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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 ε4 versus ε3 allele yielding a pooled OR of 1.18 (95% *CI:* 1.09-1.28; $P<0.001$). For *ApoE* genotypes, compared with ε3/ε3 genotype, *ε*2/*ε*2 genotype showed a possible association with T2DM (OR=1.46; 95% *CI*：1.11-1.93；$P=0.007$), *ε*3/*ε*4 genotype had a 1.11-fold risk of developing T2DM (OR=1.11; 95% *CI*： 1.01-1.22； $P=0.039$), and *ε*4/*ε*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 ε4 and genotypes (ε2/ε2, ε3/ε4, and ε4/ε4) 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

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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: ε2 (T to C substitution at position 158), the most common ε3, and ε4 (C to T substitution at position 112); 3 isoforms: ApoE2 (Cys112, 158Cys), ApoE3 (Cys112, 158Arg), and ApoE4 (Arg112, 158Arg); and 6

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genotypes having 3 homozygous: ε2/ε2, ε3/ε3, and ε4/ε4, and 3 heterozygous: ε2/ε3, ε2/ε4, and ε3/ε4 (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.

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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

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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 ($I^2 \geq 50\%$ 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* $\varepsilon 2$ with $\varepsilon 3$ allele (I^2=62%), and the pooled *OR* was 1.16 (95% *CI*: 0.98-1.37; *P*=0.079) when *ApoE* $\varepsilon 2$ was compared with $\varepsilon 3$ using the random-effects model (Figure 2); however, there was

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not heterogeneity in the comparison of *ApoE* ε4 with ε3 allele (I^2=36%), and the pooled *OR* was 1.18 (95% *CI*: 1.09-1.28; *P*<0.001) when *ApoE*ε4 was compared with ε3 using the fixed-effects model (Figure 3), suggesting that *ApoE* ε4 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 (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε*4*,and ε4/ε4) were compared with ε3/ε3 genotype. No significant heterogeneity was found whenthe ε2/ε2 genotype was compared with ε3/ε3 genotype (I^2=0%), and the yielded *OR* of ε2/ε2 genotype versus ε3/ε3 genotype using a fixed-effects model was 1.46 (95% *CI*：1.11-1.93；*P*=0.007) (Figure 4), suggesting that the ε2/ε2 genotype may have a harmful effect on type 2 diabetes. However, when ε2/ε3 genotype was compared with ε3/ε3 genotype, there was significant heterogeneity (I^2=55%), and the yielded *OR* of ε2/ε3 genotype versus ε3/ε3 genotype using a random-effects model was 1.09 (95% *CI*：0.90-1.32；*P*=0.397) (Figure 5). Compared with ε3/ε3 genotype, there were no significant heterogeneity between ε2/ε4, ε3/ε4, and ε4/ε4 genotype, respectively (I^2=0%, I^2=39%, and I^2=0%). The yielded *OR* of ε2/ε4 genotype versus ε3/ε3 genotype using a fixed-effects model was 1.15 (95% *CI*：0.90-1.46；*P*=0.276) (Figure 6). The yielded *OR* of ε3/ε4 genotype versus ε3/ε3 genotype using a fixed-effects model was 1.11 (95% *CI*：1.01-1.22；*P*=0.039) (Figure 7). For the comparition of ε4/ε4 genotype with ε3/ε3 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* ε2 with ε3 allele (I^2=62%) and the comparison of ε2/ε3 genotype with ε3/ε3 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).

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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% *CIs* in the comparison of *ApoE* ε4 with ε3 allele or in the comparison of *ApoE* ε2/ε3, ε2/ε4, and ε4/ε4 with genotype ε3/ε3 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% *CIs* in the comparison of *ApoE* ε2 with ε3 allele or in the comparison of *ApoE* ε2/ε2 and ε3/ε4 with genotype ε3/ε3 genotype (Figure 9, Figure 11, and Figure 14).

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Table 1 Main characteristics of the included studies

Study	Year	Region	Ethnicity	Genotyping method	Sample size (case/control)	Quality score	HWE Y/N(P)	ε2/ε2(n)+ε2/ε3(n)		ε2/ε4(n)+ε3/ε3(n)		ε3/ε4(n)+ε4/ε4(n)	
								case	control	case	control	case	control
Singh(Singh *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 1995)	1995	USA	Caucasian	IEF-immunoblottin and PCR	116/659	6	Y(0.992)	0+23	6+88	5+62	19+382	26+0	150+14
Ng(Ng *et al.* 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 *et al.* 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

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Morbois Trabut(Morbois-Trabut *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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

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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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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

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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 ε4 and genotypes (ε2/ε2, ε3/ε4, and ε4/ε4) are associated with the increased risk for the development of T2DM, however, allele ε2 and genotypes (ε2/ε3 and ε2/ε4) 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 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.

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* ε4 allele and the genotypes (ε3/ε4 and ε4/ε4) were associated with increased risk of T2DM. Subjects carrying the ε4 alleles had higher plasma total cholesterol levels compared to subjects carrying the ε3/ε3 genotype, and HDL cholesterol was significantly lower in the ε3/ε4 than in the ε3/ε3 individuals(Dallongeville *et al.* 1992); individuals carrying the ε2/ε2 genotype had about 31% lower mean LDL than those with the ε4/ε4 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* ε4 allele and the genotypes (ε3/ε4 and ε4/ε4) were associated with an increased risk of T2DM through affecting the lipid metabolism.

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We found the genotype ε2/ε2 was associated with increased risk of T2DM, but not allele ε2 or genotype ε2/ε3; which are not in agreement with the results of previous meta-analyses (YIN *et al.* 2014). The results from Yan et al' showed that ε2 and genotype ε2/ε3 were associated with increased risk of T2DM, genotype ε2/ε2 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 ε2-carriers genotypes (ε2/ε2， ε2/ε3, and ε2/ε4) compared to ε3/ε3 were greater than 1.00. The slight difference between the present study and Anthopoulos et al' is that the OR of ε2/ε2 in our study reaches statistical significance while the OR of ε2/ε3 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 ε2 (ε2/ε3 and ε2/ε4) are not at the risk of T2DM while those carrying two ε2 allele (ε2/ε2) possess higher risk for T2DM, which also coincides with the finding that the higher frequency of the ε2/*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 ε4 and genotypes (ε2/ε2, ε3/ε4, and ε4/ε4) 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.

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Conflict of interest

The authors declare no conflict of interest.

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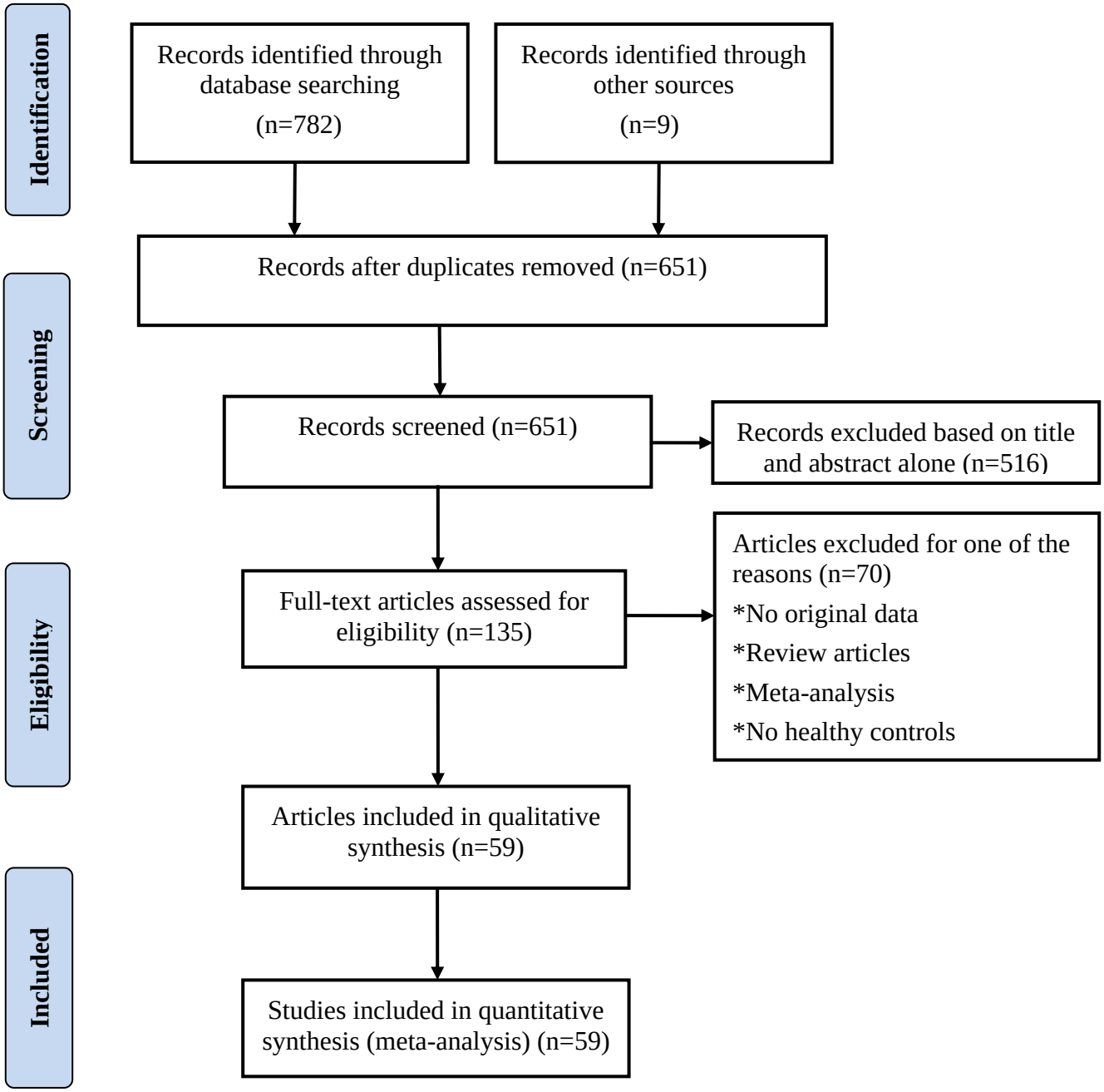
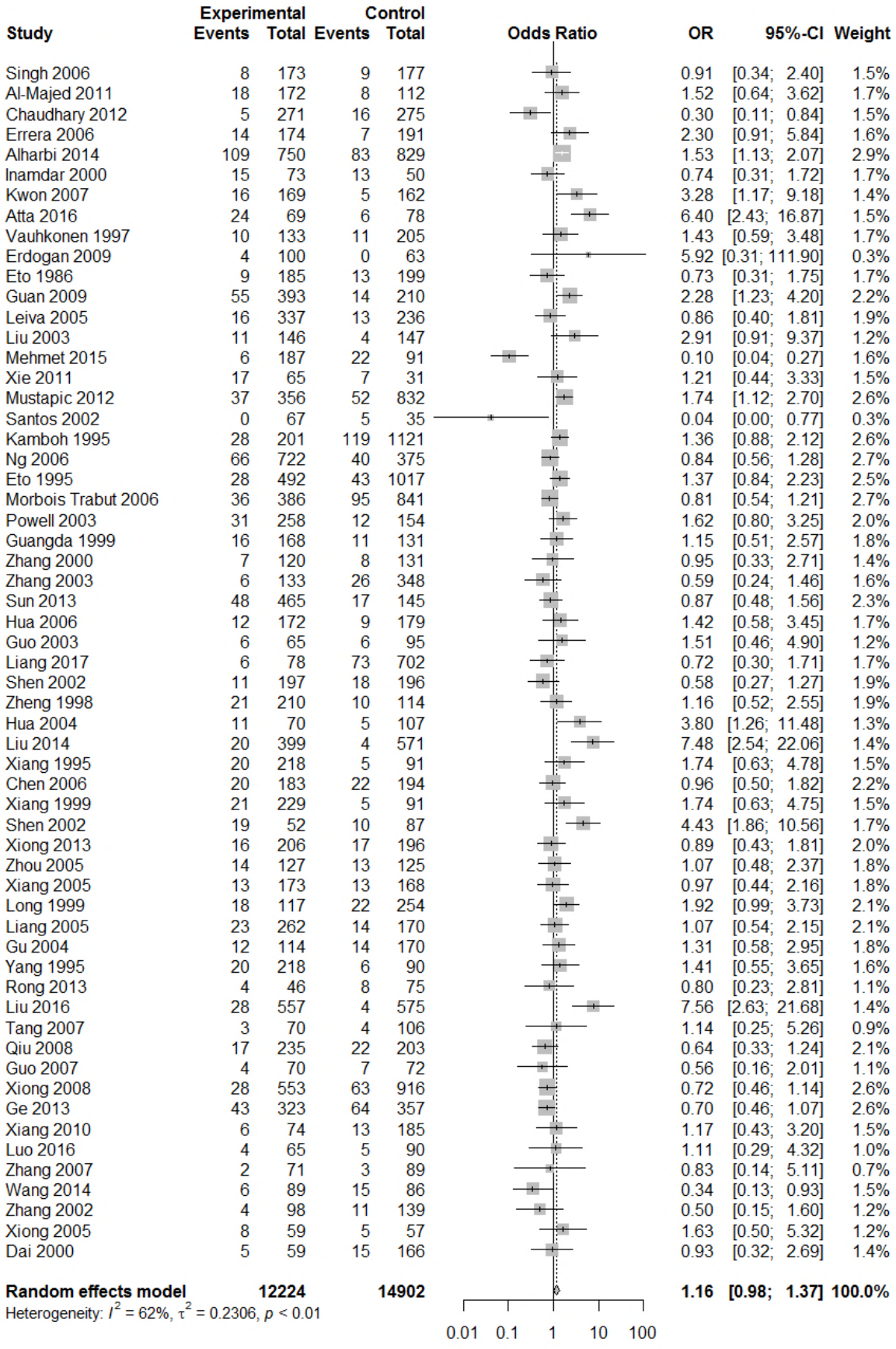
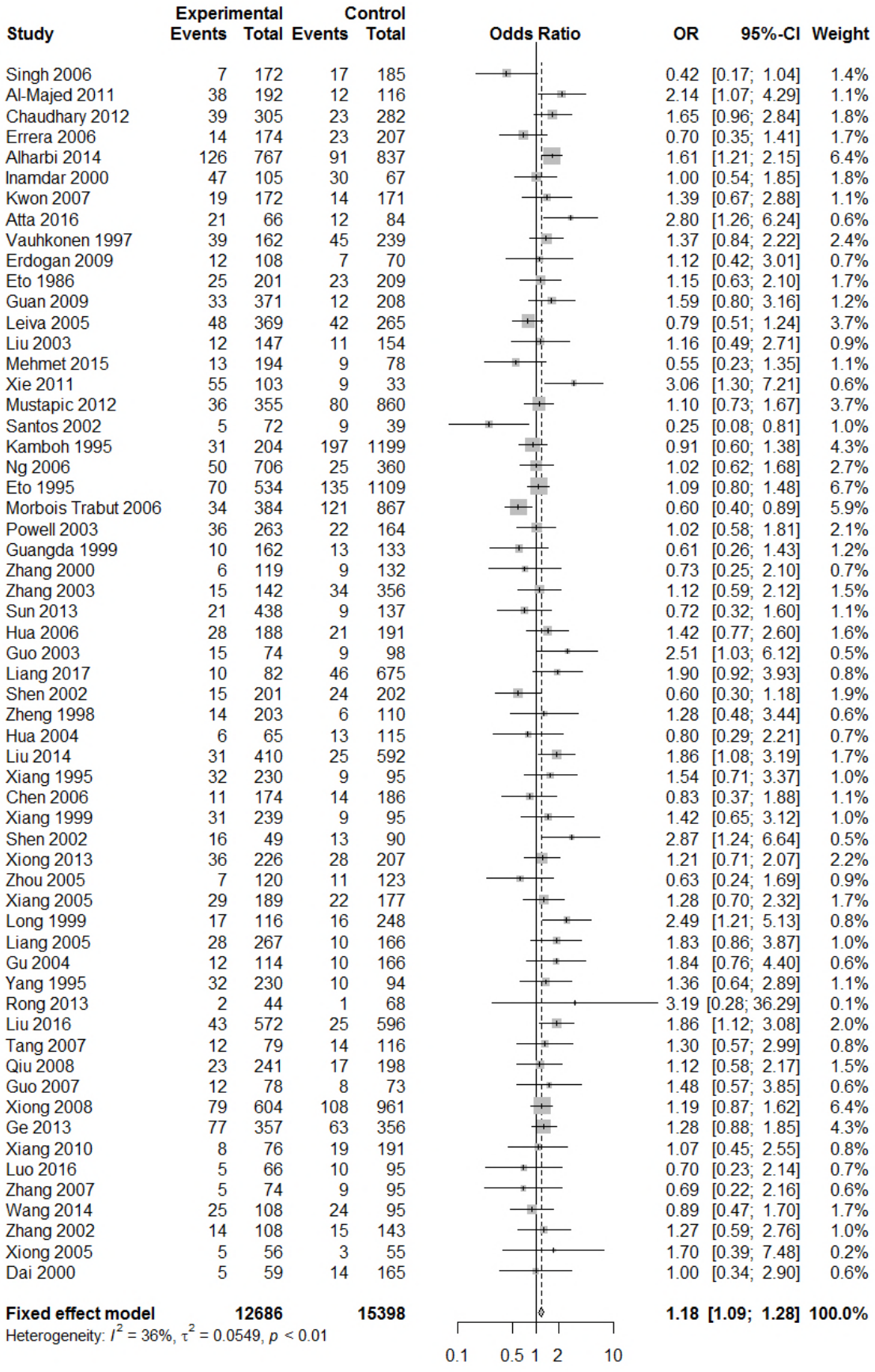
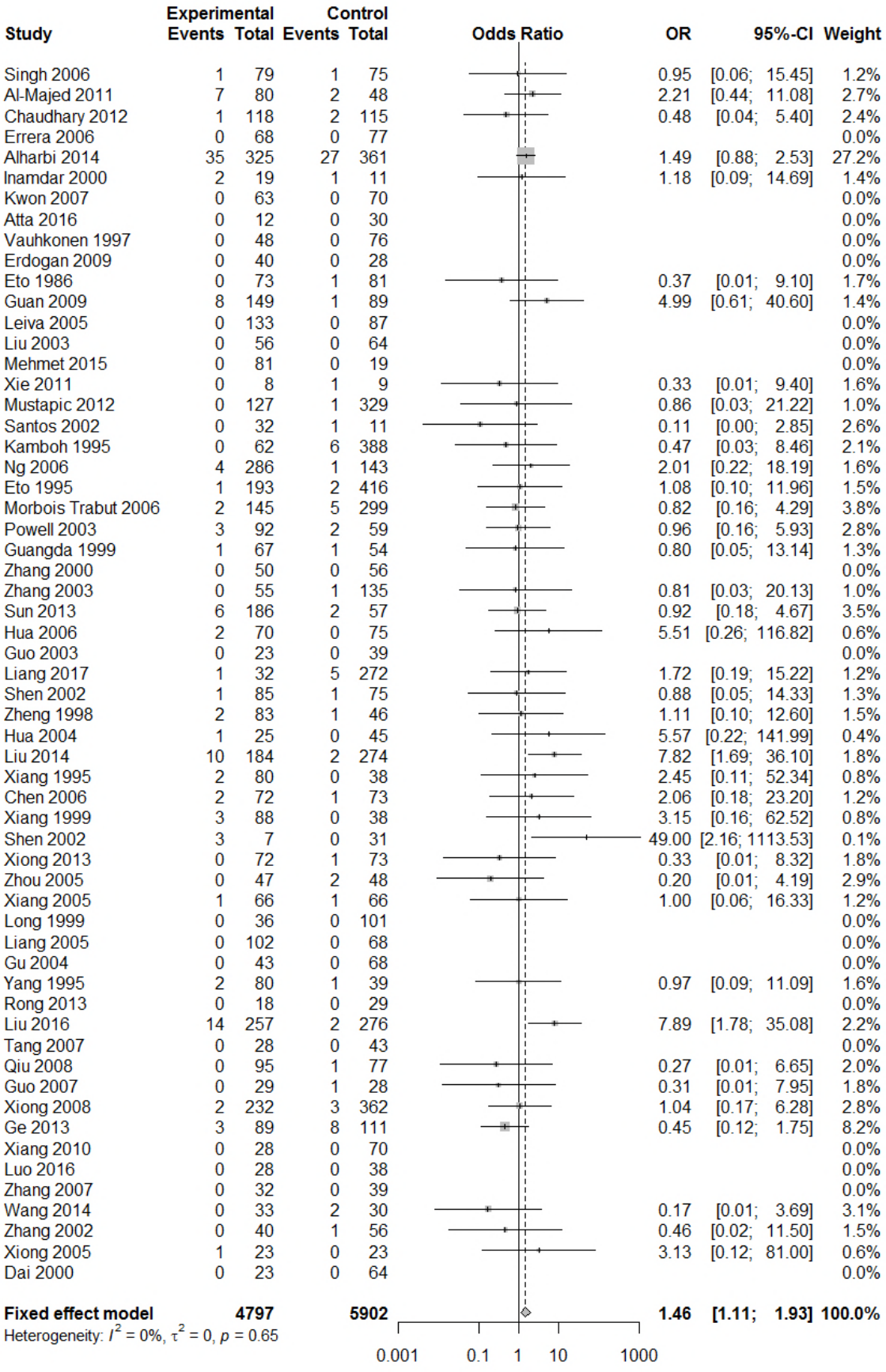
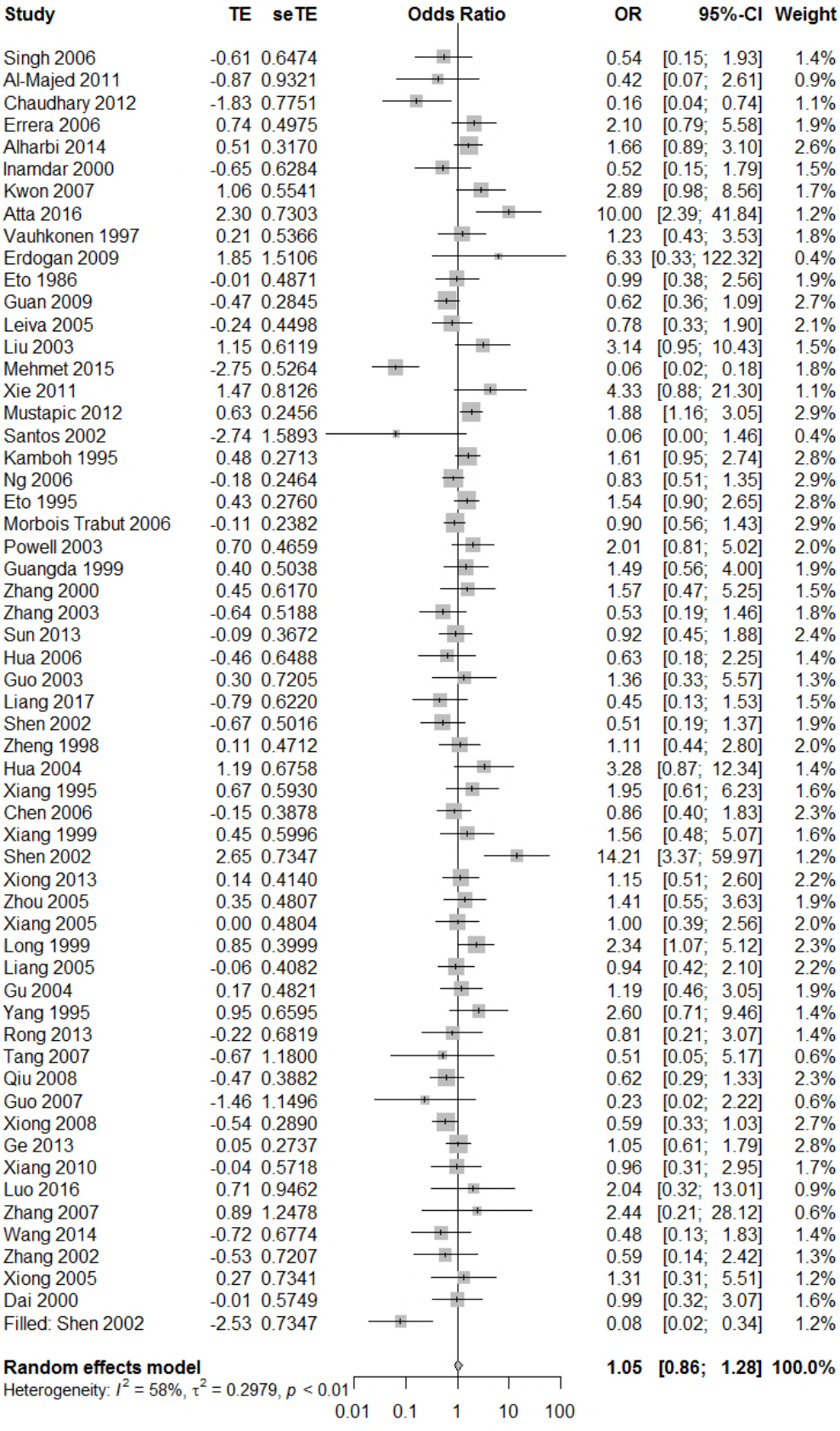
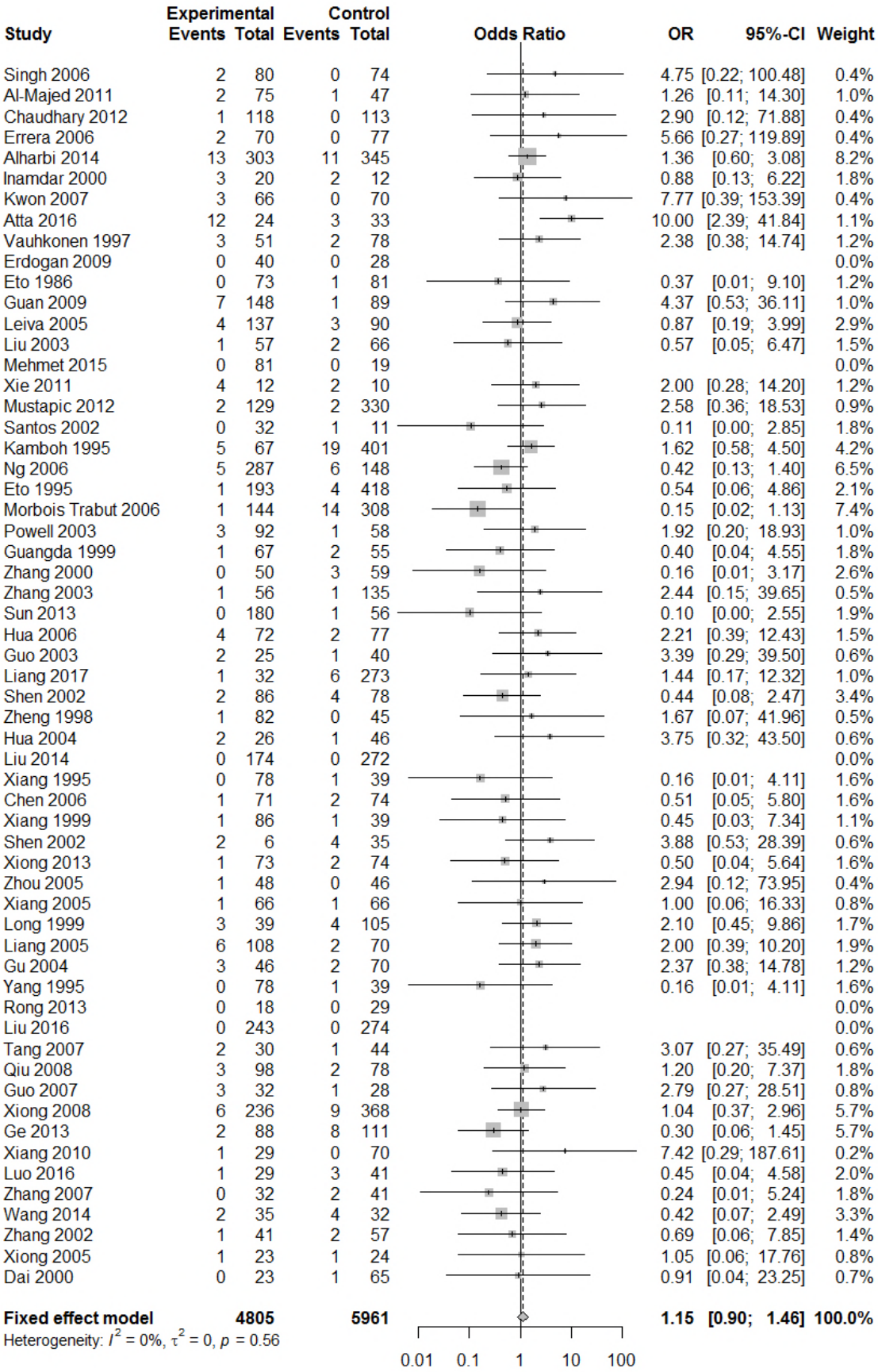


