

Association between *TCF7L2* polymorphisms and gestational diabetes mellitus: A meta-analysis

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Keywords

Gestational diabetes mellitus, Polymorphism, *TCF7L2*

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ABSTRACT

Aims/Introduction: Studies have been carried out to evaluate the correlation between *TCF7L2* genetic polymorphisms and gestational diabetes mellitus (GDM) risk. However, the conclusions from these studies are incomplete, because partial single nucleotide polymorphisms (SNPs) were analyzed. We carried out a meta-analysis aimed to systematically evaluate *TCF7L2* gene polymorphisms and GDM susceptibility in all population and racial/ethnic subgroups to afford a foundation for future research.

Materials and Methods: Published studies censoring *TCF7L2* variants and GDM risk were captured from the EMBASE, PubMed, CNKI and Wanfang databases. The meta-analysis was processed using software of RevMan 5.2 and Stata13. The relationship between *TCF7L2* polymorphism and GDM occurrence was evaluated by pooled odds ratios. Stratified analysis based on race/ethnicity was also carried out. The allele-specific odds ratios and 95% confidence intervals were counted, and based on homogeneity evaluated using the I^2 -test, fixed- or random-effects pooled measures were selected.

Results: A total of 22 studies were covered, capturing eight *TCF7L2* SNPs and involving 5,573 cases and 13,266 controls. Six of eight SNPs showed significant relationships with GDM occurrence, of which the SNPs rs7903146, rs12255372 and rs7901695 were the most powerful. Stratified analysis by race/ethnicity showed discrepant results in these three SNPs. In Caucasians and other races, all these SNPs were found to have a significant association with GDM risk, but in Asians, only SNP rs7903146 showed a significant association.

Conclusions: Six of eight SNPs were found to have significant associations between *TCF7L2* variants and GDM risk in the overall population, with the most powerful in SNPs being rs7903146, rs12255372 and rs7901695, but the contribution of these SNPs to GDM risk were variable among different racial/ethnic groups.

INTRODUCTION

Gestational diabetes mellitus (GDM), defined as impaired glucose tolerance with onset or first identification during pregnancy, is one of the most frequent complications of pregnancy. The prevalence is estimated to be 5–10%, and the incidence rate has shown a gradual upward trend^{1,2}, making it a growing health issue³. GDM increases the risk of adverse pregnancy outcomes, and has adverse effects for both mothers and their children, including susceptibility to obesity, metabolic syndrome

and type 2 diabetes mellitus in later life^{3–5}. Furthermore, GDM occurrence is confused in different populations or ethnic groups. Therefore, it is necessary to systematically evaluate *TCF7L2* gene polymorphisms and GDM susceptibility in all population and racial/ethnic subgroups.

GDM is a heterogeneous metabolic disorder, with mixed genetic etiology and phenotypes⁶. Insulin resistance is regarded as an important factor to contribute to GDM. Furthermore, there are heritable elements, and GDM could share some risk factors of genetics with type 2 diabetes mellitus⁷. Transcription factor 7-like 2 (*TCF7L2*) expresses in pancreatic β -cells⁸, and belongs to the high mobility group-box family as a

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transcription factor⁹ that plays a crucial role in the maintenance of glucose homeostasis. Recent findings suggest that the *TCF7L2* contributes to GDM risk¹⁰.

So far, *TCF7L2* has multiple single nucleotide polymorphisms (SNPs), eight of which have been reported, including rs7903146^{11–28}; rs12255372^{16–21,26,28–30}; rs7901695^{18,20,25,29,31}; rs290487^{28,32,33}; rs11196205^{28,32}; rs11196218^{32,34}; rs12243326^{25,29}; and rs4506565.^{25,29} The SNP rs7903146 has been most widely researched, and has been associated with an increased risk of GDM in Scandinavian women⁷. A study of Mexican Americans showed that SNP rs12255372 of *TCF7L2* has a relationship with GDM risk and affected the insulin response to oral glucose in propends with GDM³⁰, and rs7901695 has been shown to benefit individuals with type 2 diabetes mellitus and GDM risk¹⁸. The SNPs rs7903146 C>T, rs12255372 G>T and rs7901695 T>C are the strongest to be beneficial to GDM risk³⁵, and lie within a well-defined linkage disequilibrium block^{36–38}. A study has also shown that SNPs were susceptible to type 2 diabetes mellitus occurrence through damaging insulin secretion, possibly attributable to a potential mechanism in β -cells³⁹. The other five SNPs have been less studied, and conflicting findings exist. Furthermore, individual studies might be limited by relatively inadequate sample sizes, and might be unable to receive convincing results. Therefore, we carried out

a meta-analysis to examine the association between *TCF7L2* polymorphisms and the risk of GDM.

MATERIALS AND METHODS

Literature search

A retrieve was carried out for related available articles published in four databases including PubMed and EMBASE for English articles, and China National Knowledge Infrastructure and Wanfang for Chinese articles. 'TCF7L2', 'transcription factor 7-like 2', 'polymorphism', 'SNP', 'GDM', 'gestational diabetes mellitus', 'Gestational diabetes' and 'Screening for gestational diabetes' as keywords were used to search. We also evaluated the references in the retrieved studies, and recognized extra-published articles not captured in review articles by search strategy from these databases.

