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The genetic association between apolipoprotein E gene polymorphism and Parkinson disease

A meta-analysis of 47 studies

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Abstract

Objective: Although the relationship between apolipoprotein E (ApoE) gene polymorphisms and the risk of Parkinson disease (PD) has been established, the results were inconsistent and inconclusive.

Methods: A comprehensive search examining the association between APOE polymorphisms and PD through PubMed, Embase, Chinese National Knowledge Infrastructure (CNKI), and Cochrane Library databases was performed without published year limited.

Results: A total of 47 studies with 7533 cases and 14442 controls were included in present study. The results showed statistically significant association between risk factor ApoE ε4 allele and PD in Asian population ($P = .003$, odds ratio, OR [95% confidence interval, CI] = 1.43 [1.13,1.80]). Genotype ε2ε4 have significantly associated with PD in Asian population ($P = .004$, OR [95% CI] = 4.43 [1.62,12.10]). Genotype ε3ε4 was significantly associated with PD in Latin-American population ($P = .01$, OR [95% CI] = 1.44 [1.08,1.91]). In addition, the frequency of the genotype ε3ε4 is lower in PD group than that in the control group in Caucasian population, and the difference of genotype ε3ε4 is also statistically significant ($P = .006$, OR [95% CI] = 0.86 [0.77,0.96]). Although significant heterogeneity was observed among all studies, the results were shown to be stabilized by sensitive analysis. No publish bias was observed.

Conclusions: This meta-analysis suggests that the APOE ε4, but no ε2, might be a risk factor for PD in Asian population. Furthermore, the genotype ε2ε4 may be a susceptible factor for PD in Asian population, and the genotype ε3ε4 may be a susceptible factor for PD in both Caucasian and Latin-American populations.

Abbreviations: ApoE = apolipoprotein E, CI = confidence interval, CNKI = Chinese National Knowledge Infrastructure, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa Scale, OR = odds ratio, PD = Parkinson disease, SNP = single nuclear polymrphism.

Keywords: apolipoprotein E, meta-analysis, Parkinson disease, polymorphism

1. Introduction

Apolipoprotein E (Apo-E), plays a key role in lipid metabolism, is considered as one of the most powerful genetic risk factors for Alzheimer disease (AD).[1–3] Three common polymorphisms (ε2, ε3, and ε4) and 6 genotypes (ε2/ε2, ε3/ε3, ε4/ε4, ε3/ε2, ε4/ε2, ε4/ε3) were included in the ApoE gene. The ε3 allele is predominant in all populations, followed by ε4 and ε2 alleles. While, the frequencies of ε2, ε3, and ε4 varied among populations.[4–5] The APOE gene, especially for the ε4 allele, was identified to be a susceptible factor for AD and lower age at disease onset.[6–7] In addition, Parkinson disease (PD) was revealed to share some clinical, neurochemical, and pathologic features with AD.[8] For example, patients with PD frequently develop dementia, and patients with AD often develop parkinsonism.[9] Both the 2 diseases are characterized by neuronal death and protein deposition (eg, amyloid or α-synuclein).[10] For these reasons, the APOE gene has been hypothesized to be an important susceptible factor for PD.

Previous studies have evaluated the role of APOE in dementia associated with PD.[11–12] In contrast to AD, the results on the genetic association between APOE polymorphisms and PD were controversial. The APOE ε4 allele was a major susceptible factor for sporadic PD in Spain,[13] Mexican,[14] and Indian[15] populations. However, most of other publications have reported no significant association between the APOE ε4 allele and PD risk.[16–18] In contrast, the APOE ε2 allele seems to occur with lower frequency in PD, which indicated a protective factor for APOE ε2 allele in PD. Pulkes et al[19] and Li et al[20] have shown that the frequency of APOE ε2 allele in PD were significantly higher than that in the control group in Thailand and Chinese

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populations. While, most of other researches suggested no association between APOE ε2 and PD risk.[21–22] Furthermore, the APOE genotype ε2/ε4 was reported to be associated with an increased risk of PD in Japanese population.[21] The APOE genotype ε3/ε4 was reported to be associated with an increased risk of PD in Mexican[23] and Indian[15] populations. While, this positive results cannot be replicated in other studies.[24–25]

Considered the relatively small sample size and contradictory conclusions in individual study, we attempt to performed a meta-analysis of existing studies to clarify whether APOE alleles (ε2, ε3, and ε4) and genotype contributes significantly to the risk of PD.

2. Materials and methods

2.1. Patient and public involvement

There was no patient and public involvement in present meta-analysis. An ethical approval is not necessary for a meta-analysis.

2.2. Literature search strategy

This meta-analysis followed the Cochrane collaboration definition and PRISMA 2009 guidelines for meta-analysis and systematic review.[26] A exhaustive search was performed through Embase, Cochrane Library, PubMed, and Chinese National Knowledge Infrastructure (CNKI) data bases for relevant studies using the following terms: "apolipoprotein E," "APOE," "polymorphism," "single nuclear polymorphism (SNP)," "Parkinson disease," "PD." No language and published year were limited. Other relevant references of identified studies were retrieved by cross-references.

2.3. Inclusion/exclusion criteria

The following criteria were used for the literature inclusion: articles should concern APOE polymorphism and PD risk; case-control and/or cohort designed studies; contained SNP genotype data both in case and control groups; adequate data for the calculation of odds ratios (ORs) and 95% confidence intervals (CIs); and the genotype distribution in control groups was in Hardy–Weinberg equilibrium (HWE). In addition, studies were excluded when they were: studies that contained overlapping data with other literature; data came from case-reports, reviews or abstracts; not case-control and/or cohort designed studies; genotype frequencies were unavailable; and control group did not confirm to HWE.

2.4. Data extraction

Two independent authors (JL and LL) simultaneously selected the relevant articles according to the inclusion and exclusion criteria and performed the data extraction process. The following terms were extracted: the first author, published year, ethnicity, age, gender, genotyping methods, diagnostic criteria, number of cases and controls, and number of genotype. All discrepancies were resolved by a consensus achieved by a third author (JML).

2.5. Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to evaluate the study quality.[27] Adequacy of case definition, representativeness of the cases, selection of controls, definition of controls, comparability cases/controls, comparability cases/controls, same method of ascertainment, and non-response rate were taken into account and given a corresponding score. Total score ranged from 0 (lowest quality) to 8 (highest quality). A study with a score of 6 or higher was classified as high quality.

