# **Original Article**



# Association between *ApoE* Polymorphism and Type 2 Diabetes: A Meta-Analysis of 59 Studies<sup>\*</sup>

CHEN Da Wei<sup>1</sup>, SHI Ji Kang<sup>2</sup>, LI Yun<sup>3</sup>, YANG Yu<sup>4</sup>, and REN Shu Ping<sup>5,#</sup>

1. Department of Radiation Protection, School of Public Health, Jilin University, Changchun 130021, Jilin, China; 2. Department of Epidemiology and Statistics, School of Public Health, Jilin University, Changchun 130021, Jilin, China; 3. Department of Ophthalmology, China-Japan Union Hospital, Jilin University, Changchun 130033 Jilin, China; 4. Function Experiment Center of College of Basic Medicine, Jilin University, Changchun 130021, Jilin, China; 5. Department of Occupational and Environmental Health, School of Public Health, Jilin University, Changchun 130021, Jilin, China

## Abstract

**Objective** To identify the important risk factors for type 2 Diabetes Mellitus (T2DM) and develop effective strategies to address the problem of T2DM. Our study aimed to evaluate the association between apolipoprotein E (*ApoE*) genetic polymorphism and type 2 diabetes, and to provide clues for the etiology of T2DM.

**Methods** Based on the criteria of inclusion and exclusion, we extracted, pooled, analyzed and assessed the case-control studies of *ApoE* polymorphism and T2DM published in PubMed, Web of Science, Medline, WanFang, VIP, and CNKI databases by R soft-ware (version 3.4.3). We used Random-effect models when heterogeneity was present in between-study, and fixed-effect models otherwise.

**Results** We had 59 studies covering 6,872 cases with T2DM and 8,250 controls, and compared the alleles and genotypes of *ApoE* between cases and controls. When we conducted a comparison between *ApoE*  $\epsilon$ 4 and  $\epsilon$ 3 alleles, we produced a pooled *OR* of 1.18 (95% *Cl*: 1.09-1.28; *P* < 0.001). *ApoE*  $\epsilon$ 2/ $\epsilon$ 2 genotype displayed a possible association with T2DM (*OR* = 1.46; 95% *Cl*: 1.11-1.93; *P* = 0.007),  $\epsilon$ 3/ $\epsilon$ 4 genotype showed a 1.11-fold risk (*OR* = 1.11; 95% *Cl*: 1.01-1.22; *P* = 0.039) and  $\epsilon$ 4/ $\epsilon$ 4 genotype had a 1.71-fold risk of developing T2DM (*OR* = 1.71; 95% *Cl*: 1.33-2.19; *P* < 0.001) when they were compared with  $\epsilon$ 3/ $\epsilon$ 3 genotype.

**Conclusions** There is an association between *ApoE* polymorphism and T2DM: allele  $\varepsilon 4$  and genotypes ( $\varepsilon 2/\varepsilon 2$ ,  $\varepsilon 3/\varepsilon 4$ , and  $\varepsilon 4/\varepsilon 4$ ) are associated with the increased risk for the development of T2DM, and they may be risk factors for T2DM.

Key words: Apolipoprotein E; Polymorphism; Type 2 diabetes; Meta-analysis									
Biomed Environ Sci, 2019; 32(11): 823-838 doi: 10.3967/bes2019.104 ISSN: 0895-3									
www.besjournal.com (full text)	CN: 11-2816/Q	Copyright ©2019 by China CDC							

This work was supported by the Jipa Ruida Environmental Inspection Corporation Limited, Beijing under Grant Radioactive Diagnosis and Treatment Construction Project-Radiation Protection and Evaluation [Grant No. 2016YX137]; and Jilin Province Pharmacy Operation Corporation, Limited [Grant No.371182093427].

<sup>&</sup>lt;sup>#</sup>Correspondence should be addressed to REN Shu Ping, PhD, E-mail: rensp@jlu.edu.cn, Tel: 86-431-85619453

Biographical note of the first author: CHEN Da Wei, male, born in 1962, PhD, majoring in effects of environmental exposure on health.

#### INTRODUCTION

t is estimated that only half of the 79 million adults with type 2 diabetes will have adequate access to insulin by 2,030 if the current levels of access is not improved<sup>[1]</sup>. Moreover, one of the significant causes of worldwide mortality and morbidity is diabetes<sup>[2]</sup>, especially type 2 diabetes mellitus (T2DM), which is also the major cause of substantial global economic burden<sup>[3]</sup>. Therefore, there is an urgent need to identify the important risk factors for T2DM and develop effective strategies to address the problem of T2DM.

It is well accepted that genetic factor, environmental factors, and lifestyle contribute to the development of T2DM. Complex interactions between multiple genes and a range of environmental factors are involved in the onset and progression of type 2 diabetes<sup>[4]</sup>. A better understanding of the contribution of genetic factors in the etiology of T2DM will facilitate the development of effective preventive strategies to reduce the ever increasing incidence of T2DM<sup>[5]</sup>, it will also improve the effectiveness and precision of treatment and prevention strategies<sup>[6]</sup>.

It is reported that ApoE alleles are important genetic markers for dyslipidaemias<sup>[7]</sup>, and previous studies indicate that ApoE is among the candidate genes which are most likely associated with CAD in T2DM patients<sup>[8]</sup>. *ApoE* draws much attention due to some reports supporting the association between *ApoE* polymorphism and T2DM<sup>[9-11]</sup>. In humans, *ApoE* gene is located on the chromosome at position 19q13.2 with 3 isoforms, ApoE2, ApoE3, and ApoE4; and 6 genotypes having 3 homozygous:  $\varepsilon 2/\varepsilon 2$ ,  $\varepsilon 3/\varepsilon 3$ , and  $\varepsilon 4/\varepsilon 4$ , and 3 heterozygous:  $\varepsilon 2/\varepsilon 3$ ,  $\varepsilon 2/\varepsilon 4$ , and  $\varepsilon 3/\varepsilon 4^{[12]}$ . Besides T2DM, *ApoE* is also involved in many diseases, such as coronary heart disease (CHD)<sup>[13]</sup>, ischemic cerebrovascular disease (ICD)<sup>[14]</sup>, and Alzheimer's disease<sup>[15]</sup>.

Much of the recent research has studied the association between the *ApoE* gene polymorphism and the risk of T2DM, however, there are inconsistencies between the results of the different studies. The inconsistency may result from the difference of included population, sample size, and genotyping methods. Moreover, 18 new papers<sup>[9,16-32]</sup> have been published since the publication of latest meta-analysis of the association between *ApoE* gene polymorphism and T2DM in 2014<sup>[33]</sup>. Thus, we conducted a further meta-analysis to explore whether *ApoE* polymorphism is associated with the increased risk of T2DM by including these new

published articles.

#### METHODS

#### Search Strategy

We performed this meta-analysis by extensive literature search in PubMed, Web of Science, Medline, WanFang, VIP, and CNKI databases (last search on February 28, 2019). We used the following terms for our search strategy, ('ApoE' OR 'Apolipoprotein E') AND ('polymorphism, Genetic' OR ''variant' OR 'mutation') AND ('type 2 diabetes mellitus' OR 'type 2 diabetes' OR 'T2DM' OR 'noninsulin dependent diabetes' OR 'NIDDM'). The equivalent Chinese terms were used in the Chinese databases. In addition, we retrieved related articles that had not been identified in the initial search to replenish literatures.

#### Inclusion/Exclusion Criteria

Studies included in this meta-analysis were based on the following criteria: (1) case–control studies; (2) assessing the association between *ApoE* polymorphism and type 2 diabetes. The exclusion criteria met the follows: (1) duplicate articles; (2) no healthy controls; (3) insufficient information on genotype or allele frequencies.

#### Data Extraction

We extracted the main characteristics of each eligible study, including first author's last name, date of publication, region, population's ethnicity, genotyping method, number of cases and controls, and counts of the *ApoE* genotype or allele. Hardy-Weinberg equilibrium (HWE) was collected and calculated among the controls.

#### **Quality Assessment**

We used the Newcastle-Ottawa scale (NOS) to assess the quality of each article by a 'star' rating system covering selection, comparability, and exposure. A score of 1 point was awarded for each condition a study met, and no point (0 score) if the condition or requirement was not met. We calculated the total Quality Score of each study. Two authors (Jikang Shi and Shuping Ren) assessed the quality of included studies independently. When inconformity occurred between the two authors, we discussed with the third investigator (CHEN Da Wei) and came to a conformity. We included those studies with poor quality score to avoid selection bias.

## **Statistical Analysis**

We calculated the allele and genotype frequencies of ApoE for each study to evaluate the HWE through Goodness of fit Chi-square test among control groups, and P < 0.05 was seen as a significant deviation from HWE. The strength of association between ApoE polymorphisms and type 2 diabetes susceptibility was assessed using odds ratios (OR) and 95% confidence intervals (95% CI) because outcome variable was binary. Heterogeneity was assessed by the Chi-square test based Q-statistic and quantified by  $l^2$ -statistic<sup>[34]</sup>. Random-effect models (DerSimonian and Laird methods) were applied to calculate OR and 95% CI when P value of Q test was more than 0.10 or  $l^2$  value was more than 50%; otherwise, fixed-effect models (Mantel and Haenszel methods) were used  $(I^2 \ge 50\%)$  considered heterogeneity existed in between-study in this metaanalysis). Subgroup analyses stratified by ethnicity, quality score and Hardy-Weinberg equilibrium were calculated to trace main sources of heterogeneity and to identify the association between ApoE polymorphisms and type 2 diabetes in different groups. Publication bias was evaluated using funnel plots, and quantified by the Begg's and Egger's tests (P < 0.05 considered statistically significant publication bias)<sup>[35]</sup>. Sensitivity analysis was performed to examine stability of results by omitting each study in each turn. All data management and statistical analyses were used R soft-ware (version 3.4.3), *P*value < 0.05 was considered statistically significant.

#### RESULTS

#### **Study Characteristics**

Our meta-analysis initially collected 791 published articles, including 782 papers collected by our search strategy and 9 papers through the references. After scanning the abstracts and full texts according to the inclusion and exclusion criteria, we included 59 eligible articles with 6,872 cases and 8,250 controls in this paper. The protocol of the process for literature identification and selection is listed in Figure 1, and the baseline characteristics of the included studies are summarized in Table 1, all the results of meta-analysis is shown in Table 2.

## Association between Alleles of ApoE and Type 2 Diabetes

We found a significant heterogeneity when we comparing ApoE  $\varepsilon 2$  with  $\varepsilon 3$  allele ( $I^2 = 62\%$ ), and had

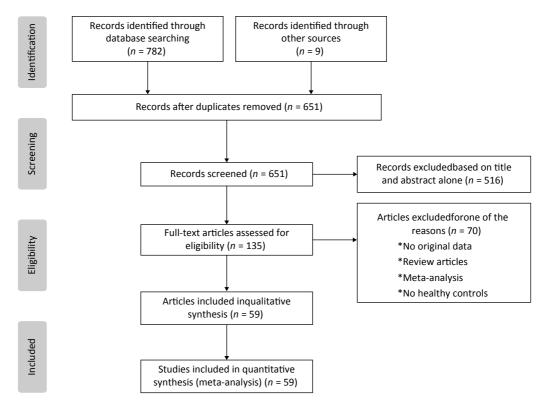


Figure 1. Flow chart of the process for literature identification and selection.

Study	Year	Region	Ethnicity	Genotyping		Quality		-	2(n)+ :3(n)	-	4(n)+ :3(n)	-	ε3/ε4(n)+ ε4/ε4(n)	
		U		method	(case/ control)	score	,	case	control	case	control	case	control	
Singh <sup>[36]</sup>	2006	India	Asian	PCR-RELP	90/97	9	Y(0.184)	1+4	1+7	2+78	0+74	5+0	13+2	
Al-Majed <sup>[16]</sup>	2011	Kuwait	Other	PCR-RELP	105/62	6	N(0.006)	7+2	2+3	2+73	2+46	6+15	9+1	
Chaudhary <sup>[9]</sup>	2012	Bangkok	Other	PCR-RELP	155/149	8	Y(0.121)	1+2	2+12	1+117	0+113	30+4	21+1	
Errera <sup>[37]</sup>	2006	Brazil	Other	PCR-RELP	95/107	7	Y(0.584)	0+13	0+7	2+68	0+77	12+0	23+0	
Alharbi <sup>[17]</sup>	2014	Riyadh	Other	TaqMan	438/460	7	N(< 0.001)	35+26	27+18	13+290	11+334	35+39	60+10	
Inamdar <sup>[38]</sup>	2000	India	Asian	Flat gel isoelectric focusing	60/40	8	Y(0.054)	2+8	1+9	3+17	2+10	16+14	8+10	
Kwon <sup>[39]</sup>	2007	Korea	Asian	PCR-RELP	94/88	7	Y(0.924)	0+13	0+5	3+63	0+70	14+1	12+1	
Atta <sup>[18]</sup>	2016	Egypt	Other	PCR-RELP	45/45	5	Y(0.098)	0+12	0+3	12+12	3+30	9+0	9+0	
Vauhkonen <sup>[40]</sup>	1997	Finland	Caucasian	PCR-RELP	86/125	8	Y(0.963)	0+7	0+9	3+48	2+76	20+8	33+5	
Erdogan <sup>[19]</sup>	2009	Turkey	Caucasian	PCR-RELP	56/35	7	N(< 0.001)	0+4	0+0	0+40	0+28	12+0	7+0	
Eto <sup>[41]</sup>	1986	Japan	Asian	Flat gel isoelectric focusing	105/111	8	Y(0.339)	0+9	1+10	0+73	1+80	21+2	16+3	
Guan <sup>[42]</sup>	2009	China	Asian	PCR-LDR	213/111	7	Y(0.499)	8+32	1+32	7+141	1+88	24+1	9+1	
Leiva <sup>[43]</sup>	2005	Chile	Other	PCR-RELP	193/139	7	Y(0.293)	0+12	0+10	4+133	3+87	43+1	39+0	
Liu <sup>[44]</sup>	2003	China	Asian	PCR-RELP	80/81	7	Y(0.217)	0+11	0+4	1+56	2+64	12+0	11+0	
Mehmet <sup>[20]</sup>	2015	Turkey	Caucasian	PCR-RELP	100/50	8	N(0.039)	0+6	0+22	0+81	0+19	13+0	9+0	
Xie <sup>[45]</sup>	2011	China	Asian	PCR-RELP	60/20	7	Y(0.936)	0+13	1+3	4+8	2+8	19+16	5+1	
Mustapic <sup>[21]</sup>	2012	Croatia	Caucasian	TaqMan	196/456	6	Y(0.331)	0+35	1+48	2+127	2+328	30+2	76+1	
Santos <sup>[46]</sup>	2002	Mexico	Other	PCR-RELP	36/22	8	Y(0.423)	0+0	1+2	0+32	1+10	3+1	8+0	
Kamboh <sup>[47]</sup>	1995	USA	Caucasian i	IEF- mmunoblottir and PCR	116/659	6	Y(0.992)	0+23	6+88	5+62	19+382	26+0	150+14	
Ng <sup>[48]</sup>	2016	China	Asian	Other	386/200	6	Y(0.168)	4+53	1+32	5+282	6+142	39+3	19+0	
Eto <sup>[49]</sup>	1995	Japan	Asian	Flat gel isoelectric	281/576	8	Y(0.609)	1+25	2+35	1+192	4+414	55+7	111+10	
Morbois Trabut <sup>[50]</sup>	2006	France	Caucasian	focusing PCR-RELP	210/481	7	Y(0.773)	2+31	5+71	1+143	14+294	33+0	87+10	
Powell <sup>[51]</sup>	2003	UK	Caucasian	PCR-RELP	187/102	7	Y(0.094)	3+22	2+7	3+89	1+57	27+3	21+0	
Guangda <sup>[52]</sup>	1999	China	Asian	PCR-RELP	89/72	7	Y(0.122)	1+13	1+7	1+66	2+53	7+1	7+2	
Zhang <sup>[53]</sup>	2000	China	Asian	PCR-RELP	63/71	8	N(0.009)	0+7	0+5	0+50	3+56	6+0	6+0	
Zhang <sup>[54]</sup>	2003	China	Asian	PCR-RELP	74/191	8	Y(0.878)	0+5	1+23	1+55	1+134	12+1	31+1	
Sun <sup>[55]</sup>	2013	China	Asian	PCR-RELP	243/78	7	Y(0.414)	6+36	2+12	0+180	1+55	21+0	6+1	
Hua <sup>[56]</sup>	2006	China	Asian	PCR-RELP	50/60	8	Y(0.190)	2+4	0+7	4+68	2+75	20+2	13+3	
Guo <sup>[57]</sup>	2003	China	Asian	PCR-RELP	40/52	7	Y(0.739)	0+4	0+5	2+23	1+39	9+2	6+1	
Liang <sup>[23]</sup>	2017	China	Asian	PCR-RELP	44/374	6	Y(0.816)	1+3	5+57	1+31	6+267	7+1	38+1	
Shen <sup>[58]</sup>	2002	China	Asian	PCR-RELP	106/110	7	Y(0.577)	1+7	1+12	2+84	4+74	11+1	18+1	
Zheng <sup>[59]</sup>	1998	China	Asian	PCR-RELP	112/60	8	Y(0.801)	2+16	1+8	1+81	0+45	11+1	6+0	
Hua <sup>[60]</sup>	2004	China	Asian	PCR-RELP	38/60	7	Y(0.434)	1+7	0+4	2+24	1+45	4+0	8+2	
Liu <sup>[24]</sup>	2014	China	Asian	PCR-RELP	215/298	7	N(< 0.001))	10+0	2+0	0+174	0+272	31+0	23+1	