Inclusion criteria

The following was the inclusion criteria, including: (i) case-control or cohort study published as an original study to assess the relationship between *TCF7L2* polymorphisms with GDM risk; (ii) precise numbers for each genotype reported in case and control groups or exposed and unexposed groups, or countable data from these numbers in the published papers; and (iii) participants from the same ethnicity and the same

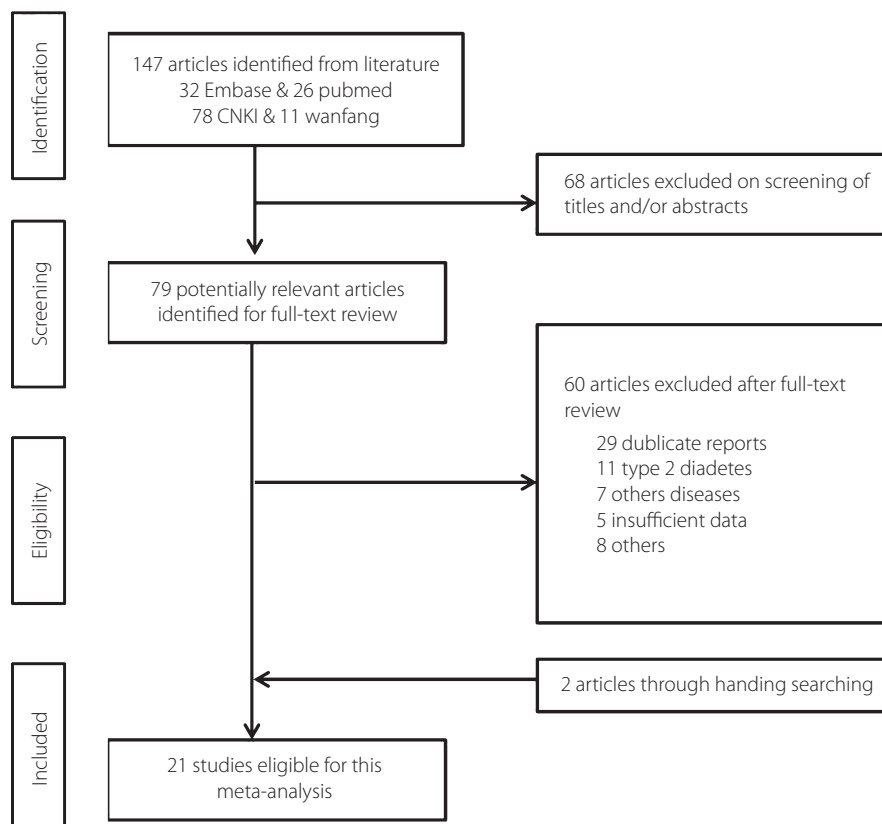


Figure 1 | Selection of studies for inclusion in the meta-analysis.

time in each research; and (iv) the nearest and integrated article was selected if a paper had been published more than once.

Data extraction

According to the inclusion criteria listed above, information was drawn from all eligible papers by two reviewers (Chang Shaoyan and Wang Zhen) independently, and the validation was tested by a third reviewer if there was disagreement. The literature were eliminated as follows: overviews or editorials, studies with cell culture or animal research, studies based on family, studies of the primary outcome exclusive of GDM, and studies with no evaluation of the relationships of GDM and *TCF7L2* polymorphisms, and studies that excluded a quality control group, or insufficient data for influence evaluations of the genetic relationships. Data were drawn from each published article as follows: first author, publication year, ethnicity, country, mean age, genotyping method, size of sample, number of cases and controls, study design, genetic variants, minor allele and allele distribution by GDM situation. If odds ratios (ORs) were accessible, but the genotype and allele distributions on the basis of GDM situation were not covered in the primitive study, the corresponding authors were contacted by email.

Quality assessment

Risk of bias was devoted to evaluate the methodological reliability of the incorporated studies. Quality was assessed based on

five questions, using different colors for low risk (green), unclear risk (yellow), and high risk (red), with more green manifesting better research quality.

Statistical analysis

A meta-analysis was carried out by RevMan version 5.2 (Cochrane Collaboration, Oxford, UK) and Stata13 software (StataCorp, College Station, Texas, USA). During the data analysis, we carried out independent meta-analyses for GDM and *TCF7L2* variants. The ORs of individual research were recounted from the accessible genotype distributions based on an allelic model, pooled using random-effects models (REMs) or fixed-effect models (FEMs) and visualized using forest plots. Heterogeneity in all qualified comparisons was evaluated by the I^2 -value and the χ^2 -test to evaluate the P -value. I^2 was the percentage of total degree of variation observed among the studies due to actual differences between the trials rather than to sampling error (chance), where $I^2 > 50\%$ is regarded as a significant heterogeneity.

RESULTS

Description of the included studies

The search generated 147 articles of which 21 were eligible for meta-analysis (Figure 1). The 22 eligible studies captured eight *TCF7L2* SNPs, and included 5,573 cases and 13,266 controls. There were 18 studies about rs7903146, 10 about rs12255372, 5 about rs7901695, 3 about rs290487, 2 about rs11196205, 2

Table 1 | Characteristics of the included studies on the association between *TCF7L2* and gestational diabetes mellitus risk

Author, (year) reference	Ethnicity	Country	Mean age (cases/controls)	Genotyping method	GDM criteria
Aris, (2012) ²⁷	Asian	Malaysia	29.7/28.5	NA	ADA
Cho, (2009) ¹⁷	Asian	Korea	32/64.7	Allelic discrimination assay	IWCGDM
de Melo, (2015) ²⁶	Hispanic/Latino	Brazil	32/24	SNP Genotyping Assay	ADA
Freathy, (2010) ¹²	Mixed	Australia and UK	NA	Illumina Golden Gate platform	OGTT
Kan, (2014) ¹⁵	Asian	China	30.7/30.9	Allelic discrimination assay	OGTT
Huerta-Chagoya, (2015) ²⁵	Hispanic/Latino	Mexico	35/28	SNP genotype (LGC)	OGTT
Hui, (2011) ³²	Asian	China	32/30	PCR-LDR	OGTT
Klein, (2012) ¹⁹	Caucasian	Australia	28.2/30.1	NA	OGTT
Liu, (2014) ³³	Asian	China	31.88/28.78	Mass spectrometry	OGTT
Pagan, (2014) ²⁹	Caucasian	Spain	34.31/31.2	Sequencing	OGTT
Papadopoulou, (2011) ²⁰	Caucasian	Sweden	NA	TaqMan allelic discrimination assay	OGTT
Reyes-López, (2014) ²¹	Mexican	Mexico	29/31	PCR	ADA
RIZK, (2011) ¹⁶	Caucasian	Qatar	NA	TaqMan allelic discrimination assay	NA
Shaat, (2007) ¹⁴	Caucasian	Scandinavia	32.3/30.5	TaqMan allelic discrimination assay	OGTT
Shi, (2014) ²⁸	Asian	China	30/29	AS-PCR	OGTT
Stuebe, (2014) ³¹	African-American	USA	24.1 (total)	Sequenom iPLEX platform	OGTT
Thomas, (2014) ²⁴	Asian	India	NA	NA	NA
Vcelak, (2012) ¹⁸	Caucasian	Czech Republic	32.8/29.9	TaqMan allelic discrimination assay	WHO
Wang, (2013) ³⁹	Asian	China	NA	PCR-LDR	OGTT
Watanabe, (2007) ³⁰	Mexican-American	USA	35.0/33.4	TaqMan allelic discrimination assay	OGTT
Zhang, (2015) ²³	Asian	China	30.58/28.75	PCR-RFLP	OGTT