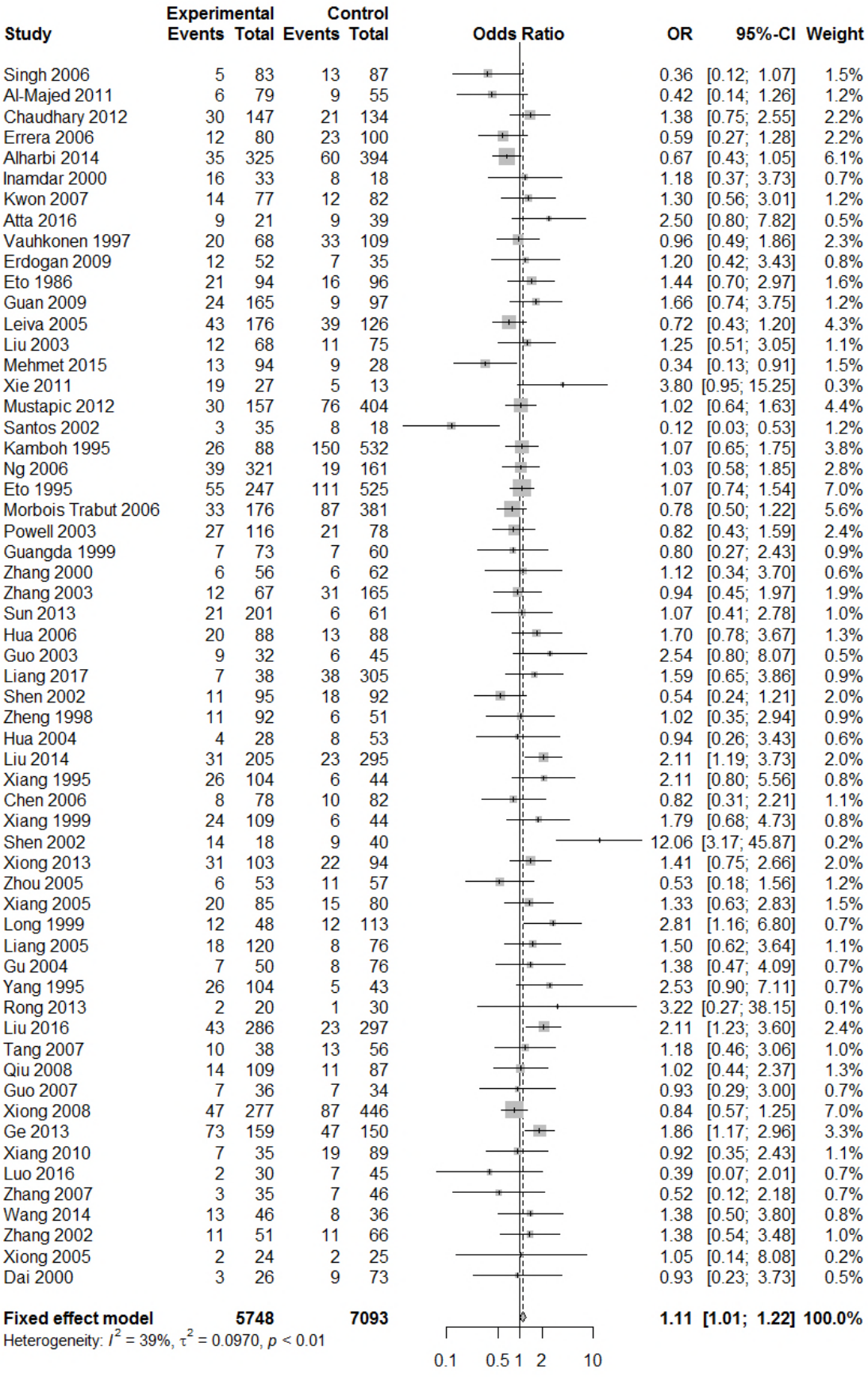

Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI Weight
Singh 2006 8 173 9 177 0.91 [0.34; 2.40] 1.5%
Al-Majed 2011 18 172 8 112 1.52 [0.64; 3.62] 1.7%
Chaudhary 2012 5 271 16 275 0.30 [0.11; 0.84] 1.5%
Errera 2006 14 174 7 191 2.30 [0.91; 5.84] 1.6%
Alharbi 2014 109 750 83 829 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 1.16 [0.98; 1.37] 100.0%
Heterogeneity: I^2 = 62%, τ^2 = 0.2306, p < 0.01
0.01 0.1 1 10 100

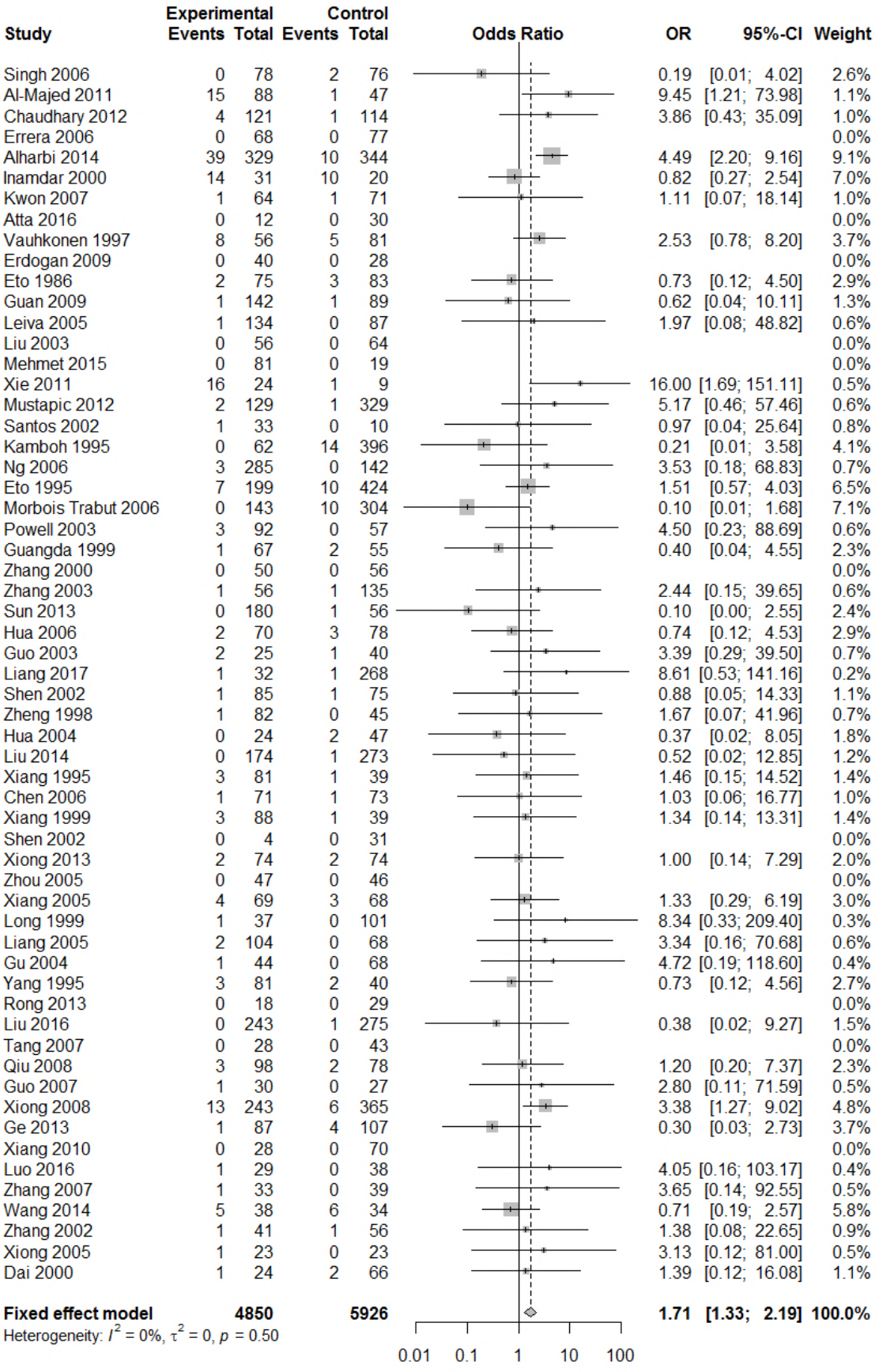

Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI Weight
Singh 2006 7 172 17 185 0.42 [0.17; 1.04] 1.4%
Al-Majed 2011 38 192 12 116 2.14 [1.07; 4.29] 1.1%
Chaudhary 2012 39 305 23 282 1.65 [0.96; 2.84] 1.8%
Errera 2006 14 174 23 207 0.70 [0.35; 1.41] 1.7%
Alharbi 2014 126 767 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 1.18 [1.09; 1.28] 100.0%
Heterogeneity: I^2 = 36%, τ^2 = 0.0549, p < 0.01
0.1 0.5 1 2 10