Table 1. Main characteristics of the included studies

Study	Year	ar Region Ethnicity Genotyping		Sample size	Quality	HWE Y/N(P)	ε2/ε2 ε2/ε		ε2/ε4(n)+ ε3/ε3(n)		Continued ε3/ε4(n)+ ε4/ε4(n)		
Study	Tear	Region	Lunnerty	method	(case/ control)	score		case	control	case	control	case	control
Xiang <sup>[61]</sup>	1995	China	Asian	PCR-RELP	125/50	7	Y(0.715)	2+16	0+4	0+78	1+38	26+3	6+1
Chen <sup>[25]</sup>	2006	China	Asian	PCR-RELP	97/105	7	Y(0.906)	2+15	1+18	1+70	2+72	8+1	10+1
Xiang <sup>[62]</sup>	1999	China	Asian	PCR-ASO	130/50	8	Y(0.715)	3+14	0+4	1+85	1+38	24+3	6+1
Shen <sup>[63]</sup>	2002	China	Asian	PCR-RELP	35/50	6	Y(0.112)	3+11	0+6	2+4	4+31	14+0	9+0
Xiong <sup>[26]</sup>	2013	China	Asian	PCR-RELP	121/112	8	Y(0.991)	0+15	1+13	1+72	2+72	31+2	22+2
Zhou <sup>[64]</sup>	2005	China	Asian	PCR-RELP	67/68	7	Y(0.263)	0+13	2+9	1+47	0+46	6+0	11+0
Xiang <sup>[65]</sup>	2005	China	Asian	PCR-ASO	101/95	7	Y(0.438)	1+10	1+10	1+65	1+65	20+4	15+3
Long <sup>[66]</sup>	1999	China	Asian	PCR-RELP	67/135	7	Y(0.124)	0+15	0+18	3+36	4+101	12+1	12+0
Liang <sup>[67]</sup>	2005	China	Asian	PCR-RELP	145/90	8	Y(0.592)	0+17	0+12	6+102	2+68	18+2	8+0
Gu <sup>[68]</sup>	2004	China	Asian	PCR-RELP	63/90	8	Y(0.592)	0+9	0+12	3+43	2+68	7+1	8+0
Yang <sup>[69]</sup>	1995	China	Asian	PCR-RELP	125/50	7	N(0.028)	2+16	1+3	0+78	1+38	26+3	5+2
Rong <sup>[32]</sup>	2013	China	Asian	PCR-RELP	18/29	7	Y(0.953)	0+4	0+8	0+18	0+29	2+0	1+0
Liu <sup>[27]</sup>	2016	China	Asian	PCR-RELP	300/300	8	N(< 0.001)	14+0	2+0	0+243	0+274	43+0	23+1
Tang <sup>[28]</sup>	2007	China	Asian	PCR-RELP	41/60	6	Y(0.80)	0+1	0+3	2+28	1+43	10+0	13+0
Qiu <sup>[70]</sup>	2008	China	Asian	PCR-RELP	129/110	8	Y(0.481)	0+14	1+18	3+95	2+76	14+3	11+2
Guo <sup>[71]</sup>	2007	China	Asian	ARMS-PCR	40/40	6	Y(0.618)	0+1	1+4	3+29	1+27	7+1	7+0
Xiong <sup>[72]</sup>	2008	China	Asian	MultiARMS PCF	316/512	6	Y(0.744)	2+18	3+48	6+230	9+359	47+13	87+6
Ge <sup>[29]</sup>	2013	China	Asian	PCR-RELP	200/210	7	Y(0.544)	3+35	8+40	2+86	8+103	73+1	47+4
Xiang <sup>[73]</sup>	2010	China	Asian	PCR-RELP	41/102	7	Y(0.473)	0+5	0+13	1+28	0+70	7+0	19+0
Luo <sup>[30]</sup>	2016	China	Asian	PCR-RELP	35/50	6	N(0.005)	0+3	0+2	1+28	3+38	2+1	7+0
Zhang <sup>[74]</sup>	2007	China	Asian	PCR-RELP	38/49	6	N(0.015)	0+2	0+1	0+32	2+39	3+1	7+0
Wang <sup>[31]</sup>	2014	China	Asian	PCR-RELP	57/55	8	N(0.027)	0+4	2+7	2+33	4+28	13+5	8+6
Zhang <sup>[75]</sup>	1999	China	Asian	PCR-RELP	56/76	5	Y(0.631)	0+3	1+7	1+40	2+55	11+1	11+1
Xiong <sup>[76]</sup>	2005	China	Asian	PCR-RELP	32/30	7	Y(0.608)	1+5	0+4	1+22	1+23	2+1	2+0
Dai <sup>[77]</sup>	2000	China	Asian	PCR-RELP	32/90	8	Y(0.253)	0+5	0+14	0+23	1+64	3+1	9+2

Note. HWE, Hardy-Weinberg equilibrium.

Table 2. Meta-analysis results of association between ApoE polymorphism and ty	ype 2 diabetes
--	----------------

Variable	OR (95% CI)	<i>I</i> <sup>2</sup> (%)	Р	
ApoE alleles				
ε2	1.16 (0.98, 1.37)	62	0.079	
ε4	1.18 (1.09, 1.28)	36	< 0.001	
ApoE genotypes				
ε2/ε2	1.46 (1.11, 1.93)	0	0.007	
ε2/ε3	1.09 (0.90, 1.32)	55	0.397	
ε2/ε4	1.15 (0.90, 1.46)	0	0.276	
ε3/ε4	1.11 (1.01, 1.22)	39	0.039	
ε4/ε4	1.71 (1.33, 2.19)	0	< 0.001	

**Note.** ApoE alleles ( $\epsilon_2$  and  $\epsilon_4$ ) and genotypes ( $\epsilon_2/\epsilon_2$ ,  $\epsilon_2/\epsilon_3$ ,  $\epsilon_2/\epsilon_4$ ,  $\epsilon_3/\epsilon_4$ , and  $\epsilon_4/\epsilon_4$ ) were compared with  $\epsilon_3$  and  $\epsilon_3/\epsilon_3$ .

the pooled *OR* of 1.16 (95% *Cl*: 0.98-1.37; *P* = 0.079) calculated by the random-effects model (Figure 2); however, there was not heterogeneity in the comparison of *ApoE*  $\varepsilon$ 4 with  $\varepsilon$ 3 allele ( $l^2$  = 36%), and the pooled *OR* was 1.18 (95% *Cl*: 1.09-1.28; *P* < 0.001) when the fixed-effects model was applied to compare *ApoE*  $\varepsilon$ 4 with  $\varepsilon$ 3 (Figure 3), indicating that *ApoE*  $\varepsilon$ 4 allele may be a risk factor for type 2 diabetes.

## Association between Genotypes of ApoE and Type 2 Diabetes

There were five genotypes ( $\varepsilon 2/\varepsilon 2$ ,  $\varepsilon 2/\varepsilon 3$ ,  $\varepsilon 2/\varepsilon 4$ ,  $\varepsilon 3/\varepsilon 4$ , and  $\varepsilon 4/\varepsilon 4$ ) were compared with  $\varepsilon 3/\varepsilon 3$ genotype. No significant heterogeneity was found when the comparison was performed between the  $\epsilon^2/\epsilon^2$  and  $\epsilon^3/\epsilon^3$  genotypes ( $I^2 = 0\%$ ), and the yielded OR of  $\varepsilon 2/\varepsilon 2$  genotype versus  $\varepsilon 3/\varepsilon 3$  genotype using a fixed-effects model was 1.46 (95% CI: 1.11-1.93; P = 0.007) (Figure 4), indicating that the  $\varepsilon 2/\varepsilon 2$  genotype might produce a harmful effect on type 2 diabetes. However, when  $\varepsilon 2/\varepsilon 3$  genotype was compared with  $\varepsilon 3/\varepsilon 3$  genotype, there was significant heterogeneity  $(I^2 = 55\%)$ , and the yielded OR of  $\varepsilon 2/\varepsilon 3$  genotype versus  $\varepsilon 3/\varepsilon 3$  genotype using a random-effects model was 1.09 (95% CI: 0.90-1.32; P = 0.397) (Figure 5). Compared with  $\varepsilon 3/\varepsilon 3$  genotype, there were no significant heterogeneity between  $\varepsilon 2/\varepsilon 4$ ,  $\varepsilon 3/\varepsilon 4$ , and  $\varepsilon 4/\varepsilon 4$  genotype, respectively ( $I^2 = 0\%$ ,  $I^2 = 39\%$ , and  $I^2$ = 0%). The yielded OR of  $\varepsilon 2/\varepsilon 4$  genotype versus  $\epsilon 3/\epsilon 3$  genotype using a fixed-effects model was 1.15 (95% CI: 0.90-1.46; P = 0.276) (Figure 6). The yielded OR of  $\varepsilon 3/\varepsilon 4$  genotype versus  $\varepsilon 3/\varepsilon 3$  genotype using a fixed-effects model was 1.11 (95% Cl: 1.01-1.22; P = 0.039) (Figure 7). For the comparison of  $\varepsilon 4/\varepsilon 4$ genotype with  $\varepsilon 3/\varepsilon 3$  genotype, the yielded OR showed a 1.71-fold risk of type 2 diabetes (OR = 1.71; 95% CI: 1.33-2.19; P < 0.001) using the fixedeffects model (Figure 8).

#### Subgroup Analysis

We conducted subgroup analysis stratified by ethnicity, quality score and Hardy–Weinberg equilibrium in order to identify main sources of heterogeneity. There were significant heterogeneity in the comparison of *ApoE*  $\epsilon$ 2 with  $\epsilon$ 3 allele ( $l^2 = 62\%$ ) and the comparison of  $\epsilon 2/\epsilon$ 3 genotype with  $\epsilon 3/\epsilon$ 3 genotype ( $l^2 = 55\%$ ) in our paper; however, we could not identify the sources of heterogeneity and there was no significant association between *ApoE* polymorphisms and type 2 diabetes in different subgroups (Supplementary Figures S1-S3, available in www.besjournal.com).

#### **Publication Bias**

Funnel plots was used to assess and Begg's and Egger's tests to quantify the publication bias. All the funnel plots for *ApoE* allele and *ApoE* genotypes seemed symmetrical (Supplementary Figures S4-S5, available in www.besjournal.com), and the results of Begg's and Egger's tests revealed that no publication bias was present for the association between *ApoE* allele and type 2 diabetes and between the *ApoE* genotypes and type 2 diabetes (all P > 0.05).

#### Sensitivity Analysis

According to our results of sensitivity analysis, no individual study produced influence on the corresponding pooled *ORs* and 95% *Cls* in the comparison of *ApoE* allele with  $\varepsilon$ 3 allele or in the comparison of *ApoE* genotypes with genotype  $\varepsilon$ 3/ $\varepsilon$ 3 genotype, which indicated these results were relatively stable and credible.

#### DISCUSSION

In this meta-analysis, we included 59 literatures with 6,872 cases and 8,250 controls to explore the association between the *ApoE* gene polymorphism and type 2 diabetes mellitus. The major findings of our study are that allele  $\varepsilon 4$  and genotypes ( $\varepsilon 2/\varepsilon 2$ ,  $\varepsilon 3/\varepsilon 4$ , and  $\varepsilon 4/\varepsilon 4$ ) are associated with the increased risk for the development of T2DM, however, allele  $\varepsilon 2$  and genotypes ( $\varepsilon 2/\varepsilon 3$  and  $\varepsilon 2/\varepsilon 4$ ) are not associated with T2DM.

