

Association between *ApoE* polymorphism and type 2 diabetes:

A meta-analysis of 59 studies

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Abstract

(1) Aims: Due to the ever increasing incidence of T2DM, it is estimated that only half of the 79 million adults with type 2 diabetes (T2DM) will have adequate access to insulin by 2030 if the current levels of access is not improved. It is urgent to identify the important risk factors for 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 and even molecular marker of targeted therapy for the treatment of T2DM.

(2) Methods: Case-control studies of *ApoE* polymorphism and T2DM, which were included in PubMed, Web of Science, Medline, WanFang, VIP, and CNKI databases, were selected and evaluated according to criteria of inclusion and exclusion. Eligible data were extracted and pooled, and were analyzed and assessed using R soft-ware (version 3.4.3). Random-effect models were used when heterogeneity existed in between-study, and fixed-effect models were applied otherwise.

(3) Results: A total of 59 studies that consisted of 6,872 cases with T2DM and 8,250 controls were selected. Alleles and genotypes of *ApoE* between cases and controls were compared. For *ApoE* alleles, we observed the contrast of $\epsilon 4$ versus $\epsilon 3$ allele yielding a pooled OR of 1.18 (95% *CI*: 1.09-1.28; $P < 0.001$). For *ApoE* genotypes, compared with $\epsilon 3/\epsilon 3$ genotype, $\epsilon 2/\epsilon 2$ genotype showed a possible association with T2DM (OR=1.46; 95% *CI*: 1.11-1.93; $P = 0.007$), $\epsilon 3/\epsilon 4$ genotype had a 1.11-fold risk of developing T2DM (OR=1.11; 95% *CI*: 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% *CI*: 1.33-2.19; $P < 0.001$).

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

Keywords: apolipoprotein E; meta-analysis; polymorphism; type 2 diabetes

1. Introduction

It is estimated that only half of the 79 million adults with type 2 diabetes will have adequate access to insulin by 2030 if the current levels of access is not improved (BASU *et al.* 2019). Moreover, one of the significant causes of worldwide mortality and morbidity is diabetes (2016), especially type 2 diabetes mellitus, which is also the major cause of substantial global economic burden (BOMMER *et al.* 2017). 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 (SCHEUNER *et al.* 2008). 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 (DAVIES and THIRLAWAY 2013), it will also improve the effectiveness and precision of treatment and prevention strategies (O'RAHILLY *et al.* 2005).

ApoE gene is one of the most studied genes which is responsible for stabilizing and solubilizing circulating lipoproteins in our body (CHAUDHARY *et al.* 2012). *ApoE* is a plasma glycoprotein of 34 kDa with 299-amino acids, and acts as a high affinity ligand for several hepatic lipoprotein receptors such as low-density lipoprotein receptor (LDLR) and LDL-related protein (LRP) (CHAUDHARY *et al.* 2012). *ApoE* is also involved in the process of cellular incorporation of several lipoproteins for transport and digestion (MAHLEY and RALL 2000) and is associated with several other plasma glycoproteins, such as high density lipoprotein (HDL), very low density lipoprotein (VLDL), and chylomicrons (SINGH *et al.* 2006b). In humans, *apoE* gene is located on the chromosome at position 19q13.2 with SNPs at positions 112 (rs 429358) and 158 (rs 7412), and includes three major alleles: ϵ 2 (T to C substitution at position 158), the most common ϵ 3, and ϵ 4 (C to T substitution at position 112); 3 isoforms: ApoE2 (Cys112, 158Cys), ApoE3 (Cys112, 158Arg), and ApoE4 (Arg112, 158Arg); and 6

genotypes having 3 homozygous: $\epsilon 2/\epsilon 2$, $\epsilon 3/\epsilon 3$, and $\epsilon 4/\epsilon 4$, and 3 heterozygous: $\epsilon 2/\epsilon 3$, $\epsilon 2/\epsilon 4$, and $\epsilon 3/\epsilon 4$ (SINGH *et al.* 2006b).

ApoE is involved in many diseases, such as coronary heart disease (CHD))(SONG *et al.* 2004), ischemic cerebrovascular disease (ICD))(McCARRON *et al.* 1999), Alzheimer's disease (FARRER *et al.* 1997) and diabetes.

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(CHEN 2006; TANG *et al.* 2007; ERDOGAN *et al.* 2009; AL-MAJED *et al.* 2011; CHAUDHARY *et al.* 2012; MUSTAPIC *et al.* 2012; GE *et al.* 2013; RONG *et al.* 2013; SUN *et al.* 2013a; XIONG *et al.* 2013; ALHARBI *et al.* 2014; LIU 2014; WANG *et al.* 2014; ATTA *et al.* 2016; LIU *et al.* 2016; LUO *et al.* 2016; MEHMET *et al.* 2016; LIANG *et al.* 2017) have been published since the publication of latest meta-analysis of the association between *ApoE* gene polymorphism and T2DM in 2014(YIN *et al.* 2014). Therefore, we enrolled these new published articles, and performed a further meta-analysis to investigate whether *ApoE* polymorphism is associated with the increased risk of T2DM.

2. Materials and Methods

2.1. 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 November 19, 2018). The terms used for searching were (“*ApoE*” OR “Apolipoprotein E”) AND (“polymorphism, Genetic” OR “variant” OR “mutation”) AND (“type 2 diabetes mellitus” OR “type 2 diabetes” OR “T2DM” OR “non-insulin 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.

2.2. 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) lack of sufficient information on genotype or allele frequencies.

2.3. 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. We collected and calculated Hardy–Weinberg equilibrium (HWE) among the controls.

2.4. Quality assessment

The Newcastle-Ottawa scale (NOS) was used to evaluate quality of each article through a “star” rating system consisting of selection, comparability, and exposure. We allocated a score of 1 point for each condition a study met, and no point (0 score) if the condition or requirement was lacking. 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 existed between the two authors, the results were requested to discuss with the third investigator (Dawei Chen). To avoid selection bias, studies with poor quality score were not excluded.

2.5. Statistical analysis

Allele and genotype frequencies of *ApoE* were calculated for each study to evaluate the HWE using Goodness of fit Chi-square test among control groups, and $P < 0.05$ was considered 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 evaluated by the Chi-square test based *Q*-statistic and quantified by *I*²-statistic (HIGGINS *et al.* 2003). Random-effect models (DerSimonian and Laird methods) were used to calculate *OR* and 95% *CI* when *P* value of *Q* test was more than 0.10 or *I*² value was more than 50%; otherwise, fixed-effect models (Mantel and Haenszel methods) were applied (*I*²≥50% considered heterogeneity existed in between-study in this meta-analysis). Subgroup analyses stratified by ethnicity, quality score and Hardy–Weinberg equilibrium were performed to identify main sources of heterogeneity and to observe the association between *ApoE* polymorphisms and type 2 diabetes in different groups. Publication bias was assessed using funnel plots, and quantified by the Begg’s and Egger’s tests (*P*<0.05 considered statistically significant publication bias) (BEGG and MAZUMDAR 1994). 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.

3. Results

3.1. Study Characteristics

Our meta-analysis initially collected 791 published articles, including 782 papers identified using our search strategy and 9 papers identified through the references. After abstracts and full texts were scanned according to the inclusion and exclusion criteria, 59 eligible articles with 6,872 cases and 8,250 controls were finally included 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.

3.2. Association between alleles of *ApoE* and type 2 diabetes

There was significant heterogeneity in the comparison of *ApoE* ϵ 2 with ϵ 3 allele (*I*²=62%), and the pooled *OR* was 1.16 (95% *CI*: 0.98-1.37; *P*=0.079) when *ApoE* ϵ 2 was compared with ϵ 3 using the random-effects model (Figure 2); however, there was

not heterogeneity in the comparison of *ApoE* $\epsilon 4$ with $\epsilon 3$ allele ($I^2=36\%$), and the pooled *OR* was 1.18 (95% *CI*: 1.09-1.28; $P<0.001$) when *ApoE* $\epsilon 4$ was compared with $\epsilon 3$ using the fixed-effects model (Figure 3), suggesting that *ApoE* $\epsilon 4$ allele may be a risk factor for type 2 diabetes.

3.3. Association between genotypes of *ApoE* and type 2 diabetes

There were five 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 $\epsilon 3/\epsilon 3$ genotype. No significant heterogeneity was found when the $\epsilon 2/\epsilon 2$ genotype was compared with $\epsilon 3/\epsilon 3$ genotype ($I^2=0\%$), and the yielded *OR* of $\epsilon 2/\epsilon 2$ genotype versus $\epsilon 3/\epsilon 3$ genotype using a fixed-effects model was 1.46 (95% *CI*: 1.11-1.93; $P=0.007$) (Figure 4), suggesting that the $\epsilon 2/\epsilon 2$ genotype may have a harmful effect on type 2 diabetes. However, when $\epsilon 2/\epsilon 3$ genotype was compared with $\epsilon 3/\epsilon 3$ genotype, there was significant heterogeneity ($I^2=55\%$), and the yielded *OR* of $\epsilon 2/\epsilon 3$ genotype versus $\epsilon 3/\epsilon 3$ genotype using a random-effects model was 1.09 (95% *CI*: 0.90-1.32; $P=0.397$) (Figure 5). Compared with $\epsilon 3/\epsilon 3$ genotype, there were no significant heterogeneity between $\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$ genotype, respectively ($I^2=0\%$, $I^2=39\%$, and $I^2=0\%$). The yielded *OR* of $\epsilon 2/\epsilon 4$ 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 $\epsilon 3/\epsilon 4$ genotype versus $\epsilon 3/\epsilon 3$ genotype using a fixed-effects model was 1.11 (95% *CI*: 1.01-1.22; $P=0.039$) (Figure 7). For the comparison of $\epsilon 4/\epsilon 4$ genotype with $\epsilon 3/\epsilon 3$ 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 fixed-effects model (Figure 8).

3.4. 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 ($I^2=62\%$) and the comparison of $\epsilon 2/\epsilon 3$ genotype with $\epsilon 3/\epsilon 3$ genotype ($I^2=55\%$) in our paper; however, we did not investigate sources of heterogeneity and there was no significant association between *ApoE* polymorphisms and type 2 diabetes in different subgroups (Supplementary Figure S1-S3).

3.5. Publication bias

Publication bias was assessed by funnel plots and quantified by Begg's and Egger's tests. All the funnel plots for *ApoE* allele and *ApoE* genotypes seemed symmetrical (Supplementary Figure S4-S5), and the results of Begg's and Egger's tests showed that there was no publication bias for the association between *ApoE* allele and type 2 diabetes and for the association between the *ApoE* genotypes and type 2 diabetes (all $P > 0.05$).

3.6. Sensitivity analysis

Our results of sensitivity analysis showed that none of individual study influenced on the corresponding pooled *ORs* and 95% *CI*s in the comparison of *ApoE* $\epsilon 4$ with $\epsilon 3$ allele or in the comparison of *ApoE* $\epsilon 2/\epsilon 3$, $\epsilon 2/\epsilon 4$, and $\epsilon 4/\epsilon 4$ with genotype $\epsilon 3/\epsilon 3$ genotype (Figure 10, Figure 12, Figure 13, and Figure 15), suggesting that these results were relatively stable and credible. However, there were slight effects of individual study on the corresponding pooled *ORs* and 95% *CI*s in the comparison of *ApoE* $\epsilon 2$ with $\epsilon 3$ allele or in the comparison of *ApoE* $\epsilon 2/\epsilon 2$ and $\epsilon 3/\epsilon 4$ with genotype $\epsilon 3/\epsilon 3$ genotype (Figure 9, Figure 11, and Figure 14).

Table 1 Main characteristics of the included studies

Study	Year	Region	Ethnicity	Genotyping method	Sample size (case/control)	Quality score	HWE Y/N(P)	$\epsilon 2/\epsilon 2(n)+\epsilon 2/\epsilon 3(n)$		$\epsilon 2/\epsilon 4(n)+\epsilon 3/\epsilon 3(n)$		$\epsilon 3/\epsilon 4(n)+\epsilon 4/\epsilon 4(n)$	
								case	control	case	control	case	control
Singh(SINGH <i>et al.</i> 2006a)	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(AL-MAJED <i>et al.</i> 2011)	2011	Kuwait	Other	PCR-RELP	105/62	6	N(0.006)	7+2	2+3	2+73	2+46	6+15	9+1
Chaudhary(CHAUDHARY <i>et al.</i> 2012)	2012	Bangkok	Other	PCR-RELP	155/149	8	Y(0.121)	1+2	2+12	1+117	0+113	30+4	21+1
Errera(ERRERA <i>et al.</i> 2006)	2006	Brazil	Other	PCR-RELP	95/107	7	Y(0.584)	0+13	0+7	2+68	0+77	12+0	23+0
Alharbi(ALHARBI <i>et al.</i> 2014)	2014	Riyadh	Other	TaqMan	438/460	7	N(<0.001)	35+26	27+18	13+290	11+334	35+39	60+10
Inamdar(INAMDAR <i>et al.</i> 2000)	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(KWON <i>et al.</i> 2007)	2007	Korea	Asian	PCR-RELP	94/88	7	Y(0.924)	0+13	0+5	3+63	0+70	14+1	12+1
Atta(ATTA <i>et al.</i> 2016)	2016	Egypt	Other	PCR-RELP	45/45	5	Y(0.098)	0+12	0+3	12+12	3+30	9+0	9+0
Vauhkonen(VAUHKONEN <i>et al.</i> 1997)	1997	Finland	Caucasian	PCR-RELP	86/125	8	Y(0.963)	0+7	0+9	3+48	2+76	20+8	33+5
Erdogan(ERDOGAN <i>et al.</i> 2009)	2009	Turkey	Caucasian	PCR-RELP	56/35	7	N(<0.001)	0+4	0+0	0+40	0+28	12+0	7+0
Eto(ETO <i>et al.</i> 1986)	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(GUAN <i>et al.</i> 2009)	2009	Hong Kong	Asian	PCR-LDR	213/111	7	Y(0.499)	8+32	1+32	7+141	1+88	24+1	9+1
Leiva(LEIVA <i>et al.</i> 2005)	2005	Chile	Other	PCR-RELP	193/139	7	Y(0.293)	0+12	0+10	4+133	3+87	43+1	39+0
Liu(LIU <i>et al.</i> 2003)	2003	Shanghai	Asian	PCR-RELP	80/81	7	Y(0.217)	0+11	0+4	1+56	2+64	12+0	11+0
Mehmet(MEHMET <i>et al.</i> 2016)	2015	Turkey	Caucasian	PCR-RELP	100/50	8	N(0.039)	0+6	0+22	0+81	0+19	13+0	9+0
Xie(XIE <i>et al.</i> 2011)	2011	Hainan	Asian	PCR-RELP	60/20	7	Y(0.936)	0+13	1+3	4+8	2+8	19+16	5+1
Mustapic(MUSTAPIC <i>et al.</i> 2012)	2012	Croatia	Caucasian	TaqMan	196/456	6	Y(0.331)	0+35	1+48	2+127	2+328	30+2	76+1
Santos(SANTOS <i>et al.</i> 2002)	2002	Mexico	Other	PCR-RELP	36/22	8	Y(0.423)	0+0	1+2	0+32	1+10	3+1	8+0
Kamboh(KAMBOH <i>et al.</i> 1995)	1995	USA	Caucasian	IEF-immunoblotting and PCR	116/659	6	Y(0.992)	0+23	6+88	5+62	19+382	26+0	150+14
Ng(NG <i>et al.</i> 2006)	2016	Hong Kong	Asian	Other	386/200	6	Y(0.168)	4+53	1+32	5+282	6+142	39+3	19+0
Eto(ETO <i>et al.</i> 1995)	1995	Japan	Asian	Flat gel isoelectric focusing	281/576	8	Y(0.609)	1+25	2+35	1+192	4+414	55+7	111+10