2.6. Statistical analyses

All statistical analyses were performed using the STATA 12.0 (StataCorp, College Station, TX) and Revman 5 (Cochrane Collaboration, London, United Kingdom). The strength of relationship between APOE ε2, ε3, ε4 alleles, ε2ε2, ε2ε3, ε2ε4, ε3ε3, ε3ε4, and ε4ε4 genotypes and PD susceptibility was evaluated using crude ORs with 95% CI. Subsequently, stratified analyses by ethnicity were also performed out. A χ^2-based Cochran Q test and Higgins I^2 statistic was used to evaluate the between-study heterogeneity of the studies. A P value of less than .05 was considered significant. I^2 values of >50% indicate heterogeneity among studies. A fixed effect model (the Mantel–Haenszel method) was adopted if there was no significant heterogeneity ($I^2 < 50\%$). Otherwise, the random effect model (the DerSimonian and Laird method) was used. The stability of the results was assessed using sensitivity analysis, which omitting single study each time to evaluate the influence of each study on the pooled OR. Funnel plots were used to assess publication bias by the methods of Begg test and Egger test. A t test was performed to determine the significance of the asymmetry. An asymmetric plot suggested possible publication bias ($P \geq .05$ suggests no bias).

3. Results

3.1. Characteristics of the published studies

As shown in Figure 1, a total of 2584 studies were retrieved initially. 957 studies were excluded for duplicated data. After reviewing the titles, abstracts, and full texts, 1475 were excluded for not related to the genetic association between APOE gene polymorphism and PD risk. And 105 were excluded for being review, short communication, letter, and conference abstract. Finally, 47 individual studies were enrolled in present meta-analysis.[13–25,28–61] Among these studies, 16 were conducted in Chinese population, 27 were in Caucasian population, and 4 were in Latin American population. The quality assessments and NOS scores for each study were list in Table 1[13–25,28–61] and Table s1, http://links.lww.com/MD/C565.

3.2. Meta-analysis: APOE alleles and PD

The results of the association between APOE alleles and PD risk were listed in Table 2. A total of 47 studies reported the relation of APOE ε2, ε3, and ε4 and PD. and significant association between APOE ε2 and PD were observed ($P = .04$, OR [95% CI] = 1.23 [1.01, 1.50]), suggesting this allele might be a risk factor for PD. Both the distributions of APOE ε3 and ε4 were not statistically different in PD population and healthy population ($P > .05$) (Table 2, Figs. 2–4). Subgroup analysis stratified by ethnicity shown that the significant difference for distribution of APOE ε2 between PD population and healthy population didn't exist anymore ($P > .05$). However, the APOE ε4 was shown to be significantly associated with the PD risk in Asian population ($P = .003$, OR [95% CI] = 1.43 [1.13, 1.80]) (Table 2).

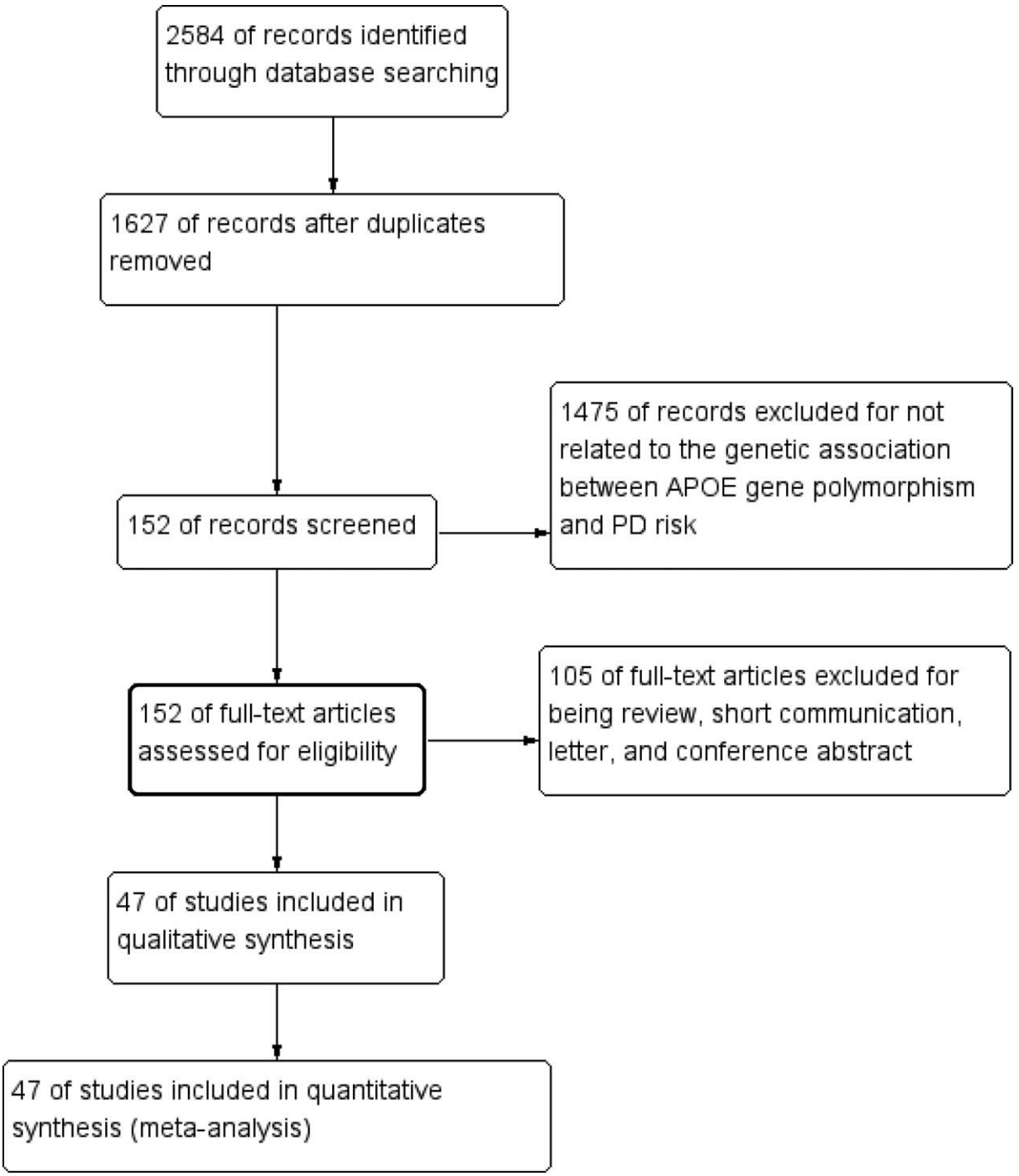


Figure 1. PRISMA flow chart of studies inclusion and exclusion.

