Original Article

Association between *ApoE* Polymorphism and Type 2 Diabetes: A Meta-Analysis of 59 Studies*

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Abstract

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

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

Results We had 59 studies covering 6,872 cases with T2DM and 8,250 controls, and compared the alleles and genotypes of *ApoE* between cases and controls. When we conducted a comparison between *ApoE* ε4 and ε3 alleles, we produced a pooled *OR* of 1.18 (95% *CI*: 1.09-1.28; $P < 0.001$). *ApoE* $\varepsilon2/\varepsilon2$ genotype displayed a possible association with T2DM (*OR* = 1.46; 95% *CI*: 1.11-1.93; $P = 0.007$), $\varepsilon3/\varepsilon4$ genotype showed a 1.11-fold risk (*OR* = 1.11; 95% *CI*: 1.01-1.22; $P = 0.039$) and $\varepsilon4/\varepsilon4$ genotype had a 1.71-fold risk of developing T2DM (*OR* = 1.71; 95% *CI*: 1.33-2.19; $P < 0.001$) when they were compared with $\varepsilon3/\varepsilon3$ genotype.

Conclusions There is an association between *ApoE* polymorphism and T2DM: allele ε4 and genotypes ($\varepsilon2/\varepsilon2$, $\varepsilon3/\varepsilon4$, and $\varepsilon4/\varepsilon4$) are associated with the increased risk for the development of T2DM, and they may be risk factors for T2DM.

Key words: Apolipoprotein E; Polymorphism; Type 2 diabetes; Meta-analysis

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

INTRODUCTION

It is estimated that only half of the 79 million adults with type 2 diabetes will have adequate access to insulin by 2,030 if the current levels of access is not improved[1]. Moreover, one of the significant causes of worldwide mortality and morbidity is diabetes[2], especially type 2 diabetes mellitus (T2DM), which is also the major cause of substantial global economic burden[3]. 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[4]. 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[5], it will also improve the effectiveness and precision of treatment and prevention strategies[6].

It is reported that ApoE alleles are important genetic markers for dyslipidaemias[7], and previous studies indicate that ApoE is among the candidate genes which are most likely associated with CAD in T2DM patients[8]. *ApoE* draws much attention due to some reports supporting the association between *ApoE* polymorphism and T2DM[9-11]. In humans, *ApoE* gene is located on the chromosome at position 19q13.2 with 3 isoforms, ApoE2, ApoE3, and ApoE4; and 6 genotypes having 3 homozygous: ε2/ε2, ε3/ε3, and ε4/ε4, and 3 heterozygous: ε2/ε3, ε2/ε4, and ε3/ε4[12]. Besides T2DM, *ApoE* is also involved in many diseases, such as coronary heart disease (CHD)[13], ischemic cerebrovascular disease (ICD)[14], and Alzheimer's disease[15].

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[9,16-32] have been published since the publication of latest meta-analysis of the association between *ApoE* gene polymorphism and T2DM in 2014[33]. Thus, we conducted a further meta-analysis to explore whether *ApoE* polymorphism is associated with the increased risk of T2DM by including these new published articles.

METHODS

Search Strategy

We performed this meta-analysis by extensive literature search in PubMed, Web of Science, Medline, WanFang, VIP, and CNKI databases (last search on February 28, 2019). We used the following terms for our search strategy, ('ApoE' OR 'Apolipoprotein E') AND ('polymorphism, Genetic' OR ''variant' OR 'mutation') AND ('type 2 diabetes mellitus' OR 'type 2 diabetes' OR 'T2DM' OR '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.

Inclusion/Exclusion Criteria

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

Data Extraction

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

Quality Assessment

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

Statistical Analysis

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

RESULTS

Study Characteristics

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

Association between Alleles of ApoE and Type 2 Diabetes

We found a significant heterogeneity when we comparing *ApoE* ε2 with ε3 allele ($I^2 = 62\%$), and had

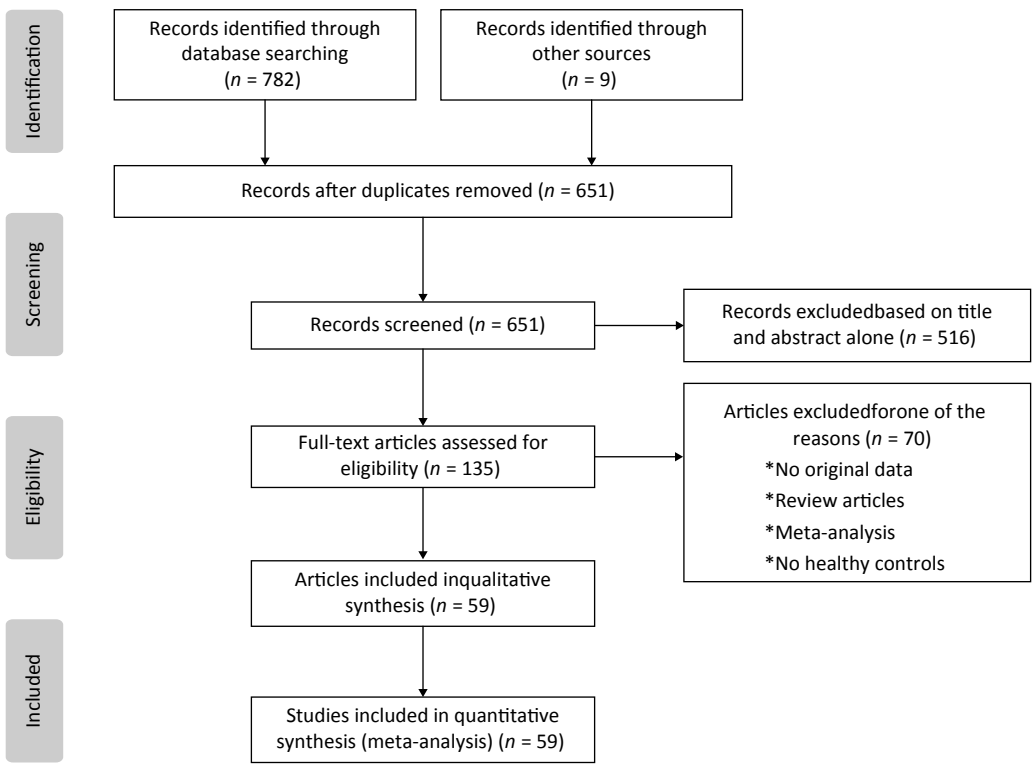

Figure 1. Flow chart of the process for literature identification and selection.

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

Continued

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

Note. HWE, Hardy-Weinberg equilibrium.

Table 2. Meta-analysis results of association between *ApoE* polymorphism and type 2 diabetes

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

Note. *ApoE* alleles (ε2 and ε4) and genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε4, and ε4/ε4) were compared with ε3 and ε3/ε3.

the pooled *OR* of 1.16 (95% *CI*: 0.98-1.37; *P* = 0.079) calculated by the random-effects model (Figure 2); however, there was not heterogeneity in the comparison of *ApoE* ε4 with ε3 allele (I^2 = 36%), and the pooled *OR* was 1.18 (95% *CI*: 1.09-1.28; *P* < 0.001) when the fixed-effects model was applied to compare *ApoE* ε4 with ε3 (Figure 3), indicating that *ApoE* ε4 allele may be a risk factor for type 2 diabetes.

Association between Genotypes of ApoE and Type 2 Diabetes

There were five genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε4, and ε4/ε4) were compared with ε3/ε3 genotype. No significant heterogeneity was found when the comparison was performed between the ε2/ε2 and ε3/ε3 genotypes (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), indicating that the ε2/ε2 genotype might produce 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 comparison 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).

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 could not identify the sources of heterogeneity and there was no significant association between *ApoE* polymorphisms and type 2 diabetes in different subgroups (Supplementary Figures S1-S3, available in www.besjournal.com).

Publication Bias

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

Sensitivity Analysis

According to our results of sensitivity analysis, no individual study produced influence on the corresponding pooled *OR*s and 95% *CI*s in the comparison of *ApoE* allele with ε3 allele or in the comparison of *ApoE* genotypes with genotype ε3/ε3 genotype, which indicated these results were relatively stable and credible.