Morbois Trabut(MORBOIS- TRABUT <i>et al.</i> 2006)	2006	France	Caucasian	PCR-RELP	210/481	7	Y(0.773)	2+31	5+71	1+143	14+294	33+0	87+10
Powell(POWELL <i>et al.</i> 2003)	2003	UK	Caucasian	PCR-RELP	187/102	7	Y(0.094)	3+22	2+7	3+89	1+57	27+3	21+0
Guangda(GUANGDA <i>et al.</i> 1999)	1999	Wuhan	Asian	PCR-RELP	89/72	7	Y(0.122)	1+13	1+7	1+66	2+53	7+1	7+2
Zhang(ZHANG <i>et al.</i> 2000)	2000	Zhejiang	Asian	PCR-RELP	63/71	8	N(0.009)	0+7	0+5	0+50	3+56	6+0	6+0
Zhang(ZHANG <i>et al.</i> 2003)	2003	Sichuan	Asian	PCR-RELP	74/191	8	Y(0.878)	0+5	1+23	1+55	1+134	12+1	31+1
Sun(SUN <i>et al.</i> 2013b)	2013	Beijing	Asian	PCR-RELP	243/78	7	Y(0.414)	6+36	2+12	0+180	1+55	21+0	6+1
Hua(HUA <i>et al.</i> 2006)	2006	Jiangsu	Asian	PCR-RELP	50/60	8	Y(0.190)	2+4	0+7	4+68	2+75	20+2	13+3
Guo(GUO <i>et al.</i> 2003)	2003	Tianjin	Asian	PCR-RELP	40/52	7	Y(0.739)	0+4	0+5	2+23	1+39	9+2	6+1
Liang(LIANG <i>et al.</i> 2017)	2017	guangdong	Asian	PCR-RELP	44/374	6	Y(0.816)	1+3	5+57	1+31	6+267	7+1	38+1
Shen(SHEN <i>et al.</i> 2002a)	2002	Shanghai	Asian	PCR-RELP	106/110	7	Y(0.577)	1+7	1+12	2+84	4+74	11+1	18+1
Zheng(ZHENG <i>et al.</i> 1998)	1998	Shanghai	Asian	PCR-RELP	112/60	8	Y(0.801)	2+16	1+8	1+81	0+45	11+1	6+0
Hua(HUA <i>et al.</i> 2004)	2004	Suzhou	Asian	PCR-RELP	38/60	7	Y(0.434)	1+7	0+4	2+24	1+45	4+0	8+2
Liu(LIU 2014)	2014	Kunming	Asian	PCR-RELP	215/298	7	N(<0.001)	10+0	2+0	0+174	0+272	31+0	23+1
Xiang(GUANGDA <i>et al.</i> 1999)	1995	Kunming	Asian	PCR-RELP	125/50	7	Y(0.715)	2+16	0+4	0+78	1+38	26+3	6+1
Chen(CHEN 2006)	2006	Fujian	Asian	PCR-RELP	97/105	7	Y(0.906)	2+15	1+18	1+70	2+72	8+1	10+1
Xiang(GUANGDA XIANG 1999)	1999	Wuhan	Asian	PCR-ASO	130/50	8	Y(0.715)	3+14	0+4	1+85	1+38	24+3	6+1
Shen(SHEN <i>et al.</i> 2002b)	2002	Fujian	Asian	PCR-RELP	35/50	6	Y(0.112)	3+11	0+6	2+4	4+31	14+0	9+0
Xiong(XIONG <i>et al.</i> 2013)	2013	Hannan	Asian	PCR-RELP	121/112	8	Y(0.991)	0+15	1+13	1+72	2+72	31+2	22+2
Zhou(ZHOU <i>et al.</i> 2005)	2005	Heilongjiang	Asian	PCR-RELP	67/68	7	Y(0.263)	0+13	2+9	1+47	0+46	6+0	11+0
Xiang(GUANGDA XIANG 2005)	2005	Wuhan	Asian	PCR-ASO	101/95	7	Y(0.438)	1+10	1+10	1+65	1+65	20+4	15+3
Long(JIANQIU LONG 1999)	1999	Shanghai	Asian	PCR-RELP	67/135	7	Y(0.124)	0+15	0+18	3+36	4+101	12+1	12+0
Liang(SHU LIANG 2005)	2005	Jiangsu	Asian	PCR-RELP	145/90	8	Y(0.592)	0+17	0+12	6+102	2+68	18+2	8+0
Gu(LIQUN GU 2004)	2004	jiangsu	Asian	PCR-RELP	63/90	8	Y(0.592)	0+9	0+12	3+43	2+68	7+1	8+0

Yang(XIANGJIU YANG 1995)	1995	Hubei	Asian	PCR-RELP	125/50	7	N(0.028)	2+16	1+3	0+78	1+38	26+3	5+2
Rong(RONG <i>et al.</i> 2013)	2013	Guangdong	Asian	PCR-RELP	18/29	7	Y(0.953)	0+4	0+8	0+18	0+29	2+0	1+0
Liu(LIU <i>et al.</i> 2016)	2016	Yunnan	Asian	PCR-RELP	300/300	8	N(<0.001)	14+0	2+0	0+243	0+274	43+0	23+1
Tang(TANG <i>et al.</i> 2007)	2007	Zhenan	Asian	PCR-RELP	41/60	6	Y(0.80)	0+1	0+3	2+28	1+43	10+0	13+0
Qiu(QIU 2008)	2008	Zhejiang	Asian	PCR-RELP	129/110	8	Y(0.481)	0+14	1+18	3+95	2+76	14+3	11+2
Guo(JINJING GUO 2007)	2007	Gansu	Asian	ARMS-PCR	40/40	6	Y(0.618)	0+1	1+4	3+29	1+27	7+1	7+0
Xiong(YU XIONG 2008)	2008	Wuhan	Asian	MultiARMS PCR	316/512	6	Y(0.744)	2+18	3+48	6+230	9+359	47+13	87+6
Ge(GE <i>et al.</i> 2013)	2013	Inner Mongolia	Asian	PCR-RELP	200/210	7	Y(0.544)	3+35	8+40	2+86	8+103	73+1	47+4
Xiang(QIAN XIANG 2010)	2010	Yunnan	Asian	PCR-RELP	41/102	7	Y(0.473)	0+5	0+13	1+28	0+70	7+0	19+0
Luo(LUO <i>et al.</i> 2016)	2016	Guangdong	Asian	PCR-RELP	35/50	6	N(0.005)	0+3	0+2	1+28	3+38	2+1	7+0
Zhang(GUANGWU ZHANG 2007)	2007	Zhejiang	Asian	PCR-RELP	38/49	6	N(0.015)	0+2	0+1	0+32	2+39	3+1	7+0
Wang(WANG <i>et al.</i> 2014)	2014	Guangdong	Asian	PCR-RELP	57/55	8	N(0.027)	0+4	2+7	2+33	4+28	13+5	8+6
Zhang(LI ZHANG 1999)	2002	Anhui	Asian	PCR-RELP	56/76	5	Y(0.631)	0+3	1+7	1+40	2+55	11+1	11+1
Xiong(BIN XIONG 2005)	2005	Gansu	Asian	PCR-RELP	32/30	7	Y(0.608)	1+5	0+4	1+22	1+23	2+1	2+0
Dai(QINGFU DAI 2000)	2000	Fujian	Asian	PCR-RELP	32/90	8	Y(0.253)	0+5	0+14	0+23	1+64	3+1	9+2

4. 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 $\epsilon 4$ and genotypes ($\epsilon 2/\epsilon 2$, $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$) are associated with the increased risk for the development of T2DM, however, allele $\epsilon 2$ and genotypes ($\epsilon 2/\epsilon 3$ and $\epsilon 2/\epsilon 4$) are not associated with T2DM.

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 meta-analysis 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 heterogeneity in our study. We did the subgroup analysis on HWE, genotyping methods and ethnicities, but we did not trace the source of heterogeneity; 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.

The findings of our meta-analysis are in accordance with the previous studies (ANTHOPOULOS *et al.* 2010; QIU XU 2010; AIMEI LONG 2013; YIN *et al.* 2014), showing that both *ApoE* $\epsilon 4$ allele and the genotypes ($\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$) were associated with increased risk of T2DM. Subjects carrying the $\epsilon 4$ alleles had higher plasma total cholesterol levels compared to subjects carrying the $\epsilon 3/\epsilon 3$ genotype, and HDL cholesterol was significantly lower in the $\epsilon 3/\epsilon 4$ than in the $\epsilon 3/\epsilon 3$ individuals (DALLONGEVILLE *et al.* 1992); individuals carrying the $\epsilon 2/\epsilon 2$ genotype had about 31% lower mean LDL than those with the $\epsilon 4/\epsilon 4$ genotype (BENNET *et al.* 2007). Insulin resistance is known to be strongly associated with metabolic dyslipidemia and the correlation of lipid profiles with diabetic phenotypes is significant. Therefore, *ApoE* $\epsilon 4$ 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 the results of previous meta-analyses (YIN *et al.* 2014). The results from Yan *et al.* showed that $\epsilon 2$ and genotype $\epsilon 2/\epsilon 3$ 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 (ANTHOPOULOS *et al.* 2010) which reveals that the ORs for the other $\epsilon 2$ -carriers genotypes ($\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, and $\epsilon 2/\epsilon 4$) compared to $\epsilon 3/\epsilon 3$ were greater than 1.00. The slight difference between the present study and Anthopoulos *et al.* is that the OR of $\epsilon 2/\epsilon 2$ 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 (ERRERA *et al.* 2006).

The significance of the present study is that we identified significant association between *ApoE* gene polymorphism and T2DM, which will provide clues for the etiology of T2DM and even molecular marker of targeted therapy for the treatment of T2DM. However, it is essential to further investigate the interaction between gene and gene as well as the gene and environment since T2DM is the result of interaction between genetic and environmental factors.

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

Author Contributions

Conception and design: Shuping Ren. Provision of study materials: Dawei Chen, Jikang Shi, and Yun Li. Collection and assembly of data: Dawei Chen, Jikang Shi, Yun Li, and Yu Yang. Data analysis and interpretation: Jikang Shi and Hui Yang. Manuscript writing: Dawei Chen, Shuping Ren. Revised the language/article: All authors. Final approval of manuscript: All authors.

Conflict of interest

The authors declare no conflict of interest.

