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Genetic polymorphisms of interleukin genes and the risk of Alzheimer's disease: An update meta-analysis

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ABSTRACT

Objectives: Recently, several meta-analyses have reported an association between interleukin (IL) gene polymorphisms and the risk of Alzheimer's disease (AD). Several further papers discussing the relationship with the risk of AD have recently been published. The aim of this meta-analysis was to re-evaluate and update the associations between IL gene polymorphisms and the risk of AD.
Methods: The search sources were PubMed, Science Direct, Scopus, and Google Scholar up to July 2015, and the following search terms were used: "interleukin 1 or interleukin 6 or interleukin 10" and "variant or polymorphism or SNP" in combination with "Alzheimer's disease". A meta-analysis using the pooled odds ratios and 95% confidence intervals was carried out to assess the associations between four polymorphisms of IL genes (−889C>T in IL-1α, −511C>T in IL-1β, −174G>C in IL-6 and −1082G>A in IL-10) and the risk of AD under the heterozygous, homozygous, dominant, and recessive models with fixed- or random-effects models.
Results: A total of 21,864 cases and 40,321 controls from 93 individual studies were included in this meta-analysis. Our results indicated that the −889C>T polymorphism was strongly associated with the increased risk of AD. However, three polymorphisms were not associated with the risk of AD.
Conclusions: Similar to previous meta-analyses, our updated meta-analysis suggested that the −889C>T polymorphism may be a factor in AD. However, the results of our meta-analysis of the −174G>C polymorphism differed from those of previous meta-analyses. Consequently, we suggest that the −174G>C polymorphism may not be a risk factor for AD.

1. Introduction

Dementia is an overall term for conditions characterized by a decline in memory, cognitive and other thinking skills that affect a person's abilities. The total number of people with dementia worldwide was estimated at 35.6 million in 2010, and is projected to be 65.7 million in 2030 and 115.4 million in 2050 (WHO, 2012). Among the several types of dementia, Alzheimer's disease (AD) is the most common. AD was first identified more than 100 years ago. However, its symptoms, causes and risk factors were only discovered in the last 30 years (Alzheimer's Association, 2014).

Several cytokines including interleukin 1 (IL-1), IL-6, tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β) have been reported to be associated with AD (Wilson et al., 2002). Interleukins (ILs) are important components of the immune system, and a deficiency in them may lead to autoimmune disease or immune deficiency. Several studies have suggested that IL-1 is related to the pathogenesis of AD. Griffin et al. reported that IL-1 immunoreactivity was increased in AD compared with non-AD subjects (Griffin et al., 1989). Sheng et al. suggested that overexpression of IL-1 was associated with evolution of neuritic plaques from diffuse amyloid-β (Aβ) deposits in AD (Sheng et al., 1995). In addition, IL-1 promotes the amyloid precursor protein (APP) cleavage pathway (Buxbaum et al., 1992). Similarly, IL-6 has been reported to be involved in AD pathogenesis. Quintanilla et al. reported that IL-6 was associated with increased levels of hyperphosphorylated tau protein in neurons (Quintanilla et al., 2004). Furthermore, Braida et al. suggested that IL-6 deficiency was associated with learning and memory skills in mice (Braida et al., 2004). These findings suggested ILs to be important factors in AD pathogenesis.

Several epidemiological studies have investigated the association between genetic polymorphisms of IL genes and the risk of AD, including −889C>T (rs1800587) in IL-1α, −511C>T (rs16944) in IL-1β, −174C>G (rs1800795) in IL-6 and −1082G>A (rs1800896) in IL-10 (Bagli et al., 2000; Bhojak et al., 2000; Du et al., 2000;

Abbreviations: OR, odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium; SNP, sing nucleotide polymorphism; AD, Alzheimer's disease; IL, Interleukin.