The findings of our meta-analysis are in accordance with the previous studies<sup>[33,78-80]</sup>, showing that both *ApoE* ε4 allele and the genotypes ( $\varepsilon 3/\varepsilon 4$  and  $\varepsilon 4/\varepsilon 4$ ) were associated with increased risk of T2DM. Subjects carrying the ɛ4 alleles had higher plasma total cholesterol levels compared to subjects carrying the  $\varepsilon 3/\varepsilon 3$  genotype, and HDL cholesterol was significantly lower in the  $\epsilon 3/\epsilon 4$  than in the  $\epsilon 3/\epsilon 3$  individuals<sup>[81]</sup>; individuals carrying the  $\epsilon 2/\epsilon 2$  genotype had about 31% lower mean LDL than those with the  $\varepsilon 4/\varepsilon 4$  genotype<sup>[82]</sup>. Insulin resistance is known to be strongly associated with metabolic dyslipidemia and the correlation of lipid profiles with diabetic phenotypes is significant. Therefore, ApoE ɛ4 allele and the genotypes ( $\epsilon 3/\epsilon 4$  and  $\epsilon 4/\epsilon 4$ ) were associated with an increased risk of T2DM through affecting the lipid metabolism.

We found the genotype  $\epsilon 2/\epsilon 2$  was associated with increased risk of T2DM, but not allele  $\epsilon 2$  or genotype  $\epsilon 2/\epsilon 3$ ; which are not in agreement with

# ApoE polymorphism and type 2 diabetes

Study	Experimen Events To		ontrol Total	Odds Ratio	OR	95%-CI	Weight
Singh 2006		73 9	177		0.91	[0.34; 2.40]	1.5%
Al-Majed 2011		72 8	112		1.52	[0.64; 3.62]	1.7%
Chaudhary 2012	5 2	71 16	275		0.30	[0.11; 0.84]	1.5%
Errera 2006		74 7	191		2.30	[0.91; 5.84]	1.6%
Alharbi 2014		50 83	829		1.53	[1.13; 2.07]	2.9%
Inamdar 2000		73 13	50		0.74	[0.31; 1.72]	1.7%
Kwon 2007 Atta 2016		69 5 69 6	162 78		3.28	[1.17; 9.18] [2.43; 16.87]	1.4% 1.5%
Vauhkonen 1997		33 11	205		1.43	[2.43, 10.07]	1.5%
Erdogan 2009		00 0	63			[0.31; 111.90]	0.3%
Eto 1986		85 13	199		0.73	[0.31; 1.75]	1.7%
Guan 2009		93 14	210	-	2.28	[1.23; 4.20]	2.2%
Leiva 2005		37 13	236		0.86	[0.40; 1.81]	1.9%
Liu 2003		46 4	147		2.91	[0.91; 9.37]	1.2%
Mehmet 2015 Xie 2011		87 22 65 7	91 31		0.10 1.21	[0.04; 0.27] [0.44; 3.33]	1.6% 1.5%
Mustapic 2012		56 52	832	<b>F</b>	1.74	[1.12; 2.70]	2.6%
Santos 2002		67 5	35		0.04	[0.00; 0.77]	0.3%
Kamboh 1995		01 119	1,121	-	1.36	[0.88; 2.12]	2.6%
Ng 2006		22 40	375		0.84	[0.56; 1.28]	2.7%
Eto 1995		92 43	1,017	_=	1.37	[0.84; 2.23]	2.5%
Morbois Trabut 2006		86 95	841		0.81	[0.54; 1.21]	2.7%
Powell 2003 Guangda 1999		58 12 68 11	154 131		1.62 1.15	[0.80; 3.25] [0.51; 2.57]	2.0% 1.8%
Zhang 2000		20 8	131		0.95	[0.33; 2.71]	1.4%
Zhang 2003		33 26	348		0.59	[0.24; 1.46]	1.6%
Sun 2013		65 17	145	<del></del>	0.87	[0.48; 1.56]	2.3%
Hua 2006		72 9	179	- <u>+</u> -	1.42	[0.58; 3.45]	1.7%
Guo 2003		65 6	95		1.51	[0.46; 4.90]	1.2%
Liang 2017		78 73	702		0.72	[0.30; 1.71]	1.7%
Shen 2002 Zheng 1998		97 18 10 10	196 114		0.58	[0.27; 1.27] [0.52; 2.55]	1.9% 1.9%
Hua 2004		70 5	107	<b></b>	3.80		1.3%
Liu 2014		99 4	571		7.48		1.4%
Xiang 1995	20 2	18 5	91		1.74	[0.63; 4.78]	1.5%
Chen 2006		83 22	194	÷.	0.96	[0.50; 1.82]	2.2%
Xiang 1999		29 5	91		1.74	[0.63; 4.75]	1.5%
Shen 2002		52 10	87		4.43		1.7%
Xiong 2013 Zhou 2005		06 17 27 13	196 125	-	0.89 1.07	[0.43; 1.81] [0.48; 2.37]	2.0% 1.8%
Xiang 2005		73 13	168	- <del></del>	0.97	[0.44; 2.16]	1.8%
Long 1999		17 22	254		1.92	[0.99; 3.73]	2.1%
Liang 2005	23 2	62 14	170	-	1.07	[0.54; 2.15]	2.1%
Gu 2004		14 14	170		1.31	[0.58; 2.95]	1.8%
Yang 1995		18 6	90		1.41	[0.55; 3.65]	1.6%
Rong 2013 Liu 2016		46 8 57 4	75 575			[0.23; 2.81] [2.63; 21.68]	1.1% 1.4%
Tang 2007		70 4	106		1.14	[0.25; 5.26]	0.9%
Qiu 2008		35 22	203		0.64	[0.33; 1.24]	2.1%
Guo 2007		70 7	72		0.56	[0.16; 2.01]	1.1%
Xiong 2008		53 63	916	-	0.72	[0.46; 1.14]	2.6%
Ge 2013		23 64	357	1	0.70	[0.46; 1.07]	2.6%
Xiang 2010		74 13	185		1.17	[0.43; 3.20]	1.5%
Luo 2016 Zhang 2007		65 5 71 3	90 89		1.11 0.83	[0.29; 4.32] [0.14; 5.11]	1.0% 0.7%
Wang 2014		89 15	86		0.34	[0.13; 0.93]	1.5%
Zhang 2002		98 11	139		0.50	[0.15; 1.60]	1.2%
Xiong 2005		59 5	57	- <u> </u> =	1.63	[0.50; 5.32]	1.2%
Dai 2000	5	59 15	166		0.93	[0.32; 2.69]	1.4%
Random effects mode			14,902		1.16	[0.98; 1.37]	100.0%
Heterogeneity: $I^2 = 62\%$ , $\tau$	<sup>2</sup> = 0.2306, <i>p</i> <	0.01				-	
				0.01 0.1 1 10 100			

**Figure 2.** Forest plot for the result of association between type 2 diabetes and *ApoE*  $\epsilon$ 2 allele *vs*.  $\epsilon$ 3 allele based on a random-effects model.

Study	Experii Events		C Events	ontrol Total	Odds Ratio	OR	95%-Cl	Weight
Singh 2006	7	172	17	185	;	0.42	[0.17; 1.04]	1.4%
Al-Majed 2011	38	192	12	116			[1.07; 4.29]	1.1%
Chaudhary 2012	39	305	23	282			[0.96; 2.84]	1.8%
Errera 2006	14	174	23	207			[0.35; 1.41]	1.7%
Alharbi 2014	126	767	91	837	<u> </u>	1.61	[1.21; 2.15]	6.4%
Inamdar 2000	47	105	30	67	- <u>+</u>		[0.54; 1.85]	1.8%
Kwon 2007	19	172	14	171			[0.67; 2.88]	1.1%
Atta 2016	21	66	12	84			[1.26; 6.24]	0.6%
Vauhkonen 1997 Erdegen 2000	39	162 108	45 7	239 70			[0.84; 2.22]	2.4%
Erdogan 2009 Eto 1986	12 25	201	23	209	<u> </u>		[0.42; 3.01] [0.63; 2.10]	0.7% 1.7%
Guan 2009	33	371	12	203	- <u>[i=</u>		[0.80; 3.16]	1.2%
Leiva 2005	48	369	42	265			[0.51; 1.24]	3.7%
Liu 2003	12	147	11	154	<del>,</del>		[0.49; 2.71]	0.9%
Mehmet 2015	13	194	9	78		0.55	[0.23; 1.35]	1.1%
Xie 2011	55	103	9	33		3.06	[1.30; 7.21]	0.6%
Mustapic 2012	36	355	80	860			[0.73; 1.67]	3.7%
Santos 2002	5	72	9	39			[0.08; 0.81]	1.0%
Kamboh 1995	31	204	197	1,199			[0.60; 1.38]	4.3%
Ng 2006 Eto 1995	50 70	706 534	25 135	360 1,109	<u> </u>		[0.62; 1.68] [0.80; 1.48]	2.7% 6.7%
Morbois Trabut 2006		384	121	867			[0.40; 0.89]	5.9%
Powell 2003	36	263	22	164	i		[0.58; 1.81]	2.1%
Guangda 1999	10	162	13	133			[0.26; 1.43]	1.2%
Zhang 2000	6	119	9	132			[0.25; 2.10]	0.7%
Zhang 2003	15	142	34	356	<u>F</u>		[0.59; 2.12]	1.5%
Sun 2013	21	438	9	137			[0.32; 1.60]	1.1%
Hua 2006	28	188	21	191	1		[0.77; 2.60]	1.6%
Guo 2003	15	74	9	98			[1.03; 6.12]	0.5%
Liang 2017 Shen 2002	10 15	82 201	46 24	675 202			[0.92; 3.93] [0.30; 1.18]	0.8% 1.9%
Zheng 1998	14	203	6	110			[0.48; 3.44]	0.6%
Hua 2004	6	65	13	115			[0.29; 2.21]	0.7%
Liu 2014	31	410	25	592	<u>+</u> =		[1.08; 3.19]	1.7%
Xiang 1995	32	230	9	95			[0.71; 3.37]	1.0%
Chen 2006	11	174	14	186			[0.37; 1.88]	1.1%
Xiang 1999	31	239	9	95			[0.65; 3.12]	1.0%
Shen 2002 Xiong 2013	16 36	49 226	13 28	90 207			[1.24; 6.64] [0.71; 2.07]	0.5% 2.2%
Zhou 2005	7	120	11	123			[0.24; 1.69]	0.9%
Xiang 2005	29	189	22	177			[0.70; 2.32]	1.7%
Long 1999	17	116	16	248			[1.21; 5.13]	0.8%
Liang 2005	28	267	10	166	+	1.83	[0.86; 3.87]	1.0%
Gu 2004	12	114	10	166			[0.76; 4.40]	0.6%
Yang 1995	32	230	10	94			[0.64; 2.89]	1.1%
Rong 2013 Liu 2016	2 43	44 572	1 25	68 596			[0.28; 36.29] [1.12; 3.08]	0.1% 2.0%
Tang 2007	12	79	14	116			[0.57; 2.99]	0.8%
Qiu 2008	23	241	17	198	<u> </u>		[0.58; 2.17]	1.5%
Guo 2007	12	78	8	73			[0.57; 3.85]	0.6%
Xiong 2008	79	604	108	961		1.19	[0.87; 1.62]	6.4%
Ge 2013	77	357	63	356			[0.88; 1.85]	4.3%
Xiang 2010	8	76	19	191			[0.45; 2.55]	0.8%
Luo 2016	5 5	66	10	95			[0.23; 2.14]	0.7%
Zhang 2007 Wang 2014	э 25	74 108	9 24	95 95	-		[0.22, 2.16]	0.6% 1.7%
Zhang 2002	14	108	15	143	<u> </u>		[0.59; 2.76]	1.0%
Xiong 2005	5	56	3	55			[0.39; 7.48]	0.2%
Dai 2000	5	59	14	165			[0.34; 2.90]	0.6%
Fixed effect model		12,686		15,398	6	1.18	[1.09; 1.28]	100.0%
Heterogeneity: $I^2 = 360$	$\%, \tau^2 = 0.0$		< 0.01					
					0.1 0.5 1 2 10			

**Figure 3.** Forest plot for the result of association between type 2 diabetes and *ApoE* ɛ4 allele *vs*. ɛ3 allele based on a fixed-effects model.

## ApoE polymorphism and type 2 diabetes

	Experimenta		ontrol				
Study	Events Tota			Odds Ratio	OR	95%-Cl	Weight
Singh 2006	1 7	9 1	75		0.95	[0.06; 15.45]	1.2%
Al-Majed 2011	7 8		48		2.21	[0.44; 11.08]	2.7%
Chaudhary 2012	1 11	8 2	115		0.48	[0.04; 5.40]	2.4%
Errera 2006	0 6		77				0.0%
Alharbi 2014	35 32		361		1.49	[0.88; 2.53]	27.2%
Inamdar 2000	2 1		11		1.18	[0.09; 14.69]	1.4%
Kwon 2007	0 6		70				0.0%
Atta 2016 Vauhkonen 1997	0 1 0 4		30 76				0.0% 0.0%
Erdogan 2009	04		28				0.0%
Eto 1986	0 7		81		0.37	[0.01; 9.10]	1.7%
Guan 2009	8 14		89		4.99	[0.61; 40.60]	1.4%
Leiva 2005	0 13	3 0	87				0.0%
Liu 2003	0 5	60	64				0.0%
Mehmet 2015	0 8		19		_		0.0%
Xie 2011		8 1	9		0.33	[0.01; 9.40]	1.6%
Mustapic 2012	0 12		329		0.86	[0.03; 21.22]	1.0%
Santos 2002	0 3		200		0.11	[0.00; 2.85]	2.6%
Kamboh 1995 Ng 2006	0 6 4 28		388 143		0.47 2.01	[0.03; 8.46] [0.22; 18.19]	2.1% 1.6%
Eto 1995	1 19		416		1.08	[0.10; 11.96]	1.5%
Morbois Trabut 2006			299		0.82	[0.16; 4.29]	3.8%
Powell 2003	3 9		59	<u> </u>	0.96	[0.16; 5.93]	2.8%
Guangda 1999	1 6		54		0.80	[0.05; 13.14]	1.3%
Zhang 2000	0 5	0 0	56				0.0%
Zhang 2003	0 5		135		0.81	[0.03; 20.13]	1.0%
Sun 2013	6 18		57		0.92	[0.18; 4.67]	3.5%
Hua 2006	2 7		75		5.51	[0.26; 116.82]	0.6%
Guo 2003	0 2		39	<u>i</u>	4 70	10 10: 15 221	0.0%
Liang 2017 Shen 2002	1 8		272 75		1.72 0.88	[0.19; 15.22] [0.05; 14.33]	1.2% 1.3%
Zheng 1998	2 8		46		1.11	[0.10; 12.60]	1.5%
Hua 2004	1 2		45		5.57		0.4%
Liu 2014	10 18		274		7.82		1.8%
Xiang 1995	2 8	0 0	38		2.45	[0.11; 52.34]	0.8%
Chen 2006	2 7		73		2.06	[0.18; 23.20]	1.2%
Xiang 1999	3 8		38		3.15		0.8%
Shen 2002		70	31 73			[2.16; 1113.53]	0.1%
Xiong 2013 Zhou 2005	0 7		48		0.33	[0.01; 8.32] [0.01; 4.19]	1.8% 2.9%
Xiang 2005	1 6		66		1.00	[0.06; 16.33]	1.2%
Long 1999	0 3		101			[0.00, 10.00]	0.0%
Liang 2005	0 10	2 0	68				0.0%
Gu 2004	0 4	3 0	68				0.0%
Yang 1995	2 8		39		0.97	[0.09; 11.09]	1.6%
Rong 2013	0 1		29		7.00		0.0%
Liu 2016	14 25		276		7.89	[1.78; 35.08]	2.2%
Tang 2007 Qiu 2008	0 2 0 9		43 77		0.27	0.01: 6.651	0.0% 2.0%
Guo 2007	0 9		28		0.27	[0.01; 6.65] [0.01; 7.95]	1.8%
Xiong 2008	2 23		362	<u> </u>	1.04	[0.17; 6.28]	2.8%
Ge 2013	3 8		111	— <u>=</u>	0.45	[0.12; 1.75]	8.2%
Xiang 2010	0 2	8 0	70			. , ,	0.0%
Luo 2016	0 2		38				0.0%
Zhang 2007	0 3		39				0.0%
Wang 2014	0 3		30		0.17	[0.01; 3.69]	3.1%
Zhang 2002	0 4		56		0.46	[0.02; 11.50]	1.5%
Xiong 2005 Dai 2000	1 2 0 2		23 64		3.13	[0.12; 81.00]	0.6% 0.0%
Dai 2000	0 2	5 0	04				0.070
Fixed effect model	4,79		5,902	<b>\</b>	1.46	[1.11; 1.93]	100.0%
Heterogeneity: $I^2 = 0\%$	$t_{0}, \tau^{2} = 0, P = 0.6$	65	I				
			0.0	01 0.1 1 10 1,00	00		

