.412	1.015-1.965	2.049	0.040	0.308	0.009
	TT+TC vs. CC	Random	64.18	0.039	1.416	1.052-1.906	2.294	0.022	0.089	≤0.001
	TT vs. TC+CC	Fixed	0.00	0.953	1.287	1.007-1.644	2.015	0.044	1.000	0.637

NA: Not Applicable

Table 2. Summary Risk Estimates for Association of TCF7L2 Polymorphisms with GDM Risk (Continued)

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
rs12255372										
Overall	T vs. G	Random	67.30	0.005	1.433	1.104-1.860	2.705	0.007	0.367	0.376
	TT vs. GG	Fixed	0.00	0.419	1.535	1.188-1.982	3.279	0.001	1.000	0.494
	TG vs. GG	Random	61.90	0.015	1.609	1.149-2.253	2.767	0.006	0.763	0.320
	TT+TC vs. GG	Random	65.78	0.008	1.649	1.177-2.309	2.911	0.004	1.000	0.346
	TT vs. TG+GG	Fixed	0.00	0.484	1.302	1.019-1.664	2.107	0.035	1.000	0.643
Ethnicity										
Asians	T vs. G	Fixed	0.00	0.515	1.557	0.928-2.611	1.678	0.093	NA	NA
	TT vs. GG	Fixed	0.00	1.000	2.273	0.598-8.640	1.205	0.228	NA	NA
	TG vs. GG	Fixed	0.00	0.848	2.903	1.239-6.832	2.452	0.014	NA	NA
	TT+TC vs. GG	Fixed	0.00	0.897	2.792	1.205-6.465	2.396	0.017	NA	NA
	TT vs. TG+GG	Fixed	0.00	1.000	1.011	0.344-2.972	0.019	0.985	NA	NA
Caucasians	T vs. G	Fixed	0.00	0.688	1.307	1.157-1.477	4.293	≤0.001	0.296	0.023
	TT vs. GG	Fixed	0.00	0.993	1.575	1.181-2.102	3.090	0.002	1.000	0.430
	TG vs. GG	Fixed	0.00	0.379	1.360	1.153-1.604	3.652	≤0.001	0.296	0.074
	TT+TC vs. GG	Fixed	0.00	0.464	1.396	1.194-1.633	4.180	≤0.001	0.296	0.068
	TT vs. TG+GG	Fixed	0.00	0.954	1.384	1.047-1.829	2.281	0.023	0.296	0.105
Mixed	T vs. G	Random	94.01	≤0.001	2.448	0.463-12.957	1.053	0.292	NA	NA
	TT vs. GG	Random	76.08	0.041	2.044	0.356-11.744	0.802	0.423	NA	NA
	TG vs. GG	Random	90.08	0.001	2.980	0.521-17.042	1.227	0.220	NA	NA
	TT+TC vs. GG	Random	92.29	≤0.001	2.836	0.499-16.123	1.176	0.240	NA	NA
	TT vs. TG+GG	Fixed	71.88	0.059	1.071	0.594-1.931	0.228	0.820	NA	NA
rs7901695										
Overall	C vs. T	Fixed	0.00	0.746	1.434	1.290-1.595	6.663	≤0.001	0.452	0.186
	CC vs. TT	Fixed	0.00	0.950	1.898	1.483-2.429	5.090	≤0.001	0.707	0.483
	CT vs. TT	Random	56.50	0.042	0.269	0.180-0.403	-6.363	≤0.001	0.707	0.987
	CC+CT vs. TT	Fixed	0.00	0.555	1.618	1.403-1.866	6.612	≤0.001	0.259	0.350
	CC vs. CT+TT	Fixed	0.00	0.960	1.510	1.196-1.906	3.464	0.001	0.452	0.662

NA: Not Applicable

1.157-1.477, P ≤ 0.001; TT vs. GG: OR = 1.575, 95% CI 1.181-2.102, P = 0.002; TG vs. GG: OR = 1.360, 95% CI 1.153-1.604, P ≤ 0.001; TT+TC vs. GG: OR = 1.360, 95% CI 1.194-1.633, P ≤ 0.001; and TT vs. TG+GG: OR = 1.384, 95% CI 1.047-1.829, P = 0.023) women with GDM. Moreover, stratified analyses revealed that the *TCF7L2 rs12255372* polymorphism was associated with GDM by GDM Criteria and genotyping methods (Table 2).

