Systematic Review and Meta-Analysis

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Association of uncoupling protein-2 -866G/A and Ala55Val polymorphisms with susceptibility to type 2 diabetes mellitus

A meta-analysis of case-control studies

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Abstract

Background: Recently, the relationships between uncoupling protein-2 (UCP2) -866G/A (*rs659366*) and Ala55Val (*rs660339*) polymorphisms and the risk of type 2 diabetes mellitus (T2DM) have been explored considerably, but the results are greatly inconsistent. This meta-analysis was performed to further identify the association of UCP2 *rs659366* and *rs660339* with the risk of T2DM.

Methods: Eligible studies were searched from PubMed, Embase, Cochrane Library, VIP database, Chinese National Knowledge Infrastructure, and Chinese WanFang database until March 8, 2020. The odds ratios with corresponding 95% confidence intervals (CIs), and *P*-values were used to assess the strength of the association.

Results: A total of 26 studies were included in this study. UCP2 *rs659366* was associated with the risk of T2DM in allele model (OR: 1.112, 95%CI: 1.009-1.224, $P=0.032$), dominant model (OR: 1.189, 95%CI: 1.035–1.366, $P=0.014$), and heterozygous model (OR: 1.177, 95%CI: 1.032–1.342, $P=.015$). A significantly increased risk of T2DM was detected in Asians by UCP2 *rs659366* allele (OR: 1.132, 95%CI: 1.016–1.262, $P=.025$), dominant (OR: 1.218, 95%CI: 1.046–1.418, $P=.011$), homozygous (OR: 1.254, 95% CI: 1.022–1.540, $P=.031$) or heterozygous (OR: 1.198, 95%CI: 1.047–1.371, $P=.009$) models. There was no significant correlation between UCP2 *rs660339* and the risk of T2DM ($P>.05$).

Conclusions: The UCP2 *rs65366* is significantly associated with the risk of T2DM, especially in Asian population, while no evidence is found between the UCP2 *rs660339* and the susceptibility to T2DM.

Abbreviations: ATP = adenosine triphosphate, CIs = confidence intervals, NOS = Newcastle-Ottawa scale, PCR-RFLP = polymerase chain reaction–restriction fragment length polymorphism, *rs659366* = -866G/A, *rs660339* = Ala55Val, T2DM = type 2 diabetes mellitus, UCP2 = uncoupling protein-2.

Keywords: -866G/A, Ala55Val, type 2 diabetes mellitus, uncoupling protein-2

1. Introduction

Type 2 diabetes mellitus (T2DM) is a serious public health hazard characterized by inadequate secretion and utilization of insulin, with increasing morbidity and mortality worldwide.[1] As a multifactorial disease, the susceptibility of T2DM is affected by the combination of various genetic and environmental factors.[2] It is believed that the environmental factors only affect the presence of T2DM genetic background, while genetic factors are considered to play a crucial role in the pathogenesis and chronic

Editor: Sabbir Khan.

This work was supported by the Project of the Priority Academic Program Development of Jiangsu Higher Education Institutions (Integration of Chinese and Western Medicine).

For this type of article, ethics approval is not necessary.

The authors have no conflicts of interest to disclose.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Xu L, Chen S, Zhan L. Association of uncoupling protein-2 -866G/A and Ala55Val polymorphisms with susceptibility to type 2 diabetes mellitus: a meta-analysis of case-control studies. Medicine 2021;100:6(e24464).

Received: 1 July 2020 / Received in final form: 21 November 2020 / Accepted: 6 January 2021

http://dx.doi.org/10.1097/MD.0000000000024464

complications of T2DM.[2] Therefore, genetically susceptible subjects who are exposed to the environmental risk factors are easier to develop the T2DM.

As a family member of the mitochondrial anion transporter proteins, uncoupling protein-2 (UCP2) is broadly expressed in tissues and cell types.[3,4] UCP2 mediates proton leakage across the inner membrane by uncoupling the substrate oxidation from the adenosine triphosphate (ATP) synthesis, causing the decrease of ATP production by the mitochondrial respiratory chain.[5] Therefore, the glucose-stimulated insulin secretion which is regulated by the ATP/ADP ratio may be suppressed by the UCP2 activity.[6,7] This mechanism is closely associated with the pathogenesis and chronic complications of T2DM. The UCP2 promoter -866G/A (*rs659366*) polymorphism, which serves as a binding site for insulin promotor factor 1 and the pancreatic transcription factor parried box-containing 6, is found to have the association with increased UCP2 mRNA levels, decreased insulin secretion and higher T2DM risk.[8–10] In addition, the Ala55Val (C/T; rs660339) polymorphism in exon 4 has also been confirmed to be associated with a reduced uncoupling degree and energy expenditure, as well as an increased risk of obesity and diabetes.[11,12]

Recently, the relationships between UCP2 -866G/A (*rs659366*) and Ala55Val (*rs660339*) polymorphisms and T2DM risk have been explored in various studies. However, the results of these studies are greatly inconsistent. A few studies demonstrated that UCP2 *rs659366* and *rs660339* polymorphisms were correlated with T2DM risk,[13,14] while some other studies failed to discover the association.[15–17] The identification of the relationship between UCP2 and T2DM susceptibility will help the diagnosis, prevention, and treatment of T2DM. Hence, we conducted this meta-analysis by systematically reviewing the current evidence to clarify the relationship between UCP2 *rs659366* and *rs660339* polymorphisms and risk of T2DM.