3.3. Meta-analysis: APOE genotypes and PD

Significant association was only found between ε2ε4 ($P = .02$, OR [95% CI] = 1.69 [1.10, 2.62]) and PD risk. Subgroup analysis stratified by ethnicity shown that the significant association between ε2ε4 and PD was only in Asian population ($P = .004$, OR [95% CI] = 4.43 [1.62, 12.10]), but not in Caucasian and Latin-American populations ($P > .05$). In addition, the distribution of ε3ε4 was significantly different in PD and control group in both Caucasian ($P = .006$, OR [95% CI] = 0.86 [0.77, 0.96]) and Latin-American populations ($P = .01$, OR [95% CI] = 1.44 [1.08, 1.91]), but not in Asian population ($P = .93$, OR [95% CI] = 0.99 [0.83, 1.18])(Table 3).

3.4. Test of heterogeneity

Significant heterogeneity was detected in allele models of APOE ε2, ε3, and ε4 (Table 2). Therefore, subgroup analysis stratified

Table 1

Characteristics of included studies.

Author	Year	Ethnicity	Age, y, (case/control)	Gender, F%, (case/control)	Genotyping methods	Diagnostic criteria	Case	Control
Hao et al[55]	2001	Chinese	63±11/62±11	42.1/47.5	PCR-RFLP	NA	64	101
Zeng et al[54]	2000	Chinese	68.2±6.1/59.2±16.3	31.5/32.5	PCR-RFLP	DSM- IV	54	234
Li et al[20]	1998	Chinese	58.8±12.6/NA	40.3/NA	PCR-RFLP	DSM- IV	52	438
Qin et al[56]	1998	Chinese	66.6±10.3/68.1±9.2	33.3/8.3	PCR-RFLP	DSM-III-R	36	60
Wang et al[57]	2001	Chinese	66.13±7.32/65.5±8.07	30.0/42.3	PCR-RFLP	DSM-III-R	40	52
Zhang et al[61]	1999	Chinese	60.67±11.68/65.88±9.50	NA	PCR-RFLP	DSM-III-R	72	66
Zhao et al[58]	2003	Chinese	63±11/68±13	41.2/46.4	PCR-RFLP	DSM-III-R	68	110
Zhou et al[59]	2004	Chinese	67.4±10.2/69.4±11.4	27.5/36.5	PCR-RFLP	DSM- IV	36	52
Whitehead et al[69]	1996	Iran	56.9±6.6/58.0±7.1	34.9/37.7	NA	NA	189	162
Kiyohara et al[21]	2011	Japanese	68.5±8.68/69.7±5.63	61.8/61/5	TaqMan	DSM- IV	238	296
Pulkes et al[19]	2011	Thailand	NA	43.5/NA	PCR-RFLP	DSM- IV	155	158
Singh et al[15]	2014	Indian	58.01±8.62/59.71±8.11	45.7/39.0	PCR-RFLP	MMSE	70	100
Ryu et al[17]	2010	Korean	71.1±8.2/72.2±4.9	70.9/49.5	TaqMan	MMSE	234	192
Higuchi et al[43]	2000	Japanese	65.5±9.5/74.0±5.6	56.4/69.4	PCR-RFLP	MMSE	140	382
Tang et al[52]	2002	Chinese	65.61±5.42/55.81±15.46	48.5/52.5	PCR-RFLP	DSM- IV	68	160
Yamamoto et al[53]	1997	Japanese	NA	60.8/NA	PCR-RFLP	NA	163	576
Buchanan et al[22]	2007	Australian	66.95±9.80/64.16±10.83	43.4/70.5	PCR-RFLP	DSM- IV	422	387
Bon et al[31]	1999	Netherland	NA	NA	PCR-RFLP	MMSE	199	96
Eerola et al[33]	2002	Finland	67.2±6.77/65.8±8.20	40.8/63.5	PCR-RFLP	DSM- IV	147	137
Egensperger et al[34]	1996	Germany	76.0±6.2/71.2±9.5	NA	PCR-RFLP	DSM- IV	20	54
Marca et al	2013	UK	61.35±10.19/54.61±6.73	50.3/55.1	PCR-RFLP	DSM- IV	163	176
McCulloch et al[24]	2008	American	67.3±12.2/66.6±10.0	31.8/61.0	PCR-RFLP	DSM- IV	932	664
Oliveri et al[48]	1999	Italian	65.8±9.01/66.3±8.5	42.9/52.1	PCR-RFLP	MMSE	126	119
Papapetropoulos et al[25]	2007	UK	77.±7.9/79.1±12.8	28/52.7	sequencing	NA	118	91
Parsian et al[49]	2002	American	NA	NA	NA	NA	166	94
Harrington et al[41]	1994	UK	77.7±7.1/78.1±7.7	49.0/51.7	TaqMan	NA	51	58
Arai et al[29]	1994	American	NA	NA	NA	DSM-III-R	98	48
Gao et al[36]	2011	Caucasians	NA	23.7/21.2	MassARRAY	NA	786	1537
Harhangi et al[40]	2000	Rotterdam	75.8±7.8/69.0±8.6	63.0/55.2	PCR-RFLP	DSM-III-R	81	4805
Koller et al[44]	1995	American	67.4±7.9/69.9±6.5	37.7/52.6	PCR-dot-blot	NA	61	78
Rubinsztein et al[50]	1994	UK	NA	NA	PCR-RFLP	NA	33	34
Williams-Gray et al[11]	2009	UK	62.5±12.8/NA	40/52	Taqman	DSM-IV	505	478
Ghebremedhin et al[37]	2006	UK	75.1±6.9/73.4±7.4	42.6/42.6	PCR-RFLP	MMSE	108	108
Blázquez et al[13]	2006	Spain	72.0±9.6/70.9±8	45.4/48.1	PCR-RFLP	MMSE	185	212
Troster et al[16]	2006	USA	65.6±8.2/71.5±7.2	25.8/51	dot-blot	DSM-IV	62	146
Martinoli et al[47]	1995	USA	NA	NA	PCR-RFLP	DSM-III-R	10	243
Helisalmi et al[42]	1996	Finland	71±6/69±8	46.7/53.3	PCR-RFLP	NA	100	100
Grasbon-Frodl et al[39]	1999	German	NA	70/58.5	PCR-RFLP	NA	62	53
Ballering et al[30]	1997	Netherland	NA	NA	NA	NA	50	107
Goetz et al[38]	2001	Chicago	NA	NA	PCR-RFLP	NA	44	44
Dürr et al	1997	France	NA	NA	PCR-RFLP	NA	46	387
Schulte et al[51]	2003	UK	67.5±10.5/72.0±4.3	46/48	PCR-RFLP	NA	382	306
Kruger et al[45]	1999	Germany	66.53±11.08/NA	44/NA	PCR-RFLP	NA	193	177
Ezquerra et al[35]	2008	Barcelona	56±8.4/57.4±8.7	NA	PCR-RFLP	DSM- IV	138	91
Gregório et al[18]	2013	Brazil	69.2±11.1/71.7±8.5	38/52	PCR-RFLP	DSM- IV	232	137
Gallegos-Arreola et al[14]	2009	Mexican	63±9/50±14	40/56	PCR-RFLP	NA	105	107
López et al[23]	2010	Mexican	62.28±12.85/63.97±11.23	39/7/39.7	NA	DSM-IV	229	229