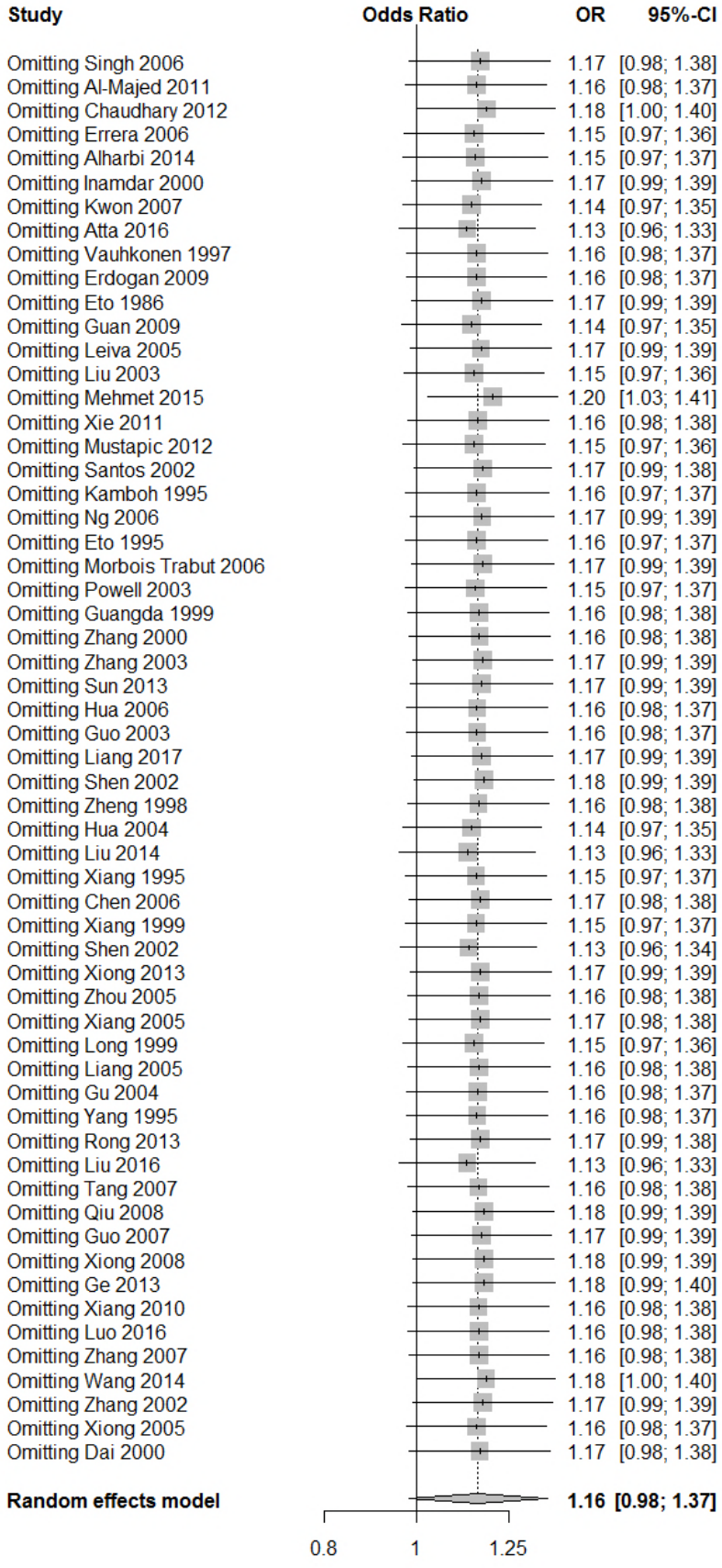

Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI Weight
Singh 2006 1 79 1 75 0.95 [0.06; 15.45] 1.2%
Al-Majed 2011 7 80 2 48 2.21 [0.44; 11.08] 2.7%
Chaudhary 2012 1 118 2 115 0.48 [0.04; 5.40] 2.4%
Errera 2006 0 68 0 77 0.0%
Alharbi 2014 35 325 27 361 1.49 [0.88; 2.53] 27.2%
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 5902 1.46 [1.11; 1.93] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.65
0.001 0.1 1 10 1000

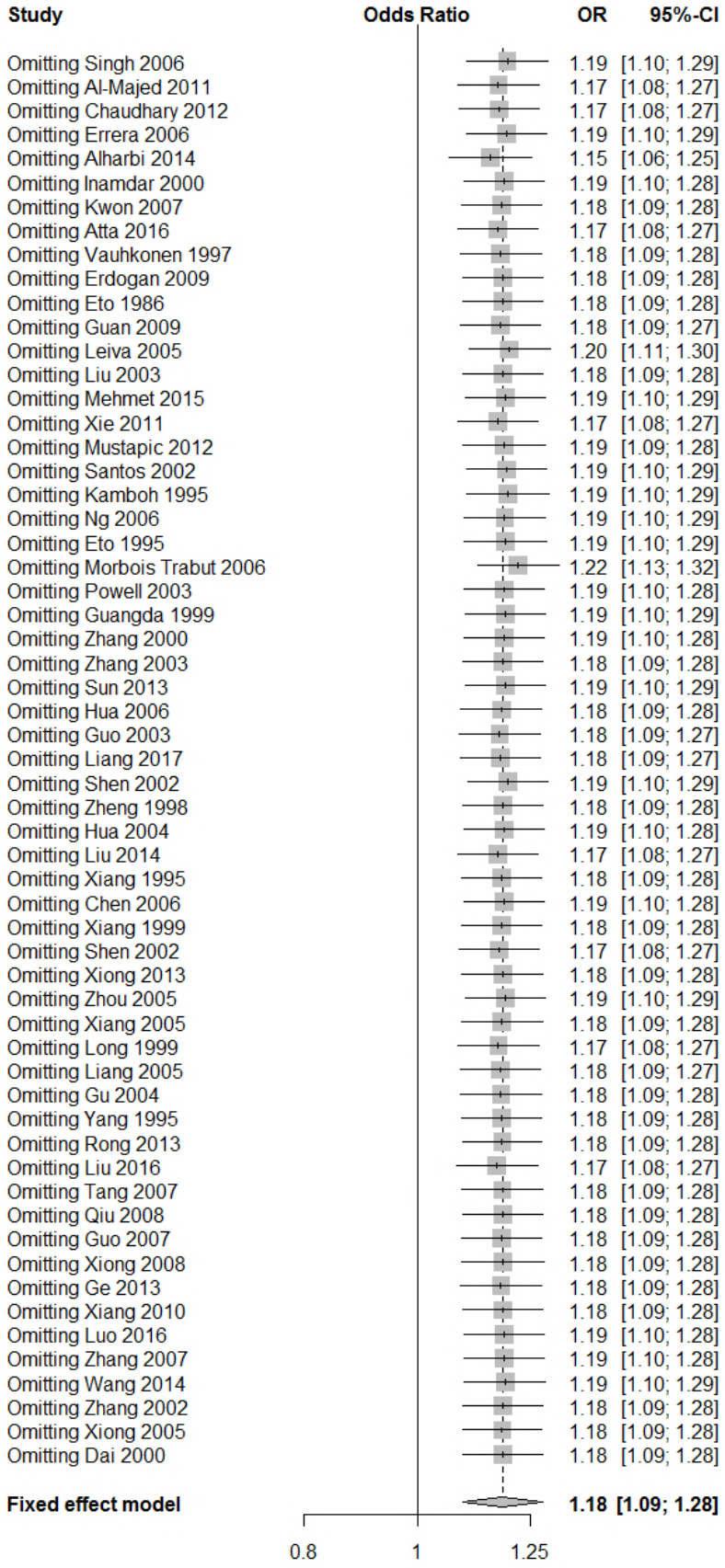

Study
TE
seTE
Odds Ratio
OR
95%-CI
Weight
Singh 2006 -0.61 0.6474 0.54 [0.15; 1.93] 1.4%
Al-Majed 2011 -0.87 0.9321 0.42 [0.07; 2.61] 0.9%
Chaudhary 2012 -1.83 0.7751 0.16 [0.04; 0.74] 1.1%
Errera 2006 0.74 0.4975 2.10 [0.79; 5.58] 1.9%
Alharbi 2014 0.51 0.3170 1.66 [0.89; 3.10] 2.6%
Inamdar 2000 -0.65 0.6284 0.52 [0.15; 1.79] 1.5%
Kwon 2007 1.06 0.5541 2.89 [0.98; 8.56] 1.7%
Atta 2016 2.30 0.7303 10.00 [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 6.33 [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 [0.95; 10.43] 1.5%
Mehmet 2015 -2.75 0.5264 0.06 [0.02; 0.18] 1.8%
Xie 2011 1.47 0.8126 4.33 [0.88; 21.30] 1.1%
Mustapic 2012 0.63 0.2456 1.88 [1.16; 3.05] 2.9%
Santos 2002 -2.74 1.5893 0.06 [0.00; 1.46] 0.4%
Kamboh 1995 0.48 0.2713 1.61 [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%
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 [0.19; 1.37] 1.9%
Zheng 1998 0.11 0.4712 1.11 [0.44; 2.80] 2.0%
Hua 2004 1.19 0.6758 3.28 [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%
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 0.95 0.6595 2.60 [0.71; 9.46] 1.4%
Rong 2013 -0.22 0.6819 0.81 [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%
Xiang 2010 -0.04 0.5718 0.96 [0.31; 2.95] 1.7%
Luo 2016 0.71 0.9462 2.04 [0.32; 13.01] 0.9%
Zhang 2007 0.89 1.2478 2.44 [0.21; 28.12] 0.6%
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 0.27 0.7341 1.31 [0.31; 5.51] 1.2%
Dai 2000 -0.01 0.5749 0.99 [0.32; 3.07] 1.6%
Filled: Shen 2002 -2.53 0.7347 0.08 [0.02; 0.34] 1.2%
Random effects model 1.05 [0.86; 1.28] 100.0%
Heterogeneity: I^2 = 58%, τ^2 = 0.2979, p < 0.01
0.01
0.1
1
10
100

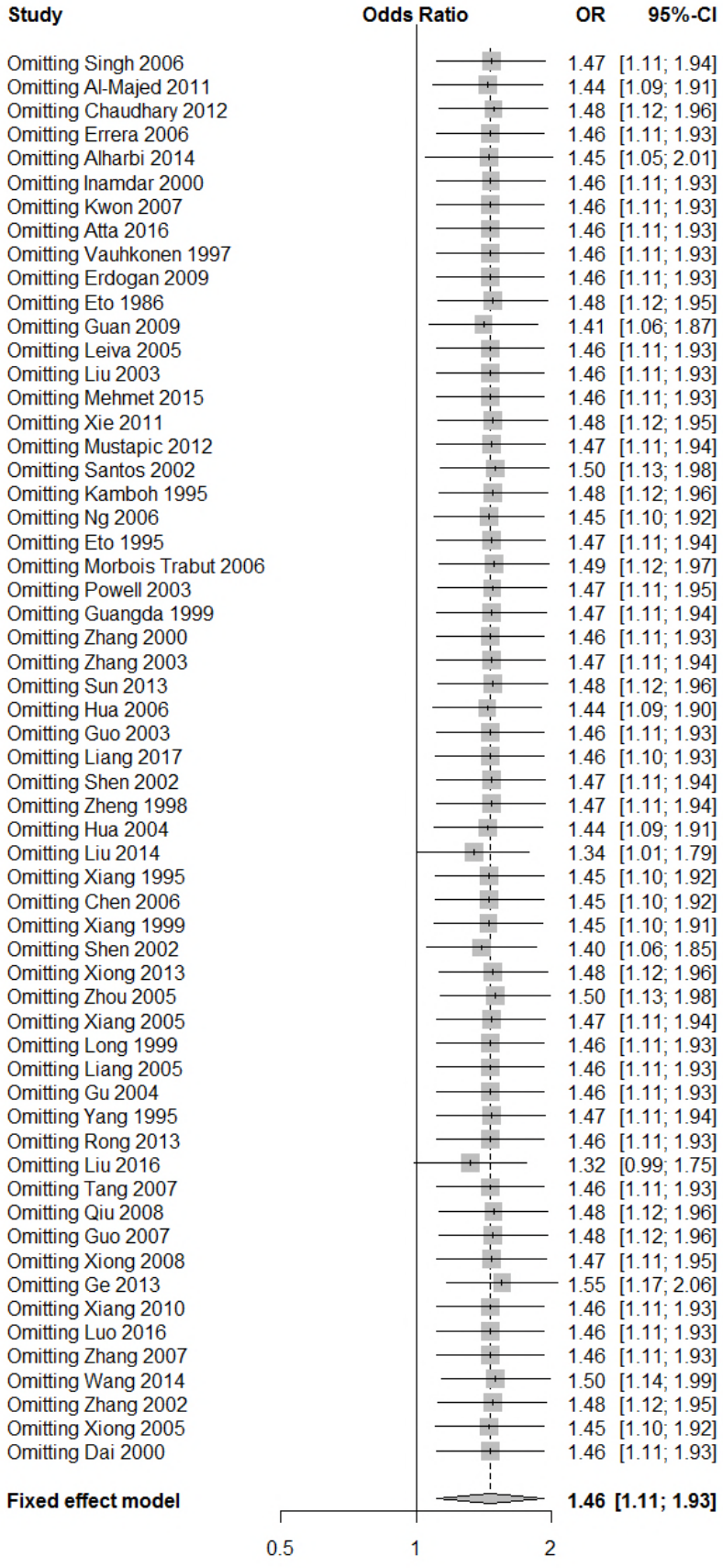

Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI Weight
Singh 2006 2 80 0 74 4.75 [0.22; 100.48] 0.4%
Al-Majed 2011 2 75 1 47 1.26 [0.11; 14.30] 1.0%
Chaudhary 2012 1 118 0 113 2.90 [0.12; 71.88] 0.4%
Errera 2006 2 70 0 77 5.66 [0.27; 119.89] 0.4%
Alharbi 2014 13 303 11 345 1.36 [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 5961 1.15 [0.90; 1.46] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.56
0.01 0.1 1 10 100

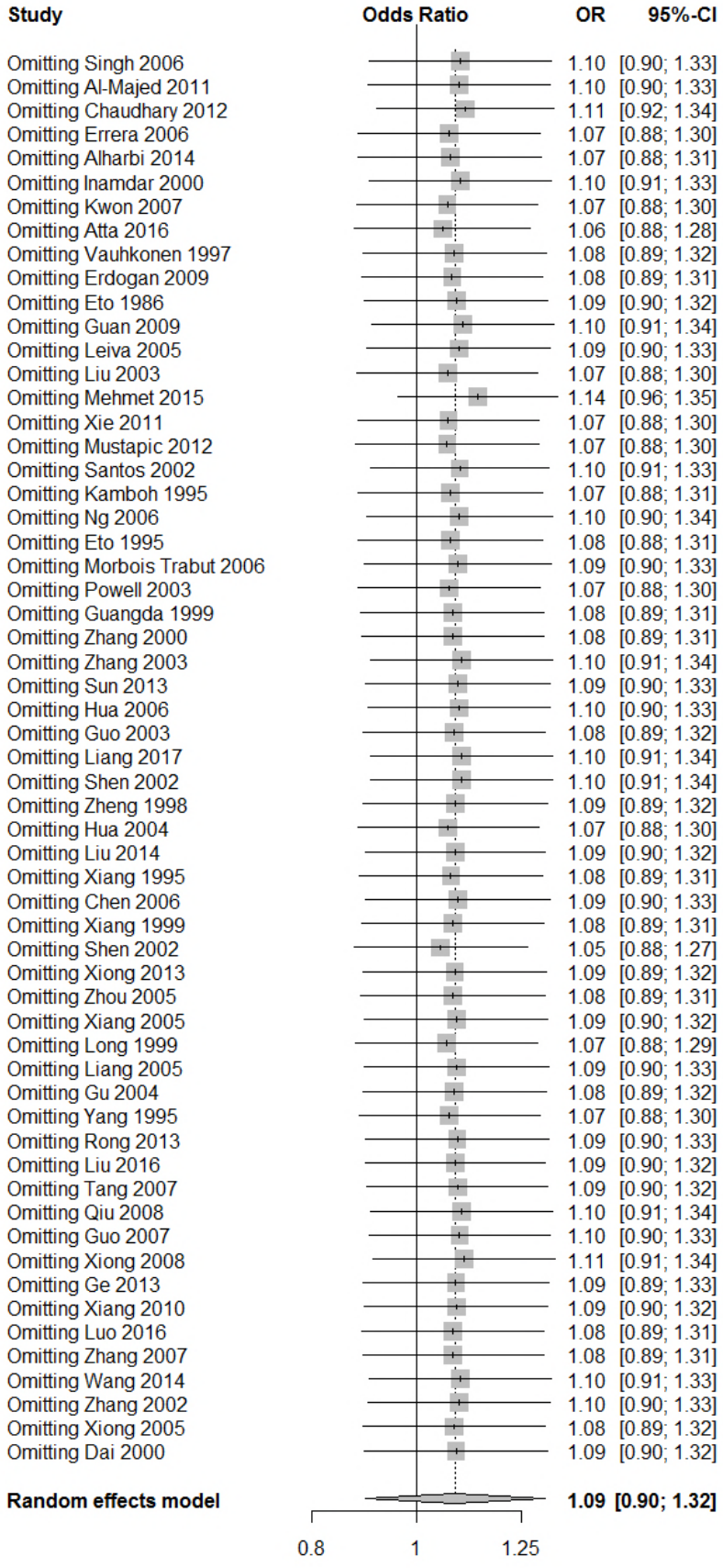

Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI Weight
Singh 2006 5 83 13 87 0.36 [0.12; 1.07] 1.5%
Al-Majed 2011 6 79 9 55 0.42 [0.14; 1.26] 1.2%
Chaudhary 2012 30 147 21 134 1.38 [0.75; 2.55] 2.2%
Errera 2006 12 80 23 100 0.59 [0.27; 1.28] 2.2%
Alharbi 2014 35 325 60 394 0.67 [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 1.11 [1.01; 1.22] 100.0%
Heterogeneity: I^2 = 39%, τ^2 = 0.0970, p < 0.01
0.1 0.5 1 2 10

