Int J Clin Exp Med 2016;9(3):5334-5346
www.ijcem.com /ISSN:1940-5901/IJCEM0020341

Review Article

Relationship between apolipoprotein E gene polymorphism and Parkinson's disease: a meta-analysis

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Received November 23, 2015; Accepted February 13, 2016; Epub March 15, 2016; Published March 30, 2016

Abstract: The Apolipoprotein E (*APOE*) gene, with its 3 common isoforms (E2, E3 and E4), was such a candidate risk gene in Parkinson's disease explored by many case-control studies, but the conclusion still remains contradictory and inconclusive. To identify the association between *APOE* gene polymorphism and the risk of PD, we performed this meta-analysis. A total of 63 eligible published studies including 8546 PD cases and 10403 health controls were searched up to 5th, 2015 in the final analysis. All literature was searched in PUBMED, EMBASE, Web of science, Wanfang Data and China National Knowledge Infrastructure. Overall, no significant association was found between *APOE* gene polymorphism and Parkinson's disease risk under four genetic models (E2 allele vs. E3 allele: OR = 1.16, 95% = 0.967-1.398, P = 0.11; E4 allele vs. E3 allele: OR = 1.10, 95% = 0.9998-1.2179, P = 0.0507; E2 carriers vs. E3 carriers: OR = 1.07, 95% CI = 0.873-1.305, P = 0.52; E4 carriers vs. E3E3: OR = 1.12, 95% CI = 0.992-1.264, P = 0.066). The results of subgroup analysis by ethnicity showed no significant association was observed in both Caucasians and Asians. No potential publication bias was detected in any genetic model in our meta-analysis which suggested the stability of our results. In conclusion, our study suggests that *APOE* gene polymorphism were not associated with PD risk.

Keywords: *APOE*, polymorphism, Parkinson's disease, meta-analysis

Introduction

Parkinson's disease (PD) is the 2nd most common neurodegenerative disorder among the elderly population, which affects about 2% of the population older than 65 years of age, although it has been observed in younger people [1, 2]. It is clinically characterized by parkinsonism (resting tremors, rigidity, slowness of movement, postural imbalance) [3] and pathologically by the loss of neurons in the substantia nigra and in association with the presence of ubiquitinated protein deposits in the cytoplasm of neurons [4]. After English doctor James Parkinson describe this disorder for the first time, people argue whether hereditary or environmental factor is the main factor of PD. With the discovering of disease-causing gene α-synuclein and Parkin, the role of hereditary factor has been recognized gradually [5, 6]. Significant researches have been conducted to establish the relationship between the functional variants of genes and the risk of PD in different ethnic groups across the world, including UCHL1 (ubiquitin carboxy-terminal hydrolase L1), NURR1 (nuclear receptor-related 1), DJ-1, PINK1 genes and so on [7, 8].

Apolipoprotein E (*APOE*), located on chromosome 19, with 3 common isoforms (E2, E3 and E4) and 6 genotypes (E2E2, E2E3, E2E4, E3E3, E3E4 and E4E4), encodes a major lipid-binding protein, which serves as a cholesterol carrier [9]. These isoforms are defined by amino acid changes at positions 112 (rs.429358) and 158 (rs.7412) and alleles (E2, E3 and E4) are defined. E3 is the most common isoform, with a frequency of approximately 70-80% [10]. *APOE* is highly polymorphic and plays an imperative role in endogenous lipoprotein metabolism and tissue distribution. It has been discovered that the presence of the *APOE* E4 allele is associated with higher levels of total and LDL serum cholesterol while *APOE* E2 is associated with the lower effect with reference to cholesterol effects from E3 allele [11]. Huang et al [12]

reported the association of lower serum low-density lipoprotein cholesterol level with PD patients which suggested that abnormality in gene of lipid metabolic pathway may contribute to PD.

Numerous case-control studies investigating a role for *APOE* in PD, however, results in these studies are conflicting. The results of previous meta-analysis have suggested *APOE*-E2 was a risk factor for susceptibility to Parkinson's disease [13, 14]. Even so, there are still no consistent perspective about the role of *APOE* and PD. Therefore, this comprehensive meta-analysis were designed to overcome the limitations of independent studies, resolve inconsistence, reduce the likelihood that random errors were responsible for false association and reveal the real association between *APOE* polymorphism and the development of PD.

Materials and methods

Literature search

Relevant studies evaluating the *APOE* gene polymorphism and PD were searched by the following electronic database: Pubmed, Web of Science, Embase, China national Knowledge Infrastructure (CNKI), Wanfang Data, with the last updated search conducted before April 2015. We used various combinations of keywords as search terms, including "apolipoprotein E or *APOE*", "Parkinson disease or Parkinson's disease or PD" without language restriction.

Inclusion and exclusion criteria

The criteria used to include studies in this meta-analysis were as follows: (1) providing information evaluating the association of *APOE* gene polymorphism with PD; (2) using a case-control or nest case-control design; (3) containing genotype frequency information for calculating an odds ratio (OR) and its 95% confidence interval (CI). If one article was published for more than one time, the one with more comprehensive data would be selected. Reasons for exclusion of studies were: (1) lack of control group; (2) overlapping study populations. A total of 1000 relevant studies were searched, and 900 were excluded, only 63 met all inclusion criteria.