**Figure 4.** Forest plot for the result of association between type 2 diabetes and *ApoE*  $\epsilon 2/\epsilon 2$  genotype *vs*.  $\epsilon 3/\epsilon 3$  genotype based on a fixed-effects model.

|--|

Study	TE seTE	Odds Ratio	OR	95%- <i>ci</i> Weigh	t
Singh 2006	-0.61 0.6474		0.54	[0.15; 1.93] 1.4%	ò
Al-Majed 2011	-0.87 0.9321		0.42	[0.07; 2.61] 0.9%	
Chaudhary 2012	-1.83 0.7751		0.16	[0.04; 0.74] 1.1%	
Errera 2006	0.74 0.4975		2.10	[0.79; 5.58] 1.9%	
Alharbi 2014 Inamdar 2000	0.51 0.3170		1.66	[0.89; 3.10] 2.6% [0.15; 1.79] 1.5%	
Kwon 2007	-0.65 0.6284 1.06 0.5541		0.52 2.89	[0.15; 1.79] 1.5% [0.98; 8.56] 1.7%	
Atta 2016	2.30 0.7303			[2.39; 41.84] 1.2%	
Vauhkonen 1997	0.21 0.5366		1.23	[0.43; 3.53] 1.8%	
Erdogan 2009	1.85 1.5106			[0.33; 122.32] 0.4%	
Eto 1986	-0.01 0.4871	-+-	0.99	[0.38; 2.56] 1.9%	
Guan 2009	-0.47 0.2845		0.62	[0.36; 1.09] 2.7%	
Leiva 2005	-0.24 0.4498		0.78	[0.33; 1.90] 2.1%	
Liu 2003	1.15 0.6119		3.14		
Mehmet 2015	-2.75 0.5264		0.06	[0.02; 0.18] 1.8%	
Xie 2011	1.47 0.8126	-		[0.88; 21.30] 1.1%	
Mustapic 2012	0.63 0.2456 -2.74 1.5893 -		1.88	[1.16; 3.05] 2.9%	
Santos 2002 Kamboh 1995	-2.74 1.5893 -		0.06 1.61	[0.00; 1.46] 0.4% [0.95; 2.74] 2.8%	
Ng 2006	-0.18 0.2464		0.83	[0.51; 1.35] 2.9%	
Eto 1995	0.43 0.2760		1.54	[0.90; 2.65] 2.8%	
Morbois Trabut 2006	-0.11 0.2382		0.90	[0.56; 1.43] 2.9%	
Powell 2003	0.70 0.4659		2.01	[0.81; 5.02] 2.0%	
Guangda 1999	0.40 0.5038		1.49	[0.56; 4.00] 1.9%	
Zhang 2000	0.45 0.6170		1.57	[0.47; 5.25] 1.5%	
Zhang 2003	-0.64 0.5188		0.53	[0.19; 1.46] 1.8%	b
Sun 2013	-0.09 0.3672		0.92	[0.45; 1.88] 2.4%	
Hua 2006	-0.46 0.6488		0.63	[0.18; 2.25] 1.4%	
Guo 2003	0.30 0.7205	-	1.36	[0.33; 5.57] 1.3%	
Liang 2017	-0.79 0.6220		0.45	[0.13; 1.53] 1.5%	
Shen 2002	-0.67 0.5016		0.51 1.11	[0.19; 1.37] 1.9%	
Zheng 1998 Hua 2004	0.11 0.4712 1.19 0.6758		3.28	[0.44; 2.80] 2.0% [0.87; 12.34] 1.4%	
Xiang 1995	0.67 0.5930		1.95	[0.61; 6.23] 1.6%	
Chen 2006	-0.15 0.3878		0.86	[0.40; 1.83] 2.3%	
Xiang 1999	0.45 0.5996		1.56	[0.48; 5.07] 1.6%	
Shen 2002	2.65 0.7347		14.21	[3.37; 59.97] 1.2%	b
Xiong 2013	0.14 0.4140		1.15	[0.51; 2.60] 2.2%	
Zhou 2005	0.35 0.4807		1.41	[0.55; 3.63] 1.9%	
Xiang 2005	0.00 0.4804		1.00	[0.39; 2.56] 2.0%	
Long 1999	0.85 0.3999		2.34	[1.07; 5.12] 2.3%	
Liang 2005	-0.06 0.4082		0.94	[0.42; 2.10] 2.2%	
Gu 2004	0.17 0.4821		1.19	[0.46; 3.05] 1.9%	
Yang 1995 Rong 2013	0.95 0.6595 -0.22 0.6819		2.60 0.81	[0.71; 9.46] 1.4% [0.21; 3.07] 1.4%	
Tang 2007	-0.67 1.1800		0.51	[0.05; 5.17] 0.6%	
Qiu 2008	-0.47 0.3882		0.62	[0.29; 1.33] 2.3%	
Guo 2007	-1.46 1.1496		0.23	[0.02; 2.22] 0.6%	
Xiong 2008	-0.54 0.2890	-	0.59	[0.33; 1.03] 2.7%	
Ge 2013	0.05 0.2737	+	1.05	[0.61; 1.79] 2.8%	b
Xiang 2010	-0.04 0.5718	_ <del></del>	0.96	[0.31; 2.95] 1.7%	D
Luo 2016	0.71 0.9462		2.04		
Zhang 2007	0.89 1.2478	- *	2.44		
Wang 2014	-0.72 0.6774		0.48	[0.13; 1.83] 1.4%	
Zhang 2002	-0.53 0.7207		0.59	[0.14; 2.42] 1.3%	
Xiong 2005 Dai 2000	0.27 0.7341		1.31	[0.31; 5.51] 1.2% [0.32; 3.07] 1.6%	
Filled: Shen 2002	-0.01 0.5749 -2.53 0.7347		0.99 0.08	[0.02; 0.34] 1.2%	
Filled, Shell 2002	-2.33 0.1341		0.00	[v.vz, v.34] 1.2%	,
Random effects mod	lel	4	1.05	[0.86; 1.28] 100.0%	0
Heterogeneity: $I^2 = 58\%$		1		,,	
	(	0.01 0.1 1 10 100			

**Figure 5.** Forest plot for the result of association between type 2 diabetes and *ApoE*  $\epsilon 2/\epsilon 3$  genotype vs.  $\epsilon 3/\epsilon 3$  genotype based on a random-effects model.

## ApoE polymorphism and type 2 diabetes

	Experimenta	C	ontrol				
Study	Events Tota			Odds Ratio	OR	95%-CI	Weight
Singh 2006	2 80	0	74		4.75	[0.22; 100.48]	0.4%
Al-Majed 2011	2 75	i 1	47		1.26	[0.11; 14.30]	1.0%
Chaudhary 2012	1 118		113		2.90	[0.12; 71.88]	0.4%
Errera 2006	2 70		77	<u> </u>		[0.27; 119.89]	0.4%
Alharbi 2014	13 303		345			[0.60; 3.08]	8.2%
Inamdar 2000	3 20		12			[0.13; 6.22]	1.8%
Kwon 2007	3 66 12 24		70 33			[0.39; 153.39]	0.4%
Atta 2016 Vauhkonen 1997	12 24 3 51		78			[2.39; 41.84] [0.38; 14.74]	1.1%
Erdogan 2009	0 40		28		2.50	[0.50, 14.14]	0.0%
Eto 1986	0 73		81		0.37	[0.01; 9.10]	1.2%
Guan 2009	7 148	1	89			[0.53; 36.11]	1.0%
Leiva 2005	4 137	3	90		0.87	[0.19; 3.99]	2.9%
Liu 2003	1 57	2	66		0.57	[0.05; 6.47]	1.5%
Mehmet 2015	0 81		19			ar 200 80.	0.0%
Xie 2011	4 12		10			[0.28; 14.20]	1.2%
Mustapic 2012	2 129		330			[0.36; 18.53]	0.9%
Santos 2002	0 32		11			[0.00; 2.85]	1.8%
Kamboh 1995 Ng 2006	5 67 5 287		401 148		1.62		4.2% 6.5%
Eto 1995	1 193		418		0.42		2.1%
Morbois Trabut 2006			308		0.15		7.4%
Powell 2003	3 92		58			[0.20; 18.93]	1.0%
Guangda 1999	1 67		55		0.40		1.8%
Zhang 2000	0 50	3	59		0.16	[0.01; 3.17]	2.6%
Zhang 2003	1 56	; 1	135		2.44	[0.15; 39.65]	0.5%
Sun 2013	0 180		56		0.10	[0.00; 2.55]	1.9%
Hua 2006	4 72		77			[0.39; 12.43]	1.5%
Guo 2003	2 25		40			[0.29; 39.50]	0.6%
Liang 2017	1 32 2 86		273	141		[0.17; 12.32]	1.0%
Shen 2002 Zheng 1998	2 86 1 82		78 45			[0.08; 2.47]	3.4% 0.5%
Hua 2004	2 26		40			[0.32; 43.50]	0.6%
Liu 2014	0 174		272		5.15	[0.02, 40.00]	0.0%
Xiang 1995	0 78	2 E	39		0.16	[0.01; 4.11]	1.6%
Chen 2006	1 71	2	74		0.51	[0.05; 5.80]	1.6%
Xiang 1999	1 86	i 1	39		0.45	[0.03; 7.34]	1.1%
Shen 2002	2 6		35			[0.53; 28.39]	0.6%
Xiong 2013	1 73		74			[0.04; 5.64]	1.6%
Zhou 2005	1 48		46 66			[0.12; 73.95] [0.06; 16.33]	0.4%
Xiang 2005 Long 1999	3 39		105			[0.45; 9.86]	0.8%
Liang 2005	6 108		70			[0.39; 10.20]	1.9%
Gu 2004	3 46		70			[0.38; 14.78]	1.2%
Yang 1995	0 78		39			[0.01; 4.11]	1.6%
Rong 2013	0 18		29			2 . E PORTO ( 1997) ( 1997) ( 1997)	0.0%
Liu 2016	0 243		274				0.0%
Tang 2007	2 30		44			[0.27; 35.49]	0.6%
Qiu 2008	3 98		78			[0.20; 7.37]	1.8%
Guo 2007	3 32		28			[0.27; 28.51]	0.8%
Xiong 2008 Ge 2013	6 236 2 88		368 111	E		[0.37; 2.96]	5.7% 5.7%
Xiang 2010	1 29		70			[0.29; 187.61]	0.2%
Luo 2016	1 29		41			[0.04; 4.58]	2.0%
Zhang 2007	0 32		41			[0.01; 5.24]	1.8%
Wang 2014	2 35		32			[0.07; 2.49]	3.3%
Zhang 2002	1 41	2	57			[0.06; 7.85]	1.4%
Xiong 2005	1 23		24			[0.06; 17.76]	0.8%
Dai 2000	0 23	1	65		0.91	[0.04; 23.25]	0.7%
Fixed effect model	4,80	5	5,961		1 15	[0.90; 1.46]	100 0%
Heterogeneity: $I^2 = 0\%$						[0.00, 1.40]	
3				0 01 01 1 10 100			

**Figure 6.** Forest plot for the result of association between type 2 diabetes and *ApoE*  $\epsilon 2/\epsilon 4$  genotype *vs*.  $\epsilon 3/\epsilon 3$  genotype based on a fixed-effects model.