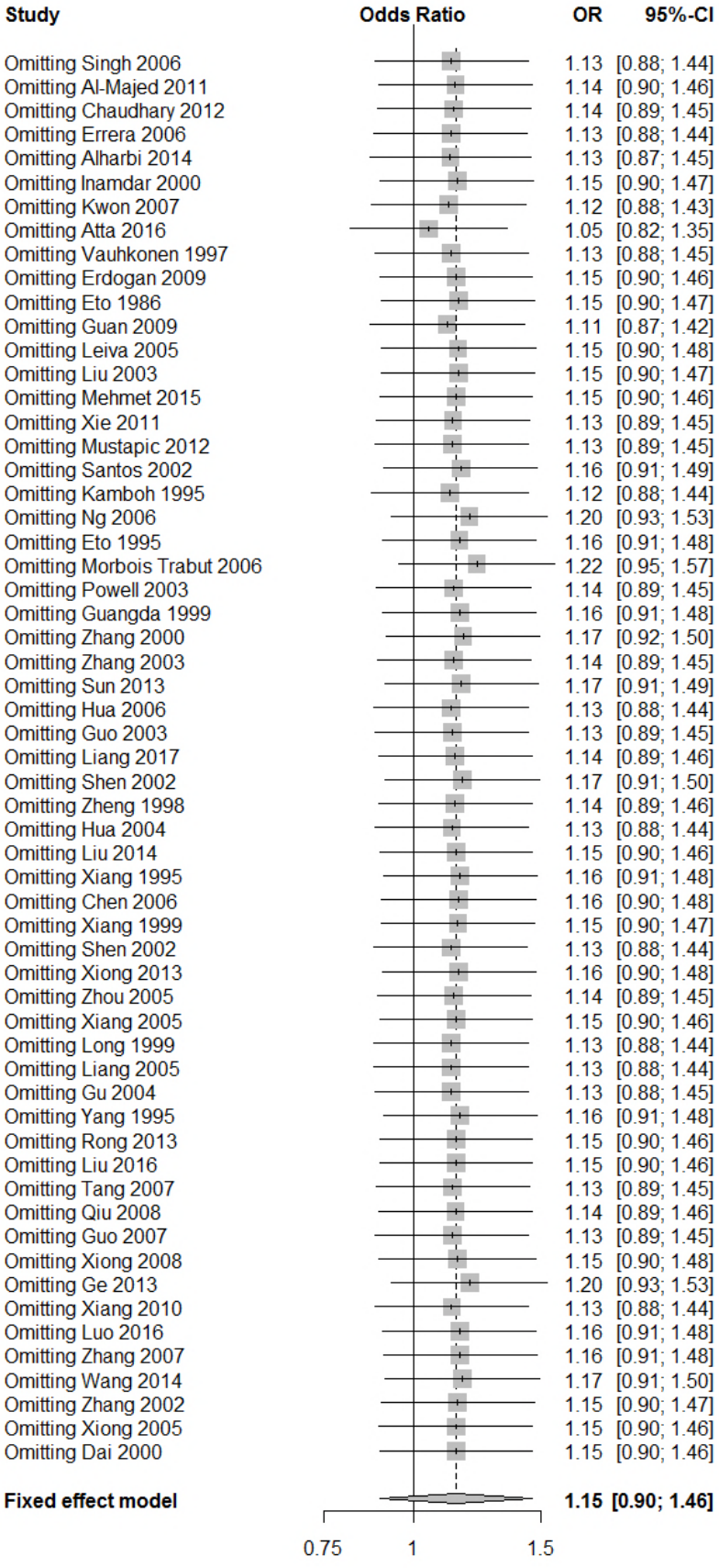

Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI Weight
Singh 2006 0 78 2 76 0.19 [0.01; 4.02] 2.6%
Al-Majed 2011 15 88 1 47 9.45 [1.21; 73.98] 1.1%
Chaudhary 2012 4 121 1 114 3.86 [0.43; 35.09] 1.0%
Errera 2006 0 68 0 77 0.0%
Alharbi 2014 39 329 10 344 4.49 [2.20; 9.16] 9.1%
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 5926 1.71 [1.33; 2.19] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.50
0.01 0.1 1 10 100


Study
Odds Ratio
OR
95%-CI
Omitting Singh 2006 1.17 [0.98; 1.38]
Omitting Al-Majed 2011 1.16 [0.98; 1.37]
Omitting Chaudhary 2012 1.18 [1.00; 1.40]
Omitting Errera 2006 1.15 [0.97; 1.36]
Omitting Alharbi 2014 1.15 [0.97; 1.37]
Omitting Inamdar 2000 1.17 [0.99; 1.39]
Omitting Kwon 2007 1.14 [0.97; 1.35]
Omitting Atta 2016 1.13 [0.96; 1.33]
Omitting Vauhkonen 1997 1.16 [0.98; 1.37]
Omitting Erdogan 2009 1.16 [0.98; 1.37]
Omitting Eto 1986 1.17 [0.99; 1.39]
Omitting Guan 2009 1.14 [0.97; 1.35]
Omitting Leiva 2005 1.17 [0.99; 1.39]
Omitting Liu 2003 1.15 [0.97; 1.36]
Omitting Mehmet 2015 1.20 [1.03; 1.41]
Omitting Xie 2011 1.16 [0.98; 1.38]
Omitting Mustapic 2012 1.15 [0.97; 1.36]
Omitting Santos 2002 1.17 [0.99; 1.38]
Omitting Kamboh 1995 1.16 [0.97; 1.37]
Omitting Ng 2006 1.17 [0.99; 1.39]
Omitting Eto 1995 1.16 [0.97; 1.37]
Omitting Morbois Trabut 2006 1.17 [0.99; 1.39]
Omitting Powell 2003 1.15 [0.97; 1.37]
Omitting Guangda 1999 1.16 [0.98; 1.38]
Omitting Zhang 2000 1.16 [0.98; 1.38]
Omitting Zhang 2003 1.17 [0.99; 1.39]
Omitting Sun 2013 1.17 [0.99; 1.39]
Omitting Hua 2006 1.16 [0.98; 1.37]
Omitting Guo 2003 1.16 [0.98; 1.37]
Omitting Liang 2017 1.17 [0.99; 1.39]
Omitting Shen 2002 1.18 [0.99; 1.39]
Omitting Zheng 1998 1.16 [0.98; 1.38]
Omitting Hua 2004 1.14 [0.97; 1.35]
Omitting Liu 2014 1.13 [0.96; 1.33]
Omitting Xiang 1995 1.15 [0.97; 1.37]
Omitting Chen 2006 1.17 [0.98; 1.38]
Omitting Xiang 1999 1.15 [0.97; 1.37]
Omitting Shen 2002 1.13 [0.96; 1.34]
Omitting Xiong 2013 1.17 [0.99; 1.39]
Omitting Zhou 2005 1.16 [0.98; 1.38]
Omitting Xiang 2005 1.17 [0.98; 1.38]
Omitting Long 1999 1.15 [0.97; 1.36]
Omitting Liang 2005 1.16 [0.98; 1.38]
Omitting Gu 2004 1.16 [0.98; 1.37]
Omitting Yang 1995 1.16 [0.98; 1.37]
Omitting Rong 2013 1.17 [0.99; 1.38]
Omitting Liu 2016 1.13 [0.96; 1.33]
Omitting Tang 2007 1.16 [0.98; 1.38]
Omitting Qiu 2008 1.18 [0.99; 1.39]
Omitting Guo 2007 1.17 [0.99; 1.39]
Omitting Xiong 2008 1.18 [0.99; 1.39]
Omitting Ge 2013 1.18 [0.99; 1.40]
Omitting Xiang 2010 1.16 [0.98; 1.38]
Omitting Luo 2016 1.16 [0.98; 1.38]
Omitting Zhang 2007 1.16 [0.98; 1.38]
Omitting Wang 2014 1.18 [1.00; 1.40]
Omitting Zhang 2002 1.17 [0.99; 1.39]
Omitting Xiong 2005 1.16 [0.98; 1.37]
Omitting Dai 2000 1.17 [0.98; 1.38]
Random effects model 1.16 [0.98; 1.37]
0.8
1
1.25


Study
Odds Ratio
OR
95%-CI
Omitting Singh 2006 1.19 [1.10; 1.29]
Omitting Al-Majed 2011 1.17 [1.08; 1.27]
Omitting Chaudhary 2012 1.17 [1.08; 1.27]
Omitting Errera 2006 1.19 [1.10; 1.29]
Omitting Alharbi 2014 1.15 [1.06; 1.25]
Omitting Inamdar 2000 1.19 [1.10; 1.28]
Omitting Kwon 2007 1.18 [1.09; 1.28]
Omitting Atta 2016 1.17 [1.08; 1.27]
Omitting Vauhkonen 1997 1.18 [1.09; 1.28]
Omitting Erdogan 2009 1.18 [1.09; 1.28]
Omitting Eto 1986 1.18 [1.09; 1.28]
Omitting Guan 2009 1.18 [1.09; 1.27]
Omitting Leiva 2005 1.20 [1.11; 1.30]
Omitting Liu 2003 1.18 [1.09; 1.28]
Omitting Mehmet 2015 1.19 [1.10; 1.29]
Omitting Xie 2011 1.17 [1.08; 1.27]
Omitting Mustapic 2012 1.19 [1.09; 1.28]
Omitting Santos 2002 1.19 [1.10; 1.29]
Omitting Kamboh 1995 1.19 [1.10; 1.29]
Omitting Ng 2006 1.19 [1.10; 1.29]
Omitting Eto 1995 1.19 [1.10; 1.29]
Omitting Morbois Trabut 2006 1.22 [1.13; 1.32]
Omitting Powell 2003 1.19 [1.10; 1.28]
Omitting Guangda 1999 1.19 [1.10; 1.29]
Omitting Zhang 2000 1.19 [1.10; 1.28]
Omitting Zhang 2003 1.18 [1.09; 1.28]
Omitting Sun 2013 1.19 [1.10; 1.29]
Omitting Hua 2006 1.18 [1.09; 1.28]
Omitting Guo 2003 1.18 [1.09; 1.27]
Omitting Liang 2017 1.18 [1.09; 1.27]
Omitting Shen 2002 1.19 [1.10; 1.29]
Omitting Zheng 1998 1.18 [1.09; 1.28]
Omitting Hua 2004 1.19 [1.10; 1.28]
Omitting Liu 2014 1.17 [1.08; 1.27]
Omitting Xiang 1995 1.18 [1.09; 1.28]
Omitting Chen 2006 1.19 [1.10; 1.28]
Omitting Xiang 1999 1.18 [1.09; 1.28]
Omitting Shen 2002 1.17 [1.08; 1.27]
Omitting Xiong 2013 1.18 [1.09; 1.28]
Omitting Zhou 2005 1.19 [1.10; 1.29]
Omitting Xiang 2005 1.18 [1.09; 1.28]
Omitting Long 1999 1.17 [1.08; 1.27]
Omitting Liang 2005 1.18 [1.09; 1.27]
Omitting Gu 2004 1.18 [1.09; 1.28]
Omitting Yang 1995 1.18 [1.09; 1.28]
Omitting Rong 2013 1.18 [1.09; 1.28]
Omitting Liu 2016 1.17 [1.08; 1.27]
Omitting Tang 2007 1.18 [1.09; 1.28]
Omitting Qiu 2008 1.18 [1.09; 1.28]
Omitting Guo 2007 1.18 [1.09; 1.28]
Omitting Xiong 2008 1.18 [1.09; 1.28]
Omitting Ge 2013 1.18 [1.09; 1.28]
Omitting Xiang 2010 1.18 [1.09; 1.28]
Omitting Luo 2016 1.19 [1.10; 1.28]
Omitting Zhang 2007 1.19 [1.10; 1.28]
Omitting Wang 2014 1.19 [1.10; 1.29]
Omitting Zhang 2002 1.18 [1.09; 1.28]
Omitting Xiong 2005 1.18 [1.09; 1.28]
Omitting Dai 2000 1.18 [1.09; 1.28]
Fixed effect model 1.18 [1.09; 1.28]
0.8
1
1.25


Study
Odds Ratio
OR
95%-CI
Omitting Singh 2006 1.47 [1.11; 1.94]
Omitting Al-Majed 2011 1.44 [1.09; 1.91]
Omitting Chaudhary 2012 1.48 [1.12; 1.96]
Omitting Errera 2006 1.46 [1.11; 1.93]
Omitting Alharbi 2014 1.45 [1.05; 2.01]
Omitting Inamdar 2000 1.46 [1.11; 1.93]
Omitting Kwon 2007 1.46 [1.11; 1.93]
Omitting Atta 2016 1.46 [1.11; 1.93]
Omitting Vauhkonen 1997 1.46 [1.11; 1.93]
Omitting Erdogan 2009 1.46 [1.11; 1.93]
Omitting Eto 1986 1.48 [1.12; 1.95]
Omitting Guan 2009 1.41 [1.06; 1.87]
Omitting Leiva 2005 1.46 [1.11; 1.93]
Omitting Liu 2003 1.46 [1.11; 1.93]
Omitting Mehmet 2015 1.46 [1.11; 1.93]
Omitting Xie 2011 1.48 [1.12; 1.95]
Omitting Mustapic 2012 1.47 [1.11; 1.94]
Omitting Santos 2002 1.50 [1.13; 1.98]
Omitting Kamboh 1995 1.48 [1.12; 1.96]
Omitting Ng 2006 1.45 [1.10; 1.92]
Omitting Eto 1995 1.47 [1.11; 1.94]
Omitting Morbois Trabut 2006 1.49 [1.12; 1.97]
Omitting Powell 2003 1.47 [1.11; 1.95]
Omitting Guangda 1999 1.47 [1.11; 1.94]
Omitting Zhang 2000 1.46 [1.11; 1.93]
Omitting Zhang 2003 1.47 [1.11; 1.94]
Omitting Sun 2013 1.48 [1.12; 1.96]
Omitting Hua 2006 1.44 [1.09; 1.90]
Omitting Guo 2003 1.46 [1.11; 1.93]
Omitting Liang 2017 1.46 [1.10; 1.93]
Omitting Shen 2002 1.47 [1.11; 1.94]
Omitting Zheng 1998 1.47 [1.11; 1.94]
Omitting Hua 2004 1.44 [1.09; 1.91]
Omitting Liu 2014 1.34 [1.01; 1.79]
Omitting Xiang 1995 1.45 [1.10; 1.92]
Omitting Chen 2006 1.45 [1.10; 1.92]
Omitting Xiang 1999 1.45 [1.10; 1.91]
Omitting Shen 2002 1.40 [1.06; 1.85]
Omitting Xiong 2013 1.48 [1.12; 1.96]
Omitting Zhou 2005 1.50 [1.13; 1.98]
Omitting Xiang 2005 1.47 [1.11; 1.94]
Omitting Long 1999 1.46 [1.11; 1.93]
Omitting Liang 2005 1.46 [1.11; 1.93]
Omitting Gu 2004 1.46 [1.11; 1.93]
Omitting Yang 1995 1.47 [1.11; 1.94]
Omitting Rong 2013 1.46 [1.11; 1.93]
Omitting Liu 2016 1.32 [0.99; 1.75]
Omitting Tang 2007 1.46 [1.11; 1.93]
Omitting Qiu 2008 1.48 [1.12; 1.96]
Omitting Guo 2007 1.48 [1.12; 1.96]
Omitting Xiong 2008 1.47 [1.11; 1.95]
Omitting Ge 2013 1.55 [1.17; 2.06]
Omitting Xiang 2010 1.46 [1.11; 1.93]
Omitting Luo 2016 1.46 [1.11; 1.93]
Omitting Zhang 2007 1.46 [1.11; 1.93]
Omitting Wang 2014 1.50 [1.14; 1.99]
Omitting Zhang 2002 1.48 [1.12; 1.95]
Omitting Xiong 2005 1.45 [1.10; 1.92]
Omitting Dai 2000 1.46 [1.11; 1.93]
Fixed effect model 1.46 [1.11; 1.93]
0.5
1
2


Study
Odds Ratio
OR
95%-CI
Omitting Singh 2006 1.10 [0.90; 1.33]
Omitting Al-Majed 2011 1.10 [0.90; 1.33]
Omitting Chaudhary 2012 1.11 [0.92; 1.34]
Omitting Errera 2006 1.07 [0.88; 1.30]
Omitting Alharbi 2014 1.07 [0.88; 1.31]
Omitting Inamdar 2000 1.10 [0.91; 1.33]
Omitting Kwon 2007 1.07 [0.88; 1.30]
Omitting Atta 2016 1.06 [0.88; 1.28]
Omitting Vauhkonen 1997 1.08 [0.89; 1.32]
Omitting Erdogan 2009 1.08 [0.89; 1.31]
Omitting Eto 1986 1.09 [0.90; 1.32]
Omitting Guan 2009 1.10 [0.91; 1.34]
Omitting Leiva 2005 1.09 [0.90; 1.33]
Omitting Liu 2003 1.07 [0.88; 1.30]
Omitting Mehmet 2015 1.14 [0.96; 1.35]
Omitting Xie 2011 1.07 [0.88; 1.30]
Omitting Mustapic 2012 1.07 [0.88; 1.30]
Omitting Santos 2002 1.10 [0.91; 1.33]
Omitting Kamboh 1995 1.07 [0.88; 1.31]
Omitting Ng 2006 1.10 [0.90; 1.34]
Omitting Eto 1995 1.08 [0.88; 1.31]
Omitting Morbois Trabut 2006 1.09 [0.90; 1.33]
Omitting Powell 2003 1.07 [0.88; 1.30]
Omitting Guangda 1999 1.08 [0.89; 1.31]
Omitting Zhang 2000 1.08 [0.89; 1.31]
Omitting Zhang 2003 1.10 [0.91; 1.34]
Omitting Sun 2013 1.09 [0.90; 1.33]
Omitting Hua 2006 1.10 [0.90; 1.33]
Omitting Guo 2003 1.08 [0.89; 1.32]
Omitting Liang 2017 1.10 [0.91; 1.34]
Omitting Shen 2002 1.10 [0.91; 1.34]
Omitting Zheng 1998 1.09 [0.89; 1.32]
Omitting Hua 2004 1.07 [0.88; 1.30]
Omitting Liu 2014 1.09 [0.90; 1.32]
Omitting Xiang 1995 1.08 [0.89; 1.31]
Omitting Chen 2006 1.09 [0.90; 1.33]
Omitting Xiang 1999 1.08 [0.89; 1.31]
Omitting Shen 2002 1.05 [0.88; 1.27]
Omitting Xiong 2013 1.09 [0.89; 1.32]
Omitting Zhou 2005 1.08 [0.89; 1.31]
Omitting Xiang 2005 1.09 [0.90; 1.32]
Omitting Long 1999 1.07 [0.88; 1.29]
Omitting Liang 2005 1.09 [0.90; 1.33]
Omitting Gu 2004 1.08 [0.89; 1.32]
Omitting Yang 1995 1.07 [0.88; 1.30]
Omitting Rong 2013 1.09 [0.90; 1.33]
Omitting Liu 2016 1.09 [0.90; 1.32]
Omitting Tang 2007 1.09 [0.90; 1.32]
Omitting Qiu 2008 1.10 [0.91; 1.34]
Omitting Guo 2007 1.10 [0.90; 1.33]
Omitting Xiong 2008 1.11 [0.91; 1.34]
Omitting Ge 2013 1.09 [0.89; 1.33]
Omitting Xiang 2010 1.09 [0.90; 1.32]
Omitting Luo 2016 1.08 [0.89; 1.31]
Omitting Zhang 2007 1.08 [0.89; 1.31]
Omitting Wang 2014 1.10 [0.91; 1.33]
Omitting Zhang 2002 1.10 [0.90; 1.33]
Omitting Xiong 2005 1.08 [0.89; 1.32]
Omitting Dai 2000 1.09 [0.90; 1.32]
Random effects model 1.09 [0.90; 1.32]
0.8
1
1.25