Data extraction

Two reviewers independently viewed all the papers searched from the electronic data and standard protocol was used for data extraction. A third reviewer as served as an arbiter when different opinion occurred. The information extracted from each eligible study: The last name of the first author, publication year, ethnicity of the population studied, number of cases and controls, baseline characteristics of population in each studies, genotype information and frequencies of alleles, Hardy-Weinberg equilibrium (HWE) in controls. It should be noticed that the genotype information were not reported in some papers. Therefore, the frequency of each allele was extracted from each paper or calculated manually if not reported explicitly.

Statistical analysis

Pooled OR (odds ratio) and CI (corresponding 95% confidence intervals) were estimated for the association between *APOE* gene polymorphism and PD risk. HWE for the controls was assessed in each study by the Chi-square test or Fisher exact test goodness of fit. Genotype E3E3, well accepted as the 'wild-type' genotype, is the most common genotype between the healthy population and PD cases with the frequency about 67% [15]. Therefore, genotype E3E3 and allele E3 are designated as reference category. Risk of E2 carriers (E2E2, E2E3 and E2E4 genotypes), E4 carriers (E4E4, E3E4 and E2E4 genotypes) allele E2 and allele E4 are compared with E3E3 and allele E3 respectively. Heterogeneity among studies was measured by Q statistic ($P<0.10$ was considered statistically significant heterogeneity) and I^2 statistic. I^2 values of 25%, 50% and 75% were defined as low, moderate and high heterogeneity respectively. Association of *APOE* gene polymorphism and PD risk were measured using random or fixed effect models according to the heterogeneity of the study. Begg's funnel plot and egger's test [16] was used for assessment of publication bias.

Results

Study characteristics

1864 published papers were relevant to the initial literature search. Finally, 63 eligible stud-

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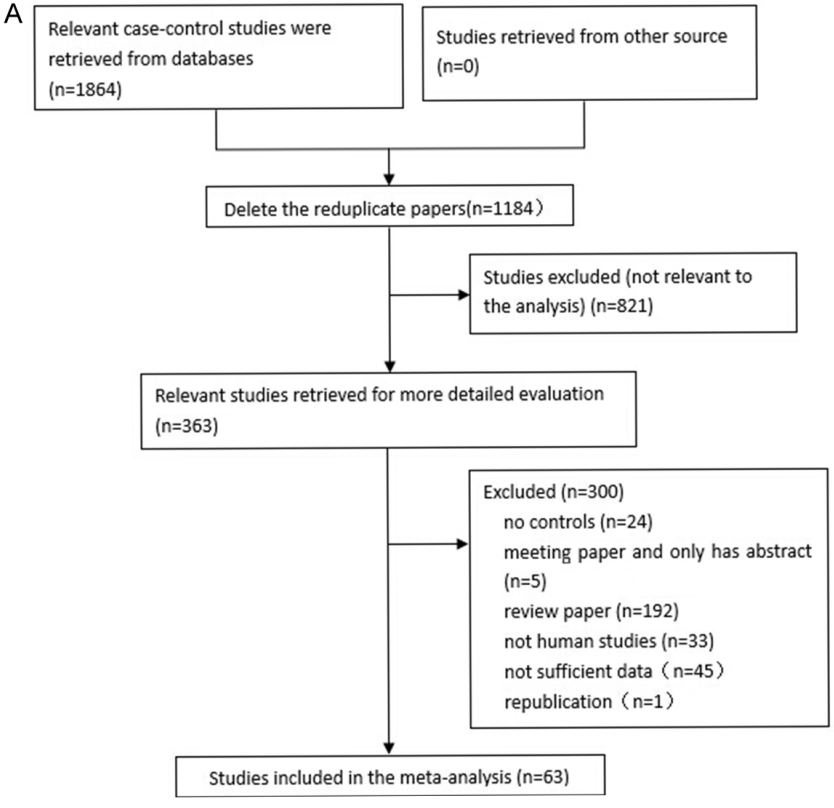
Relevant case-control studies were retrieved from databases (n=1864)
Studies retrieved from other source (n=0)
Delete the reduplicate papers(n=1184）
Studies excluded (not relevant to the analysis) (n=821)
Relevant studies retrieved for more detailed evaluation (n=363)
Excluded (n=300)
no controls (n=24)
meeting paper and only has abstract (n=5)
review paper (n=192)
not human studies (n=33)
not sufficient data（n=45）
republication（n=1）
Studies included in the meta-analysis (n=63)