DSM = Diagnostic and Statistical Manual of Mental Disorders, MMSE = Mini-mental State Examination, NA = not available, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, UK = United Kingdom, USA = United States of America.

Table 2

The association between APOE polymorphisms and Parkinson's disease.

Alleles	Subgroups	Number of studies	Numbers		Test of association		Model	Test of heterogeneity	
			Case	Control	OR [95% CI]	*P*		*P*	I^2 (%)
ε2	Total	47	14866	28848	1.23 [1.01, 1.50]	.04	R	<.00001	75
	Caucasian	27	10100	21478	1.19 [0.98, 1.45]	.08	R	<.0001	59
	Asian	16	3358	6242	1.16 [0.70, 1.92]	.57	R	<.00001	87
	Latin-American	4	1408	1128	1.33 [0.73, 2.42]	.36	F	.27	24
ε3	Total	47	15066	28696	0.85 [0.66, 1.10]	.21	R	<.00001	94
	Caucasian	27	10300	21264	1.12 [0.90, 1.39]	.32	R	<.00001	87
	Asian	16	3358	6278	0.56 [0.29, 1.10]	.09	R	<.00001	97
	Latin-American	4	1408	1128	0.71 [0.44, 1.13]	.15	R	.005	76
ε4	Total	47	14986	28650	1.11 [0.95, 1.30]	.18	R	<.00001	75
	Caucasian	27	10300	21478	0.94 [0.77, 1.13]	.50	R	<.00001	75
	Asian	16	3278	6044	1.43 [1.13, 1.80]	.003	R	.005	54
	Latin-American	4	1408	1128	1.41 [0.90, 2.21]	.13	R	.03	66

APOE = apolipoprotein E, CIs = confidence intervals, F = fixed model, OR = odds ratios, R = random model.

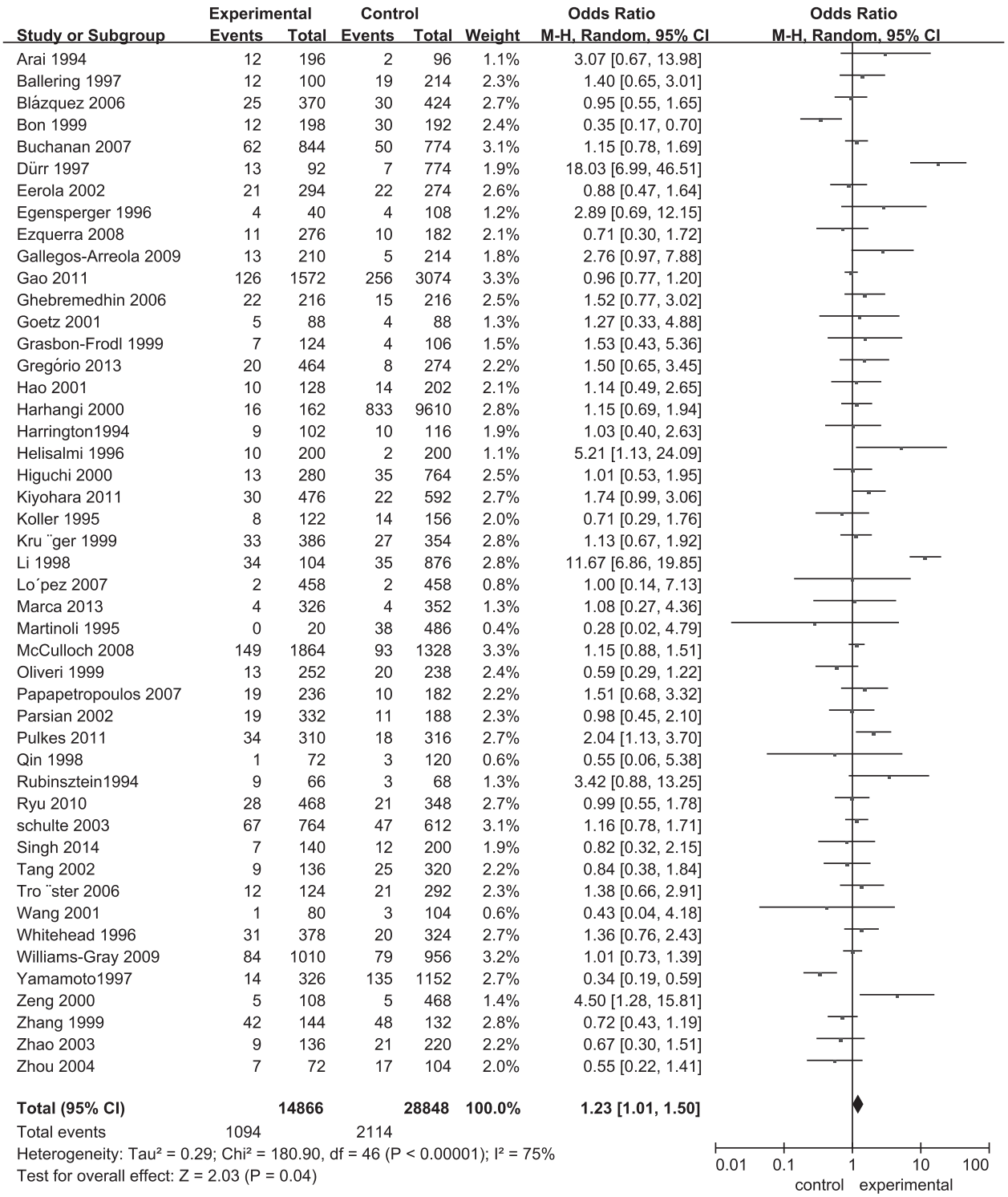


Figure 2. Forest plots of odds ratios for the association between APOE ε2 and Parkinson disease.