2. Methods

2.1. Search strategy

Articles were retrieved from PubMed, Embase, Cochrane Library, VIP database, Chinese National Knowledge Infrastructure, and Chinese WanFang database until March 8st, 2020. Key words and subject terms used for search included 'Type 2 Diabetes' OR 'Type 2 diabetes mellitus' OR 'T2DM' AND 'Uncoupling protein 2' OR 'UCP2' AND 'variation' OR 'mutation' OR 'variant' OR 'polymorphism' OR 'single nucleotide polymorphism.'

2.2. Inclusion and exclusion criteria

All involved articles were screened by the following inclusion criteria:

(1) case-control studies investigating the association of UCP2 *rs659366* and *rs660339* polymorphisms with T2DM;
(2) clear definition of T2DM;
(3) cases of diabetes ≥ 50;
(4) sufficient data on the genotype distribution;
(5) articles published in peer-reviewed journals;
(6) language in English or Chinese;
(7) evidence of Hardy-Weinberg equilibrium (HWE) >0.05.

Exclusion criteria were as follows:

(1) reviews, letters, meetings;
(2) duplicated reports;
(3) outcomes not relevant to *rs659366* or *rs660339*;
(4) studies using genome wide association study to detect the genotyping.

2.3. Methodological quality appraisal

Two researchers independently assessed the methodological quality of the included studies using the Newcastle-Ottawa scale (NOS).[18] The NOS evaluates quality of observational study based on 3 aspects: selection, comparability and ascertainment of exposure and outcomes. Three aspects assign a maximum score of 4, 2 and 3, respectively, and the assessment score for each study ranges from 0 to 9. Studies with a NOS score of 7 or more were regarded as high-quality study. Any disagreements were settled by the consensus.

2.4. Data extraction

The following data were extracted from each independent study: first author, year of publication, country, ethnicity, sample size, source of control, genotyping method, single nucleotide polymorphism type, HWE, and NOS score. All data were extracted from the included studies, and we did not contact the authors for additional data.

2.5. Statistical analysis

To investigate the relationships of *UCP2* rs659366 and rs660339 polymorphisms with T2DM risk, we conducted the meta-analyses using a series of genetic models, including allele model (A vs G for *rs659366* and T vs C for *rs660339*), homozygous model (AA vs GG for *rs659366* and TT vs CC for *rs660339*), dominant model (AG/AA vs GG for *rs659366* and TC/TT vs CC for *rs660339*), recessive model (AA vs GG/AG for *rs659366* and TT vs CC/TC for *rs660339*), and heterozygous model (AG vs GG for *rs659366* and CT vs TT for *rs660339*). Besides, subgroup analyses were carried out according to ethnicity, source of control, genotyping method, and quality of articles.

The strength of correlation between UCP2 variants and T2DM was measured by odds ratios and the corresponding 95% confidence intervals (CIs). Between-study heterogeneity was evaluated by the χ^2-based Q-test and I^2 statistics. P value of Q-test $< .10$ and $I^2 > 50\%$ indicated evidence of heterogeneity, and then a random-effect model was used to count the summary risk estimate; otherwise, the fixed-effect model was performed. Harbord test was used to estimate the potential publication bias. All above statistical analyses were performed using Stata 14.0 (Stata Corporation, College Station, TX), and P values were 2-sided with a statistical significance level of 0.05, except for tests of heterogeneity where a level of 0.10 was used.

3. Results

3.1. Characteristics of included studies

A total of 322 relevant articles were recognized from electronic databases. 110 duplicate articles were excluded, 152 articles were removed by screening titles and abstracts, and further 34 articles were excluded based on appraising the full text. Finally, 26 case-control studies meeting all inclusion criteria were included in this