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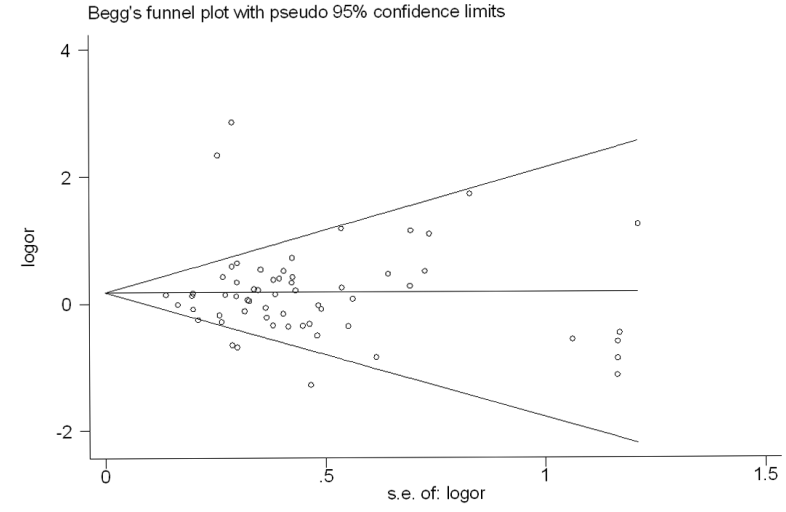
Begg's funnel plot with pseudo 95% confidence limits
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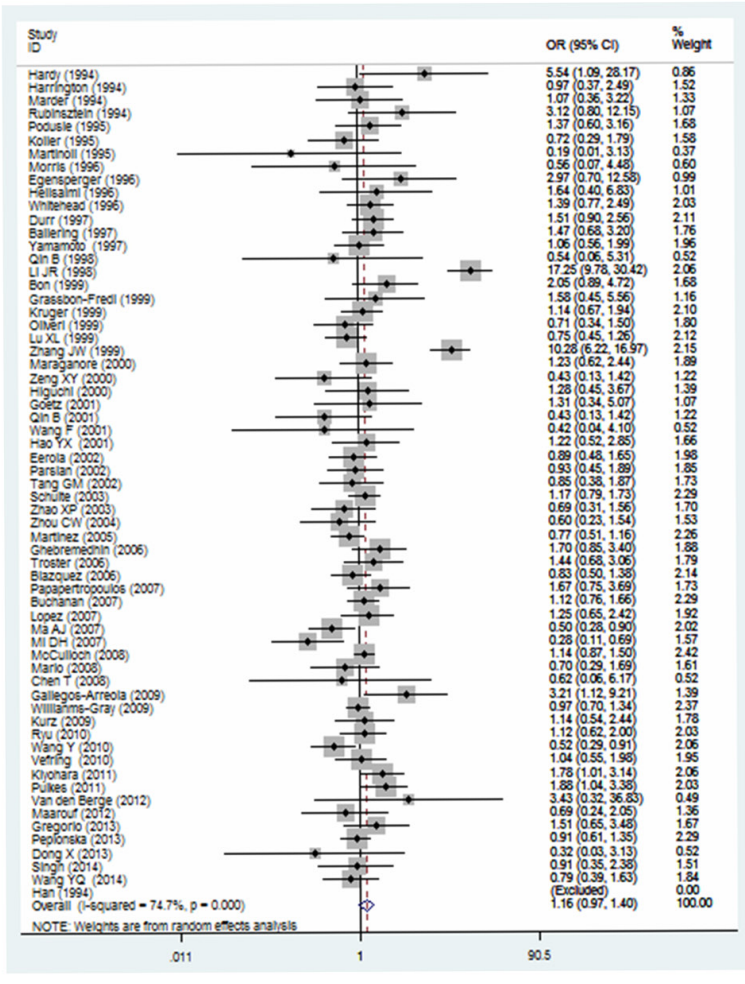
Study ID
OR (95% CI)
% Weight
Hardy (1994) 5.54 (1.09, 28.17) 0.86
Harrington (1994) 0.97 (0.37, 2.49) 1.52
Mardet (1994) 1.07 (0.36, 3.22) 1.33
Rubinsztein (1994) 3.12 (0.80, 12.15) 1.07
Podusle (1995) 1.37 (0.60, 3.16) 1.68
Koller (1995) 0.72 (0.29, 1.79) 1.58
Martinoli (1995) 0.19 (0.01, 3.13) 0.37
Morris (1996) 0.56 (0.07, 4.48) 0.60
Egensperger (1996) 2.97 (0.70, 12.58) 0.99
Hellsalmi (1996) 1.64 (0.40, 6.83) 1.01
Whitehead (1996) 1.39 (0.77, 2.49) 2.03
Durr (1997) 1.51 (0.90, 2.56) 2.11
Ballering (1997) 1.47 (0.68, 3.20) 1.76
Yamamoto (1997) 1.06 (0.56, 1.99) 1.96
Qin B (1998) 0.54 (0.06, 5.31) 0.52
Li JR (1998) 17.25 (9.78, 30.42) 2.06
Bon (1999) 2.05 (0.89, 4.72) 1.68
Grassbon-Fredl (1999) 1.58 (0.45, 5.56) 1.16
Kruger (1999) 1.14 (0.67, 1.94) 2.10
Olivieri (1999) 0.71 (0.34, 1.50) 1.80
Lu XL (1999) 0.75 (0.45, 1.26) 2.12
Zhang JW (1999) 10.28 (6.22, 16.97) 2.15
Maraganore (2000) 1.23 (0.62, 2.44) 1.89
Zeng XY (2000) 0.43 (0.13, 1.42) 1.22
Higuchi (2000) 1.28 (0.45, 3.67) 1.39
Goetz (2001) 1.31 (0.34, 5.07) 1.07
Qin B (2001) 0.43 (0.13, 1.42) 1.22
Wang F (2001) 0.42 (0.04, 4.10) 0.52
Hao YX (2001) 1.22 (0.52, 2.85) 1.66
Eerola (2002) 0.89 (0.48, 1.65) 1.98
Parsian (2002) 0.93 (0.45, 1.89) 1.85
Tang GM (2002) 0.85 (0.38, 1.87) 1.73
