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SYSTEMATIC REVIEWS

KCNQ1 rs2237895 gene polymorphism increases susceptibility to type 2 diabetes mellitus in Asian populations

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Abstract

BACKGROUND

The association of single nucleotide polymorphism of *KCNQ1* gene rs2237895 with type 2 diabetes mellitus (T2DM) is currently controversial. It is unknown whether this association can be gene realized across different populations.

AIM

To determine the association of *KCNQ1* rs2237895 with T2DM and provide reliable evidence for genetic susceptibility to T2DM.

METHODS

We searched PubMed, Embase, Web of Science, Cochrane Library, Medline, Baidu Academic, China National Knowledge Infrastructure, China Biomedical Literature Database, and Wanfang to investigate the association between *KCNQ1* gene rs2237895 and the risk of T2DM up to January 12, 2022. Review Manager 5.4 was used to analyze the association of the *KCNQ1* gene rs2237895 polymorphism with T2DM and to evaluate the publication bias of the selected literature.

RESULTS

Twelve case–control studies (including 11273 cases and 11654 controls) met our inclusion criteria. In the full population, allelic model [odds ratio (OR): 1.19; 95% confidence interval (95%CI): 1.09–1.29; $P < 0.0001$], recessive model (OR: 1.20; 95%CI: 1.11–1.29; $P < 0.0001$), dominant model (OR: 1.27. 95%CI: 1.14–1.42; $P <$

0.0001), and codominant model (OR: 1.36; 95%CI: 1.15–1.60; *P* = 0.0003) (OR: 1.22; 95%CI: 1.10–1.36; *P* = 0.0002) indicated that the *KCNQ1* gene rs2237895 polymorphism was significantly correlated with susceptibility to T2DM. In stratified analysis, this association was confirmed in Asian populations: allelic model (OR: 1.25; 95%CI: 1.13–1.37; *P* < 0.0001), recessive model (OR: 1.29; 95%CI: 1.11–1.49; *P* = 0.0007), dominant model (OR: 1.35; 95%CI: 1.20–1.52; *P* < 0.0001), codominant model (OR: 1.49; 95%CI: 1.22–1.81; *P* < 0.0001) (OR: 1.26; 95%CI: 1.16–1.36; *P* < 0.0001). In non-Asian populations, this association was not significant: Allelic model (OR: 1.06, 95%CI: 0.98–1.14; *P* = 0.12), recessive model (OR: 1.04; 95%CI: 0.75–1.42; *P* = 0.83), dominant model (OR: 1.06; 95%CI: 0.98–1.15; *P* = 0.15), codominant model (OR: 1.08; 95%CI: 0.82–1.42; *P* = 0.60. OR: 1.15; 95%CI: 0.95–1.39; *P* = 0.14).

CONCLUSION

KCNQ1 gene rs2237895 was significantly associated with susceptibility to T2DM in an Asian population. Carriers of the C allele had a higher risk of T2DM. This association was not significant in non-Asian populations.

Key Words: Type 2 diabetes mellitus; KCNQ1; rs2237895; Single nucleotide polymorphism; Asian populations

Core Tip: In Asian populations, the rs2237895 polymorphism in the *KCNQ1* gene was significantly associated with susceptibility to type 2 diabetes mellitus (T2DM), and C allele carriers had an increased risk of developing T2DM. The CC and AC genotypes of *KCNQ1* rs2237895 significantly increased the susceptibility to T2DM. In non-Asian populations, this association was not significant.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a common multifactorial, metabolic disease whose pathogenesis is influenced by a combination of genetic and environmental factors. The rise and large-scale application of genome-wide association studies have contributed to the understanding of genetic factors related to T2DM. T2DM remains a health problem that plagues the world to this day. As of January 4, 2021, the number of people with diabetes worldwide had reached 537 million. Even more alarmingly, this number is expected to increase to 643 million by 2030. The various expenditures due to diabetes have exceeded $966 billion, and this figure has grown at an annual rate of 63% since 2006[1]. The etiology of T2DM is complex and has not yet been fully elucidated. T2DM is characterized by defective insulin secretion and reduced sensitivity, leading to chronic hyperglycemia and severe metabolic dysfunction in patients[2,3]. Hyperglycemia affects the physiological function of several tissues and organs in the body, among which the most common are neuropathy and vascular complications[1].

Studies have not provided an accurate description of the etiology of T2DM, and a genome-wide scan of Japanese by Nawata *et al*[4] showed that *KCNQ1* is a susceptibility gene for T2DM in Japan. In addition, genes such as *ADRA2A, KCNJ11 and CDKAL1* may be associated with the development of T2DM[4,5]. *KCNQ1* is a potassium channel subunit that is mainly found in adipose and pancreatic tissues. It was found that *KCNQ1* affects the process of islet β-cell depolarization by regulating potassium channel currents, thereby limiting insulin secretion from pancreatic β-cells and leading to the development of T2DM[6].

Previous studies have found that C allele carriers of the *KCNQ1* gene rs2237895 may have an increased risk of developing T2DM[7]. rs2237895 is present in three genotypes in the population, AA, AC and CC. The A gene is wild type and the C gene is mutant, and their gene frequencies in the population are approximately 66% and 34%[8]. A study by Cui *et al*[7] in Kazakhs living in China showed that rs2237895 single nucleotide polymorphism (SNP) of *KCNQ1* gene was not significantly associated with T2DM. A study by Afshardoost *et al*[9] on Iranians also showed no significant association between rs2237895 and T2DM; while in a study by Khan *et al*[10] on Indians, they confirmed a significant association between the SNP of rs2237895 and T2DM. Previously, a similar study has been conducted by Sun *et al*[11], but we consider that their inclusion criteria were more lenient and the strength of the proof may be weakened. Meanwhile, their work was > 10 years old and many new studies have been published during this period and that meta-analysis is in urgent need of updating. To address the above issues, we performed the present meta-analysis.