Study
Odds Ratio
OR
95%-CI
Omitting Singh 2006 1.13 [0.88; 1.44]
Omitting Al-Majed 2011 1.14 [0.90; 1.46]
Omitting Chaudhary 2012 1.14 [0.89; 1.45]
Omitting Errera 2006 1.13 [0.88; 1.44]
Omitting Alharbi 2014 1.13 [0.87; 1.45]
Omitting Inamdar 2000 1.15 [0.90; 1.47]
Omitting Kwon 2007 1.12 [0.88; 1.43]
Omitting Atta 2016 1.05 [0.82; 1.35]
Omitting Vauhkonen 1997 1.13 [0.88; 1.45]
Omitting Erdogan 2009 1.15 [0.90; 1.46]
Omitting Eto 1986 1.15 [0.90; 1.47]
Omitting Guan 2009 1.11 [0.87; 1.42]
Omitting Leiva 2005 1.15 [0.90; 1.48]
Omitting Liu 2003 1.15 [0.90; 1.47]
Omitting Mehmet 2015 1.15 [0.90; 1.46]
Omitting Xie 2011 1.13 [0.89; 1.45]
Omitting Mustapic 2012 1.13 [0.89; 1.45]
Omitting Santos 2002 1.16 [0.91; 1.49]
Omitting Kamboh 1995 1.12 [0.88; 1.44]
Omitting Ng 2006 1.20 [0.93; 1.53]
Omitting Eto 1995 1.16 [0.91; 1.48]
Omitting Morbois Trabut 2006 1.22 [0.95; 1.57]
Omitting Powell 2003 1.14 [0.89; 1.45]
Omitting Guangda 1999 1.16 [0.91; 1.48]
Omitting Zhang 2000 1.17 [0.92; 1.50]
Omitting Zhang 2003 1.14 [0.89; 1.45]
Omitting Sun 2013 1.17 [0.91; 1.49]
Omitting Hua 2006 1.13 [0.88; 1.44]
Omitting Guo 2003 1.13 [0.89; 1.45]
Omitting Liang 2017 1.14 [0.89; 1.46]
Omitting Shen 2002 1.17 [0.91; 1.50]
Omitting Zheng 1998 1.14 [0.89; 1.46]
Omitting Hua 2004 1.13 [0.88; 1.44]
Omitting Liu 2014 1.15 [0.90; 1.46]
Omitting Xiang 1995 1.16 [0.91; 1.48]
Omitting Chen 2006 1.16 [0.90; 1.48]
Omitting Xiang 1999 1.15 [0.90; 1.47]
Omitting Shen 2002 1.13 [0.88; 1.44]
Omitting Xiong 2013 1.16 [0.90; 1.48]
Omitting Zhou 2005 1.14 [0.89; 1.45]
Omitting Xiang 2005 1.15 [0.90; 1.46]
Omitting Long 1999 1.13 [0.88; 1.44]
Omitting Liang 2005 1.13 [0.88; 1.44]
Omitting Gu 2004 1.13 [0.88; 1.45]
Omitting Yang 1995 1.16 [0.91; 1.48]
Omitting Rong 2013 1.15 [0.90; 1.46]
Omitting Liu 2016 1.15 [0.90; 1.46]
Omitting Tang 2007 1.13 [0.89; 1.45]
Omitting Qiu 2008 1.14 [0.89; 1.46]
Omitting Guo 2007 1.13 [0.89; 1.45]
Omitting Xiong 2008 1.15 [0.90; 1.48]
Omitting Ge 2013 1.20 [0.93; 1.53]
Omitting Xiang 2010 1.13 [0.88; 1.44]
Omitting Luo 2016 1.16 [0.91; 1.48]
Omitting Zhang 2007 1.16 [0.91; 1.48]
Omitting Wang 2014 1.17 [0.91; 1.50]
Omitting Zhang 2002 1.15 [0.90; 1.47]
Omitting Xiong 2005 1.15 [0.90; 1.46]
Omitting Dai 2000 1.15 [0.90; 1.46]
Fixed effect model 1.15 [0.90; 1.46]
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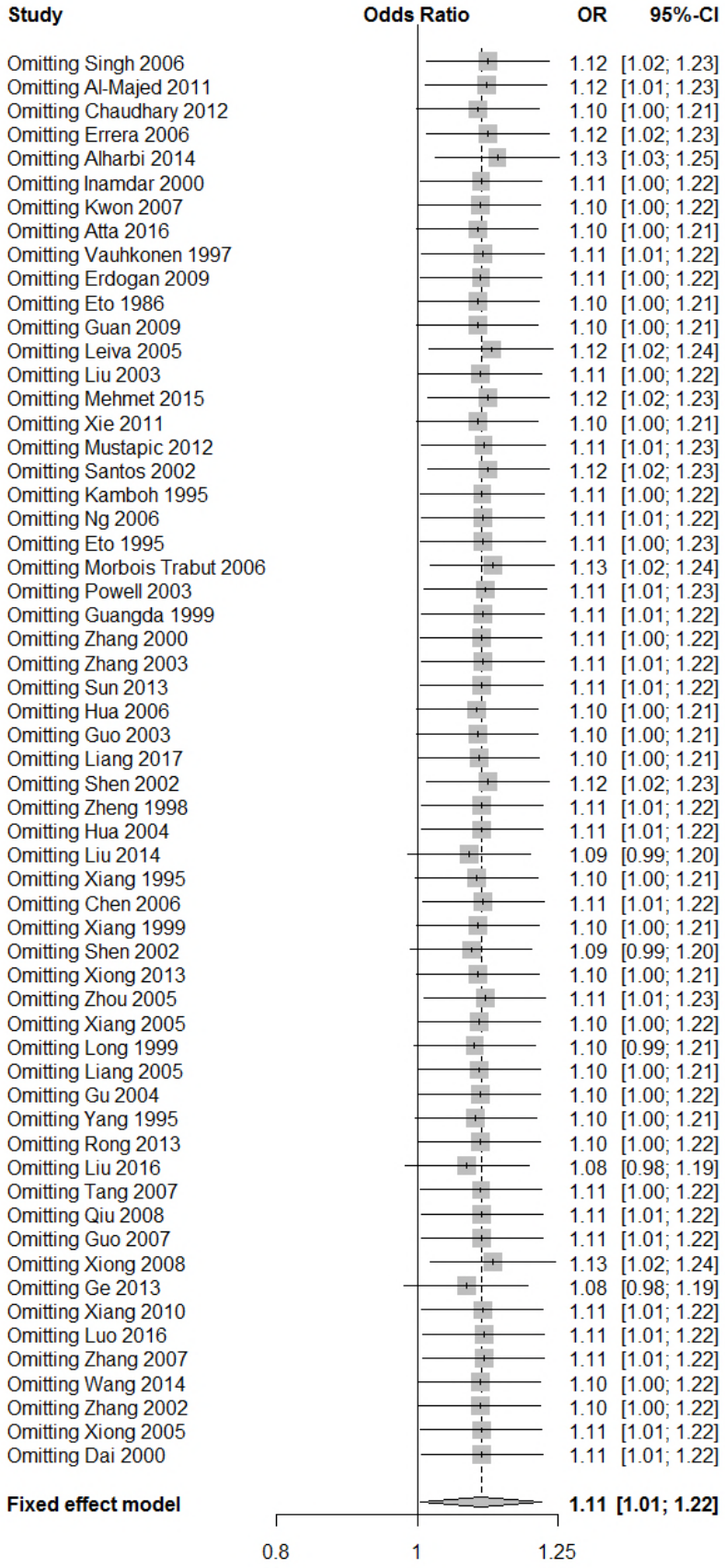
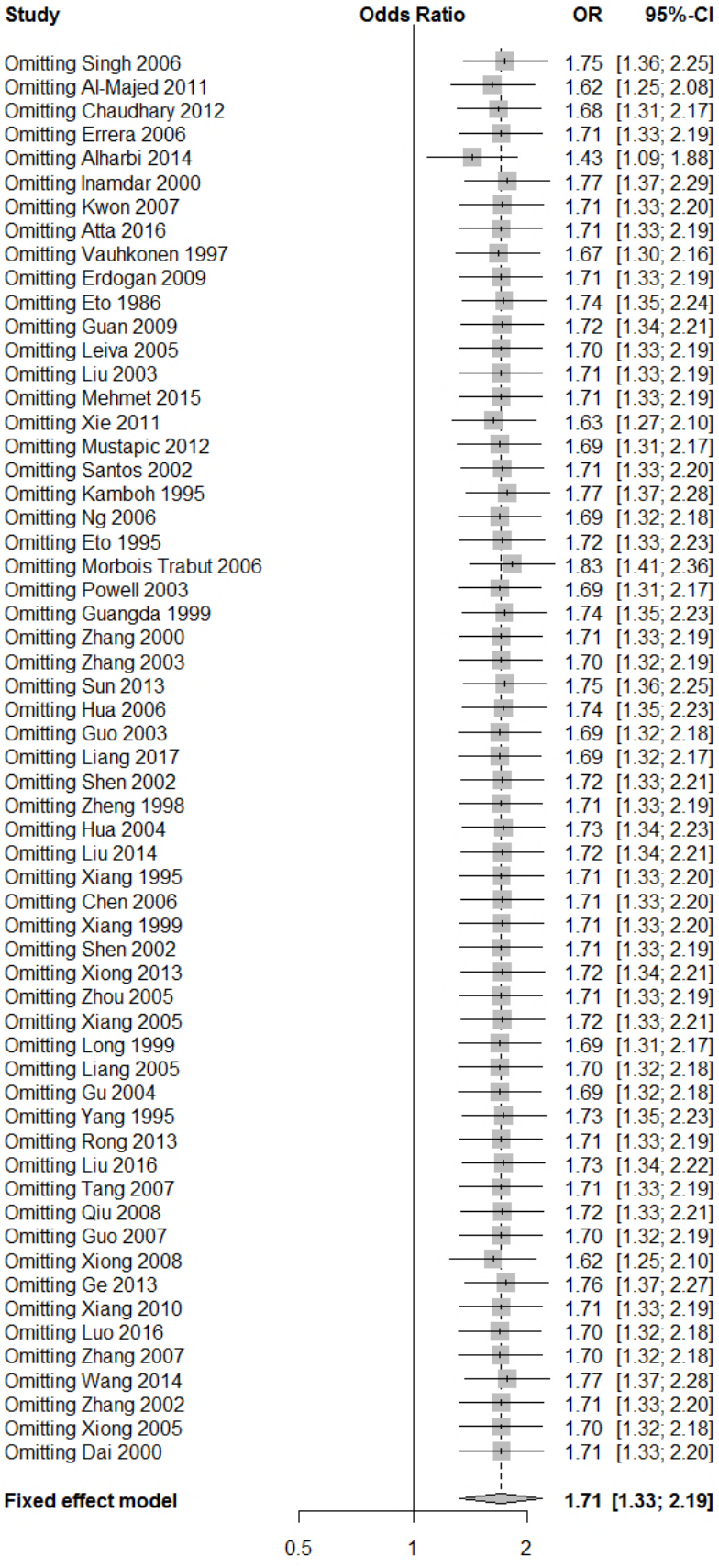
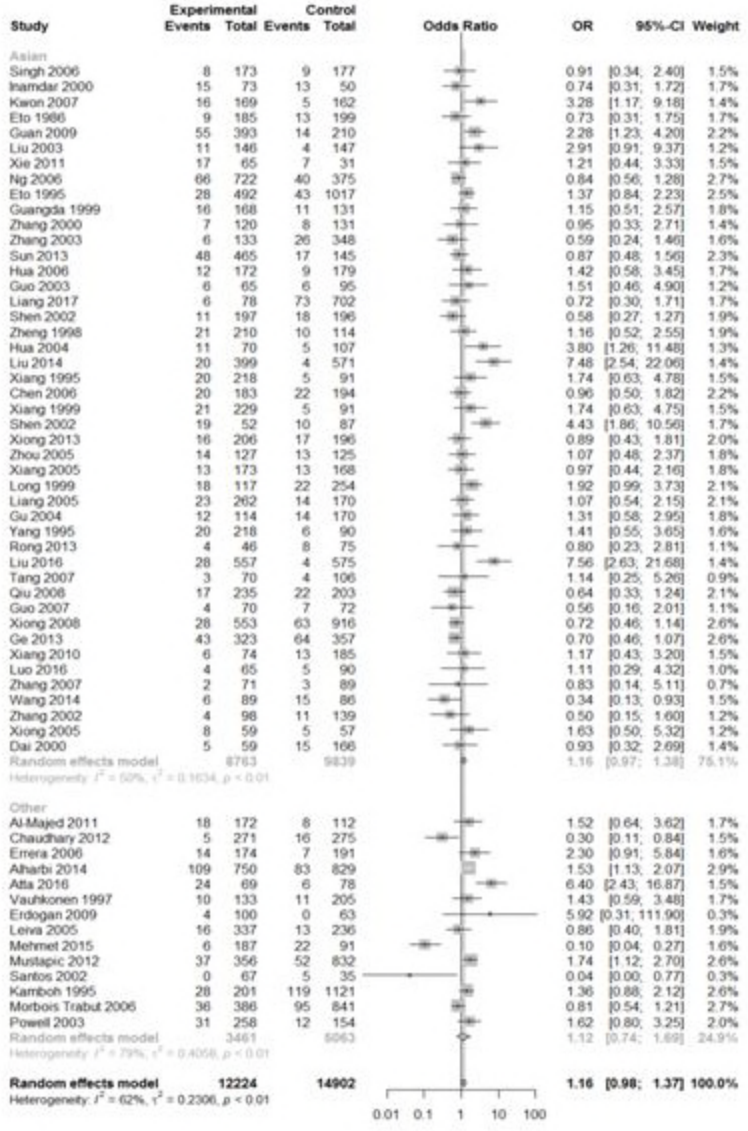
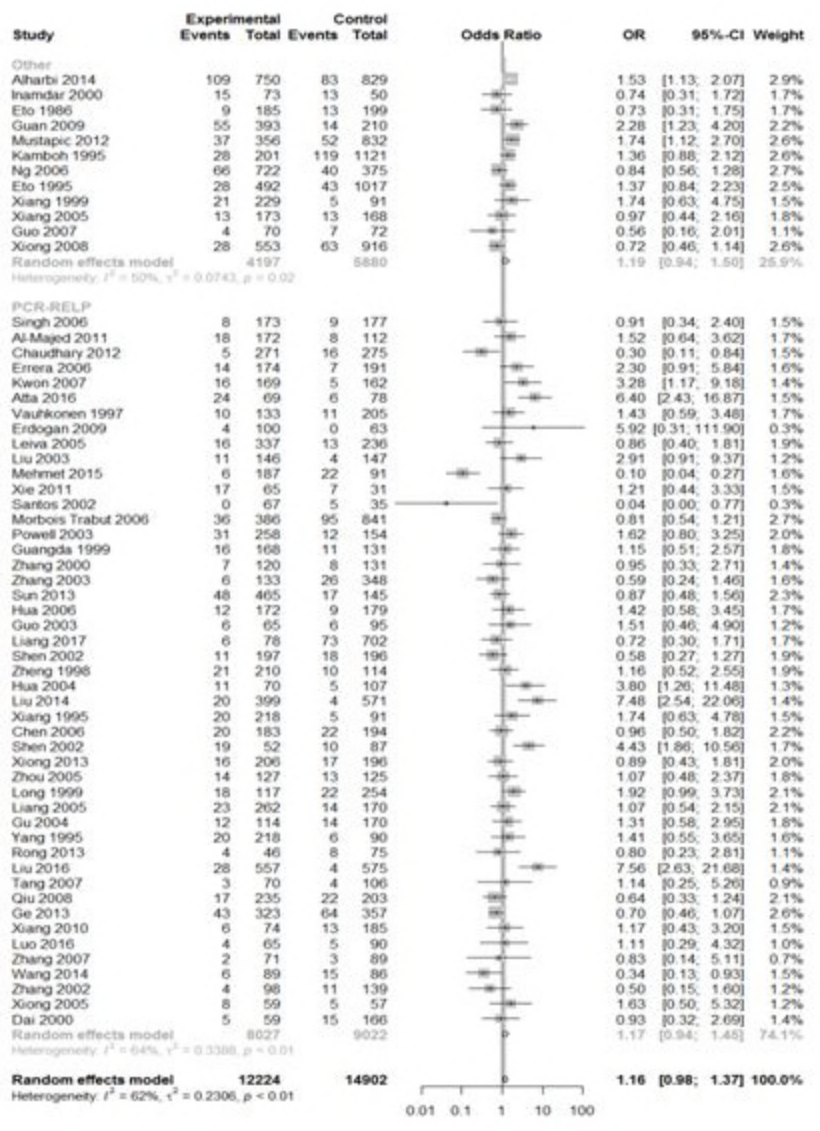
1.5