DISCUSSION

In this meta-analysis, we included 59 literatures with 6,872 cases and 8,250 controls to explore the association between the *ApoE* gene polymorphism and type 2 diabetes mellitus. The major findings of our study are that allele 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 findings of our meta-analysis are in accordance with the previous studies[33,78-80], 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[81]; individuals carrying the ε2/ε2 genotype had about 31% lower mean LDL than those with the ε4/ε4 genotype[82]. 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.

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

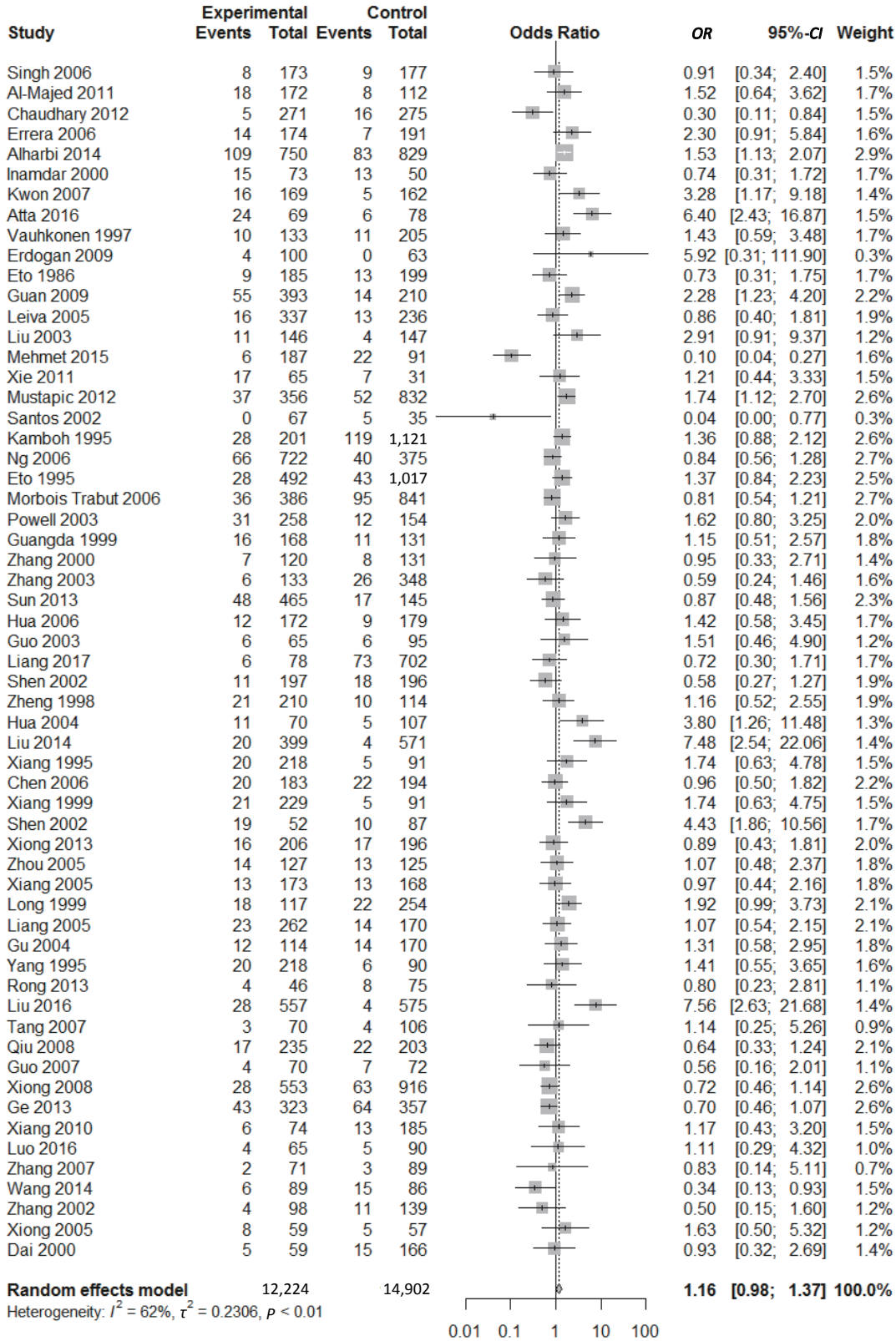

Figure 2. Forest plot for the result of association between type 2 diabetes and *ApoE* ε2 allele *vs*. ε3 allele based on a random-effects model.

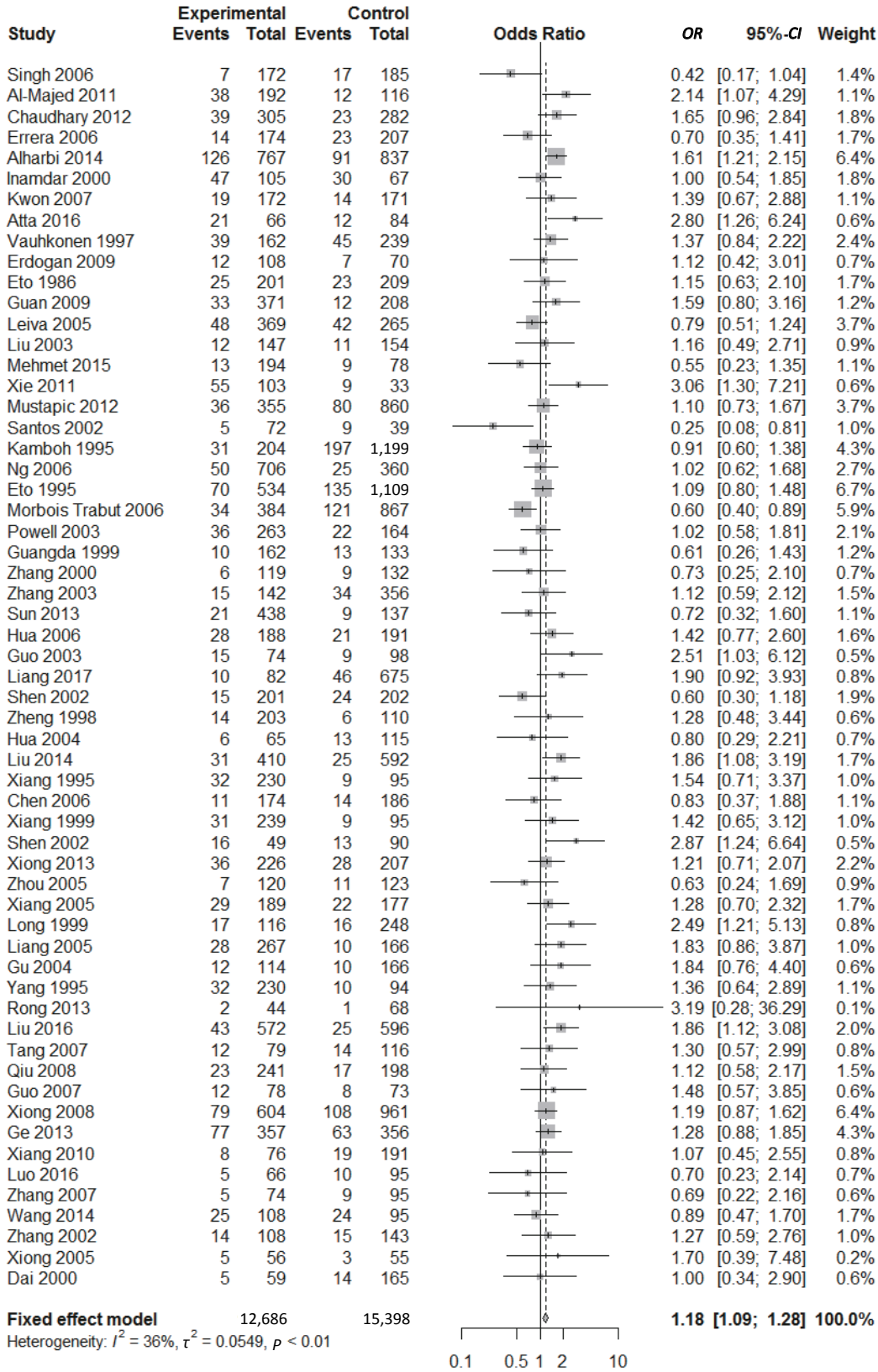

Figure 3. Forest plot for the result of association between type 2 diabetes and *ApoE* ε4 allele *vs*. ε3 allele based on a fixed-effects model.

