Meta-Analysis of Observational Studies in Epidemiology

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Association of the CDKAL1 polymorphism rs10946398 with type 2 diabetes mellitus in adults

A meta-analysis

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Abstract

Previous studies had reported that the CDKAL1 (cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like 1) rs10946398 C/A polymorphism associated with type 2 diabetes mellitus (T2DM) in various ethnic groups, however, inconsistent results have been obtained in studies of different populations.

We performed a meta-analysis of 13 studies for rs10946398 of CDKAL1 on genetic susceptibility for T2DM.

The results showed that CDKAL1 rs10946398 C/A polymorphism associated with T2DM under allelic (odds risk (OR): 1.17, 95% CI: 1.07–1.28, $P = .0007$), homozygous (OR: 1.39, 95% CI: 1.15–1.69, $P = .0008$), and dominant models (OR: 1.26, 95% CI: 1.09–1.46, $P = .001$).

We found that rs10946398 C/A polymorphism was associated with T2DM, and this association was significantly in population of western country (Europe and United States) and Asian populations.

Abbreviations: 95% C.I = 95% confidence intervals, BMI = body mass index, CDKAL1 = cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like 1, OR = odds ratios, SNP = ingle nucleotide polymorphism, T2DM = type 2 diabetes mellitus.

Keywords: cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like 1, rs10946398, type 2 diabetes mellitus, meta-analysis

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic syndrome caused by a combination of genetic and environmental factors. According to the International Diabetes Federation, in 2011, there were approximately 366 million patients with diabetes mellitus worldwide.[1] Large-scale studies in 2010 have shown that approximately 113.9 million and 493.4 million adults in China had T2DM and pre-diabetes, respectively, indicating that China has the highest incidence worldwide; these patients were predominantly young and middle-aged. Therefore, methods for the prevention of T2DM are urgently needed.[2]

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XL and HG contributed equally to this work.

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This study is a meta-analysis, so the ethics approval and requirement for consent are not applicable.

We, all authors, consent to publish this study in Medicine.

All data generated or analyzed during this study are included in this manuscript.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available. All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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The CDKAL1 (cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like 1) gene spans 697,948 bp on chromosome 6p22.3 and encodes a 65-kD protein.[3] The synonymous single nucleotide polymorphism (SNP) rs10946398 in CDKAL1 has been identified as a candidate SNP for T2DM. A number of case-control studies have examined the association between the CDKAL1 rs10946398 C/A polymorphism and T2DM.[2,4–6] However, inconsistent results have been obtained in studies of different populations. Variation in rs10946398 was significantly associated with T2DM in studies conducted in India[7] and China,[8] but not in the United States.[9] These discrepancies could be related to racial or regional differences in the CDKAL1 polymorphism frequency. Therefore, we performed a meta-analysis to examine the association between the CDKAL1 rs10946398 C/A polymorphism and T2DM in adults.

2. Materials and methods

2.1. Literature search strategy

A professional librarian was invited to help us search the following databases for relevant studies: PubMed, Medline, Embase, ISI Web of Knowledge, Biosis Preview, Ovid, Science Direct, and The Cochrane Library. Two investigators (Jun Liang and XueKui Liu) searched all of these databases using appropriate descriptions according to the particular database. For example, the search strategy for the PubMed database was "(CDKAL1 or CDKAL1 protein, human) and (rs10946398) and (Diabetes Mellitus, Type 2 or T2DM or Type 2 Diabetes Mellitus or NIDDM)" in the title and abstract. The search was limited to studies of humans. The search language was English, and the searches were performed up to August 2019.

2.2. Inclusion and exclusion criteria

The studies included in this meta-analysis satisfied the following criteria:

(1) case-control studies focusing on the association between the CDKAL1 rs10946398 C/A polymorphism and T2DM in adults,
(2) a clear description of the diagnostic criteria for T2DM and sources of subjects,
(3) genotype frequencies for rs10946398 in T2DM and control groups or odds ratios (OR) and 95% confidence intervals (CI),
(4) Hardy–Weinberg equilibrium (HWE) in the control group, and published in English.

