Int J Clin Exp Med 2016;9(8):15400-15413
www.ijcem.com /ISSN:1940-5901/IJCEM0032743

Original Article

TNF-α (rs1800629), CDKAL1 (rs7754840, rs7756992), MTNR1B (rs10830963, rs1387153) polymorphisms were linked to gestational diabetes mellitus (GDM) risks: based on an updated meta-analysis

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Received May 24, 2016; Accepted August 2, 2016; Epub August 15, 2016; Published August 30, 2016

Abstract: The rs1800629 of TNF-α (Tumor Necrosis Factor-alpha), rs7754840, rs7756992 of CDKAL1 (CDK5 regulatory subunit associated protein 1-like 1), rs10830963, rs1387153 of MTNR1B (Melatonin Receptor 1B) have been reported previously. Our study aims at investigating the potential role of the above SNPs (Single Nucleotide polymorphisms) in the risks of GDM (Gestational Diabetes Mellitus). An updated meta-analysis was thus conducted via Stata/SE 12.0 software. The six online databases (PubMed, EMBASE, WOS, EBSCO, WANFANG and CNKI) were searched to obtain the relevant literature. 8 articles for TNF-α gene, 6 articles for CDKAL1 gene and 10 articles for MTNR1B gene were finally included. The *p* value, OR (odd radio) and 95% CI (confidence interval) from Mantel-Haenszel statistics were then calculated. Compared with the control group, a significantly increased GDM risk was observed for TNF-α rs1800629, CDKAL1 rs7754840, rs7756992, MTNR1B rs10830963 and rs1387153, in the overall or Asian population under almost genetic comparisons (OR>1, $p<0.05$). The potential publication bias was excluded by Begg's test and Egger's test. Sensitivity meta-analyses further indicated the stable results. In summary, it is more likely that TNF-α (rs1800629), CDKAL1 (rs7754840, rs7756992), MTNR1B (rs10830963, rs1387153) polymorphisms are associated with an increased GDM risk.

Keywords: TNF-α, CDKAL1, MTNR1B, SNP, GDM, meta-analysis

Introduction

Abnormal glucose tolerance that first diagnosed in pregnant women is considered as GDM (Gestational Diabetes Mellitus), a type of metabolic disease [1, 2]. GDM has been one of the most common medical problems, and multiple environmental, social or genetic factors are related to the etiology and pathophysiology of GDM [3, 4]. A number of gene polymorphisms were reported to be involved in the occurrence, progression and prognosis of GDM [5-7]. In the present study, we targeted the SNPs of TNF-α, CDKAL1, MTNR1B gene and investigated their association with GDM susceptibility via literature-based meta-analysis.

TNF-α protein, encoding by TNF-α gene, is linked to cellular differentiation, apoptosis, and insulin resistance [8-10]. The rs1800629 (Y308) polymorphism in TNF-α gene has been identified as the risk factor for the occurrence of male infertility or non-Hodgkin lymphomas [11, 12]. CDKAL1 gene, locates in chromosome 6p22.3 and encodes the CDKAL1 protein, which is involved in the processes of tRNA decoration, glucose regulation and insulin secretion/action [13, 14]. Two intronic variants (rs7756992 and rs6931514) have been identified for CDKAL1 loci and were found to be associated with the susceptibility to T2DM (type 2 diabetes mellitus) [15]. MTNR1B gene locates on human chromosome 11q21–22, and encodes a melatonin receptor, which is related to insulin release, glucose tolerance and circadian rhythms [16, 17]. rs10830963 and rs1083-0962 were found in MTNR1B gene and might be associated with T2DM risks [18, 19].

Meta-analysis is efficient for the assessment of genetic effects by increasing the effective sample size [20]. Even though several previous meta-analyses on the association of TNF-α,

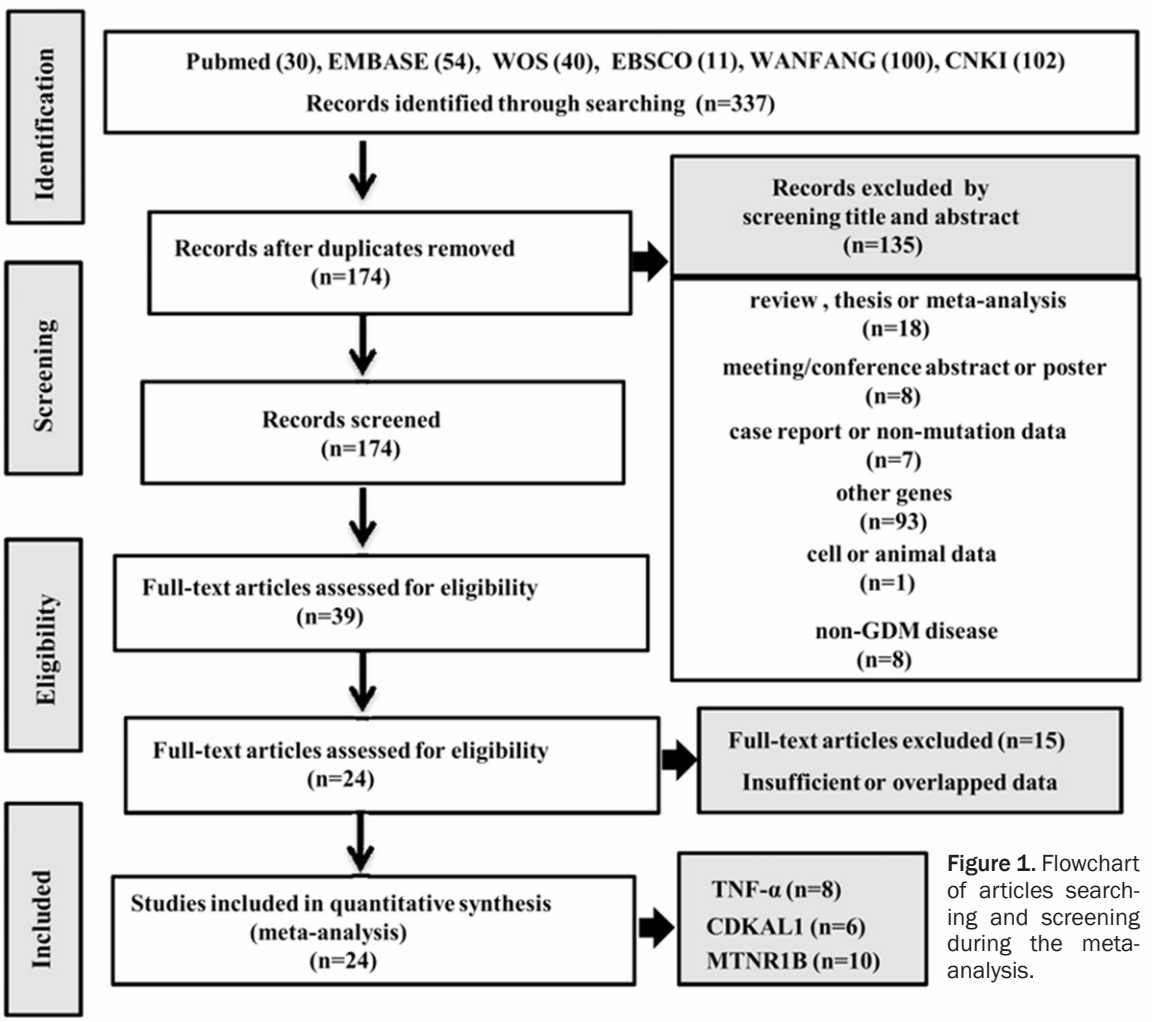

Figure 1. Flowchart of articles searching and screening during the meta-analysis.

