

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, metaanalysis

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

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

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

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 rs10946398C/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:

- 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.



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 subunitassociated protein 1-like 1 rs10946398 C/A polymorphism and type 2 diabetes mellitus.

					Body ma (Mear	ass index 1 \pm SD)	Age	(yr)	(fre	T2DN equen	l Icy)	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 Ganesh 2	2010 2010	India India	Asian Asian	1019/1006 1467/1672	25.0 (22–29.2) 25.8 (22.8–29.6)	23.9 (20.2–28.6) 20.4 (17.6–23.6)	53 (45–62) 46 (40–52)	50 (44–60) 33 (29–37)	59 107	372 578	589 782	44 113	334 643	628 916	1.00
Xueyao Han Ving Lin	2010	Chinese	Asian	1024/1005	25.0 ± 3.1	25.0 ± 3.3	56 ± 12	58 ± 9	236	554 757	277 463	177 107	490 671	338 571	1.00
Dimitry A.	2010	Russia	Europe	772/773	23.3 ± 2.7 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 C. Herder	2009 2008	South Korea America	Asian America	145/444 433/1438	NA 30.9±5.0	NA 27.7 <u>+</u> 4.3	42.6±9.1 65.2±8.3	37.4±9.3 61.9±10.2	42 56	72 200	31 177	90 129	220 604	134 705	1.00 1.00
JESSICA N M. Cruz	2012	America Mexico	America	1150/567 519/547	33.7 ± 7.6	29.5 ± 7.6	46.0 ± 12.3	48.6 ± 13.0	428 52	547 225	175 242	184 ⊿q	278 229	105 270	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 Y. Liu	2008 2008	America Chinese	America Asian	993/1054 1822/1903	NA 25.3 <u>+</u> 3.4	NA 24.5 <u>+</u> 3.2	NA 63.8±9	NA 58.1 ± 9	376 293	470 903	147 707	357 372	513 862	184 588	1.00 .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

A

С

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

Genetic model	Pooled OR (95% CI)	Z-value	P-value	Study number	T2DM size	Control size	l 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.

	T2D	M	Cont	rol		Odds Ratio		C	dds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	í	M-H, F	Random, 95%	CI	
C.Herder 2008	312	866	862	2876	7.3%	1.32 [1.12, 1.54]			-		
Cheng Hu 2009	1632	3700	1478	3570	8.5%	1.12 [1.02, 1.23]			-		
Dimitry A 2011	535	1538	470	1534	7.5%	1.21 [1.04, 1.40]			-		
Eun Seok Kang 2009	156	290	400	888	5.2%	1.42 [1.09, 1.85]			-		
Ganesh Chauhan 1 2010	490	2040	422	2012	7.5%	1.19 [1.03, 1.38]			-		
Ganesh Chauhan 2 2010	792	2934	869	3344	8.2%	1.05 [0.94, 1.18]			+		
JESSICA N. COOKE 2012	1403	2300	646	1134	7.6%	1.18 [1.02, 1.37]			-		
Joshua P. Lewis 2008	1222	1986	1227	2108	8.0%	1.15 [1.01, 1.30]			-		
M.Cruz 2010	329	1038	327	1096	6.8%	1.09 [0.91, 1.31]			+		
Oswald NN 2017	801	1948	6393	17868	8.5%	1.25 [1.14, 1.38]			-		
Kueyao Han 2010	1026	2134	844	2010	8.0%	1.28 [1.13, 1.45]			-		
Y.Liu 2008	1489	3806	1606	3644	8.6%	0.82 [0.74, 0.89]			-		
Ying Lin 2010	1377	3060	1065	2878	8.4%	1.39 [1.26, 1.55]			-		
Total (95% CI)		27640		44962	100.0%	1.17 [1.07, 1.28]			•		
Total events	11564		16609								
Heterogeneity: Tau ² = 0.02; 0	Chi ² = 81.2	23, df = 1	12 (P < 0.	00001);	l ² = 85%		- 01	0.1	-	10	100
Test for overall effect: Z = 3.4	40 (P = 0.0)	0007)		20000			0.01	0.1	1	10	100