The following studies were excluded:

(1) those that were not designed as case-control studies;
(2) reviews, abstracts (without data), comments (without data), and duplicate publications (for multiple studies of the same population by different investigators or overlapping data obtained by the same authors, the complete article with the largest number of subjects was included);
(3) studies with control groups that deviated from HWE;
(4) studies with participants diagnosed with secondary T2DM or other serious diseases;
(5) studies that did not include adults.

2.3. Data extraction

Two researchers (Houfa Geng and XueKui Liu) independently reviewed all studies to determine whether an individual study could be retained for the meta-analysis and extracted all relevant information and data. All disagreements were discussed with a third reviewer (Jun Liang) until consensus was reached. The following information was obtained from each study: the last name of the first author, year of publication, country, gender and age of the enrolled subjects, genotype counts in cases and controls, and HWE in each control group. If necessary, data were not reported in the primary paper, the corresponding authors were contacted by e-mail to request the missing data.

2.4. Statistical analysis

A meta-analysis was performed using the Cochrane Collaboration RevMan 5.3 and STATA package version 14.0 (Stata Corporation, College Station, TX). The pooled OR and 95% CI were calculated to evaluate the association between the CDKAL1 rs10946398 C/A polymorphism and T2DM risk. A χ^2-test based on the Q statistic was performed to assess between-study heterogeneity. $I^2 > 50\%$ and $P < 0.1$ indicated significant heterogeneity, and the random effects model was used to analyze the results. The fixed effects model was used for homogeneous data. Egger test was used to assess publication bias. HWE was examined using the χ^2 test. $P < .05$ was considered significant.

3. Results

3.1. Study characteristics

Figure 1 provides a flow chart of the literature search and selection procedure. A total of 326 studies published in English were initially identified through the database search. Among these, 196 studies with duplicate titles and 82 articles that were reviews or assessed unrelated diseases were excluded. We carefully reviewed the main text of 47 studies and excluded 21 papers that assessed unrelated polymorphisms, were not case-control designs, were conducted in non-adult populations, or did not report necessary parameters. Finally, 13 studies,[7,10–20] including 13,820 cases and 22,481 controls, related to the CDKAL1 rs10946398 C/A polymorphism and T2DM were eligible for the meta-analysis.

Table 1 summarizes the information extracted from 13,820 T2DM cases and 22,481 controls, including body mass index (BMI), age, genotype and allele frequencies in cases and controls, and HWE. Seven studies were carried out in Asia, 4 were performed in the United States, and 1 was performed in Europe.

As summarized in Table 2 and Figures. 2–4, a significant association was found between the CDKAL1 rs10946398 C/A polymorphism and T2DM under allelic (OR: 1.17, 95% CI: 1.07–1.28, $P = .0007$), homozygous (OR: 1.39, 95% CI: 1.15–1.69, $P = .0008$), and dominant models (OR: 1.26, 95% CI: 1.09–1.46, $P = .001$).

In a subgroup analysis of the Asian population, a significant association was found between the CDKAL1 rs10946398 C/A polymorphism and T2DM for the allelic genetic model (OR: 1.16, 95% CI: 1.02–1.33, $P = .003$). The homozygous genetic model (OR: 1.37, 95% CI: 1.03–1.82, $P = .03$) and dominant genetic model (OR: 1.25, 95% CI: 1.00–1.56, $P = .05$) indicated a significant association.