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Grimaldi et al., 2000; Minster et al., 2000; Nicoll et al., 2000; Rebeck, 2000; Ki et al., 2001; Prince et al., 2001; Combarros et al., 2002; Fidani et al., 2002; Green et al., 2002; Hedley et al., 2002; Mattila et al., 2002; Pirskanen et al., 2002; Pola et al., 2002; Shibata et al., 2002; Clarimon et al., 2003; Depboylu et al., 2003; Faltraco et al., 2003; Kuo et al., 2003; Licastro et al., 2003; Lio et al., 2003; Ma et al., 2003; McCarron et al., 2003; Sciacca et al., 2003; Tsai et al., 2003; Arosio et al., 2004; Capurso et al., 2004; Depboylu et al., 2004; Hayes et al., 2004; Li et al., 2004; McCulley et al., 2004; Nishimura et al., 2004; Scassellati et al., 2004; Zhang et al., 2004; Koivisto et al., 2005; Ma et al., 2005; Seripa et al., 2005; Wang et al., 2005; Culpan et al., 2006; Ramos et al., 2006; Ravaglia et al., 2006; Zhou et al., 2006; Bagnoli et al., 2007; Wang et al., 2007; Combarros et al., 2008; Deniz-Naranjo et al., 2008; Paradowski et al., 2008; Dursun et al., 2009; Hu et al., 2009; Klimkowicz-Mrowiec et al., 2009; Serretti et al., 2009; Vural et al., 2009; Capurso et al., 2010; Combarros et al., 2010; Klimkowicz-Mrowiec et al., 2010; Ribizzi et al., 2010; Shawkatova et al., 2010; Cousin et al., 2011; Vendramini et al., 2011; Heun et al., 2012; Mansoori et al., 2012; Payao et al., 2012; Moraes et al., 2013; Rasmussen et al., 2013; Torres et al., 2013; Flex et al., 2014; Kang et al., 2014; Tian et al., 2015; Toral-Rios et al., 2015). However, these epidemiological studies have reported inconsistent results. In addition, several previous meta-analyses have assessed the associations between four polymorphisms of the IL genes and the risk of AD. However, several further papers regarding this relationship between IL gene polymorphisms and the risk of AD have been published recently. It is thus necessary to update the data regarding the association between IL gene polymorphisms and the risk of AD.

Therefore, we have re-evaluated and updated the associations between the polymorphisms of four IL genes and the risk of AD using published studies.

2. Materials and methods

2.1. Search strategy

Two clinical researchers independently searched and reviewed the literature. We conducted a meta-analysis of the published literature to analyze the associations between IL gene polymorphisms and Alzheimer's disease. The search sources were the PubMed, Science Direct, Scopus, and Google Scholar databases, the search was conducted up to July 2015, and the following search terms were used: “interleukin 1 or interleukin 6 or interleukin 10” and “variant or polymorphism or SNP” in combination with “Alzheimer's disease”. The reference lists in the published articles were reviewed to identify any studies missing from the database search. The workflow of the literature search is shown in Fig 1.

2.2. Selection criteria

All articles reporting the genotype frequencies of the following IL gene single-nucleotide polymorphisms (SNPs) were included: −889C>T, −511C>T, −174C>G and −1082G>A. As the studies were heterogeneous in terms of the number of cases and controls, racial composition, and the polymorphisms analyzed, we used the following inclusion criteria: hospital-based or population-based case–control studies on the associations of IL gene polymorphisms with AD, genotype frequencies of each polymorphism provided for cases and controls, genotype distribution in the control group confirmed by Hardy–Weinberg equilibrium (HWE), and English-language articles only. If overlapping cases and controls between studies were identified, only the most-complete study was included in this meta-analysis.

2.3. Data extraction

Data extraction was performed by two reviewers. The following data were extracted from each study: last name of the first author, publication year, study region, participants' ethnicity, sample size, genotype distribution of the polymorphisms of four interleukin genes in both cases and controls, and *p*-values for the HWE of genotype distribution of controls (p value less than 0.05 of HWE was considered to indicate significance).

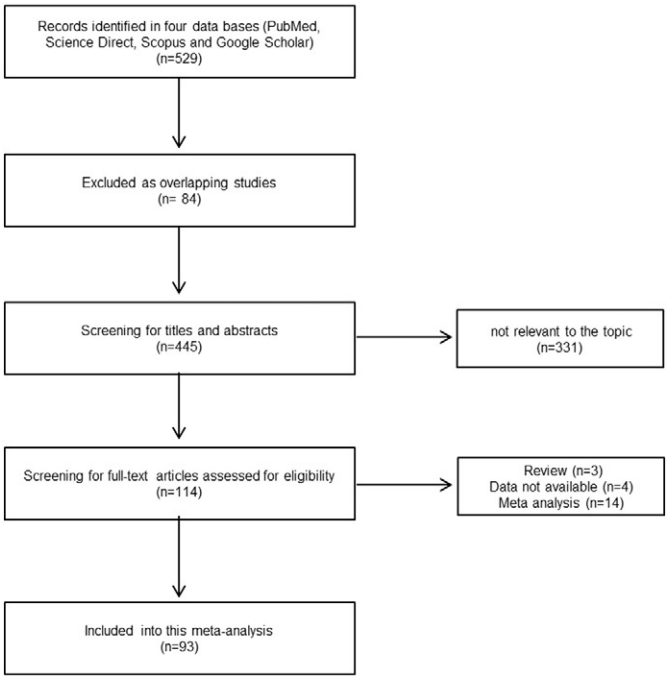

Fig. 1. Flow chart of the selection of studies for inclusion in our meta-analysis.