	T2D	м	Cont	rol		Odds Ratio			Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% C	1	M-H	Random, 95	% CI	
Cheng Hu 2009	1632	3700	1478	3570	13.3%	1.12 [1.02, 1.23]			-		
Eun Seok Kang 2009	156	290	400	888	9.2%	1.42 [1.09, 1.85]			-		
Ganesh Chauhan 1 2010	490	2040	422	2012	12.1%	1.19 [1.03, 1.38]			-		
Ganesh Chauhan 2 2010	792	2934	869	3344	12.9%	1.05 [0.94, 1.18]			+		
Oswald NN 2017	801	1948	6393	17868	13.3%	1.25 [1.14, 1.38]			-		
Xueyao Han 2010	1026	2134	844	2010	12.7%	1.28 [1.13, 1.45]			-		
Y.Liu 2008	1489	3806	1606	3644	13.3%	0.82 [0.74, 0.89]			-		
Ying Lin 2010	1377	3060	1065	2878	13.1%	1.39 [1.26, 1.55]					
Total (95% CI)		19912		36214	100.0%	1.16 [1.02, 1.33]			٠		
Total events	7763		13077								
Heterogeneity: Tau ² = 0.03	; Chi ² = 76	.93, df =	= 7 (P < 0	.00001);	l ² = 91%		-			1	100
Test for overall effect: Z = 2	2.21 (P = 0	.03)					0.01	0.1	1	10	100

	T2D	N	Cont	lo		Odds Ratio			Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-	H. Fixed. 95%	CI	
C.Herder 2008	312	866	862	2876	16.2%	1.32 [1.12, 1.54]			+		
Dimitry A 2011	535	1538	470	1534	19.5%	1.21 [1.04, 1.40]			-		
JESSICA N. COOKE 2012	1403	2300	646	1134	21.4%	1.18 [1.02, 1.37]			-		
Joshua P. Lewis 2008	1222	1986	1227	2108	29.1%	1.15 [1.01, 1.30]			-		
M.Cruz 2010	329	1038	327	1096	13.8%	1.09 [0.91, 1.31]			+		
Total (95% CI)		7728		8748	100.0%	1.19 [1.11, 1.27]			٠		
Total events	3801		3532								
Heterogeneity: Chi ² = 2.72, c	f = 4 (P =	0.61);	$^{2} = 0\%$					1		1	
Test for overall effect: Z = 5.	01 (P < 0.0	00001)					0.01	0.1	1	10	100

Figure 2. Association between the cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like 1 rs10946398 C/A polymorphism and T2DM for the allelic genetic model (Total (a)\ Asian subgroup (b) and Europe and America subgroup (c)).