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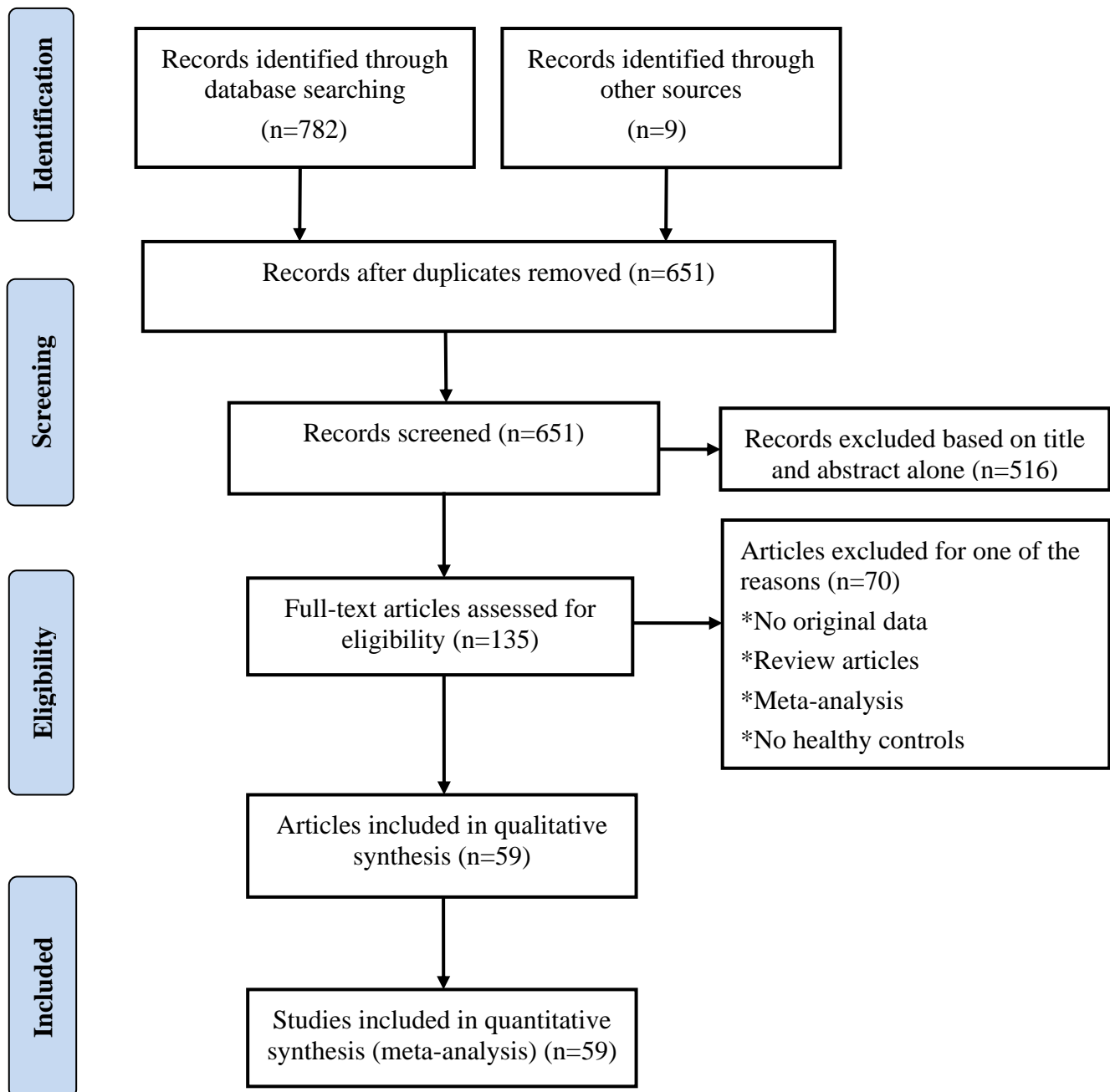
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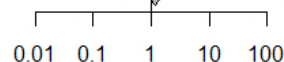
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Study	Experimental		Control		Odds Ratio	OR	95%-CI	Weight
	Events	Total	Events	Total				
Singh 2006	8	173	9	177		0.91	[0.34; 2.40]	1.5%
Al-Majed 2011	18	172	8	112		1.52	[0.64; 3.62]	1.7%
Chaudhary 2012	5	271	16	275		0.30	[0.11; 0.84]	1.5%
Errera 2006	14	174	7	191		2.30	[0.91; 5.84]	1.6%
Alharbi 2014	109	750	83	829		1.53	[1.13; 2.07]	2.9%
Inamdar 2000	15	73	13	50		0.74	[0.31; 1.72]	1.7%
Kwon 2007	16	169	5	162		3.28	[1.17; 9.18]	1.4%
Atta 2016	24	69	6	78		6.40	[2.43; 16.87]	1.5%
Vauhkonen 1997	10	133	11	205		1.43	[0.59; 3.48]	1.7%
Erdogan 2009	4	100	0	63		5.92	[0.31; 111.90]	0.3%
Eto 1986	9	185	13	199		0.73	[0.31; 1.75]	1.7%
Guan 2009	55	393	14	210		2.28	[1.23; 4.20]	2.2%
Leiva 2005	16	337	13	236		0.86	[0.40; 1.81]	1.9%
Liu 2003	11	146	4	147		2.91	[0.91; 9.37]	1.2%
Mehmet 2015	6	187	22	91		0.10	[0.04; 0.27]	1.6%
Xie 2011	17	65	7	31		1.21	[0.44; 3.33]	1.5%
Mustapic 2012	37	356	52	832		1.74	[1.12; 2.70]	2.6%
Santos 2002	0	67	5	35		0.04	[0.00; 0.77]	0.3%
Kamboh 1995	28	201	119	1121		1.36	[0.88; 2.12]	2.6%
Ng 2006	66	722	40	375		0.84	[0.56; 1.28]	2.7%
Eto 1995	28	492	43	1017		1.37	[0.84; 2.23]	2.5%
Morbois Trabut 2006	36	386	95	841		0.81	[0.54; 1.21]	2.7%
Powell 2003	31	258	12	154		1.62	[0.80; 3.25]	2.0%
Guangda 1999	16	168	11	131		1.15	[0.51; 2.57]	1.8%
Zhang 2000	7	120	8	131		0.95	[0.33; 2.71]	1.4%
Zhang 2003	6	133	26	348		0.59	[0.24; 1.46]	1.6%
Sun 2013	48	465	17	145		0.87	[0.48; 1.56]	2.3%
Hua 2006	12	172	9	179		1.42	[0.58; 3.45]	1.7%
Guo 2003	6	65	6	95		1.51	[0.46; 4.90]	1.2%
Liang 2017	6	78	73	702		0.72	[0.30; 1.71]	1.7%
Shen 2002	11	197	18	196		0.58	[0.27; 1.27]	1.9%
Zheng 1998	21	210	10	114		1.16	[0.52; 2.55]	1.9%
Hua 2004	11	70	5	107		3.80	[1.26; 11.48]	1.3%
Liu 2014	20	399	4	571		7.48	[2.54; 22.06]	1.4%
Xiang 1995	20	218	5	91		1.74	[0.63; 4.78]	1.5%
Chen 2006	20	183	22	194		0.96	[0.50; 1.82]	2.2%
Xiang 1999	21	229	5	91		1.74	[0.63; 4.75]	1.5%
Shen 2002	19	52	10	87		4.43	[1.86; 10.56]	1.7%
Xiong 2013	16	206	17	196		0.89	[0.43; 1.81]	2.0%
Zhou 2005	14	127	13	125		1.07	[0.48; 2.37]	1.8%
Xiang 2005	13	173	13	168		0.97	[0.44; 2.16]	1.8%
Long 1999	18	117	22	254		1.92	[0.99; 3.73]	2.1%
Liang 2005	23	262	14	170		1.07	[0.54; 2.15]	2.1%
Gu 2004	12	114	14	170		1.31	[0.58; 2.95]	1.8%
Yang 1995	20	218	6	90		1.41	[0.55; 3.65]	1.6%
Rong 2013	4	46	8	75		0.80	[0.23; 2.81]	1.1%
Liu 2016	28	557	4	575		7.56	[2.63; 21.68]	1.4%
Tang 2007	3	70	4	106		1.14	[0.25; 5.26]	0.9%
Qiu 2008	17	235	22	203		0.64	[0.33; 1.24]	2.1%
Guo 2007	4	70	7	72		0.56	[0.16; 2.01]	1.1%
Xiong 2008	28	553	63	916		0.72	[0.46; 1.14]	2.6%
Ge 2013	43	323	64	357		0.70	[0.46; 1.07]	2.6%
Xiang 2010	6	74	13	185		1.17	[0.43; 3.20]	1.5%
Luo 2016	4	65	5	90		1.11	[0.29; 4.32]	1.0%
Zhang 2007	2	71	3	89		0.83	[0.14; 5.11]	0.7%
Wang 2014	6	89	15	86		0.34	[0.13; 0.93]	1.5%
Zhang 2002	4	98	11	139		0.50	[0.15; 1.60]	1.2%
Xiong 2005	8	59	5	57		1.63	[0.50; 5.32]	1.2%
Dai 2000	5	59	15	166		0.93	[0.32; 2.69]	1.4%

Random effects model 12224 14902

Heterogeneity: $I^2 = 62\%$, $\tau^2 = 0.2306$, $p < 0.01$



Study	Experimental Events	Experimental Total	Control Events	Control Total	Odds Ratio	OR	95%-CI	Weight
Singh 2006	7	172	17	185		0.42	[0.17; 1.04]	1.4%
Al-Majed 2011	38	192	12	116		2.14	[1.07; 4.29]	1.1%
Chaudhary 2012	39	305	23	282		1.65	[0.96; 2.84]	1.8%
Errera 2006	14	174	23	207		0.70	[0.35; 1.41]	1.7%
Alharbi 2014	126	767	91	837		1.61	[1.21; 2.15]	6.4%
Inamdar 2000	47	105	30	67		1.00	[0.54; 1.85]	1.8%
Kwon 2007	19	172	14	171		1.39	[0.67; 2.88]	1.1%
Atta 2016	21	66	12	84		2.80	[1.26; 6.24]	0.6%
Vauhkonen 1997	39	162	45	239		1.37	[0.84; 2.22]	2.4%
Erdogan 2009	12	108	7	70		1.12	[0.42; 3.01]	0.7%
Eto 1986	25	201	23	209		1.15	[0.63; 2.10]	1.7%
Guan 2009	33	371	12	208		1.59	[0.80; 3.16]	1.2%
Leiva 2005	48	369	42	265		0.79	[0.51; 1.24]	3.7%
Liu 2003	12	147	11	154		1.16	[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		1.10	[0.73; 1.67]	3.7%
Santos 2002	5	72	9	39		0.25	[0.08; 0.81]	1.0%
Kamboh 1995	31	204	197	1199		0.91	[0.60; 1.38]	4.3%
Ng 2006	50	706	25	360		1.02	[0.62; 1.68]	2.7%
Eto 1995	70	534	135	1109		1.09	[0.80; 1.48]	6.7%
Morbois Trabut 2006	34	384	121	867		0.60	[0.40; 0.89]	5.9%
Powell 2003	36	263	22	164		1.02	[0.58; 1.81]	2.1%
Guangda 1999	10	162	13	133		0.61	[0.26; 1.43]	1.2%
Zhang 2000	6	119	9	132		0.73	[0.25; 2.10]	0.7%
Zhang 2003	15	142	34	356		1.12	[0.59; 2.12]	1.5%
Sun 2013	21	438	9	137		0.72	[0.32; 1.60]	1.1%
Hua 2006	28	188	21	191		1.42	[0.77; 2.60]	1.6%
Guo 2003	15	74	9	98		2.51	[1.03; 6.12]	0.5%
Liang 2017	10	82	46	675		1.90	[0.92; 3.93]	0.8%
Shen 2002	15	201	24	202		0.60	[0.30; 1.18]	1.9%
Zheng 1998	14	203	6	110		1.28	[0.48; 3.44]	0.6%
Hua 2004	6	65	13	115		0.80	[0.29; 2.21]	0.7%
Liu 2014	31	410	25	592		1.86	[1.08; 3.19]	1.7%
Xiang 1995	32	230	9	95		1.54	[0.71; 3.37]	1.0%
Chen 2006	11	174	14	186		0.83	[0.37; 1.88]	1.1%
Xiang 1999	31	239	9	95		1.42	[0.65; 3.12]	1.0%
Shen 2002	16	49	13	90		2.87	[1.24; 6.64]	0.5%
Xiong 2013	36	226	28	207		1.21	[0.71; 2.07]	2.2%
Zhou 2005	7	120	11	123		0.63	[0.24; 1.69]	0.9%
Xiang 2005	29	189	22	177		1.28	[0.70; 2.32]	1.7%
Long 1999	17	116	16	248		2.49	[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		1.84	[0.76; 4.40]	0.6%
Yang 1995	32	230	10	94		1.36	[0.64; 2.89]	1.1%
Rong 2013	2	44	1	68		3.19	[0.28; 36.29]	0.1%
Liu 2016	43	572	25	596		1.86	[1.12; 3.08]	2.0%
Tang 2007	12	79	14	116		1.30	[0.57; 2.99]	0.8%
Qiu 2008	23	241	17	198		1.12	[0.58; 2.17]	1.5%
Guo 2007	12	78	8	73		1.48	[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		1.28	[0.88; 1.85]	4.3%
Xiang 2010	8	76	19	191		1.07	[0.45; 2.55]	0.8%
Luo 2016	5	66	10	95		0.70	[0.23; 2.14]	0.7%
Zhang 2007	5	74	9	95		0.69	[0.22; 2.16]	0.6%
Wang 2014	25	108	24	95		0.89	[0.47; 1.70]	1.7%
Zhang 2002	14	108	15	143		1.27	[0.59; 2.76]	1.0%
Xiong 2005	5	56	3	55		1.70	[0.39; 7.48]	0.2%
Dai 2000	5	59	14	165		1.00	[0.34; 2.90]	0.6%

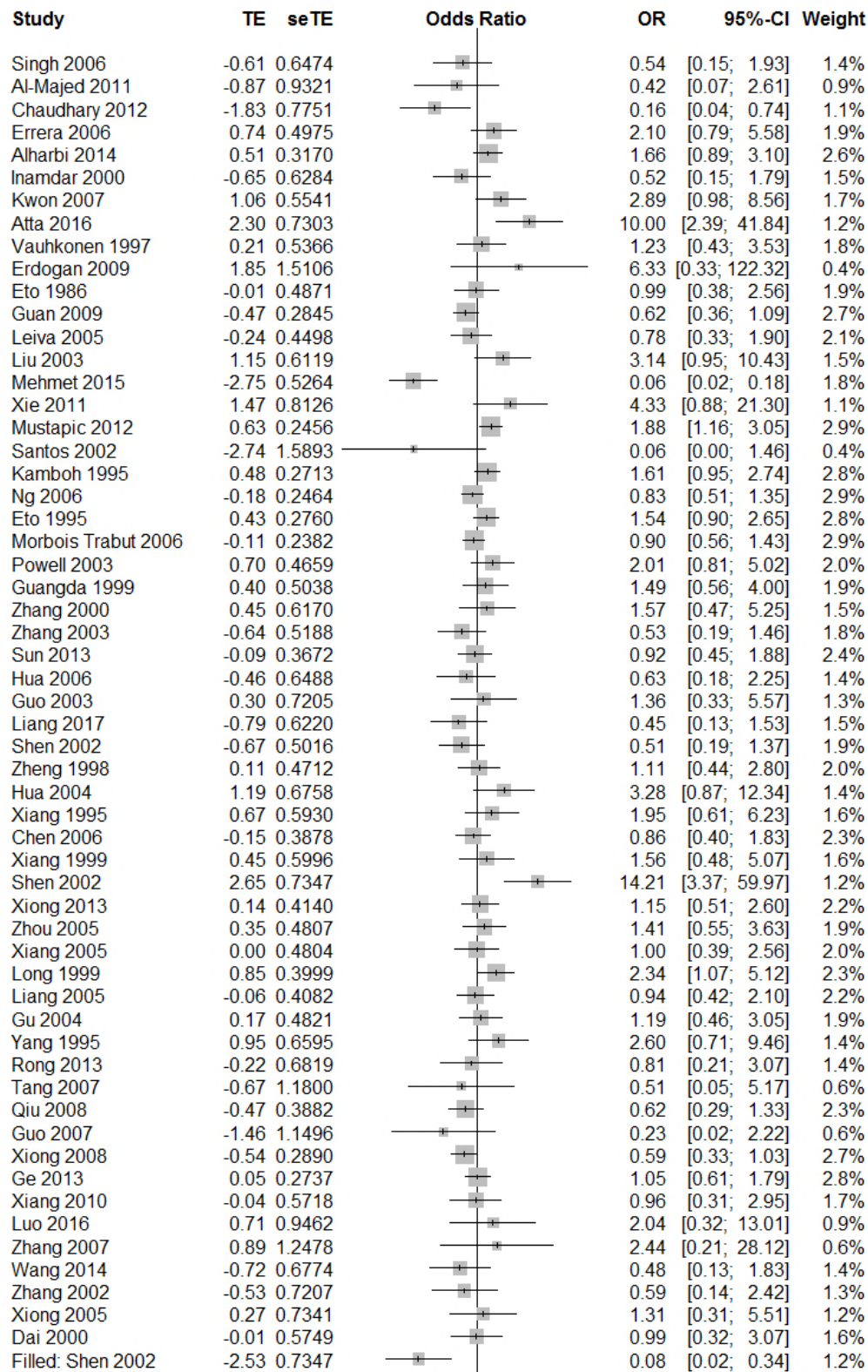
Fixed effect model 12686 15398
Heterogeneity: $I^2 = 36\%$, $\tau^2 = 0.0549$, $p < 0.01$