Schulte (2003) 1.17 (0.79, 1.73) 2.29
Zhao XP (2003) 0.69 (0.31, 1.56) 1.70
Zhou CW (2004) 0.60 (0.23, 1.54) 1.53
Martinez (2005) 0.77 (0.51, 1.16) 2.26
Ghebremedhin (2006) 1.70 (0.85, 3.40) 1.88
Troster (2006) 1.44 (0.68, 3.06) 1.79
Blazquez (2006) 0.83 (0.50, 1.38) 2.14
Papapertropoulos (2007) 1.67 (0.75, 3.69) 1.73
Buchanan (2007) 1.12 (0.76, 1.66) 2.29
Lopez (2007) 1.25 (0.65, 2.42) 1.92
Ma AJ (2007) 0.50 (0.28, 0.90) 2.02
MI DH (2007) 0.28 (0.11, 0.69) 1.57
McCulloch (2008) 1.14 (0.87, 1.50) 2.42
Mario (2008) 0.70 (0.29, 1.69) 1.61
Chen T (2008) 0.62 (0.06, 6.17) 0.52
Gallegos-Arreola (2009) 3.21 (1.12, 9.21) 1.39
Williahms-Gray (2009) 0.97 (0.70, 1.34) 2.37
Kurz (2009) 1.14 (0.54, 2.44) 1.78
Ryu (2010) 1.12 (0.62, 2.00) 2.03
Wang Y (2010) 0.52 (0.29, 0.91) 2.06
Vefring (2010) 1.04 (0.55, 1.98) 1.95
Kiyohara (2011) 1.78 (1.01, 3.14) 2.06
Pulkes (2011) 1.88 (1.04, 3.38) 2.03
Van den Berge (2012) 3.43 (0.32, 36.83) 0.49
Maarouf (2012) 0.69 (0.24, 2.05) 1.36
Gregorio (2013) 1.51 (0.65, 3.48) 1.67
Peplonska (2013) 0.91 (0.61, 1.35) 2.29
Dong X (2013) 0.32 (0.03, 3.13) 0.52
Singh (2014) 0.91 (0.35, 2.38) 1.51
Wang YQ (2014) 0.79 (0.39, 1.63) 1.84
Han (1994) (Excluded) 0.00
Overall (I-squared = 74.7%, p = 0.000) 1.16 (0.97, 1.40) 100.00
NOTE: Weights are from random effects analysis
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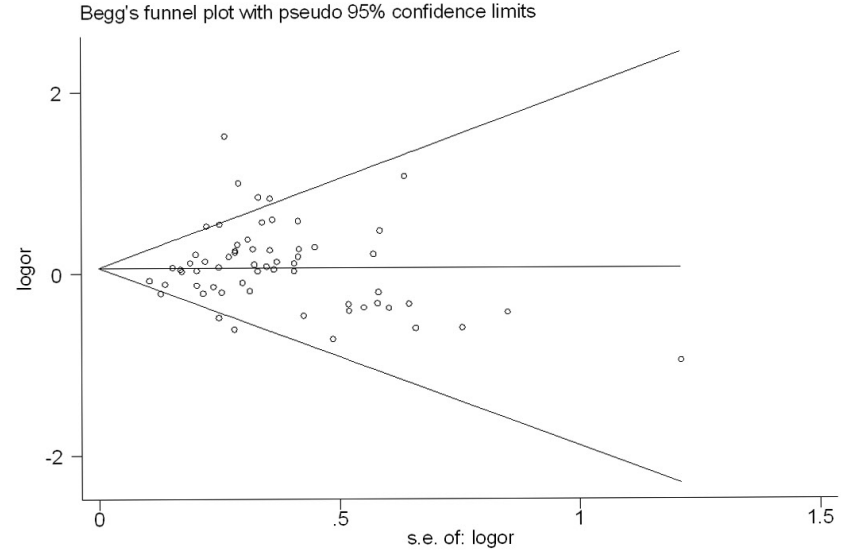
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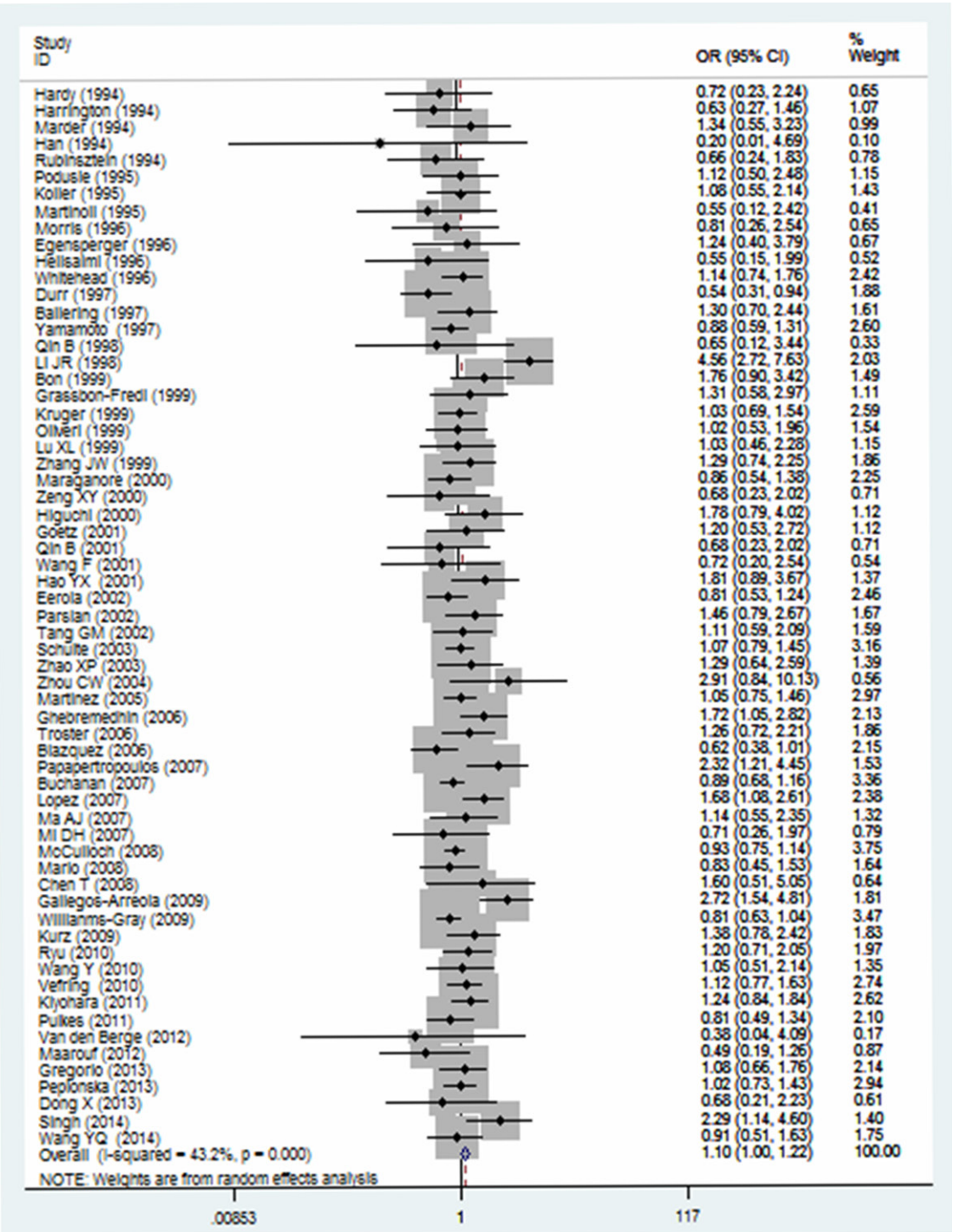