2.4. Statistical analysis

The chi-squared test was used to determine whether the distribution of genotypes in the control group was in agreement with HWE. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the associations between four IL gene polymorphisms (−889C>T, −511C>T, −174C>G and–1082G>A) and AD risk under the heterozygous, homozygous, dominant, and recessive models with fixed-effects (Mantel–Haenszel method) and random-effects models (Mantel–Haenszel method). Statistical heterogeneity between studies was evaluated using the I^2 statistic. A random-effects model was used to calculate the pooled OR and 95% CI when I^2 values > 50% were considered to indicate significant heterogeneity between studies. A fixed-effects model was used when I^2 values <50% were considered to indicate low heterogeneity between studies. We also performed subgroup analyses by ethnicity (Caucasian and Asian). The risk of small study bias, such as publication bias, was measured using funnel plots and further evaluated with Egger's linear regression test. It was assumed that large-sized studies would plot close to the mean in the absence of publication bias, whereas small-sized studies would be spread smoothly on both sides of the mean. All meta-statistical analyses were performed using the RevMan ver. 5.1 software (Cochrane Collaboration, Copenhagen, Denmark) and confirmed using the Comprehensive Meta-Analysis trial version. Two-sided *p*-values < 0.05 were considered to indicate significance.

3. Results

3.1. Characteristics of the included studies

A total of 529 papers published before July 2015 was identified in the search of the four databases. Of them, a total of 21,864 cases and 40,321 controls from 93 individual studies were included in our meta-

Table 1
Description of this meta-analysis of the association of four polymorphisms of IL genes with risk of Alzheimer's disease.