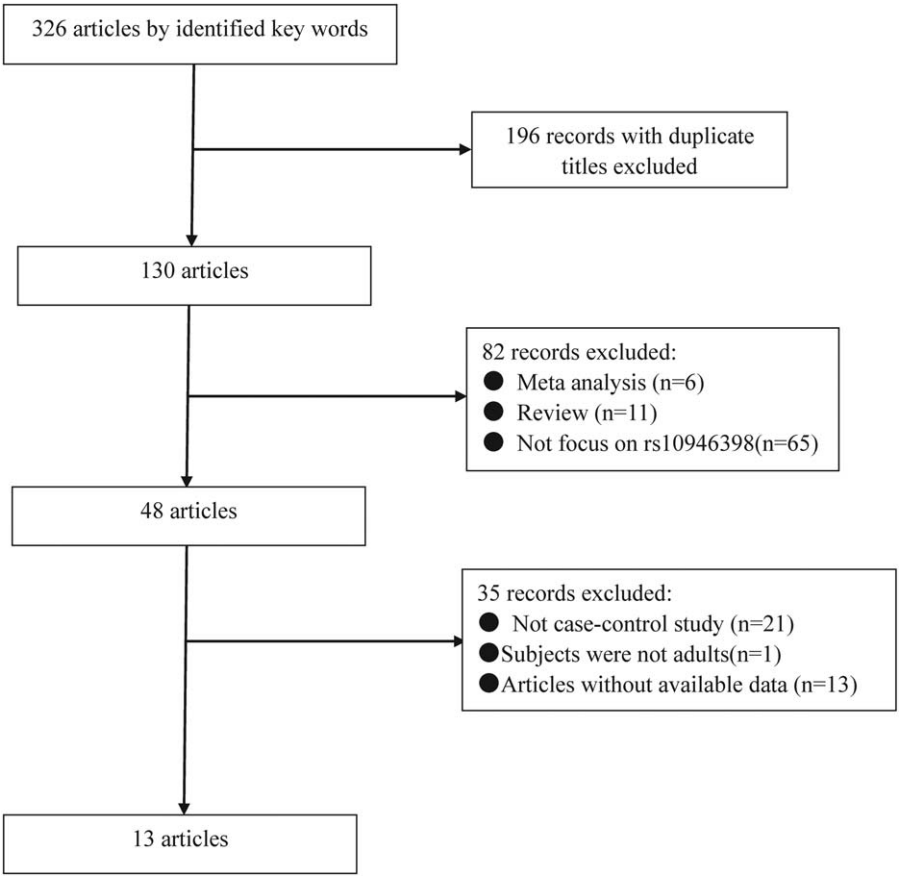

Figure 1. Flow diagram of eligible study selection.

In a subgroup analysis of the Europe and United States populations, the 3 models all indicated a significant association between the CDKAL1 rs10946398 C/A polymorphism and T2DM. Significant results were obtained for the allelic genetic model (OR: 1.19, 95% CI: 1.11–1.27, $P < .0001$), homozygous genetic model (OR: 1.43, 95% CI: 1.27–1.60, $P < .0001$), and dominant genetic model (OR: 1.26, 95% CI: 1.16–1.37, $P < .0001$).

Table 1

Characteristics of the investigated studies of the association between the cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like 1 rs10946398 C/A polymorphism and type 2 diabetes mellitus.

					Body mass index (Mean ± SD)		Age (yr)		T2DM (frequency)			Control (frequency)			HEW
Author	Yr	Country/ regions	Subgroup	Sample/size (T2DM/control)	T2DM	Control	T2DM	Control	CC	CA	AA	CC	CA	AA	*P*
Ganesh 1	2010	India	Asian	1019/1006	25.0 (22–29.2)	23.9 (20.2–28.6)	53 (45–62)	50 (44–60)	59	372	589	44	334	628	1.00
Ganesh 2	2010	India	Asian	1467/1672	25.8 (22.8–29.6)	20.4 (17.6–23.6)	46 (40–52)	33 (29–37)	107	578	782	113	643	916	1.00
Xueyao Han	2010	Chinese	Asian	1024/1005	25.0 ± 3.1	25.0 ± 3.3	56 ± 12	58 ± 9	236	554	277	177	490	338	1.00
Ying Lin	2010	Chinese	Asian	1529/1439	23.9 ± 2.7	23.5 ± 2.8	60.2 ± 10.1	58.1 ± 10.8	310	757	463	197	671	571	1.00
Dimitry A.	2011	Russia	Europe	772/773	28.3 ± 5.9	26.9 ± 4.8	59.9 ± 7.9	61.6 ± 9.7	99	337	333	70	330	367	.94
Eun Seok	2009	South Korea	Asian	145/444	NA	NA	42.6 ± 9.1	37.4 ± 9.3	42	72	31	90	220	134	1.00
C. Herder	2008	America	America	433/1438	30.9 ± 5.0	27.7 ± 4.3	65.2 ± 8.3	61.9 ± 10.2	56	200	177	129	604	705	1.00
JESSICA N	2012	America	America	1150/567	33.7 ± 7.6	29.5 ± 7.6	46.0 ± 12.3	48.6 ± 13.0	428	547	175	184	278	105	1.00
M. Cruz	2010	Mexico	America	519/547	29.25 ± 4.76	27.50 ± 3.55	53.44 ± 7.42	43.60 ± 6.63	52	225	242	49	229	270	1.00
Cheng Hu	2009	Chinese	Asian	1849/1785	24.04 ± 3.51	23.57 ± 3.25	61.21 ± 12.62	57.39 ± 12.37	360	912	578	306	866	613	1.00
Joshua P	2008	America	America	993/1054	NA	NA	NA	NA	376	470	147	357	513	184	1.00
Y. Liu	2008	Chinese	Asian	1822/1903	25.3 ± 3.4	24.5 ± 3.2	63.8 ± 9	58.1 ± 9	293	903	707	372	862	588	.23
Oswald NN	2017	Taiwan	Asian	974/8934	NA	NA	55.65 ± 9.19	47.60 ± 10.80	180	441	353	1166	4061	3707	.22