Figure 1. A. Flow chart of the literature selection; B. Forest plot of the meta-analysis of E2 versus E3; C. Forest plot of the meta-analysis of E4 versus E3; D. Funnel plot of the meta-analysis of E2 versus E3; E. Funnel plot of the meta-analysis of E4 versus E3.

ies, including 8546 PD cases and 10403 health controls, which reported *APOE* polymorphism and the risk of PD, were included in this meta-analysis [14, 17-77]. The flow chart of the literature selection was provided in **Figure 1**. Of the 63 studies, 34 studies conducted in Caucasian, 22 conducted in Asian and 6 studies conducted in mixed population. 55 studies

Table 1. Characteristic of studies included in the meta-analysis

Reference	Year	Country	Numbers		characteristics of included studies		Genotyping method	HWE in controls P	NOS
			PD	Control	PD group	Controls group			
Hardy	1994	USA/UK	24	35	Age = 75±7	NA	NA	\	4
Harrington	1994	UK	51	58	Male: 26 age = 77.7 (7.1)	Male: 28 age = 78.1 (7.7)	PCR-RFLP	0.233	6
Marder	1994	US	59	44	Age = 71.2	Age = 72.6	PCR-RFLP	0.101	7
Han	1994	US	5	6	Age = 82±6 male: 5	Age = 70±10 male: 3	PCR-RFLP	\	4
Rubinsztein	1994	UK	34	34	Male: 26 age = 57	Age and sex matched	PCR-RFLP	0.416	5
Podusle	1995	USA	54	77	Age = 74.1±7.5	Age = 71.9±7.4	PCR-RFLP	\	5
Koller	1995	USA	61	78	Male: 38 age = 67.4±7.9	Male: 37 age = 69.9±6.5	PCR	0.063	6
Martinoli	1995	Canada	10	243	Age = 24-86	Age = NA	PCR-RFLP	0.147	5
Morris	1996	UK	11	99	NA	NA	PCR-RFLP	\	4
Egensperger	1996	Germany/Austria	20	54	Age = 76±6.2	Age = 71.2±9.5	PCR-RFLP	0.462	5
Helisalmi	1996	Finland	15	60	Male: 8 age = 71±6	Male: 28 age = 69±8	PCR-RFLP	0.016	5
Whitehead	1996	Ireland	189	162	Male: 123 age = 56.9 (6.6)	Male: 101 age = 58 (7.1)	PCR-RFLP	0.242	8
Durr	1997	France	103	387	Male: 56 age = 56.6	Male: 215 age = 67	PCR	0.426	6
Ballering	1997	The netherland	50	107	NA	NA	Semi-nested PCR	0.959	5
Yamamoto	1997	Japan	163	576	Male: 65 age = 59.3	Aged 32-86 years	PCR-RFLP	0.259	5
Qin B	1998	China	36	60	Male: 24 age = 66.6±10.3	Male: 55 age = 68.1±9.2	PCR-RFLP	0.014	5
Li JR	1998	China	52	438	Male: 31 age = 58.8±12.6	Male: 228 age = 53.16±13.3	PCR-RFLP	0.003	4
Grassbon-Frodl	1999	Germany	62	53	Male: 29 age = 70	Male: 22 age = 71	PCR-RFLP	0.459	6
Bon	1999	The Netherland	50	96	NA	NA	Semi-nested PCR	\	4
Kruger	1999	Germany	193	177	Male: 108 age = 66.53 (11.08)	Resemble age and sex of PD group	PCR-RFLP	0.186	6
Oliveri	1999	Italy	126	119	Male: 72 age = 65.8 (9.01)	Male: 57 age = 66.3 (8.5)	PCR-RFLP	<0.001	6
Lu XL	1999	China	72	66	Male: 46 age = 60.7±11.8	Male: 39 age = 77±7.5	PCR-RFLP	<0.001	5
Zhang JW	1999	China	72	438	Age = 60.67±11.68	Age = 65.88±9.5	PCR-RFLP	0.003	5
Maraganore	2000	USA	139	113	Male: 90 age = 69 (39-91)	Male: 39 age = 62 (31-82)	PCR	0.325	7
Zeng XY	2000	China	54	234	Male: 37 age = 68±6.1	Male: 158 age = 59.2±16.3	PCR-RFLP	<0.001	5
Higuchi	2000	Japan	140	382	Male: 61 age = 56.5±9.5	Male: 117 age = 74.0±5.6	PCR	\	6
Goetz	2001	US	44	44	NA	NA	PCR-RFLP	0.811	5
Qin B	2001	China	54	234	Male: 37 age = 68.2±6.1	Male: 158 age = 59.2±16.3	PCR-RFLP	<0.001	6
Wang F	2001	China	40	52	Male: 28 age = 66.13±7.32	Male: 30 age = 65.50±8.07	PCR-RFLP	0.745	6
Hao YX	2001	China	64	101	Male: 37 age = 63±11	Male: 53 age = 62±11	PCR-RFLP	<0.001	7
Eerola	2002	Finland	147	137	Male: 87 age = 65.8	Male: 50 age = 67.2	PCR-RFLP	0.516	7
Parsian	2002	US	318	94	Male: 99 age = 67±13.7	Male: 33 age = 62±14	PCR-RFLP	0.331	6
Tang GM	2002	China	68	160	Male: 35 age = 65.61±5.42	Male: 84 age = 55.81±15.46	PCR-RFLP	<0.001	7
Schulte	2003	Germany	382	306	Male: 206 age = 67.5 (10.5)	Male: 159 age = 72 (4.3)	PCR-RFLP	0.544	6