0.1 0.5 1 2 10

Study	Experimental		Control		Odds Ratio	OR	95%-CI	Weight
Events	Total	Events	Total					
Singh 2006	1	79	1	75		0.95	[0.06; 15.45]	1.2%
Al-Majed 2011	7	80	2	48		2.21	[0.44; 11.08]	2.7%
Chaudhary 2012	1	118	2	115		0.48	[0.04; 5.40]	2.4%
Errera 2006	0	68	0	77				0.0%
Alharbi 2014	35	325	27	361		1.49	[0.88; 2.53]	27.2%
Inamdar 2000	2	19	1	11		1.18	[0.09; 14.69]	1.4%
Kwon 2007	0	63	0	70				0.0%
Atta 2016	0	12	0	30				0.0%
Vauhkonen 1997	0	48	0	76				0.0%
Erdogan 2009	0	40	0	28				0.0%
Eto 1986	0	73	1	81		0.37	[0.01; 9.10]	1.7%
Guan 2009	8	149	1	89		4.99	[0.61; 40.60]	1.4%
Leiva 2005	0	133	0	87				0.0%
Liu 2003	0	56	0	64				0.0%
Mehmet 2015	0	81	0	19				0.0%
Xie 2011	0	8	1	9		0.33	[0.01; 9.40]	1.6%
Mustapic 2012	0	127	1	329		0.86	[0.03; 21.22]	1.0%
Santos 2002	0	32	1	11		0.11	[0.00; 2.85]	2.6%
Kamboh 1995	0	62	6	388		0.47	[0.03; 8.46]	2.1%
Ng 2006	4	286	1	143		2.01	[0.22; 18.19]	1.6%
Eto 1995	1	193	2	416		1.08	[0.10; 11.96]	1.5%
Morbois Trabut 2006	2	145	5	299		0.82	[0.16; 4.29]	3.8%
Powell 2003	3	92	2	59		0.96	[0.16; 5.93]	2.8%
Guangda 1999	1	67	1	54		0.80	[0.05; 13.14]	1.3%
Zhang 2000	0	50	0	56				0.0%
Zhang 2003	0	55	1	135		0.81	[0.03; 20.13]	1.0%
Sun 2013	6	186	2	57		0.92	[0.18; 4.67]	3.5%
Hua 2006	2	70	0	75		5.51	[0.26; 116.82]	0.6%
Guo 2003	0	23	0	39				0.0%
Liang 2017	1	32	5	272		1.72	[0.19; 15.22]	1.2%
Shen 2002	1	85	1	75		0.88	[0.05; 14.33]	1.3%
Zheng 1998	2	83	1	46		1.11	[0.10; 12.60]	1.5%
Hua 2004	1	25	0	45		5.57	[0.22; 141.99]	0.4%
Liu 2014	10	184	2	274		7.82	[1.69; 36.10]	1.8%
Xiang 1995	2	80	0	38		2.45	[0.11; 52.34]	0.8%
Chen 2006	2	72	1	73		2.06	[0.18; 23.20]	1.2%
Xiang 1999	3	88	0	38		3.15	[0.16; 62.52]	0.8%
Shen 2002	3	7	0	31		49.00	[2.16; 1113.53]	0.1%
Xiong 2013	0	72	1	73		0.33	[0.01; 8.32]	1.8%
Zhou 2005	0	47	2	48		0.20	[0.01; 4.19]	2.9%
Xiang 2005	1	66	1	66		1.00	[0.06; 16.33]	1.2%
Long 1999	0	36	0	101				0.0%
Liang 2005	0	102	0	68				0.0%
Gu 2004	0	43	0	68				0.0%
Yang 1995	2	80	1	39		0.97	[0.09; 11.09]	1.6%
Rong 2013	0	18	0	29				0.0%
Liu 2016	14	257	2	276		7.89	[1.78; 35.08]	2.2%
Tang 2007	0	28	0	43				0.0%
Qiu 2008	0	95	1	77		0.27	[0.01; 6.65]	2.0%
Guo 2007	0	29	1	28		0.31	[0.01; 7.95]	1.8%
Xiong 2008	2	232	3	362		1.04	[0.17; 6.28]	2.8%
Ge 2013	3	89	8	111		0.45	[0.12; 1.75]	8.2%
Xiang 2010	0	28	0	70				0.0%
Luo 2016	0	28	0	38				0.0%
Zhang 2007	0	32	0	39				0.0%
Wang 2014	0	33	2	30		0.17	[0.01; 3.69]	3.1%
Zhang 2002	0	40	1	56		0.46	[0.02; 11.50]	1.5%
Xiong 2005	1	23	0	23		3.13	[0.12; 81.00]	0.6%
Dai 2000	0	23	0	64				0.0%

Fixed effect model 4797
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.65$

5902 1.46 [1.11; 1.93] 100.0%
0.001 0.1 1 10 1000



1.05 [0.86; 1.28] 100.0%

Study	Experimental Events Total	Control Events Total	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	1 47		1.26	[0.11; 14.30]	1.0%
Chaudhary 2012	1 118	0 113		2.90	[0.12; 71.88]	0.4%
Errera 2006	2 70	0 77		5.66	[0.27; 119.89]	0.4%
Alharbi 2014	13 303	11 345		1.36	[0.60; 3.08]	8.2%
Inamdar 2000	3 20	2 12		0.88	[0.13; 6.22]	1.8%
Kwon 2007	3 66	0 70		7.77	[0.39; 153.39]	0.4%
Atta 2016	12 24	3 33		10.00	[2.39; 41.84]	1.1%
Vauhkonen 1997	3 51	2 78		2.38	[0.38; 14.74]	1.2%
Erdogan 2009	0 40	0 28				0.0%
Eto 1986	0 73	1 81		0.37	[0.01; 9.10]	1.2%
Guan 2009	7 148	1 89		4.37	[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	0 19				0.0%
Xie 2011	4 12	2 10		2.00	[0.28; 14.20]	1.2%
Mustapic 2012	2 129	2 330		2.58	[0.36; 18.53]	0.9%
Santos 2002	0 32	1 11		0.11	[0.00; 2.85]	1.8%
Kamboh 1995	5 67	19 401		1.62	[0.58; 4.50]	4.2%
Ng 2006	5 287	6 148		0.42	[0.13; 1.40]	6.5%
Eto 1995	1 193	4 418		0.54	[0.06; 4.86]	2.1%
Morbois Trabut 2006	1 144	14 308		0.15	[0.02; 1.13]	7.4%
Powell 2003	3 92	1 58		1.92	[0.20; 18.93]	1.0%
Guangda 1999	1 67	2 55		0.40	[0.04; 4.55]	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	1 56		0.10	[0.00; 2.55]	1.9%
Hua 2006	4 72	2 77		2.21	[0.39; 12.43]	1.5%
Guo 2003	2 25	1 40		3.39	[0.29; 39.50]	0.6%
Liang 2017	1 32	6 273		1.44	[0.17; 12.32]	1.0%
Shen 2002	2 86	4 78		0.44	[0.08; 2.47]	3.4%
Zheng 1998	1 82	0 45		1.67	[0.07; 41.96]	0.5%
Hua 2004	2 26	1 46		3.75	[0.32; 43.50]	0.6%
Liu 2014	0 174	0 272				0.0%
Xiang 1995	0 78	1 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	1 39		0.45	[0.03; 7.34]	1.1%
Shen 2002	2 6	4 35		3.88	[0.53; 28.39]	0.6%
Xiong 2013	1 73	2 74		0.50	[0.04; 5.64]	1.6%
Zhou 2005	1 48	0 46		2.94	[0.12; 73.95]	0.4%
Xiang 2005	1 66	1 66		1.00	[0.06; 16.33]	0.8%
Long 1999	3 39	4 105		2.10	[0.45; 9.86]	1.7%
Liang 2005	6 108	2 70		2.00	[0.39; 10.20]	1.9%
Gu 2004	3 46	2 70		2.37	[0.38; 14.78]	1.2%
Yang 1995	0 78	1 39		0.16	[0.01; 4.11]	1.6%
Rong 2013	0 18	0 29				0.0%
Liu 2016	0 243	0 274				0.0%
Tang 2007	2 30	1 44		3.07	[0.27; 35.49]	0.6%
Qiu 2008	3 98	2 78		1.20	[0.20; 7.37]	1.8%
Guo 2007	3 32	1 28		2.79	[0.27; 28.51]	0.8%
Xiong 2008	6 236	9 368		1.04	[0.37; 2.96]	5.7%
Ge 2013	2 88	8 111		0.30	[0.06; 1.45]	5.7%
Xiang 2010	1 29	0 70		7.42	[0.29; 187.61]	0.2%
Luo 2016	1 29	3 41		0.45	[0.04; 4.58]	2.0%
Zhang 2007	0 32	2 41		0.24	[0.01; 5.24]	1.8%
Wang 2014	2 35	4 32		0.42	[0.07; 2.49]	3.3%
Zhang 2002	1 41	2 57		0.69	[0.06; 7.85]	1.4%
Xiong 2005	1 23	1 24		1.05	[0.06; 17.76]	0.8%
Dai 2000	0 23	1 65		0.91	[0.04; 23.25]	0.7%

Fixed effect model 4805
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.56$

5961

1.15 [0.90; 1.46] 100.0%

0.01 0.1 1 10 100

Study	Experimental Events	Experimental Total	Control Events	Control Total	Odds Ratio	OR	95%-CI	Weight
Singh 2006	5	83	13	87		0.36	[0.12; 1.07]	1.5%
Al-Majed 2011	6	79	9	55		0.42	[0.14; 1.26]	1.2%
Chaudhary 2012	30	147	21	134		1.38	[0.75; 2.55]	2.2%
Errera 2006	12	80	23	100		0.59	[0.27; 1.28]	2.2%
Alharbi 2014	35	325	60	394		0.67	[0.43; 1.05]	6.1%
Inamdar 2000	16	33	8	18		1.18	[0.37; 3.73]	0.7%
Kwon 2007	14	77	12	82		1.30	[0.56; 3.01]	1.2%
Atta 2016	9	21	9	39		2.50	[0.80; 7.82]	0.5%
Vauhkonen 1997	20	68	33	109		0.96	[0.49; 1.86]	2.3%
Erdogan 2009	12	52	7	35		1.20	[0.42; 3.43]	0.8%
Eto 1986	21	94	16	96		1.44	[0.70; 2.97]	1.6%
Guan 2009	24	165	9	97		1.66	[0.74; 3.75]	1.2%
Leiva 2005	43	176	39	126		0.72	[0.43; 1.20]	4.3%
Liu 2003	12	68	11	75		1.25	[0.51; 3.05]	1.1%
Mehmet 2015	13	94	9	28		0.34	[0.13; 0.91]	1.5%
Xie 2011	19	27	5	13		3.80	[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		0.12	[0.03; 0.53]	1.2%
Kamboh 1995	26	88	150	532		1.07	[0.65; 1.75]	3.8%
Ng 2006	39	321	19	161		1.03	[0.58; 1.85]	2.8%
Eto 1995	55	247	111	525		1.07	[0.74; 1.54]	7.0%
Morbois Trabut 2006	33	176	87	381		0.78	[0.50; 1.22]	5.6%
Powell 2003	27	116	21	78		0.82	[0.43; 1.59]	2.4%
Guangda 1999	7	73	7	60		0.80	[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		0.94	[0.45; 1.97]	1.9%
Sun 2013	21	201	6	61		1.07	[0.41; 2.78]	1.0%
Hua 2006	20	88	13	88		1.70	[0.78; 3.67]	1.3%
Guo 2003	9	32	6	45		2.54	[0.80; 8.07]	0.5%
Liang 2017	7	38	38	305		1.59	[0.65; 3.86]	0.9%
Shen 2002	11	95	18	92		0.54	[0.24; 1.21]	2.0%
Zheng 1998	11	92	6	51		1.02	[0.35; 2.94]	0.9%
Hua 2004	4	28	8	53		0.94	[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		2.11	[0.80; 5.56]	0.8%
Chen 2006	8	78	10	82		0.82	[0.31; 2.21]	1.1%
Xiang 1999	24	109	6	44		1.79	[0.68; 4.73]	0.8%
Shen 2002	14	18	9	40		12.06	[3.17; 45.87]	0.2%
Xiong 2013	31	103	22	94		1.41	[0.75; 2.66]	2.0%
Zhou 2005	6	53	11	57		0.53	[0.18; 1.56]	1.2%
Xiang 2005	20	85	15	80		1.33	[0.63; 2.83]	1.5%
Long 1999	12	48	12	113		2.81	[1.16; 6.80]	0.7%
Liang 2005	18	120	8	76		1.50	[0.62; 3.64]	1.1%
Gu 2004	7	50	8	76		1.38	[0.47; 4.09]	0.7%
Yang 1995	26	104	5	43		2.53	[0.90; 7.11]	0.7%
Rong 2013	2	20	1	30		3.22	[0.27; 38.15]	0.1%
Liu 2016	43	286	23	297		2.11	[1.23; 3.60]	2.4%
Tang 2007	10	38	13	56		1.18	[0.46; 3.06]	1.0%
Qiu 2008	14	109	11	87		1.02	[0.44; 2.37]	1.3%
Guo 2007	7	36	7	34		0.93	[0.29; 3.00]	0.7%
Xiong 2008	47	277	87	446		0.84	[0.57; 1.25]	7.0%
Ge 2013	73	159	47	150		1.86	[1.17; 2.96]	3.3%
Xiang 2010	7	35	19	89		0.92	[0.35; 2.43]	1.1%
Luo 2016	2	30	7	45		0.39	[0.07; 2.01]	0.7%
Zhang 2007	3	35	7	46		0.52	[0.12; 2.18]	0.7%
Wang 2014	13	46	8	36		1.38	[0.50; 3.80]	0.8%
Zhang 2002	11	51	11	66		1.38	[0.54; 3.48]	1.0%
Xiong 2005	2	24	2	25		1.05	[0.14; 8.08]	0.2%
Dai 2000	3	26	9	73		0.93	[0.23; 3.73]	0.5%