HEW = Hardy–Weinberg equilibrium, T2DM = Type 2 diabetes mellitus.

Table 2

Summary of the meta-analysis of the association between cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like 1 rs10946398C/A polymorphism and type 2 diabetes mellitus.

Genetic model	Pooled OR (95% CI)	*Z*-value	*P*-value	Study number	T2DM size	Control size	I^2
Allelic genetic model							
Total	1.17 (1.07–1.28)	3.40	.0007	13	27640	44962	85%
Asian subgroup	1.16 (1.02–1.33)	2.21	.03	8	19912	36214	91%
Europe and America subgroup	1.19 (1.11–1.27)	3.02	<.0001	5	7728	8748	0%
Homozygous genetic model							
Total	1.39 (1.15–1.69)	3.34	.0008	13	14904	24760	93%
Asian subgroup	1.37 (1.03–1.82)	2.17	.03	8	10734	19920	95%
Europe and America subgroup	1.43 (1.27–1.60)	6.03	<.0001	5	4170	4840	20%
Dominant genetic model							
Total	1.26 (1.09–1.46)	3.18	.001	13	27640	44962	90%
Asian subgroup	1.25 (1.00–1.56)	1.97	.05	8	19912	36214	94%
Europe and America subgroup	1.26 (1.16–1.37)	5.66	<.0001	5	7728	8748	25%

95% C.I = 95% confidence intervals, OR = odds ratios, T2DM = Type 2 diabetes mellitus.