ADA, American Diabetes Association; AS-PCR, allele-specific polymerase chain reaction; GDM, gestational diabetes mellitus; IWCGDM, International Workshop-Conference on Gestational Diabetes Mellitus; LGC, LGC Bioresearch Technologies; OGTT, oral glucose tolerance test; NA, not available; PCR, polymerase chain reaction; PCR-LDR, ligase detection reaction–polymerase chain reaction; SNP, single nucleotide polymorphism; WHO, World Health Organization.

Table 2 | *TCF7L2* allele distribution among GDM cases and controls in the included studies

Author (year)	Variant (minor allele)	No. cases		Genotypes in GDM case			Genotypes in GDM control			Minor allele frequency (%)		<i>P</i> for HWE
		Case	Control	AA	AB	BB	AA	AB	BB	Case	Control	
Aris (2012)	rs7903146(T)	173	114	129	43	1	99	15	0	87	93.4	0.686
Cho (2009)		868	627	2	63	803	0	31	596	3.9	2.5	1
de Melo (2015)		200	200	20	104	76	16	86	98	36	29.5	0.633
Freathy (2010)		614	3,811	75	246	293	370	1,557	1,884	32.2	30.1	0.29
Freathy (2010)		384	1,332	0	46	338	3	108	1,211	6	4.3	0.73
Huerta-Chagoya (2015)		408	342	19	124	265	10	67	265	19.9	12.7	0.03
Kan (2014)		100	100	1	15	84	0	5	95	8.5	5	>0.05
Klein (2012)		125	125	5	112	8	8	107	10	48.8	49.2	NA
Lauenborg (2009)		276	2,353	33	125	118	198	863	1,292	34.6	26.8	>0.05
Pagan (2014)		45	24	8	18	19	2	12	10	38	33	1
Papadopoulou (2011)		803	1,110	88	352	363	82	384	644	32.9	24.7	0.02
PAPPA (2011)		148	107	18	81	49	7	38	62	39.53	24.29	0.792
Reyes-López (2014)		90	108	6	29	55	4	23	81	23	14	NA
RIZK (2011)		40	74	6	18	16	8	37	29	37.5	37.2	0.706
Shaat (2007)		585	1,111	59	255	271	69	392	650	31.9	23.8	0.363
Shi (2014)		100	100	24	36	40	7	38	55	42	26	>0.05
Thomas (2014)		117	49	16	46	55	4	18	27	33.3	26.5	0.452
Vcelak (2012)		261	376	17	102	142	35	185	156	33.8	26.1	0.067
Zhang (2015)		113	115	0	17	96	0	5	110	7.52	2.17	>0.05
Cho (2009)	rs12255372(T)	867	630	0	7	860	0	2	628	0.4	0.2	NA
de Melo (2015)		200	200	20	88	92	23	75	102	32	30.3	0.633
Klein (2012)		125	125							39.6	28	NA
Pagan (2014)		45	25	6	20	19	2	14	9	36	36	0.4095
Papadopoulou (2011)		801	1,102	81	333	387	84	385	633	30.9	25.1	0.02
Reyes-López (2014)		90	108	7	23	60	2	5	101	20	5	NA
RIZK (2011)		40	74	6	28	6	11	38	25	50	40.5	0.108
Shi (2014)		100	100	0	0	100	0	0	100	0	0	>0.05
Vcelak (2012)		260	376	22	115	124	23	147	206	30	25.7	0.067
Watanabe (2007)		94	58							39.4	20.7	NA
Huerta-Chagoya (2015)	rs7901695(C)	408	342	NA	NA	NA	NA	NA	NA	20.3	13.6	0.03
Pagan (2014)		45	25	8	20	17	2	13	10	40	34	0.6626
Papadopoulou (2011)		794	1,102	95	356	343	90	405	607	34.4	26.5	0.02
Stuebe (2014)		56	842	9	30	17	70	357	415	42.9	29.5	>0.05
Stuebe (2014)		24	366	4	15	5	79	162	121	47.9	43.7	>0.05
Vcelak (2012)		261	376	25	130	106	24	147	205	34.4	26.9	0.067
Hui (2011)	rs290487(C)	480	631	90	220	170	88	282	261	41.7	36.3	0.2076
Shi (2014)		100	90	12	36	52	6	34	50	30	33	>0.05
Wang (2013)		70	70	11	37	22	9	33	28	42.2	36.5	NA
Hui (2011)	rs11196205(G)	479	623	461	18	0	591	32	0	98.1	97.4	1
Shi (2014)		100	100	99	0	1	100	0	0	99	100	>0.05
Hui (2011)	rs11196218(A)	471	625	30	201	240	43	256	326	27.7	27.4	0.1449
Liu (2014)		144	144	9	58	77	5	53	86	26	22	>0.05
Huerta-Chagoya (2015)	rs12243326(C)	408	342	NA	NA	NA	NA	NA	NA	16.8	9.6	0.03
Pagan (2014)		45	25	7	20	18	2	13	10	38	34	0.6626
Huerta-Chagoya (2015)	rs4506565(T)	408	342	NA	NA	NA	NA	NA	NA	21.3	14	0.03
Pagan (2014)		45	25	9	20	16	0	12	13	42	24	0.2762

GDM, gestational diabetes mellitus; HWE, Hardy–Weinberg equilibrium; NA, not available.

about rs11196218, 2 about rs12243326 and 2 about rs4506565. Characteristics of the included studies, and the genotype and allele distributions of SNPs among GDM cases and controls are shown in Tables 1 and 2.