Fixed effect model **5748** **7093**

Heterogeneity: $I^2 = 39\%$, $\tau^2 = 0.0970$, $p < 0.01$

0.1 0.5 1 2 10

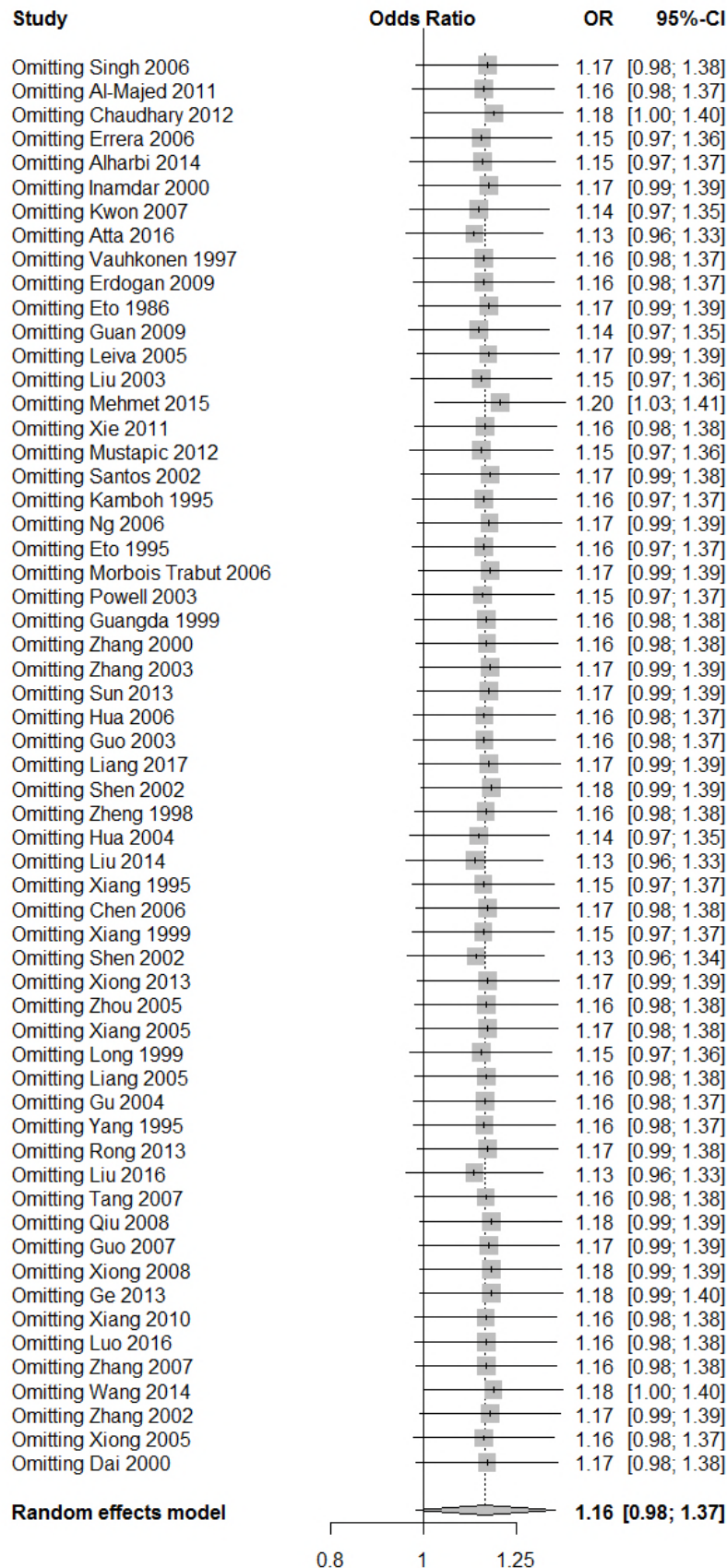
1.11 [1.01; 1.22] 100.0%

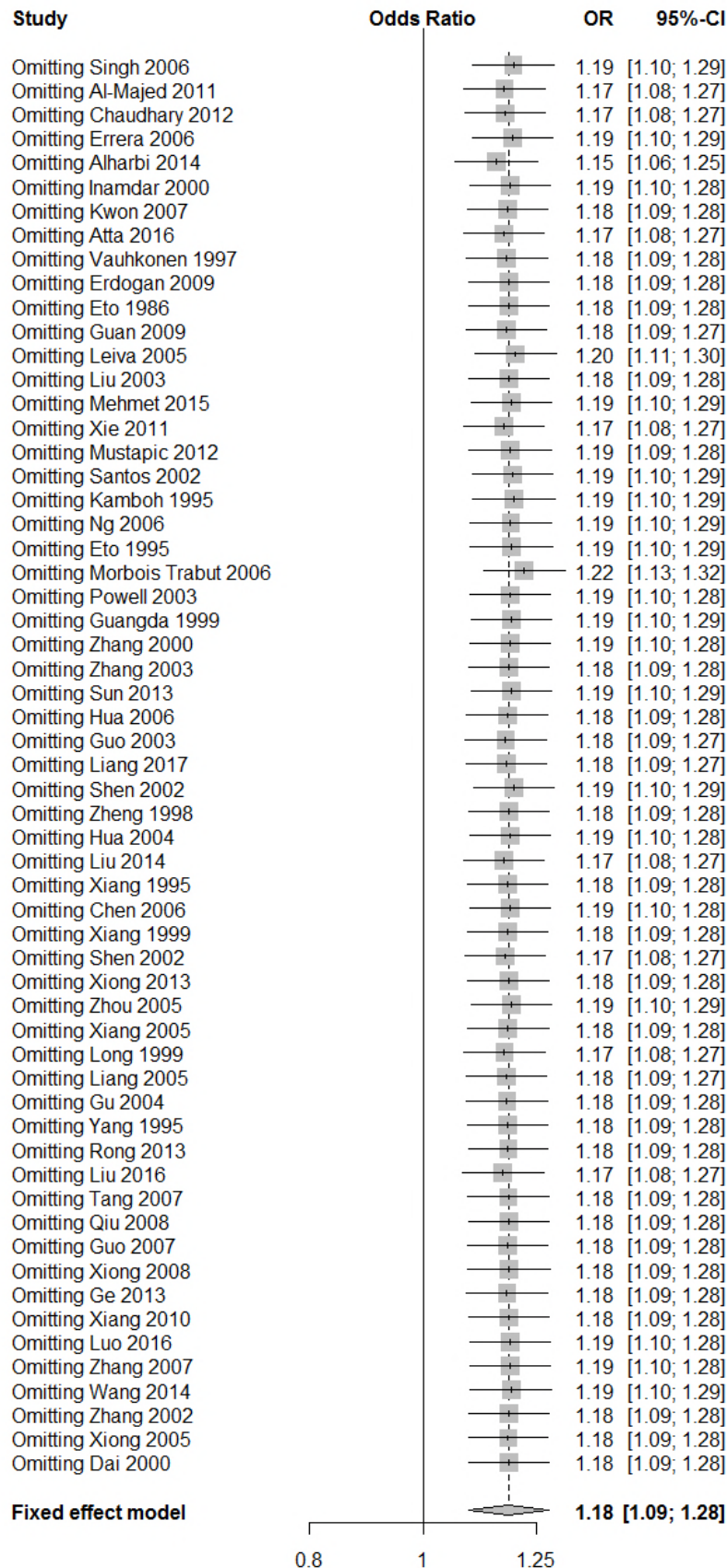
Study	Experimental Events Total	Control Events Total	Odds Ratio	OR	95%-CI	Weight
Singh 2006	0 78	2 76		0.19	[0.01; 4.02]	2.6%
Al-Majed 2011	15 88	1 47		9.45	[1.21; 73.98]	1.1%
Chaudhary 2012	4 121	1 114		3.86	[0.43; 35.09]	1.0%
Errera 2006	0 68	0 77				0.0%
Alharbi 2014	39 329	10 344		4.49	[2.20; 9.16]	9.1%
Inamdar 2000	14 31	10 20		0.82	[0.27; 2.54]	7.0%
Kwon 2007	1 64	1 71		1.11	[0.07; 18.14]	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				0.0%
Eto 1986	2 75	3 83		0.73	[0.12; 4.50]	2.9%
Guan 2009	1 142	1 89		0.62	[0.04; 10.11]	1.3%
Leiva 2005	1 134	0 87		1.97	[0.08; 48.82]	0.6%
Liu 2003	0 56	0 64				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	1 329		5.17	[0.46; 57.46]	0.6%
Santos 2002	1 33	0 10		0.97	[0.04; 25.64]	0.8%
Kamboh 1995	0 62	14 396		0.21	[0.01; 3.58]	4.1%
Ng 2006	3 285	0 142		3.53	[0.18; 68.83]	0.7%
Eto 1995	7 199	10 424		1.51	[0.57; 4.03]	6.5%
Morbois Trabut 2006	0 143	10 304		0.10	[0.01; 1.68]	7.1%
Powell 2003	3 92	0 57		4.50	[0.23; 88.69]	0.6%
Guangda 1999	1 67	2 55		0.40	[0.04; 4.55]	2.3%
Zhang 2000	0 50	0 56				0.0%
Zhang 2003	1 56	1 135		2.44	[0.15; 39.65]	0.6%
Sun 2013	0 180	1 56		0.10	[0.00; 2.55]	2.4%
Hua 2006	2 70	3 78		0.74	[0.12; 4.53]	2.9%
Guo 2003	2 25	1 40		3.39	[0.29; 39.50]	0.7%
Liang 2017	1 32	1 268		8.61	[0.53; 141.16]	0.2%
Shen 2002	1 85	1 75		0.88	[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	[0.02; 8.05]	1.8%
Liu 2014	0 174	1 273		0.52	[0.02; 12.85]	1.2%
Xiang 1995	3 81	1 39		1.46	[0.15; 14.52]	1.4%
Chen 2006	1 71	1 73		1.03	[0.06; 16.77]	1.0%
Xiang 1999	3 88	1 39		1.34	[0.14; 13.31]	1.4%
Shen 2002	0 4	0 31				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		1.33	[0.29; 6.19]	3.0%
Long 1999	1 37	0 101		8.34	[0.33; 209.40]	0.3%
Liang 2005	2 104	0 68		3.34	[0.16; 70.68]	0.6%
Gu 2004	1 44	0 68		4.72	[0.19; 118.60]	0.4%
Yang 1995	3 81	2 40		0.73	[0.12; 4.56]	2.7%
Rong 2013	0 18	0 29				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	[0.20; 7.37]	2.3%
Guo 2007	1 30	0 27		2.80	[0.11; 71.59]	0.5%
Xiong 2008	13 243	6 365		3.38	[1.27; 9.02]	4.8%
Ge 2013	1 87	4 107		0.30	[0.03; 2.73]	3.7%
Xiang 2010	0 28	0 70				0.0%
Luo 2016	1 29	0 38		4.05	[0.16; 103.17]	0.4%
Zhang 2007	1 33	0 39		3.65	[0.14; 92.55]	0.5%
Wang 2014	5 38	6 34		0.71	[0.19; 2.57]	5.8%
Zhang 2002	1 41	1 56		1.38	[0.08; 22.65]	0.9%
Xiong 2005	1 23	0 23		3.13	[0.12; 81.00]	0.5%
Dai 2000	1 24	2 66		1.39	[0.12; 16.08]	1.1%