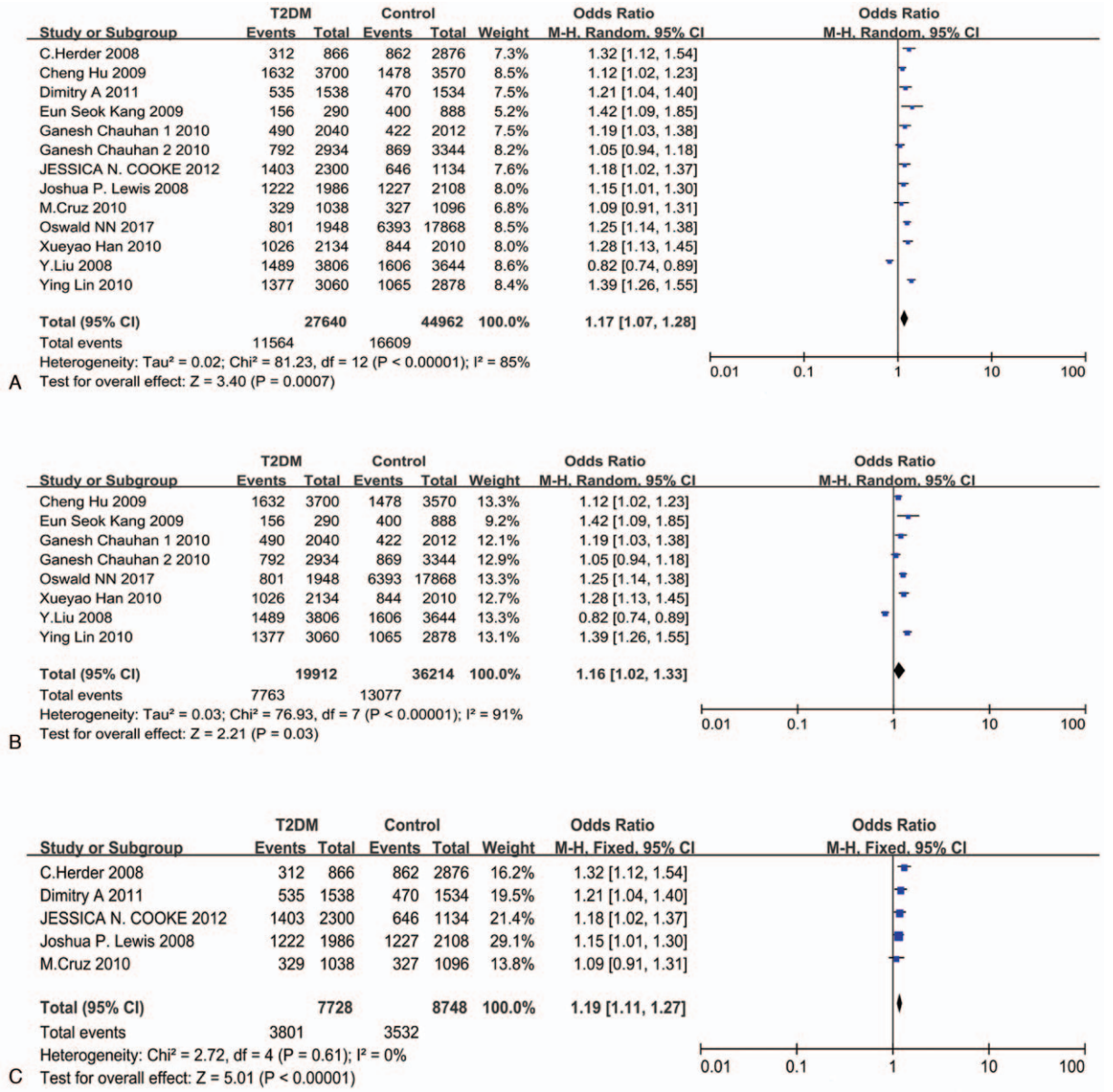

Figure 2. Association between the cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like 1 rs10946398C/A polymorphism and T2DM for the allelic genetic model (Total (a)\ Asian subgroup (b) and Europe and America subgroup (c)).