Study
Odds Ratio
OR
95%-CI
Omitting Singh 2006 1.12 [1.02; 1.23]
Omitting Al-Majed 2011 1.12 [1.01; 1.23]
Omitting Chaudhary 2012 1.10 [1.00; 1.21]
Omitting Errera 2006 1.12 [1.02; 1.23]
Omitting Alharbi 2014 1.13 [1.03; 1.25]
Omitting Inamdar 2000 1.11 [1.00; 1.22]
Omitting Kwon 2007 1.10 [1.00; 1.22]
Omitting Atta 2016 1.10 [1.00; 1.21]
Omitting Vauhkonen 1997 1.11 [1.01; 1.22]
Omitting Erdogan 2009 1.11 [1.00; 1.22]
Omitting Eto 1986 1.10 [1.00; 1.21]
Omitting Guan 2009 1.10 [1.00; 1.21]
Omitting Leiva 2005 1.12 [1.02; 1.24]
Omitting Liu 2003 1.11 [1.00; 1.22]
Omitting Mehmet 2015 1.12 [1.02; 1.23]
Omitting Xie 2011 1.10 [1.00; 1.21]
Omitting Mustapic 2012 1.11 [1.01; 1.23]
Omitting Santos 2002 1.12 [1.02; 1.23]
Omitting Kamboh 1995 1.11 [1.00; 1.22]
Omitting Ng 2006 1.11 [1.01; 1.22]
Omitting Eto 1995 1.11 [1.00; 1.23]
Omitting Morbois Trabut 2006 1.13 [1.02; 1.24]
Omitting Powell 2003 1.11 [1.01; 1.23]
Omitting Guangda 1999 1.11 [1.01; 1.22]
Omitting Zhang 2000 1.11 [1.00; 1.22]
Omitting Zhang 2003 1.11 [1.01; 1.22]
Omitting Sun 2013 1.11 [1.01; 1.22]
Omitting Hua 2006 1.10 [1.00; 1.21]
Omitting Guo 2003 1.10 [1.00; 1.21]
Omitting Liang 2017 1.10 [1.00; 1.21]
Omitting Shen 2002 1.12 [1.02; 1.23]
Omitting Zheng 1998 1.11 [1.01; 1.22]
Omitting Hua 2004 1.11 [1.01; 1.22]
Omitting Liu 2014 1.09 [0.99; 1.20]
Omitting Xiang 1995 1.10 [1.00; 1.21]
Omitting Chen 2006 1.11 [1.01; 1.22]
Omitting Xiang 1999 1.10 [1.00; 1.21]
Omitting Shen 2002 1.09 [0.99; 1.20]
Omitting Xiong 2013 1.10 [1.00; 1.21]
Omitting Zhou 2005 1.11 [1.01; 1.23]
Omitting Xiang 2005 1.10 [1.00; 1.22]
Omitting Long 1999 1.10 [0.99; 1.21]
Omitting Liang 2005 1.10 [1.00; 1.21]
Omitting Gu 2004 1.10 [1.00; 1.22]
Omitting Yang 1995 1.10 [1.00; 1.21]
Omitting Rong 2013 1.10 [1.00; 1.22]
Omitting Liu 2016 1.08 [0.98; 1.19]
Omitting Tang 2007 1.11 [1.00; 1.22]
Omitting Qiu 2008 1.11 [1.01; 1.22]
Omitting Guo 2007 1.11 [1.01; 1.22]
Omitting Xiong 2008 1.13 [1.02; 1.24]
Omitting Ge 2013 1.08 [0.98; 1.19]
Omitting Xiang 2010 1.11 [1.01; 1.22]
Omitting Luo 2016 1.11 [1.01; 1.22]
Omitting Zhang 2007 1.11 [1.01; 1.22]
Omitting Wang 2014 1.10 [1.00; 1.22]
Omitting Zhang 2002 1.10 [1.00; 1.22]
Omitting Xiong 2005 1.11 [1.01; 1.22]
Omitting Dai 2000 1.11 [1.01; 1.22]
Fixed effect model 1.11 [1.01; 1.22]
0.8
1
1.25

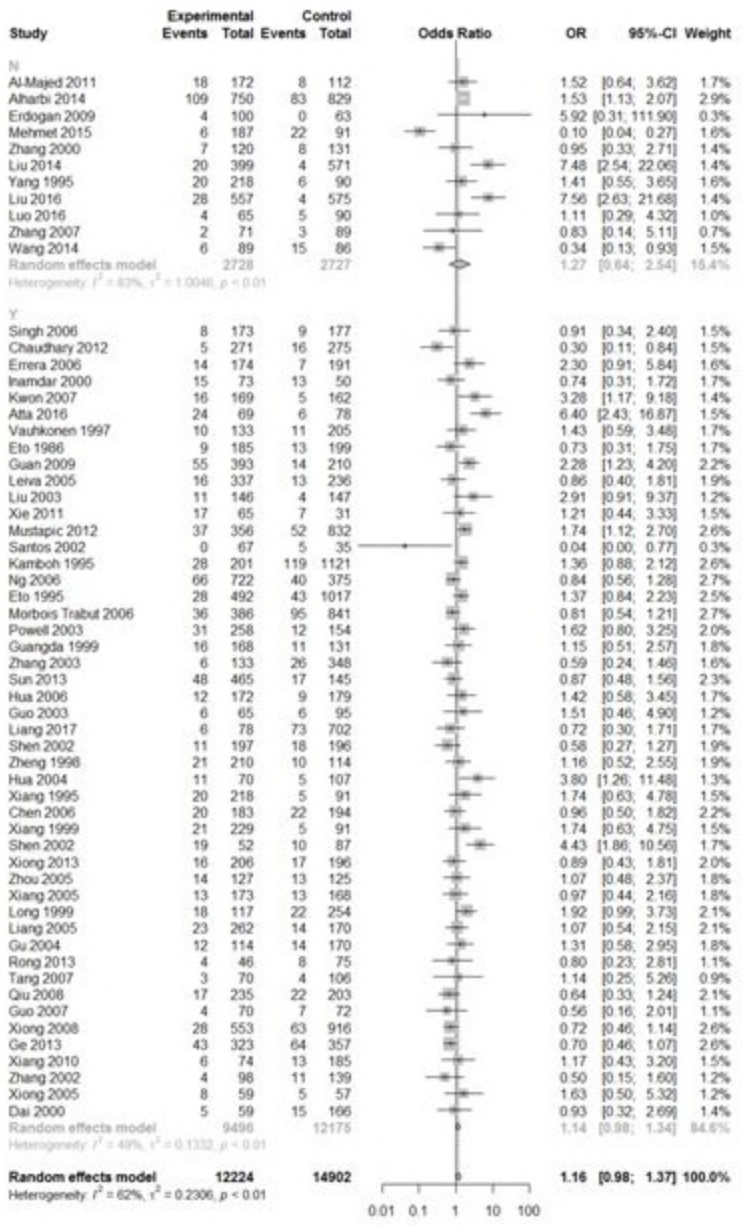

Study
Odds Ratio
OR
95%-CI
Omitting Singh 2006 1.75 [1.36; 2.25]
Omitting Al-Majed 2011 1.62 [1.25; 2.08]
Omitting Chaudhary 2012 1.68 [1.31; 2.17]
Omitting Errera 2006 1.71 [1.33; 2.19]
Omitting Alharbi 2014 1.43 [1.09; 1.88]
Omitting Inamdar 2000 1.77 [1.37; 2.29]
Omitting Kwon 2007 1.71 [1.33; 2.20]
Omitting Atta 2016 1.71 [1.33; 2.19]
Omitting Vauhkonen 1997 1.67 [1.30; 2.16]
Omitting Erdogan 2009 1.71 [1.33; 2.19]
Omitting Eto 1986 1.74 [1.35; 2.24]
Omitting Guan 2009 1.72 [1.34; 2.21]
Omitting Leiva 2005 1.70 [1.33; 2.19]
Omitting Liu 2003 1.71 [1.33; 2.19]
Omitting Mehmet 2015 1.71 [1.33; 2.19]
Omitting Xie 2011 1.63 [1.27; 2.10]
Omitting Mustapic 2012 1.69 [1.31; 2.17]
Omitting Santos 2002 1.71 [1.33; 2.20]
Omitting Kamboh 1995 1.77 [1.37; 2.28]
Omitting Ng 2006 1.69 [1.32; 2.18]
Omitting Eto 1995 1.72 [1.33; 2.23]
Omitting Morbois Trabut 2006 1.83 [1.41; 2.36]
Omitting Powell 2003 1.69 [1.31; 2.17]
Omitting Guangda 1999 1.74 [1.35; 2.23]
Omitting Zhang 2000 1.71 [1.33; 2.19]
Omitting Zhang 2003 1.70 [1.32; 2.19]
Omitting Sun 2013 1.75 [1.36; 2.25]
Omitting Hua 2006 1.74 [1.35; 2.23]
Omitting Guo 2003 1.69 [1.32; 2.18]
Omitting Liang 2017 1.69 [1.32; 2.17]
Omitting Shen 2002 1.72 [1.33; 2.21]
Omitting Zheng 1998 1.71 [1.33; 2.19]
Omitting Hua 2004 1.73 [1.34; 2.23]
Omitting Liu 2014 1.72 [1.34; 2.21]
Omitting Xiang 1995 1.71 [1.33; 2.20]
Omitting Chen 2006 1.71 [1.33; 2.20]
Omitting Xiang 1999 1.71 [1.33; 2.20]
Omitting Shen 2002 1.71 [1.33; 2.19]
Omitting Xiong 2013 1.72 [1.34; 2.21]
Omitting Zhou 2005 1.71 [1.33; 2.19]
Omitting Xiang 2005 1.72 [1.33; 2.21]
Omitting Long 1999 1.69 [1.31; 2.17]
Omitting Liang 2005 1.70 [1.32; 2.18]
Omitting Gu 2004 1.69 [1.32; 2.18]
Omitting Yang 1995 1.73 [1.35; 2.23]
Omitting Rong 2013 1.71 [1.33; 2.19]
Omitting Liu 2016 1.73 [1.34; 2.22]
Omitting Tang 2007 1.71 [1.33; 2.19]
Omitting Qiu 2008 1.72 [1.33; 2.21]
Omitting Guo 2007 1.70 [1.32; 2.19]
Omitting Xiong 2008 1.62 [1.25; 2.10]
Omitting Ge 2013 1.76 [1.37; 2.27]
Omitting Xiang 2010 1.71 [1.33; 2.19]
Omitting Luo 2016 1.70 [1.32; 2.18]
Omitting Zhang 2007 1.70 [1.32; 2.18]
Omitting Wang 2014 1.77 [1.37; 2.28]
Omitting Zhang 2002 1.71 [1.33; 2.20]
Omitting Xiong 2005 1.70 [1.32; 2.18]
Omitting Dai 2000 1.71 [1.33; 2.20]
Fixed effect model 1.71 [1.33; 2.19]
0.5
1
2


Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI Weight
Asian
Singh 2006 8 173 9 177 0.91 [0.34; 2.40] 1.5%
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%
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%
Liu 2003 11 146 4 147 2.91 [0.91; 9.37] 1.2%
Xie 2011 17 65 7 31 1.21 [0.44; 3.33] 1.5%
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%
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 8763 9839 1.16 [0.97; 1.38] 75.1%
Heterogeneity: I^2 = 50%, τ^2 = 0.1634, p < 0.01
Other
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%
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%
Leiva 2005 16 337 13 236 0.86 [0.40; 1.81] 1.9%
Mehmet 2015 6 187 22 91 0.10 [0.04; 0.27] 1.6%
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%
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%
Random effects model 3461 5063 1.12 [0.74; 1.69] 24.9%
Heterogeneity: I^2 = 79%, τ^2 = 0.4058, p < 0.01
Random effects model 12224 14902 1.16 [0.98; 1.37] 100.0%
Heterogeneity: I^2 = 62%, τ^2 = 0.2306, p < 0.01
0.01 0.1 1 10 100

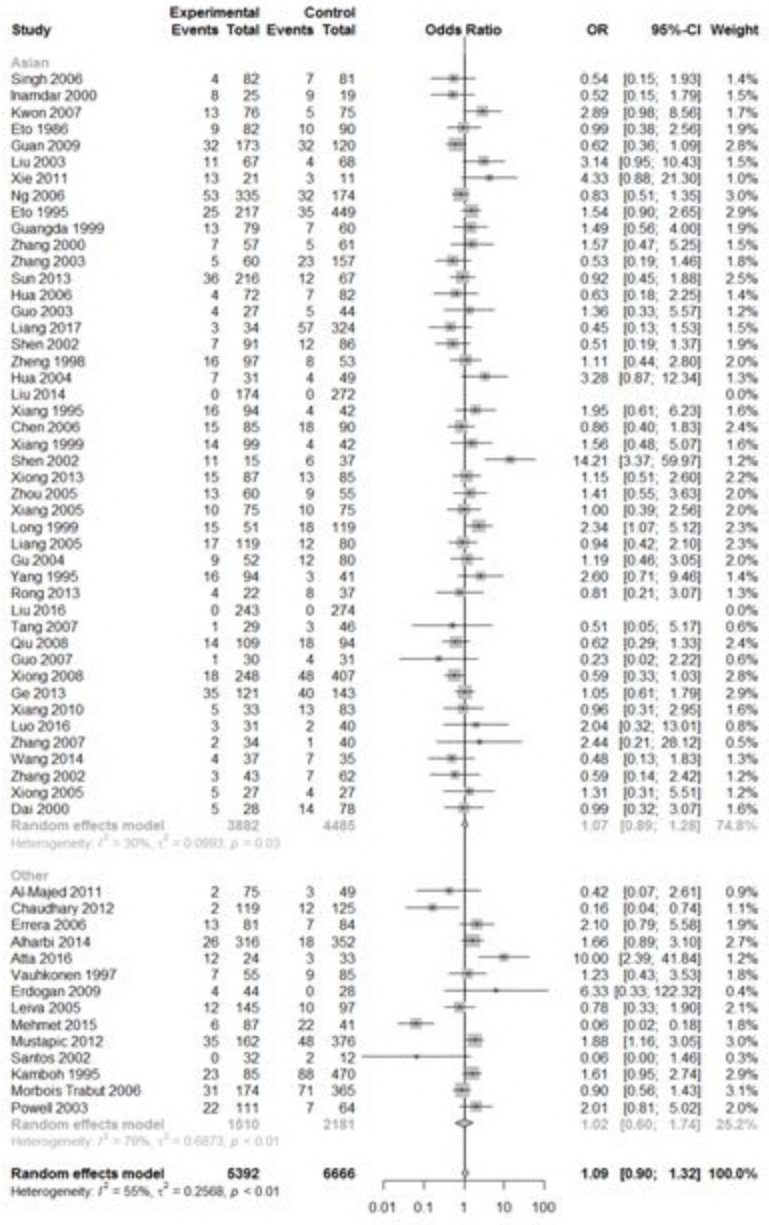
A


Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI Weight
Other
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%
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%
Mustapic 2012 37 356 52 832 1.74 [1.12; 2.70] 2.6%
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%
Xiang 1999 21 229 5 91 1.74 [0.63; 4.75] 1.5%
Xiang 2005 13 173 13 168 0.97 [0.44; 2.16] 1.8%
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%
Random effects model 4197 5880 1.19 [0.94; 1.50] 25.9%
Heterogeneity: I^2 = 50%, τ^2 = 0.0743, p = 0.02
PCR-RELP
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%
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%
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%
Santos 2002 0 67 5 35 0.04 [0.00; 0.77] 0.3%
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%
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%
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%
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 8027 9022 1.17 [0.94; 1.45] 74.1%
Heterogeneity: I^2 = 64%, τ^2 = 0.3388, p < 0.01
Random effects model 12224 14902 1.16 [0.98; 1.37] 100.0%
Heterogeneity: I^2 = 62%, τ^2 = 0.2306, p < 0.01
0.01 0.1 1 10 100

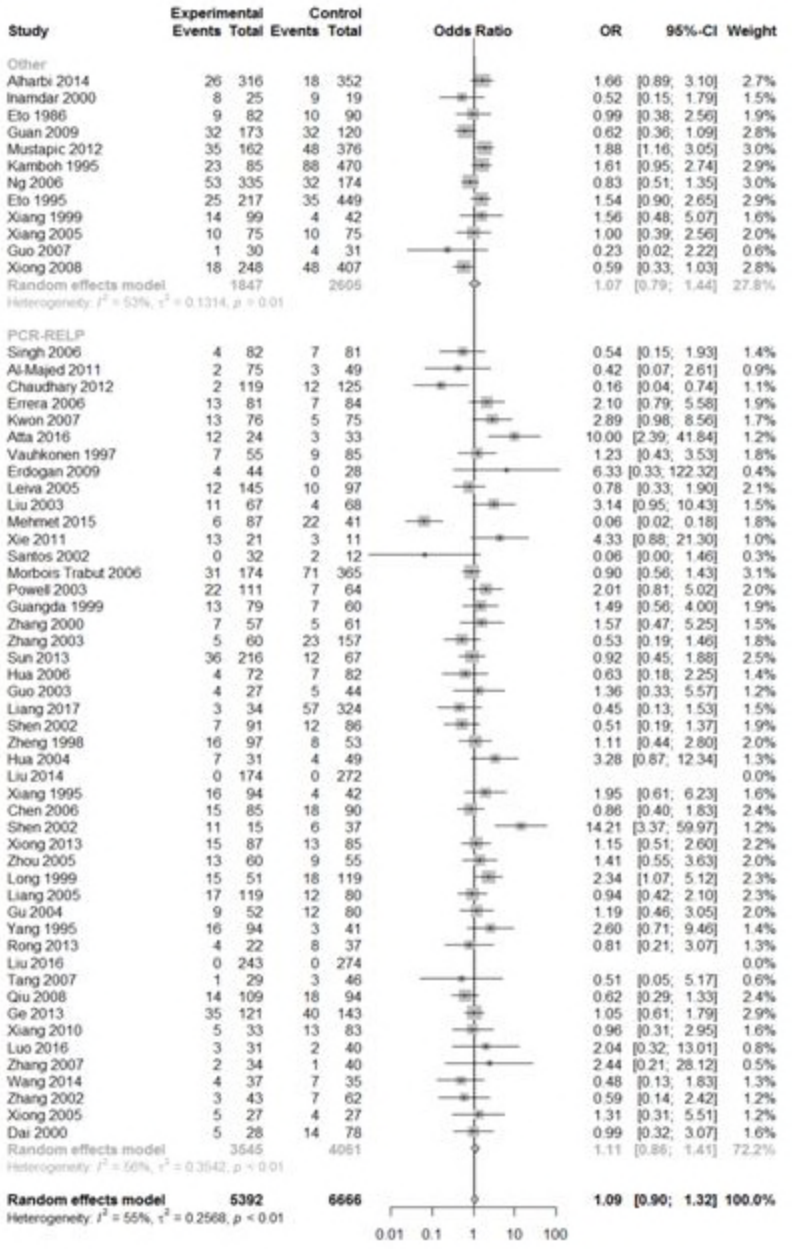
B


Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI Weight
N
Al-Majed 2011 18 172 8 112 1.52 [0.64; 3.62] 1.7%
Alharbi 2014 109 750 83 829 1.53 [1.13; 2.07] 2.9%
Erdogan 2009 4 100 0 63 5.92 [0.31; 111.90] 0.3%
Mehmet 2015 6 187 22 91 0.10 [0.04; 0.27] 1.6%
Zhang 2000 7 120 8 131 0.95 [0.33; 2.71] 1.4%
Liu 2014 20 399 4 571 7.48 [2.54; 22.06] 1.4%
Yang 1995 20 218 6 90 1.41 [0.55; 3.65] 1.6%
Liu 2016 28 557 4 575 7.56 [2.63; 21.68] 1.4%
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%
Random effects model 2728 2727 1.27 [0.64; 2.54] 15.4%
Heterogeneity: I^2 = 83%, τ^2 = 1.0046, p < 0.01
Y
Singh 2006 8 173 9 177 0.91 [0.34; 2.40] 1.5%
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%
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%
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%
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 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%
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%
Rong 2013 4 46 8 75 0.80 [0.23; 2.81] 1.1%
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%
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 9496 12175 1.14 [0.98; 1.34] 84.6%
Heterogeneity: I^2 = 49%, τ^2 = 0.1332, p < 0.01
Random effects model 12224 14902 1.16 [0.98; 1.37] 100.0%
Heterogeneity: I^2 = 62%, τ^2 = 0.2306, p < 0.01
0.01 0.1 1 10 100