by ethnicity was performed. Notable, the significant heterogeneity of allele model of APOE ε2, ε3, and ε4 still exist (Except for APOE ε2 in Latin-American population) ($P=.27$, $I^2\%=24$) (Table 2). For the genotypes, significant heterogeneity were also detected in ε2ε4 ($P<.0001$, $I^2\%=58$) and ε3ε3 ($P<.0001$, $I^2\%=80$). Subgroup analysis stratified by ethnicity shown the significant heterogeneity for ε2ε4 was only detected in Asian population ($P<.0001$, $I^2\%=72$) but not in Caucasian ($P=.47$, $I^2\%=0$) and Latin-American populations ($P=.57$, $I^2\%=0$). Furthermore, significant heterogeneity for ε3ε3 were detected in

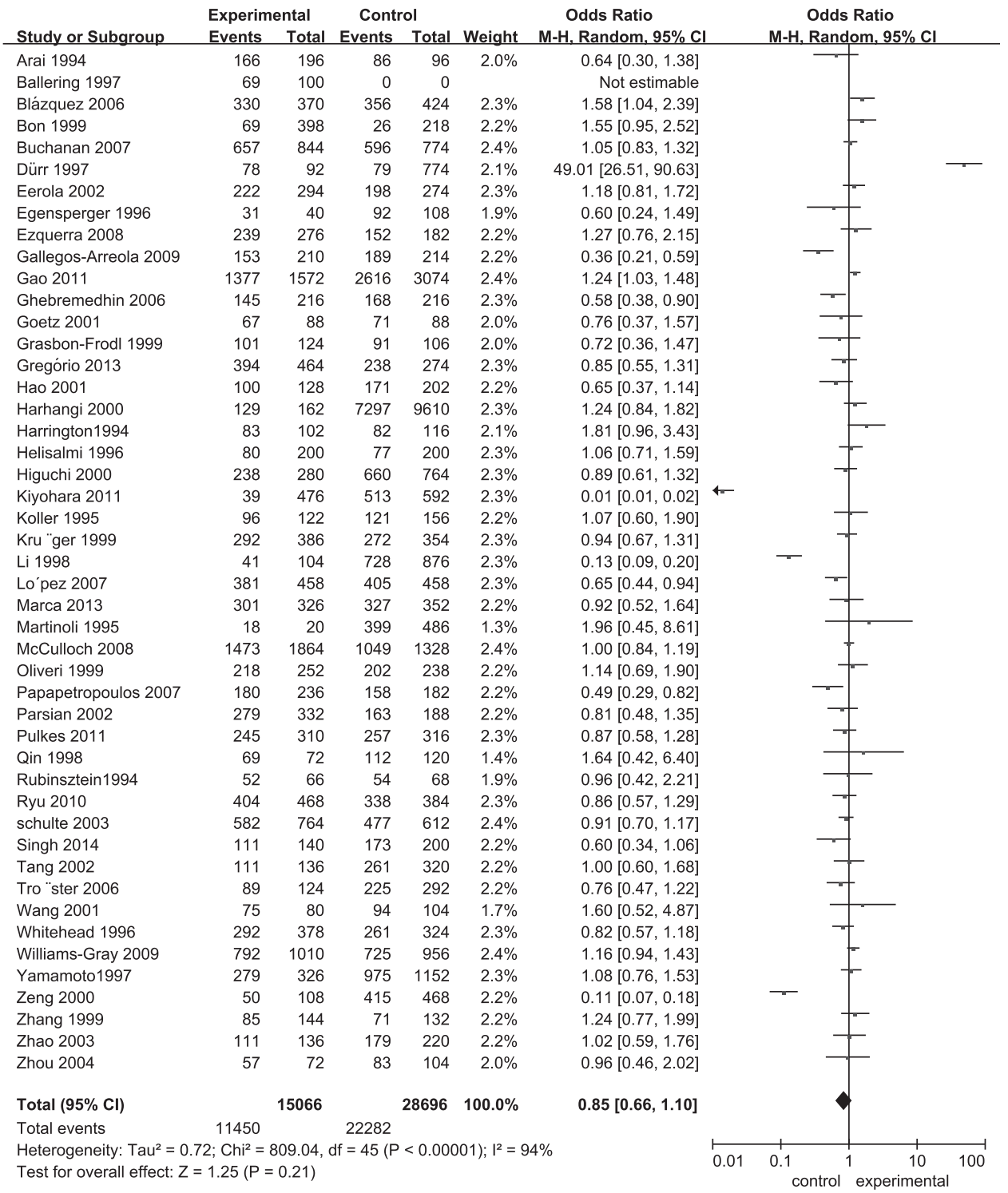


Figure 3. Forest plots of odds ratios for the association between APOE ε3 and Parkinson disease.

Asian ($P=.0004$, $I^2\%=64$) and Latin-American populations ($P<.00001$, $I^2\%=98$), but not in Caucasian population ($P=.31$, $I^2\%=11$) (Table 2).

3.5. Sensitivity analysis and publication bias

Sensitivity analysis on the overall risk estimate by excluding one study at a time was confirmed. The ORs were not significantly altered in APOE ε2, ε3, and ε4 allele analysis (Fig. 5). Begg test and Egger test were used to evaluate publication bias. The *P* value for Egger linear regression test is shown in Figure 6. The results revealed that there was no obvious publication bias in overall analysis for ε2 ($P_{egger}=.367$), ε3 ($P_{egger}=.586$) and ε4 ($P_{egger}=.069$) in APOE.