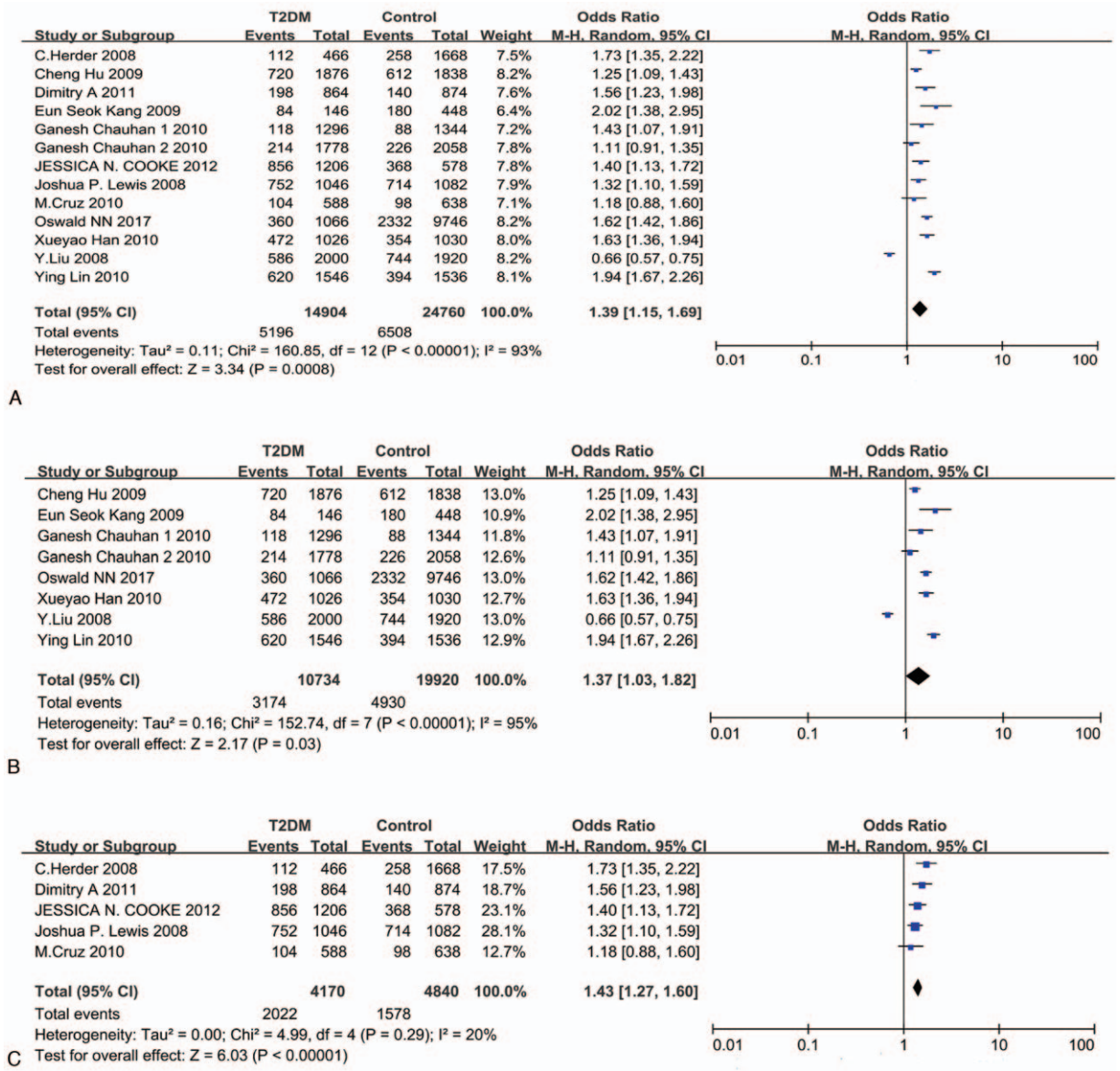

Figure 3. Association between the cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like 1 rs10946398 C/A polymorphism and T2DM for the homozygous genetic model (Total (a)\ Asian subgroup (b) and Europe and America subgroup (c)).

3.2. Publication bias

We evaluated publication bias using Egger test with STATA 14.0. Funnel plots were obtained using RevMan 5.2 to evaluate the quality of 13 papers. Based on Egger test, the publication bias was not significant (total: $t=0.96$, $P=.356$; Asian subgroup: $t=0.78$, $P=.465$; European-American subgroup: $t=1.47$, $P=.142$). Three funnel plots were nearly symmetrical, suggesting that there was no publication bias for the CDKAL1 rs10946398 C/A polymorphism (Figs. 5–7).

4. Discussion

The results of our meta-analysis indicated that the rs10946398 C/A polymorphism of CDKAL1 was significantly associated with T2DM at a large scale, that is, in 36,301subjects, including 13,820 patients with T2DM and 22,481 controls. The average ages were 55.4 ± 5.27 and 50.6 ± 7.54 years in the case group and control group, respectively. The average BMI in the case group ($27.1\pm2.13\,kg/m^2$) was greater than that in the control group ($25.2\pm2.12\,kg/m^2$).

In our previous study,[21] we confirmed that the CDKAL1 rs10946398 C/A polymorphism was associated with markers of impaired insulin secretion in Chinese adults. Impaired insulin secretion is an early symptom of T2DM. In this review, we included 8 case-control studies of Asian populations, and found the significantly association between CDKAL1 rs10946398 C/A polymorphism and T2DM. A study of the Icelandic population suggested that the effect of genotype was substantially stronger in homozygous carriers than in heterozygous carriers, consistent with our results.[22] Some previous studies have confirmed that the CDKAL1 gene plays a role in cell-cycle control in β-cells; the C allele of rs10946398 decreases insulin secretion from β-cells and reduces the insulin response.[8] The effects of the rs10946398