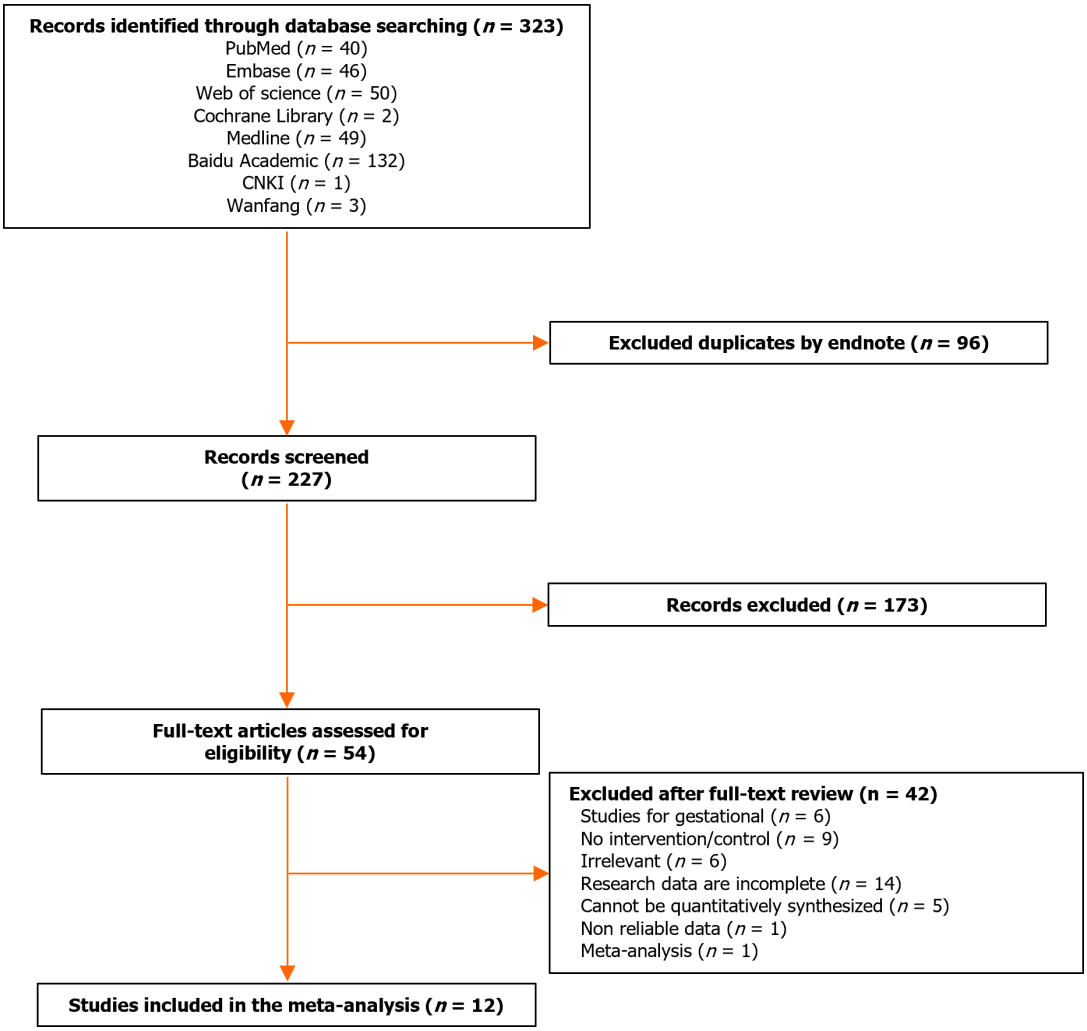


Figure 1 Literature screening process.

MATERIALS AND METHODS

Literature search

The following nine electronic databases were searched: PubMed, Embase, Web of Science, Cochrane Library, Medline, Baidu Academic, China National Knowledge Infrastructure (CNKI), China Biomedical Literature Database (CBM), and Wanfang Database, with the following search formulas: Subject (T2DM) and keywords (KCNQ1) and keywords (rs2237895). The last search date was January 12, 2022. Chinese and English literature on the association of the rs2237895 SNP in the *KCNQ1* gene with T2DM was collected. The inclusion criteria for the articles were: (1) T2DM patients in the case group met the diagnostic criteria for diabetes published by WHO in 1999 or American Diabetes Association in 2010; (2) the type of experiment was a case–control study or a cohort study; (3) there was sufficient information in the text to describe the genotype and allele frequencies of the case and control groups; (4) the patients in the control group all met the Hardy–Weinberg genetic equilibrium model; (5) patients were randomly selected with no special restrictions on age, sex, or family history; and (6) for duplicate or data-identical literature, the one with the most complete information. Exclusion criteria were: (1) Incomplete study data; (2) literature reviews; (3) studies with gestational diabetes as an endpoint; and (4) exclusion of studies with familial diabetes as a basis.

Data extraction

Two researchers independently performed literature screening and extraction of information based on the above criteria. A third researcher was required to discuss and agree on the results when difficult differences were encountered. For each article, we collected the basic information that needed to be used for Meta-analysis, and the literature screening process is shown in Figure 1.

Statistical analysis

The data were processed using Review Manager 5.4. The strength of association between SNPs in the *KCNQ1* gene rs2237895 and the risk of T2DM was assessed using the odds ratio (OR) and its corresponding 95% confidence interval (95%CI) as a criterion in the data statistics. The forest plots were used to show the OR and its 95%CI for each study. The

Table 1 Characteristics of the included literature

Ref.	Ethnicity	*N*		Age (yr)		Case			Control		
		Case	Control	Case	Control	AA	AC	CC	AA	AC	CC
Cui *et al*[7], 2016	Kazakh	100	100	51.21 ± 11.60	49.85 ± 12.41	40	49	11	32	51	17
Khan *et al*[10], 2020	Indian	300	100	40.33 ± 9.76	35.29 ± 7.96	90	153	57	50	36	14
Liu *et al*[12], 2009	Chinese	1885	1994	63.9 ± 9.50	58.10 ± 9.40	790	886	209	942	883	169
Zhang[13], 2010	Chinese	100	97	63.90 ± 9.50	58.1 ± 9.40	25	36	39	43	34	20
Dai *et al*[14], 2012	Chinese	367	214	49.13 ± 10.79	47.55 ± 10.93	134	168	65	99	87	28
Li *et al*[15], 2020	Chinese	1194	1292	52.49 ± 12.10	52.70 ± 10.52	509	568	117	621	552	119
Hu *et al*[16], 2021	Chinese	277	279	52.26 ± 9.49	52.26 ± 9.49	121	123	33	145	113	21
Saif-Ali *et al*[17], 2011	Malaysian	300	230	49.80 ± 7.42	52.90 ± 9.15	123	147	30	120	96	14
Almawi *et al*[18], 2013	Arabs	995	1076	58.6 ± 13.40	57.30 ± 10.40	324	497	174	413	511	152
Al-Shammari *et al*[19], 2017	Arabs	320	516	51.50 ± 8.75	48.75 ± 6.85	122	150	58	202	223	91
van Vliet-Ostaptchouk *et al*[20], 2012	Dutch	4549	5182	64.36 ± 10.6	51.16 ± 10.10	1522	2158	869	1803	2516	863
Turki *et al*[21], 2012	Arabs	886	574	61.20 ± 9.70	52.00 ± 11.9	350	429	107	233	261	80

pooled results were directly observed on the forest plots. The difference was considered significant when the 95%CI did not include 1. Allelic model (C *vs* A), recessive model (CC *vs* AA + AC), dominant model (CC + AC *vs* AA) and codominant model (CC *vs* AA and AC *vs* AA) were used to assess the genetic effects of the genes. The significance level was set at $P < 0.05$. The random-effect model was used to calculate the effect size when the heterogeneity was $I^2 > 50\%$, and the fixed-effect model was used when I^2 was < 50%. Publication bias was assessed by Egger's test and funnel plot. In the funnel plot, the dashed line perpendicular to the horizontal axis indicated the combined effect size. It suggested that the studies were without publication bias when the distribution of studies in the funnel plot was approximately symmetrical.

RESULTS

According to the research strategy, 323 relevant papers were retrieved from the databases. Some duplicates were found and we removed them by Endnote software. We also screened the citations of the paper to ensure the comprehensiveness of the search. After a stepwise screening process, 12 eligible papers were finally included for meta-analysis, which included 11273 patients with T2DM and 11654 controls. Five of the datasets were from China[12-16], five from the rest of Asia[7,10,17-19], one from Europe[20], and one from Africa[21]. The basic information of the studies is shown in Table 1.

The 12 datasets that met the inclusion criteria were pooled for meta-analysis, and allelic, recessive, dominant, and codominant models were used to investigate the association of rs2237895 with T2DM. Since the study population was predominantly Asian, we performed stratified analysis of Asian and non-Asian populations (Figure 2 and Figure 3).

In the full population, allelic model (OR: 1.19; 95%CI: 1.09–1.29; $P < 0.0001$), recessive model (OR: 1.20; 95%CI: 1.11–1.29; $P < 0.0001$), dominant model (OR: 1.27. 95%CI: 1.14–1.42; $P < 0.0001$), and codominant model (OR: 1.36; 95%CI: 1.15–1.60; $P = 0.0003$. OR: 1.22; 95%CI: 1.10–1.36; $P = 0.0002$) all showed significant association between rs2237895 and T2DM. In the subgroup of the Asian population, allelic model (OR: 1.25; 95%CI: 1.13–1.37; $P < 0.0001$), recessive model (OR: 1.29; 95%CI: 1.11–1.49; $P = 0.0007$), dominant model (OR: 1.35; 95%CI: 1.20–1.52; $P < 0.0001$), and codominant model (OR: 1.49; 95%CI: 1.22–1.81; $P < 0.0001$. OR: 1.26; 95% CI: 1.16–1.36; $P < 0.0001$) also showed a significant association between rs2237895 and T2DM, which was consistent with the whole population. C allele carriers had an increased risk of developing T2DM. The CC and AC genotypes significantly increased the risk of T2DM compared to the AA genotype. However, in the non-Asian population subgroup, allelic model (OR: 1.06; 95%CI: 0.98–1.14; $P = 0.12$), recessive model (OR: 1.04; 95%CI: 0.75–1.42; $P = 0.83$), dominant model (OR: 1.06; 95%CI: 0.98–1.15; $P = 0.15$), and codominant model (OR: 1.08; 95%CI: 0.82–1.42; $P = 0.60$) (OR: 1.15; 95%CI: 0.95–1.39; $P = 0.14$) all showed no significant association between rs2237895 and T2DM.