Zhao XP	2003	China	68	110	Male: 40 age = 63±11	Male: 59 age = 75±9	PCR-RFLP	0.080	7
Zhou CW	2004	China	36	52	Age = 67.4±10.2	Male: 33 age = 69.4±11.4	PCR-RFLP	0.024	5
Martinez	2005	Mixed	387	257	NA	NA	PCR-RFLP	0.488	6
Ghebremedhin	2006	The Netherland	108	108	Male: 62 age = 75.1±6.9	Male: 62 age = 75.1±6.9	PCR	0.008	6
Troster	2006	USA	62	146	NA	NA	PCR	0.135	5
Blazquez	2006	Spain	276	212	Male: 162 age = 71.1±10.2	Male: 110 age = 70.9±8	PCR-RFLP	0.104	6
Papapertropoulos	2007	USA	118	91	Male: 85 age = 77±7.9	Male: 43 age = 79.1±12.8	PCR	0.619	5
Buchanan	2007	USA	422	387	Male: 239 age = 66.95±9.8	Male: 114 age = 64.16±10.83	PCR	0.505	7
Lopez	2007	Mexico	229	229	Male: 138 age = 62.28±12.85	Male: 138 age = 63.97±11.23	PCR-RFLP	0.681	6
Ma AJ	2007	China	133	105	Male: 73 age = 68.38±9.18	Male: 62 age = 68.26±9.18	PCR-RFLP	0.362	6
Mi DH	2007	China	68	56	Male: 41 age = 67±7.09	Male: 30 age = 68.26±9.18	PCR-RFLP	0.558	6
McCulloch	2008	USA	932	664	Male: 636 age = 67.3	Male: 73 age = 67.3	PCR-RFLP	\	6
Mario	2008	Spain	138	91	Male: 80 age = 56±8.4	Male: 40 age = 67±9.2	PCR-RFLP	0.087	5
Chen T	2008	China	26	49	Age = 73.38±9.68	Male: 40 age = 70.1±8.4	PCR-RFLP	0.729	6
Gallegos-Arreola	2009	Mexico	105	107	Male: 63 age = 63±9	Male: 47 age = 50±14	PCR-RFLP	<0.001	4
Willianms-Gray	2009	UK	505	478	Male: 303 age = 62.5±11.8	Male: 229	Taqman	0.304	6
Kurz	2009	Norway	95	73	NA	NA	PCR-RFLP	0.000	5
Ryu	2010	Korea	234	192	Male: 68 age = 71.1±8.2	Male: 97 age = 72.2±4.4	PCR	0.404	7
Wang Y	2010	China	150	100	Male: 88 age = 68.38±9.18	Male: 55 age = 68.26±9.18	PCR	0.389	6
Vefring	2010	Norway	203	187	Male: 120 age = 68.2±9.1	Male = 99 age = 66.2±9.6	LightCycler	\	6
Kiyohara	2011	Japan	238	296	Male: 91 age = 68.5±8.68	Male: 114 age = 69.7±5.63	Taqman	0.086	5
Pulkes	2011	Thailand	155	158	Male: 88 age = 61.2±9.8	Age: older than 65	PCR-RFLP	0.423	5
van den Berge	2012	The Netherland	9	10	Male: 7 age = 79	Male: 7 age = 82	NA	0.050	4
Maarouf	2012	USA	43	49	Male: 30 age = 79 (64-90)	Male: 31 age = 83 (68-97)	NA	\	5
Gregorio	2013	Brazil	232	137	Male: 143 age = 69.2±11.1	Male: 66 age = 71.7±8.5	PCR-RFLP	0.515	6
Peplonska	2013	Poland	407	305	Male: 223 age = 64.2±11.6	Male: 85 age = 70.36±5.9	taqman	0.195	7
Dong X	2013	China	50	50	Male: 34 age = 65.93±11.28	Male: 30 age = 65.02±9.19	PCR-RFLP	0.734	6
Singh	2014	India	70	100	Male: 38 age = 58.01±8.62	Male: 61 age = 59.71±8.11	PCR-RFLP	0.588	5
Wang YQ	2014	China	85	280	Male: 50 age = 65.53±6.54	Male: 141 age = 66.74±7.25	PCR	0.343	5