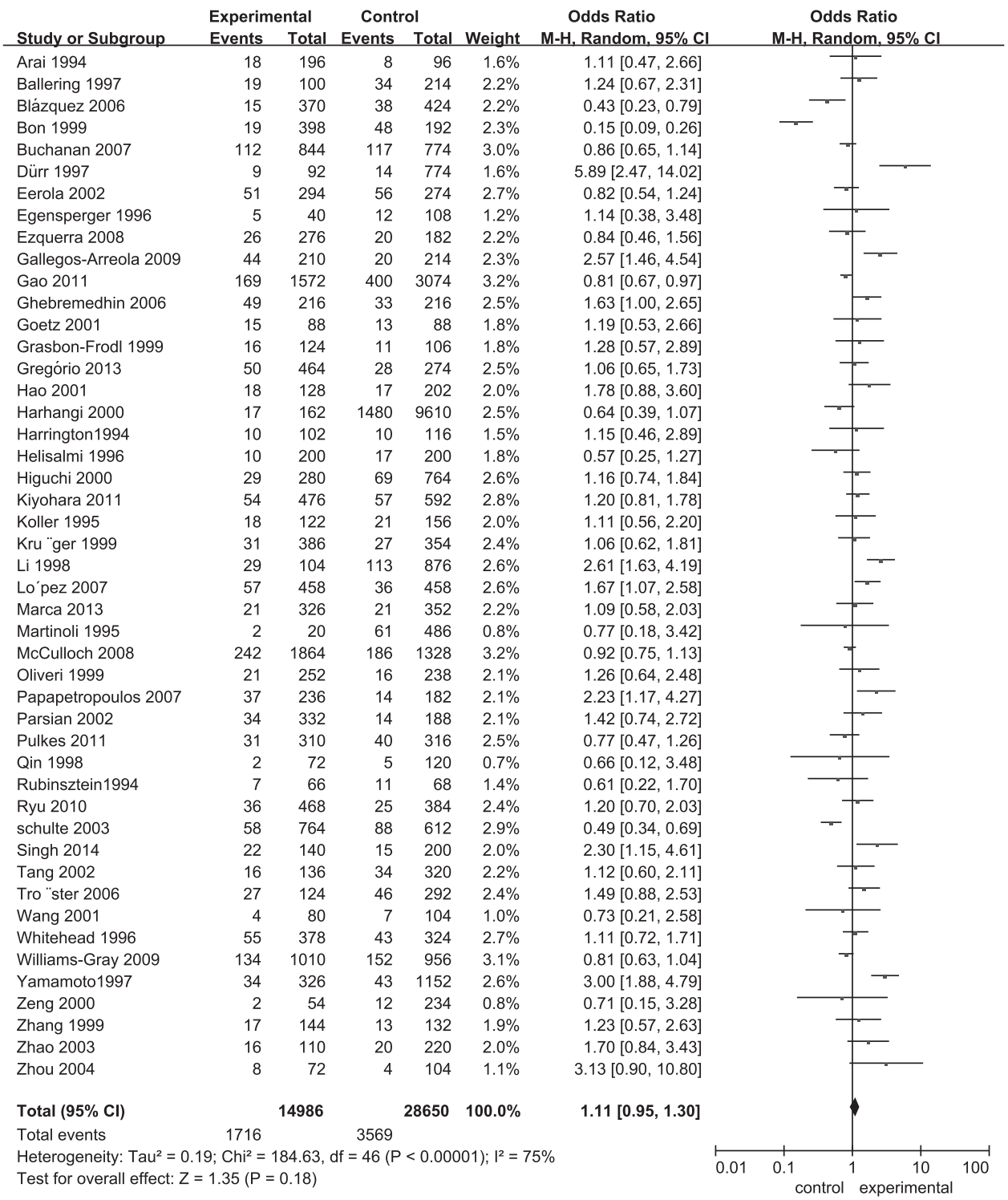


Figure 4. Forest plots of odds ratios for the association between APOE ε4 and Parkinson disease.

4. Discussion

It has suggested that the AD and PD may share several similar pathogenesis. Both the two diseases were characterized by neuronal loss and protein aggregation.[62] And both the clinical features included dementia and extra-pyramidal symptoms.[63] The APOE gene was a major cholesterol carrier that supports lipid transport and injury repair in the brain, which located on chromosome 19q13.2.[64–65] It was considered to be a plausible candidate gene for influencing the neurodegenerative process in

Table 3

The association between APOE polymorphisms and Parkinson disease.

Genotypes	subgroups	Number of studies	Numbers		Test of association		Model	Test of heterogeneity	
			case	control	OR [95% CI]	*P*		*P*	I^2 (%)
ε2ε2	Total	24	4056	11049	0.99 [0.65, 1.51]	.98	F	.96	0
	Caucasian	13	2819	8625	1.09 [0.64, 1.86]	.75	F	.91	0
	Asian	10	1132	2317	0.67 [0.31, 1.45]	.31	F	.86	0
	Latin-American	1	105	107	4.20 [0.46, 38.20]	.20	–	–	–
ε2ε3	Total	42	5979	13040	1.11 [0.99, 1.24]	.07	F	.17	17
	Caucasian	23	3736	9719	1.12 [0.98, 1.28]	.10	F	.34	9
	Asian	15	1539	2757	1.02 [0.82, 1.28]	.84	F	.06	40
	Latin-American	4	704	564	1.36 [0.86, 2.17]	.19	F	.67	0
ε2ε4	Total	36	5528	12363	1.69 [1.10, 2.62]	.02	R	<.00001	58
	Caucasian	20	3397	9206	1.05 [0.78, 1.41]	.76	F	.47	0
	Asian	12	1427	2593	4.43 [1.62, 12.10]	.004	R	<.0001	72
	Latin-American	4	704	564	0.52 [0.15, 1.72]	.28	F	.57	0
ε3ε3	Total	42	5979	13040	0.98 [0.81, 1.17]	.80	R	<.00001	80
	Caucasian	23	3736	9719	1.02 [0.92, 1.13]	.74	F	.31	11
	Asian	15	1539	2757	0.86 [0.66, 1.12]	.26	R	.0004	64
	Latin-American	4	704	564	1.93 [0.26, 14.23]	.52	R	<.00001	98
ε3ε4	Total	41	5813	12946	0.94 [0.86, 1.02]	.14	F	.01	36
	Caucasian	22	3570	9652	0.86 [0.77, 0.96]	.006	F	.64	0
	Asian	15	1539	2757	0.99 [0.83, 1.18]	.93	F	.10	33
	Latin-American	4	704	564	1.44 [1.08, 1.91]	.01	R	.007	35
ε4ε4	Total	35	5361	12447	1.11 [0.86, 1.43]	.42	F	.84	0
	Caucasian	20	3534	9536	1.11 [0.84, 1.46]	.48	F	.54	0
	Asian	11	1123	2347	0.94 [0.47, 1.91]	.87	F	.83	0
	Latin-American	4	704	564	1.62 [0.56, 4.67]	.37	F	.58	0

APOE = apolipoprotein E, CIs = confidence intervals, F = fixed model, OR = odds ratios, R = random model.