rs7901695: The summary of association between the *TCF7L2 rs7901695* polymorphism with GDM risk is presented in Table 2. The pooled data showed that the *TCF7L2 rs7901695* polymorphism was significantly associated with an increased risk of GDM risk under all five genetic models, i.e., allele (T vs. C: OR = 1.434, 95% CI 1.290-1.595, P ≤ 0.001), homozygote (TT vs. CC: OR = 1.898, 95% CI 1.483-2.429, P ≤ 0.001), heterozygote (TC vs. CC: OR = 0.269, 95% CI 0.180-0.403, P ≤ 0.001, Figure 4A), dominant (TT+TC vs. CC: OR = 1.618, 95% CI 1.403-1.866, P ≤ 0.001, Figure 4B) and recessive (TT vs. TC+CC: OR = 1.510, 95% CI 1.196-1.906, P = 0.001) in the whole population.

Test of heterogeneity: The heterogeneity in whole population and subgroups was shown in table 2. Among the studies on TCF7L2 rs7903146 and rs12255372, there was significant between-study heterogeneity under most genetic models in overall population. Thus, we assessed the heterogeneity for all genetic models by ethnicity, GDM criteria, genotyping methods, and HWE.

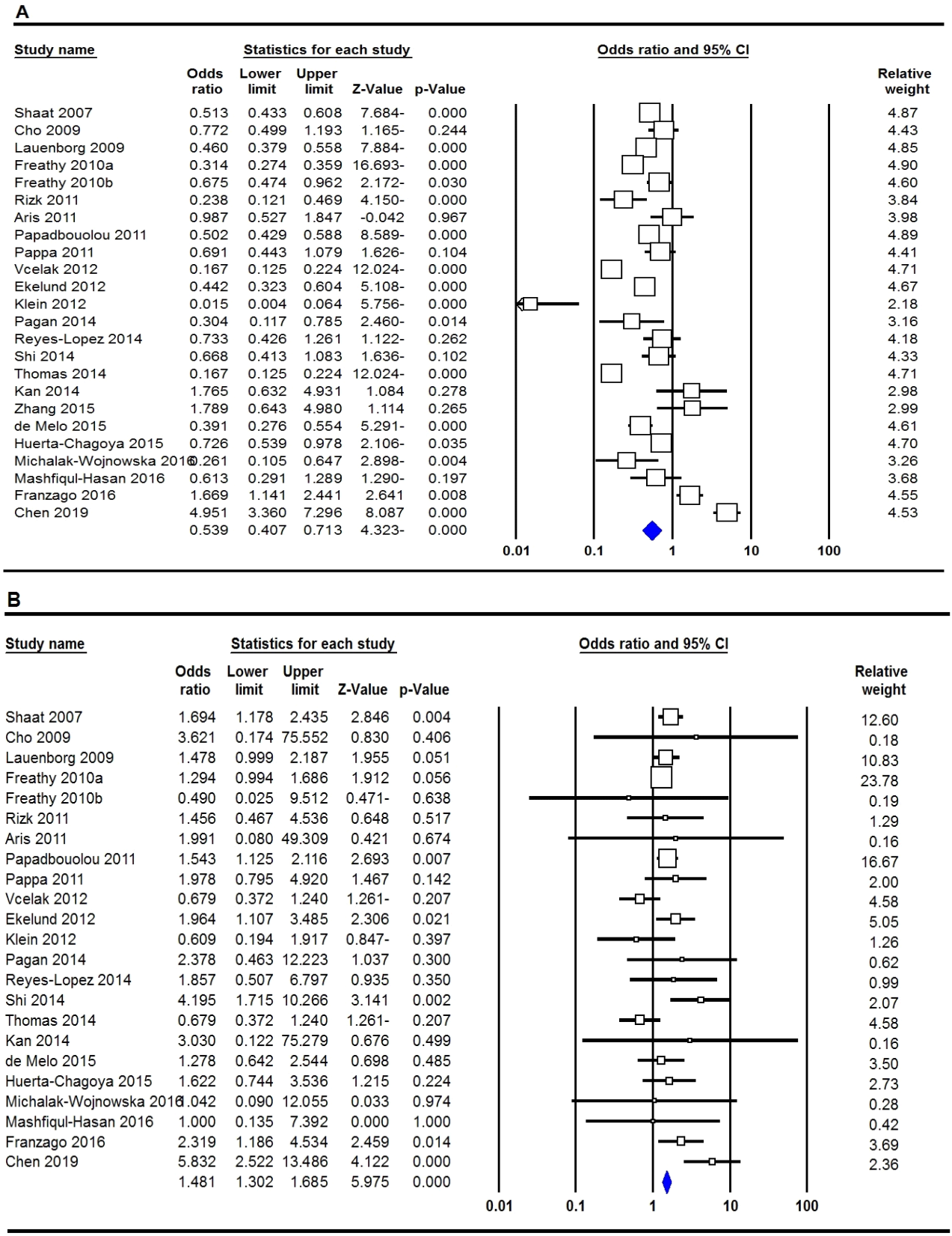

Figure 2. Forest Plots for Association between the TCF7L2 rs7903146 Polymorphism and GDM Risk in Whole Population. A: Allele model (T vs. C); B: Recessive model (TT vs. TC+CC)

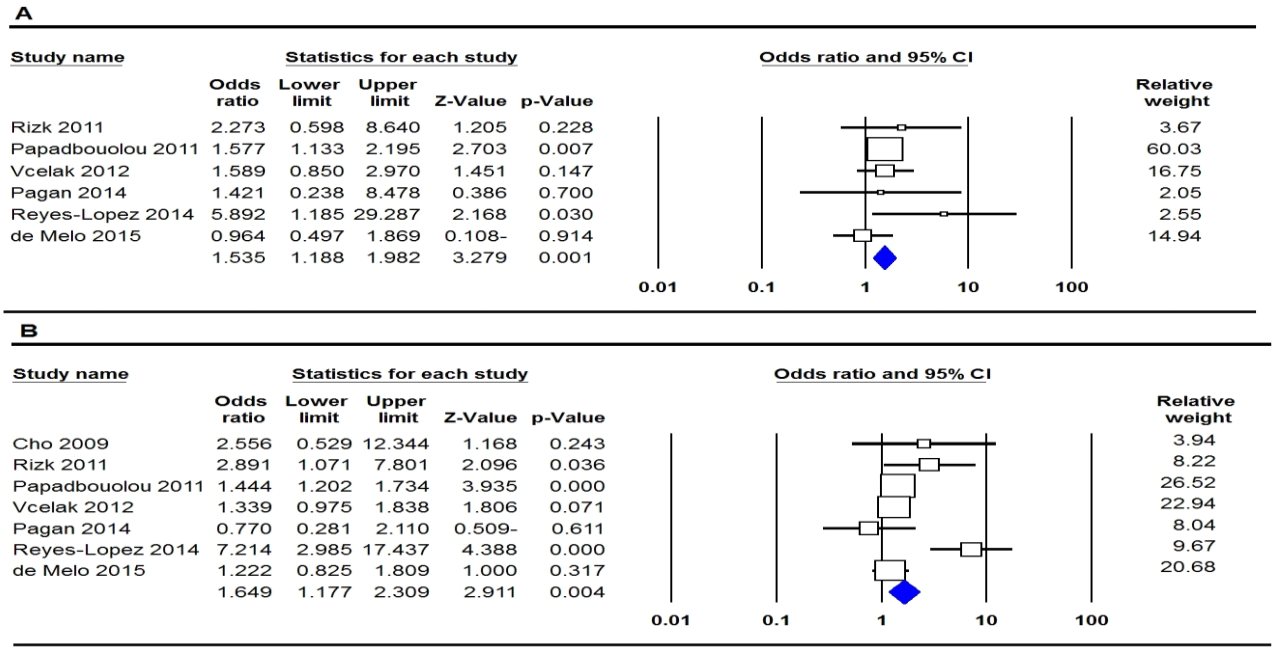

Figure 3. Forest Plots for Association between the TCF7L2 rs12255372 Polymorphism and GDM Risk in Whole Population. A: Homozygote model (TT vs. GG); B: Dominant model (TT+TC vs. CC)

However, we found that heterogeneity could be explained by GDM criteria and ethnicity for TCF7L2 rs7903146 and rs12255372, respectively.