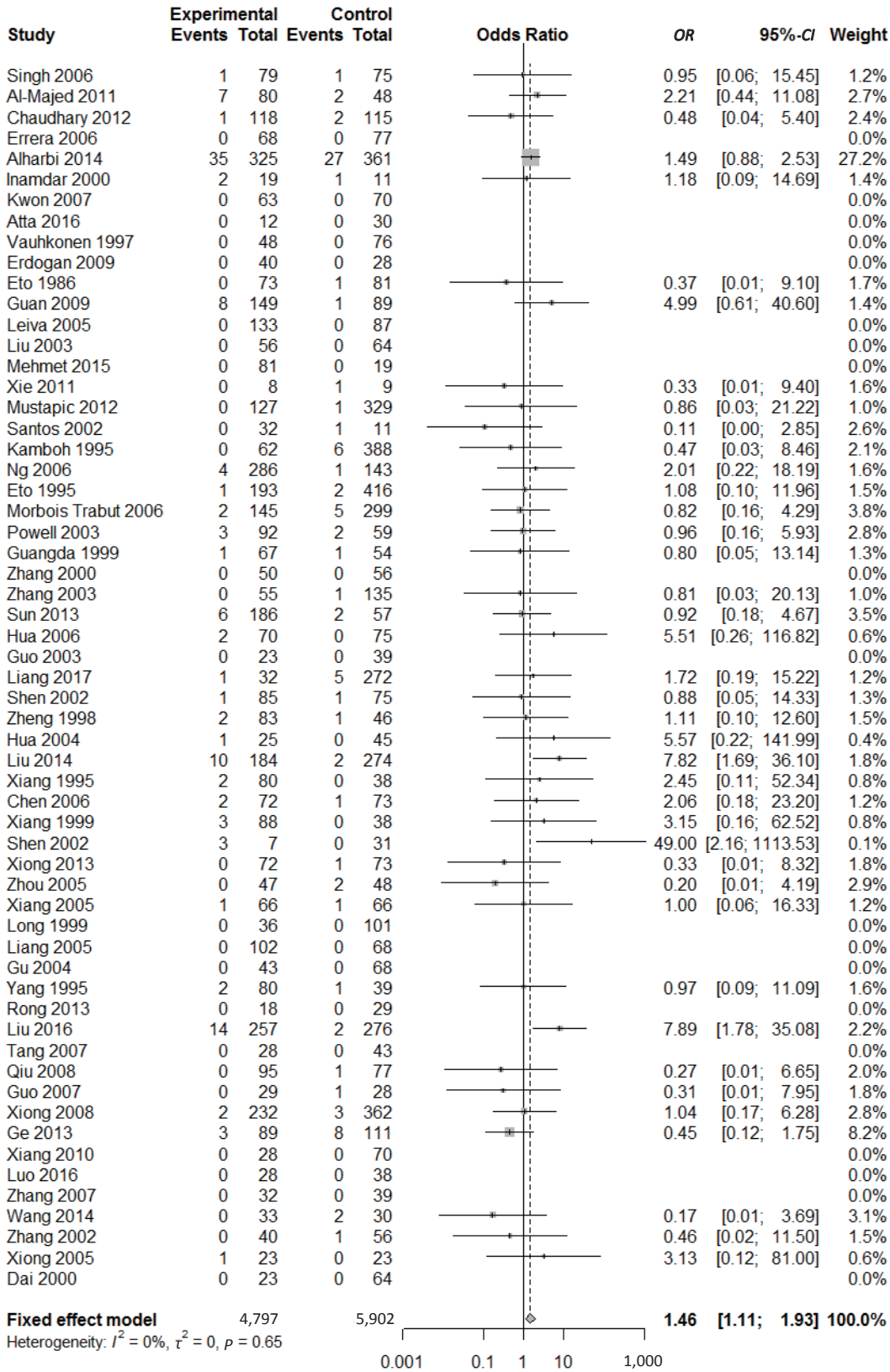

Figure 4. Forest plot for the result of association between type 2 diabetes and *ApoE* ε2/ε2 genotype *vs*. ε3/ε3 genotype based on a fixed-effects model.

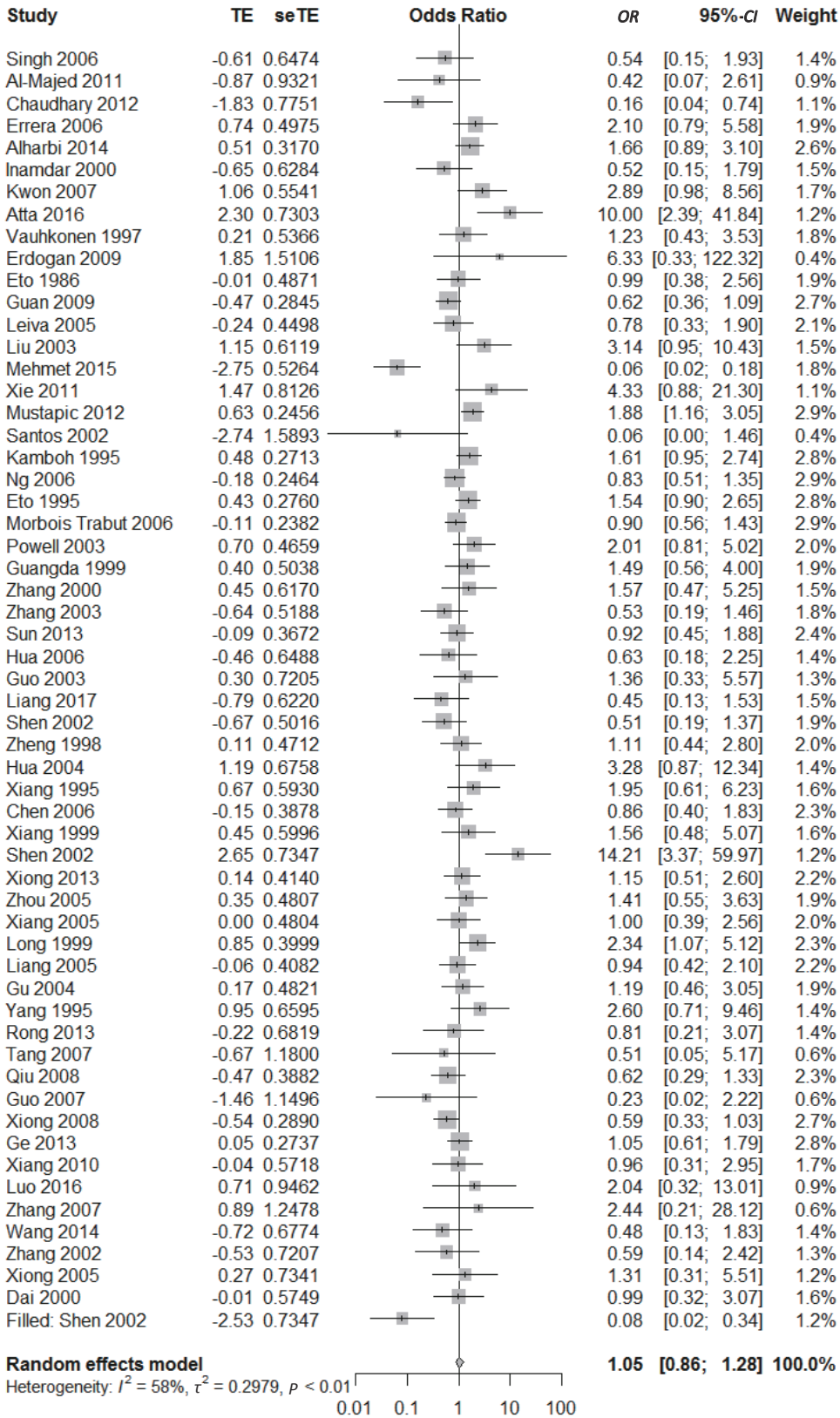

Figure 5. Forest plot for the result of association between type 2 diabetes and *ApoE* ε2/ε3 genotype *vs*. ε3/ε3 genotype based on a random-effects model.