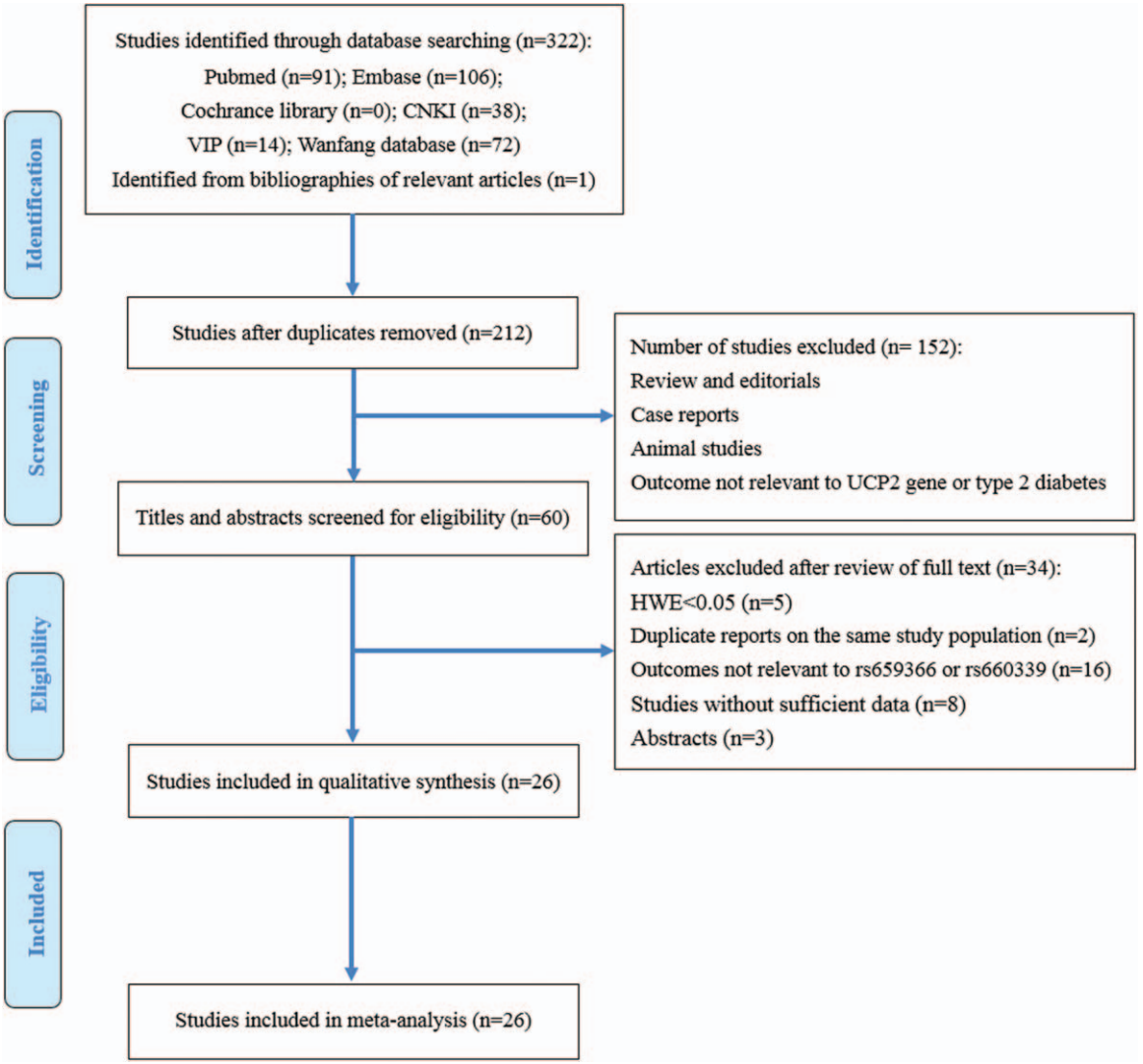

Figure 1. The flow diagram of the meta-analysis.

meta-analysis.[1,8,14–16,19–39] The flow diagram was shown in the Figure 1.

Among the included studies, 19 studies were performed in Asian population, and 7 in Caucasian population. Polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) was adopted for genotyping of UCP2 *rs659366* and *rs660339* in most studies. The detailed characteristics and quality assessment of all included studies were listed in the Table 1.

3.2. Correlation between UCP2 rs659366 polymorphism and risk of T2DM

20 studies[1,14,16,20–23,24–34,36,38] including 6895 T2DM cases and 4999 controls were pooled to estimate the relationship of UCP2 *rs659366* polymorphism with T2DM risk. Significant correlations were discovered in allele model (OR: 1.112, 95%CI: 1.009–1.224, P=0.032), dominant model (OR: 1.189, 95%CI: 1.035–1.366, P=.014), and heterozygous model (OR: 1.177, 95%CI: 1.032–1.342, P=.015), while no evidence of association was found in recessive model (OR: 1.086, 95%CI: 0.945–1.248, P=.246) and homozygous model (OR: 1.207, 95%CI: 0.997–1.461, P=.054). (Table 2, Fig. 2).

Due to the significant heterogeneity in the genetic models among included studies, subgroup analyses were performed to identify the source of heterogeneity based on the ethnicity, source of control, genotyping method and quality assessment. For ethnicity, a significantly increased risk of T2DM was detected in Asians by allele (OR: 1.132, 95%CI: 1.016–1.262, P=.025), dominant (OR: 1.218, 95%CI: 1.046–1.418, P=.011), homozygous (OR: 1.254, 95%CI: 1.022–1.540, P=.031), or heterozygous (OR: 1.198, 95%CI: 1.047–1.371, P=.009) models, while no statistical significance was found in the recessive model (OR: 1.105, 95%CI: 0.963–1.268, P=.154). Regarding the source of control, significant differences were presented between T2DM risk and UCP2 *rs659366* allele (OR: 1.212, 95%CI: 1.104–1.330, P<.001), dominant (OR: 1.342, 95%CI: 1.151–1.565, P<.001), recessive (OR: 1.215, 95%CI: 1.077–1.371, P=.002), homozygous (OR: 1.424, 95%CI: 1.204–1.684, P<.001), or heterozygous (OR: 1.308, 95%CI: 1.114–1.535, P=.001) models in hospital-based studies. For genotyping methods, the risk of T2DM was found to be associated with

Table 1

Basic characteristics of the studies included in this meta-analysis.