Sensitivity analysis: We carried out sensitivity analysis to assess the effect of excluding a single study, in turns. The results showed that no individual study had an influence on the pooled OR all involved polymorphisms at *TCF7L2* gene in the current meta-analysis. Moreover, we performed the sensitivity analysis by excluding those studies did not in agreement with HWE. The results indicated that the pooled ORs were not materially altered by excluding those studies on *TCF7L2* rs7903146 and rs12255372 polymorphisms, suggesting the stability of our meta-analysis.

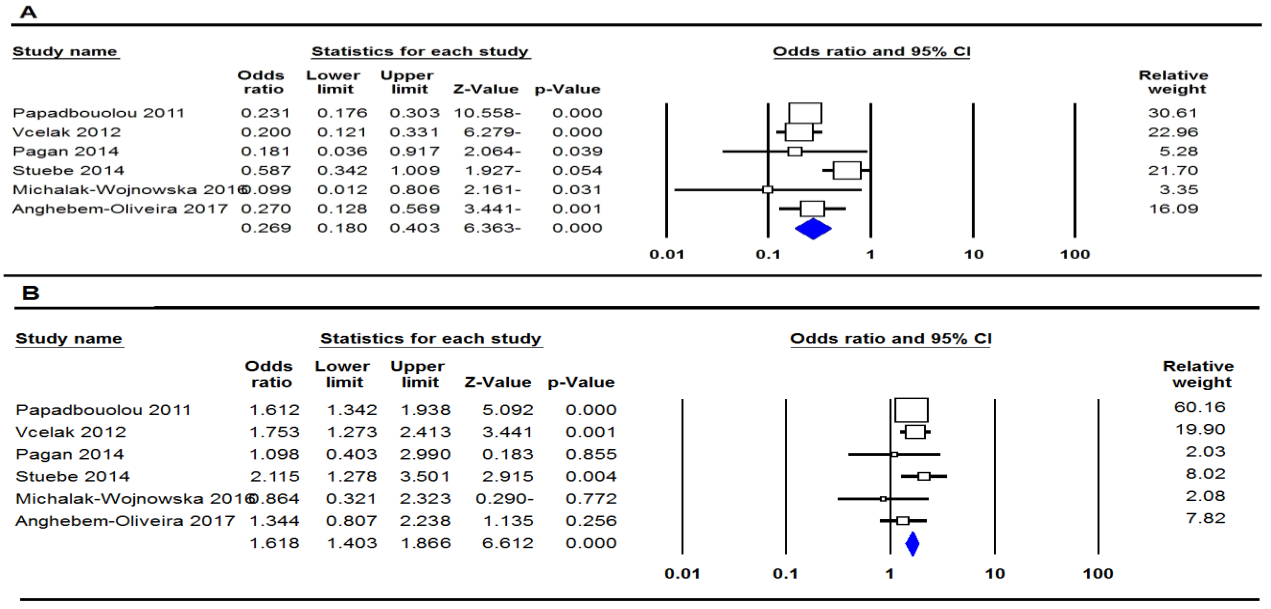

Figure 4. Forest Plots for Association between the TCF7L2 rs7901695 Polymorphism and GDM Risk in Whole Population. A: Heterozygote model (CT vs. TT); B: Dominant model (CC+CT vs. TT)