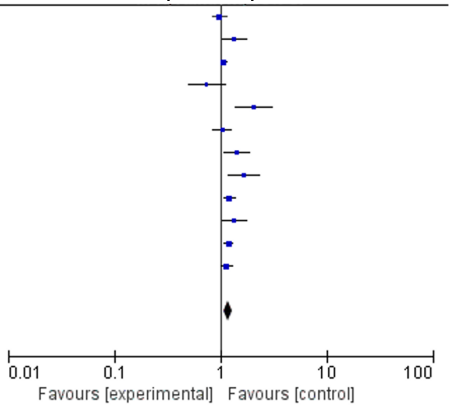
The funnel plots showed no significant publication bias was found in the meta-analysis (Figure 4 and Figure 5). Egger's test showed no significant publication bias for the allelic model ($t = 1.84$, $P = 0.095$), recessive model ($t = 0.48$, $P = 0.64$), dominant model ($t = 1.44$, $P = 0.18$), and codominant model ($t = 1.33$, $P = 0.21$; $t = 1.79$, $P = 0.10$).

We performed a sensitivity analysis. After sequentially excluding one study in the allelic model, recessive model, dominant model, and codominant model, we calculated the pooled effect sizes for the remaining studies. By calculation, no qualitative change occurred between the pooled results of the remaining studies and the original results. Sensitivity analysis proved that the results of the meta-analysis were reliable.

A

Study or subgroup	T2DM Events	T2DM Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95%CI
Amira Turki 2012	643	1772	421	1148	10.2%	0.98 [0.84, 1.15]
Fulan Hu 2021	189	554	155	558	6.4%	1.35 [1.04, 1.74]
Jana V. van Vliet-Ostaptchouk 2012	3896	9098	4242	10364	14.7%	1.08 [1.02, 1.14]
L.J. Cui 2016	71	200	85	200	3.4%	0.74 [0.50, 1.11]
Li Zhang 2010	114	200	77	197	3.4%	2.07 [1.38, 3.08]
Maha S. Al-Shammari 2017	266	660	405	1032	8.3%	1.05 [0.86, 1.28]
Riyadh Saif-Ali 2011	207	600	124	460	6.0%	1.43 [1.09, 1.86]
Vasiuddin Khan 2020	264	600	64	200	4.4%	1.67 [1.19, 2.34]
Wassim Y. Almawi 2013	845	1990	815	2152	11.7%	1.21 [1.07, 1.37]
Xing-Ping Dai 2012	298	734	143	428	6.5%	1.36 [1.06, 1.75]
Y. Liu 2009	1304	3770	1221	3988	13.1%	1.20 [1.09, 1.32]
Yiping Li 2020	802	2388	790	2584	11.9%	1.15 [1.02, 1.29]
Total (95% CI)		**22566**		**23311**	**100.0%**	**1.19 [1.09, 1.29]**
Total events	8899		8542			

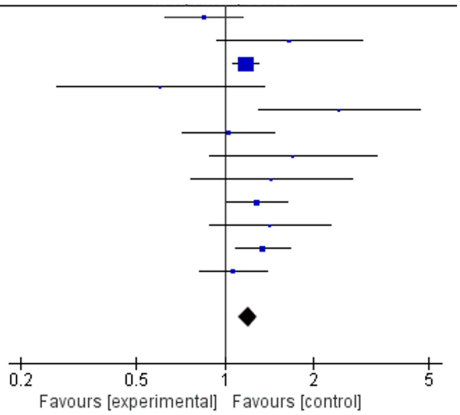
Heterogeneity: Tau² = 0.01; Chi² = 33.54, df = 11 (P = 0.0004); I² = 67%
Test for overall effect: Z = 4.09 (P < 0.0001)



B

Study or subgroup	T2DM Events	T2DM Total	Control Events	Control Total	Weight	Odds ratio M-H, fixed, 95%CI
Amira Turki 2012	107	886	80	574	6.7%	0.85 [0.62, 1.16]
Fulan Hu 2021	33	277	21	279	1.5%	1.66 [0.94, 2.95]
Jana V. van Vliet-Ostaptchouk 2012	869	4549	863	5182	51.4%	1.18 [1.07, 1.31]
L.J. Cui 2016	11	100	17	100	1.2%	0.60 [0.27, 1.36]
Li Zhang 2010	39	100	20	97	1.0%	2.46 [1.30, 4.65]
Maha S. Al-Shammari 2017	58	320	91	516	4.5%	1.03 [0.72, 1.49]
Riyadh Saif-Ali 2011	30	300	14	230	1.1%	1.71 [0.89, 3.31]
Vasiuddin Khan 2020	57	300	14	100	1.3%	1.44 [0.76, 2.72]
Wassim Y. Almawi 2013	174	995	152	1076	9.5%	1.29 [1.02, 1.63]
Xing-Ping Dai 2012	65	367	28	214	2.3%	1.43 [0.89, 2.31]
Y. Liu 2009	209	1885	169	1994	11.5%	1.35 [1.09, 1.67]
Yiping Li 2020	117	1194	119	1292	8.1%	1.07 [0.82, 1.40]
Total (95% CI)		**11273**		**11654**	**100.0%**	**1.20 [1.11, 1.29]**
Total events	1769		1588			

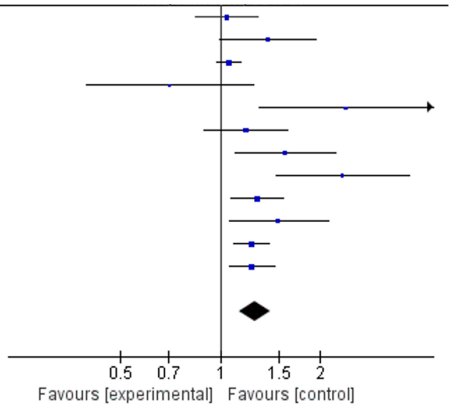
Heterogeneity: Chi² = 18.51, df = 11 (P = 0.07); I² = 41%
Test for overall effect: Z = 4.82 (P < 0.00001)



C

Study or subgroup	T2DM Events	T2DM Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95%CI
Amira Turki 2012	536	886	341	574	10.2%	1.05 [0.84, 1.30]
Fulan Hu 2021	156	277	134	279	6.7%	1.40 [1.00, 1.95]
Jana V. van Vliet-Ostaptchouk 2012	3027	4549	3379	5182	15.0%	1.06 [0.98, 1.15]
L.J. Cui 2016	60	100	68	100	3.0%	0.71 [0.40, 1.26]
Li Zhang 2010	75	100	54	97	2.8%	2.39 [1.31, 4.37]
Maha S. Al-Shammari 2017	208	320	314	516	7.8%	1.19 [0.89, 1.60]
Riyadh Saif-Ali 2011	177	300	110	230	6.4%	1.57 [1.11, 2.22]
Vasiuddin Khan 2020	210	300	50	100	4.3%	2.33 [1.47, 3.71]
Wassim Y. Almawi 2013	671	995	663	1076	11.5%	1.29 [1.08, 1.55]
Xing-Ping Dai 2012	233	367	115	214	6.5%	1.50 [1.06, 2.11]
Y. Liu 2009	1095	1885	1052	1994	13.5%	1.24 [1.09, 1.41]
Yiping Li 2020	685	1194	671	1292	12.3%	1.25 [1.06, 1.46]
Total (95% CI)		**11273**		**11654**	**100.0%**	**1.27 [1.14, 1.42]**
Total events	7133		6951			