Meta-analysis results

The SNP rs7903146 of *TCF7L2* was the most extensively studied variant, and showed a conflicting correlation across different populations. The results of the allele distribution are described

in detail in Table 2. We found a significant correlation between the T allele of SNP rs7903146 and the risk of GDM (REM, OR 1.36, 95% CI: 1.17–1.57) by meta-analysis. Further subgroup analyses were carried out based on race/ethnicity, and the results showed significant relationships in all populations including in Caucasian (REM, OR 1.27, 95% CI: 1.04–1.55), Asian (REM, OR 1.55, 95% CI: 1.05–2.31) and other populations (REM, OR 1.39, 95% CI: 1.08–1.80; Figure 2).

The rs12255372 polymorphism was also widely studied with the results of different relationships with GDM risk in different populations. There was a significant relationship between the T allele of SNP rs12255372 and the risk of GDM (REM,

OR 1.55, 95% CI: 1.23–1.96) by meta-analysis. Further subgroup analyses showed significant correlations in Caucasian (REM, OR 1.32, 95% CI: 1.17–1.48) and other populations (REM, OR 2.11, 95% CI: 1.17–3.82), but no correlation in Asian populations (REM, OR 2.55, 95% CI: 0.53–12.29; Figure 3).

Additionally, a significant relationship was discovered between the C allele of SNP rs7901695 and GDM risk by meta-analysis with 1.49 (95% CI: 1.34–1.66) of overall OR (FEM). Further subgroup analyses showed significant correlations in Caucasian (FEM, OR 1.48, 95% CI: 1.32–1.66) and other populations (FEM, OR 1.53, 95% CI: 1.19–1.97; Figure 4).

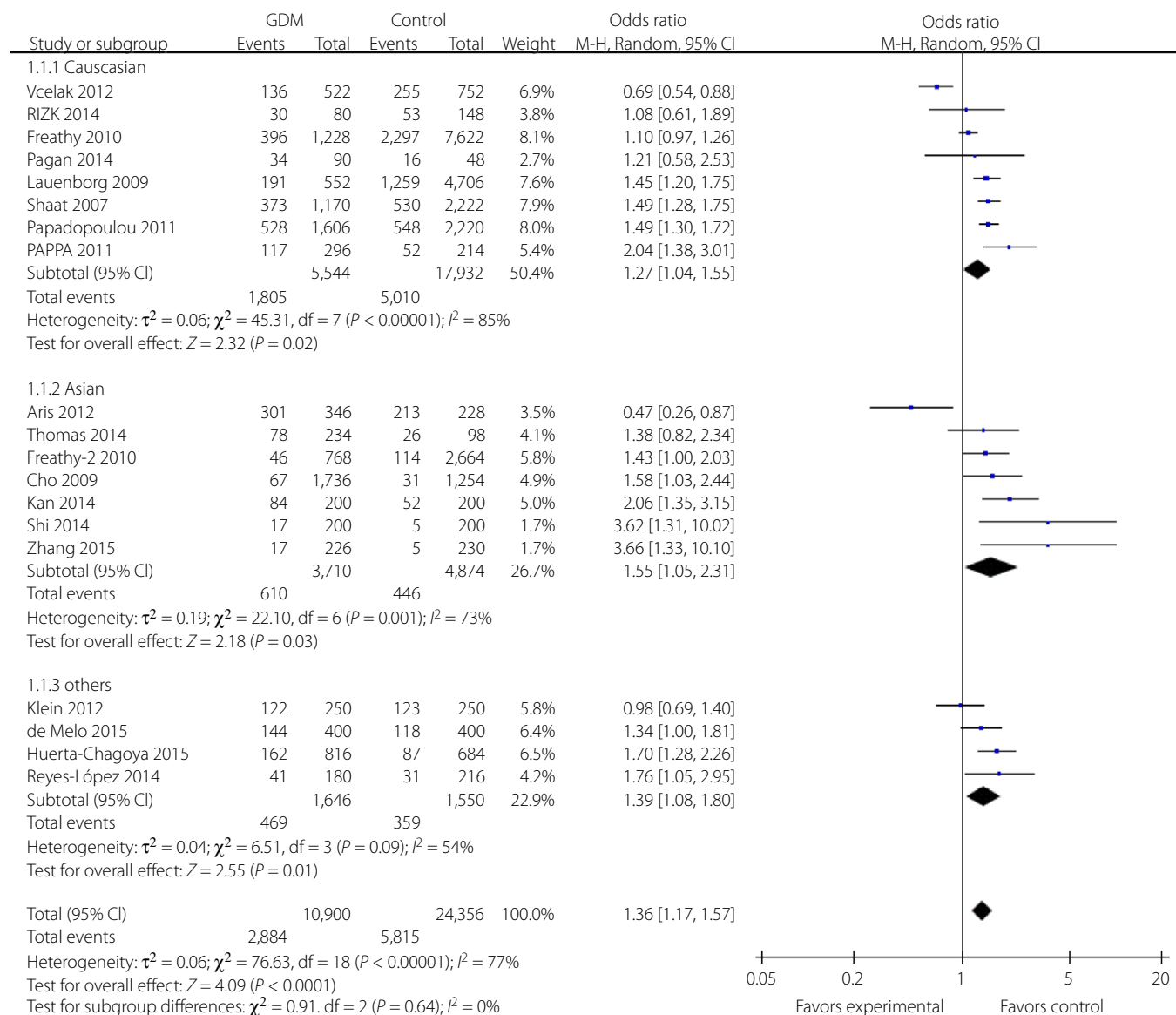


Figure 2 | Forest plots of the relationship between *TCF7L2* rs7903146 polymorphism and the risk of gestational diabetes mellitus across different populations. Black diamonds denote the pooled odds ratio. Blue squares indicate the odds ratio in each study, with square sizes inversely proportional to the standard error of the odds ratio. Horizontal lines represent 95% confidence intervals (CI).