CDKAL1, MTNR1B mutation and GDM risks have been reported respectively, an updated systematic meta-analysis is still required [18, 21, 22]. In addition, to our knowledge, no meta-analysis has been carried out to investigate the correlation between CDKAL1 rs7756992 polymorphism and GDM susceptibility. The present updated meta-analysis was thus performed. We found that there was a positive association between TNF-α (rs1800629), CDKAL1 (rs7754840, rs7756992), MTNR1B (rs10830963, rs1387153) and increased GDM risks.

Materials and methods

Article searching

The following databases, including PubMed, EMBASE (Excerpta Medica Database), WOS (Web of Science), EBSCO (Elton B. Stephens. Company), WANFANG and CNKI (Chinese National Knowledge Infrastructure), were systematically researched to obtain the articles (published until April. 25th, 2016) without any language limitation. In addition, the main index words, such as GDM, Gestational Diabetes Mellitus; polymorphism, mutation, SNP, Single Nucleotide Polymorphism; CDK5 regulatory subunit associated protein 1-like 1, CDKAL1; Tumor Necrosis Factor-alpha, TNF-alpha, TNF-α; melatonin receptor type 1B, Melatonin Receptor 1B, and MTNR1B, were utilized.

Exclusion and inclusion criteria

Our meta-analysis was performed under the modified guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [23]. After the initial retrieval, the articles were screened according to the exclusion and inclusion criteria. The exclusion criteria: duplicated articles; review, thesis,

Table 1. The characteristics of eligible studies in this meta-analysis

First author	Year	Country	Ethnicity	Gene	SNP	Case			Control			Source of controls	Method	HWE	
						AA	Aa	aa	AA	Aa	aa			χ^2	*P*
Chang [31]	2005	China	Asian	TNF-α	rs1800629	10	7	18	22	5	8	PB	PCR-RFLP	15.24	**0.00**
Cho [38]	2009	Korean	Asian	CDKAL1	rs7754840	171	389	303	178	319	133	PB	Taqman assay	0.20	0.65
					rs7756992	145	374	331	137	325	170	PB		0.62	0.43
Deng [44]	2011	China	Asian	MTNR1B	rs10830963	23	38	26	31	45	15	PB	PCR-DNA sequencing	0.04	0.84
Gueuvoghlanian-Silva [37]	2012	Brazil	Mixed	TNF-α	rs1800629	59	18	2	133	31	4	PB	PCR-RFLP	1.71	0.19
Guzman-Flores [9]	2013	Mexico	Caucasian	TNF-α	rs1800629	43	7	1	39	5	0	PB	PCR-RFLP	0.16	0.69
Hu [41]	2014	China	Asian	CDKAL1	rs7754840	61	65	50	101	42	42	PB	Multiplex SnaPshot	45.24	**0.00**
Huopio [47]	2013	Finland	Caucasian	MTNR1B	rs10830963	282[#]	251[&]		265[#]	142[&]		PB	Sequenom iPlex and TaqMan Assays	NA	>0.05
				MTNR1B	rs1387153	298[#]	235[&]		260[#]	147[&]		PB		NA	>0.05
Junior [52]	2015	Brazil	Caucasian	MTNR1B	rs10830963	102	61	20	113	66	4	PB	Real-time PCR with fluorescent probes	2.54	0.11
Kanthimathi [42]	2015	Idian	Asian	CDKAL1	rs7756992	258	182	52	556	306	48	PB	MassARRAY system	0.48	0.49
				CDKAL1	rs7754840	274	172	49	558	306	46	PB		0.23	0.63
Kim [45]	2015	Korea	Asian	MTNR1B	rs10830963	217	435	256	294	469	203	PB	Taqman assay	0.40	0.53
				MTNR1B	rs1387153	235	433	241	313	455	204	PB		2.61	0.11
Lauenborg [39]	2009	Denmark	Caucasian	CDKAL1	rs7756992	124	127	24	1229	929	181	PB	Taqman assay	0.09	0.77
Li [48]	2013	China	Asian	MTNR1B	rs10830963	113	158	79	172	233	75	PB	Direct sequencing	0.07	0.79
Liu [18]	2015	China	Asian	MTNR1B	rs10830963	162	334	178	195	362	117	PB	Taqman assay	5.31	**0.02**
					rs1387153	341	228	105	367	246	77	PB		12.39	**0.00**
Montazeri [36]	2010	Malaysia	Asian	TNF-α	rs1800629	103	4	3	94	6	2	PB	PCR-RFLP	13.89	**0.00**
Qi [49]	2013	China	Asian	MTNR1B	rs10830963	25	52	33	37	50	23	PB	PCR-DNA sequencing	0.63	0.43
Si [33]	2007	China	Asian	TNF-α	rs1800629	9	3	22	21	7	6	PB	PCR-RFLP	8.12	**0.00**
Vejrazkova [50]	2014	Czech	Caucasian	MTNR1B	rs10830963	169	227	62	206	184	32	PB	Taqman assay	1.08	0.30
Vlassi [46]	2012	Greece	Caucasian	MTNR1B	rs10830963	30	31	16	56	30	12	PB	Multiplex PCR-SNaPshot analysis	0.72	0.28
				MTNR1B	rs1387153	39	26	12	52	35	11	PB		1.76	0.18
Wang [51]	2011	China	Asian	CDKAL1	rs7754840	199	339	159	311	512	197	PB	Taqman assay	0.28	0.60
				MTNR1B	rs10830963	199	364	137	329	509	191	PB		0.06	0.81
Wang [40]	2014	China	Asian	MTNR1B	rs10830963	62	89	33	69	121	45	PB	PCR-RFLP	0.39	0.53
				MTNR1B	rs1387153	55	93	36	101	109	25	PB		0.30	0.58
Wu [43]	2015	China	Asian	CDKAL1	rs7754840	45	79	29	52	95	33	PB	PCR-RFLP	0.82	0.37
Yang [32]	2005	China	Asian	TNF-α	rs1800629	91	25	4	106	14	0	PB	PCR-RFLP	0.46	0.50
Zhang [35]	2008	China	Asian	TNF-α	rs1800629	8	19	3	19	11	0	PB	PCR-RFLP	1.51	0.22
Zhou [34]	2007	China	Asian	TNF-α	rs1800629	21	20	37	48	14	16	PB	PCR-RFLP	25.20	**0.00**

A: major allele; a: minor allele; [#]major allele frequency; [&]minor allele frequency; PB, population-based; NA: not available; HWE: Hardy-Weinberg Equilibrium; PCR-RFLP: polymerase chain reaction–restriction fragment length polymorphism; Significant *p* values are given in bold.