			M	Con	trol		Odds Ratio		Odds Ratio						
Stuc	dy or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	3	M-H	Random, 959	% CI				
C.He	erder 2008	112	466	258	1668	7.5%	1.73 [1.35, 2.22]			-					
Cher	eng Hu 2009	720	1876	612	1838	8.2%	1.25 [1.09, 1.43]	l.		-					
Dimi	itry A 2011	198	864	140	874	7.6%	1.56 [1.23, 1.98]			-					
Eun	Seok Kang 2009	84	146	180	448	6.4%	2.02 [1.38, 2.95]								
Gan	nesh Chauhan 1 2010	118	1296	88	1344	7.2%	1.43 [1.07, 1.91]			_					
Gan	nesh Chauhan 2 2010	214	1778	226	2058	7.8%	1.11 [0.91, 1.35]			_					
JES	SICA N. COOKE 2012	856	1206	368	578	7.8%	1.40 [1.13, 1.72]			-					
Josh	hua P. Lewis 2008	152	1046	/14	1082	7.9%	1.32 [1.10, 1.59]			-					
M.Cr	ruz 2010	104	1066	98	038	7.1%	1.18 [0.88, 1.60]			-					
Vue	vaid NN 2017	472	1000	2332	9740	0.2%	1.02 [1.42, 1.00]			-					
VIII	1 2008	596	2000	744	1030	9.0%	0.66 [0.57, 0.75]			-					
Ying	Lin 2010	620	1546	394	1536	8.1%	1.94 [1.67, 2.26]			-					
_															
Tota	al (95% Cl)		14904		24760	100.0%	1.39 [1.15, 1.69]			-					
Tota	al events	5196		6508			22	-	- T						
Hete Test	erogeneity: Tau ² = 0.11; 0 t for overall effect: Z = 3.3	$Chi^2 = 160$ 34 (P = 0.0	.85, df = 0008)	= 12 (P <	0.00001); l ² = 93%	6	0.01	0.1	i	10	100			
A															
		TODA		Cont			Odda Datia								
		TZDA		Cont			Udds Ratio			Odds Ratio					
Stud	dy or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C		M-H	, Random, 95	6 CI				
Che	eng Hu 2009	720	1876	612	1838	13.0%	1.25 [1.09, 1.43]			-					
Eun	n Seok Kang 2009	84	146	180	448	10.9%	2.02 [1.38, 2.95]			_					
Gan	nesh Chauhan 1 2010	118	1296	88	1344	11.8%	1.43 [1.07, 1.91]								
Gan	nesh Chauhan 2 2010	214	1778	226	2058	12.6%	1.11 [0.91, 1.35]			-					
Osw	wald NN 2017	360	1066	2332	9746	13.0%	1.62 [1.42, 1.86]			-					
Xue	evao Han 2010	472	1026	354	1030	12.7%	1.63 [1.36, 1.94]			-					
YL	iu 2008	586	2000	744	1920	13.0%	0.66 [0.57, 0.75]			-					
Ying	g Lin 2010	620	1546	394	1536	12.9%	1.94 [1.67, 2.26]			-					
Tota	al (95% CI)		10734		19920	100.0%	1 37 [1 03 1 82]			•					
Tete		2474	10104	1020	10020	100.070	1.07 [1.00, 1.02]								
TOLA	al events	31/4		4930	00004	12 050									
Hete	erogeneity: Tau ² = 0.16;	Chi ² = 152	2.74, df	= / (P <)	0.00001); 1² = 95%		0.01	0.1	1	10	10			
Test 3	at for overall effect: Z = 2.	17 (P = 0.	03)												
		T2D	М	Cont	rol		Odds Ratio			Odds Ratio					
Stuc	dy or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% C	1	M-H.	Random, 95%	6 CI				
C.He	erder 2008	112	466	258	1668	17.5%	1.73 [1.35, 2.22]			-					
Dimi	itry A 2011	198	864	140	874	18.7%	1.56 [1.23, 1.98]								
JES	SICA N. COOKE 2012	856	1206	368	578	23.1%	1.40 [1.13, 1.72]			-					
Josh	hua P. Lewis 2008	752	1046	714	1082	28.1%	1.32 [1.10, 1.59]			-					
M.C	Cruz 2010	104	588	98	638	12.7%	1.18 [0.88, 1.60]			-					
Tota	al (95% CI)		4170		4840	100.0%	1.43 [1.27, 1.60]			•					
Tota	al events	2022		1578											
Hoto	erogeneity: Tau ² = 0.00	$Chi^2 = 4.0$	q df = d	(P=0.3	Q). 12 - 1	20%			1						
nele	$e_1 \cup u_2 = 1010$, $1 du = 0.00$.	- 4.9	J. UI - 4	- U.2		2070									

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)).

0.01

0.1

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).