First author, year	Country	Ethnicity	Case/Control	Source of control	Genotyping method	SNP type	HWE	NOS score
Gomathi 2019[1]	India	Asian	318/312	Hospital-based	PCR-RFLP	rs659366	0.490	7
Su 2018[19]	China	Asian	397/409	Population-based	Mass ARRAY system	rs660399	0.751	7
Shen 2014[20]	China	Asian	479/479	Hospital-based	DNA sequencing	rs659366, rs660399	0.160/0.117	6
Sun 2013[21]	China	Asian	471/78	Hospital-based	PCR-RFLP	rs659366	0.630	5
Qin 2013[22]	China	Asian	352/363	Hospital-based	PCR-RFLP	rs659366, rs660399	0.487/0.022	6
Souza 2013[15]	Brazil	Caucasian	981/534	Hospital-based	TaqMan	rs659366, rs660399	0.932/0.536	6
Hu 2010[23]	China	Asian	104/114	Unknown	PCR+DHPLC	rs660339	0.460	5
Hedari 2010[24]	Iran	Asian	75/75	Population-based	PCR-RFLP	rs659366	0.125	7
Crispim 2010[25]	Brazil	Caucasian	240/258	Hospital-based	TaqMan	rs659366, rs660399	0.997/0.613	6
Beitelshees 2010[26]	Italy	Caucasian	107/341	Hospital-based	Pyrosequencing/TaqMan	rs659366	0.192	7
Wang 2009[27]	China	Asian	470/217	Population-based	PCR-RFLP	rs659366	0.634	6
She 2009[28]	China	Asian	370/166	Hospital-based	PCR-RFLP	rs659366	0.076	7
Li 2008[29]	China	Asian	192/101	Hospital-based	PCR-RFLP	rs659366	0.395	6
Shen 2007[30]	China	Asian	229/196	Hospital-based	PCR-RFLP	rs659366	0.894	5
Gu 2007[31]	China	Asian	278/162	Population-based	PCR-RFLP	rs659366	0.671	8
Yu 2006[32]	China	Asian	122/55	Hospital-based	PCR-RFLP	rs659366	0.893	7
Pinelli 2006[33]	Italy	Caucasian	342/305	Population-based	ASA/RT-PCR	rs659366	0.315	6
Bullota 2005[34]	Italy	Caucasian	746/327	Population-based	Unknown	rs659366	0.633	7
Xiu 2004[35]	China	Asian	173/177	Hospital-based	PCR-RFLP	rs660339	0.327	6
Sasahara 2004[16]	Japan	Asian	413/172	Hospital-based	PCR-RFLP	rs659366	0.446	4
Ji 2004[36]	Japan	Asian	342/134	Unknown	PCR-RFLP	rs659366	0.689	3
D'Adamo 2004[14]	Italy	Caucasian	483/565	Hospital-based	TaqMan	rs659366	0.069	3
Cho 2004[37]	Korea	Asian	504/133	Unknown	PCR-RFLP	rs660339	0.097	4
Krempler 2002[8]	Austria	Caucasian	201/291	Hospital-based	PCR-RFLP	rs659366	0.132	6
Zheng 2000[38]	China	Asian	166/193	Population-based	PCR-RFLP	rs660339	0.121	4
Kubota 1998[39]	Japan	Asian	210/218	Unknown	PCR-RFLP	rs660339	0.107	3

DHPLC = denaturing high-performance liquid chromatography, HWE = Hardy-Weinberg equilibrium, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism, RT-PCR = (Real-time reverse transcription)-polymerase chain reaction.

UCP2 *rs659366* allele (OR: 1.161, 95%CI: 1.031–1.308, $P = .014$), dominant (OR: 1.273, 95%CI: 1.072–10512, $P = .006$), homozygous (OR: 1.301, 95%CI: 1.044–1.621, $P = .019$), or heterozygous (OR: 1.258, 95%CI: 1.071–1.477, $P = .005$) models when PCR-RFLP was used. Additionally, high-quality studies showed that there was the association between the risk of T2DM and UCP2 *rs659366* dominant (OR: 1.239, 95% CI: 1.045–1.469, $P = .014$) and heterozygous (OR: 1.239, 95% CI: 1.064–1.442, $P = .006$) models. (Table 2).

3.3. Correlation between UCP2 rs660339 polymorphism and risk of T2DM

There were 9 studies on the correlation between UCP2 *rs660339* and the risk of T2DM,[15,19,20,22,23,25,37,39,40] including 3042 T2DM cases and 2388 controls. Pooled analysis exhibited that no significant difference was presented between *rs660339* and the risk of T2DM (all $P > .05$). Details were shown in the Table 3 and Figure 3.

Table 2

Stratified meta-analyses of the correlation between UCP2 rs659366 polymorphism and risk of T2DM.

			A vs. G (allele model)		AG+AA vs. GG (dominant model)		AA vs. GG+AG (recessive model)		AA vs. GG (homozygous model)		AG vs. GG (heterozygous model)	
Characteristics	No. of studies	Sample size (case/control)	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Total	20	6985/4999	1.112 (1.009–1.224)	.032	1.189 (1.035–1.366)	.014	1.086 (0.945–1.248)	.246	1.207 (0.997–1.461)	.054	1.177 (1.032–1.342)	.015
Ethnicity												
Asian	13	4088/2479	1.132 (1.016–1.262)	.025	1.218 (1.046–1.418)	.011	1.105 (0.963–1.268)	.154	1.254 (1.022–1.540)	.031	1.198 (1.047–1.371)	.009
Caucasian	7	2897/2520	1.079 (0.896–1.298)	.423	1.154 (0.890–1.496)	.279	1.022 (0.750–1.393)	.891	1.117 (0.756–1.651)	.577	1.161 (0.899–1.499)	.252
Source of control												
Hospital-based	14	4732/3779	1.212 (1.104–1.330)	<.001	1.342 (1.151–1.565)	<.001	1.215 (1.077–1.371)	.002	1.424 (1.204–1.684)	<.001	1.308 (1.114–1.535)	.001
Population-based	5	1911/1086	0.841 (0.752–0.940)	.002	0.839 (0.716–0.984)	.031	0.725 (0.587–0.897)	.003	0.669 (0.525–0.851)	.001	0.896 (0.758–1.060)	.202
Unknown	1	342/134	1.098 (0.827–1.457)	.517	1.101 (0.702–1.726)	.675	1.175 (0.723–1.909)	.515	1.216 (0.684–2.164)	.505	1.054 (0.656–1.695)	.828
Genotyping method												
Others	7	3150/2677	1.040 (0.887–1.218)	.631	1.077 (0.873–1.330)	.488	1.011 (0.760–1.347)	.938	1.065 (0.751–1.512)	.723	1.076 (0.880–1.317)	.475
PCR-RFLP	13	3835/2322	1.161 (1.031–1.308)	.014	1.273 (1.072–1.512)	.006	1.117 (0.966–1.291)	.136	1.301 (1.044–1.621)	.019	1.258 (1.071–1.477)	.005
Quality												
High	16	5377/3964	1.126 (0.996–1.274)	.058	1.239 (1.045–1.469)	.014	1.048 (0.888–1.238)	.578	1.207 (0.948–1.538)	.127	1.239 (1.064–1.442)	.006
Low	4	1608/1035	1.069 (0.951–1.202)	.265	1.004 (0.848–1.190)	.960	1.245 (1.002–1.547)	.048	1.251 (0.980–1.598)	.073	0.938 (0.784–1.124)	.489