NA: Not available; HWE: Hardy-Weinberg equilibrium; PCR-RFLP: Polymerase chain reaction with restriction fragment length polymorphism; NOS: Newcastle-ottawa quality assessment scale case control studies; PD: Parkinson's disease.

Table 2. Main result of meta-analysis

Polymorphism	Group	No. of studies	Test of association		P_z[a] value	Test of heterogeneity		*P* value
			OR	95% CI		Model[b]	I^2 (%)	
E2 allele vs. E3 allele	ALL	62	1.16	0.97-1.40	0.110	R	74.70%	<0.001
	ALL in HWE	40	1.03	0.91-1.17	0.646	R	23.40%	0.096
	Ethnicity							
	Caucasians	39	1.12	1.01-1.24	0.029	F	0.00%	0.634
	Asians	23	1.00	0.60-1.65	0.989	R	89.20%	<0.001
	High quality	56	1.06	0.91-1.24	0.430	R	61.20%	<0.001
E4 allele vs. E3 allele	ALL	63	1.10	0.99983-1.22	0.0507	R	43.20%	<0.001
	ALL in HWE	40	1.01	0.93-1.11	0.813	F	11.30%	0.269
	Ethnicity							
	Caucasians	40	1.05	0.94-1.16	0.392	R	34.00%	0.021
	Asians	23	1.23	0.99-1.52	0.058	R	50.50%	0.003
	High quality	56	1.06	0.99-1.13	0.516	F	11.80%	0.232
E2 carriers vs. E3E3	ALL	54	1.17	0.94-1.45	0.165	R	74.50%	<0.001
	ALL in HWE	40	1.03	0.90-1.18	0.656	R	22.70%	0.104
	Ethnicity							
	Caucasians	32	1.10	0.97-1.24	0.132	F	0.00%	0.716
	Asians	22	1.02	0.59-1.77	0.935	R	88.30%	<0.001
	High quality	51	1.07	0.89-1.29	0.459	R	63.50%	<0.001
E4 carriers vs. E3E3	ALL	55	1.12	0.99-1.26	0.066	R	43.80%	<0.001
	ALL in HWE	40	1.00	0.91-1.10	0.979	F	10.70%	0.28
	Ethnicity							
	Caucasians	33	1.06	0.92-1.21	0.415	R	37.40%	0.017
	Asians	22	1.23	0.98-1.56	0.080	R	49.10%	0.005
	High quality	51	1.05	0.95-1.15	0.361	R	13.10%	0.014

a, Z test used to determine the significant of overall OR. P<0.05 was considered to be significant; b, Model, F: Fixed-effects model; R: Random-effects model; Q test used to determine heterogeneity. P>0.1 & I^2≤40%, Fixed-effects model was used, P≤0.1 & I^2>40%, Random-effects model was used; OR: Odds ratio; CI: Confidence interval; PD: Parkinson's disease; *APOE*: Apolipoprotein.

provided the data of genotypes while 8 studies only provide the alleles frequencies. Of these 55 studies, the genotype frequencies in 40 are in line with HWE among the controls, and other 15 deviated from HWE. According to the Newcastle-ottawa quality assessment scale case control studies, 56 studies were rated as high quality and 7 were rated as low quality. The characteristics of studies were presented in **Table 1**.

Main results of meta-analysis

The main results of meta-analysis regarding the relationship between E2, E4 and PD were showed in **Table 2**.

No significant association was found between *APOE-E2* allele and PD risk under two genetic models (E2 allele vs. E3 allele: OR = 1.16, 95% = 0.967-1.398, P = 0.11; E2 carriers vs. E3E3: OR = 1.07, 95% CI = 0.873-1.305, P = 0.52). In the subgroup analyses according to ethnicity, no significant association was observed in Asians but a significantly increased risk for *APOE*-E2 allele and PD risk in Caucasians population (E2 allele vs. E3 allele: OR = 1.12, 95% = 1.012-1.237, P = 0.029). No significant association were found in the stratified analysis by studies conformed to HWE and quality of studies.

The similar results were obtained in *APOE-E4* allele and PD risk under two genetic models (E4 allele vs. E3 allele: OR = 1.104, 95% = 0.9998-1.2197, P = 0.051; E4 carriers vs. E3E3: OR = 1.12, 95% CI = 0.992-1.264, P = 0.066). When stratified by ethnicity, conformed to HWE and quality of studies, no significant association

was observed. The stratified analysis by ethnicity conformed to HWE and quality of studies.