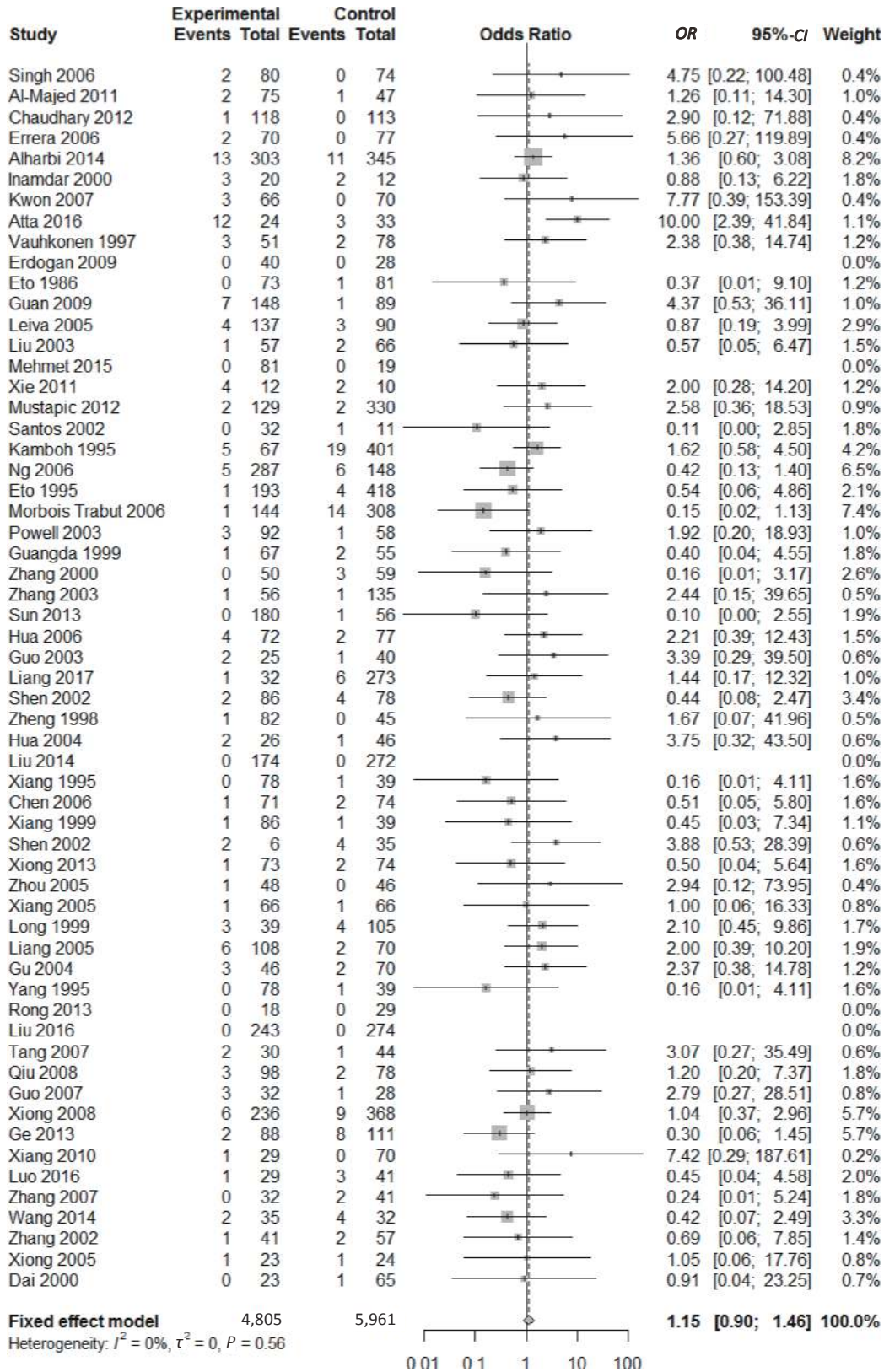

Figure 6. Forest plot for the result of association between type 2 diabetes and *ApoE* ε2/ε4 genotype *vs*. ε3/ε3 genotype based on a fixed-effects model.

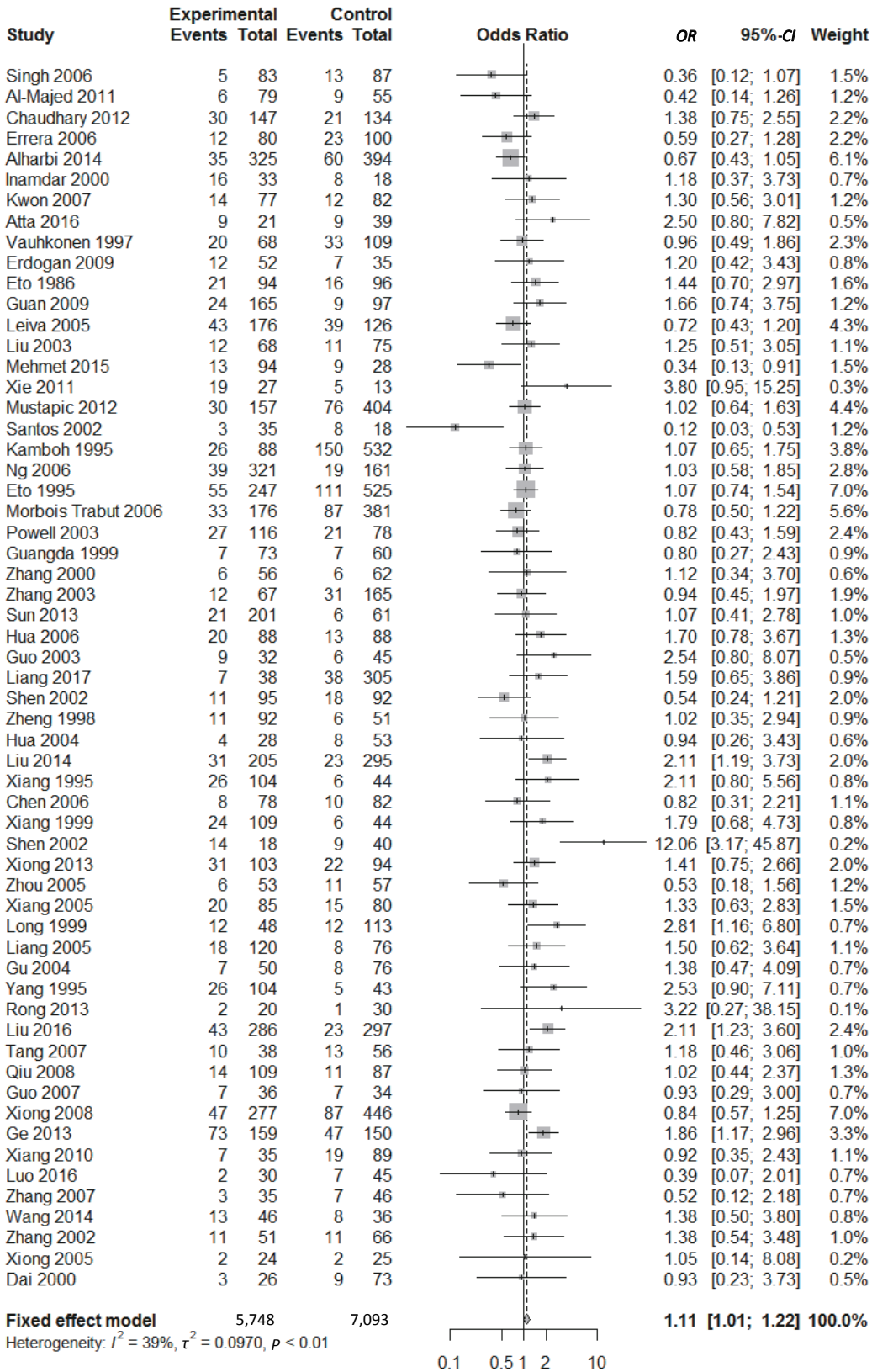

Figure 7. Forest plot for the result of association between type 2 diabetes and *ApoE* ε3/ε4 genotype *vs*. ε3/ε3 genotype based on a fixed-effects model.