0 to the	Experim			ntrol			05%	14/-:
Study	Events	Iotai	Events	lotal	Odds Ratio	OR		Weight
Singh 2006	5	83	13	87			[0.12; 1.07]	1.5%
Al-Majed 2011	6	79	9	55			[0.14; 1.26]	1.2%
Chaudhary 2012 Errera 2006	30 12	147 80	21 23	134 100			[0.75; 2.55]	2.2% 2.2%
Alharbi 2000	35	325	23 60	394			[0.27; 1.28] [0.43; 1.05]	2.2 <i>%</i> 6.1%
Inamdar 2000	16	33	8	18	i		[0.37; 3.73]	0.7%
Kwon 2007	14	77	12	82			[0.56; 3.01]	1.2%
Atta 2016	9	21	9	39			[0.80; 7.82]	0.5%
Vauhkonen 1997	20	68	33	109			[0.49; 1.86]	2.3%
Erdogan 2009	12	52	7	35			[0.42; 3.43]	0.8%
Eto 1986	21	94 165	16	96 97			[0.70; 2.97]	1.6% 1.2%
Guan 2009 Leiva 2005	24 43	176	9 39	97 126			[0.74; 3.75] [0.43; 1.20]	4.3%
Liu 2003	12	68	11	75			[0.43, 1.20]	1.1%
Mehmet 2015	13	94	9	28			[0.13; 0.91]	1.5%
Xie 2011	19	27	5	13	÷ +		[0.95; 15.25]	0.3%
Mustapic 2012	30	157	76	404		1.02	[0.64; 1.63]	4.4%
Santos 2002	3	35	8	18			[0.03; 0.53]	1.2%
Kamboh 1995	26	88	150	532	- <u>+</u> -		[0.65; 1.75]	3.8%
Ng 2006 Eto 1995	39 55	321 247	19 111	161 525	 		[0.58; 1.85] [0.74; 1.54]	2.8% 7.0%
Morbois Trabut 2006		176	87	381			[0.74, 1.34]	5.6%
Powell 2003	27	116	21	78			[0.43; 1.59]	2.4%
Guangda 1999	7	73	7	60			[0.27; 2.43]	0.9%
Zhang 2000	6	56	6	62		1.12	[0.34; 3.70]	0.6%
Zhang 2003	12	67	31	165			[0.45; 1.97]	1.9%
Sun 2013	21	201	6	61			[0.41; 2.78]	1.0%
Hua 2006	20	88	13	88			[0.78; 3.67]	1.3%
Guo 2003 Liang 2017	9 7	32 38	6 38	45 305			[0.80; 8.07] [0.65; 3.86]	0.5% 0.9%
Shen 2002	11	95	18	92			[0.03, 3.80]	2.0%
Zheng 1998	11	92	6	51	<u>+</u>		[0.35; 2.94]	0.9%
Hua 2004	4	28	8	53			[0.26; 3.43]	0.6%
Liu 2014	31	205	23	295		2.11	[1.19; 3.73]	2.0%
Xiang 1995	26	104	6	44			[0.80; 5.56]	0.8%
Chen 2006	8	78	10	82			[0.31; 2.21]	1.1%
Xiang 1999 Shen 2002	24 14	109 18	6 9	44 40			[0.68; 4.73] [3.17; 45.87]	0.8% 0.2%
Xiong 2013	31	103	22	40 94	- <u>i</u>		[0.75; 2.66]	2.0%
Zhou 2005	6	53	11	57			[0.18; 1.56]	1.2%
Xiang 2005	20	85	15	80			[0.63; 2.83]	1.5%
Long 1999	12	48	12	113			[1.16; 6.80]	0.7%
Liang 2005	18	120	8	76			[0.62; 3.64]	1.1%
Gu 2004	7	50	8	76			[0.47; 4.09]	0.7%
Yang 1995 Rong 2013	26 2	104 20	5 1	43 30			[0.90; 7.11] [0.27; 38.15]	0.7% 0.1%
Liu 2016	43	286	23	297			[1.23; 3.60]	2.4%
Tang 2007	10	38	13	56			[0.46; 3.06]	1.0%
Qiu 2008	14	109	11	87	<u> </u>		[0.44; 2.37]	1.3%
Guo 2007	7	36	7	34	<u>_</u>	0.93	[0.29; 3.00]	0.7%
Xiong 2008	47	277	87	446			[0.57; 1.25]	7.0%
Ge 2013	73	159	47	150			[1.17; 2.96]	3.3%
Xiang 2010	7	35	19	89 45			[0.35; 2.43]	1.1%
Luo 2016 Zhang 2007	2 3	30 35	7 7	45 46			[0.07; 2.01] [0.12; 2.18]	0.7% 0.7%
Wang 2014	13	46	8	36			[0.12, 2.10]	0.8%
Zhang 2002	11	51	11	66			[0.54; 3.48]	1.0%
Xiong 2005	2	24	2	25	l		[0.14; 8.08]	0.2%
Dai 2000	3	26	9	73			[0.23; 3.73]	0.5%
Fixed effect model		5,748	-	7,093	L 6-	1 11	[1.01; 1.22]	100.0%
Heterogeneity: $I^2 = 399$				,000			[	
	,	1 (			0.1 0.5 1 2 10			

**Figure 7.** Forest plot for the result of association between type 2 diabetes and *ApoE*  $\epsilon$ 3/ $\epsilon$ 4 genotype *vs*.  $\epsilon$ 3/ $\epsilon$ 3 genotype based on a fixed-effects model.

## ApoE polymorphism and type 2 diabetes

	Experimental	Control				
Study	Events Total	Events Total	Odds Ratio	OR	95%-Cl	Weight
Singh 2006	0 78	2 76		0.19		2.6%
Al-Majed 2011	15 88	1 47			[1.21; 73.98]	1.1%
Chaudhary 2012	4 121	1 114		3.86	[0.43; 35.09]	1.0%
Errera 2006 Alharbi 2014	0 68 39 329	0 77 10 344		4.49	[2.20; 9.16]	0.0% 9.1%
Inamdar 2000	14 31	10 20			[0.27; 2.54]	7.0%
Kwon 2007	1 64	1 71		1.11		1.0%
Atta 2016	0 12	0 30			. , .	0.0%
Vauhkonen 1997	8 56	5 81	+ =	2.53	[0.78; 8.20]	3.7%
Erdogan 2009	0 40	0 28	_	0.70	10 40 4 501	0.0%
Eto 1986	2 75 1 142	3 83 1 89		0.73	L	2.9% 1.3%
Guan 2009 Leiva 2005	1 142	0 87			[0.04; 10.11] [0.08; 48.82]	0.6%
Liu 2003	0 56	0 64		1.57	[0.00, 40.02]	0.0%
Mehmet 2015	0 81	0 19				0.0%
Xie 2011	16 24	1 9		16.00	[1.69; 151.11]	0.5%
Mustapic 2012	2 129				[0.46; 57.46]	0.6%
Santos 2002	1 33	0 10			[0.04; 25.64]	0.8%
Kamboh 1995	0 62 3 285	14 396 0 142		0.21	[0.01; 3.58]	4.1%
Ng 2006 Eto 1995	3 285 7 199	10 424		3.55	[0.18; 68.83] [0.57; 4.03]	0.7% 6.5%
Morbois Trabut 2006		10 304		0.10		7.1%
Powell 2003	3 92	0 57			[0.23; 88.69]	0.6%
Guangda 1999	1 67	2 55		0.40		2.3%
Zhang 2000	0 50	0 56				0.0%
Zhang 2003	1 56	1 135			[0.15; 39.65]	0.6%
Sun 2013	0 180	1 56			[0.00; 2.55]	2.4%
Hua 2006 Guo 2003	2 70 2 25	3 78 1 40		0.74	[0.12; 4.53] [0.29; 39.50]	2.9% 0.7%
Liang 2017	1 32	1 268			[0.53; 141.16]	0.2%
Shen 2002	1 85	1 75			[0.05; 14.33]	1.1%
Zheng 1998	1 82	0 45		1.67	[0.07; 41.96]	0.7%
Hua 2004	0 24	2 47		0.37		1.8%
Liu 2014	0 174	1 273			[0.02; 12.85]	1.2%
Xiang 1995 Chen 2006	3 81 1 71	1 39 1 73			[0.15; 14.52] [0.06; 16.77]	1.4% 1.0%
Xiang 1999	3 88	1 39			[0.14; 13.31]	1.4%
Shen 2002	0 4	0 31		1.04	[0.14, 10.01]	0.0%
Xiong 2013	2 74	2 74		1.00	[0.14; 7.29]	2.0%
Zhou 2005	0 47	0 46				0.0%
Xiang 2005	4 69	3 68			[0.29; 6.19]	3.0%
Long 1999	1 37	0 101			[0.33; 209.40]	0.3%
Liang 2005 Gu 2004	2 104 1 44	0 68 0 68			[0.16; 70.68] [0.19; 118.60]	0.6% 0.4%
Yang 1995	3 81	2 40			[0.12; 4.56]	2.7%
Rong 2013	0 18	0 29		0.10	[0.12, 1.00]	0.0%
Liu 2016	0 243	1 275		0.38	[0.02; 9.27]	1.5%
Tang 2007	0 28	0 43				0.0%
Qiu 2008	3 98	2 78		1.20		2.3%
Guo 2007	1 30	0 27			[0.11; 71.59]	0.5%
Xiong 2008 Ge 2013	13 243 1 87	6 365 4 107		3.38	[1.27; 9.02] [0.03; 2.73]	4.8% 3.7%
Xiang 2010	0 28	0 70	-	0.00	[0.00, 2.10]	0.0%
Luo 2016	1 29	0 38		4.05	[0.16; 103.17]	0.4%
Zhang 2007	1 33	0 39			[0.14; 92.55]	0.5%
Wang 2014	5 38	6 34			[0.19; 2.57]	5.8%
Zhang 2002	1 41	1 56			[0.08; 22.65]	0.9%
Xiong 2005	1 23	0 23			[0.12; 81.00]	0.5%
Dai 2000	1 24	2 66		1.39	[0.12; 16.08]	1.1%
Fixed effect model	4,850		4	1.71	[1.33; 2.19]	100.0%
Heterogeneity: $I^2 = 0\%$						
- /	- **		0.01 0.1 1 10 100			

**Figure 8.** Forest plot for the result of association between type 2 diabetes and *ApoE*  $\epsilon$ 4/ $\epsilon$ 4 genotype *vs*.  $\epsilon$ 3/ $\epsilon$ 3 genotype based on a fixed-effects model.

There is an association between ApoE polymorphism and T2DM: allele ɛ4 and genotypes  $(\epsilon 2/\epsilon 2, \epsilon 3/\epsilon 4, \text{ and } \epsilon 4/\epsilon 4)$  are associated with the increased risk for the development of T2DM, and they may be risk factors for T2DM.

## ACKNOWLEDGEMENT

The funding body has no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

### AUTHOR CONTRIBUTIONS

REN Shu Ping concepted and designed the study; CHEN Da Wei, SHI Ji Kang, LI Yun, and YANG Yu collected, and assembled the data; CHEN Da Wei and SHI Ji Kang analyzed and interpreted the data; CHEN Da Wei, SHI Ji Kang, and REN Shu Ping contributed to the writing process.

Received: May 31, 2019; Accepted: September 17, 2019

#### REFERENCES

- 1. Basu S, Yudkin JS, Kehlenbrink S, et al. Estimation of global insulin use for type 2 diabetes, 2018-30: a microsimulation analysis. Lancet Diabetes Endocrinol, 2019; 7, 25-33.
- 2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 populationbased studies with 4.4 million participants. Lancet, 2016; 387, 1513 - 30
- 3. Bommer C, Heesemann E, Sagalova V, et al. The global economic burden of diabetes in adults aged 20-79 years: a cost-of-illness study. Lancet Diabetes Endocrinol, 2017; 5, 423-30.
- 4. Scheuner MT, Sieverding P, Shekelle PG. Delivery of genomic medicine for common chronic adult diseases: a systematic review. JAMA, 2008; 299, 1320-34.
- 5. Davies LE, Thirlaway K. The influence of genetic explanations of type 2 diabetes on patients' attitudes to prevention, treatment and personal responsibility for health. Public Health Genomics, 2013; 16, 199-207.
- 6. O'Rahilly S, Barroso I, Wareham NJ. Genetic factors in type 2 diabetes: the end of the beginning? Science, 2005; 307, 370–3.
- 7. Hsu CC, Kao WH, Coresh J, et al. Apolipoprotein E and progression of chronic kidney disease. JAMA, 2005; 293, 2892-9
- 8. Luo JQ, Ren H, Banh HL, et al. The Associations between Apolipoprotein E Gene Epsilon2/Epsilon3/Epsilon4 Polymorphisms and the Risk of Coronary Artery Disease in Patients with Type 2 Diabetes Mellitus. Front Physiol, 2017; 8, 1031.
- 9. Chaudhary R, Likidlilid A, Peerapatdit T, et al. Apolipoprotein E gene polymorphism: effects on plasma lipids and risk of type 2 diabetes and coronary artery disease. Cardiovasc Diabetol,

from Yan et al. showed that  $\varepsilon 2$  and genotype  $\varepsilon 2/\varepsilon 3$ were associated with increased risk of T2DM, genotype  $\epsilon 2/\epsilon 2$  was not associated with increased risk of T2DM. The inconsistency may be caused by the different subjects included. Yan et al. research included only Chinese Han. Furthermore, we did not reveal the difference in the association of ApoE gene polymorphism with T2DM between ethnicities through subgroup analysis. In addition, our findings are consistent with those of Anthopoulos et al. study<sup>[78]</sup> which reveals that the ORs for the other  $\varepsilon^2$ carriers genotypes ( $\epsilon 2/\epsilon 2$ ,  $\epsilon 2/\epsilon 3$ , and  $\epsilon 2/\epsilon 4$ ) compared to  $\varepsilon 3/\varepsilon 3$  were greater than 1.00. The slight difference between the present study and Anthopoulos et al' is that the OR of  $\varepsilon 2/\varepsilon 2$  in our study reaches statistical significance while the OR of  $\epsilon 2/\epsilon 3$  in Anthopoulos et al' reaches statistical significance. However, the estimates of the results from Anthopoulos et al' study are likely to be attenuated due to the small sample size. Our findings demonstrate that individuals with the genotype carrying single allele  $\epsilon 2$  ( $\epsilon 2/\epsilon 3$  and  $\epsilon 2/\epsilon 4$ ) are not at the risk of T2DM while those carrying two  $\epsilon 2$  allele ( $\epsilon 2/\epsilon 2$ ) possess higher risk for T2DM, which also coincides with the finding that the higher frequency of the  $\epsilon 2/APOE$  allele might be primarily related to T2DM<sup>[37]</sup>

The strengths of the present study are that, 1) we included all the published literatures on the association between ApoE gene polymorphism and T2DM regardless of regions or ethnicities; 2) we had a large sample size. There are 18 new published papers discussing the association between ApoE gene polymorphism and T2DM since the last metaanalysis published in 2014, all of them are included in our present meta-analysis, which will provide more convincing evidence to the association of ApoE gene polymorphism with T2DM; 3) the results of our sensitivity analysis demonstrate that the conclusion of the present study is very stable; 4) the results of publication bias analysis reveal that the conclusion of our study is absent of publication bias. However, our study also has several weaknesses, 1) presence of heterogenicity in our study. We did the subgroup analysis on HWE, genotyping methods and ethnicities, but we did not trace the source of heterogenicity; 2) since the present study is a case-control study, the findings of our study cannot provide the causal relationship between ApoE gene polymorphism and T2DM, only the association of ApoE gene polymorphism with T2DM.

2012; 11, 36.