IL-1α (−889C>T) study (author/year)	Study region	Ethnicity	Criteria	Sample size (case/control)	Genotype distribution (case/control)			HWE (*p*-value)	Reference
					CC	CT	TT		
Clarimon et al. (2003)	Spain	Caucasian	NINCDS-ADRDA	111/89	61/42	41/34	9/13	0.171	Clarimon et al. (2003)
Combarros et al. (2002)	Spain	Caucasian	NINCDS-ADRDA	298/306	161/195	119/104	18/7	0.108	Combarros et al. (2002)
Combarros et al. (2010) (I)	Bonn	Caucasian	NINCDS-ADRDA-CERAD	235/210	123/111	93/78	19/21	0.192	Combarros et al. (2010))
Combarros et al. (2010) (II)	Bristol	Caucasian		198/56	87/24	8629	25/3	0.125	
Combarros et al. (2010) (III)	Nottingham	Caucasian		83/96	36/46	38/38	9/12	0.353	
Combarros et al. (2010) (IV)	OPTIMA	Caucasian		233/237	124/102	80/110	29/25	0.56	
Combarros et al. (2010) (V)	Oviedo	Caucasian		187/109	95/52	77/50	15/7	0.269	
Combarros et al. (2010) (VI)	Rotterdam	Caucasian		391/5110	185/2574	162/2111	44/425	0.789	
Combarros et al. (2010) (VII)	Santander	Caucasian		302/374	162/220	114/127	26/27	0.15	
Cousin et al. (2011)	France	Caucasian	NINCDS-ADRDA	129/190	60/90	61/85	8/15	0.409	Cousin et al. (2011)
Deniz-Naranzo et al. (2008)	Spain	Caucasian	NINCDS-ADRDA	282/312	138/168	118/121	26/23	0.85	Deniz-Naranjo et al. (2008)
Du et al. (2000)	Germany	Caucasian	NINCDS-ADRDA	259/191	141/126	97/62	21/3	0.131	Du et al. (2000)
Dursun et al. (2009)	Turkey	Caucasian	DSM-IV	104/103	60/45	41/52	3/6	0.07	Dursun et al. (2009)
Fidani et al. (2002)	USA	Caucasian	NINCDS-ADRDA	142/119	73/59	59/49	10/11	0.858	Fidani et al. (2002)
Green et al. (2002)	UK/France	Caucasian	NINCDS-ADRDA-DSM-III-R	294/503	134/221	126/217	34/65	0.309	Green et al. (2002)
Grimaldi et al. (2000)	Italy	Caucasian	NINCDS-ADRDA	318/335	140/142	125/163	53/30	0.08	Grimaldi et al. (2000)
Hayes et al. (2004)	UK	Caucasian	CERAD	68/503	30/221	31/220	7/62	0.528	Hayes et al. (2004)
Hedley et al. (2002)	Australian	Caucasian	NINCDS-ADRDA	221/351	98/153	94/168	29/30	0.087	Hedley et al. (2002)
Hu et al. (2009)	China	Asian	NINCDS-ADRDA-DSM-III-R	344/224	272/183	61/37	11/4	0.198	Hu et al. (2009)
Ki et al. (2001)	Korean	Asian	NINCDS-ADRDA	126/221	106/184	20/27	0/0	0.321	Ki et al. (2001)
Kuo et al. (2003)	Taiwan	Asian	NINCDS-ADRDA	125/93	104/72	20/21	1/0	0.22	Kuo et al. (2003)
Li et al. (2004)	China	Asian	NINCDS-ADRDA-DSM-IV	145/181	103/128	41/52	1/1	0.076	Li et al. (2004)
Mattila et al. (2002)	Finland	Caucasian	NINCDS-ADRDA-CERAD	110/73	42/33	39/29	29/11	0.281	Mattila et al. (2002)
McCarron et al. (2003)	US/UK	Caucasian	CERAD	232/167	103/82	99/74	30/11	0.291	McCarron et al. (2003)
Minster et al. (2000)	USA	Caucasian	NINCDS-ADRDA-DSM-III-R	297/204	139/102	126/86	32/16	0.717	Minster et al. (2000)
Moraes et al. (2013)	Brazil	Caucasian	NINCDS-ADRDA	120/412	64/209	45/168	11/35	0.88	Moraes et al. (2013)
Nicoll et al. (2000)	US/UK	Caucasian	CERAD	232/167	103/82	99/74	30/11	0.291	Nicoll et al. (2000)
Nishmura et al. (2004)	Japan	Asian	NINCDS-ADRDA	172/163	141/126	31/37	0/0	0.102	Nishimura et al. (2004)
Pirskanen et al. (2002)	Finland	Caucasian	NINCDS-ADRDA	237/513	123/248	91/209	23/56	0.235	Pirskanen et al. (2002)
Prince et al. (2001)	Sweden	Caucasian	NINCDS-ADRDA	198/175	89/93	89/65	20/17	0.264	Prince et al. (2001)
Rebeck et al. (2000)	USA	Caucasian	CERAD	247/187	119/97	103/74	25/16	0.725	Rebeck (2000))
Ribizzi et al. (2010)	Italy	Caucasian	NINCDS-ADRDA	19/20	12/7	3/10	4/3	0.852	Ribizzi et al. (2010)
Sciacca et al. (2003)	Italy	Caucasian	NINCDS-ADRDA	353/482	165/229	153/219	35/34	0.057	Sciacca et al. (2003)
Seripa et al. (2005) I)	Italy	Caucasian	NINCDS-ADRDA	225/143	117/83	90/56	18/4	0.128	Seripa et al. (2005)
Seripa et al. (2005) (II)	USA	Caucasian	NINCDS-ADRDA	121/93	52/40	59/42	10/11	0.996	
Serretti (2009) (I)	Greece	Caucasian	DSM-IV	86/113	45/66	34/39	7/8	0.504	Serretti et al. (2009)
Serretti (2009) (II)	Italy	Caucasian	NINCDS-ADRDA	24/17	12/12	8/4	4/1	0.432	
Tian et al. (2015)	China	Asian	NINCDS-ADRDA	201/257	153/217	45/37	3/3	0.328	Tian et al. (2015)
Tsai et al. (2003)	China	Asian	NINCDS-ADRDA	234/170	212/147	21/22	1/1	0.858	Tsai et al. (2003)
Vendramini et al. (2011)	Brazil	Caucasian	NINCDS-ADRDA	199/241	96/136	84/91	19/14	0.811	Vendramini et al. (2011)
Wang et al. (2007)	Taiwan	Asian	NINCDS-ADRDA	219/209	182/174	37/33	0/2	0.756	Wang et al. (2007)
Zhou et al. (2006) (abstract)	China	Asian	–	520/505	369/407	134/92	17/6	0.756	Zhou et al. (2006)