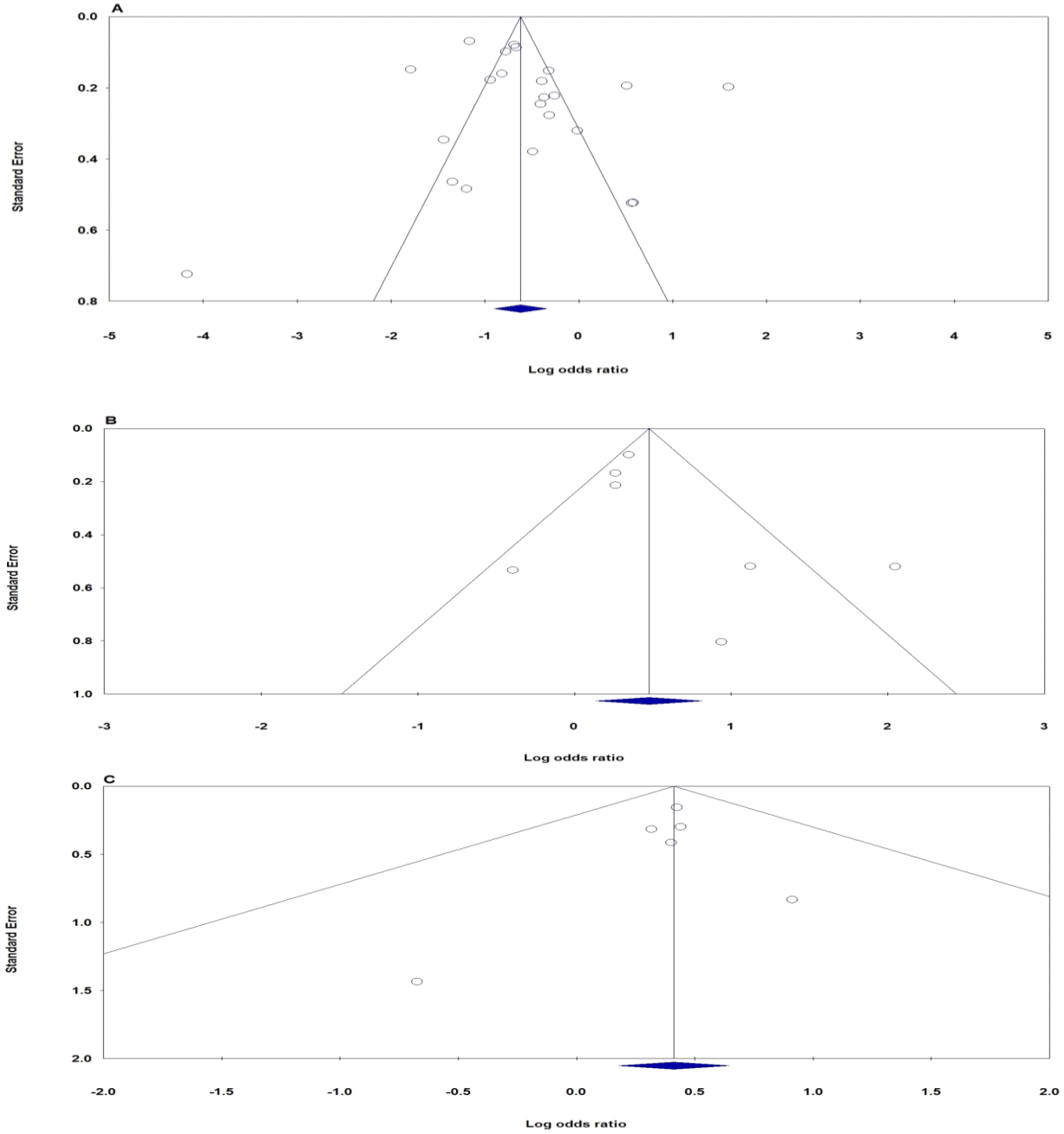

Figure 5. Begg's Funnel Plot for Publication Bias Test for Association between the TCF7L2 Polymorphisms with GDM Risk. A: rs7903146 (Allele Model: T vs. C); B: rs12255372 (Heterozygote Model: TG vs. GG); and C: rs7901695 (Recessive Model: CC vs. CT+TT)

Publication bias: Begg's funnel plot and Egger's test were used to evaluate the potential publication bias of included studies on *TCF7L2 rs7903146*, *rs12255372* and *rs7901695* polymorphisms. The Egger's test results for the *TCF7L2* polymorphisms under all five genetic models are presented in table 2. Begg's funnel did not statistically reveal a significant publication bias in any of the models for all involved polymorphisms at *TCF7L2* gene (Figure 5A-5C).