- Mahley RW, Rall SC Jr. Apolipoprotein E: far more than a lipid transport protein. Annu Rev Genomics Hum Genet, 2000; 1, 507–37.
- Li T, Shi Y, Yin J, et al. The association between lipid metabolism gene polymorphisms and nephropathy in type 2 diabetes: a meta-analysis. Int Urol Nephrol, 2015; 47, 117–30.
- Singh PP, Singh M, Mastana SS. APOE distribution in world populations with new data from India and the UK. Ann Hum Biol, 2006; 33, 279–308.
- Song Y, Stampfer MJ, Liu S. Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease. Ann Intern Med, 2004; 141, 137–47.
- McCarron MO, Delong D, Alberts MJ. APOE genotype as a risk factor for ischemic cerebrovascular disease: a meta-analysis. Neurology, 1999; 53, 1308–11.
- Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA, 1997; 278, 1349–56.
- Al-Majed HT, Qasem JA, Al-Sherifi AK, et al. Association between apolipoprotein E-polymorphism and Ischemic heart disease patients with or without type 2 diabetes mellitus: a preliminary study in Kuwait. Arch Iran Med, 2011; 14, 385–8.
- Alharbi KK, Khan IA, Syed R. Association of apolipoprotein E polymorphism with type 2 diabetes mellitus in a Saudi population. DNA Cell Biol, 2014; 33, 637–41.
- Atta MI, Abo Gabal K, El-Hadidi K, et al. Apolipoprotein E genotyping in Egyptian diabetic nephropathy patients. IUBMB Life, 2016; 68, 58–64.
- 19. Erdogan M, Eroglu Z, Biray C, et al. The relationship of the apolipoprotein E gene polymorphism Turkish Type 2 diabetic patients with and without nephropathy. J Endocrinol Invest, 2009; 32, 219–22.
- Mehmet E, Zuhal E, Mustafa K, et al. The relationship of the apolipoprotein E gene polymorphism in Turkish Type 2 Diabetic Patients with and without diabetic foot ulcers. Diabetes Metab Syndr, 2016; 10(1 Suppl 1), S30–33.
- Mustapic M, Popovic Hadzija M, Pavlovic M, et al. Alzheimer's disease and type 2 diabetes: the association study of polymorphisms in tumor necrosis factor-alpha and apolipoprotein E genes. Metab Brain Dis, 2012; 27, 507–12.
- 22. Sun L, Wang S, Shi X, et al. Interactionsbetween APOE and M THFR M utationsisAssociated with the Risk for Type2 Diabetic Nephropathy. Journal of Medical Molecular Biology, 2013; 10, 95–9.
- Liang A, He S, Hua X, et al. Correlation between ApoE gene polymorphism and chronic cardiovascular disease and blood ipid levels of patients. International Journal of laboratory medicine, 2017; 38, 1601–2+1605.
- Liu W. FOXC2, APOE, eNOS gene polymorphism with type 2 diabetes in Yunnan Naxi correlation. Kunming Medical University, 2014.
- 25. Chen X. Relationship between paraoxonase 1, paraoxonase 2 and apoliplprotein E gene polymorphisms and type 2 diabetes nephropathy. Fujian Medical University, 2006.
- 26. Xiong Y, Pei H, Qian S, et al. Study on the correlation between dyslipidemia and apolipoprotein E gene polymorphism in Li nationality population T2DM patients. Chinese Journal of Diabetes, 2013; 21, 822–4.
- Liu W, Yang L, Nian X, et al. The correlation between ApoE gene polymorphism with type 2 diabetes in Yuannan Naxi minority. Chinese Journal of Diabetes, 2016; 24, 402–6.
- Tang L, Wang X, Yu K, et al. Correlativ e analysis of apolipoprotein B,E gene polymorphism and several common

diseases in southern area of Zhejiang Province. Journal of Wenzhou Medical College, 2007; 1, 14–7.

- 29. Ge B, Chen J, Tian G, et al. The relationship between apolipoprotein E polymorphism and dyslipidemia in patients with type 2 diabetes. China Medical Herald, 2013; 10, 17–9+23.
- 30. Luo E, Yang Q, Li X. Analysis on the association between Apolipoprotein E Gene Polymorphism and renal Complications in Chinese Type 2 Diabetic Patients. Journal of Qiqihar University of Medicine, 2016; 37, 3130–2.
- Wang Y, Xiao Z, Huang P. Studies on relationshp between apolipoprotein E genotype polymorphism and diabetic nephropathy in Chinese Han population of Guangdong Province. Journal of practical Medicine, 2014; 30, 3090–2.
- Rong Y, Xie Y, Chen X, et al. Analysis fo the correlation among insulin resistance ApoE gene polymorphism and mild cognitive impairment. Hebei Medicine, 2013; 19, 1604–7.
- 33. Yin YW, Qiao L, Sun QQ, H, et al. Influence of apolipoprotein E gene polymorphism on development of type 2 diabetes mellitus in Chinese Han population: a meta-analysis of 29 studies. Metabolism, 2014; 63, 532–41.
- Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ, 2003; 327, 557–60.
- 35. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics, 1994; 50, 1088–101.
- 36. Singh PP, Naz I, Gilmour A, et al. Association of APOE (Hha1) and ACE (I/D) gene polymorphisms with type 2 diabetes mellitus in North West India. Diabetes Res Clin Pract, 2006; 74, 95–102.
- 37. Errera FI, Silva ME, Yeh E, et al. Effect of polymorphisms of the MTHFR and APOE genes on susceptibility to diabetes and severity of diabetic retinopathy in Brazilian patients. Braz J Med Biol Res, 2006; 39, 883–8.
- Inamdar PA, Kelkar SM, Devasagayam TP, et al. Apolipoprotein E polymorphism in non-insulin-dependent diabetics of Mumbai, India and its effect on plasma lipids and lipoproteins. Diabetes Res Clin Pract, 2000; 47, 217–23.
- 39. Kwon MK, Rhee SY, Chon S, et al. Association between apolipoprotein E genetic polymorphism and the development of diabetic nephropathy in type 2 diabetic patients. Diabetes Res Clin Pract, 2007; 77(Suppl 1), S228–232.
- Vauhkonen I, Niskanen L, Ryynanen M, et al. Divergent association of apolipoprotein E polymorphism with vascular disease in patients with NIDDM and control subjects. Diabet Med, 1997; 14, 748–56.
- 41. Eto M, Watanabe K, Iwashima Y, et al. Apolipoprotein E polymorphism and hyperlipemia in type II diabetics. Diabetes, 1986; 35, 1374–82.
- 42. Guan J, Zhao HL, Baum L, et al. Apolipoprotein E polymorphism and expression in type 2 diabetic patients with nephropathy: clinicopathological correlation. Nephrol Dial Transplant, 2009; 24, 1889–95.
- Leiva E, Mujica V, Orrego R, et al. Apolipoprotein E polymorphism in type 2 diabetic patients of Talca, Chile. Diabetes Res Clin Pract, 2005; 68, 244–9.
- 44. Liu L, Xiang K, Zheng T, et al. Co-inheritance of specific genotypes of HSPG and ApoE gene increases risk of type 2 diabetic nephropathy. Mol Cell Biochem, 2003; 254, 353–8.
- 45. Xie YQ, Wang H, Wu YP, et al. Association of APOE polymorphisms and insulin resistance with TCM syndromes in type 2 diabetes patients with macroangiopathy. Mol Med Rep, 2011; 4, 1219–23.
- 46. Santos A, Salguero ML, Gurrola C, et al. The epsilon4 allele of apolipoprotein E gene is a potential risk factor for the severity of macular edema in type 2 diabetic Mexican patients.

Ophthalmic Genet, 2002; 23, 13–9.

- 47. Kamboh MI, Aston CE, Hamman RF. The relationship of APOE polymorphism and cholesterol levels in normoglycemic and diabetic subjects in a biethnic population from the San Luis Valley, Colorado. Atherosclerosis, 1995; 112, 145–59.
- 48. Ng MC, Baum L, So WY, et al. Association of lipoprotein lipase S447X, apolipoprotein E exon 4, and apoC3 -455T>C polymorphisms on the susceptibility to diabetic nephropathy. Clin Genet, 2006; 70, 20–8.
- Eto M, Horita K, Morikawa A, et al. Increased frequency of apolipoprotein epsilon 2 allele in non-insulin dependent diabetic (NIDDM) patients with nephropathy. Clin Genet, 1995; 48, 288–92.
- Morbois-Trabut L, Chabrolle C, Garrigue MA, et al. Apolipoprotein E genotype and plasma lipid levels in Caucasian diabetic patients. Diabetes Metab, 2006; 32, 270–5.
- Powell DS, Maksoud H, Charge SB, et al. Apolipoprotein E genotype, islet amyloid deposition and severity of Type 2 diabetes. Diabetes Res Clin Pract, 2003; 60, 105–10.
- Guangda X, Bangshun X, Xiujian L, et al. Apovarepsilon(4) allele increases the risk for exercise-induced silent myocardial ischemia in non-insulin-dependent diabetes mellitus. Atherosclerosis, 1999; 147, 293–6.
- 53. Zhang W, Zhang G, Zhang H, et al. Relationship between Apo E gene polymorphism and type 2 diabetes mellitus with its cardiovascular complication in Chinese. Medical Journal of Chinese Civil Administration, 2000; 4, 206–9.
- 54. Zhang X, Liu B, Bai H, et al. Study on Apolipoprotein E Gene Polymorphism in Chinese Type 2 Diabetes Mellitus. J Sichuan Univ (Med Sci Edi), 2003; 1, 75–7.
- 55. Sun L, Wang S, Shi X, et al. Interactionsbetween APOE and M THFR M utationsisAssociated with the Risk for Type2 Diabetic Nephropathy. J Med Mol Biol, 2013; 10, 95–9.
- 56. Hua F, Liu W, Hu W, et al. Research on the association of ApoE gene polymorphism and type 2 diabetes mellitus with nephropathy. Suzhou Univers Ity Journal of Medical Science, 2006; 05, 837–838+860.
- 57. Guo J, Li P, Su Z. Preliminary analysis on relationship between ApoE gene polymorphism and type 2 diabetes. Journal of Tianjin Medical University, 2003; 4, 532–4.
- 58. Shen H, Liu L, Xiang K, et al. Relationship between ApoE gene polymorphism and type 2 diabetes mellitus with its nephropathy in Chinese. Chinese Journal of Diabetes, 2002; 1, 2–4.
- 59. Zheng Y, Sun R, Li X, et al. Relationshipbetween ApoE gene polymorphism and type 2 diabetes mellitus with its cardiovascular complications in Chinese. Chin J Endocrinol Metab, 1998; 1, 14–7.
- 60. Hua F, Shen Y, Hua W, et al. Association of carrier protein E gene polymorphism with diabetes mellitus with gallstone. Jiangsu Med J, 2004; 3, 182–4.
- 61. Xiang GD, Yang XJ, Ding XH, et al. The distribution of Apolipoprotein E genotype among different vascular complications in non-insulin-dependent diabetes mellitus. Chinese Journal of Medical Genetics, 1995; 4, 197–200.
- Xiang G, He Y, Le L, et al. The relationship of Apo E2 and renal insufficiency lipid levels in NIDDM. Natl Med J China, 1999; 5, 339.
- 63. Shen Q, Chen X, Li P, et al. Relationship between polymorphism of APOE gene and plasma catenin and protein C in elderly type 2 diabetes mellitus. F J Medical Journal, 2002; 1, 75–7.
- 64. Zhou J, Xue Y, Guan Y, et al. Association Study of Apolipoprotein E Gene Polymorphism and Cerebral Infarction in Type 2 Diabetic Patients. HEREDITAS, 2005; 27, 35–8.

- 65. Xiang G, Jiang W, Hu T. Apolipoproteine 4 allele is associated with the decrease of endothelium-dependent arterial dilation in female patients with type 2 diabetes mellitus. Chin J Endocrinol Metab, 2005; 21, 9–12.
- 66. Long J, Yang S, Gao J, et al. The Determination of Apolipoprotein E Genetic Polymorphism in Diabetics. Journal of Navy Medicine, 1999; 1, 42–4.
- 67. Liang S, Cheng H, Guan H, et al. Relationship of angiotensin converting enzyme and apolipoprotein E gene polymorphism with diabetic retinopathy. International Journal of Ophthamology, 2005; 5, 1156–9.
- Gu L, Pan M, Chen H, et al. Study in the Relationships between Apolipoprotein E Gene Polymorphism and Diabetic Retinopathy. Chinese Journal of Misdiagnostics, 2004; 4, 664–6.
- 69. Yang X, Ding X, Fan Y, et al. Relationship between coronary heart disease and apolipoprotein E genotype in patients with type 2 diabetes mellitus in Wuhan. Chinese Journal of Endocrine and Metabolism, 1995; 4, 206–210+250.
- Qiu Y. Relationship between variation of apolipoprotein E gene and type 2 diabetes mellitus with carotid atherosclerosis. Zhejiang Practical Medicine, 2008; 3, 157–159+168.
- 71. Guo J, Xu X. Association of apolipoprotein E gene polymorphism, hypersensitive C-reactive protein and type 2 diabetes mellitus with coronary heart disease. Shuanxi Medical Journal, 2007; 12, 1613–1616.
- Xiong Y, Liu S, Yang Y, et al. The Association of Apolipoprotein E Genotype with Type 2 Diabetes Mellitus. Chinese Journal of Microcirculation, 2008; 18, 28–29,33,23.
- Xiang Q, Song D, Liu H, et al. The study of the association of apolipoprotein E(ApoE) gene polymorphism with diabetic nephropathy in type 2 diabetic patients. Chinese Journal of Diabetes, 2010; 18, 185–6.
- 74. Zhang G, Xu Z. Study on the relationship between apolipoprotein E(Apo E)gene polymorphism and Chinese patients with type 2 diabetes mellitus and diabetogenous nephropathy(DN). Zhejiang Journal of Clinical Medicine, 2007; 9, 735–6.
- 75. Zhang L. Association between apolipoprotein E gene polymorphism and type II diabetic nephropathy. Acta Universitatis Medicinalis Anhui, 1999; 34, 102.
- 76. Xiong B, Zhu X. Relativity between apolipoprotein E,fatty acid binding 2 polymorphism and type 2 diabetes mellitus patients with nephropathy. CLINICAL FOCUS, 2005; 20, 367–70.
- 77. Qingfu Dai. A studies on the relationship between apo e sevels and genotypes in diabetie-nephropathy. Modern Journal of Integrated Chinese and Western Medicine, 2000; 23, 2321–2.
- Anthopoulos PG, Hamodrakas SJ, Bagos PG. Apolipoprotein E polymorphisms and type 2 diabetes: a meta-analysis of 30 studies including 5423 cases and 8197 controls. Mol Genet Metab, 2010; 100, 283–91.
- 79. Xu Q, Yang G, Li L, et al. Association of ApoE gene polymorphisms and type 2 diabetes mellitus in Chinese population: a Meta-analysisstudy. Cta Academiae Medicinae Militaris Tertiae, 2010; 32, 164–8.
- Long A, Huang X, Shen M, et al. Meta-Analysis: Association of Apolipoprotein E Gene Polymorphism with Type 2 Diabetes Mellitus in Chinese Population. The Journal of Evidence-Based Medicine, 2013; 13, 57–60.
- Dallongeville J, Lussier-Cacan S, Davignon J. Modulation of plasma triglyceride levels by apoE phenotype: a meta-analysis. J Lipid Res, 1992; 33, 447–54.
- Bennet AM, Di Angelantonio E, Ye Z, et al. Association of apolipoprotein E genotypes with lipid levels and coronary risk. JAMA, 2007; 298, 1300–11.