IL-1β (−511C>T) study (author/year)	Study region	Ethnicity	Criteria	Sample size (case/control)	Genotype distribution (case/control)			HWE (*p*-value)	Reference
					CC	CT	TT		
Deniz-Naranzo et al. (2008)	Spain	Caucasian	NINCDS-ADRDA	282/312	117/158	127/129	38/25	0.852	Deniz-Naranjo et al. (2008)
Grimaldi et al. (2000)	Italy	Caucasian	NINCDS-ADRDA	317/305	141/126	130/144	46/35	0.523	Grimaldi et al. (2000)
Hayes et al. (2004)	UK	Caucasian	CERAD	68/479	34/211	24/220	10/48	0.395	Hayes et al. (2004)
Hedley et al. (2002)	Australian	Caucasian	NINCDS-ADRDA	220/351	106/154	84/160	30/37	0.631	Hedley et al. (2002)
Kang et al. (2014)	Korea	Asian	NINCDS-ADRDA-DSM-IV	86/625	27/207	46/320	13/98	0.161	Kang et al. (2014)
Klimkowicz-Mrowiec et al. (2009)	Poland	Caucasian	NINCDS-ADRDA	331/219	152/118	147/85	32/16	0.897	Klimkowicz-Mrowiec et al. (2009)
Li et al. (2004)	China	Asian	NINCDS-ADRDA-DSM-IV	145/181	34/44	69/84	42/53	0.35	Li et al. (2004)
Ma et al. (2003)	China	Asian	NINCDS-ADRDA	90/100	26/22	26/33	38/45	0.002	Ma et al. (2003)
Mattila et al. (2002)	Finland	Caucasian	NINCDS-ADRDA-CERAD	92/52	35/25	47/25	10/2	0.159	Mattila et al. 2002)
McCulley et al. (2004)	UK	Caucasian	NINCDS-ADRDA	133/156	65/82	59/59	9/15	0.365	McCulley et al. (2004)
Minster et al. (2000)	USA	Caucasian	NINCDS-DSM-III-R-ADRDA	335/203	131/72	164/112	40/19	0.009	Minster et al. (2000)
Nishmura et al. (2004)	Japan	Asian	NINCDS-ADRDA	172/163	61/44	77/82	34/37	0.919	Nishimura et al. (2004)
Payao et al. (2012)	Brazil	Caucasian	NINCDS-ADRDA	188/263	38/48	107/132	43/83	0.722	Payao et al. (2012)
Ravaglia et al. (2006)	Italy	Caucasian	NINCDS-ADRDA	105/644	52/283	46/287	7/74	0.923	Ravaglia et al. (2006)
Ribizzi et al. (2010)	Italy	Caucasian	NINCDS-ADRDA	19/20	5/3	14/12	0/5	0.343	Ribizzi et al. (2010)
Seripa et al. (2005) (I)	Italy	Caucasian	NINCDS-ADRDA	225/143	103/54	97/70	25/19	0.62	Seripa et al. (2005)
Seripa et al. (2005) (II)	USA	Caucasian	NINCDS-ADRDA	121/93	50/38	60/40	11/15	0.419	Wang et al. (2005)
Wang et al. (2005)	Taiwan	Asian	NINCDS-ADRDA	46/103	17/27	13/52	16/24	0.915	Wang et al. (2007)
Wang et al. (2007)	Taiwan	Asian	NINCDS-ADRDA-DSM-IV	219/209	74/56	107/105	38/48	0.928	Wang et al. (2005)

(continued on next page)

Table 1 (*continued*)