Comparison of prevalence of E2 vs. E3 alleles, under a random-effect model, among cases and controls showed no significant association (E2 allele vs. E3 allele: OR = 1.16).

Sensitivity analysis

Sensitivity analysis was conducted to evaluate the influence of single study on the pooled results by omitting individual studies in turn. After excluding the studies deviating from HWE, we obtained almost the same results, suggesting that our results were statistically robust.

Public bias

Begg's test and Egger's test were examined to assess publication bias. The shape of the funnel plots showed no evidence of obvious asymmetry in any genetic models. (E2 allele vs. E3 allele: P = 0.619; E4 allele vs. E3 allele: P = 0.889; E2 carriers vs. E3E3: P = 0.975; E4 carriers vs. E3E3: P = 0.864).

The results of Egger's test also indicated a lack of publication bias for all genetic models (E2 allele vs. E3 allele: t = -0.22, P = 0.829; E4 allele vs. E3 allele: t = 0.82, P = 0.415; E2 carriers vs. E3E3: t = -0.08, P = 0.937; E4 carriers vs. E3E3: t = 1.01, P = 0.317).

Discussion

The roles of genetic polymorphisms of *APOE* in susceptibility to PD had been well investigated by many case-control studies but the results still remains contradictory. Kiyohara [72] suggested that the *APOE* polymorphism might play an important role in PD susceptibility in Japanese population, while Gregorio [75] found that the *APOE* polymorphism did not distinguish PD patients from controls. Estimation of the correlation might be conducted on small sample size, and the confused results were concluded unsurprisingly. To summarize the published literature and clarify the relationship between *APOE* polymorphism and PD. Therefore, a meta-analysis of all studies available is imperative to estimate this relationship and provide a reliable evidence on statistical power.

In this meta-analysis, systematic literature search in different databases were carried out and included 63 independent studies of 8546 PD cases and 10403 health controls. The present meta-analysis suggested that there was no significant association of *APOE* gene polymorphism and PD risk in overall comparisons and subgroup analyses by studies conformed to HWE and quality of studies. Therefore the polymorphism of *APOE* gene may not play a vital role in the risk of PD, which conflicted with the conclusion of previous meta-analysis [14, 21, 22].

Subgroup analysis was performed by ethnicity. In Asians, pooled estimates showed that the association between *APOE*-E2, *APOE*-E4 and PD were not significant in contrast of genetic mode of E2 allele vs. E3 allele, E2 carriers vs. E3E3, E4 allele vs. E3 allele and E4 carriers vs. E3E3. However the analyses by ethnicity found that *APOE* gene polymorphism was significant associated with an increased risk for PD under genetic mode of E2 allele vs. E3 allele in Caucasians, which suggested that the association of *APOE* gene polymorphism and PD might be different in Asians and Caucasians. The differences may be explained by genetic diversity and gene-gene, gene-environment interactions varied greatly by different ethnic background.

APOE E4 allele has been associated with high levels of serum cholesterol and low-density lipoprotein cholesterol (LDL cholesterol) while E2 allele has been associated with low levels of serum cholesterol and LDL cholesterol [69]. Huang [12] found the association of lower serum LDL cholesterol level with PD patients which suggest that altered lipid metabolism and abnormalities in genes/proteins of the lipid metabolic pathway may contribute to PD risk.

It is noteworthy that only 40 of 63 studies conformed to HWE in our meta-analysis, 8 literatures did not have genotype information and other 15 studies deviated from HWE in controls. Deviation from HWE may induce genotyping error, ethnic heterogeneity, publication bias or other factors. The results, including all studies in agreement with HWE, showed that the association between E2 and PD were not significant, different with the results that including all studies. The difference of the results may be explained by heterogeneity of studies.

In our meta-analysis, we observed heterogeneity in overall comparisons of E2 allele vs. E3 allele, E2 carriers vs. E3E3, E4 allele vs. E3

allele and E4 carriers vs. E3E3, which may affect the stability of this study. When stratified by ethnicity, severe heterogeneity was observed among Asians only in E4 allele vs. E3 allele model. Hence, the ethnicity may contribute to the heterogeneity. When significant heterogeneity was detected in any genetic models, random effects model was adopted for the analysis. Publication bias is a potential factor that may influence the results of our study. In this meta-analysis no obvious publication bias were identified in any genetic models, which strengthening this conclusion.

Although quite a few studies were included in our meta-analysis, some limitations should be taken into account. Firstly, due to the lack of genotypes information, the data which could be used for genotype models were less than that of allele models. Secondly, the controls of each eligible study came from different population that some were based on community population while others were based on hospital population, therefore, the controls may not be representative of the underlying source population. Thirdly, the controls of several studies were not accord with Hardy-Weinberg equilibrium expectations. Fourthly, our results were based on unadjusted evaluate due to the insufficient of original data. Furthermore, for the sufficient of original data, such as individual gender and age information, it was hard for us to perform further subgroup analysis which would help to detect heterogeneity of this study. Finally, we only searched the literature in English or Chinese in published. It is possible that several unpublished articles with negative results or studies in other languages were missed.

In conclusion, our meta-analysis demonstrates that *APOE* polymorphism was not associated with altered risk for Parkinson's disease. Considering the limitation of this meta-analysis, further well-designed and large sample sizes regarding the association of *APOE* polymorphism and PD should be conducted in the future.

Disclosure of conflict of interest

None.

Abbreviations

APOE, Apolipoprotein E; PD, Parkinson's disease; OR, odds ratio; CI, confidential interval.

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