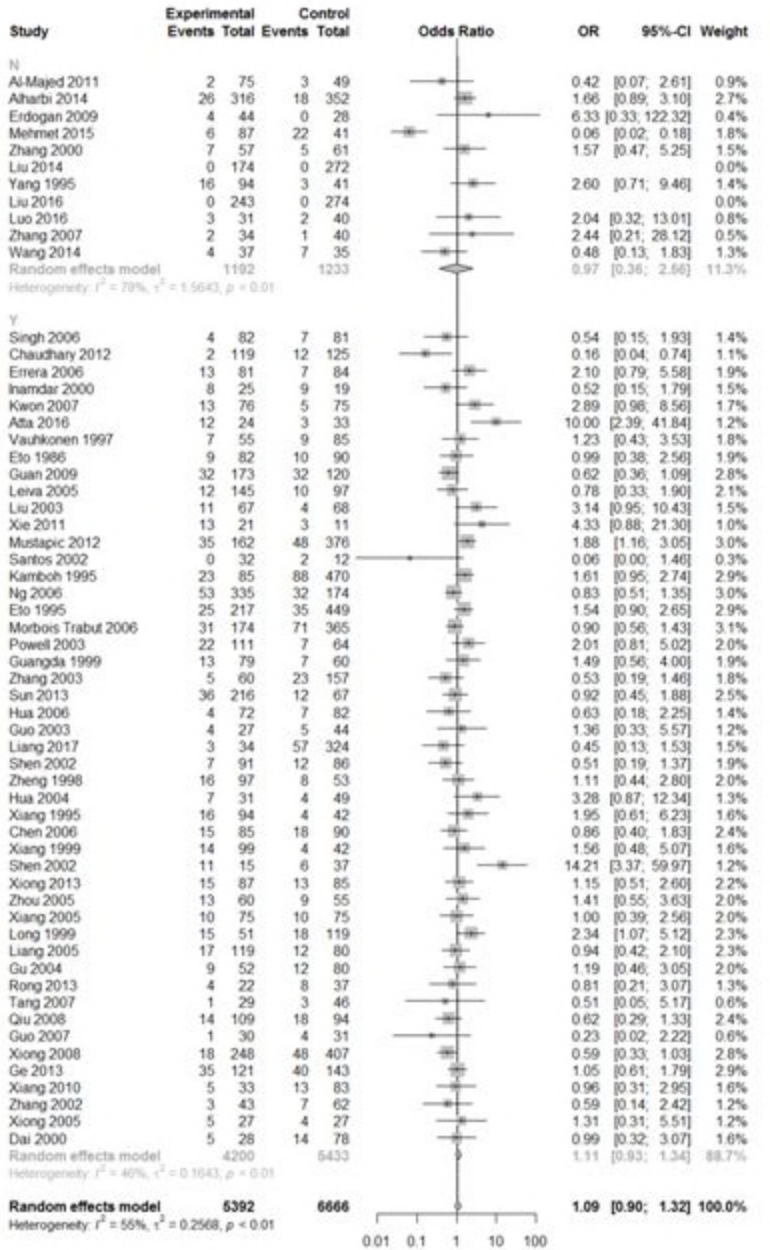
A


Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI Weight
Asian
Singh 2006 4 82 7 81 0.54 [0.15; 1.93] 1.4%
Inamdar 2000 8 25 9 19 0.52 [0.15; 1.79] 1.5%
Kwon 2007 13 76 5 75 2.89 [0.98; 8.56] 1.7%
Eto 1986 9 82 10 90 0.99 [0.38; 2.56] 1.9%
Guan 2009 32 173 32 120 0.62 [0.36; 1.09] 2.8%
Liu 2003 11 67 4 68 3.14 [0.95; 10.43] 1.5%
Xie 2011 13 21 3 11 4.33 [0.88; 21.30] 1.0%
Ng 2006 53 335 32 174 0.83 [0.51; 1.35] 3.0%
Eto 1995 25 217 35 449 1.54 [0.90; 2.65] 2.9%
Guangda 1999 13 79 7 60 1.49 [0.56; 4.00] 1.9%
Zhang 2000 7 57 5 61 1.57 [0.47; 5.25] 1.5%
Zhang 2003 5 60 23 157 0.53 [0.19; 1.46] 1.8%
Sun 2013 36 216 12 67 0.92 [0.45; 1.88] 2.5%
Hua 2006 4 72 7 82 0.63 [0.18; 2.25] 1.4%
Guo 2003 4 27 5 44 1.36 [0.33; 5.57] 1.2%
Liang 2017 3 34 57 324 0.45 [0.13; 1.53] 1.5%
Shen 2002 7 91 12 86 0.51 [0.19; 1.37] 1.9%
Zheng 1998 16 97 8 53 1.11 [0.44; 2.80] 2.0%
Hua 2004 7 31 4 49 3.28 [0.87; 12.34] 1.3%
Liu 2014 0 174 0 272 0.0%
Xiang 1995 16 94 4 42 1.95 [0.61; 6.23] 1.6%
Chen 2006 15 85 18 90 0.86 [0.40; 1.83] 2.4%
Xiang 1999 14 99 4 42 1.56 [0.48; 5.07] 1.6%
Shen 2002 11 15 6 37 14.21 [3.37; 59.97] 1.2%
Xiong 2013 15 87 13 85 1.15 [0.51; 2.60] 2.2%
Zhou 2005 13 60 9 55 1.41 [0.55; 3.63] 2.0%
Xiang 2005 10 75 10 75 1.00 [0.39; 2.56] 2.0%
Long 1999 15 51 18 119 2.34 [1.07; 5.12] 2.3%
Liang 2005 17 119 12 80 0.94 [0.42; 2.10] 2.3%
Gu 2004 9 52 12 80 1.19 [0.46; 3.05] 2.0%
Yang 1995 16 94 3 41 2.60 [0.71; 9.46] 1.4%
Rong 2013 4 22 8 37 0.81 [0.21; 3.07] 1.3%
Liu 2016 0 243 0 274 0.0%
Tang 2007 1 29 3 46 0.51 [0.05; 5.17] 0.6%
Qiu 2008 14 109 18 94 0.62 [0.29; 1.33] 2.4%
Guo 2007 1 30 4 31 0.23 [0.02; 2.22] 0.6%
Xiong 2008 18 248 48 407 0.59 [0.33; 1.03] 2.8%
Ge 2013 35 121 40 143 1.05 [0.61; 1.79] 2.9%
Xiang 2010 5 33 13 83 0.96 [0.31; 2.95] 1.6%
Luo 2016 3 31 2 40 2.04 [0.32; 13.01] 0.8%
Zhang 2007 2 34 1 40 2.44 [0.21; 28.12] 0.5%
Wang 2014 4 37 7 35 0.48 [0.13; 1.83] 1.3%
Zhang 2002 3 43 7 62 0.59 [0.14; 2.42] 1.2%
Xiong 2005 5 27 4 27 1.31 [0.31; 5.51] 1.2%
Dai 2000 5 28 14 78 0.99 [0.32; 3.07] 1.6%
Random effects model 3882 4485 1.07 [0.89; 1.28] 74.8%
Heterogeneity: I^2 = 30%, τ^2 = 0.0993, p = 0.03
Other
Al-Majed 2011 2 75 3 49 0.42 [0.07; 2.61] 0.9%
Chaudhary 2012 2 119 12 125 0.16 [0.04; 0.74] 1.1%
Errera 2006 13 81 7 84 2.10 [0.79; 5.58] 1.9%
Alharbi 2014 26 316 18 352 1.66 [0.89; 3.10] 2.7%
Atta 2016 12 24 3 33 10.00 [2.39; 41.84] 1.2%
Vauhkonen 1997 7 55 9 85 1.23 [0.43; 3.53] 1.8%
Erdogan 2009 4 44 0 28 6.33 [0.33; 122.32] 0.4%
Leiva 2005 12 145 10 97 0.78 [0.33; 1.90] 2.1%
Mehmet 2015 6 87 22 41 0.06 [0.02; 0.18] 1.8%
Mustapic 2012 35 162 48 376 1.88 [1.16; 3.05] 3.0%
Santos 2002 0 32 2 12 0.06 [0.00; 1.46] 0.3%
Kamboh 1995 23 85 88 470 1.61 [0.95; 2.74] 2.9%
Morbois Trabut 2006 31 174 71 365 0.90 [0.56; 1.43] 3.1%
Powell 2003 22 111 7 64 2.01 [0.81; 5.02] 2.0%
Random effects model 1510 2181 1.02 [0.60; 1.74] 25.2%
Heterogeneity: I^2 = 79%, τ^2 = 0.6873, p < 0.01
Random effects model 5392 6666 1.09 [0.90; 1.32] 100.0%
Heterogeneity: I^2 = 55%, τ^2 = 0.2568, p < 0.01
0.01 0.1 1 10 100

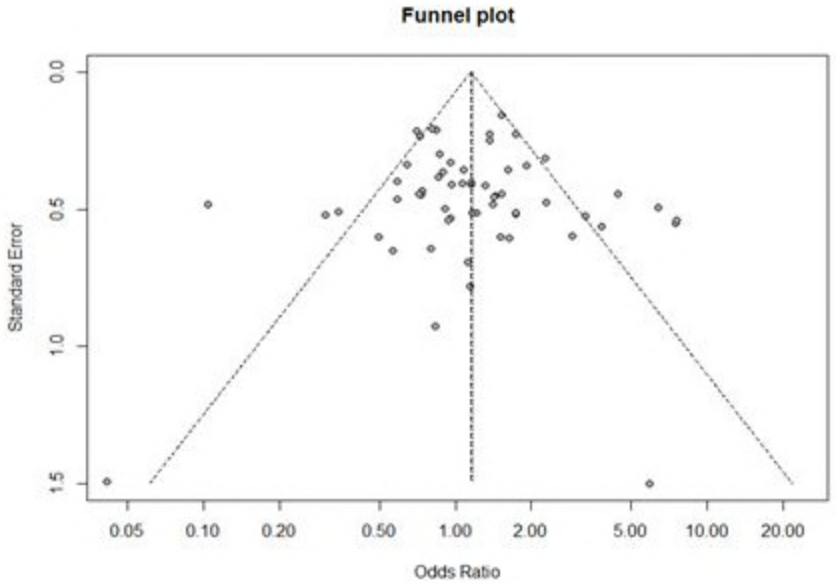
B


Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI Weight
Other
Alharbi 2014 26 316 18 352 1.66 [0.89; 3.10] 2.7%
Inamdar 2000 8 25 9 19 0.52 [0.15; 1.79] 1.5%
Eto 1986 9 82 10 90 0.99 [0.38; 2.56] 1.9%
Guan 2009 32 173 32 120 0.62 [0.36; 1.09] 2.8%
Mustapic 2012 35 162 48 376 1.88 [1.16; 3.05] 3.0%
Kamboh 1995 23 85 88 470 1.61 [0.95; 2.74] 2.9%
Ng 2006 53 335 32 174 0.83 [0.51; 1.35] 3.0%
Eto 1995 25 217 35 449 1.54 [0.90; 2.65] 2.9%
Xiang 1999 14 99 4 42 1.56 [0.48; 5.07] 1.6%
Xiang 2005 10 75 10 75 1.00 [0.39; 2.56] 2.0%
Guo 2007 1 30 4 31 0.23 [0.02; 2.22] 0.6%
Xiong 2008 18 248 48 407 0.59 [0.33; 1.03] 2.8%
Random effects model 1847 2605 1.07 [0.79; 1.44] 27.8%
Heterogeneity: I^2 = 53%, τ^2 = 0.1314, p = 0.01
PCR-RELP
Singh 2006 4 82 7 81 0.54 [0.15; 1.93] 1.4%
Al-Majed 2011 2 75 3 49 0.42 [0.07; 2.61] 0.9%
Chaudhary 2012 2 119 12 125 0.16 [0.04; 0.74] 1.1%
Errera 2006 13 81 7 84 2.10 [0.79; 5.58] 1.9%
Kwon 2007 13 76 5 75 2.89 [0.98; 8.56] 1.7%
Atta 2016 12 24 3 33 10.00 [2.39; 41.84] 1.2%
Vauhkonen 1997 7 55 9 85 1.23 [0.43; 3.53] 1.8%
Erdogan 2009 4 44 0 28 6.33 [0.33; 122.32] 0.4%
Leiva 2005 12 145 10 97 0.78 [0.33; 1.90] 2.1%
Liu 2003 11 67 4 68 3.14 [0.95; 10.43] 1.5%
Mehmet 2015 6 87 22 41 0.06 [0.02; 0.18] 1.8%
Xie 2011 13 21 3 11 4.33 [0.88; 21.30] 1.0%
Santos 2002 0 32 2 12 0.06 [0.00; 1.46] 0.3%
Morbois Trabut 2006 31 174 71 365 0.90 [0.56; 1.43] 3.1%
Powell 2003 22 111 7 64 2.01 [0.81; 5.02] 2.0%
Guangda 1999 13 79 7 60 1.49 [0.56; 4.00] 1.9%
Zhang 2000 7 57 5 61 1.57 [0.47; 5.25] 1.5%
Zhang 2003 5 60 23 157 0.53 [0.19; 1.46] 1.8%
Sun 2013 36 216 12 67 0.92 [0.45; 1.88] 2.5%
Hua 2006 4 72 7 82 0.63 [0.18; 2.25] 1.4%
Guo 2003 4 27 5 44 1.36 [0.33; 5.57] 1.2%
Liang 2017 3 34 57 324 0.45 [0.13; 1.53] 1.5%
Shen 2002 7 91 12 86 0.51 [0.19; 1.37] 1.9%
Zheng 1998 16 97 8 53 1.11 [0.44; 2.80] 2.0%
Hua 2004 7 31 4 49 3.28 [0.87; 12.34] 1.3%
Liu 2014 0 174 0 272 0.0%
Xiang 1995 16 94 4 42 1.95 [0.61; 6.23] 1.6%
Chen 2006 15 85 18 90 0.86 [0.40; 1.83] 2.4%
Shen 2002 11 15 6 37 14.21 [3.37; 59.97] 1.2%
Xiong 2013 15 87 13 85 1.15 [0.51; 2.60] 2.2%
Zhou 2005 13 60 9 55 1.41 [0.55; 3.63] 2.0%
Long 1999 15 51 18 119 2.34 [1.07; 5.12] 2.3%
Liang 2005 17 119 12 80 0.94 [0.42; 2.10] 2.3%
Gu 2004 9 52 12 80 1.19 [0.46; 3.05] 2.0%
Yang 1995 16 94 3 41 2.60 [0.71; 9.46] 1.4%
Rong 2013 4 22 8 37 0.81 [0.21; 3.07] 1.3%
Liu 2016 0 243 0 274 0.0%
Tang 2007 1 29 3 46 0.51 [0.05; 5.17] 0.6%
Qiu 2008 14 109 18 94 0.62 [0.29; 1.33] 2.4%
Ge 2013 35 121 40 143 1.05 [0.61; 1.79] 2.9%
Xiang 2010 5 33 13 83 0.96 [0.31; 2.95] 1.6%
Luo 2016 3 31 2 40 2.04 [0.32; 13.01] 0.8%
Zhang 2007 2 34 1 40 2.44 [0.21; 28.12] 0.5%
Wang 2014 4 37 7 35 0.48 [0.13; 1.83] 1.3%
Zhang 2002 3 43 7 62 0.59 [0.14; 2.42] 1.2%
Xiong 2005 5 27 4 27 1.31 [0.31; 5.51] 1.2%
Dai 2000 5 28 14 78 0.99 [0.32; 3.07] 1.6%
Random effects model 3545 4061 1.11 [0.86; 1.41] 72.2%
Heterogeneity: I^2 = 56%, τ^2 = 0.3542, p < 0.01
Random effects model 5392 6666 1.09 [0.90; 1.32] 100.0%
Heterogeneity: I^2 = 55%, τ^2 = 0.2568, p < 0.01
0.01 0.1 1 10 100