Il-6 (−174g>c) study (author/year)	Study region	Ethnicity	Criteria	Sample size (case/control)	Genotype distribution (case/control)			HWE (*p*-value)	Reference
					GG	GC	CC		
Arosio et al. (2004)	Italy	Caucasian	NINCDS-ADRDA-DSM-IV	59/64	17/32	34/27	8/5	0.833	Arosio et al. (2004)
Bagli et al. (2000)	Germany	Caucasian	NINCDS-ADRDA	102/351	33/99	56/208	13/44	<0.001	Bagli et al. (2000)
Bhojak et al. (2000)	USA	Caucasian	NINCDS-ADRDA	464/337	178/126	221/155	65/56	0.478	Bhojak et al. (2000)
Capurso et al. (2004)	Italy	Caucasian	NINCDS-ADRDA	168/220	90/129	71/82	7/9	0.364	Capurso et al. (2004)
Capurso et al. (2010)	Italy	Caucasian	NINCDS-ADRDA	149/298	81/172	61/111	7/15	0.590	Capurso et al. (2010)
Combarros et al. (2010) (i)	Bonn	Caucasian	NINCDS-ADRDA-CERAD	241/224	81/77	123/95	37/52	0.035	Combarros et al. (2010)
Combarros et al. (2010) (ii)	Bristol	Caucasian		189/54	66/9	83/29	40/16	0.497	
Combarros et al. (2010) (iii)	Nottingham	Caucasian		84/95	33/32	36/41	15/22	0.215	
Combarros et al. (2010) (iv)	OPTIMA	Caucasian		243/240	88/65	106/141	49/34	0.002	
Combarros et al. (2010) (v)	Oviedo	Caucasian		190/119	89/60	82/51	19/8	0.517	
Combarros et al. (2010) (vi)	Rotterdam	Caucasian		391/5110	127/1824	191/2426	73/860	0.270	
Combarros et al. (2010) (vii)	Santander	Caucasian		333/381	148/169	137/163	48/49	0.328	
Cousin et al. (2011)	France	Caucasian	NINCDS-ADRDA	231/470	96/171	100/229	35/70	0.639	Cousin et al. (2011)
Depboylu et al. (2004)	Germany	Caucasian	NINCDS-ADRDA	113/108	33/26	65/64	15/18	0.046	Depboylu et al. (2004)
Faltraco et al. (2003)	Germany	Caucasian	NINCDS-ADRDA	101/133	44/43	47/70	10/20	0.326	Faltraco et al. (2003)
Flex et al. (2014)	Italy	Caucasian	NINCDS-ADRDA	533/713	216/160	241/337	76/216	0.192	Flex et al. (2014)
Klimkowicz-mrowiec et al. (2010	Poland	Caucasian	NINCDS-ADRDA	361/200	119/66	185/91	57/43	0.271	Klimkowicz-Mrowiec et al. (2010)
Koivisto et al. (2005)	Finland	Caucasian	–	65/542	18/136	32/260	15/146	0.349	Koivisto et al. (2005)
Licastro et al. (2003)	Italy	Caucasian	NINCDS-ADRDA-DSM-IV-R	332/393	137/209	161/165	34/19	0.057	Licastro et al. (2003)
Mansoori et al. (2012)	India	Caucasian	NINCDS-ADRDA	80/120	55/88	24/29	1/3	0.743	Mansoori et al. (2012)
Moraes et al. (2013)	Brazil	Caucasian	NINCDS-ADRDA-DSM-IV	120/412	71/260	38/136	11/16	0.732	Moraes et al. (2013)
Paradowski et al. (2008)	Poland	Caucasian	NINCDS-ADRDA	51/36	11/12	31/16	9/8	0.549	Paradowski et al. (2008)
Pola et al. (2002)	Italy	Caucasian	NINCDS-ADRDA	124/134	56/29	51/58	17/47	0.170	Pola et al. (2002)
Rasmussen et al. (2013)	Brazil	Caucasian	NINCDS-ADRDA-DSM-IV	197/163	88/82	91/65	18/16	0.557	Rasmussen et al. (2013)
Ravaglia et al. (2006)	Italy	Caucasian	NINCDS-ADRDA	105/644	50/251	43/304	12/89	0.842	Ravaglia et al. 2006)
Shawkatová et al. (2010)	Slovakia	Caucasian	NINCDS-ADRDA	50/140	23/53	21/66	6/21	0.951	Shawkatova et al. (2010)
Shibata et al. (2002)	Japan	Asian	NINCDS-ADRDA	128/83	4/7	74/23	50/53	0.068	Shibata et al. (2002)
Toral-rios et al. (2015)	Mexico	Caucasian	NINCDS-ADRDA	94/100	5/3	23/15	66/82	0.040	Toral-Rios et al. (2015)
Vural et al. (2009)	Turkey	Caucasian	NINCDS-ADRDA	101/138	54/76	43/51	4/11	0.556	Vural et al. (2009)
Zhang et al. (2004)	UK	Caucasian	NINCDS-ADRDA-DSM-III-R	356/434	132/152	171/213	53/69	0.695	Zhang et al. (2004)