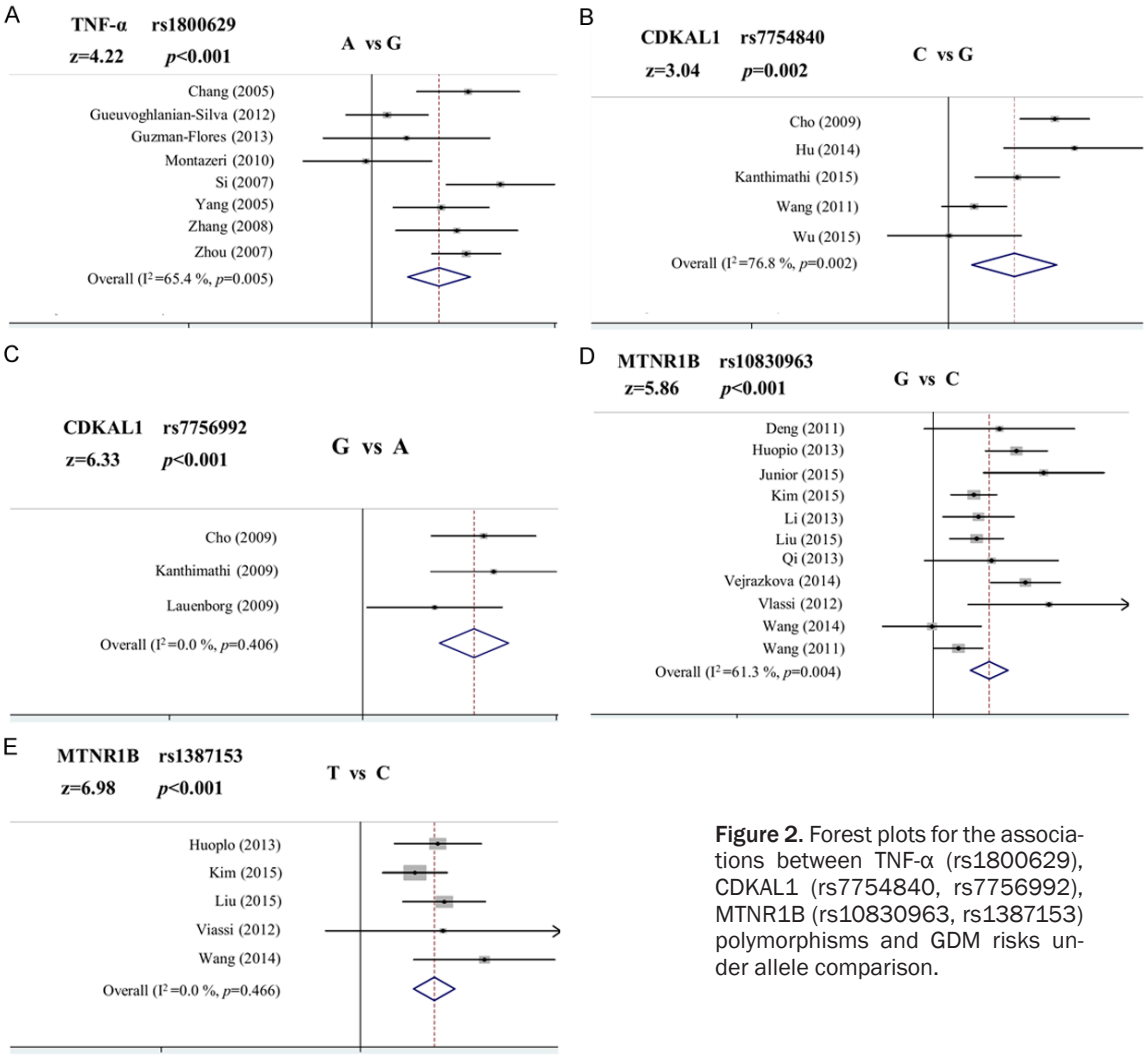

Figure 2. Forest plots for the associations between TNF-α (rs1800629), CDKAL1 (rs7754840, rs7756992), MTNR1B (rs10830963, rs1387153) polymorphisms and GDM risks under allele comparison.

meta-analysis; meeting/conference abstract, poster; case report or non-mutation data; other genes; cell or animal data; non-GDM disease; insufficient or overlapped data. The included eligible studies should contain the data on the allele or genotype frequencies of TNF-α, CDKAL1 and MTNR1B polymorphisms.

Data extraction

Three authors (Fang Gao, Jinxiu Xu and Guangya Wang) independently extracted the data from the selected articles and provided the relative characteristics information, including first author, year, country, ethnicity, gene, genotype frequencies in the case/control group, the source of control, genotyping method and Hardy-Weinberg Equilibrium (HWE) test in the control group. The other two authors (Dongxia Fu and Ningning Guo) were enrolled to resolve the disagreement during data extraction.

Statistical analysis

Mantel-Haenszel statistics via Stata/SE 12.0 (Stata Corporation, USA) were applied to calculate OR, 95% CI and *p* value. $p<0.05$ was regarded as statistically significant. The degree of heterogeneity among studies was evaluated via the Q test and I^2 values (0%~100%). The *p* value of Q test >0.10 or I^2 values<25% led to the utilization of fixed-effect model [24-27]. The combined ORs and *p* value were estimated for allele, homozygote, heterozygote, dominant, recessive and carrier comparisons, respectively. Subgroup analyses were also performed, based on ethnicity or HWE. In addition, Begg's test (Begg's funnel plot with pseudo 95% confi-

Table 2. Meta analysis for the association between TNF-α rs1800629 polymorphism and GDM risks