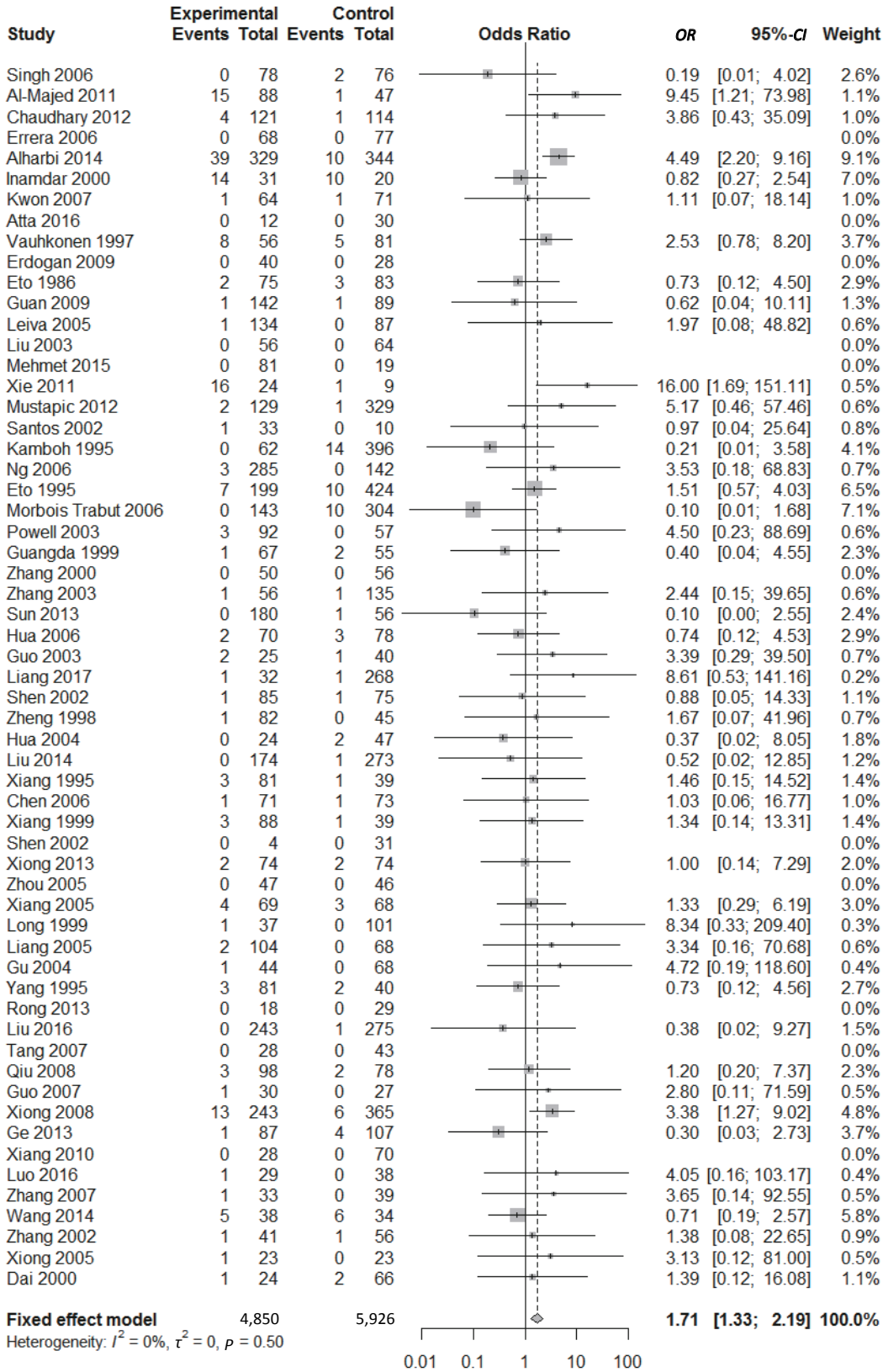

Figure 8. Forest plot for the result of association between type 2 diabetes and *ApoE* ε4/ε4 genotype *vs*. ε3/ε3 genotype based on a fixed-effects model.

the results of previous meta-analyses[33]. 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[78] which reveals that the *OR*s 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[37].

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.

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.