C Test for overall effect: Z = 6.03 (P < 0.00001)

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 $(27.1 \pm 2.13 \text{ kg/m}^2)$ was greater than that in the control group $(25.2 \pm 2.12 \text{ kg/m}^2).$

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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 B-cells and reduces the insulin response.^[8] The effects of the rs10946398

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	120	IVI	0011						oudo mano		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% C	1	M-H.	Random. 95	% CI	
C.Herder 2008	112	866	258	2876	7.2%	1.51 [1.19, 1.91]	1		-		
Cheng Hu 2009	720	3700	612	3570	8.4%	1.17 [1.04, 1.32]			-		
Dimitry A 2011	198	1538	140	1534	7.3%	1.47 [1.17, 1.85]			-		
Eun Seok Kang 2009	84	290	180	888	6.4%	1.60 [1.19, 2.17]	Î.				
Ganesh Chauhan 1 2010	118	2040	88	2012	6.7%	1.34 [1.01, 1.78]			-		
Ganesh Chauhan 2 2010	214	2934	226	3344	7.7%	1.09 [0.89, 1.32]			+		
JESSICA N. COOKE 2012	856	2300	368	1134	8.1%	1.23 [1.06, 1.43]	i		-		
Joshua P. Lewis 2008	752	1986	714	2108	8.4%	1.19 [1.05, 1.35]			-		
M.Cruz 2010	104	1038	98	1096	6.6%	1.13 [0.85, 1.52]	Í.		+-		
Oswald NN 2017	360	1948	2332	17868	8.4%	1.51 [1.34, 1.71]	Í.		-		
Xueyao Han 2010	472	2134	354	2010	8.1%	1.33 [1.14, 1.55]	i i i i i i i i i i i i i i i i i i i		-		
Y.Liu 2008	586	3806	744	3644	8.4%	0.71 [0.63, 0.80]			-		
Ying Lin 2010	620	3060	394	2878	8.3%	1.60 [1.40, 1.84]					
Total (95% CI)		27640		44962	100.0%	1.26 [1.09, 1.46]			•		
Table	5196		6508			1			100		
I otal events											
Heterogeneity: Tau ² = 0.06; Test for overall effect: Z = 3.	Chi ² = 118 18 (P = 0.0	8.71, df = 001)	= 12 (P <	0.00001); I² = 90%	•	0.01	0.1	i	10	100
Heterogeneity: Tau ² = 0.06; Test for overall effect: Z = 3.	Chi ² = 118 18 (P = 0.0 T2DN	8.71, df = 001)	= 12 (P <	0.00001); I² = 90%	Odds Ratio	0.01	0.1	1 Odds Ratio	10	100
Total events Heterogeneity: Tau ² = 0.06; Test for overall effect: Z = 3.	Chi ² = 118 18 (P = 0.0 T2DN Events	8.71, df = 001) 1 Total	Events	0.00001 ol Total); I ² = 90% Weight	Odds Ratio M-H. Random, 95% CI	0.01	0.1 M-H.	1 Odds Ratio Random, 95%	10 % CI	100
Total events Heterogeneity: Tau ² = 0.06; Test for overall effect: Z = 3. Study or Subgroup Cheng Hu 2009	Chi ² = 118 18 (P = 0.0 T2DM Events 720	8.71, df = 001) 1 <u>Total</u> 3700	Contr Events 612	0.00001); I ² = 90% <u>Weight</u> 13.2%	Odds Ratio <u>M-H. Random. 95% CI</u> 1.17 (1.04, 1.32)	0.01	0.1 М-Н.	1 Odds Ratio Random, 95%	10 % CI	100