Comparison		Subgroup	Number (studies)	Test of association				Test of heterogeneity		Model
				OR	95% CI	z	*P*	I^2	*P*	
Allele	A vs G	Overall	8	2.50	1.63, 3.82	4.22	**<0.001**	65.4%	0.005	R
		Asian	6	3.04	2.01, 4.60	5.26	**<0.001**	53.2%	0.058	
		Caucasian	1	1.61	0.52, 4.99	0.82	0.412	-	-	
		HWE *p*>0.05	4	1.95	1.22, 3.12	2.81	**0.005**	36.0%	0.196	
		HWE *p*<0.05	4	3.07	1.64, 5.76	3.49	**<0.001**	70.5%	0.017	
Homozygote	AA vs GG	Overall	8	4.72	2.93, 7.62	6.36	**<0.001**	0.0%	0.484	F
		Asian	6	5.47	3.26, 9.17	6.44	**<0.001**	0.0%	0.625	
		Caucasian	1	2.72	0.11, 68.83	0.61	0.543	-	-	
		HWE *p*>0.05	4	3.62	1.24, 10.60	2.35	**0.019**	6.1%	0.363	
		HWE *p*<0.05	4	5.05	2.96, 8.63	5.93	**<0.001**	0.0%	0.430	
Heterozygote	GA vs GG	Overall	8	1.84	1.32, 2.56	3.59	**<0.001**	23.6%	0.241	F
		Asian	6	2.18	1.45, 3.28	3.73	**<0.001**	29.1%	0.217	
		Caucasian	1	1.27	0.37, 4.33	0.38	0.703	-	-	
		HWE *p*>0.05	4	1.81	1.20, 2.72	2.83	**0.005**	14.0%	0.322	
		HWE *p*<0.05	4	1.90	1.08, 3.34	2.22	**0.027**	46.8%	0.131	
Dominant	GA+AA vs GG	Overall	8	2.47	1.55, 3.94	3.80	**<0.001**	55.4%	0.082	R
		Asian	6	3.06	1.86, 5.04	4.39	**<0.001**	46.1%	0.098	
		Caucasian	1	1.45	0.44, 4.81	0.61	0.543	-	-	
		HWE *p*>0.05	4	2.02	1.18, 3.45	2.56	**0.011**	37.3%	0.188	
		HWE *p*<0.05	4	2.96	1.38, 6.36	2.78	**0.005**	63.3%	0.042	
Recessive	AA vs GG+GA	Overall	8	3.74	2.39, 5.86	5.76	**<0.001**	0.0%	0.548	F
		Asian	6	4.16	2.58, 6.71	5.83	**<0.001**	0.0%	0.589	
		Caucasian	1	2.64	0.11, 66.55	0.59	0.555	-	-	
		HWE *p*>0.05	4	3.04	1.02, 9.02	2.00	**0.046**	0.0%	0.499	
		HWE *p*<0.05	4	3.91	2.39, 6.40	5.42	**<0.001**	6.6%	0.360	
Carrier	Carrier A vs G	Overall	8	2.05	1.44, 2.93	3.94	**<0.001**	34.9%	0.150	R
		Asian	6	2.42	1.66, 3.53	4.60	**<0.001**	22.4%	0.265	
		Caucasian	1	1.41	0.43, 4.62	0.56	0.573	-	-	
		HWE *p*>0.05	4	1.65	1.12, 2.43	2.55	**0.011**	0.0%	0.572	
		HWE *p*<0.05	4	2.50	1.36, 4.61	2.94	**0.003**	51.2%	0.104	

F: fixed; R: random. HWE: Hardy-Weinberg Equilibrium; Significant *p* values are given in bold.

dence limits), Egger's test (Egger's publication bias plot) and sensitivity analysis were conducted to assess the potential publication bias and possible heterogeneity cause [28-30].

Results

The selection of eligible studies in the meta-analysis

Online electronic databases were researched to identify the relative articles in April 25th, 2016. And a total of 337 candidate articles, from PubMed (n=30), EMBASE (n=54), WOS (n=40), EBSCO (n=11), WANFANG (n=100) and CNKI (n=102), were retrieved initially. Next, the exclusion and inclusion criteria were utilized to select the eligible studies. 163 duplicated articles were removed. We screened title and abstract to exclude the following articles: Reviews, thesis or meta-analysis (n=18), meeting/conference abstract or poster (n=8), case report or non-mutation data (n=7), articles for other genes (n=93), article for cell or animal sample (n=1), and articles for other diseases (n=8). We then assessed the eligibility of 39 full-text articles by extracting independently the relative data. After 15 articles were excluded due to the insufficient or overlapped data, 24 eligible articles, including 8 articles for TNF-α [9, 31-37], 6 articles for CDKAL1 [38-43] and 10 articles for MTNR1B [18, 44-52], were

Table 3. Meta-analysis for the association between CDKAL1 rs7754840 and rs7756992 polymorphisms and GDM risks

SNP	Comparison	Number (studies)	Test of association				Test of heterogeneity		Model
			OR	95% CI	z	*P*	I^2	*P*	
rs7754840	C vs G	5	1.32	1.10, 1.58	3.04	**0.002**	76.8%	0.002	R
	CC vs GG	5	0.67	0.29, 1.53	0.95	0.343	96.4%	<0.001	R
	GC vs GG	5	1.24	0.98, 1.57	1.81	0.070	65.3%	0.021	R
	GC+CC vs GG	5	1.36	1.08, 1.72	2.61	**0.009**	69.6%	0.011	R
	CC vs GG+GC	5	1.53	1.16, 2.01	2.99	**0.003**	68.0%	0.014	R
	carrier C vs G	5	1.21	1.06, 1.38	2.89	**0.004**	41.8%	0.143	R
rs7756992	G vs A	3	1.37	1.24, 1.51	6.33	**<0.001**	0.0%	0.406	F
	GG vs AA	3	1.81	1.36, 2.40	4.09	**<0.001**	38.5%	0.197	R
	AG vs AA	3	1.24	1.07, 1.44	2.90	**0.004**	0.0%	0.502	F
	GA+AA vs GG	3	1.38	1.20, 1.58	4.48	**<0.001**	0.0%	0.929	F
	GG vs AA+AG	3	1.65	1.23, 2.21	3.33	**0.001**	52.9%	0.120	F
	Carrier G vs A	3	1.25	1.12, 1.40	3.92	**<0.001**	0.0%	0.773	F

F: fixed; R: random. Significant *p* values are given in bold.

involved in our meta-analysis. **Figure 1** showed the searching flowchart of relative articles, and **Table 1** presented the summarized characteristics of final eligible studies.