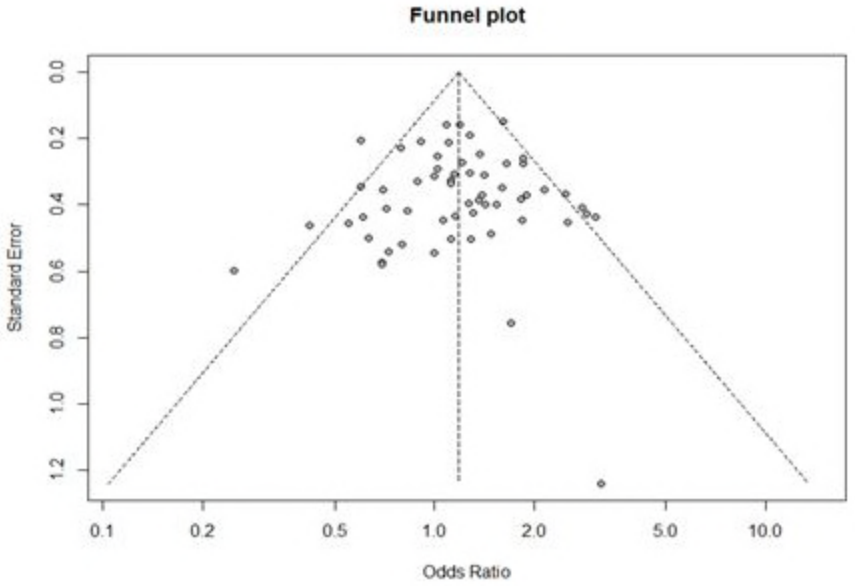
A


Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI Weight
N
Al-Majed 2011 2 75 3 49 0.42 [0.07; 2.61] 0.9%
Alharbi 2014 26 316 18 352 1.66 [0.89; 3.10] 2.7%
Erdogan 2009 4 44 0 28 6.33 [0.33; 122.32] 0.4%
Mehmet 2015 6 87 22 41 0.06 [0.02; 0.18] 1.8%
Zhang 2000 7 57 5 61 1.57 [0.47; 5.25] 1.5%
Liu 2014 0 174 0 272 0.0%
Yang 1995 16 94 3 41 2.60 [0.71; 9.46] 1.4%
Liu 2016 0 243 0 274 0.0%
Luo 2016 3 31 2 40 2.04 [0.32; 13.01] 0.8%
Zhang 2007 2 34 1 40 2.44 [0.21; 28.12] 0.5%
Wang 2014 4 37 7 35 0.48 [0.13; 1.83] 1.3%
Random effects model 1192 1233 0.97 [0.36; 2.56] 11.3%
Heterogeneity: I^2 = 78%, τ^2 = 1.5643, p < 0.01
Y
Singh 2006 4 82 7 81 0.54 [0.15; 1.93] 1.4%
Chaudhary 2012 2 119 12 125 0.16 [0.04; 0.74] 1.1%
Errera 2006 13 81 7 84 2.10 [0.79; 5.58] 1.9%
Inamdar 2000 8 25 9 19 0.52 [0.15; 1.79] 1.5%
Kwon 2007 13 76 5 75 2.89 [0.98; 8.56] 1.7%
Atta 2016 12 24 3 33 10.00 [2.39; 41.84] 1.2%
Vauhkonen 1997 7 55 9 85 1.23 [0.43; 3.53] 1.8%
Eto 1986 9 82 10 90 0.99 [0.38; 2.56] 1.9%
Guan 2009 32 173 32 120 0.62 [0.36; 1.09] 2.8%
Leiva 2005 12 145 10 97 0.78 [0.33; 1.90] 2.1%
Liu 2003 11 67 4 68 3.14 [0.95; 10.43] 1.5%
Xie 2011 13 21 3 11 4.33 [0.88; 21.30] 1.0%
Mustapic 2012 35 162 48 376 1.88 [1.16; 3.05] 3.0%
Santos 2002 0 32 2 12 0.06 [0.00; 1.46] 0.3%
Kamboh 1995 23 85 88 470 1.61 [0.95; 2.74] 2.9%
Ng 2006 53 335 32 174 0.83 [0.51; 1.35] 3.0%
Eto 1995 25 217 35 449 1.54 [0.90; 2.65] 2.9%
Morbois Trabut 2006 31 174 71 365 0.90 [0.56; 1.43] 3.1%
Powell 2003 22 111 7 64 2.01 [0.81; 5.02] 2.0%
Guangda 1999 13 79 7 60 1.49 [0.56; 4.00] 1.9%
Zhang 2003 5 60 23 157 0.53 [0.19; 1.46] 1.8%
Sun 2013 36 216 12 67 0.92 [0.45; 1.88] 2.5%
Hua 2006 4 72 7 82 0.63 [0.18; 2.25] 1.4%
Guo 2003 4 27 5 44 1.36 [0.33; 5.57] 1.2%
Liang 2017 3 34 57 324 0.45 [0.13; 1.53] 1.5%
Shen 2002 7 91 12 86 0.51 [0.19; 1.37] 1.9%
Zheng 1998 16 97 8 53 1.11 [0.44; 2.80] 2.0%
Hua 2004 7 31 4 49 3.28 [0.87; 12.34] 1.3%
Xiang 1995 16 94 4 42 1.95 [0.61; 6.23] 1.6%
Chen 2006 15 85 18 90 0.86 [0.40; 1.83] 2.4%
Xiang 1999 14 99 4 42 1.56 [0.48; 5.07] 1.6%
Shen 2002 11 15 6 37 14.21 [3.37; 59.97] 1.2%
Xiong 2013 15 87 13 85 1.15 [0.51; 2.60] 2.2%
Zhou 2005 13 60 9 55 1.41 [0.55; 3.63] 2.0%
Xiang 2005 10 75 10 75 1.00 [0.39; 2.56] 2.0%
Long 1999 15 51 18 119 2.34 [1.07; 5.12] 2.3%
Liang 2005 17 119 12 80 0.94 [0.42; 2.10] 2.3%
Gu 2004 9 52 12 80 1.19 [0.46; 3.05] 2.0%
Rong 2013 4 22 8 37 0.81 [0.21; 3.07] 1.3%
Tang 2007 1 29 3 46 0.51 [0.05; 5.17] 0.6%
Qiu 2008 14 109 18 94 0.62 [0.29; 1.33] 2.4%
Guo 2007 1 30 4 31 0.23 [0.02; 2.22] 0.6%
Xiong 2008 18 248 48 407 0.59 [0.33; 1.03] 2.8%
Ge 2013 35 121 40 143 1.05 [0.61; 1.79] 2.9%
Xiang 2010 5 33 13 83 0.96 [0.31; 2.95] 1.6%
Zhang 2002 3 43 7 62 0.59 [0.14; 2.42] 1.2%
Xiong 2005 5 27 4 27 1.31 [0.31; 5.51] 1.2%
Dai 2000 5 28 14 78 0.99 [0.32; 3.07] 1.6%
Random effects model 4200 5433 1.11 [0.93; 1.34] 88.7%
Heterogeneity: I^2 = 46%, τ^2 = 0.1643, p < 0.01
Random effects model 5392 6666 1.09 [0.90; 1.32] 100.0%
Heterogeneity: I^2 = 55%, τ^2 = 0.2568, p < 0.01
0.01 0.1 1 10 100

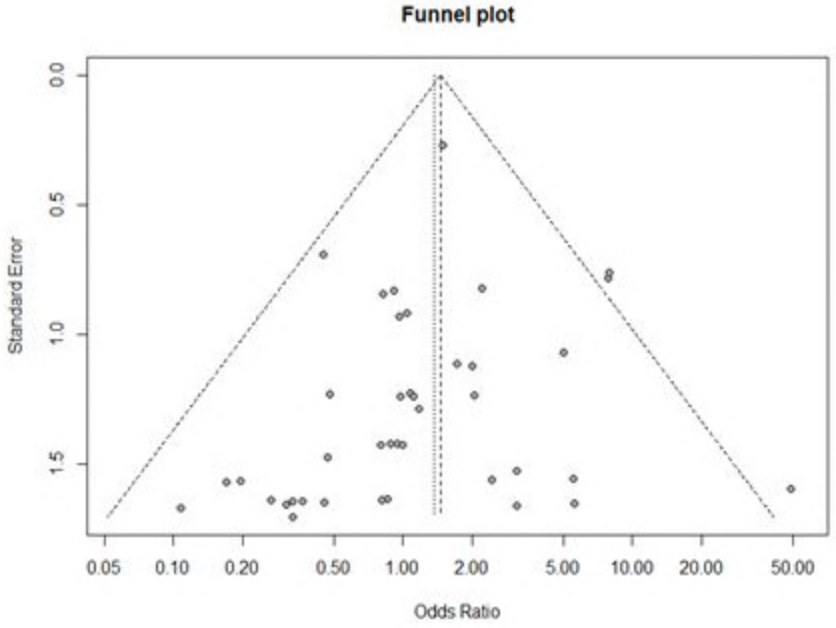
B


Funnel plot
Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
Odds Ratio

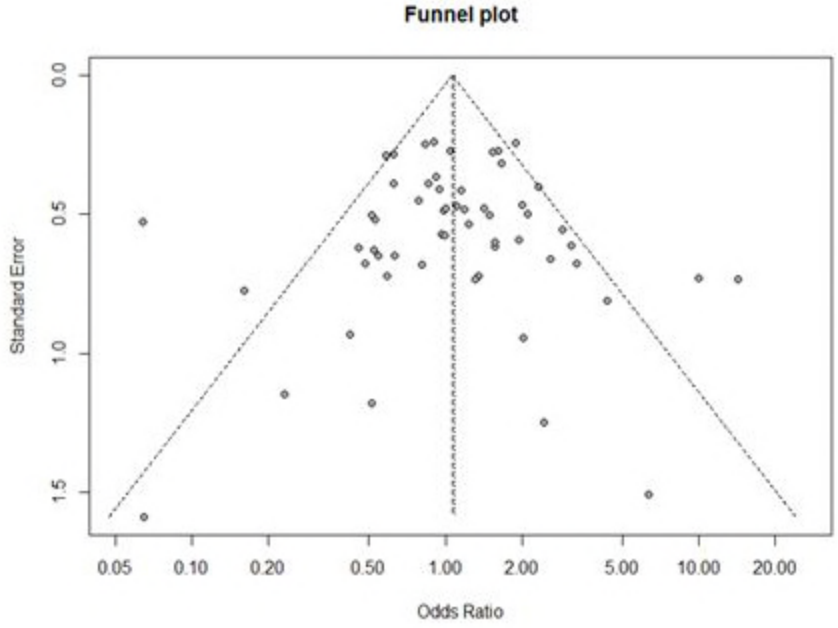
A


Funnel plot
Standard Error
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.1
0.2
0.5
1.0
2.0
5.0
10.0
Odds Ratio

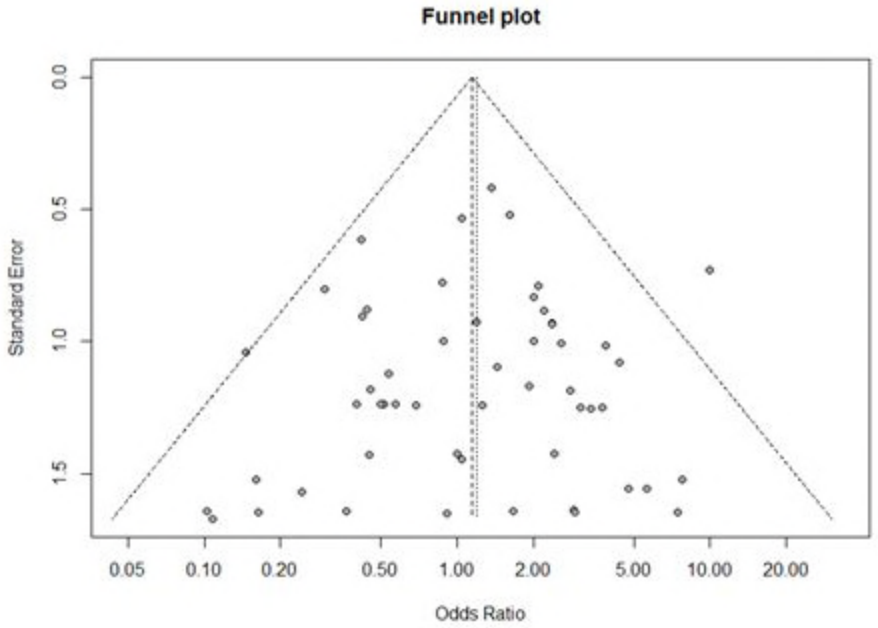
B


Funnel plot
Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
50.00
Odds Ratio

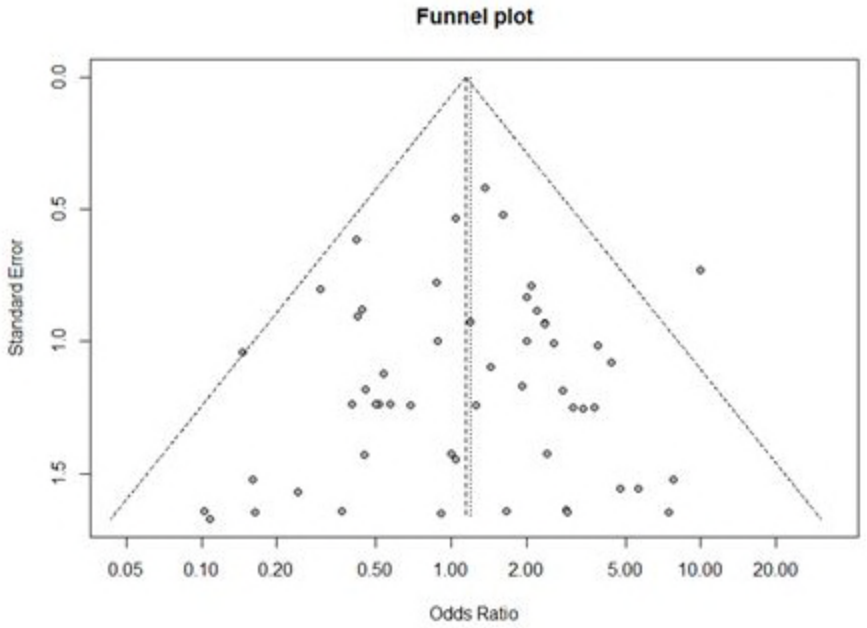
C


Funnel plot
Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
Odds Ratio

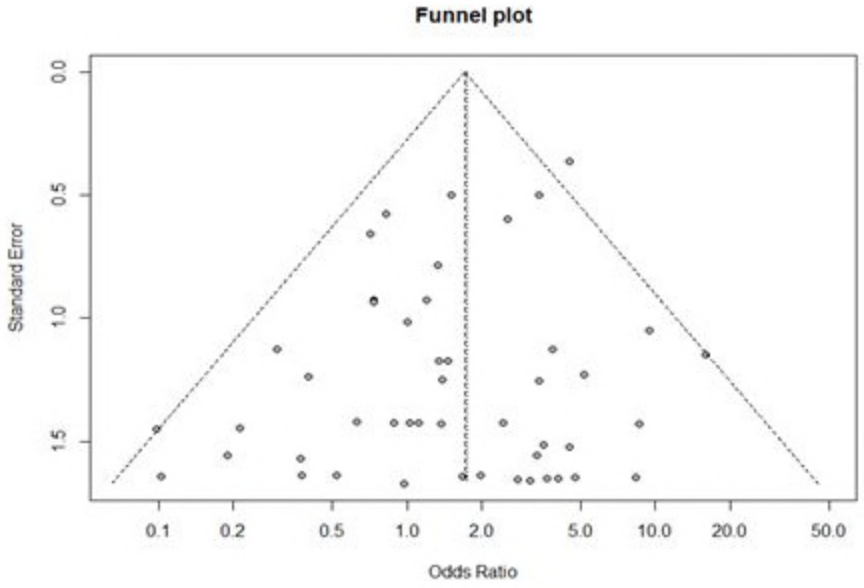
D


Funnel plot
Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
Odds Ratio

A


Funnel plot
Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
Odds Ratio

B


Funnel plot
Standard Error
0.0
0.5
1.0
1.5
0.1
0.2
0.5
1.0
2.0
5.0
10.0
20.0
50.0
Odds Ratio

C

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Figure legends:

Supplementary Figure S1 (A) Forest plot for associations between type 2 diabetes and *ApoE* ε2 allele *vs*. ε3 allele in the subgroup based on ethnicity. (B) Forest plot for associations between type 2 diabetes and *ApoE* ε2 allele *vs*. ε3 allele in the subgroup based on genotype.

Supplementary Figure S2 (A) Forest plot for associations between type 2 diabetes and *ApoE* ε2 allele *vs*. ε3 allele in the subgroup based on HWE. (B) Forest plot for associations between type 2 diabetes and *ApoE* ε2/ε3 genotype *vs*. ε3/ε3 genotype in the subgroup based on ethnicity.

Supplementary Figure S3 (A) Forest plot for associations between type 2 diabetes and *ApoE* ε2/ε3 genotype *vs*. ε3/ε3 genotype in the subgroup based on genotype. (B) Forest plot for associations between type 2 diabetes and *ApoE* ε2/ε3 genotype *vs*. ε3/ε3 genotype in the subgroup based on HWE.

Supplementary Figure S4 (A) Funnel plot of association between type 2 diabetes and *ApoE* ε2 allele *vs*. ε3 allele. (B) Funnel plot of association between type 2 diabetes and *ApoE* ε4 allele *vs*. ε3 allele. (C) Funnel plot of association between type 2 diabetes and *ApoE* ε2/ε2 genotype *vs*. and ε3/ε3 genotype. (D) Funnel plot of association between type 2 diabetes and *ApoE* ε2/ε3 genotype *vs*. and ε3/ε3 genotype.

Supplementary Figure S5 (A) Funnel plot of association between type 2 diabetes and *ApoE* ε2/ε4 genotype *vs*. and ε3/ε3 genotype. (B) Funnel plot of association between type 2 diabetes and *ApoE* ε3/ε4 genotype *vs*. and ε3/ε3 genotype.(C) Funnel plot of association between type 2 diabetes and *ApoE* ε4/ε4 genotype *vs*. and ε3/ε3 genotype.

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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* ε2 allele *vs*. ε3 allele based on a random-effects model.

Figure 3 Forest plot for the result of association between type 2 diabetes and *ApoE* ε4 allele *vs*. ε3 allele based on a fixed-effects model.

Figure 4 Forest plot for the result of association between type 2 diabetes and *ApoE* ε2/ε2 genotype *vs*. ε3/ε3 genotype based on a fixed-effects model.

Figure 5 Forest plot for the result of association between type 2 diabetes and *ApoE* ε2/ε3 genotype *vs*. ε3/ε3 genotype based on a random-effects model.

Figure 6 Forest plot for the result of association between type 2 diabetes and *ApoE* ε2/ε4 genotype *vs*. ε3/ε3 genotype based on a fixed-effects model.

Figure 7 Forest plot for the result of association between type 2 diabetes and *ApoE* ε3/ε4 genotype *vs*. ε3/ε3 genotype based on a fixed-effects model.

Figure 8 Forest plot for the result of association between type 2 diabetes and *ApoE* ε4/ε4 genotype *vs*. ε3/ε3 genotype based on a fixed-effects model.

Figure 9 Sensitivity analysis for the result of association between type 2 diabetes and *ApoE* ε2 allele *vs*. ε3 allele.

Figure 10 Sensitivity analysis for the result of association between type 2 diabetes and *ApoE* ε4 allele *vs*. ε3 allele.

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Figure 11 Sensitivity analysis for the result of association between type 2 diabetes and *ApoE* ε2/ε2 genotype *vs*. ε3/ε3 genotype.

Figure 12 Sensitivity analysis for the result of association between type 2 diabetes and *ApoE* ε2/ε3 genotype *vs*. ε3/ε3 genotype.

Figure 13 Sensitivity analysis for the result of association between type 2 diabetes and *ApoE* ε2/ε4 genotype *vs*. ε3/ε3 genotype.

Figure 14 Sensitivity analysis for the result of association between type 2 diabetes and *ApoE* ε3/ε4 genotype *vs*. ε3/ε3 genotype.

Figure 15 Sensitivity analysis for the result of association between type 2 diabetes and *ApoE* ε4/ε4 genotype *vs*. ε3/ε3 genotype.