AD, PD and PD dementia (PDD).[66–67] Among the three alleles (ε2, ε3, and ε4), the APOE ε4 was shown to be significantly associated with AD,[67] onset of late onset AD (LOAD), PD, and PDD risk.[23,67–68] The APOE ε4 is the "risk" variant for several phenotypes compared with other 2 alleles. APOE ε3 was considered to be neutral. And APOE ε2 generally was considered to be a protective factor in neurodegenerative diseases.

Three studies have reported the association between APOEε2 and/or ε4 and PD risk. Whitehead et al[69] has firstly investigated the APOE ε4 and PD risk using a case-control study and meta-analysis of 6 studies and shown no significant association between APOE ε4 and the risk of PD. Subsequently, Huang et al[70] carried out a meta-analysis with 22 publications and found the APOE ε2, but not APOE ε4, was positively associated with PD. Five years later, Williams-Gray et al[71] performed a update meta-analysis with 32 articles and detected the APOE ε4 was a susceptible factor for PD compared to healthy control. In present meta-analysis, we detected a significant increase of APOE-ε2 carriers among PD patients compared to controls. However, no association was observed between APOE-ε3 and -ε4 and PD risk in overall populations, which was similar with the results reported by Whitehead et al[69] and Huang et al,[70] but different from the results reported by Williams-Gray et al.[71] This inconsistent in the 2 meta-analysis may due to the different number of cases and controls included in the studies. In present study, we included 15 more article than that in Williams-Gray et al,[71] which may increase the power to detect the genetic association between APOE-ε4 and PD. However, no subgroup analysis stratified by ethnicity was performed out in previous meta-analysis. For the important role of gene background in PD, subgroup analysis based on ethnicity was carried out. Notable, the genetic association between APOE polymorphisms and PD varied in different populations. The significant association between APOE-ε2 and PD risk disappeared in Caucasian, Asian, and Latin-American subgroups. In addition, a statistical genetic association was found between APOE-ε4 and PD risk in Asian subgroup, but not in Caucasian and Latin-American subgroups, which might indicate the important role of genetic background in the pathogenesis of PD.

Recent researches have been shown a significant higher total- and LDL-cholesterol levels typically occur with the ε4 allele; which, forming monofibrillary peptides, precipitates and forms dense structures (amyloid plaques) that are the main component of neurofibrillary tangles.[72] However, ε3 and ε2 isoforms have affinity to the Tau protein; which confers protection from hyperphosphorylationon the Tau protein.[73] Our combined analysis suggested the APOE-ε4, but not APOE-ε2, was the susceptible factor for PD. The inconsistent results in previous meta-analyses may due to the limited number of included studies, as well as the number of subjects. Furthermore, we firstly conducted a subgroup analysis stratified by ethnicity and detected the APOE-ε4 was a risk factor for PD only in Asian population, but not in Caucasian and Latin-American populations.

Several limitations were presented in this meta-analysis. First, mixed dementia might exist in included case-control study, which was shown to increase the apparent association of APOE with PD. Second, multiple factors including genetic factors, environmental factors, as well as the interaction of the 2 factors, and other unknown risk factors should be considered in the pathogenesis of PD. Third, the number of studies and subjects was relatively small, especially in Latin-American population. To identify these genetic associations, larger number of case-control designed studies with more subjects is necessary.