A	Study	Experimental Events Total	Control Events Total		OR	95%-Cl	Weight
A	Asian Singh 2006 Inamdar 2000 Kwon 2007 Eto 1986 Guan 2009 Liu 2003 Xie 2011 Ng 2006 Eto 1995 Guangda 1999 Zhang 2000 Zhang 2000 Zhang 2003 Sun 2013 Hua 2006 Guo 2003	Events Total   8 173   15 73   16 169   9 185   55 393   11 146   17 65   66 722   28 492   16 168   7 120   6 133   48 465   12 172   6 65	Events Total   9 177   13 50   5 162   13 199   14 210   4 147   7 31   40 375   43 1,017   11 131   26 348   17 145   9 179   6 95	Odds Ratio	0.91 0.74 3.28 0.73 2.28 2.91 1.21 0.84 1.37 1.15 0.95 0.87 1.42 1.51		1.5% 1.7% 1.4% 1.7% 2.2% 1.2% 1.5% 2.7% 2.5% 1.8% 1.4% 1.6% 2.3% 1.7% 1.2%
	Liang 2017 Shen 2002 Zheng 1998 Hua 2004 Liu 2014 Xiang 1995 Chen 2006 Xiang 1999 Shen 2002 Xiong 2013 Zhou 2005 Xiang 2005 Long 1999 Liang 2005 Gu 2004 Yang 1995 Rong 2013 Liu 2016	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		0.72 0.58 1.16 3.80 7.48 1.74 0.96 1.74 4.43 0.89 1.07 0.97 1.92 1.07 1.31 1.41 0.80 7.56	[0.30; 1.71] [0.27; 1.27] [0.52; 2.55] [1.26; 11.48] [2.54; 22.06] [0.63; 4.78] [0.50; 1.82] [0.63; 4.75] [1.86; 10.56] [0.43; 1.81] [0.48; 2.37] [0.44; 2.16] [0.99; 3.73] [0.54; 2.15] [0.55; 3.65] [0.55; 3.65] [0.23; 2.81] [2.63; 21.68]	1.7% 1.9% 1.9% 1.3% 1.4% 1.5% 2.2% 1.5% 1.7% 2.0% 1.8% 1.8% 2.1% 1.8% 1.6% 1.1% 1.4%
	Tang 2007 Qiu 2008 Guo 2007 Xiong 2008 Ge 2013 Xiang 2010 Luo 2016 Zhang 2007 Wang 2014 Zhang 2002 Xiong 2005 Dai 2000 <b>Random effects model</b> Heterogeneity: $l^2 = 50\%$ , $\tau^2$ <b>Other</b>	3 70 17 235 4 70 28 553 43 323 6 74 4 65 2 71 6 89 4 98 8 59 5 59 8763 = 0.1634, p < 0.0	4 106 22 203 7 72 63 916 64 357 13 185 5 90 3 89 15 86 11 139 5 57 15 166 <b>9839</b>		1.14 0.64 0.72 0.70 1.17 1.11 0.83 0.34 0.50 1.63 0.93 1.16	[0.25; 5.26] [0.33; 1.24] [0.16; 2.01] [0.46; 1.14] [0.46; 1.07] [0.43; 3.20] [0.29; 4.32] [0.14; 5.11] [0.13; 0.93] [0.15; 1.60] [0.50; 5.32] [0.32; 2.69] [0.97; 1.38]	0.9% 2.1% 1.1% 2.6% 2.6% 1.5% 1.5% 1.5% 1.2% 1.2% 1.2% 75.1%
	Al-Majed 2011 Chaudhary 2012 Errera 2006 Alharbi 2014 Atta 2016 Vauhkonen 1997 Erdogan 2009 Leiva 2005 Mehmet 2015 Mustapic 2012 Santos 2002 Kamboh 1995 Morbois Trabut 2006 Powell 2003 <b>Random effects model</b> Heterogeneity: $I^2 = 79\%$ , $\tau^2$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		0.30 2.30 1.53 6.40 1.43 5.92 0.86 0.10 1.74 0.04 1.36 0.81 1.62	[0.64; 3.62] [0.11; 0.84] [0.91; 5.84] [1.13; 2.07] [2.43; 16.87] [0.59; 3.48] [0.31; 111.90] [0.40; 1.81] [0.04; 0.27] [1.12; 2.70] [0.00; 0.77] [0.88; 2.12] [0.54; 1.21] [0.80; 3.25] [0.74; 1.69]	1.7% 1.5% 1.6% 2.9% 1.7% 0.3% 1.6% 0.3% 2.6% 2.6% 2.6% 2.7% 2.0% 24.9%
	<b>Random effects model</b> Heterogeneity: $I^2 = 62\%$ , $\tau^2$	12,224 = 0.2306, <i>P</i> < 0.0		0.01 0.1 1 10 100	1.16	[0.98; 1.37]	100.0%

Study	Experimental Events Total	Control Events Total	Odds Ratio	OR	95%-Cl	Weight
Other Alharbi 2014 Inamdar 2000 Eto 1986 Guan 2009 Mustapic 2012 Kamboh 1995 Ng 2006 Eto 1995 Xiang 1999 Xiang 2005 Guo 2007 Xiong 2008 Random effects model Heterogeneity: $I^2 = 50\%$ , $\tau$		83 829 13 50 13 199 14 210 52 832 119 1,121 40 375 43 1,017 5 91 13 168 7 72 63 916 5880 2		1.53 0.74 0.73 2.28 1.74 1.36 0.84 1.37 1.74 0.56 0.72 1.19	[1.13; 2.07] [0.31; 1.72] [1.23; 4.20] [1.12; 2.70] [0.88; 2.12] [0.56; 1.28] [0.84; 2.23] [0.63; 4.73] [0.44; 2.16] [0.16; 2.01] [0.46; 1.14] [0.94; 1.50]	2.9% 1.7% 2.2% 2.6% 2.6% 2.5% 1.5% 1.5% 1.8% 1.1% 2.6% 25.9%
PCR-RELP Singh 2006 AI-Majed 2011 Chaudhary 2012 Errera 2006 Kwon 2007 Atta 2016 Vauhkonen 1997 Erdogan 2009 Leiva 2005 Liu 2003 Mehmet 2015 Xie 2011 Santos 2002 Morbois Trabut 2006 Powell 2003 Guangda 1999 Zhang 2000 Zhang 2000 Zhang 2003 Liang 2013 Hua 2006 Guo 2003 Liang 2017 Shen 2002 Zheng 1998 Hua 2004 Liu 2014 Xiang 1995 Chen 2006 Shen 2002 Xiong 2013 Zhoug 2013 Zhoug 2005 Long 1999 Liang 2005 Gu 2004 Yang 1995 Rong 2013 Liu 2016 Tang 2007 Qiu 2008 Ge 2013 Xiang 2010 Luo 2016 Zhang 2007 Wang 2014 Zhang 2007 Wang 2014 Zhang 2005 Dai 2000 Random effects model Heterogeneity: $J^2 = 64\%, \tau$		$\begin{array}{cccccccccccccccccccccccccccccccccccc$		$\begin{array}{c} 1.43\\ 5.92\\ 0.86\\ 2.91\\ 0.10\\ 1.21\\ 0.04\\ 0.81\\ 1.62\\ 0.59\\ 0.87\\ 1.42\\ 0.59\\ 0.87\\ 1.42\\ 0.59\\ 0.87\\ 1.42\\ 0.58\\ 1.51\\ 0.72\\ 0.58\\ 1.6\\ 1.51\\ 0.72\\ 0.58\\ 1.6\\ 1.51\\ 0.72\\ 0.58\\ 1.6\\ 1.51\\ 0.72\\ 0.58\\ 1.6\\ 0.78\\ 0.80\\ 7.66\\ 1.14\\ 0.60\\ 0.80\\ 7.56\\ 1.14\\ 0.60\\ 0.80\\ 7.56\\ 1.14\\ 0.60\\ 0.80\\ 7.56\\ 1.14\\ 0.60\\ 0.80\\ 0.80\\ 0.80\\ 0.93\\ 0.9$	[0.43; 3.20] [0.29; 4.32] [0.14; 5.11] [0.13; 0.93] [0.15; 1.60]	0.9% 2.1% 2.6% 1.5% 1.0% 0.7% 1.5% 1.2% 1.2% 1.2% 1.4%
<b>Random effects model</b> Heterogeneity: $I^2 = 62\%$ , $\tau$		14,902 1	0.01 0.1 1 10 100	1.16	[0.98; 1.37]	100.0%

**Supplementary Figure S1.** (A) Forest plot for associations between type 2 diabetes and *ApoE*  $\epsilon$ 2 allele *vs*.  $\epsilon$ 3 allele in the subgroup based on ethnicity. (B) Forest plot for associations between type 2 diabetes and *ApoE*  $\epsilon$ 2 allele vs.  $\epsilon$ 3 allele in the subgroup based on genotype.

Stu	udy	Experin Events			ontrol Total	Odds Ratio	OR	95%-Cl	Weight
N									
Al-	Majed 2011	18	172	8	112		1.52	[0.64; 3.62]	1.7%
	narbi 2014	109	750	83	829			[1.13; 2.07]	2.9%
	dogan 2009	4	100	0	63	_ *		[0.31; 111.90]	0.3%
	hmet 2015	6	187	22	91	<u> </u>	0.10	[0.04; 0.27]	1.6%
	ang 2000	7	120	8	131		0.95	[0.33; 2.71]	1.4%
	12014 ng 1005	20 20	399 218	4 6	571 90			[2.54; 22.06]	1.4%
	ng 1995 I 2016	20	557	4	90 575		1.41	[0.55; 3.65] [2.63; 21.68]	1.6% 1.4%
	o 2016	4	65	5	90		1.11	[0.29; 4.32]	1.4%
	ang 2007	2	71	3	89		0.83	[0.14; 5.11]	0.7%
	ang 2014	6	89	15	86		0.34	[0.13; 0.93]	1.5%
	ndom effects model		2728		2727	\$	1.27	[0.64; 2.54]	
Het	terogeneity: $I^2 = 83\%, \tau^2$	= 1.0046,	<i>p</i> < 0.0	1					
Y									
	ngh 2006	8	173	9	177		0.91	[0.34; 2.40]	1.5%
	audhary 2012	5	271	16	275		0.30	[0.11; 0.84]	1.5%
	rera 2006 mdar 2000	14	174	7	191 50		2.30	[0.91; 5.84]	1.6%
	mdar 2000 /on 2007	15 16	73 169	13 5	50 162		0.74 3.28	[0.31; 1.72] [1.17; 9.18]	1.7% 1.4%
	a 2016	24	69	6	78			[2.43; 16.87]	
	uhkonen 1997	10	133	11	205		1.43	[0.59; 3.48]	1.7%
	o 1986	9	185	13	199		0.73	[0.31; 1.75]	1.7%
	an 2009	55	393	14	210		2.28	[1.23; 4.20]	2.2%
	iva 2005	16	337	13	236		0.86	[0.40; 1.81]	1.9%
	2003	11	146	4	147		2.91	[0.91; 9.37]	1.2%
Xie	e 2011	17	65	7	31		1.21	[0.44; 3.33]	1.5%
	istapic 2012	37	356	52	832		1.74	[1.12; 2.70]	2.6%
	ntos 2002	0	67	5	35		0.04	[0.00; 0.77]	0.3%
	mboh 1995	28	201		1,121		1.36	[0.88; 2.12]	2.6%
	2006 0 1995	66 28	722 492	40	375 1,017		0.84 1.37	[0.56; 1.28] [0.84; 2.23]	2.7% 2.5%
	orbois Trabut 2006	36	386	43 95	841		0.81	[0.54; 2.23]	2.7%
	well 2003	31	258	12	154		1.62	[0.34, 1.21]	2.0%
	angda 1999	16	168	11	131	- <u>F</u>	1.15	[0.51; 2.57]	1.8%
	ang 2003	6	133	26	348		0.59	[0.24; 1.46]	1.6%
	n 2013	48	465	17	145	-	0.87	[0.48; 1.56]	2.3%
Hu	a 2006	12	172	9	179		1.42	[0.58; 3.45]	1.7%
Gu	o 2003	6	65	6	95		1.51	[0.46; 4.90]	1.2%
	ing 2017	6	78	73	702		0.72	[0.30; 1.71]	1.7%
	en 2002	11	197	18	196		0.58	[0.27; 1.27]	1.9%
	eng 1998	21	210	10	114		1.16	[0.52; 2.55]	1.9%
	a 2004	11	70 218	5	107 91			[1.26; 11.48]	1.3%
	ang 1995 Ien 2006	20 20	183	5 22	194		1.74 0.96	[0.63; 4.78] [0.50; 1.82]	1.5% 2.2%
	ang 1999	20	229	5	91		1.74	[0.63; 4.75]	1.5%
	en 2002	19	52	10	87	<b>—</b>		[1.86; 10.56]	1.7%
	ong 2013	16	206	17	196		0.89	[0.43; 1.81]	2.0%
	ou 2005	14	127	13	125		1.07	[0.48; 2.37]	1.8%
	ang 2005	13	173	13	168		0.97	[0.44; 2.16]	1.8%
	ng 1999	18	117	22	254	<u> </u>	1.92	[0.99; 3.73]	2.1%
	ing 2005	23	262	14	170	- <u></u>	1.07	[0.54; 2.15]	2.1%
	2004	12	114	14	170		1.31	[0.58; 2.95]	1.8%
	ng 2013	4	46	8	75		0.80	[0.23; 2.81]	1.1%
	ng 2007	3 17	70 235	4 22	106 203		1.14	[0.25; 5.26]	0.9% 2.1%
	u 2008 lo 2007	4	235	7	203 72		0.64 0.56	[0.33; 1.24] [0.16; 2.01]	2.1% 1.1%
	ong 2008	28	553	63	916	-	0.50	[0.16, 2.01]	
	e 2013	20 43	323	64	357	-	0.72	[0.46; 1.14]	2.6%
	ang 2010	-5	74	13	185		1.17	[0.43; 3.20]	1.5%
	ang 2002	4	98	11	139	<u>_</u>	0.50	[0.15; 1.60]	
	ong 2005	8	59	5	57	-	1.63	[0.50; 5.32]	1.2%
	i 2000	5	59	15	166		0.93	[0.32; 2.69]	1.4%
	ndom effects model		9496		12175	ķ	1.14	[0.98; 1.34]	
He	terogeneity: $I^2 = 49\%$ , $\tau^2$	= 0.1332,	<i>p</i> < 0.0	1					
	ndom effects model		12,224		14,902		1.16	[0.98; 1.37]	100.0%
Het	terogeneity: $I^2 = 62\%, \tau^2$	= 0.2306,	P < 0.0	1				_	
						0.01 0.1 1 10 100			