rs1800629 polymorphism of TNF-α and GDM risks

The meta-analysis for the genetic association between TNF-α rs1800629 polymorphism and susceptibility to GDM was first performed. As shown in **Figure 2A** and **Table 2**, the pooled result (Test of heterogeneity, I^2=65.4% and *p*=0.005) indicated that moderate heterogeneity among studies was present under the A vs G allele comparison. Random-effect model was thus applied. Compared with the control group, a significantly increased GDM risk was observed (**Figure 2A** and **Table 2**, Test of association, OR=2.50, z=4.22, *p*<0.001). Next, AA vs GG (homozygote), GA vs GG (heterozygote), GA+AA vs GG (dominant), AA vs GG+GA (recessive) and carrier A vs G (carrier) comparisons were then used in the meta-analysis. The GA+AA vs GG (I^2=55.4% and *p*=0.082), carrier A vs G (I^2=34.9% and *p*=0.150) data indicated the presence of between-study heterogeneity (**Table 2**). A random-effect model was thus used. The pooled results showed that increased GDM risks were observed under all genetic comparisons (**Table 2**, Test of association, all OR>1, all *p*<0.001). Moreover, the subgroup analyses under all comparisons were performed based on ethnicity and HWE. As shown in **Table 2**, a significantly increased GDM risk was observed in the Asian population (A vs G, OR=3.04, *p*<0.001; AA vs GG, OR=5.47, *p*<0.001; GA vs GG, OR=2.18, *p*<0.001; GA+AA vs GG, OR=3.06, *p*<0.001; AA vs GG+GA, OR=4.16, *p*<0.001; carrier A vs G, OR=2.42, *p*<0.001). The similar results were observed in HWE *p*>0.05 and *p*<0.05 subgroups (**Table 2**, Test of association, all OR>1, all *p*<0.05). These data demonstrated that TNF-α rs1800629 polymorphism is more likely to be associated with genetic susceptibility to GDM in the Asian population.

rs7754840, rs7756992 polymorphisms of CDKAL1 and GDM risks

A meta-analysis on the association between CDKAL1 polymorphisms (rs7754840 and rs7756992) and GDM risks was also performed. As shown in **Figure 2B** and **Table 3**, random-effect model was used for CDKAL1 rs7754840, due to the presence of moderate or high degree of heterogeneity (Test of heterogeneity, all I^2>25%). A significantly increased GDM risk was observed in the C vs G (Test of association, OR=1.32, *p*=0.002), GC+CC vs GG (OR=1.36, *p*=0.009), CC vs GG+GC (OR=1.53, *p*=0.003), carrier C vs G (OR=1.21, *p*=0.004), but not others. For CDKAL1 rs7756992, fixed-effect models were used for all comparisons, apart from GG vs AA comparison. A significantly increased GDM risk was observed in all genetic comparisons (**Figure 2C** and **Table 3**, Test of association, all OR>1, *p*<0.05). These data sug-

Table 4. Meta-analysis for the association between MTNR1B rs10830963 and rs1387153 polymorphisms and GDM risks

SNP	Comparison	Subgroup	No. of studies	Test of association				Test of heterogeneity		Model
				OR	95% CI	z	*P*	I^2	*P*	
rs10830963	G vs C	Overall	11	1.41	1.26, 1.58	5.86	**<0.001**	61.3%	0.004	R
		Asian	7	1.25	1.16, 1.35	5.79	**<0.001**	0.0%	0.581	
		Caucasian	4	1.75	1.54, 1.99	8.65	**<0.001**	0.0%	0.801	
	GG vs CC	Overall	10	1.72	1.37, 2.15	4.70	**<0.001**	56.2%	0.015	R
		Asian	7	1.52	1.23, 1.89	3.85	**<0.001**	48.7%	0.069	
		Caucasian	3	2.65	1.80, 3.91	4.92	**<0.001**	0.0%	0.374	
	CG vs CC	Overall	10	1.19	1.08, 1.32	3.42	**0.001**	8.7%	0.362	F
		Asian	7	1.15	1.02, 1.28	2.33	**0.020**	0.0%	0.633	
		Caucasian	3	1.40	1.12, 1.75	2.95	**0.003**	35.0%	0.215	
	CG+GG vs CC	Overall	10	1.31	1.16, 1.48	4.42	**<0.001**	28.0%	0.187	R
		Asian	7	1.24	1.10, 1.40	3.58	**<0.001**	12.9%	0.331	
		Caucasian	3	1.58	1.28, 1.95	4.23	**<0.001**	0.0%	0.401	
	GG vs CC+CG	Overall	10	1.53	1.26, 1.86	4.32	**<0.001**	54.5%	0.019	R
		Asian	7	1.41	1.17, 1.70	3.62	**<0.001**	49.7%	0.064	
		Caucasian	3	2.32	1.35, 3.97	3.06	**<0.001**	37.9%	0.200	
	Carrier G vs C	Overall	10	1.17	1.09, 1.26	4.32	**<0.001**	0.0%	0.665	F
		Asian	7	1.15	1.06, 1.24	3.36	**0.001**	0.0%	0.674	
		Caucasian	3	1.34	1.11, 1.60	3.11	**0.002**	0.0%	0.795	
rs1387153	T vs C	Overall	5	1.37	1.26, 1.50	6.98	**<0.001**	0.0%	0.466	F
		Caucasian	2	1.40	1.17, 1.67	3.74	**<0.001**	0.0%	0.937	
		Asian	3	1.36	1.23, 1.51	5.90	**<0.001**	43.2%	0.172	
	TT vs CC	Overall	4	1.61	1.34, 1.94	5.03	**<0.001**	0.0%	0.399	F
		Caucasian	1	1.45	0.58, 3.64	0.80	0.423	-	-	
		Asian	3	1.62	1.34, 1.95	4.97	**<0.001**	31.1%	0.234	
	CT vs CC	Overall	4	1.18	0.97, 1.43	1.69	0.092	31.3%	0.225	R
		Caucasian	1	0.99	0.51, 1.91	0.03	0.977	-	-	
		Asian	3	1.20	0.96, 1.51	1.60	0.109	51.3%	0.129	
	CT+TT vs CC	Overall	4	1.29	1.07, 1.56	2.71	**0.007**	37.0%	0.190	R
		Caucasian	1	1.10	0.61, 2.00	0.32	0.751	-	-	
		Asian	3	1.32	1.06, 1.65	2.48	**0.013**	55.6%	0.105	
	TT vs CC+CT	Overall	4	1.44	1.22, 1.70	4.36	**<0.001**	0.0%	0.605	F
		Caucasian	1	1.46	0.61, 3.52	0.84	0.399	-	-	
		Asian	3	1.44	1.22, 1.71	4.27	**<0.001**	0.0%	0.397	
	Carrier T vs C	Overall	4	1.17	1.05, 1.31	2.87	**0.004**	0.0%	0.746	F
		Caucasian	1	1.11	0.65, 1.89	0.37	0.714	-	-	
		Asian	3	1.17	1.05, 1.31	2.85	**0.004**	0.0%	0.554	

F: fixed; R: random. Significant *p* values are given in bold.

gested that both rs7754840 and rs7756992 polymorphism of CDKAL1 were linked to the increased GDM risks.

rs10830963, rs1387153 polymorphisms of MTNR1B and GDM risks

Next, we performed the meta-analysis for the association between rs10830963, rs1387153 polymorphisms of MTNR1B and GDM risks (**Figure 2D**, **2E** and **Table 4**). No or low degree of heterogeneity was obtained and fixed-effect model was thus used for CG vs CC (**Table 4**, Test of heterogeneity, I^2=8.7% and *p*=0.362) and carrier G vs C (I^2=0.0% and *p*=0.665) comparison. However, the random-effect model was used for others. The data of pooled analysis showed that the significantly increased