CI = confidence interval, OR = odds ratio, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, T2DM = type 2 diabetes mellitus, UCP2 = uncoupling protein-2.

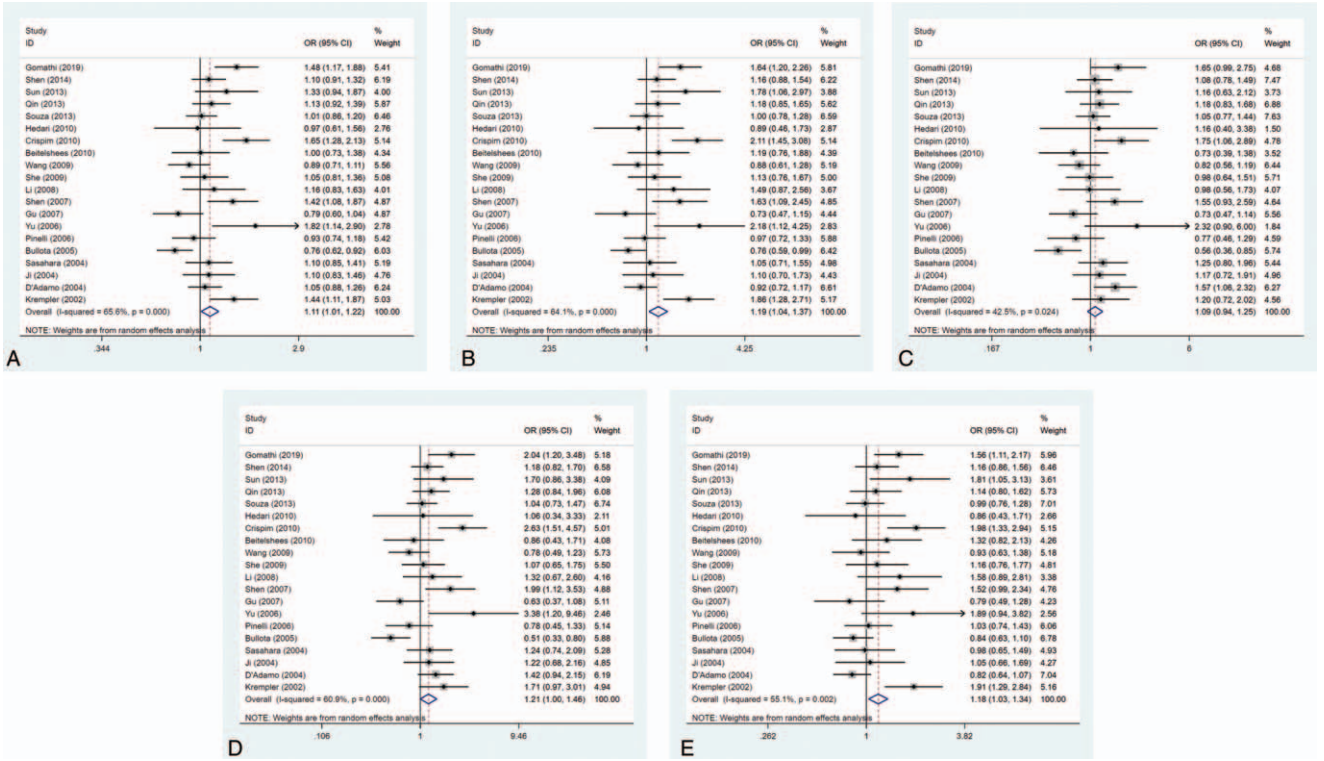

Figure 2. Forest plots for the correlation between UCP2 *rs659366* polymorphism and risk of T2DM (A. allele model; B. dominant model; C. recessive model; D. homozygous model; E. homozygous model).

3.4. Publication bias

Harbord test showed no publication bias in allele ($t=1.42$, $P=.172$), dominant (t=1.89, $P=.075$), recessive (t=0.48, $P=.638$), homozygous (t=1.98, $P=.342$) and heterozygous models (t=2.08, $P=0.052$) of UCP2 *rs659366*, as well as in allele (t=1.29, $P=.240$), dominant (t=0.91, $P=.392$), recessive (t=1.63, $P=.147$), homozygous (t=1.49, $P=.180$) and heterozygous models (t=0.69, $P=.511$) of UCP2 *rs660339*. Details were shown in the Table 4, Figs. 4 and 5.