Discussion

Pregnancy is associated with several metabolic, biochemical, physiological, hematological and immunological changes.[59-61] During pregnancy insulin resistance changes due to placental secretion of diabetogenic hormones such as progesterone, growth hormone and corticotrophin-releasing hormone to ensure an adequate supply of nutrients to the fetus.[59,60,62] Studies revealed that the *TCF7L2* variants correlated with insulin resistance and insulin secretion of patients with GDM.[63] Moreover, the *TCF7L2* variants might be associated with increased hepatic glucose production and reduced hepatic insulin sensitivity and regulated the hepatic glucose metabolism via the gluconeogenesis pathway in humans.[64,65]

Large scale association studies have found a significant association between *TCF7L2 rs7903146* polymorphism and GDM risk. However, those studies results are inconsistent and incomplete, and might have limited statistical power with individual studies having relatively small sample sizes and genotyping methods. In this study, we aimed to assess the association of the *TCF7L2 rs7903146* polymorphism with GDM risk in whole population. Our pooled data showed that the *TCF7L2 rs7903146* polymorphism was associated with an increased risk of GDM risk under all five genetic models. Moreover, subgroup analysis indicated that *TCF7L2 rs7903146* polymorphism was associated with GDM risk in Caucasians and Chinese women, but not in Asian women. Chang et al., in a meta-analysis based on 18 studies evaluated the *TCF7L2 rs7903146* polymorphism with GDM. They found that the polymorphism was associated with GDM risk in overall population. Moreover, their subgroup analyses revealed that the *TCF7L2 rs7903146* polymorphism was associated with an increased risk of GDM in in Caucasian, Asian and other populations.[66] Lin et al., in a meta-analysis including 16 studies with 4,853 cases and 10,631 controls reported that the *TCF7L2 rs7903146* polymorphism was associated with GDM risk. Moreover, their subgroup analysis showed a statistically significant association between *rs7903146* polymorphism and GDM risk in whites, Hispanics/Latinos and Asians.[67] In another meta-analysis based on 10 studies with 3404 cases and 6473 controls reported that the *TCF7L2 rs7903146* polymorphism associated with GDM risk in overall population.[68]

The *rs12255372* polymorphism was widely studied with susceptibility to GDM in different populations. Our pooled data showed that the *TCF7L2 rs12255372* polymorphism was significantly associated with an increased risk of GDM in whole population. Moreover, there was significant association by ethnicity in Asians and Caucasians women. Wang et al., in a meta-analysis reported the *TCF7L2 rs12255372* polymorphism was associated with GDM. Their pooled data indicated that this polymorphism was associated with GDM in Caucasians women. [31] Chang et al., in a meta-analysis based on ten studies reported that the *TCF7L2 rs12255372* polymorphism was associated with GDM in overall population and Caucasians, but not in Asians.[66] Moreover, our pooled data revealed that the *TCF7L2 rs7901695* polymorphism was significantly associated with an increased risk of GDM risk in whole population under all five genetic models. Moreover, two previous meta-analyses by Chang et al., Wang et al., indicated that the TCF7L2 rs7901695 polymorphism was associated with GDM.[31,66]

Some limitations of this meta-analysis should be taken into account. First, some published studies included in the current met-analysis did not conform to the HWE, which could be due to potential bias during population selection. Second, the sample size of some included studies to evaluate the association of *TCF7L2* rs7903146, rs12255372 and rs7901695 polymorphisms with GDM were relatively small. Third, the sample sizes for TF7L2 rs7903146, rs12255372 and rs7901695 polymorphisms were not large, which may lead to reduced statistical power. Fourth, the strength of the

associations was measured by unadjusted ORs for confounding factors such as age, insulin level, gestational age, and environmental factors due to the lack primary data, which might have affected our results. Finally, GDM is a multifactorial condition and interactions between genetic and environmental factors might influence the development of this disease. The evaluation of TCF7L2 variants could not clarify the susceptibility of GDM exactly. Thus, more attention should be devoted to interactions of gene-gene and gene-environment in future large multi-centric studies.

Conclusion

In summary, this meta-analysis result demonstrated that the *TCF7L2* rs7903146, rs12255372 and rs7901695 polymorphisms were associated with a significant risk of GDM in whole population. Moreover, rs7903146 was associated with an increased risk of GDM in Caucasian, mixed and Chinese women, and *TCF7L2* rs12255372 polymorphism in Asians and Caucasians women. Our results may help understand the role of *TCF7L2* polymorphisms in GDM pathogenesis.

Conflict of Interests

Authors have no conflict of interests.

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