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AUTHOR CONTRIBUTIONS

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

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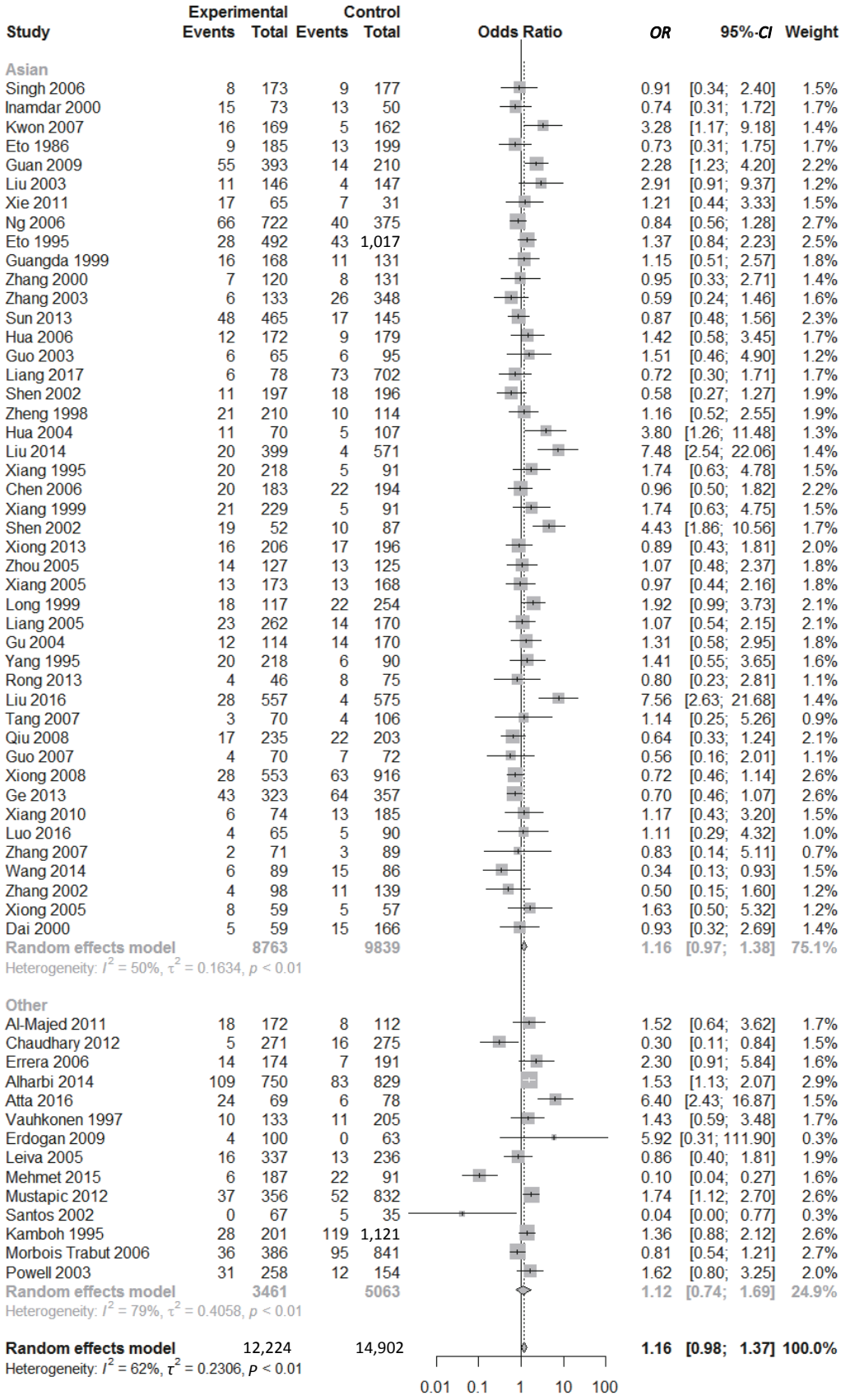
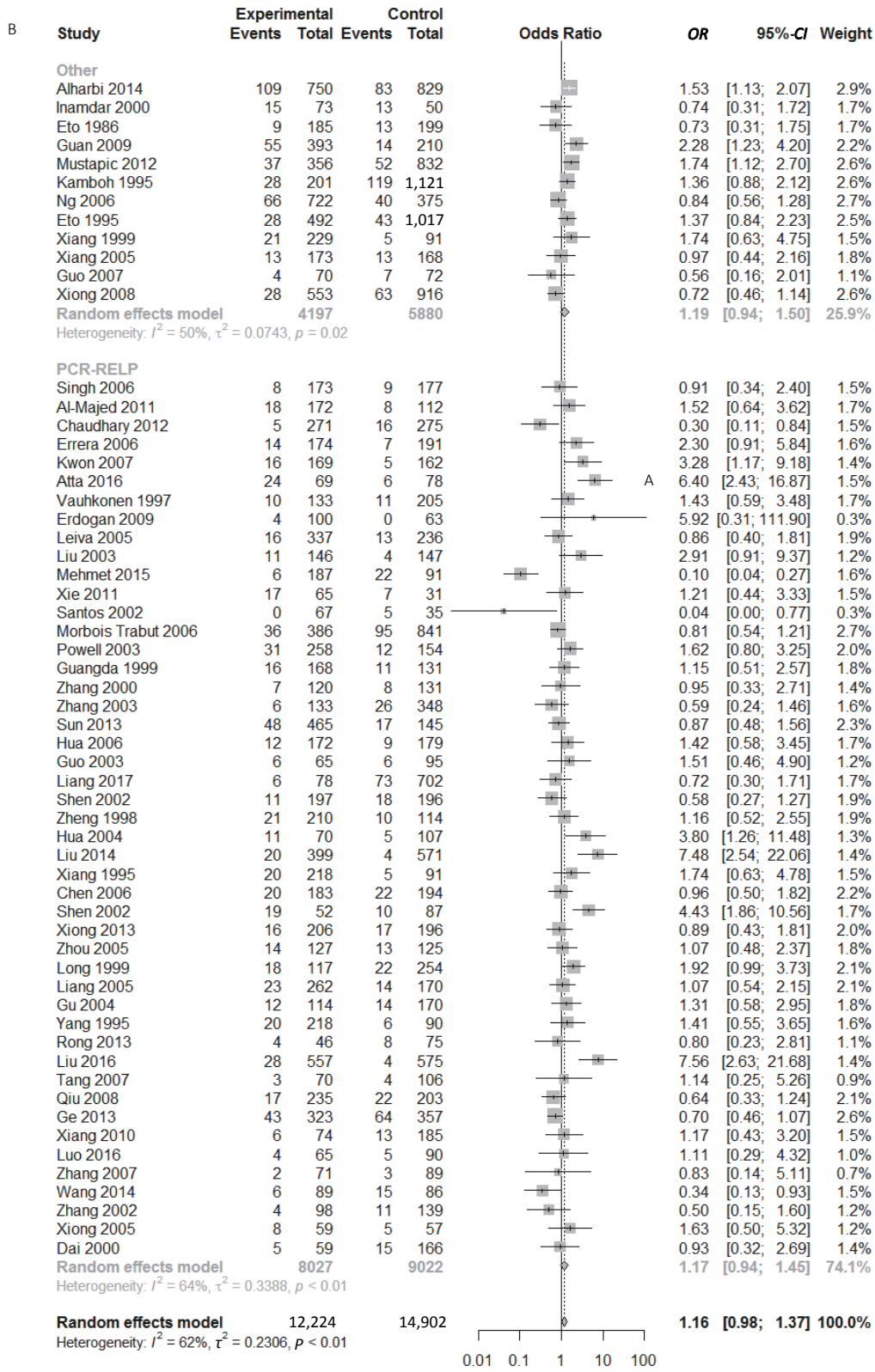
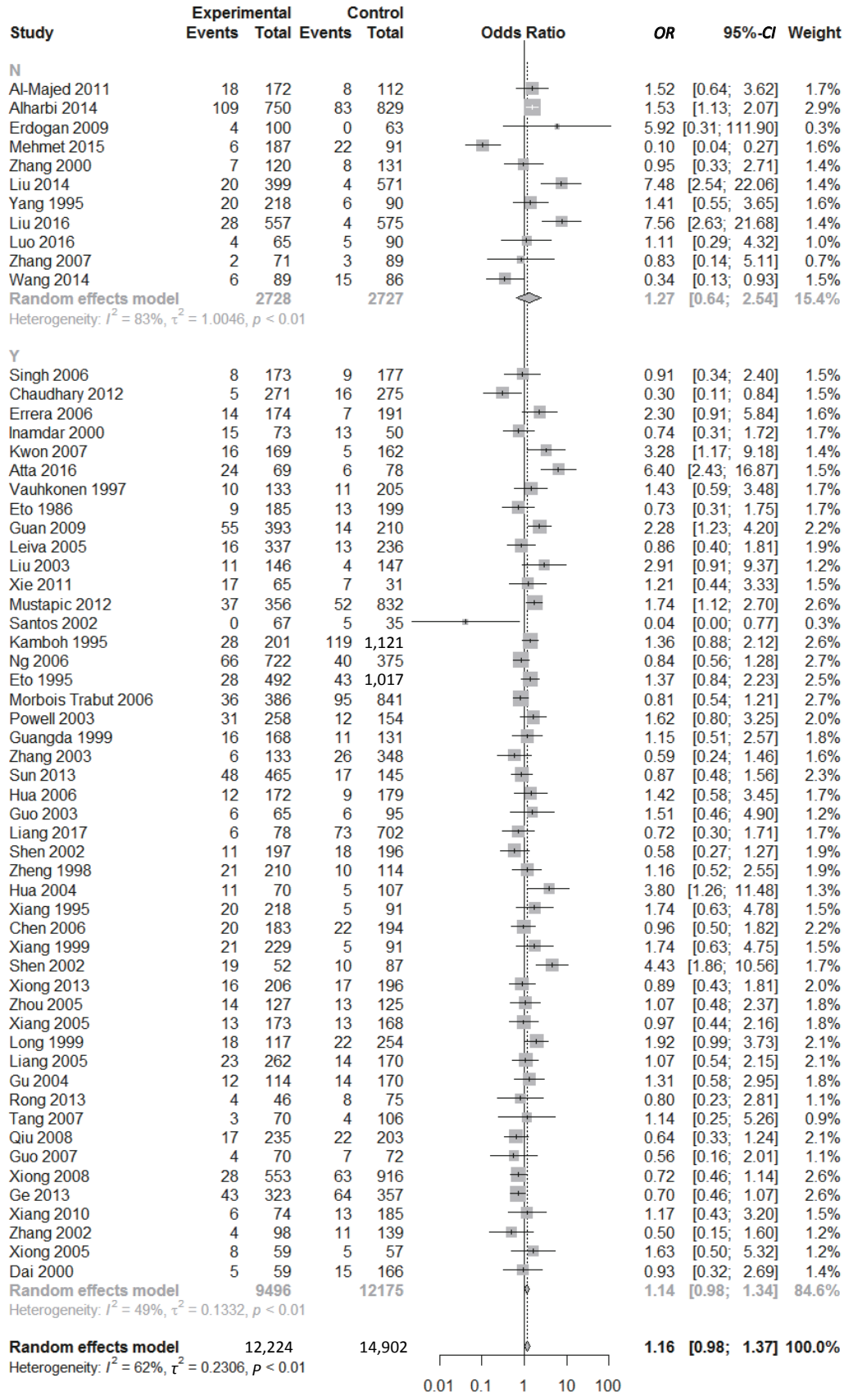
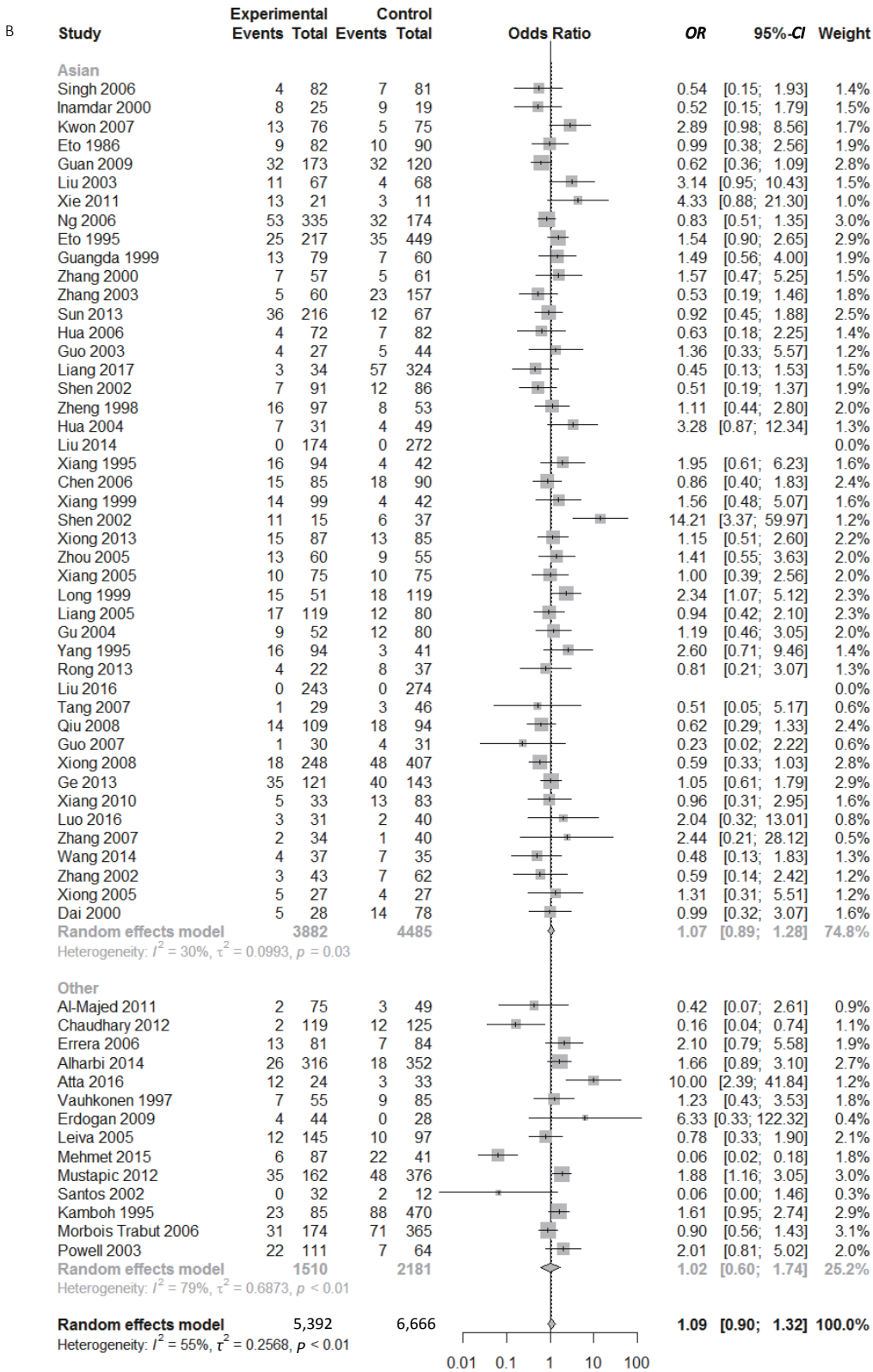