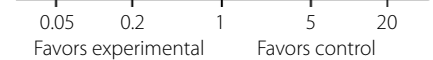
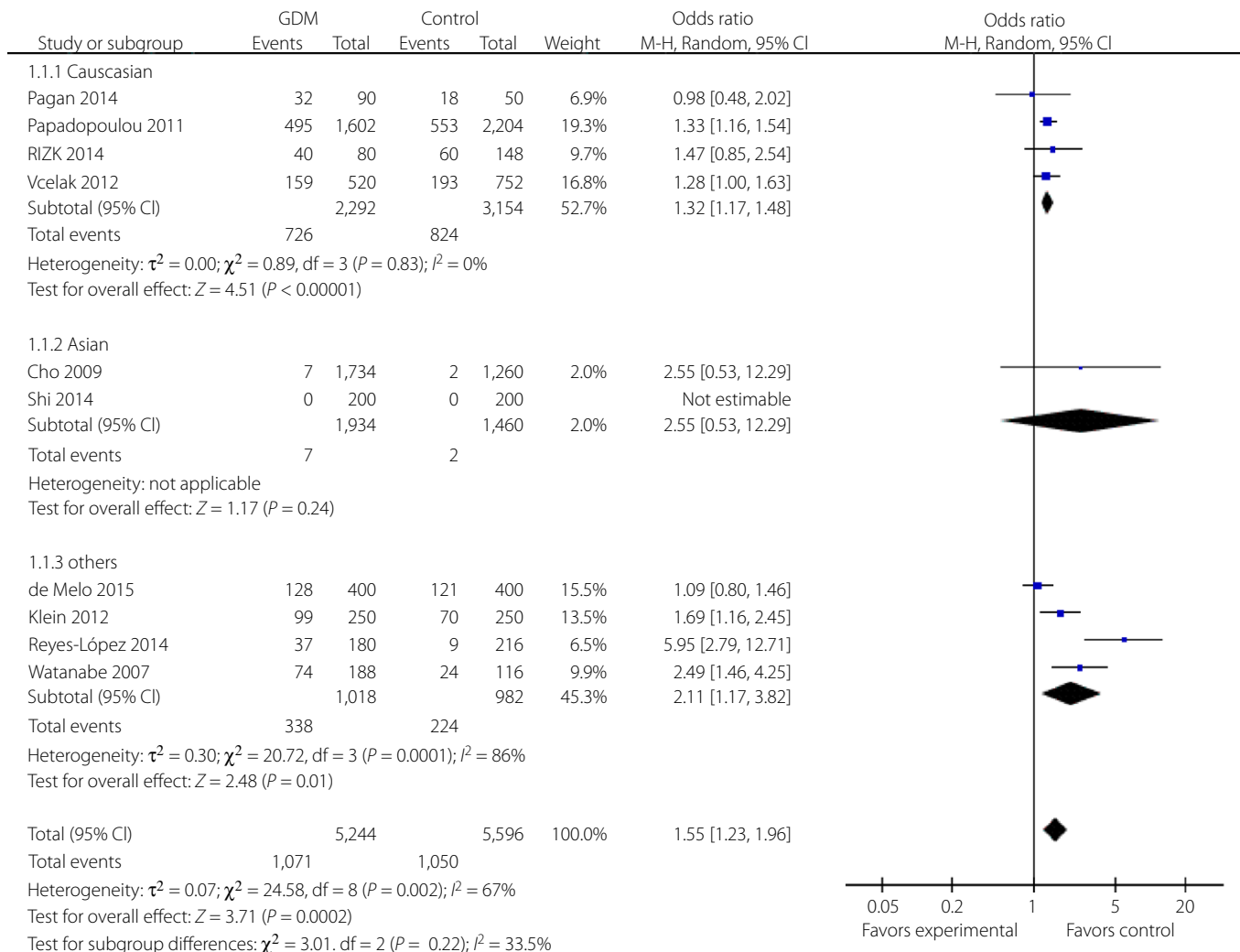


Figure 3 | Forest plots of the relationship between *TCF7L2* rs12255372 polymorphism and the risk of gestational diabetes mellitus across different populations. Black diamonds denote the pooled odds ratio. Blue squares indicate the odds ratio in each study, with square sizes inversely proportional to the standard error of the odds ratio. Horizontal lines represent 95% confidence intervals (CI).

Three variants in the *TCF7L2* gene, including rs290487, rs11196205 and rs11196218, were researched only in Chinese populations (Figures 5–7). There was a significant correlation between rs290487 (FEM, OR 1.25, 95% CI: 1.08–1.46) and GDM risk, but no correlation with rs11196205 (FEM, OR 1.24, 95% CI: 0.71–2.18) and rs11196218 (FEM, OR 1.06, 95% CI: 0.90–1.26). Two other SNPs in the *TCF7L2* gene were found only in two literature research articles with different ethnicity, and they had significant correlations between rs4506565 (FEM, OR 1.72, 95% CI: 1.33–2.23) with GDM, and rs12243326 (FEM, OR 1.76, 95% CI: 1.32–2.34) with GDM (Figures 8 and 9).

Heterogeneity

Heterogeneity between studies was measured in all comparisons. There was no heterogeneity in rs7901695, rs4506565 and

rs290487 with $I^2 = 0\%$, slight heterogeneity in rs11196205 ($I^2 = 34\%$), rs11196218 ($I^2 = 10\%$) and rs12243326 ($I^2 = 27\%$), but severe heterogeneity in rs12255372 ($I^2 = 67\%$) and rs7903146 ($I^2 = 77\%$). Except for rs12255372 and rs7903146, all SNPs in the *TCF7L2* gene were analyzed using the FEM. Although subgroup analysis according to ethnicity of rs12255372 and rs7903146 was carried out, heterogeneity was still severe. Therefore, the use of REMs was justified in these analyses.