Heterogeneity: Tau² = 0.02; Chi² = 31.32, df = 11 (P = 0.0010); I² = 65%
Test for overall effect: Z = 4.21 (P < 0.0001)



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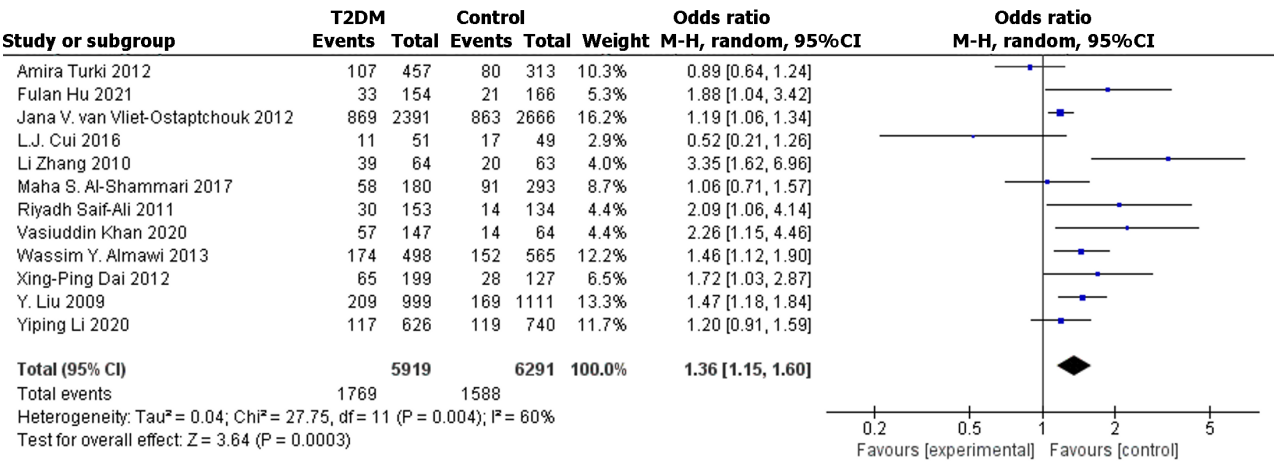

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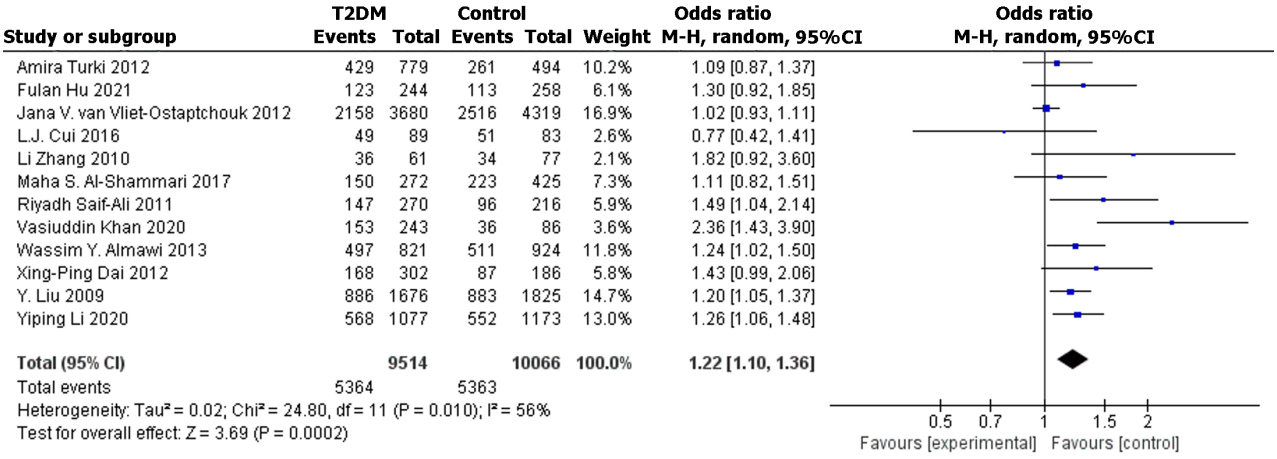


Figure 2 The forest plot of different model. A: Allelic model; B: Recessive model; C: Dominant model; D: Co-dominant model (CC *vs* AA); E: Co-dominant model (AC *vs* AA). T2DM: Type 2 diabetes mellitus.

DISCUSSION

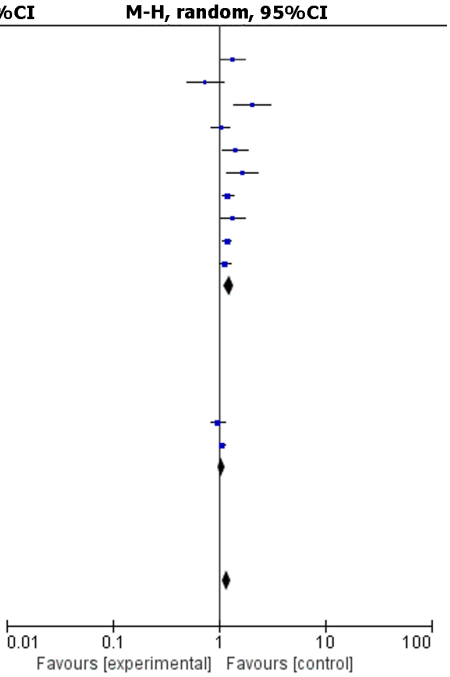
Compared with previous studies, we increased the inclusion criteria of cases, excluded the interference of other factors (*e.g.*, gestational diabetes), improved the strength of proof of the study, and made the results more reliable and stable. Our meta-analysis supported the findings of Khan *et al*[10], suggesting that the rs2237895 SNP in the *KCNQ1* gene is significantly associated with the development of T2DM in Asian populations. In the study by Cui *et al*[7], the study population had an overall overweight problem, which increased the risk of T2DM prevalence and thus confounded the findings[22].

T2DM is a multifactorial, chronic, metabolic disease[23]. The idea that genetic factors have a significant role in the development of T2DM is now more widely accepted[23], although only a few genes have been confirmed as a risk for the development of T2DM. However, many genetic characteristics associated with T2DM, such as effect sizes and risk allele frequencies, need to be explored[24]. There is a need for researchers to identify risk genetic loci for T2DM and characterize the variation at the loci, thus providing a basis for elucidating the genetic pathogenesis of T2DM.

Previous studies have shown that the *KCNQ1*, *miR-21*, and *Arg972* may be risk genes for T2DM[25,26]. *KCNQ1* gene has now been shown to be located on chromosome 11p15.5, which is approximately 400 kb in length and consists of 17 exons ranging from 47 to 1122 bp in length[27]. *KCNQ1* is associated with voltage-gated K^+ channels, and mutations in the *KCNQ1* gene lead to dysfunction of K^+ channels, which would cause diseases such as QT syndrome and familial atrial fibrillation. *KCNQ1* is expressed in many tissues[27,28], and the more studied about the *KCNQ1* gene is expressed in cardiac and pancreatic tissues[29]. Current studies suggest that the main mechanisms of T2DM development are insulin resistance and islet β-cell dysfunction[2,23]. Variants in the *KCNQ1* gene may lead to increased susceptibility to T2DM in the population by altering insulin secretion from pancreatic β-cells[30,31]. It was hypothesized that variants in the *KCNQ1* gene would lead to increased expression of *KCNQ1* protein on pancreatic β-cells, which in turn would alter the open state of voltage-gated potassium channels, decrease insulin secretion, and impair glucose storage and utilization[32].