4. Discussion

As an inner mitochondrial membrane transporter protein, UCP2 enables oxidative phosphorylation of ADP uncoupled to ATP. This may influence the specific function of tissues, such as thermogenesis, regulation of glucose and free fatty acid metabolism. The high expression of UCP2 in the pancreatic β-cells regulates the insulin negatively, resulting in the dysfunction and development of T2DM.[40,41] Considering the importance of UCP2 in the T2DM pathogenesis, the relationship

Table 3

Stratified meta-analyses of the correlation between UCP2 rs660339 polymorphism and risk of T2DM.

Characteristics	No. of studies	Sample size (case/control)	T vs. C (allele model) OR (95%CI)	P	CT+CC vs. TT (dominant model) OR (95%CI)	P	CC vs. TT+CT (recessive model) OR (95%CI)	P	CC vs. TT (homozygous model) OR (95%CI)	P	CT vs. TT (heterozygous model) OR (95%CI)	P
Total	9	3042/2388	1.066 (0.887–1.282)	.494	1.056 (0.827–1.349)	.663	1.132 (0.851–1.506)	.393	1.160 (0.803–1.676)	.430	1.026 (0.825–1.276)	.820
Ethnicity												
Asian	7	2016/1676	1.034 (0.825–1.296)	.774	0.994 (0.760–1.300)	.962	1.126 (0.767–1.653)	.545	1.107 (0.695–1.762)	.669	0.965 (0.776–1.199)	.745
Caucasian	2	1026/712	1.186 (0.777–1.808)	.429	1.291 (0.612–2.725)	.502	1.148 (0.882–1.494)	.305	1.369 (0.655–2.863)	.404	1.256 (0.592–2.668)	.553
Source of control												
Hospital-based	2	1671/1330	1.078 (0.912–1.272)	.379	1.083 (0.844–1.388)	.532	1.145 (0.840–1.560)	.391	1.176 (0.829–1.668)	.363	1.054 (0.811–1.370)	.692
Population-based	4	553/591	1.182 (0.798–1.751)	.404	1.217 (0.743–1.996)	.435	1.286 (0.717–2.309)	.399	1.431 (0.655–3.127)	.369	1.155 (0.770–1.732)	.486
Unknown	3	818/467	0.920 (0.775–1.091)	.337	0.852 (0.654–1.110)	.235	0.963 (0.665–1.395)	.843	0.865 (0.607–1.232)	.421	0.844 (0.561–1.271)	.418
Genotyping method												
Others	5	1989/1665	1.001 (0.799–1.254)	.995	1.013 (0.737–1.392)	.935	0.979 (0.734–1.306)	.886	1.005 (0.656–1.542)	.980	1.020 (0.765–1.359)	.893
PCR-RFLP	4	1053/723	1.164 (0.827–1.637)	.383	1.120 (0.723–1.737)	.612	1.397 (0.769–2.537)	.272	1.422 (0.691–2.925)	.339	1.035 (0.698–1.536)	.863
Quality												
High	6	2162/1842	1.115 (0.856–1.452)	.421	1.127 (0.809–1.570)	.480	1.191 (0.798–1.776)	.392	1.273 (0.749–2.162)	.372	1.084 (0.825–1.425)	.562
Low	3	880/546	0.975 (0.831–1.144)	.760	0.920 (0.682–1.241)	.586	1.046 (0.714–1.532)	.819	0.966 (0.695–1.343)	.837	0.904 (0.600–1.362)	.628

CI = confidence interval, OR = odds ratio, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphis, T2DM = type 2 diabetes mellitus, UCP2 = uncoupling protein-2.