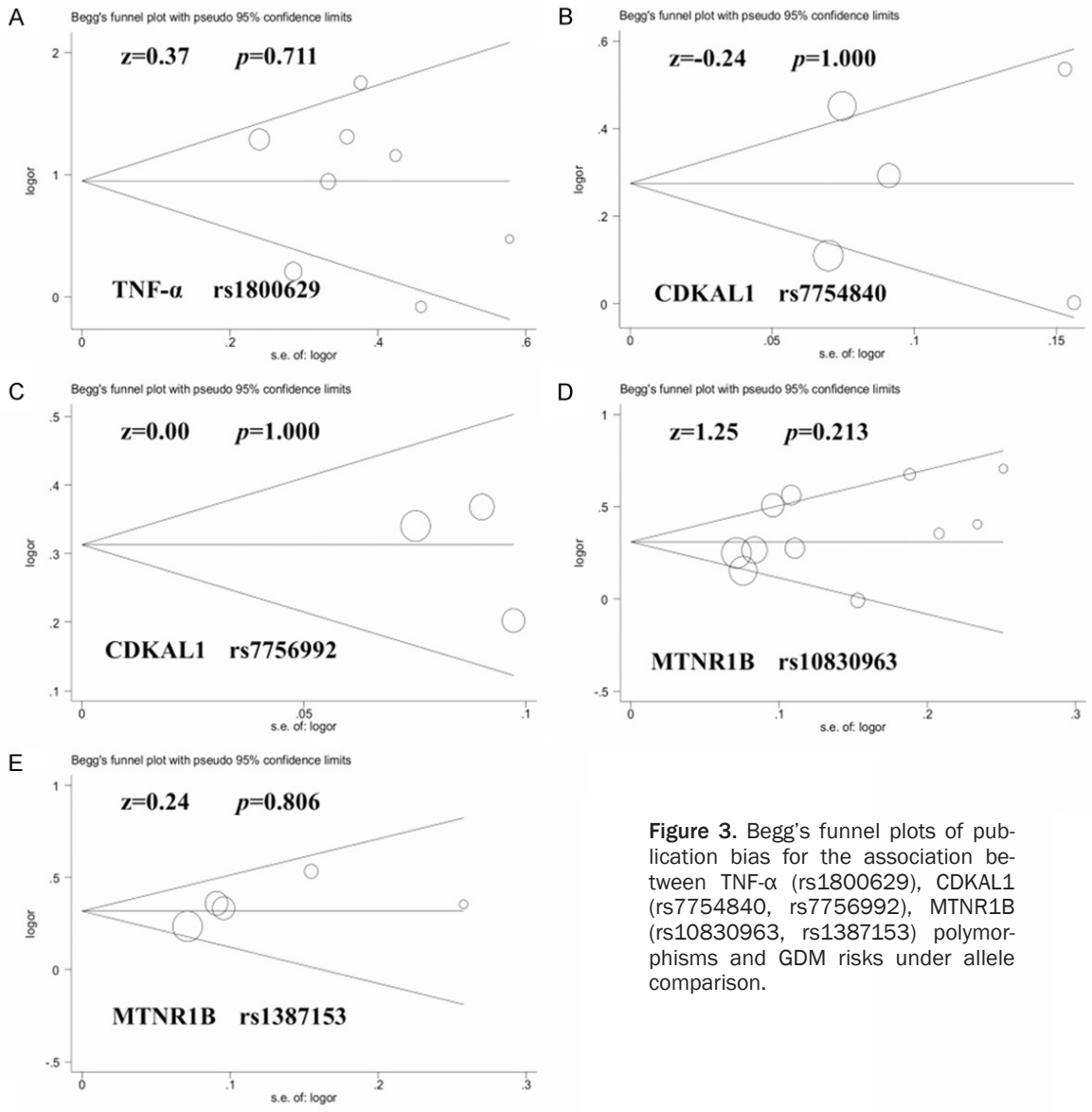

Figure 3. Begg's funnel plots of publication bias for the association between TNF-α (rs1800629), CDKAL1 (rs7754840, rs7756992), MTNR1B (rs10830963, rs1387153) polymorphisms and GDM risks under allele comparison.

GDM risks were detected in all genetic comparisons of MTNR1B rs10830963 in the overall population (**Figure 2D** and **Table 4**, Test of association, all OR>1, $p<0.05$). Moreover, the followed subgroup analysis based on ethnicity showed that the similar significant difference was observed in the Asian and Caucasian populations, which provided strong evidence for the positive correlation between MTNR1B rs10830963 and GDM risks. For MTNR1B rs1387153, fixed-effect model was used for the comparisons of T vs C, TT vs CC, TT vs CC+CT, and carrier T vs C (**Figure 2E** and **Table 4**, all $I^2<25\%$ and $p>0.1$) in the overall population. The data of meta-analysis showed that a significantly increased GDM risk was observed in the overall or Asian population under all genetic comparisons (**Figure 2E** and **Table 4**, Test of association, all OR>1, $p<0.05$), apart from the CT vs CC (Test of association, all $p>0.05$). These data suggested that rs10830963, rs1387153 polymorphisms of MTNR1B might be associated with the susceptibility to GDM.

Publication bias and sensitivity analysis

The potential publication bias among the above meta-analyses was investigated by Begg's test and Egger's test. As shown in **Figures 3**, **4** and **Table 5**, basically symmetric plot in Begg's test (MTNR1B rs10830963 GG vs CC, $p=0.049$; others $p>0.05$) and Egger's test (all $p>0.05$) indicated the absence of obvious publication