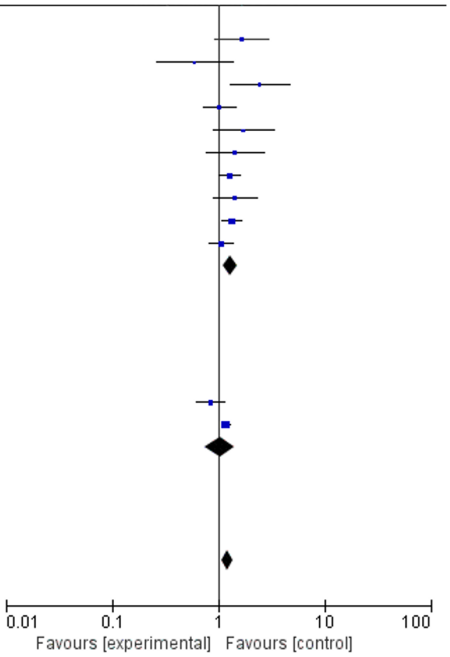
A

Study or subgroup	T2DM Events	T2DM Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95%CI
1.2.1 Asian						
Fulan Hu 2021	189	554	155	558	6.4%	1.35 [1.04, 1.74]
L.J. Cui 2016	71	200	85	200	3.4%	0.74 [0.50, 1.11]
Li Zhang 2010	114	200	77	197	3.4%	2.07 [1.38, 3.08]
Maha S. Al-Shammari 2017	266	660	405	1032	8.3%	1.05 [0.86, 1.28]
Riyadh Saif-Ali 2011	207	600	124	460	6.0%	1.43 [1.09, 1.86]
Vasiuddin Khan 2020	264	600	64	200	4.4%	1.67 [1.19, 2.34]
Wassim Y. Almawi 2013	845	1990	815	2152	11.7%	1.21 [1.07, 1.37]
Xing-Ping Dai 2012	298	734	143	428	6.5%	1.36 [1.06, 1.75]
Y. Liu 2009	1304	3770	1221	3988	13.1%	1.20 [1.09, 1.32]
Yiping Li 2020	802	2388	790	2584	11.9%	1.15 [1.02, 1.29]
Subtotal (95% CI)		**11696**		**11799**	**75.1%**	**1.25 [1.13, 1.37]**
Total events	4360		3879			
Heterogeneity: Tau² = 0.01; Chi² = 21.78, df = 9 (P = 0.010); I² = 59%						
Test for overall effect: Z = 4.38 (P < 0.0001)						
1.2.2 Non-Asian						
Amira Turki 2012	643	1772	421	1148	10.2%	0.98 [0.84, 1.15]
Jana V. van Vliet-Ostaptchouk 2012	3896	9098	4242	10364	14.7%	1.08 [1.02, 1.14]
Subtotal (95% CI)		**10870**		**11512**	**24.9%**	**1.06 [0.98, 1.14]**
Total events	4539		4663			
Heterogeneity: Tau² = 0.00; Chi² = 1.27, df = 1 (P = 0.26); I² = 21%						
Test for overall effect: Z = 1.56 (P = 0.12)						
Total (95% CI)		**22566**		**23311**	**100.0%**	**1.19 [1.09, 1.29]**
Total events	8899		8542			
Heterogeneity: Tau² = 0.01; Chi² = 33.54, df = 11 (P = 0.0004); I² = 67%						
Test for overall effect: Z = 4.09 (P < 0.0001)						
Test for subgroup differences: Chi² = 6.55, df = 1 (P = 0.01), I² = 84.7%						