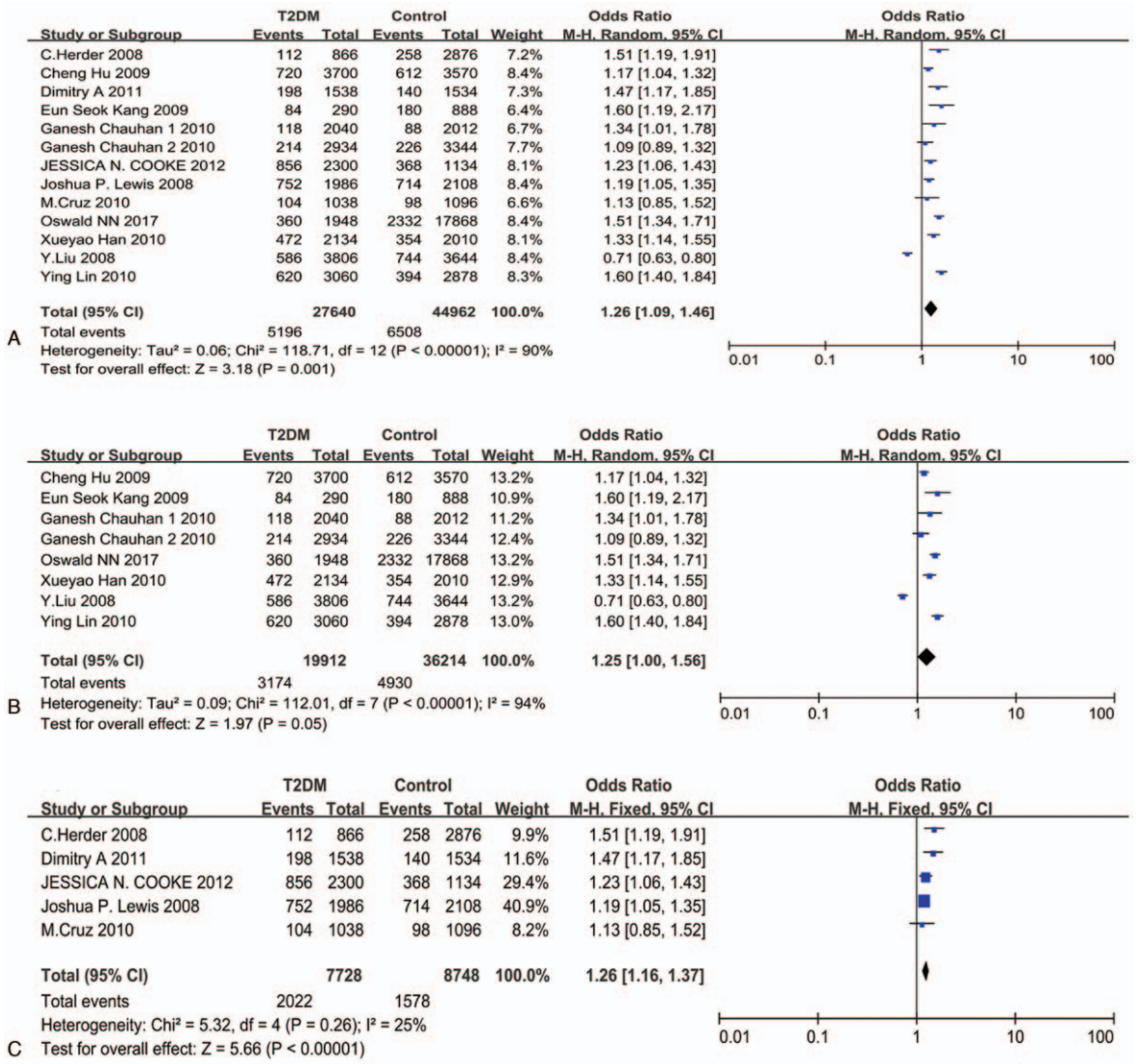

Figure 4. Association between the cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like 1 rs10946398 C/A polymorphism and T2DM for the dominant genetic model (Total (a)\ Asian subgroup (b) and Europe and America subgroup (c)).

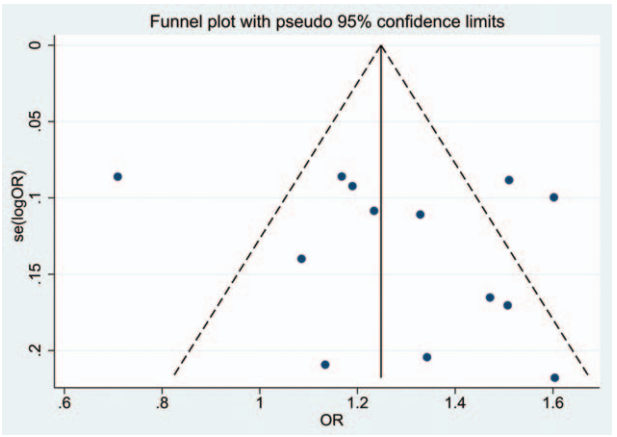

Figure 5. Funnel plot for the detection of publication bias (CC vs AA of cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like 1 rs10946398).