Experimental
Control
Study
Events
Total
Events
Total
Odds Ratio
OR
95%-CI
Weight
Asian
Singh 2006 8 173 9 177 0.91 [0.34; 2.40] 1.5%
Inamdar 2000 15 73 13 50 0.74 [0.31; 1.72] 1.7%
Kwon 2007 16 169 5 162 3.28 [1.17; 9.18] 1.4%
Eto 1986 9 185 13 199 0.73 [0.31; 1.75] 1.7%
Guan 2009 55 393 14 210 2.28 [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 1,017 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 1,121 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 12,224 14,902 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



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.

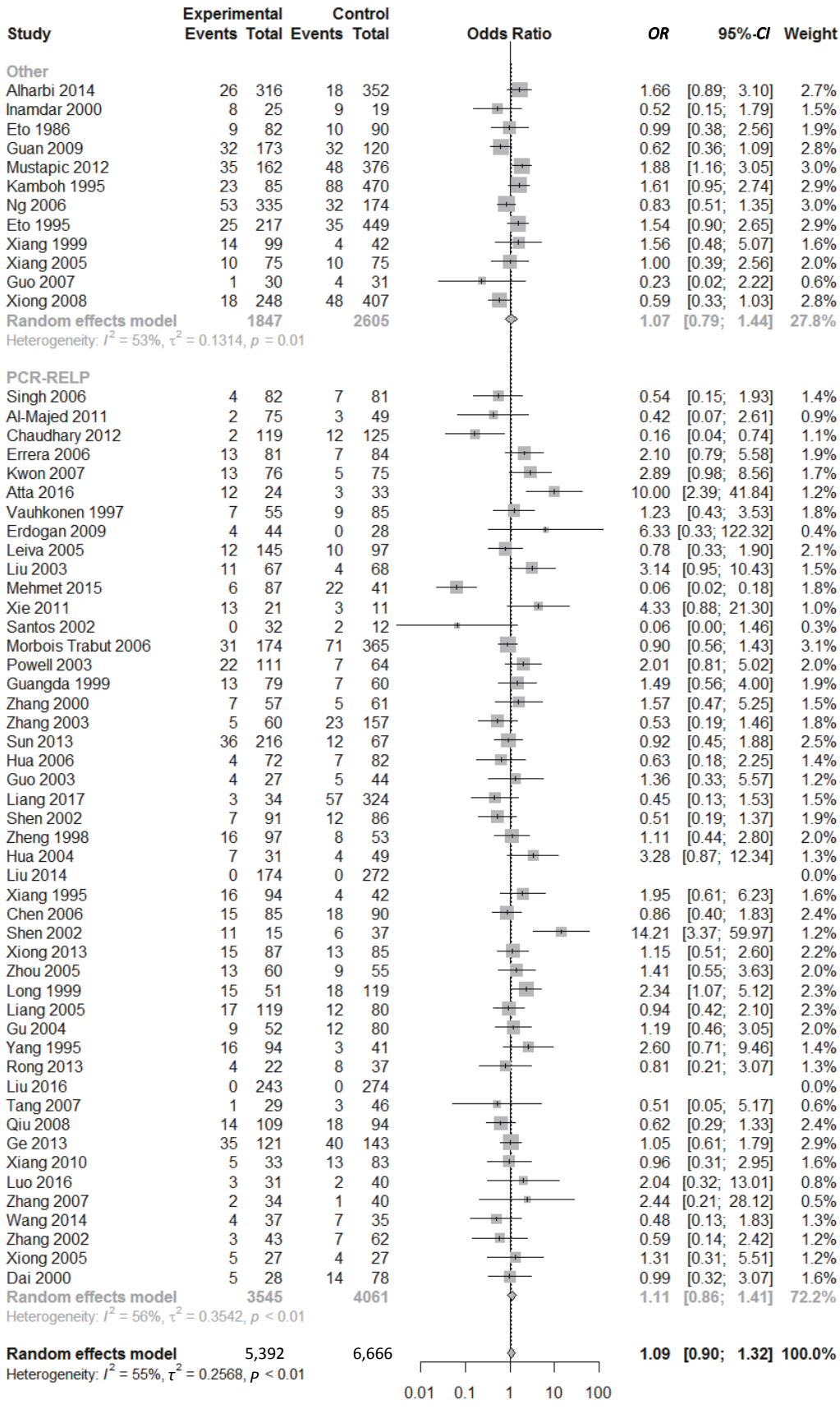
A


Experimental
Control
Study
Events Total 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 1,121 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 1,017 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 12,224 14,902 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