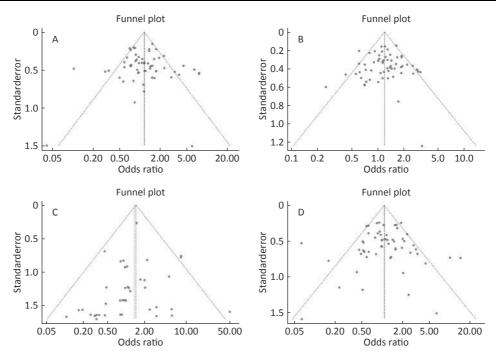
В	Study	Experimental Events Total Ev	Control vents Total	Odds Ratio	OR	95%-Cl	Weight
	Asian Singh 2006 Inamdar 2000 Kwon 2007 Eto 1986 Guan 2009 Liu 2003 Xie 2011 Ng 2006 Eto 1995 Guangda 1999 Zhang 2000 Zhang 2003 Sun 2013 Hua 2006 Guo 2003 Liang 2013 Hua 2006 Guo 2003 Liang 2017 Shen 2002 Zheng 1998 Hua 2004 Liu 2014 Xiang 1995 Chen 2006 Xiang 1999 Shen 2002 Xiong 2013 Zhou 2005 Kiang 2005 Gu 2004 Yang 1999 Liang 2005 Gu 2004 Yang 1999 Liang 2005 Gu 2004 Yang 1999 Liang 2005 Gu 2004 Yang 1995 Rong 2013 Liu 2016 Tang 2007 Qiu 2008 Ge 2013 Xiang 2010 Luo 2016 Zhang 2007 Wang 2014 Zhang 2007 Wang 2014 Zhang 2002 Xiong 2008 Ge 2013 Xiang 2007 Wang 2014 Zhang 2007 Wang 2014 Zhang 2002 Xiong 2008 Ge 2013 Xiang 2007 Wang 2014 Zhang 2007 Yang 2007 Yang 2007 Yang 2007 Yang 2014 Zhang 2007 Yang 2007 Yang 2014 Zhang 2007 Yang 2014 Zhang 2007 Yang 2014 Zhang 2007 Yang 2014 Zha	4 82 8 25 13 76 9 82 32 173 11 67 13 21 53 335 25 217 13 79 7 57 5 60 36 216 4 72 4 27 3 34 7 91 16 97 7 31 0 174 16 97 7 31 0 174 16 97 7 31 0 174 15 85 14 99 11 15 15 87 13 60 10 75 15 51 17 119 9 52 16 94 4 22 0 243 1 29 1 30 18 248 35 121 5 33 3 31 2 34 4 37 3 43 5 27 5 28 3882 = 0.0993, $p = 0.03$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		$\begin{array}{c} 4.33\\ 0.83\\ 1.54\\ 1.49\\ 1.57\\ 0.53\\ 0.92\\ 0.63\\ 1.36\\ 0.45\\ 0.51\\ 1.11\\ 3.28\\ 1.95\\ 0.86\\ 1.56\\ 14.21\\ 1.15\\ 1.41\\ 1.00\\ 2.34\\ 0.94\\ 1.19\\ 2.60\\ 0.81\\ 0.51\\ 0.62\\ 0.23\\ 0.59\\ 1.05\\ 0.96\\ 2.04\\ \end{array}$	[0.51; 2.60] [0.55; 3.63] [0.39; 2.56] [1.07; 5.12] [0.42; 2.10] [0.46; 3.05] [0.71; 9.46] [0.21; 3.07] [0.29; 1.33] [0.02; 2.22] [0.33; 1.03] [0.61; 1.79] [0.32; 13.01] [0.21; 28.12] [0.32; 13.01] [0.21; 28.12] [0.13; 1.83] [0.14; 2.42] [0.31; 5.51] [0.32; 3.07]	$\begin{array}{c} 1.4\% \\ 1.5\% \\ 1.7\% \\ 1.9\% \\ 2.8\% \\ 1.5\% \\ 1.0\% \\ 3.0\% \\ 2.9\% \\ 1.9\% \\ 1.5\% \\ 1.8\% \\ 2.5\% \\ 1.4\% \\ 1.2\% \\ 1.5\% \\ 1.9\% \\ 2.0\% \\ 1.6\% \\ 2.4\% \\ 1.6\% \\ 2.2\% \\ 2.0\% \\ 2.0\% \\ 2.0\% \\ 2.3\% \\ 2.0\% \\ 2.0\% \\ 2.3\% \\ 2.0\% \\ 1.3\% \\ 0.6\% \\ 2.4\% \\ 0.6\% \\ 2.8\% \\ 2.9\% \\ 1.6\% \\ 0.6\% \\ 2.8\% \\ 2.9\% \\ 1.6\% \\ 0.6\% \\ 2.8\% \\ 2.9\% \\ 1.6\% \\ 0.6\% \\ 1.3\% \\ 1.2\% \\ 1.6\% \\ 74.8\% \end{array}$
	Other Al-Majed 2011 Chaudhary 2012 Errera 2006 Alharbi 2014 Atta 2016 Vauhkonen 1997 Erdogan 2009 Leiva 2005 Mehmet 2015 Mustapic 2012 Santos 2002 Kamboh 1995 Morbois Trabut 2006 Powell 2003 <b>Random effects model</b> Heterogeneity: $I^2 = 79\%$ , $\tau^2$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3 49 12 125 7 84 18 352 3 33 9 85 0 28 10 97 22 41 48 376 2 12 88 470 71 365 7 64 2181		0.16 2.10 1.66 10.00 1.23 6.33 0.78 0.06 1.88 0.06 1.61 0.90 2.01		0.9% 1.1% 1.9% 2.7% 1.2% 1.8% 0.4% 2.1% 1.8% 3.0% 0.3% 2.9% 3.1% 2.0% 25.2%
	Random effects model Heterogeneity: $I^2$ = 55%, $\tau^2$	5,392 = 0.2568, <i>p</i> < 0.01	6,666	0.01 0.1 1 10 100	1.09	[0.90; 1.32]	100.0%

**Supplementary Figure S2.** (A) Forest plot for associations between type 2 diabetes and *ApoE*  $\epsilon$ 2 allele *vs*.  $\epsilon$ 3 allele in the subgroup based on HWE. (B) Forest plot for associations between type 2 diabetes and *ApoE*  $\epsilon$ 2/ $\epsilon$ 3 genotype vs.  $\epsilon$ 3/ $\epsilon$ 3 genotype in the subgroup based on ethnicity.

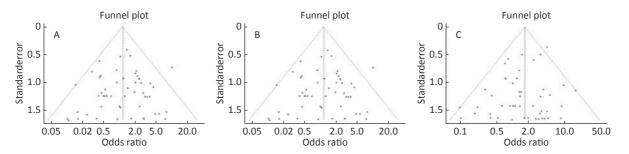
А	Study	Experimental Events Total Eve	Control ents Total	Odds Ratio	OR	95%-Cl Weight
	Other Alharbi 2014 Inamdar 2000 Eto 1986 Guan 2009 Mustapic 2012 Kamboh 1995 Ng 2006 Eto 1995 Xiang 1999 Xiang 2005 Guo 2007 Xiong 2008 Random effects model Heterogeneity: $I^2 = 53\%$ , $\tau^2$		18 352   9 19   10 90   32 120   48 376   88 470   32 174   35 449   4 42   10 75   4 31   48 407   2605		1.66 0.52 0.99 0.62 1.88 1.61 0.83 1.54 1.56 1.00 0.23 0.59 1.07	[0.38; 2.56] 1.9%   [0.36; 1.09] 2.8%   [1.16; 3.05] 3.0%   [0.95; 2.74] 2.9%   [0.51; 1.35] 3.0%   [0.90; 2.65] 2.9%   [0.48; 5.07] 1.6%   [0.32; 2.56] 2.0%   [0.33; 1.03] 2.8%
	PCR-RELP Singh 2006 Al-Majed 2011 Chaudhary 2012 Errera 2006 Kwon 2007 Atta 2016 Vauhkonen 1997 Erdogan 2009 Leiva 2005 Liu 2003 Mehmet 2015 Xie 2011 Santos 2002 Morbois Trabut 2006 Powell 2003 Guangda 1999 Zhang 2000 Zhang 2000 Zhang 2003 Sun 2013 Hua 2006 Guo 2003 Liang 2017 Shen 2002 Zheng 1998 Hua 2004 Liu 2014 Xiang 1995 Chen 2006 Shen 2002 Xiong 2013 Zhou 2005 Long 1999 Liang 2005 Gu 2004 Yang 1995 Rong 2013 Zhou 2005 Gu 2004 Yang 1995 Rong 2013 Liu 2016 Tang 2007 Qiu 2008 Ge 2013 Xiang 2010 Luo 2016 Zhang 2007 Qiu 2008 Ge 2013 Xiang 2010 Luo 2016 Zhang 2007 Wang 2014 Zhang 2007 Wang 2014 Zhang 2007 Wang 2014 Zhang 2007 Random effects model Heterogeneity: $I^2 = 56\%$ , $\tau$		$\begin{array}{cccccccccccccccccccccccccccccccccccc$		$\begin{array}{c} 10.00\\ 1.23\\ 6.33\\ 0.78\\ 3.14\\ 0.06\\ 4.33\\ 0.06\\ 0.90\\ 2.01\\ 1.49\\ 1.57\\ 0.53\\ 0.92\\ 0.63\\ 1.36\\ 0.45\\ 1.57\\ 0.51\\ 0.51\\ 1.11\\ 3.28\\ 1.95\\ 0.86\\ 14.21\\ 1.15\\ 1.41\\ 2.34\\ 0.94\\ 1.19\\ 2.60\\ 0.81\\ 0.51\\ 0.62\\ 1.05\\ 0.96\\ 2.04\\ 2.44\\ \end{array}$	
	Random effects model Heterogeneity: $I^2 = 55\%$ , $\tau^2$		6,666	0.01 0.1 1 10 100	1.09	[0.90; 1.32] 100.0%

В	Study	Experimental Events Total Eve	Control ents Total	Odds Ratio	OR	95%-Cl	Weight
	N Al-Majed 2011 Alharbi 2014 Erdogan 2009 Mehmet 2015 Zhang 2000 Liu 2014 Yang 1995 Liu 2016 Luo 2016 Zhang 2007 Wang 2014 Random effects model Heterogeneity: $I^2 = 78\%$ , T		3 49 18 352 0 28 22 41 5 61 0 272 3 41 0 272 3 41 0 274 2 40 1 40 7 35 1233		0.06 1.57 2.60 2.04 2.44 0.48	[0.07; 2.61] [0.89; 3.10] [0.33; 122.32] [0.02; 0.18] [0.47; 5.25] [0.71; 9.46] [0.32; 13.01] [0.21; 28.12] [0.13; 1.83] [0.36; 2.56]	0.9% 2.7% 0.4% 1.8% 1.5% 0.0% 1.4% 0.8% 0.5% 1.3% 11.3%
	Y Singh 2006 Chaudhary 2012 Errera 2006 Inamdar 2000 Kwon 2007 Atta 2016 Vauhkonen 1997 Eto 1986 Guan 2009 Leiva 2005 Liu 2003 Xie 2011 Mustapic 2012 Santos 2002 Kamboh 1995 Ng 2006 Eto 1995 Morbois Trabut 2006 Powell 2003 Guangda 1999 Zhang 2003 Sun 2013 Hua 2006 Guo 2003 Liang 2017 Shen 2002 Zheng 1998 Hua 2004 Xiang 1995 Chen 2006 Xiang 1999 Shen 2002 Xiong 2013 Zhou 2005 Xiang 2005 Long 2008 Guo 2007 Xiong 2008 Guo 2007 Xiong 2008 Ge 2013 Xiang 2017 Zhang 2005 Xiang 2005 Long 1999 Liang 2005 Xiang 2007 Xiong 2008 Ge 2013 Xiang 2010 Zhang 2002 Xiong 2005 Dai 2000		$\begin{array}{cccccccccccccccccccccccccccccccccccc$		$\begin{array}{c} 1.23\\ 0.99\\ 0.62\\ 0.78\\ 3.14\\ 4.33\\ 1.88\\ 0.06\\ 1.61\\ 0.83\\ 1.54\\ 0.90\\ 2.01\\ 1.49\\ 0.53\\ 0.92\\ 0.63\\ 1.56\\ 0.45\\ 0.51\\ 1.11\\ 3.28\\ 1.95\\ 0.86\\ 1.56\\ \end{array}$	[0.33; 1.03] [0.61; 1.79] [0.31; 2.95] [0.14; 2.42] [0.31; 5.51] [0.32; 3.07]	2.0% 1.9% 1.5% 1.4% 1.2% 1.5% 1.9% 2.0% 1.3% 1.6% 2.4% 1.6% 2.2% 2.0% 2.2% 2.0% 2.3% 2.3% 2.0% 1.3% 0.6% 2.4% 0.6% 2.4%
	Random effects model Heterogeneity: $I^2 = 55\%$ , $\tau$		6,666	0.01 0.1 1 10 100	1.09	[0.90; 1.32]	100.0%

**Supplementary Figure S3.** (A) Forest plot for associations between type 2 diabetes and ApoE  $\epsilon 2/\epsilon 3$  genotype vs.  $\epsilon 3/\epsilon 3$  genotype in the subgroup based on genotype. (B) Forest plot for associations between type 2 diabetes and ApoE  $\epsilon 2/\epsilon 3$  genotype vs.  $\epsilon 3/\epsilon 3$  genotype in the subgroup based on HWE.



**Supplementary Figure S4.** (A) Funnel plot of association between type 2 diabetes and *ApoE*  $\epsilon$ 2 allele *vs*.  $\epsilon$ 3 allele. (B) Funnel plot of association between type 2 diabetes and *ApoE*  $\epsilon$ 4 allele *vs*.  $\epsilon$ 3 allele. (C) Funnel plot of association between type 2 diabetes and *ApoE*  $\epsilon$ 2/ $\epsilon$ 2 genotype *vs*. and  $\epsilon$ 3/ $\epsilon$ 3 genotype. (D) Funnel plot of association between type 2 diabetes and *ApoE*  $\epsilon$ 2/ $\epsilon$ 2 genotype *vs*. and  $\epsilon$ 3/ $\epsilon$ 3 genotype.



**Supplementary Figure S5.** (A) Funnel plot of association between type 2 diabetes and ApoE  $\epsilon 2/\epsilon 4$  genotype vs. and  $\epsilon 3/\epsilon 3$  genotype. (B) Funnel plot of association between type 2 diabetes and ApoE  $\epsilon 3/\epsilon 4$  genotype vs. and  $\epsilon 3/\epsilon 3$  genotype. (C) Funnel plot of association between type 2 diabetes and ApoE  $\epsilon 4/\epsilon 4$  genotype vs. and  $\epsilon 3/\epsilon 3$  genotype.