Publication bias analysis

Publication bias of all *TCF7L2* SNPs was determined using a funnel plot of Revman 5.2, but vague results of SNPs rs7903146 and SNPs rs7903146 were found. Therefore, Egger of Stata13 was used to further confirm the results. The results

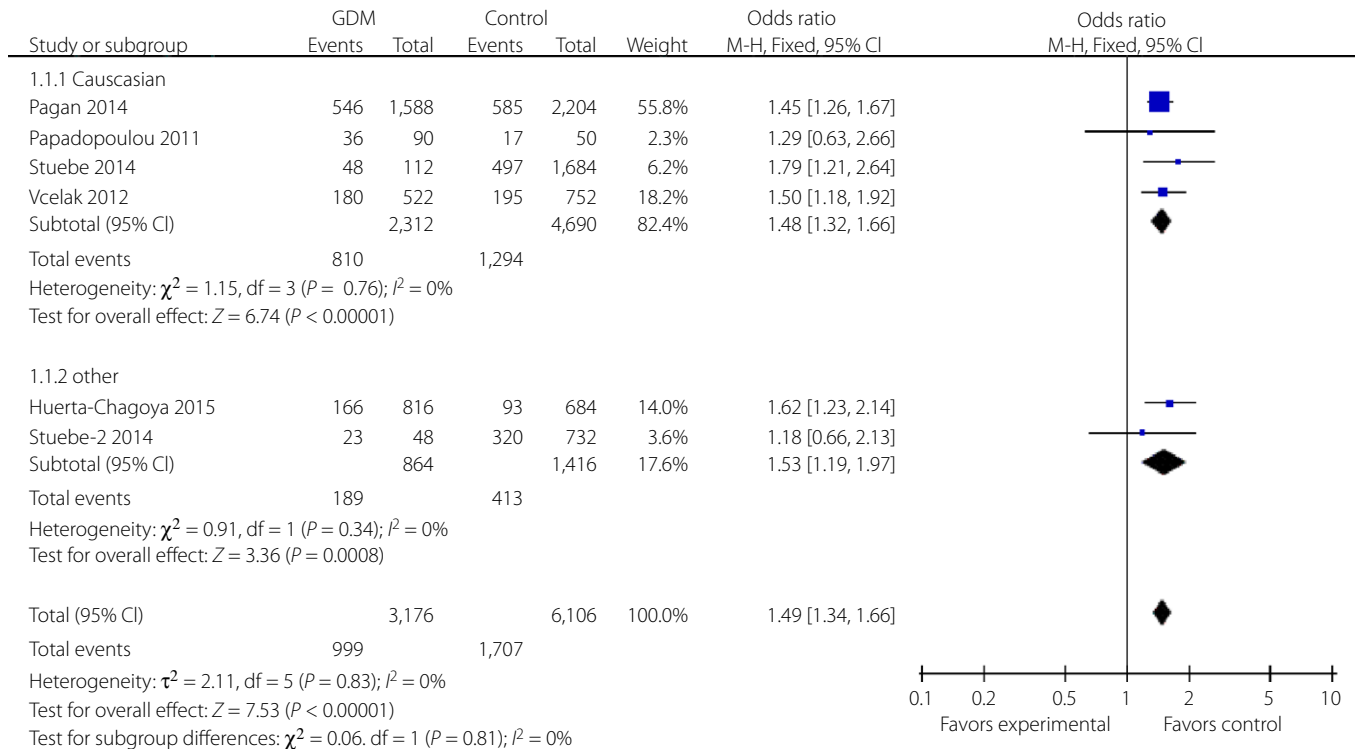


Figure 4 | Forest plots of the relationship between *TCF7L2* rs7901695 polymorphism and the risk of gestational diabetes mellitus across different populations. Black diamonds denote the pooled odds ratio. Blue squares indicate the odds ratio in each study, with square sizes inversely proportional to the standard error of the odds ratio. Horizontal lines represent 95% confidence intervals (CI).

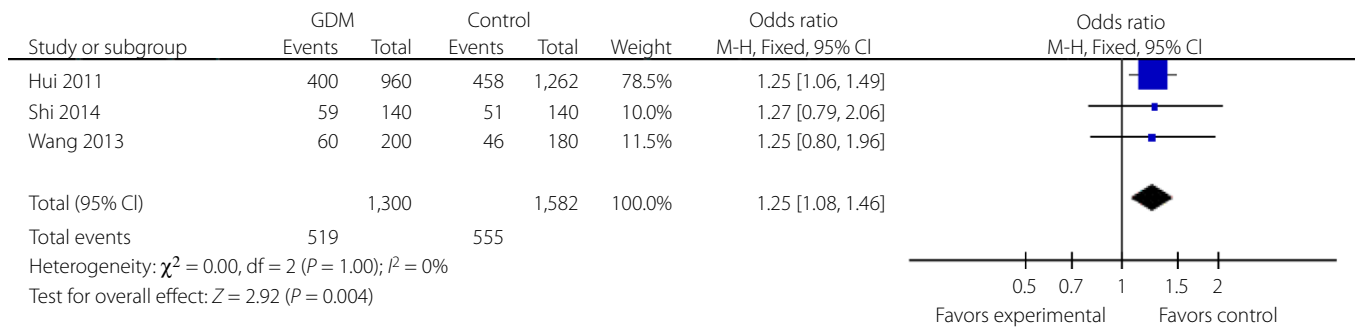


Figure 5 | Forest plots of the relationship between *TCF7L2* rs290487 polymorphism and the risk of gestational diabetes mellitus across different populations. Black diamonds denote the pooled odds ratio. Blue squares indicate the odds ratio in each study, with square sizes inversely proportional to the standard error of the odds ratio. Horizontal lines represent 95% confidence intervals (CI).

showed that no evidence of statistically significant publication bias was detected for the studies (Figure S1–S8; Tables S1–S4).