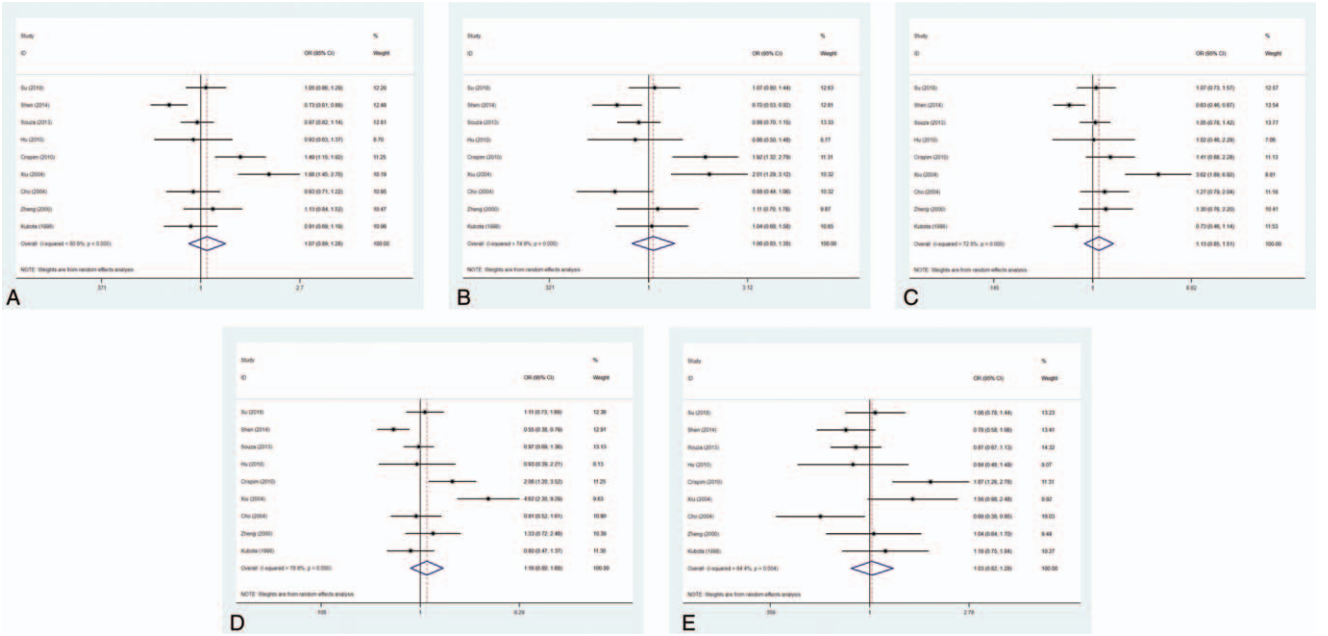

Figure 3. Forest plots for the correlation between UCP2 *rs660339* polymorphism and risk of T2DM (A. allele model; B. dominant model; C. recessive model; D. homozygous model; E. homozygous model).

between UCP2 polymorphisms and T2DM susceptibility has been studied in the current study. A total of 26 studies were finally included. Results showed that the risk of T2DM was associated with the allele model, dominant model, and heterozygous model of UCP2 *rs659366*, especially in Asians. However, we did not find the significant correlation between UCP2 *rs660339* and the risk of T2DM.

The polymorphism in the promoter region of UCP2 is reported to elevate the expression of UCP2, resulting in decreased insulin secretion and early onset of T2DM.[1] UCP2 *rs659366*, situated in the core promoter of the region with putative binding sites for 2 β-cell transcription factors, is associated with differential expression of UCP2 and increased levels of oxidative stress markers.[10] Compared with G allele, the A allele in the UCP2 *rs659366* is related to higher UCP2 mRNA expression levels.[1] Enormous studies showed that the A allele in the UCP2 *rs659366* had the association with insulin resistance and T2DM risk.[10,14,25] In our meta-analysis, the risk of T2DM was found to be associated with the allele model, dominant model, and heterozygous model of UCP2 *rs659366* in Asian population, but not Caucasian population, supported by the result of a previous meta-analysis that UCP2 *rs659366* polymorphism in European ancestry was irrelevant to T2DM risk.[15] This ethnic discrepancy in susceptibility to T2DM might be attributed to the genetic variation. In addition, our study also found significance differences between the risk of T2DM and UCP2 *rs659366* allele, dominant, homozygous or heterozygous models in the hospital-based studies and PCR-RFLP assay.

Table 4

Publication bias of each model for UCP2 polymorphisms.

SNP	*t*	*P*
rs659366		
A vs G (allele model)	1.42	.172
AG+AA vs GG (dominant model)	1.89	.075
AA vs GG+AG (recessive model)	0.48	.638
AA vs GG (homozygous model)	1.98	.342
AG vs GG (heterozygous model)	2.08	.052
rs660399		
T vs C (allele model)	1.29	.240
CT+CC vs TT (dominant model)	0.91	.392
CC vs TT+CT (recessive model)	1.63	.147
CC vs TT (homozygous model)	1.49	.180
CT vs TT (heterozygous model)	0.69	.511

SNP = single nucleotide polymorphism, UCP2 = uncoupling protein-2.

UCP2 rs660339 is located in exon 4 in the UCP2 gene where the base change can cause the changes in coding amino acids from alanine to valine. Previous studies showed that the TT of rs660339 could increase the risk of overweight, suggesting rs660339 might contribute to facilitating the development of prediabetes or T2DM via overweight.[42,43] Vimaleswaran et al. found that UCP2 rs660339 was associated with a significantly lowered risk of T2DM in Asian Indians.[13] Nevertheless, no association between UCP2 rs660339 and incidence T2DM was found in the Atherosclerosis Risk in Communities Study cohort.[44] Our results further confirmed no association of UCP2 rs660339 with susceptibility to T2DM either in Asian population or Caucasian population, which may be explained by the fact that the UCP2 gene was probably a genetic risk factor for diabetes, while UCP2 rs660339 polymorphism may not be a key variant.

Although our meta-analysis included the latest publications and conducted a series of subgroup analyses to provide a comprehensive evaluation for the relationship between UCP2 variants and T2DM risk, several potential limitations remained to be taken into consideration. First, the results of our study were based on the unadjusted estimates. The adjusted estimates might be more precise in evaluating the real relationship. Second, T2DM was a complex multifactorial disease produced by the