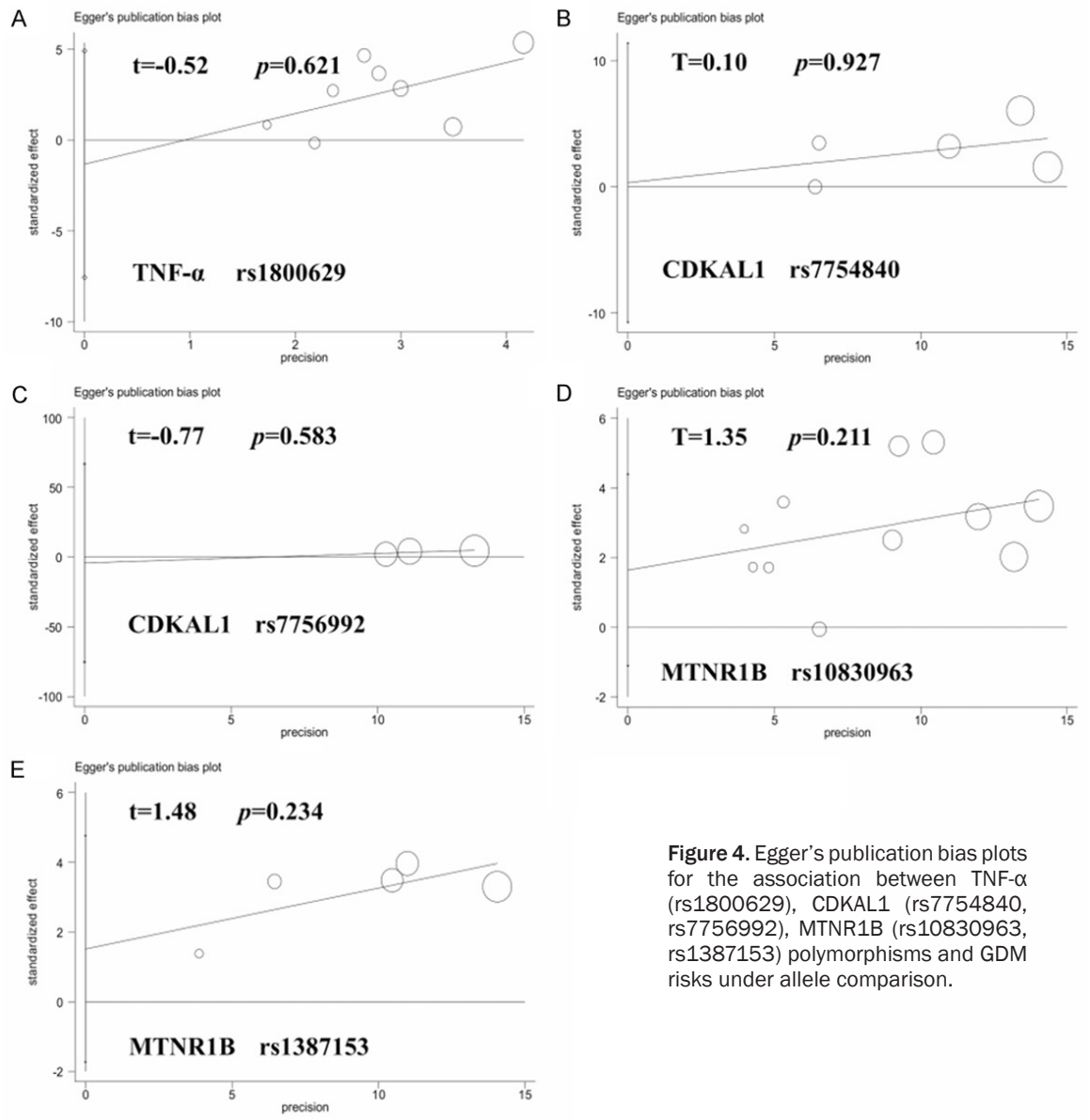

Figure 4. Egger's publication bias plots for the association between TNF-α (rs1800629), CDKAL1 (rs7754840, rs7756992), MTNR1B (rs10830963, rs1387153) polymorphisms and GDM risks under allele comparison.

bias. Furthermore, the results of sensitivity meta-analyses (**Figure 5** for allele model, and data for other models not shown) showed that similar results were observed, when each study was omitted at a time. There suggested that our conclusion was statistically stable and reliable.

Discussion

GG genotype of TNF-α rs1800629 polymorphism was linked to the increased insulin levels and insulin resistance in Mexican women with GDM [9]. However, the role of TNF-α rs1800629 polymorphism in the presence of GDM is still inconclusive. For examples, there is no association between TNF-α rs1800629 polymorphism and GDM risks in Malaysia patients [36]. To date, only one relative meta-analysis under allele comparison, containing 3 case-control studies, was performed previously by Zhang C. et al [53]. Here, 8 case-control studies were enrolled in our updated meta-analysis. Data of new 5 articles were added and analyzed [9, 32-35]. And the subgroup analysis based on the Asian/Caucasian population was performed. In addition, the homozygote, heterozygote, dominant, recessive and carrier comparisons were also detected. We found that an increased GDM risk was observed under all genetic com-

Table 5. The publication bias analysis of the included articles

Gene	SNP	Comparison	Begg's test#		Egger's test	
			z	*P*	t	*P*
TNF-α	rs1800629	A vs G	0.37	0.711	-0.52	0.621
		AA vs GG	-0.12	1.000	-0.40	0.700
		GA vs GG	0.12	0.902	-0.25	0.812
		GA+AA vs GG	0.12	0.902	0.24	0.816
		AA vs GG+GA	-0.12	1.000	-0.18	0.866
		Carrier A vs G	-0.12	1.000	-0.15	0.864
CDKAL1	rs7754840	C vs G	-0.24	1.000	0.10	0.927
		CC vs GG	0.73	0.462	-0.33	0.763
		GC vs GG	1.22	0.221	1.10	0.353
		GC+CC vs GG	0.73	0.462	0.54	0.624
		CC vs GG+GC	0.24	0.806	-0.36	0.744
		Carrier C vs G	0.24	0.806	0.28	0.795
CDKAL1	rs7756992	G vs A	0.00	1.000	-0.77	0.583
		GG vs AA	0.00	1.000	-0.27	0.831
		AG vs AA	0.00	1.000	-0.71	0.608
		GA+AA vs GG	1.04	0.296	-5.35	0.118
		GG vs AA+AG	0.00	1.000	-0.33	0.796
		Carrier G vs A	0.00	1.000	-0.68	0.622
MTNR1B	rs10830963	G vs C	1.25	0.213	1.35	0.211
		GG vs CC	1.97	0.049	1.39	0.201
		CG vs CC	0.00	1.000	0.13	0.897
		CG+GG vs CC	0.72	0.474	0.50	0.631
		GG vs CC+CG	1.25	0.210	1.52	0.166
		Carrier G vs C	1.43	0.152	1.08	0.313
MTNR1B	rs1387153	T vs C	0.24	0.806	1.48	0.234
		TT vs CC	0.34	0.734	0.71	0.552
		CT vs CC	-0.34	1.000	0.20	0.857
		CT+TT vs CC	-0.34	1.000	0.35	0.762
		TT vs CC+CT	0.34	0.734	1.26	0.335
		Carrier T vs C	-0.34	1.000	0.38	0.743

#Continuity corrected.

parisons in the Asian population with TNF-α rs1800629 polymorphism. Nevertheless, no association between TNF-α rs1800629 polymorphism and GDM risks was not observed in the meta-analysis of Zhang C. et al [53]. The more case-control studies or genetic comparison analysis might contribute to such difference. The followed Begg's test, Egger's test and sensitivity analyses further confirmed our conclusion.