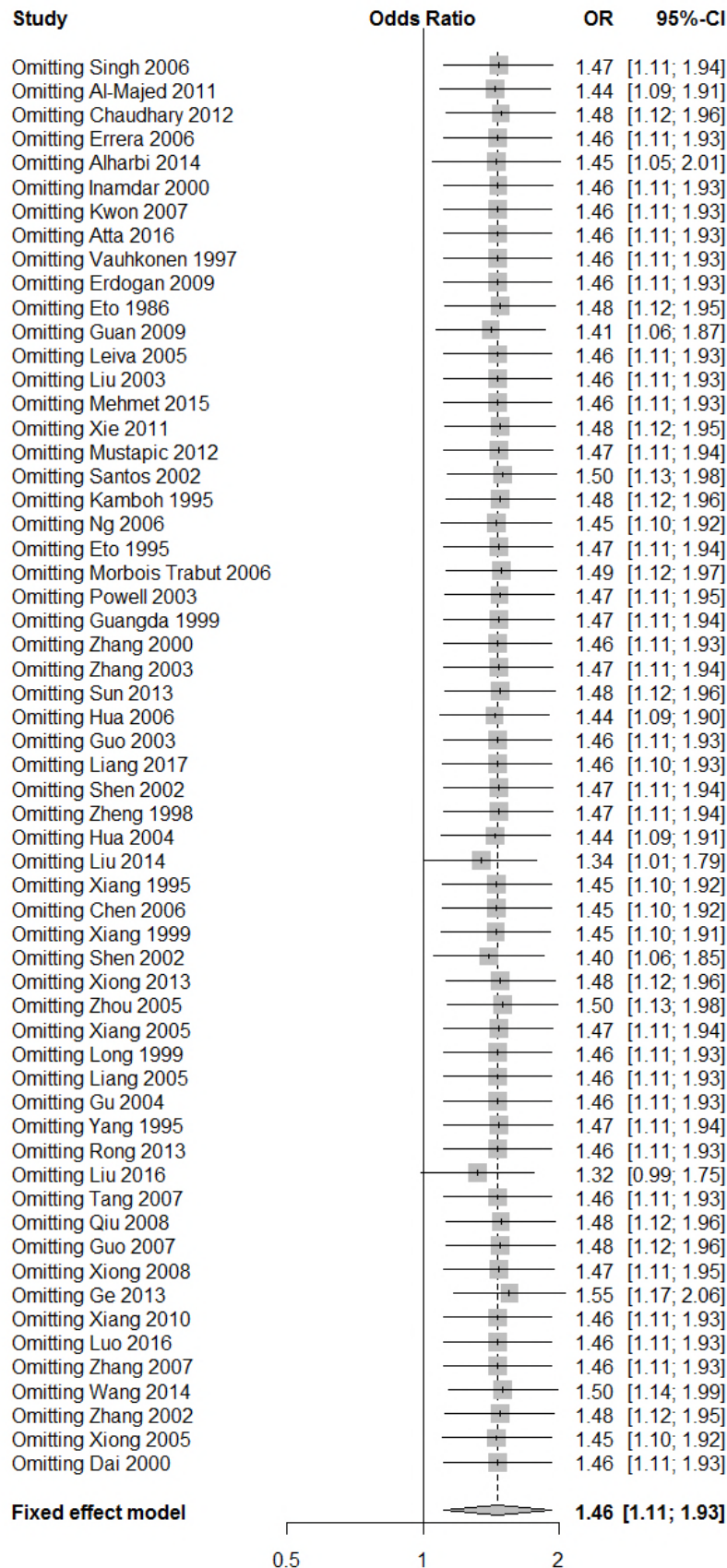
Fixed effect model 4850
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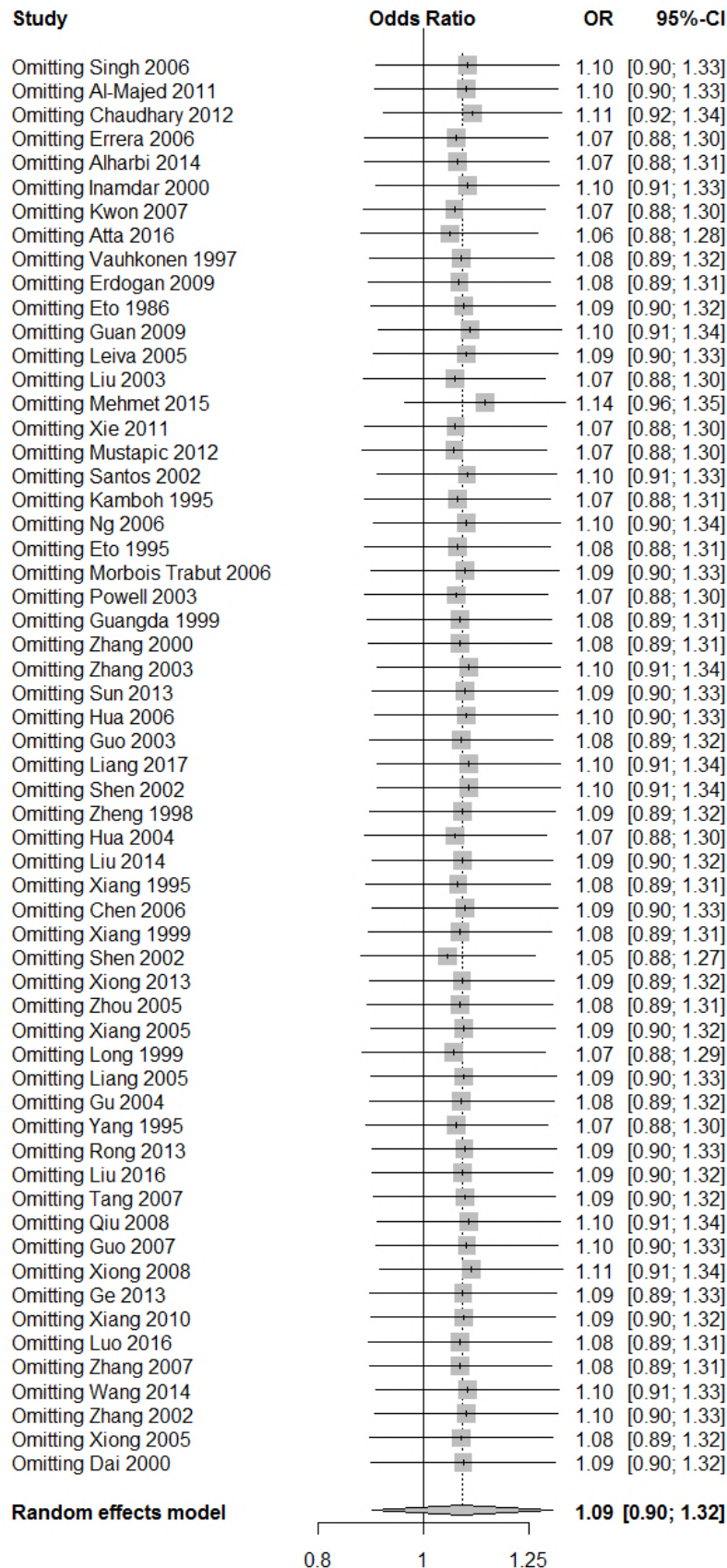
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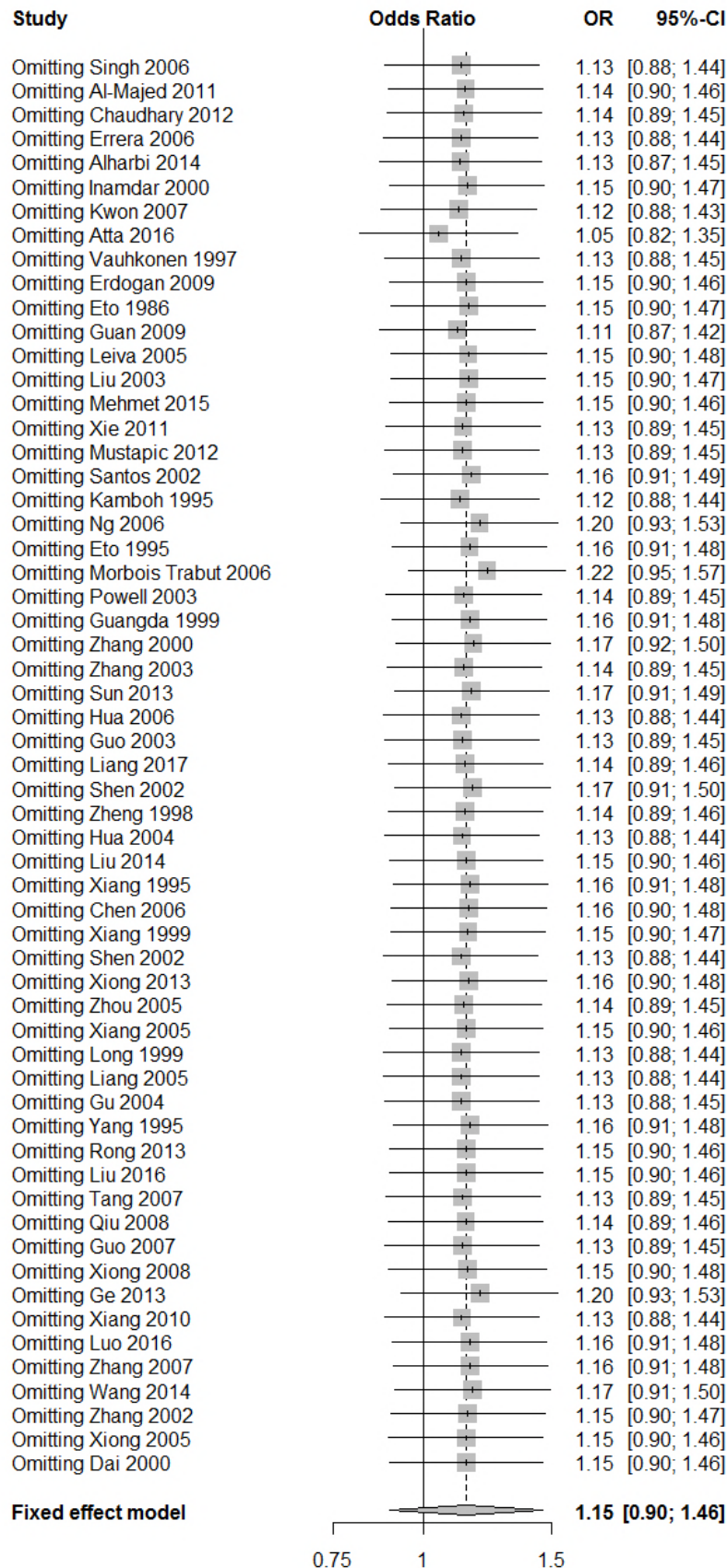
1.71 [1.33; 2.19] 100.0%
0.01 0.1 1 10 100