Study or Subgroup Cheng Hu 2009 Fun Seek Kang 2009	Chi ² = 118 18 (P = 0.0 T2DN Events 720 84	8.71, df = 001) 1 Total 3700 290	Contr Events 612 180	0.00001 rol 3570 888); I ² = 90% <u>Weight</u> 13.2% 10.9%	Odds Ratio <u>M-H. Random, 95% CI</u> 1.17 [1.04, 1.32] 1.60 (11.19, 2.17]	0.01	0.1 M-H.	1 Odds Ratio Random, 95%	10 % CI	100
Study or Subgroup Cheng Hu 2009 Eun Seok Kang 2009 Ganesh Chauhan 1 2010	Chi ² = 118 18 (P = 0.0 T2DN Events 720 84 118	8.71, df = 001) 1 <u>Total</u> 3700 290 2040	Contr Events 612 180 88	ol Total 3570 888 2012); I ² = 90% <u>Weight</u> 13.2% 10.9% 11.2%	Odds Ratio <u>M-H. Random. 95% CI</u> 1.17 [1.04, 1.32] 1.60 [1.19, 2.17] 1.34 (1.01 1.78]	0.01	0.1 M-H.	1 Odds Ratio Random, 95%	10 % CI	100
Study or Subgroup Cheng Hu 2009 Eun Seok Kang 2009 Ganesh Chauhan 1 2010 Ganesh Chauhan 2 2010	Chi ² = 118 18 (P = 0.0 T2DN Events 720 84 118 214	8.71, df = 001) 1 Total 3700 290 2040 2934	Contr Events 612 180 88 226	0.00001 Total 3570 888 2012 3344	Weight 13.2% 10.9% 11.2% 12.4%	Odds Ratio <u>M-H. Random, 95% CI</u> 1.17 [1.04, 1.32] 1.60 [1.19, 2.17] 1.34 [1.01, 1.78] 1.09 (0.89, 1.32]	0.01	0.1 M-H.	1 Odds Ratio Random, 959	10 % Cl	100
Study or Subgroup Cheng Hu 2009 Eun Seok Kang 2009 Ganesh Chauhan 1 2010 Ganesh Chauhan 2 2010	Chi ² = 118 18 (P = 0.0 T2DN Events 720 84 118 214 260	8.71, df = 001) Total 3700 290 2040 2934 1948	Contr Events 612 180 88 226	0.00001 Total 3570 888 2012 3344 17969	Weight 13.2% 10.9% 11.2% 12.4% 12.2%	Odds Ratio <u>M-H. Random. 95% CI</u> 1.17 [1.04, 1.32] 1.60 [1.19, 2.17] 1.34 [1.01, 1.78] 1.09 [0.89, 1.32] 1.51 (1.24, 1.21]	0.01	0.1 M-H.	1 Odds Ratio Random, 959	10 % CI	100
Study or Subgroup Cheng Hu 2009 Eun Seok Kang 2009 Ganesh Chauhan 1 2010 Ganesh Chauhan 2 2010 Oswald NN 2017 Xuaree Mag 2000	Chi ² = 118 18 (P = 0.0 T2DN Events 720 84 118 214 360 470	8.71, df = 001) Total 3700 290 2040 2934 1948	Contr Events 612 180 88 226 2332	0.00001 Total 3570 888 2012 3344 17868 2012	Weight 13.2% 10.9% 11.2% 12.4% 13.2%	Odds Ratio <u>M-H. Random, 95% CI</u> 1.17 [1.04, 1.32] 1.60 [1.19, 2.17] 1.34 [1.01, 1.78] 1.09 [0.89, 1.32] 1.51 [1.34, 1.71]	0.01	0.1 M-H.	1 Odds Ratio Random, 959	10 <u>% CI</u>	100