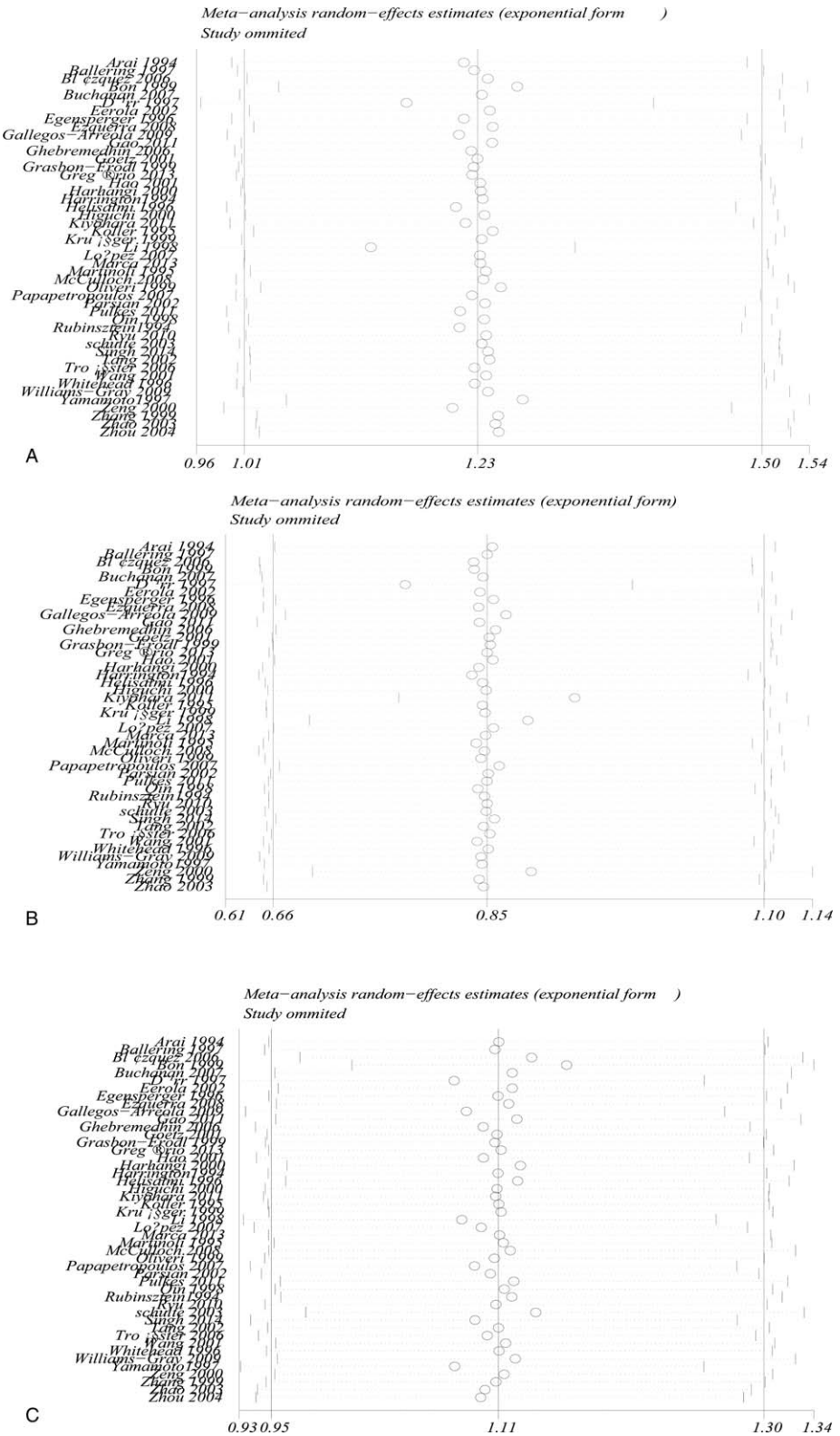
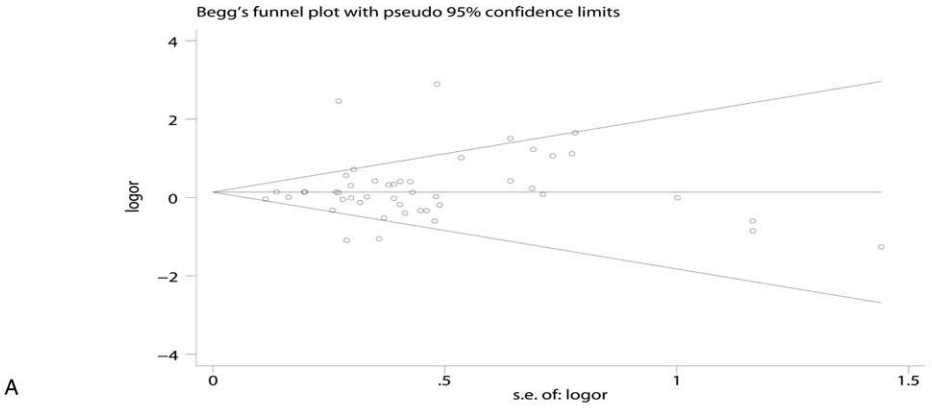
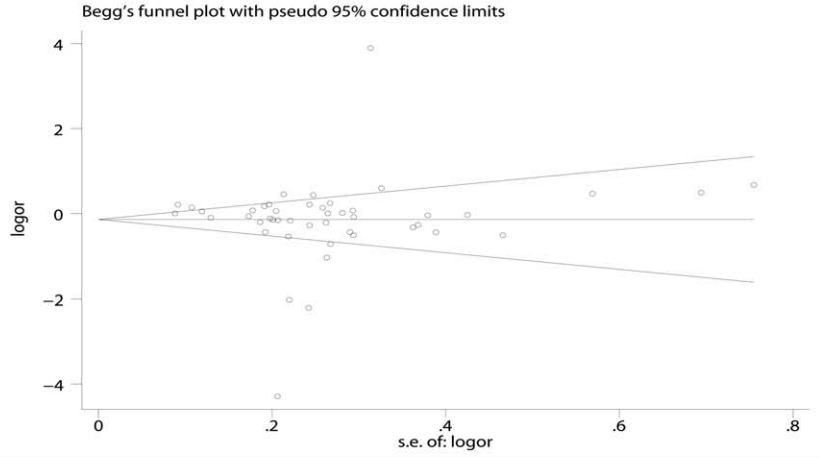


Figure 5. Sensitivity analyses between APOE and Parkinson disease. A: ε2; B: ε3; C: ε4.



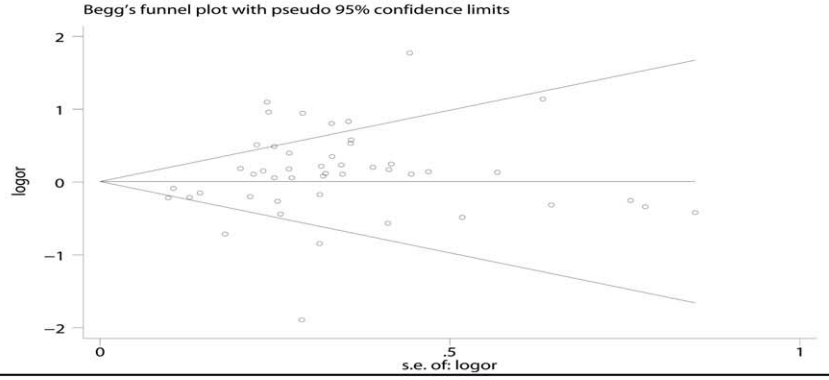
A

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.0070455	.1820687	-0.04	0.969	-.3737508	.3596597
bias	.5343134	.5859744	0.91	0.367	-.6458996	1.714526



B

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0100161	.2972768	0.03	0.973	-.589106	.6091382
bias	-.805624	1.468086	-0.55	0.586	-3.764357	2.153109



C

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.2439425	.1515164	-1.61	0.114	-.5491121	.0612272
bias	1.143009	.6127706	1.87	0.069	-.0911745	2.377192

Figure 6. Publication bias of literatures for allelic model of APOE ε2, ε3, and ε4 were tested by Begg's funnel plot and Egger's test. A: ε2; B: ε3; C: ε4.

5. Conclusion

Our meta-analysis suggests that APOE ε2 is associated with PD in total group and APOE ε4 carrier is associated with PD in Asian population. In addition, it provides a support for the risk effect of ε2ε4 in total group and ε3ε4 in Latin-American population.

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