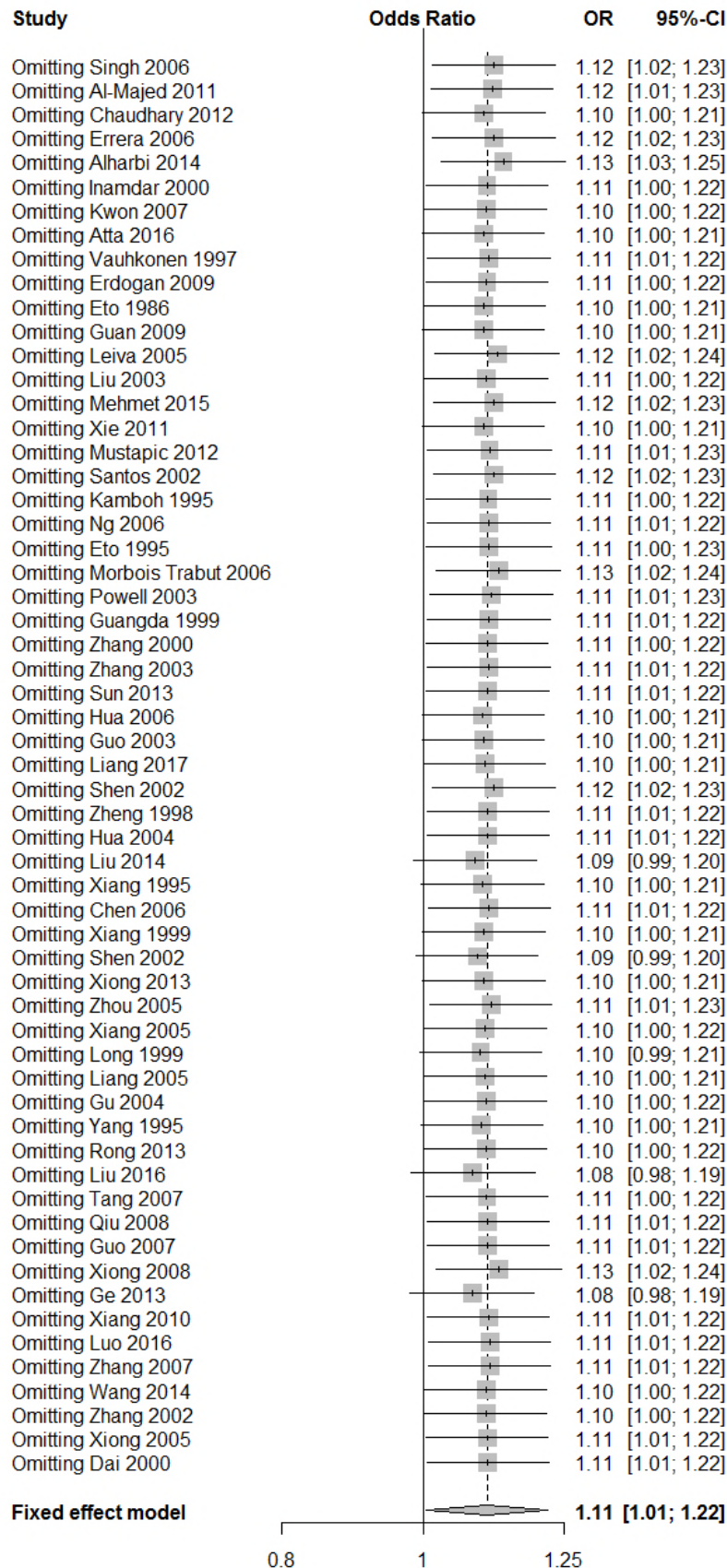


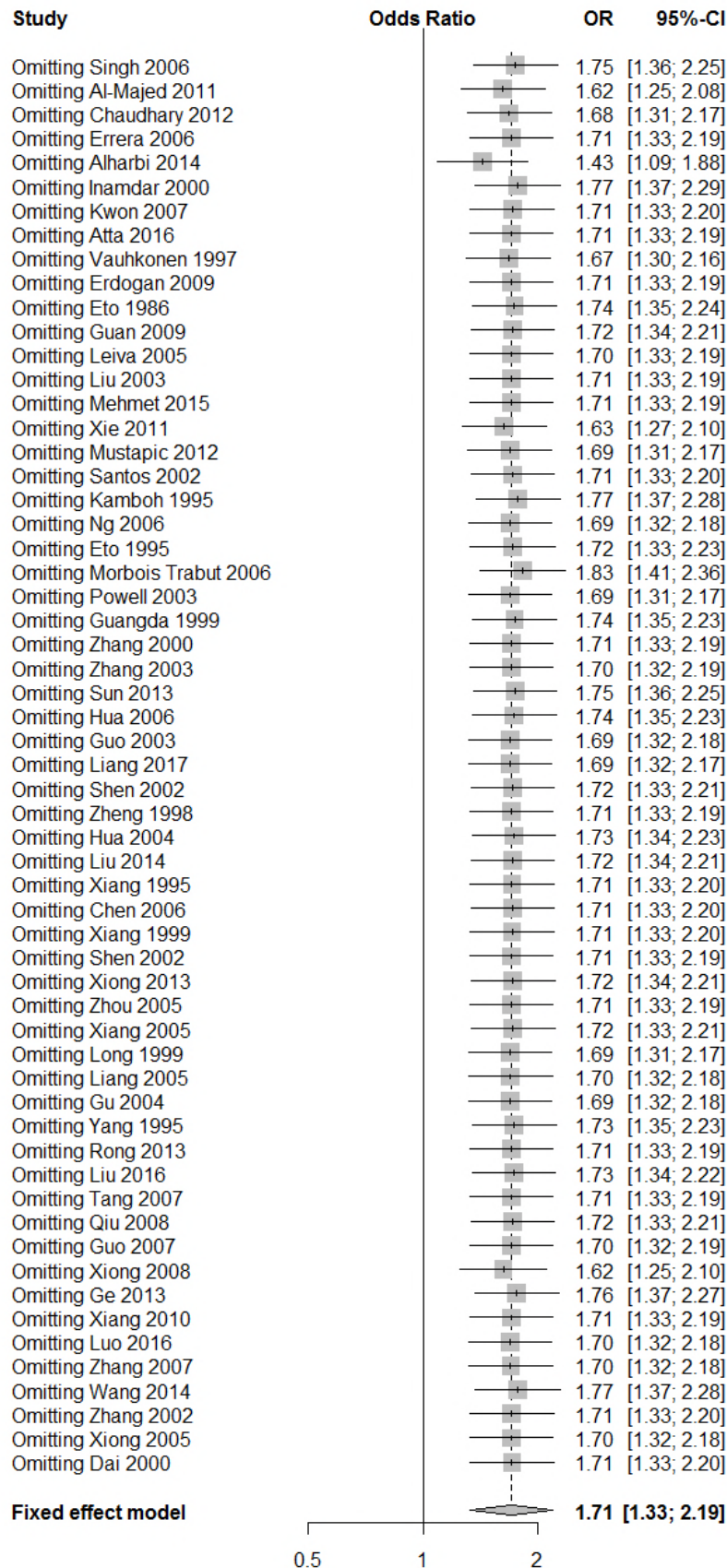


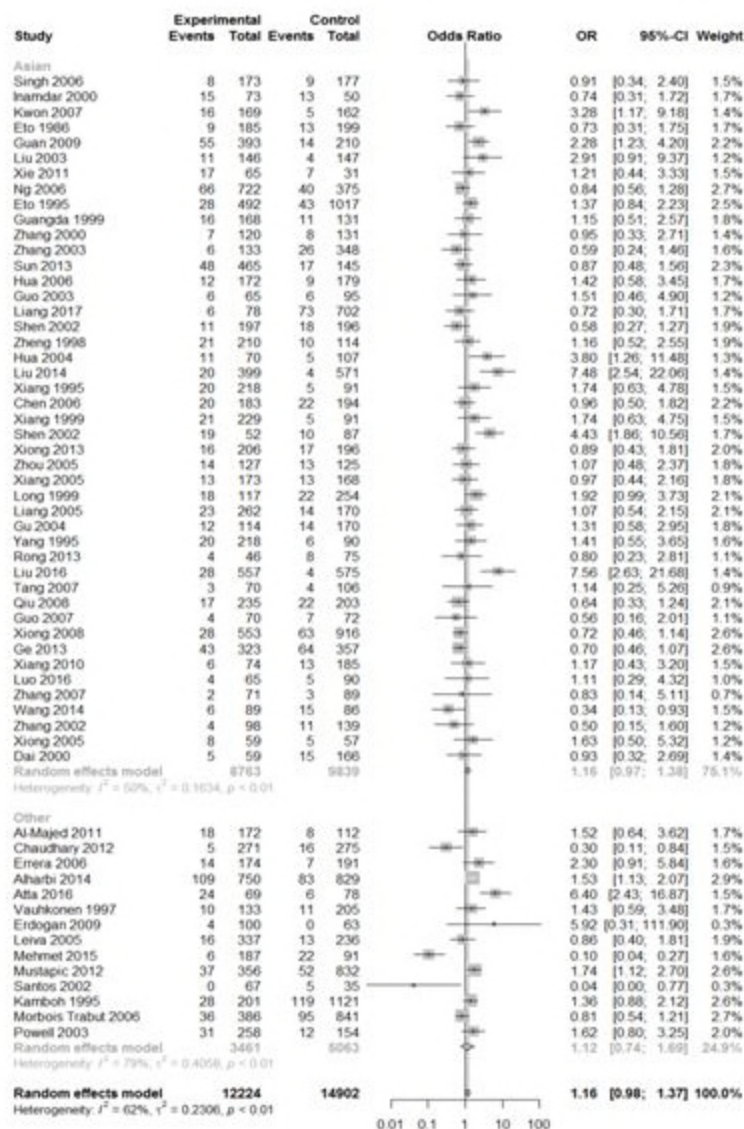




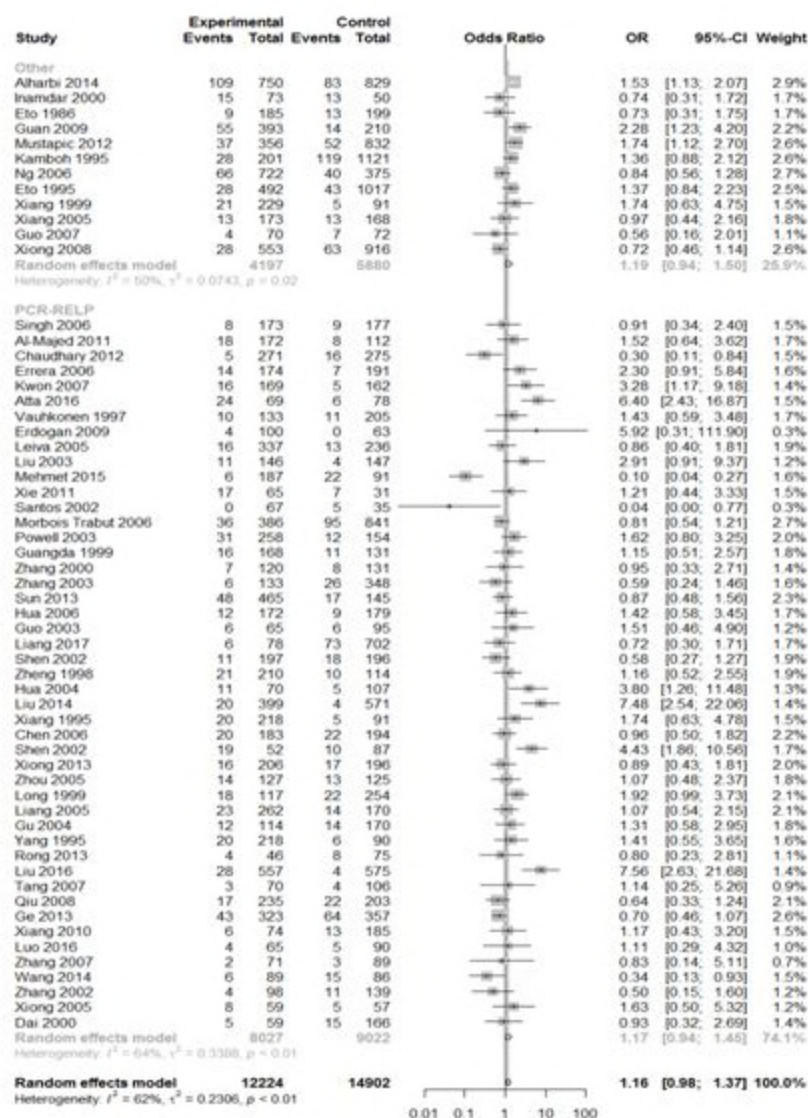


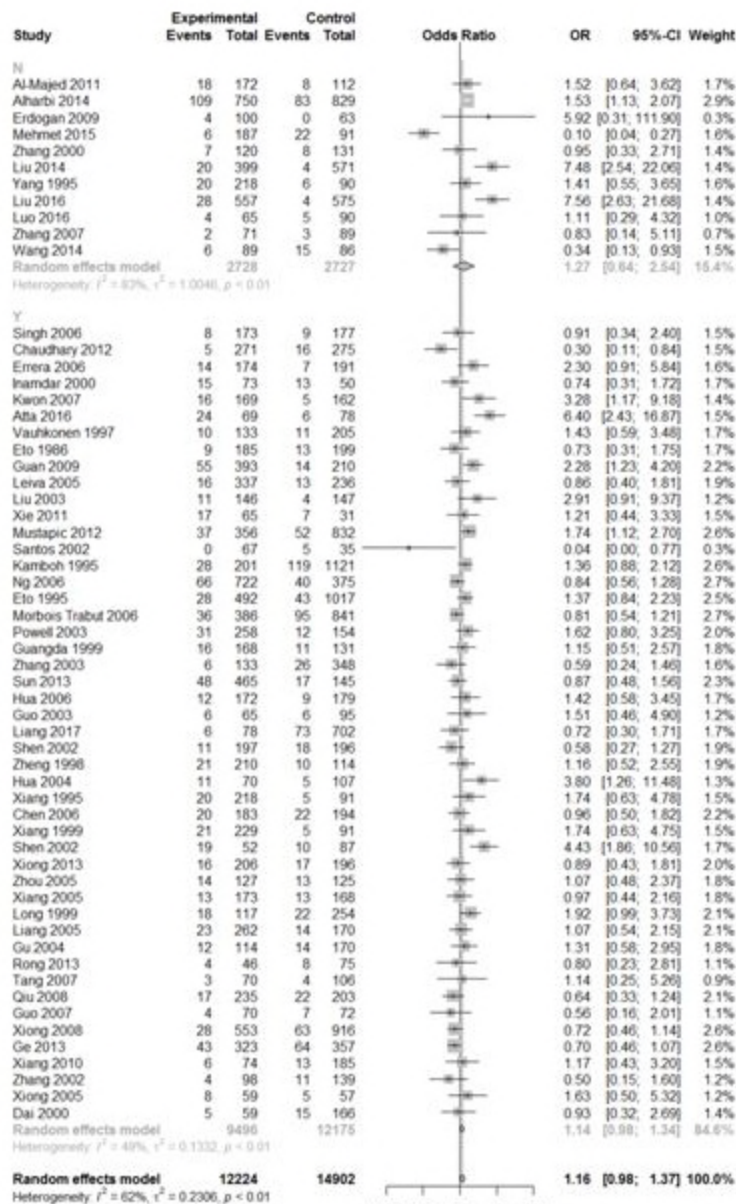




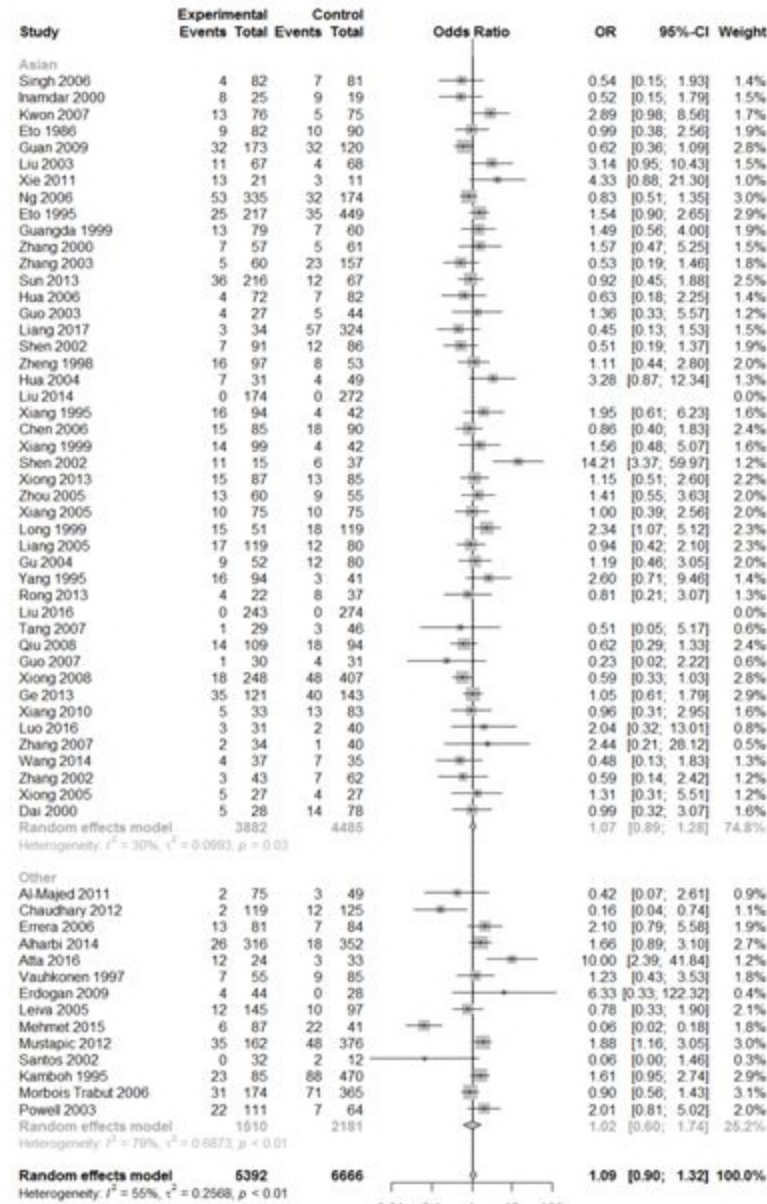


A

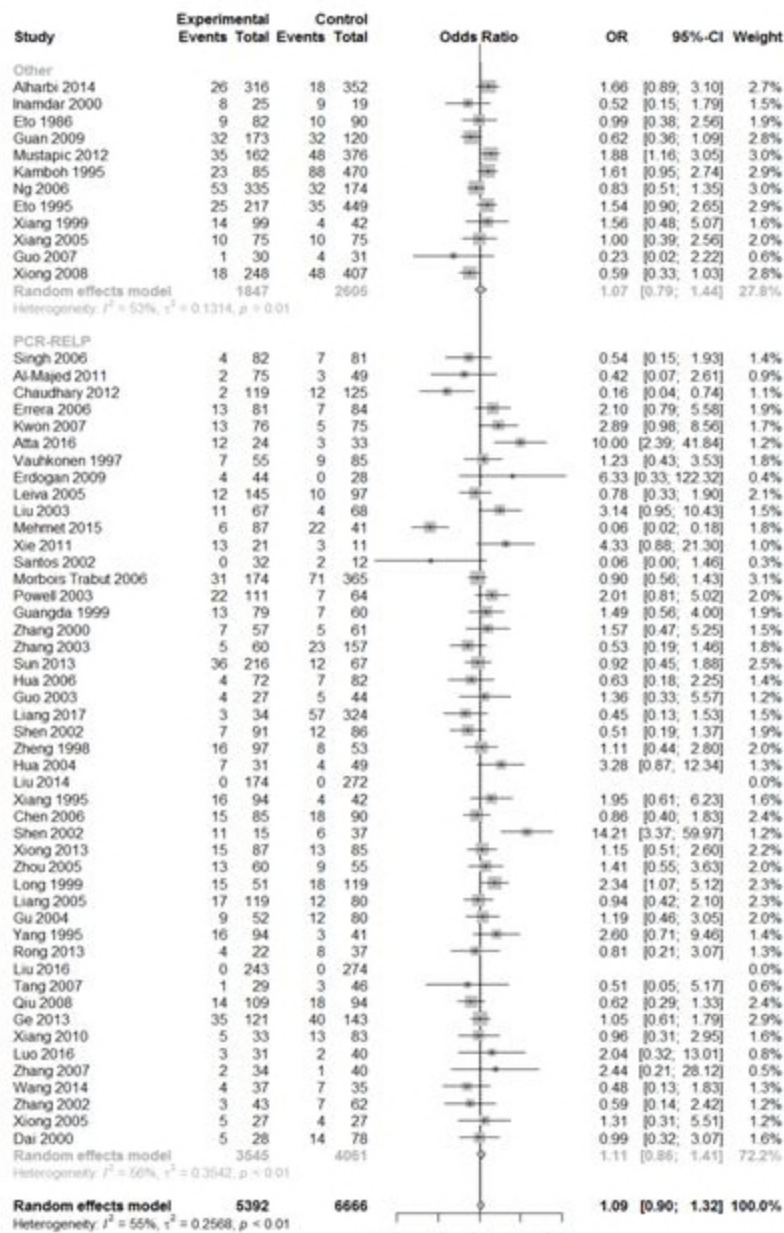




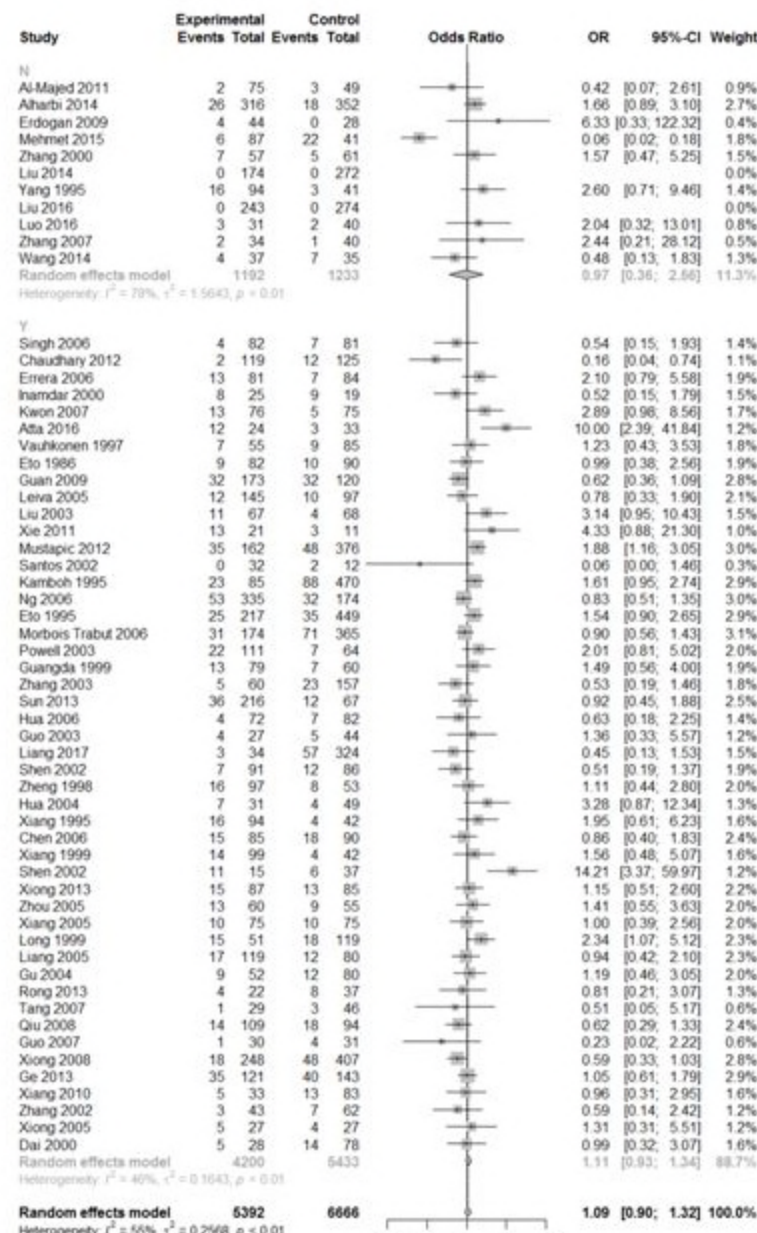
A



B

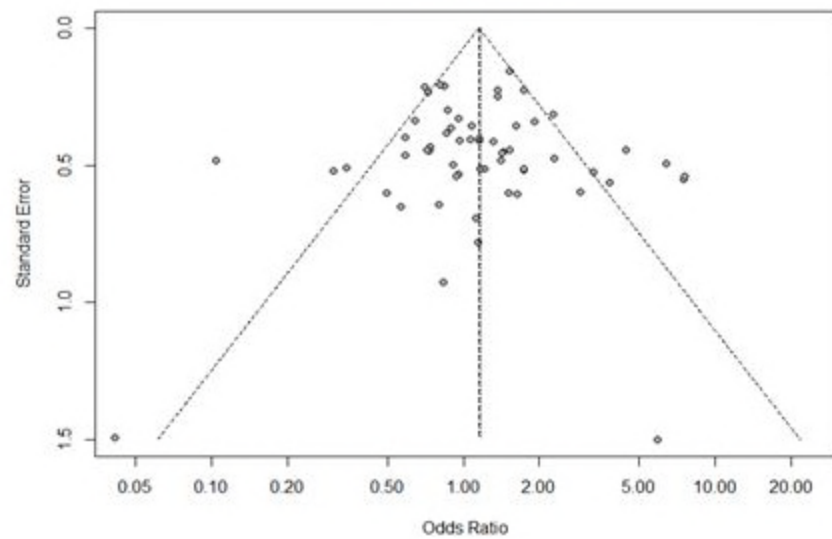


A



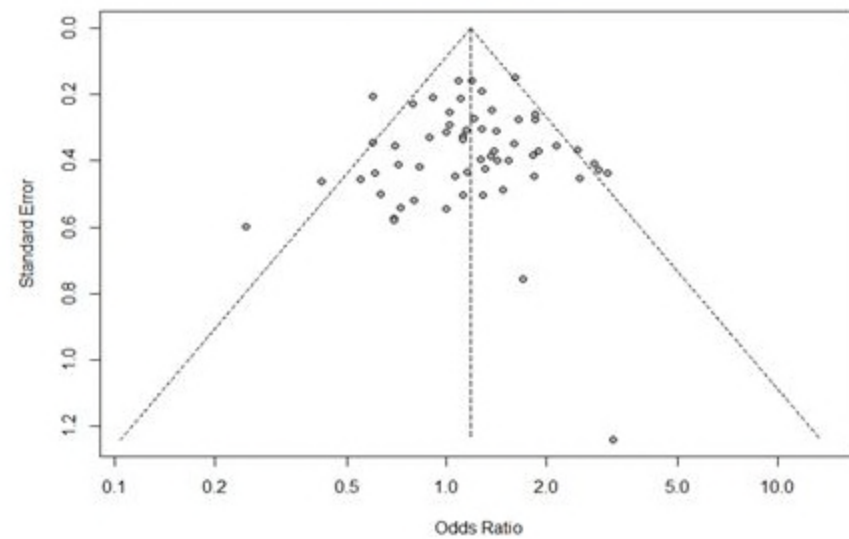
B

Funnel plot



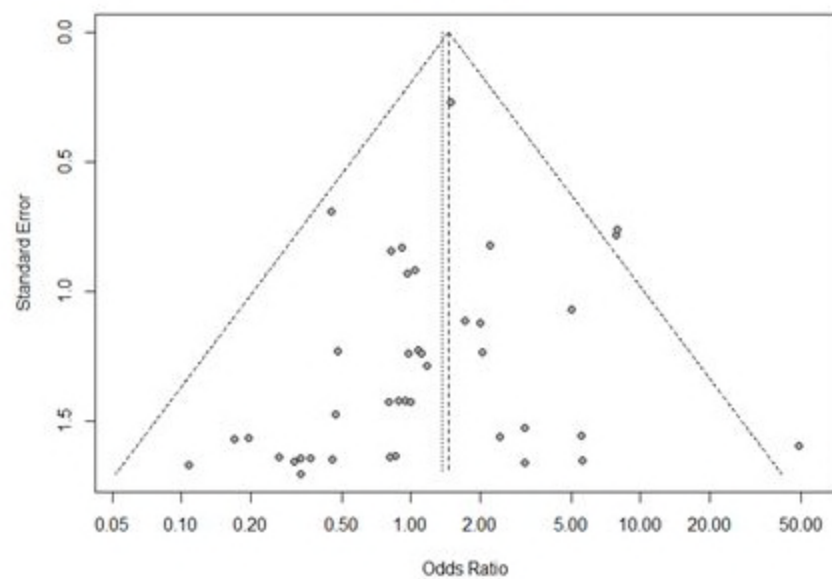
A

Funnel plot



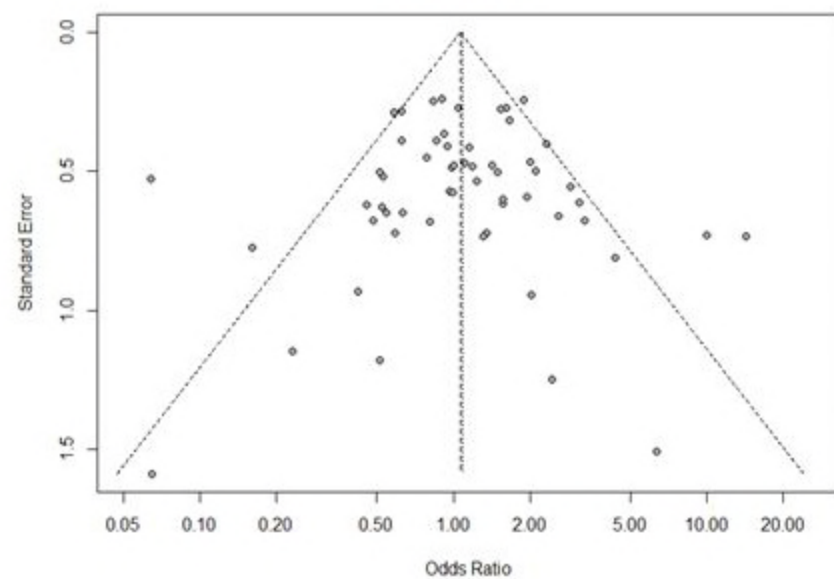
B

Funnel plot



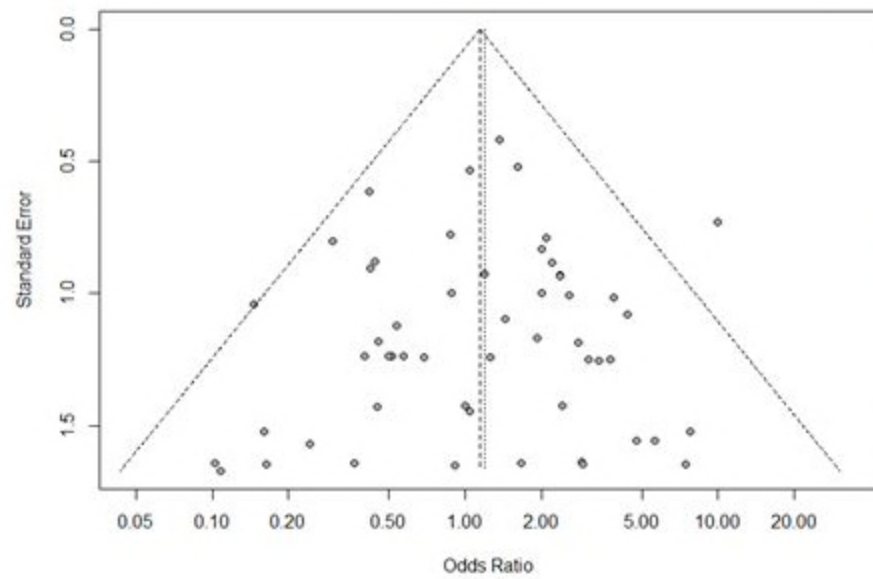
C

Funnel plot



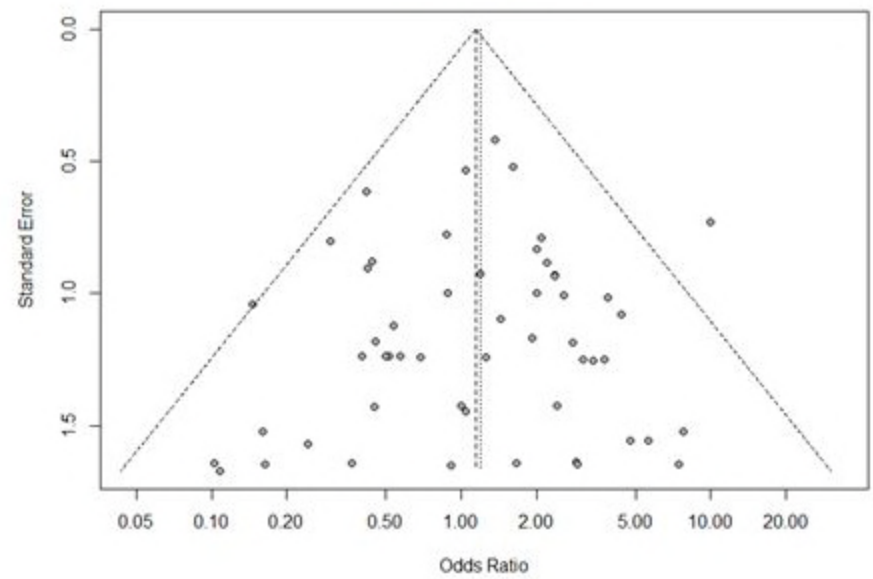
D

Funnel plot



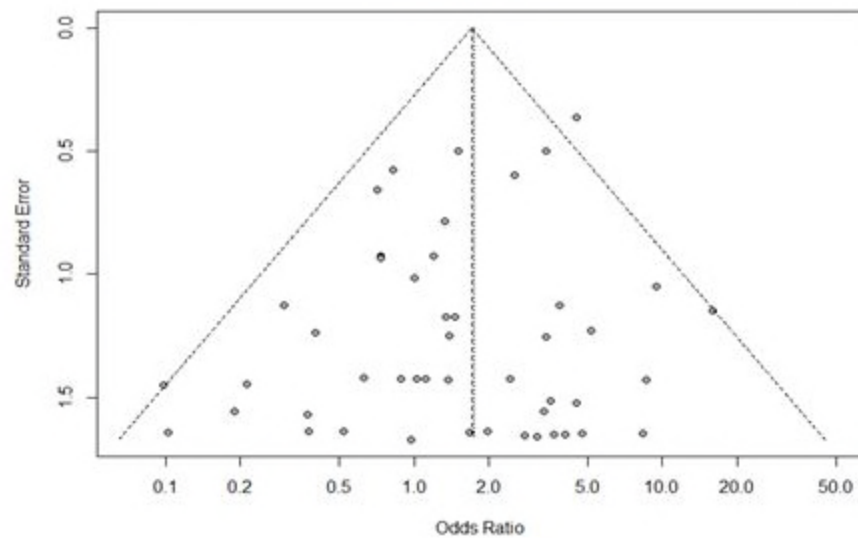
A

Funnel plot



B

Funnel plot



C

Figure legends:

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.

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.

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* $\epsilon 2/\epsilon 3$ 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.

Figure legends:

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

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.

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

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.

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.