DISCUSSION

An increasing number of studies have shown that *TCF7L2* variants are related to GDM risk. However, the results of the studies are inconsistent and incomplete, and might have limited

statistical power with individual studies having relatively small sample sizes and the analysis of partial SNPs. Therefore, we carried out the meta-analysis with the aim to provide a more comprehensive summary of the currently available evidence with respect to the relationship between *TCF7L2* variants and GDM risk. Overall, 22 eligible studies captured eight *TCF7L2* SNPs, including 5,573 cases and 13,266 controls. The SNPs rs7903146

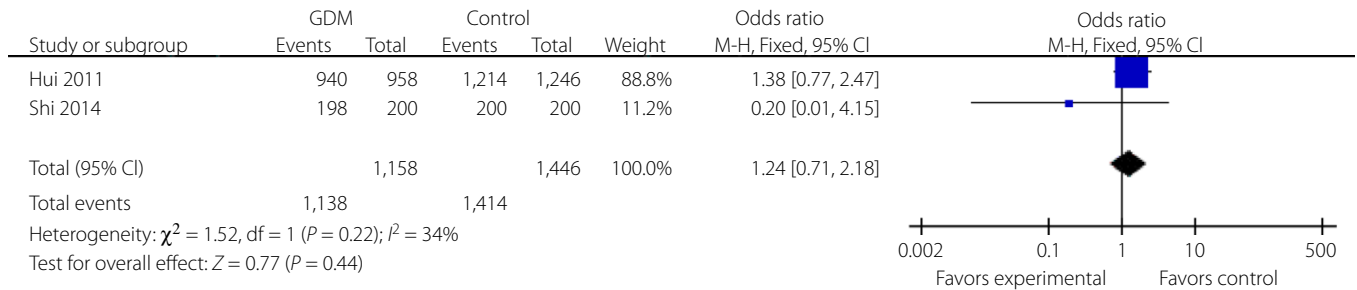


Figure 6 | Forest plots of the relationship between *TCF7L2* rs11196205 polymorphism and the risk of gestational diabetes mellitus across different populations. Black diamonds denote the pooled odds ratio. Blue squares indicate the odds ratio in each study, with square sizes inversely proportional to the standard error of the odds ratio. Horizontal lines represent 95% confidence intervals (CI).

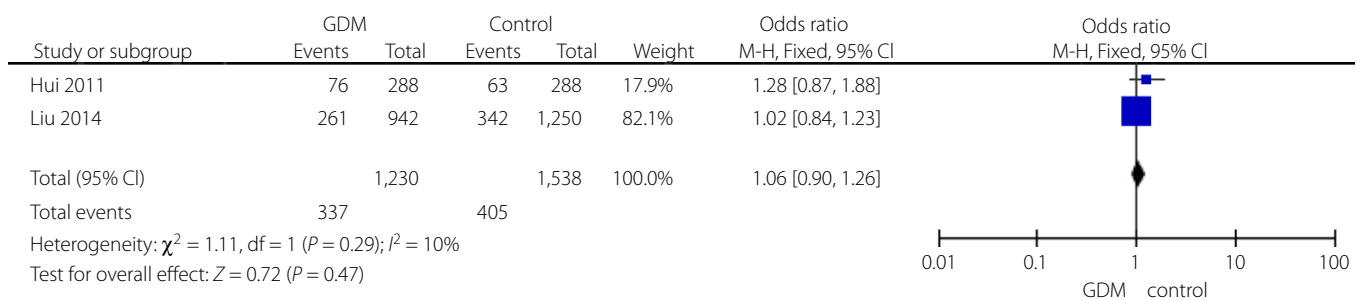


Figure 7 | Forest plots of the relationship between *TCF7L2* rs11196218 polymorphism and risk of gestational diabetes mellitus (GDM) across different populations. Black diamonds denote the pooled odds ratio. Blue squares indicate the odds ratio in each study, with square sizes inversely proportional to the standard error of the odds ratio. Horizontal lines represent 95% confidence intervals (CI).

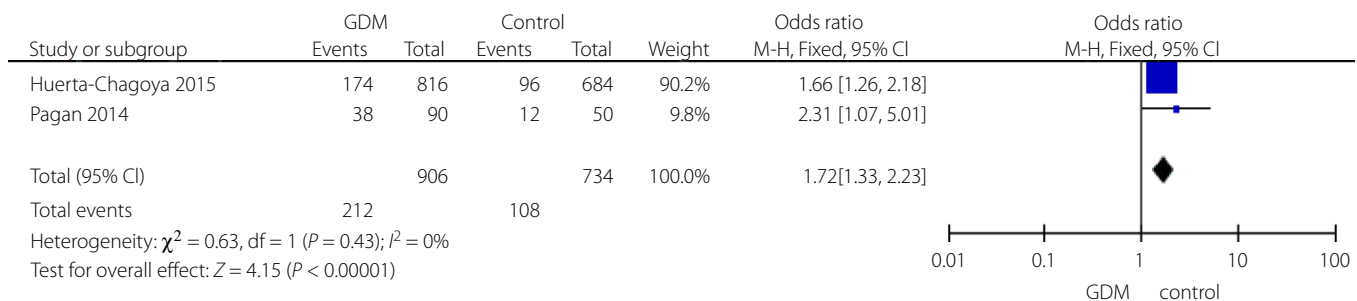


Figure 8 | Forest plots of the relationship between *TCF7L2* rs4506565 polymorphism and the risk of gestational diabetes mellitus (GDM) across different populations. Black diamonds denote the pooled odds ratio. Blue squares indicate the odds ratio in each study, with square sizes inversely proportional to the standard error of the odds ratio. Horizontal lines represent represent 95% confidence intervals (CI).

C>T, rs12255372 G>T and rs7901695 T>C were the most powerful to assess the relationship between *TCF7L2* polymorphism and the risk of GDM. The SNPs rs7903146 and rs7901695 showed significant relationships with GDM risk in the overall and subgroup analyses; however, the relationship of rs12255372 was significant and conflicting among different ethnicities.