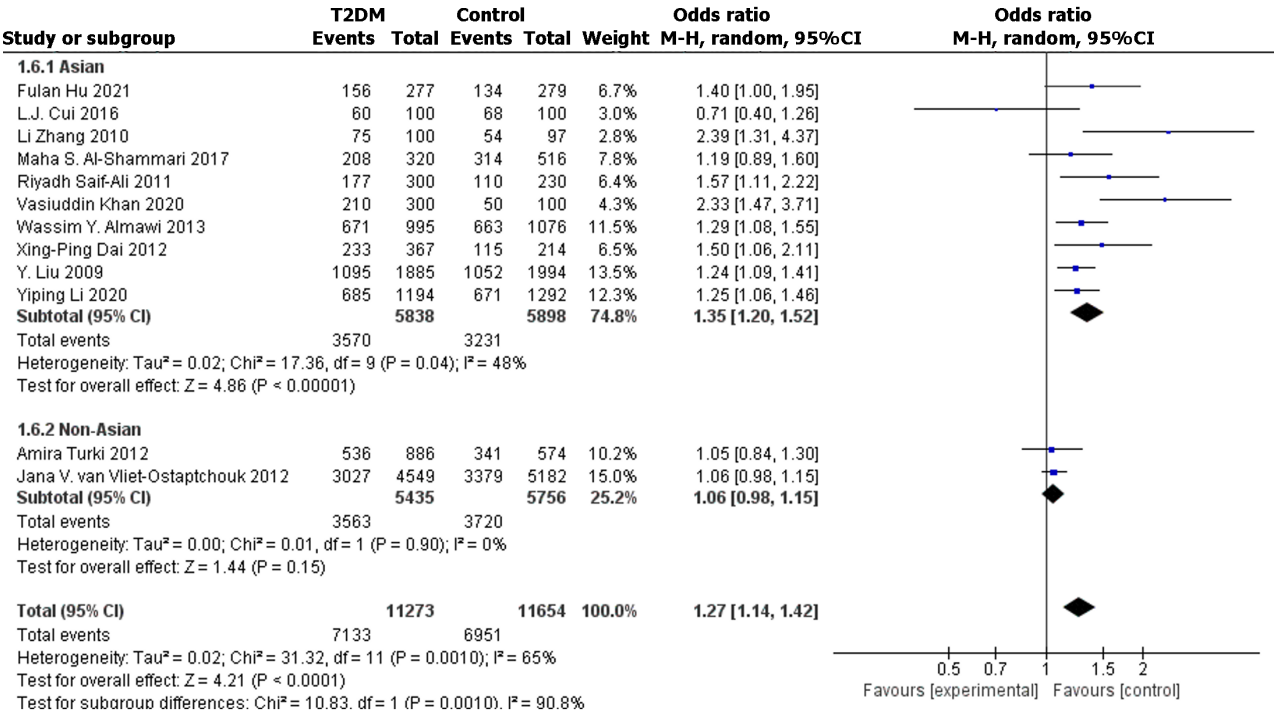


B

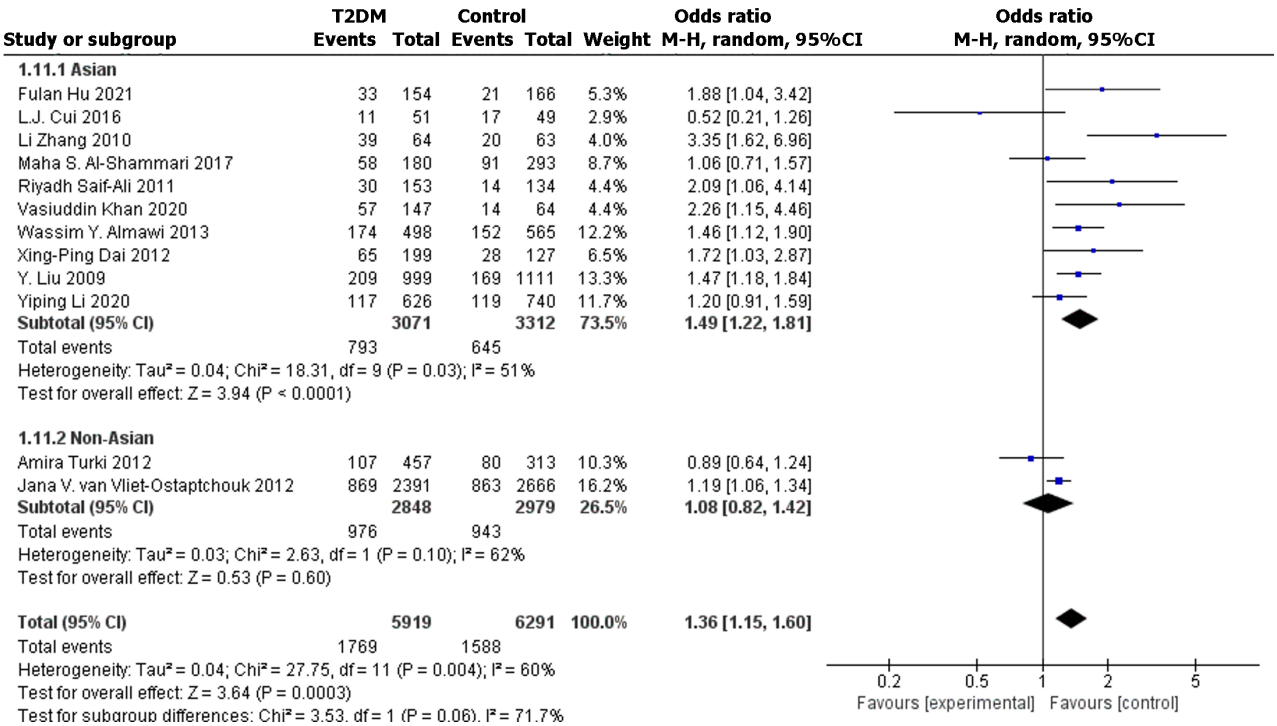
Study or subgroup	T2DM Events	T2DM Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95%CI
1.4.1 Asian						
Fulan Hu 2021	33	277	21	279	3.9%	1.66 [0.94, 2.95]
L.J. Cui 2016	11	100	17	100	2.1%	0.60 [0.27, 1.36]
Li Zhang 2010	39	100	20	97	3.3%	2.46 [1.30, 4.65]
Maha S. Al-Shammari 2017	58	320	91	516	8.0%	1.03 [0.72, 1.49]
Riyadh Saif-Ali 2011	30	300	14	230	3.1%	1.71 [0.89, 3.31]
Vasiuddin Khan 2020	57	300	14	100	3.3%	1.44 [0.76, 2.72]
Wassim Y. Almawi 2013	174	995	152	1076	13.2%	1.29 [1.02, 1.63]
Xing-Ping Dai 2012	65	367	28	214	5.3%	1.43 [0.89, 2.31]
Y. Liu 2009	209	1885	169	1994	14.6%	1.35 [1.09, 1.67]
Yiping Li 2020	117	1194	119	1292	11.6%	1.07 [0.82, 1.40]
Subtotal (95% CI)		**5838**		**5898**	**68.5%**	**1.29 [1.11, 1.49]**
Total events	793		645			
Heterogeneity: Tau² = 0.01; Chi² = 12.47, df = 9 (P = 0.19); I² = 28%						
Test for overall effect: Z = 3.38 (P = 0.0007)						
1.4.2 Non-Asian						
Amira Turki 2012	107	886	80	574	9.8%	0.85 [0.62, 1.16]
Jana V. van Vliet-Ostaptchouk 2012	869	4549	863	5182	21.7%	1.18 [1.07, 1.31]
Subtotal (95% CI)		**5435**		**5756**	**31.5%**	**1.04 [0.75, 1.42]**
Total events	976		943			
Heterogeneity: Tau² = 0.04; Chi² = 3.93, df = 1 (P = 0.05); I² = 75%						
Test for overall effect: Z = 0.21 (P = 0.83)						
Total (95% CI)		**11273**		**11654**	**100.0%**	**1.21 [1.07, 1.37]**
Total events	1769		1588			
Heterogeneity: Tau² = 0.02; Chi² = 18.51, df = 11 (P = 0.07); I² = 41%						
Test for overall effect: Z = 3.08 (P = 0.002)						
Test for subgroup differences: Chi² = 1.50, df = 1 (P = 0.22), I² = 33.2%						



C


T2DM
Control
Odds ratio
Odds ratio
Study or subgroup Events Total Events Total Weight M-H, random, 95%CI
M-H, random, 95%CI
1.6.1 Asian
Fulan Hu 2021 156 277 134 279 6.7% 1.40 [1.00, 1.95]
L.J. Cui 2016 60 100 68 100 3.0% 0.71 [0.40, 1.26]
Li Zhang 2010 75 100 54 97 2.8% 2.39 [1.31, 4.37]
Maha S. Al-Shammari 2017 208 320 314 516 7.8% 1.19 [0.89, 1.60]
Riyadh Saif-Ali 2011 177 300 110 230 6.4% 1.57 [1.11, 2.22]
Vasiuddin Khan 2020 210 300 50 100 4.3% 2.33 [1.47, 3.71]
Wassim Y. Almawi 2013 671 995 663 1076 11.5% 1.29 [1.08, 1.55]
Xing-Ping Dai 2012 233 367 115 214 6.5% 1.50 [1.06, 2.11]
Y. Liu 2009 1095 1885 1052 1994 13.5% 1.24 [1.09, 1.41]
Yiping Li 2020 685 1194 671 1292 12.3% 1.25 [1.06, 1.46]
Subtotal (95% CI) 5838 5898 74.8% 1.35 [1.20, 1.52]
Total events 3570 3231
Heterogeneity: Tau² = 0.02; Chi² = 17.36, df = 9 (P = 0.04); I² = 48%
Test for overall effect: Z = 4.86 (P < 0.00001)
1.6.2 Non-Asian
Amira Turki 2012 536 886 341 574 10.2% 1.05 [0.84, 1.30]
Jana V. van Vliet-Ostaptchouk 2012 3027 4549 3379 5182 15.0% 1.06 [0.98, 1.15]
Subtotal (95% CI) 5435 5756 25.2% 1.06 [0.98, 1.15]
Total events 3563 3720
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.44 (P = 0.15)
Total (95% CI) 11273 11654 100.0% 1.27 [1.14, 1.42]
Total events 7133 6951
Heterogeneity: Tau² = 0.02; Chi² = 31.32, df = 11 (P = 0.0010); I² = 65%
Test for overall effect: Z = 4.21 (P < 0.0001)
Test for subgroup differences: Chi² = 10.83, df = 1 (P = 0.0010), I² = 90.8%
0.5 0.7 1 1.5 2
Favours [experimental] Favours [control]

D


T2DM
Control
Odds ratio
Odds ratio
Study or subgroup Events Total Events Total Weight M-H, random, 95%CI
M-H, random, 95%CI
1.11.1 Asian
Fulan Hu 2021 33 154 21 166 5.3% 1.88 [1.04, 3.42]
L.J. Cui 2016 11 51 17 49 2.9% 0.52 [0.21, 1.26]
Li Zhang 2010 39 64 20 63 4.0% 3.35 [1.62, 6.96]
Maha S. Al-Shammari 2017 58 180 91 293 8.7% 1.06 [0.71, 1.57]
Riyadh Saif-Ali 2011 30 153 14 134 4.4% 2.09 [1.06, 4.14]
Vasiuddin Khan 2020 57 147 14 64 4.4% 2.26 [1.15, 4.46]
Wassim Y. Almawi 2013 174 498 152 565 12.2% 1.46 [1.12, 1.90]
Xing-Ping Dai 2012 65 199 28 127 6.5% 1.72 [1.03, 2.87]
Y. Liu 2009 209 999 169 1111 13.3% 1.47 [1.18, 1.84]
Yiping Li 2020 117 626 119 740 11.7% 1.20 [0.91, 1.59]
Subtotal (95% CI) 3071 3312 73.5% 1.49 [1.22, 1.81]
Total events 793 645
Heterogeneity: Tau² = 0.04; Chi² = 18.31, df = 9 (P = 0.03); I² = 51%
Test for overall effect: Z = 3.94 (P < 0.0001)
1.11.2 Non-Asian
Amira Turki 2012 107 457 80 313 10.3% 0.89 [0.64, 1.24]
Jana V. van Vliet-Ostaptchouk 2012 869 2391 863 2666 16.2% 1.19 [1.06, 1.34]
Subtotal (95% CI) 2848 2979 26.5% 1.08 [0.82, 1.42]
Total events 976 943
Heterogeneity: Tau² = 0.03; Chi² = 2.63, df = 1 (P = 0.10); I² = 62%
Test for overall effect: Z = 0.53 (P = 0.60)
Total (95% CI) 5919 6291 100.0% 1.36 [1.15, 1.60]
Total events 1769 1588
Heterogeneity: Tau² = 0.04; Chi² = 27.75, df = 11 (P = 0.004); I² = 60%
Test for overall effect: Z = 3.64 (P = 0.0003)
Test for subgroup differences: Chi² = 3.53, df = 1 (P = 0.06), I² = 71.7%
0.2 0.5 1 2 5
Favours [experimental] Favours [control]