Study or Subgroup Cheng Hu 2009 Cheng Hu 2009 Ganesh Chauhan 1 2010 Ganesh Chauhan 2 2010 Oswald NN 2017 Xueyao Han 2010	Chi ² = 118 18 (P = 0.0 T2DN Events 720 84 118 214 360 472 500	8.71, df = 001) 1 Total 3700 290 2040 2934 1948 2134 2020	Contr Events 612 180 88 226 2332 354	0.00001 Total 3570 888 2012 3344 17868 2010); I ² = 90% Weight 13.2% 10.9% 11.2% 12.4% 13.2% 12.9%	Odds Ratio <u>M-H. Random. 95% CI</u> 1.17 [1.04, 1.32] 1.60 [1.19, 2.17] 1.34 [1.01, 1.78] 1.09 [0.89, 1.32] 1.51 [1.34, 1.71] 1.33 [1.14, 1.55]	0.01	0.1 М-Н.	1 Odds Ratio Random, 95%	10 <u>% Cl</u>	100
Study or Subgroup Cheng Hu 2009 Eun Seok Kang 2009 Ganesh Chauhan 1 2010 Ganesh Chauhan 2 2010 Oswald NN 2017 Xueyao Han 2010 Y.Liu 2008	Chi ² = 118 18 (P = 0.0 T2DN Events 720 84 118 214 360 472 586	8.71, df = 001) 1 Total 3700 290 2040 2934 1948 2134 3806	Contr Events 612 180 88 226 2332 354 744	0.00001 Total 3570 888 2012 3344 17868 2010 3644	Weight 13.2% 10.9% 11.2% 12.4% 13.2% 12.9% 13.2% 13.2%	Odds Ratio <u>M-H. Random. 95% CI</u> 1.17 [1.04, 1.32] 1.60 [1.19, 2.17] 1.34 [1.01, 1.78] 1.09 [0.89, 1.32] 1.51 [1.34, 1.71] 1.33 [1.14, 1.55] 0.71 [0.63, 0.80]	0.01	0.1 М-Н,	1 Odds Ratio Random, 959	10 <u>% CI</u>	100
Study or Subgroup Cheng Hu 2009 Eun Seok Kang 2009 Ganesh Chauhan 1 2010 Ganesh Chauhan 2 2010 Oswald NN 2017 Xueyao Han 2010 Y.Liu 2008 Ying Lin 2010	Chi ² = 118 18 (P = 0.0 T2DN Events 720 84 118 214 360 472 586 620	8.71, df = 001) 1 Total 3700 290 2040 2934 1948 2134 3806 3060	Contr Events 612 180 88 226 2332 354 744 394	0.00001 Total 3570 888 2012 3344 17868 2010 3644 2878	Weight 13.2% 10.9% 11.2% 12.4% 13.2% 13.2% 13.2% 13.2% 13.2% 13.2% 13.2%	Odds Ratio <u>M-H. Random. 95% CI</u> 1.17 [1.04, 1.32] 1.60 [1.19, 2.17] 1.34 [1.01, 1.78] 1.09 [0.89, 1.32] 1.51 [1.34, 1.71] 1.33 [1.14, 1.55] 0.71 [0.63, 0.80] 1.60 [1.40, 1.84]	0.01	0.1 М-Н.	1 Odds Ratio Random, 959	10 <u>% CI</u>	100
Study or Subgroup Cheng Hu 2009 Eun Seok Kang 2009 Ganesh Chauhan 1 2010 Ganesh Chauhan 2 2010 Oswald NN 2017 Xueyao Han 2010 Y.Liu 2008 Ying Lin 2010 Total (95% CI)	Chi ² = 118 18 (P = 0.0 T2DN Events 720 84 118 214 360 472 586 620	8.71, df = 001) 1 Total 3700 290 2040 2934 1948 2134 3806 3060 19912	Contr Events 612 180 88 226 2332 354 744 394	0.00001 Total 3570 888 2012 3344 17868 2010 3644 2878 36214	Weight 13.2% 10.9% 11.2% 12.4% 13.2% 12.9% 13.2% 13.0% 100.0%	Odds Ratio <u>M-H. Random. 95% CI</u> 1.17 [1.04, 1.32] 1.60 [1.19, 2.17] 1.34 [1.01, 1.78] 1.09 [0.89, 1.32] 1.51 [1.34, 1.71] 1.33 [1.14, 1.55] 0.71 [0.63, 0.80] 1.60 [1.40, 1.84] 1.25 [1.00, 1.56]	0.01	0.1 М-Н.	1 Odds Ratio Random, 959	10 <u>% CI</u>	100