GDM can progress when a genetic susceptibility to pancreatic islet β -cell injury is exposed by incremental insulin resistance during pregnancy⁴⁰. Among the most widely studied

genes involved in GDM risk, *TCF7L2* is identified as regulating β -cell action⁴¹. It is well known that *TCF7L2* expresses in pancreatic β -cells, and belongs to the supernal mobility group-box transcription factors family and plays a vital role in maintaining glucose homeostasis. Eight SNPs in the *TCF7L2* gene have been reported, including rs7903146, rs12255372, rs7901695, rs290487, rs4506565, rs11196205, rs11196218 and rs12243326.

The most widely studied SNP was rs7903146, and a previous meta-analysis regarding this SNP found a 1.65-fold increased risk

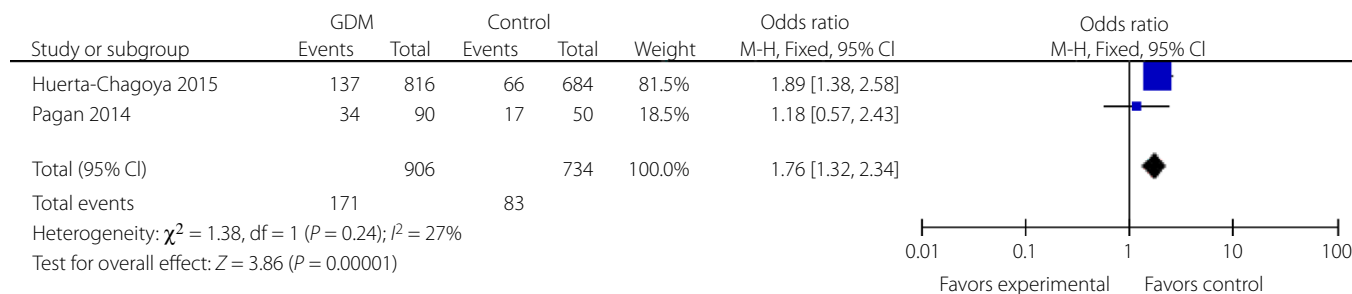


Figure 9 | Forest plots of the relationship between *TCF7L2* rs12243326 polymorphism and risk of gestational diabetes mellitus across different populations. Black diamonds denote the pooled odds ratio. Blue squares indicate the odds ratio in each study, with square sizes inversely proportional to the standard error of the odds ratio. Horizontal lines represent 95% confidence intervals (CI).

of GDM, based on six studies⁴², and 1.63-fold in 16 studies⁴³. We identified 18 studies assessing the association, and the results were consistent with the previous analysis. Furthermore, we carried out subgroup analysis based on ethnicity, and found a significant correlation in Caucasian and Asian ethnicities and others, as seen in the previous study. Combined with all results, T allele of the SNP rs7903146 of *TCF7L2* was related to GDM risk.

The rs12255372 variant was also widely studied with the results of different relationships with GDM risk in different populations. A systematic review of four studies found a significant relationship between this SNP and GDM⁴⁴. We extended the sample to nine studies, and increased the number of participants to carry out a relatively comprehensive assessment. The significant relationship remained, with rs12255372 associated with GDM, consistent with previous research. However, findings of the subgroup analysis differed, with a significant correlation in Caucasian and other groups, but no association in Asian groups. Overall, this suggests that the T allele of rs12255372 might be related to GDM risk, but to varying degrees among different ethnicities.

A significant relationship was discovered in the meta-analysis regarding the C allele of rs7901695 and the risk of GDM (OR 1.49, 95% CI: 1.34–1.66), with subgroup analysis showing a significant correlation in Caucasian, Asian and other groups.

In conclusion, different relationships between *TCF7L2* variants and GDM risk among different ethnic groups might be attributable to genetic characteristics and sample size, or selection standards of participants, but could also be because of different growth environments, body structure and variations in genetic background. Therefore, ongoing research and systematic analysis is important. Because we were unable to completely eliminate potential bias and heterogeneous factors in the present meta-analysis, further studies with rich sample capacity and using normalized unbiased genotyping methods are required to verify the present findings.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 | Funnel plots of publication bias for the relationship of TCF7L2 rs7903146 polymorphism and risk of gestational diabetes mellitus across different populations.

Figure S2 | Funnel plots of publication bias for the relationship of TCF7L2 rs12255372 polymorphism and risk of gestational diabetes mellitus across different populations.

Figure S3 | Funnel plots of publication bias for the relationship of TCF7L2 rs7901695 polymorphism and risk of gestational diabetes mellitus across different populations.

Figure S4 | Funnel plots of publication bias for the relationship of TCF7L2 rs290487 polymorphism and risk of gestational diabetes mellitus across different populations.

Figure S5 | Funnel plots of publication bias for the relationship of TCF7L2 rs4506565 polymorphism and risk of gestational diabetes mellitus across different populations.

Figure S6 | Funnel plots of publication bias for the relationship of TCF7L2 rs11196205 polymorphism and risk of gestational diabetes mellitus across different populations.

Figure S7 | Funnel plots of publication bias for the relationship of TCF7L2 rs11196218 polymorphism and risk of gestational diabetes mellitus across different populations.

Figure S8 | Funnel plots of publication bias for the relationship of TCF7L2 rs12243326 polymorphism and risk of gestational diabetes mellitus across different populations.

Table S1 | Publication bias list for the relationship of TCF7L2 rs7903146 polymorphism and risk of GDM across different populations.

Table S2 | Egger's test of publication bias for the relationship of TCF7L2 rs7903146 polymorphism and risk of GDM across different populations.

Table S3 | Publication bias list for the relationship of TCF7L2 rs12255372 polymorphism and risk of GDM across different populations.

Table S4 | Egger's test of publication bias for the relationship of TCF7L2 rs12255372 polymorphism and risk of GDM across different populations.