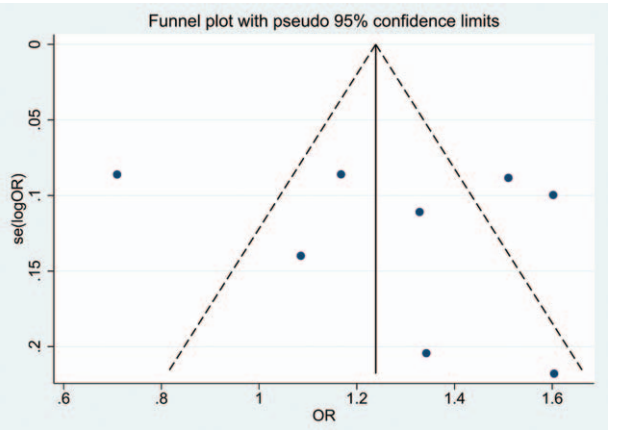

Figure 6. Funnel plot for the detection of publication bias (CC vs AA of cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like 1 cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like 1 rs10946398) (Asian subgroup).

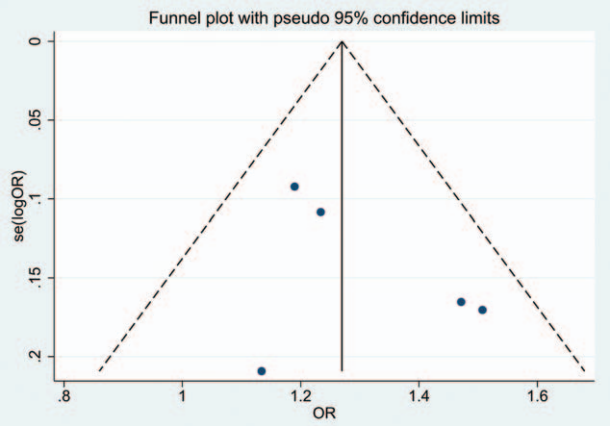

Figure 7. Funnel plot for the detection of publication bias (CC vs AA of cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like 1 rs10946398) (Europe and America subgroup).

C allele were reduced after adjusting for BMI in Asia, but adjusting for BMI had no effect in an analysis of the European population.[16] In our previous study, we found that the association between CDKAL1 and BMI only existed in East Asians.[23] Thus, we hypothesized that the BMI mediates the effect of CDKAL1 in β-cells in East Asians. In a previous study, we found that CDKAL1 is associated with a predisposition to obesity and shows a protective effect against HbA1c/2hPG/prediabetes; furthermore, BMI mediated this association.[24]

In this meta-analysis, we also found that rs10946398 of CDKAL1 was associated with T2DM in European and American populations. This association has been identified in some previous studies, but the function of the CDKAL1 protein is unknown. Steinthorsdottir et al[22] reported that the function of CDKAL1 is similar to that of another protein, that is, CDK5 regulatory subunit-associated protein 1 (encoded by CDK5RAP1). CDK5 reduces insulin secretion in response to glucose; additionally, it has a permissive role in the decrease of insulin gene expression that results from glucotoxicity as well as in the pathophysiology of β-cell dysfunction and predisposition to type 2 diabetes.[25,26]

This review had a few limitations. First, only case-control studies were included, which are less powerful than cohort studies. Second, we only screened English papers for simplicity. Third, 2 papers included in the analysis had low power owing to a small number of cases, and this might affect the results of the meta-analysis.

Despite these limitations, this is the first meta-analysis of the rs10946398 C/A polymorphism of CDKAL1. We found that this SNP was associated with T2DM. A homozygous genetic model indicated a greater risk of T2DM than an allelic or dominant genetic model.

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Author contributions

Xuekui Liu and Houfa Geng were drafted this manuscript, All authors took part in the collection of data and have approved the final version of the manuscript. J Liang is responsible for the integrity of the work as a whole.

Writing – review & editing: Jun Liang.

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