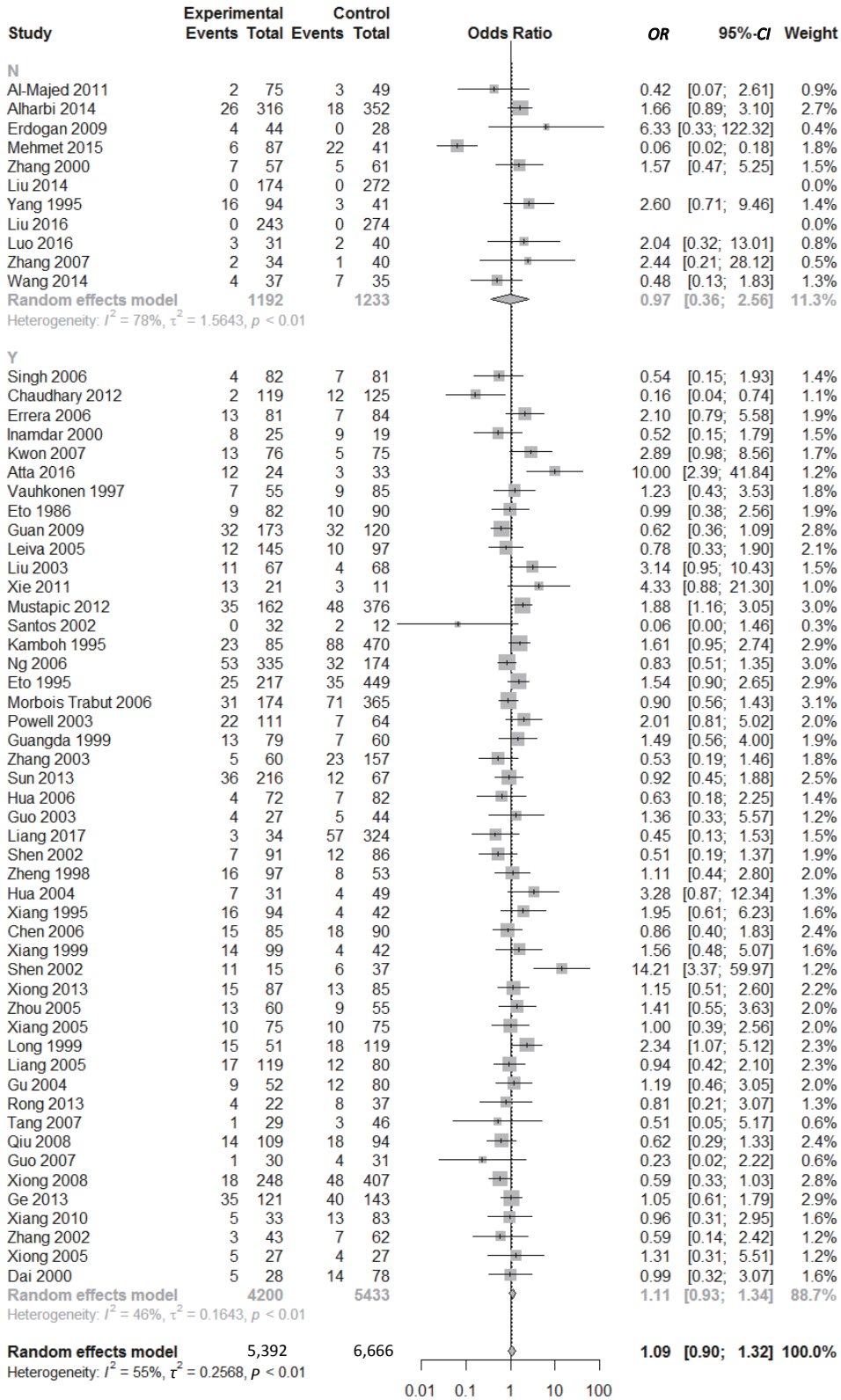


Supplementary Figure S2. (A) Forest plot for associations between type 2 diabetes and *ApoE* ε2 allele *vs*. ε3 allele in the subgroup based on HWE. (B) Forest plot for associations between type 2 diabetes and *ApoE* ε2/ε3 genotype vs. ε3/ε3 genotype in the subgroup based on ethnicity.

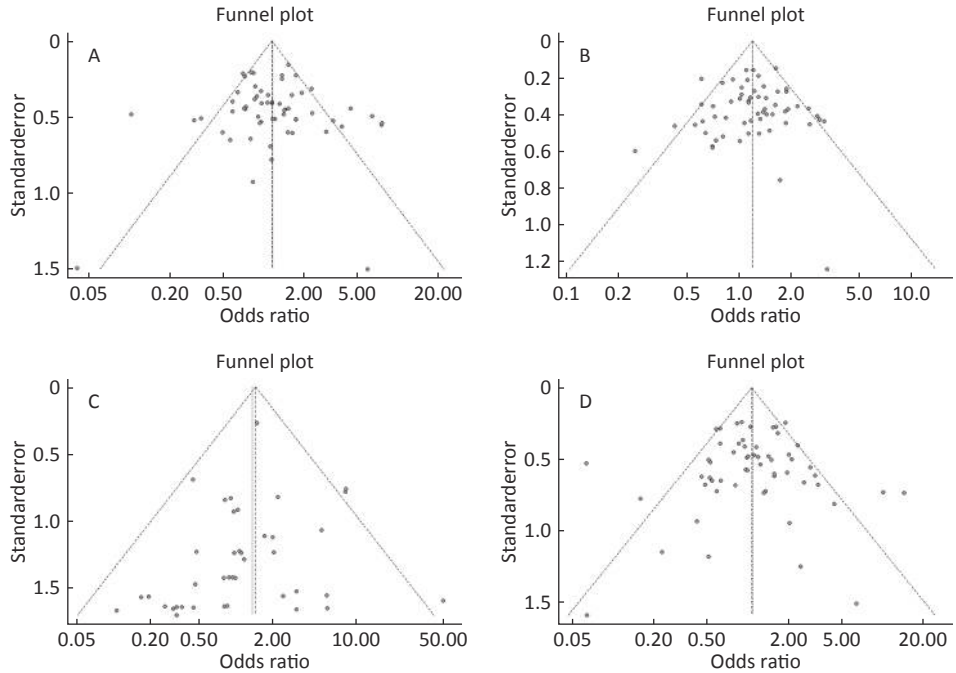
A


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 5,392 6,666 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

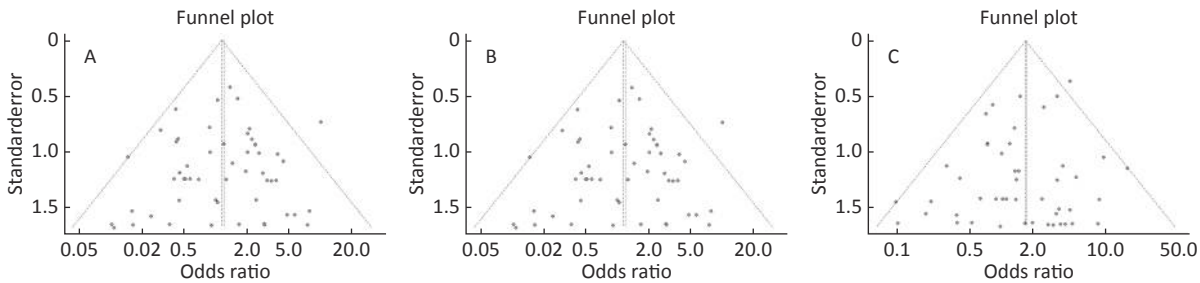
B



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.