Several studies on the role of CDKAL1 SNPs in the GDM risks have also been reported. For example, rs7754840 and rs7756992 of CDKAL1 gene were found to be associated with GDM risks in the South Indian population [42]. CDKAL1 rs7754840 may be related to GDM risks in Koreans [38]. The previous meta-analyses for CDKAL1 rs7754840 were reported in the data of Mao H. et al in 2012 [21] and Zhang C. et al in 2013 [53]. Only the allele comparison was employed in the previous meta-analysis of either 4 case-control studies of Mao H. et al or 3 studies of Zhang C. et al [21, 53]. Here, an updated meta-analysis based on 5 case-control studies was conducted under the allele, homozygote, heterozygote, dominant, recessive and carrier comparisons. Our results showed an significant association between CDKAL1 rs7754840 and increased GDM risks, which is partly in line with the previous conclusion [21, 53]. In addition, we first carried out the meta-analysis between CDKAL1 rs7756992 and GDM risks under all genetic comparisons. The significant association was also observed in the overall populations.

Several mutation analyses have been performed to investigate the relationship between MTNR1B mutations and GDM susceptibility. Forexample, MTNR1B rs10830963 was reported to be associated with an increased GDM risk in the Greek, Czech and Chinese populations [46, 48, 50]. Several related meta-analyses were published previously [18, 21, 22, 53]. For instance, Mao H. et al performed the meta-analyses of 4 case-control studies for MTNR1B rs10830963 under allele comparison [21], while Liu Q. el al performed the meta-analyses of 6 case-control studies for MTNR1B rs10830963 and 3 case-control studies for MTNR1B rs1387153 [18]. In our updated meta-analysis, 11 case-control studies were included for MTNR1B rs10830963, while 5 case-control studies were for MTNR1B rs1387153. The analyses, including subgroup analysis based on the Asian/Caucasian population, Begg's test, Egger's test and sensitivity detection, under all genetic comparisons were

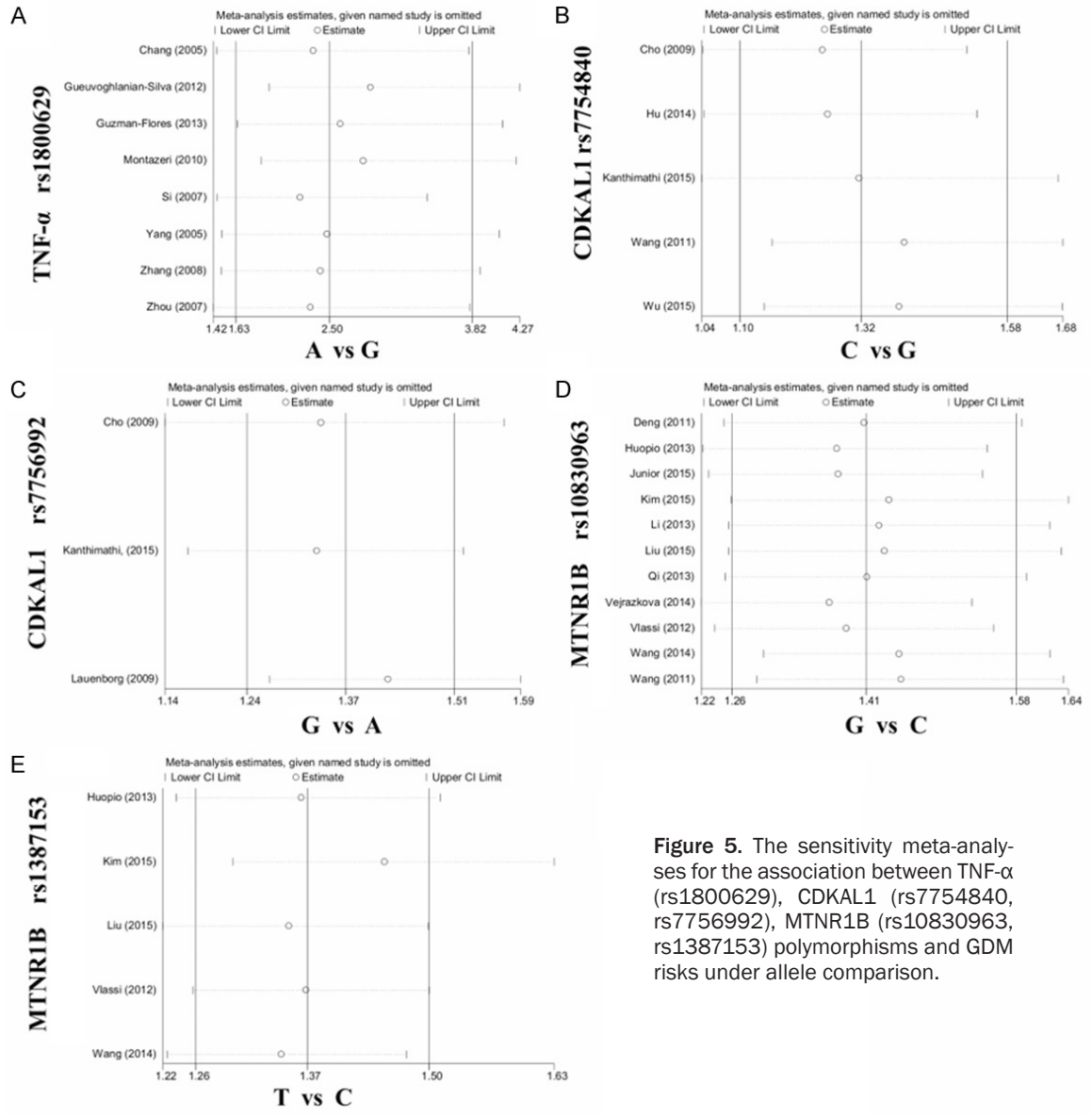

Figure 5. The sensitivity meta-analyses for the association between TNF-α (rs1800629), CDKAL1 (rs7754840, rs7756992), MTNR1B (rs10830963, rs1387153) polymorphisms and GDM risks under allele comparison.

also performed. Our data provided the evidence for the significant association between rs10830963, rs1387153 polymorphisms of MTNR1B and increased GDM risks, which further confirmed the previous conclusions [18, 21, 22, 53].

Some limitations are still present in our meta-analysis. There were small sample sizes included in our meta-analysis or subgroup analysis. For instance, only 3 case-control studies were enrolled in the meta-analysis for CDKAL1 rs7756992 polymorphism. We also sensed that only a few studies were in the Caucasian population for these measured SNPs. Five case-control studies for CDKAL1 rs7754840 were all in the Asian population. Subgroup analyses based on etiology, geography, gender, age or clinical features were not conducted, owing to the limitation of sample sizes. It is still possible that other unpublished or undetected studies are present, although we selected the eligible studies independently according to the exclusion and inclusion criteria. More studies with large sample sizes are warranted to confirm the conclusion in our meta-analysis.

Taken together, the present updated meta-analysis indicated that TNF-α (rs1800629), CDKAL1 (rs7754840, rs7756992), MTNR1B (rs10830963, rs1387153) polymorphisms seem to be the significant risks for GDM.

Disclosure of conflict of interest

None.

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