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.

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.

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.

Figure 9 Sensitivity analysis for the result of association between type 2 diabetes and *ApoE* $\epsilon 2$ allele vs. $\epsilon 3$ allele.

Figure 10 Sensitivity analysis for the result of association between type 2 diabetes and *ApoE* $\epsilon 4$ allele vs. $\epsilon 3$ allele.

Figure 11 Sensitivity analysis for the result of association between type 2 diabetes and *ApoE* $\epsilon 2/\epsilon 2$ genotype vs. $\epsilon 3/\epsilon 3$ genotype.

Figure 12 Sensitivity analysis for the result of association between type 2 diabetes and *ApoE* $\epsilon 2/\epsilon 3$ genotype vs. $\epsilon 3/\epsilon 3$ genotype.

Figure 13 Sensitivity analysis for the result of association between type 2 diabetes and *ApoE* $\epsilon 2/\epsilon 4$ genotype vs. $\epsilon 3/\epsilon 3$ genotype.

Figure 14 Sensitivity analysis for the result of association between type 2 diabetes and *ApoE* $\epsilon 3/\epsilon 4$ genotype vs. $\epsilon 3/\epsilon 3$ genotype.

Figure 15 Sensitivity analysis for the result of association between type 2 diabetes and *ApoE* $\epsilon 4/\epsilon 4$ genotype vs. $\epsilon 3/\epsilon 3$ genotype.