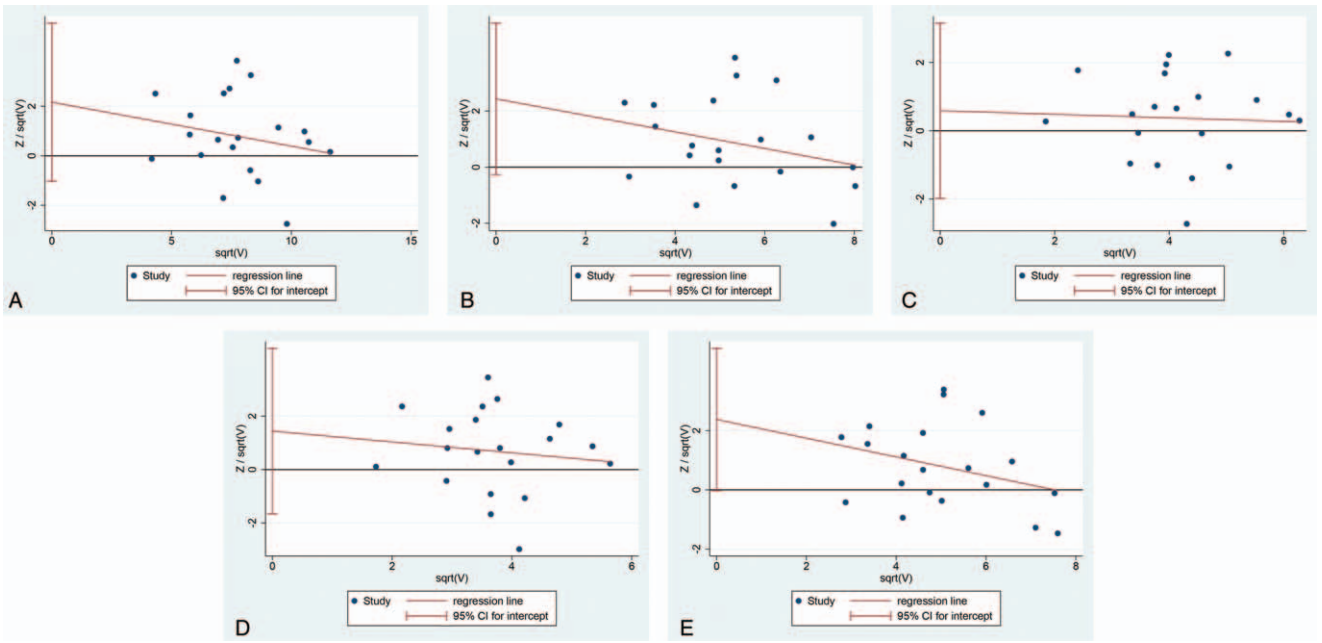

Figure 4. Begg funnel plot of publication bias for UCP2 *rs659366* (A. allele model; B. dominant model; C. recessive model; D. homozygous model; E. homozygous model).

synthesized effect of genetic and environmental risk factors. The effects of gene-gene and gene-environmental interactions were not assessed on account of lacking original data. Additionally, the accuracy of our results might be affected due to exclusion of studies with genome wide association study to detect the genotyping. In the future, further well-designed studies, especially those on gene-gene and gene-environmental interactions, will be undertaken to verify our results.

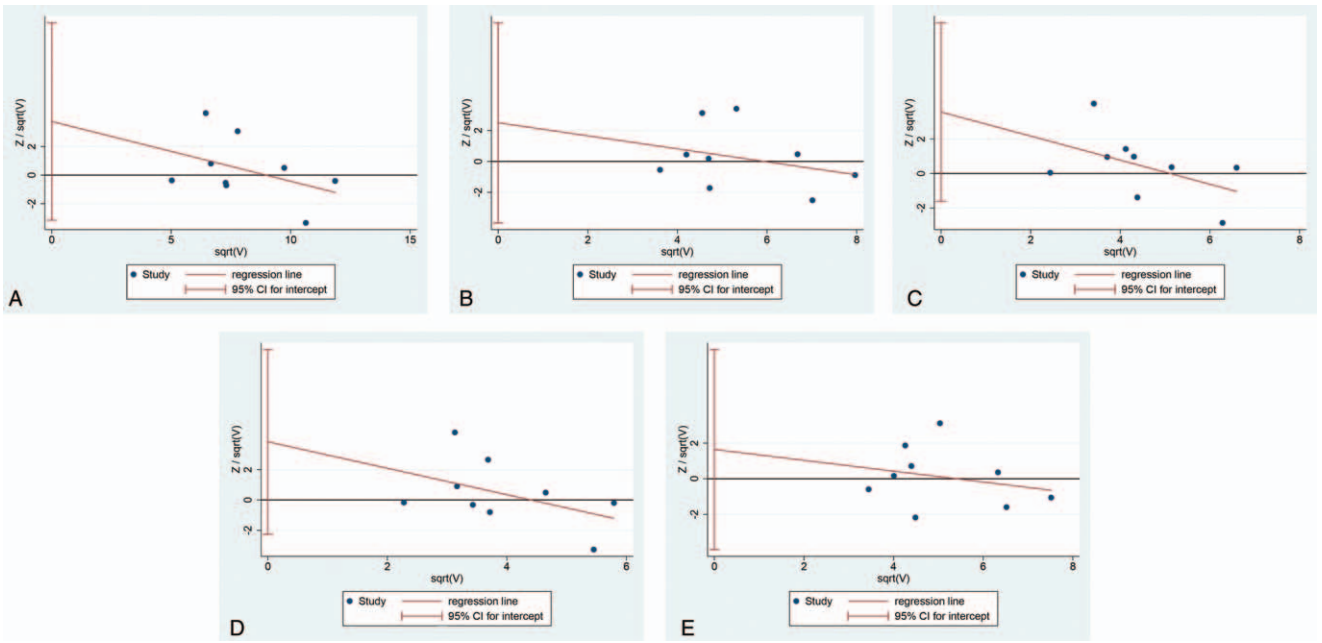

Figure 5. Begg funnel plot of publication bias for UCP2 *rs660339* (A. allele model; B. dominant model; C. recessive model; D. homozygous model; E. homozygous model).

5. Conclusions

The UCP2 *rs65366* was significantly associated with the risk of T2DM, especially in Asian population, while no evidence was found between the UCP2 *rs660339* and the susceptibility to T2DM.

Author contributions

LX and LBZ conceived and designed the study. LX wrote the manuscript and collected the data. SYC participated in data analysis and literature research. LBZ critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

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