Study or Subgroup Cheng Hu 2009 Eun Seok Kang 2009 Ganesh Chauhan 1 2010 Ganesh Chauhan 2 2010 Oswald NN 2017 Xueyao Han 2010 Y.Liu 2008 Ying Lin 2010 Total (95% CI) Total events	Chi ² = 118 18 (P = 0.0 T2DW Events 720 84 118 214 360 472 586 620 3174	8.71, df = 001) Total 3700 290 2040 2934 1948 2134 3806 3060 19912	Contr Events 612 180 88 226 2332 354 744 394 4930	0.00001 Total 3570 888 2012 3344 17868 2010 3644 2878 36214	Weight 13.2% 10.9% 11.2% 12.4% 13.2% 13.2% 13.2% 13.0% 100.0%	Odds Ratio <u>M-H. Random. 95% CI</u> 1.17 [1.04, 1.32] 1.60 [1.19, 2.17] 1.34 [1.01, 1.78] 1.09 [0.89, 1.32] 1.51 [1.34, 1.71] 1.33 [1.14, 1.55] 0.71 [0.63, 0.80] 1.60 [1.40, 1.84] 1.25 [1.00, 1.56]	0.01	0.1	1 Odds Ratio Random, 959	10 % CI	100
Study or Subgroup Cheng Hu 2009 Eun Seok Kang 2009 Ganesh Chauhan 1 2010 Ganesh Chauhan 2 2010 Oswald NN 2017 Xueyao Han 2010 Y.Liu 2008 Ying Lin 2010 Total events Heterogeneity: Tau ² = 0.09;	Chi ² = 118 18 (P = 0.0 T2DN Events 720 84 118 214 360 472 586 620 	8.71, df = 001) Total 3700 290 2040 2934 1948 2134 3806 3060 19912 2.01, df =	Contr Events 612 180 88 236 2322 354 744 394 4930 = 7 (P < 0	0.00001 Total 3570 888 2012 3344 17868 2010 3644 2878 36214	Weight 13.2% 10.9% 11.2% 12.4% 13.2% 13.2% 13.0% 100.0% ² = 94%	Odds Ratio <u>M-H. Random. 95% CI</u> 1.17 [1.04, 1.32] 1.60 [1.19, 2.17] 1.34 [1.01, 1.78] 1.09 [0.89, 1.32] 1.51 [1.34, 1.71] 1.33 [1.14, 1.55] 0.71 [0.63, 0.80] 1.60 [1.40, 1.84] 1.25 [1.00, 1.56]	0.01	0.1 M-H.	1 Odds Ratio Random, 95%	10 <u>% Cl</u>	100

	T2DI	M	Contr	lo		Odds Ratio			Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-	H. Fixed, 95%	CI	
C.Herder 2008	112	866	258	2876	9.9%	1.51 [1.19, 1.91]			-		
Dimitry A 2011	198	1538	140	1534	11.6%	1.47 [1.17, 1.85]			-		
JESSICA N. COOKE 2012	856	2300	368	1134	29.4%	1.23 [1.06, 1.43]			-		
Joshua P. Lewis 2008	752	1986	714	2108	40.9%	1.19 [1.05, 1.35]					
M.Cruz 2010	104	1038	98	1096	8.2%	1.13 [0.85, 1.52]			+		
Total (95% CI)		7728		8748	100.0%	1.26 [1.16, 1.37]			•		
Total events	2022		1578								
Heterogeneity: Chi ² = 5.32, c	if = 4 (P =	0.26); 1	² = 25%					-		10	100
Test for overall effect: Z = 5.	66 (P < 0.0	00001)					0.01	0.1	1	10	100

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 cyclindependent 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 cyclindependent 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 cyclindependent 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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