E

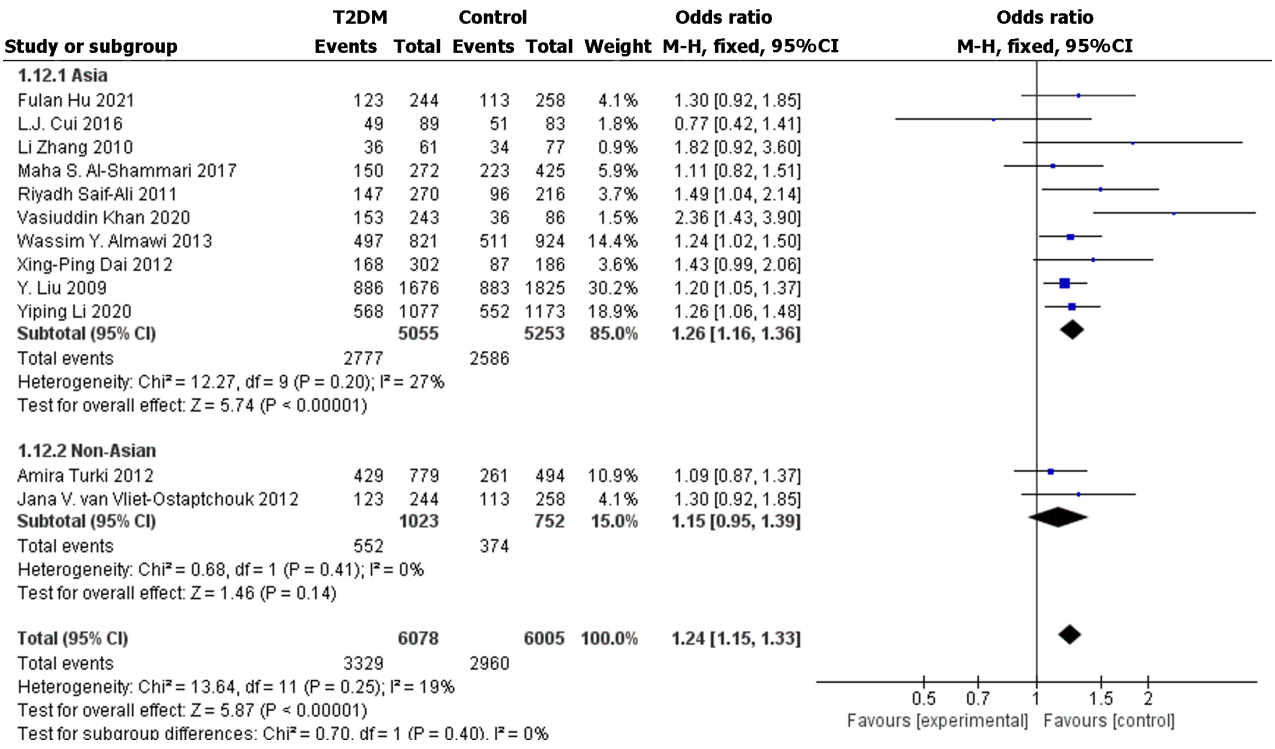


Figure 3 The forest plot for stratified analysis of different model. A: Allelic model; B: Recessive model; C: Dominant model; D: Co-dominant model (CC *vs* AA); E: Co-dominant model (AC *vs* AA). T2DM: Type 2 diabetes mellitus.

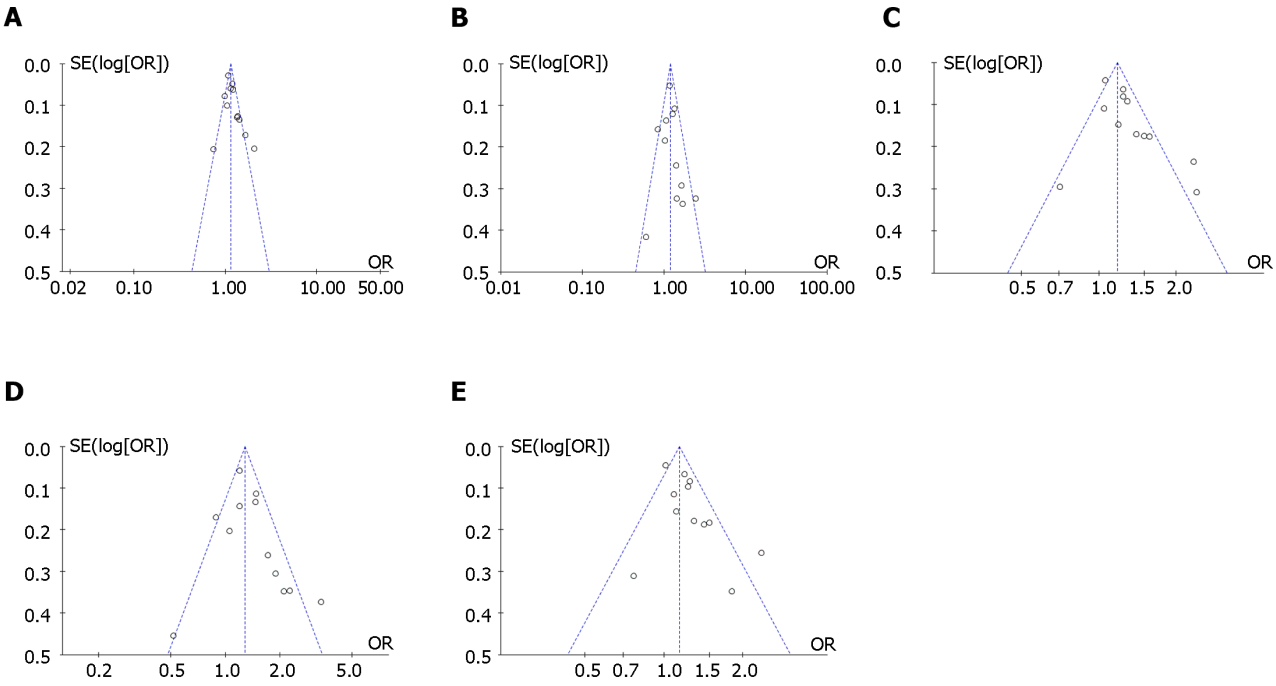


Figure 4 The funnel plot of different model. A: Allelic model; B: Recessive model; C: Dominant model; D: Co-dominant model (CC *vs* AA); E: Co-dominant model (AC *vs* AA). OR: Odds ratio.