IL-10 (−1082G>A) study (author/year)	Study region	Ethnicity	Criteria	Sample size (case/control)	Genotype distribution (case/control)			HWE (*p*-value)	Reference
					GG	GA	AA		
Arosio et al. (2004)	Italy	Caucasian	NINCDS-ADRDA-DSM-IV	63/63	4/14	28/29	31/20	0.573	Arosio et al. (2004)
Bagnoli et al. (2007)	Italy	Caucasian	DSM-IV	222/179	98/79	99/74	25/26	0.210	Bagnoli et al. (2007)
Combarros et al. (2008)	Spain	Caucasian	NINCDS-ADRDA	231/194	60/66	140/99	31/29	0.410	Combarros et al. (2008)
Cousin et al. (2011)	France	Caucasian	NINCDS-ADRDA	426/475	94/107	205/232	127/136	0.671	Cousin et al. (2011)
Culpan et al. (2006)	Sweden	Caucasian	–	160/92	41/24	79/50	40/18	0.380	Culpan et al. (2006)
Depboylu et al. (2003)	Germany	Caucasian	NINCDS-ADRDA	233/97	56/25	96/54	81/18	0.240	Depboylu et al. (2003)
Heun et al. (2012) (I)	Bonn	Caucasian	NINCDS-ADRDA-CERAD	245/216	54/45	118/109	73/62	0.819	Heun et al. (2012)
Heun et al. (2012) (II)	Bristol	Caucasian		162/52	45/12	72/25	45/15	0.799	
Heun et al. (2012) (III)	Nottingham	Caucasian		67/76	21/22	28/29	18/25	0.040	
Heun et al. (2012) (IV)	OPTIMA	Caucasian		237/241	72/58	112/123	53/60	0.747	
Heun et al. (2012) (V)	Oviedo	Caucasian		186/110	24/25	97/61	65/24	0.252	
Heun et al. (2012) (VI)	Rotterdam	Caucasian		391/5110	120/1339	190/2538	81/1233	0.656	
Heun et al. (2012) (VII)	Santander	Caucasian		311/387	38/66	182/185	91/136	0.820	
Lio et al. (2003)	Italy	Caucasian	NINCDS-ADRDA	132/213	32/86	91/118	9/9	<0.001	Lio et al. (2003)
Ma et al. (2005)	China	Asian	NINCDS-ADRDA	95/117	3/5	8/6	84/106	<0.001	Ma et al. (2005)
Moraes et al. (2013)	Brazil	Caucasian	NINCDS-ADRDA	120/412	15/35	68/189	37/188	0.192	Moraes et al. (2013)
Ramos et al. (2006)	USA	Caucasian	NINCDS-ADRDA	265/347	65/100	144/156	56/91	0.062	Ramos et al. (2006)
Ribizzi et al. (2010)	Italy	Caucasian	NINCDS-ADRDA	19/20	8/1	5/12	6/7	0.154	Ribizzi et al. (2010)
Scassellati et al. (2004)	Italy	Caucasian	NINCDS-ADRDA	215/153	35/26	109/64	71/63	0.168	Scassellati et al. (2004)
Shawkatova et al. (2010)	Slovakia	Caucasian	NINCDS-ADRDA	50/140	8/30	20/61	22/49	0.184	Shawkatova et al. (2010)
Toral-Rios et al. (2015)	Mexico	Caucasian	NINCDS-ADRDA	94/100	8/9	86/91	0/0	<0.001	Toral-Rios et al. (2015)
Torres et al. (2013)	Brazil	Caucasian	NINCDS-ADRDA-CERAD	249/98	25/12	103/40	121/46	0.476	Torres et al. (2013)
Vural et al. (2009)	Turkey	Caucasian	NINCDS-ADRDA	101/138	24/50	65/63	12/25	0.511	Vural et al. (2009)

Bonn, Ethics Review Board of the University of Bonn; Bristol, Frenchay Local Research Ethics committee Bristol; Nottingham, Nottingham Research Committee 2 (NHS); OPTIMA, Central Oxford Ethics Committee No 1656; Oviedo, Ethical Committee of the Hospital Central de Asturias; Rotterdam, Medical Ethical Committee of the Erasmus MC; Santander, Ethical Committee of the University Hospital "Marqués de Valdecilla", Santander; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association; CERAD, The Consortium to Establish a Registry for Alzheimer's Disease; DSM, Diagnostic and Statistical Manual of Mental Disorder. *Zhou et al. data from abstract.