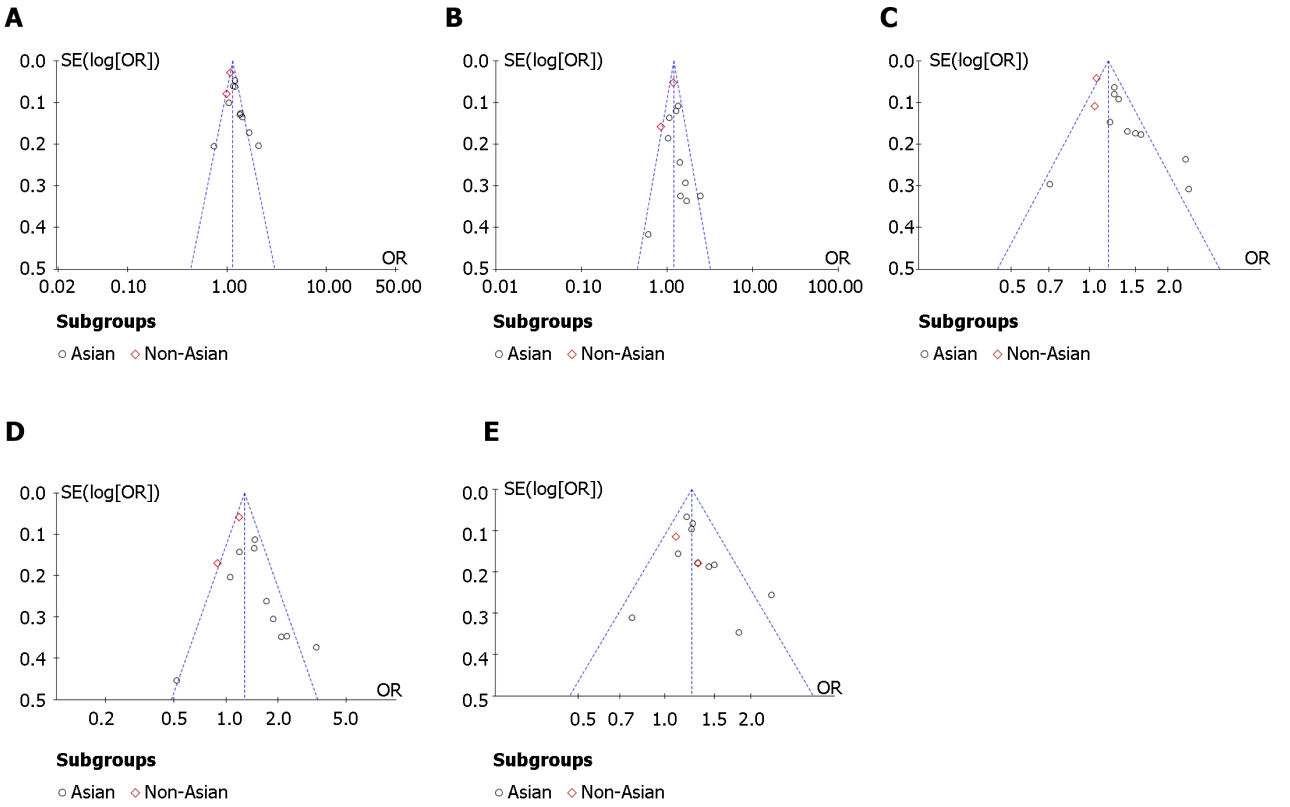


Figure 5 The funnel plot for stratified analysis of different models. A: Allelic model; B: Recessive model; C: Dominant model; D: Co-dominant model (CC *vs* AA); E: Co-dominant model (AC *vs* AA). OR: Odds ratio.

This meta-analysis of the *KCNQ1* gene rs2237895 SNP and T2DM association study involved 12 studies, including 11273 T2DM patients and 11654 controls. This analysis showed that the rs2237895 polymorphism was significantly associated with an elevated risk of developing T2DM in an Asian population, which is consistent with Khan *et al*'s[10] findings. In Asian populations, C allele carriers have an increased risk of developing T2DM. The risk of T2DM is also increased in people with the CC and AC genotypes compared to the AA genotype. This is consistent with the previous findings of Hu *et al*[16]. Also, their findings showed that rs2237895 was associated with hypertension, body mass index, and hypertriglyceridemia. In non-Asian populations, this association was not significant. A 2015 study by Ríos *et al*[33] in Europeans also showed that the *KCNQ1* gene rs2237895 SNP was not significantly associated with T2DM, which is consistent with our findings. Our work provided strong evidence for the genetic pathogenesis of T2DM and helped to fully reveal the pathogenesis of T2DM.

This study showed that the rs2237895 SNP of the *KCNQ1* gene was differentially associated with T2DM in different populations. The reasons for this variation may be mutations in the regulatory region of the *KCNQ1* gene in particular populations[33], which interfere with the expression of the *KCNQ1* gene; or it may be due to the existence of different genotypes and allele frequencies in populations with different clinical characteristics, geographical distribution and ethnic origin; or differences in the external influences associated with T2DM, such as lifestyle and behavior, in different populations[4,23-25]. The possibility of false-negative results in non-Asian populations with small study sample sizes cannot be excluded.

CONCLUSION

In the Asian population, there was a significant association between the *KCNQ1* gene rs2237895 SNP and T2DM onset. C allele carriers were at increased risk of T2DM, and the CC and AC genotypes significantly increased the susceptibility to T2DM. However, in the non-Asian population, the association between rs2237895 and T2DM onset was not significant.

ARTICLE HIGHLIGHTS

Research background

The association between the rs2237895 single nucleotide polymorphism (SNP) in the *KCNQ1* gene and the prevalence of type 2 diabetes mellitus (T2DM) has been controversial in different studies.

Research motivation

The aim of this study was to investigate the association between the *KCNQ1* gene rs2237895 and the prevalence of T2DM, and to provide help in establishing the pathogenesis of T2DM.

Research objectives

Demonstration of the association of the rs2237895 SNP in the *KCNQ1* gene with the prevalence of T2DM. Also, to explore whether this relationship differs in different populations.

Research methods

We searched nine databases. Two authors independently screened the literature according to the established inclusion and exclusion criteria. Finally, data extraction was performed and the data were meta-analyzed.

Research results

Twelve case–control studies met our inclusion criteria. After analysis, the rs2237895 SNP in the *KCNQ1* gene was associated with T2DM prevalence in Asian populations. However, this association was not significant in non-Asian populations.

Research conclusions

In Asian populations, carriers of the rs2237895 C allele of the *KCNQ1* gene were highly susceptible to T2DM compared to those who did not carry the C allele. However, in non-Asian populations, the association between the rs2237895 SNP and T2DM was not significant.

Research perspectives

We should continue to search for T2DM susceptibility genes through advanced technologies (*e.g.*, genome-wide association strategy) and gradually elucidate the pathogenesis of T2DM.

FOOTNOTES

Co-first authors: Dong-Xu Li and Li-Ping Yin.

Co-corresponding authors: Chen-Sen He and Jiang-Jie Sun.

Author contributions: Li DX, Yin LP, Sun JJ, and He CS designed this study (substantial contributions to the conception); Li DX, Yin LP, Song YQ, Shao NN, and Zhu H collected data; Li DX and Yin LP extracted and analyzed data, interpretation of data for the work; Sun JJ and He CS provided guidance for statistical analysis and provided financial support. They agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy; Li DX and Yin LP wrote the manuscript; Li DX, Yin LP, Song YQ, Shao NN, Zhu H, Sun JJ and He CS reviewed the manuscript; Li DX and Yin LP contributed equally to this work as co-first authors; Sun JJ and He CS contributed equally to this work as co-corresponding authors. The reasons for designating Li DX and Yin LP as co-first authors are as follows. First, Li DX and Yin LP contributed equal effort throughout the study. The selection of these researchers as co-first authors respects their equal contributions. Second, the research was conducted as a collaborative effort, and the designation of co-first authors accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the research and final paper. The reasons for designating Sun JJ and He CS as co-corresponding authors are as follows. First, Sun JJ and He CS put equal effort into the entire study. Second, the designation of co-corresponding authors best reflects the need for this study to have authors from different fields, which promotes the most in-depth examination of the research topic. In summary, we believe that the designation of Li DX and Yin LP as co-first authors and Sun JJ and He CS as co-corresponding authors meets the requirements of our manuscript, which reflects the spirit of equality and cooperation in our team.

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L-Editor: A

P-Editor: Chen YX

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