analysis. A total of 8641 cases and 14,214 controls from 34 studies (42 subgroup studies) that reported on the association between the IL-1α gene polymorphism (−889C>T) and risk of AD were included in the meta-analysis. A total of 3194 cases and 4621 controls from 18 studies (19 subgroup studies) that reported on the association between the IL-1β gene polymorphism (−511C>T) and risk of AD were included in the meta-analysis. A total of 5755 cases and 12,456 controls from 24 studies (30 subgroup studies) of IL-6 gene polymorphism (−174G>C) were included in the meta-analysis. Seventeen IL-10 gene polymorphism (−1082G>A) studies (23 subgroup studies) involving 4274 cases and 9030 controls were included in the meta-analysis. Most of the studies were performed in Caucasian populations. However, several studies were conducted in Asian populations (nine subgroup studies in IL-1α, six subgroup studies in IL-1β, one subgroup

study in IL-6, and one subgroup study in IL-10). The characteristics of the studies are summarized in Table 1.

3.2. IL genes polymorphisms and risk of AD

Forty-two subgroup studies involving 8641 cases and 14,214 controls identified an association between the −889C>T polymorphism and risk of AD. The distributions of the genotypes in the control groups from all studies followed HWE. Our comprehensive meta-analysis indicated that the −889C>T polymorphism was significantly associated with an increased risk of AD by three genetic models. The ORs of the homozygote (CC vs. TT), dominant (TT/CT vs. CC) and recessive (TT vs. CC/CT) models were 1.32, 1.09 and 1.32, respectively (95% CI: 1.18–1.49, 1.03–1.16 and 1.18–1.45, respectively) using a fixed-effects model (Fig. 2). However, heterozygote models (CC vs. TC) were not associated with risk of AD (OR: 1.05, 95% CI: 0.98–1.12). We also assessed the association between the −889C>T polymorphism and risk of AD in Caucasian populations by excluding nine Asian studies (Ki et al., 2001; Kuo et al., 2003; Tsai et al., 2003; Li et al., 2004; Nishimura et al., 2004; Zhou et al., 2006; Wang et al., 2007; Hu et al., 2009; Tian et al., 2015). Data from the Caucasian studies showed that three genetic models (homozygote, dominant and recessive) were related to an increased risk of AD (OR: 1.30, 95% CI: 1.15–1.47; OR: 1.07, 95% CI: 1.00–1.15; OR: 1.30, 95% CI: 1.16–1.46, respectively). However, the heterozygote model was not related to risk of AD. Nineteen subgroup studies on the −511C>T polymorphism of IL-1β included 3194 cases and 4621 controls. Of these, the distribution of genotypes in the control groups of two studies, Ma et al. 2003 and Minster et al. 2000, deviated from HWE ($p < 0.05$). Our meta-analysis with HWE revealed that the −511C>T polymorphism was not associated with risk of AD (homozygote: OR = 0.95, 95% CI = 0.81–1.12 by fixed-effects model; heterozygote: OR = 0.94, 95% CI = 0.84–1.06 by fixed-effects model; dominant: OR = 0.95, 95% CI = 0.86–1.06 by fixed-effects model; recessive: OR = 0.98, 95% CI = 0.75–1.28 by random-effects model). Therefore, our meta-analysis suggested that the −889C>T polymorphism was significantly associated with an increased risk of AD. However, the −511C>T polymorphism was not related to risk of AD.

Thirty subgroup studies on the −174G>C polymorphism included 5755 cases and 12,456 controls. Of them, five studies deviated from HWE ($p < 0.05$) (Bagli et al., 2000; Depboylu et al., 2004; Combarros et al., 2010; Toral-Rios et al., 2015). The tendency of our meta-analysis indicated that the −174G>C polymorphism was related to a decreased risk of AD. However, this polymorphism was statistically not associated with risk of AD (homozygote: OR = 0.85, 95% CI = 0.64–1.13; heterozygote: OR = 0.99, 95% CI = 0.85–1.15; dominant: OR = 0.95, 95% CI = 0.80–1.13; recessive: OR = 0.83, 95% CI = 0.67–1.03) by a random-effects model. Consequently, our results suggested that the −174G>C polymorphism was not associated with risk of AD.

Twenty-three subgroup studies involving 4274 cases and 9030 controls identified an association between the −1082G>A polymorphism and risk of AD. Two studies of the association between the −1082G>A polymorphism and AD risk were conducted in Asian populations. Among previous studies, the results of four studies departed from HWE ($p < 0.05$) (Lio et al., 2003; Ma et al., 2003; Heun et al., 2012). Our meta-analysis results showed that the −1082G>A polymorphism of IL-10 was not related to risk of AD. The ORs of four genetic

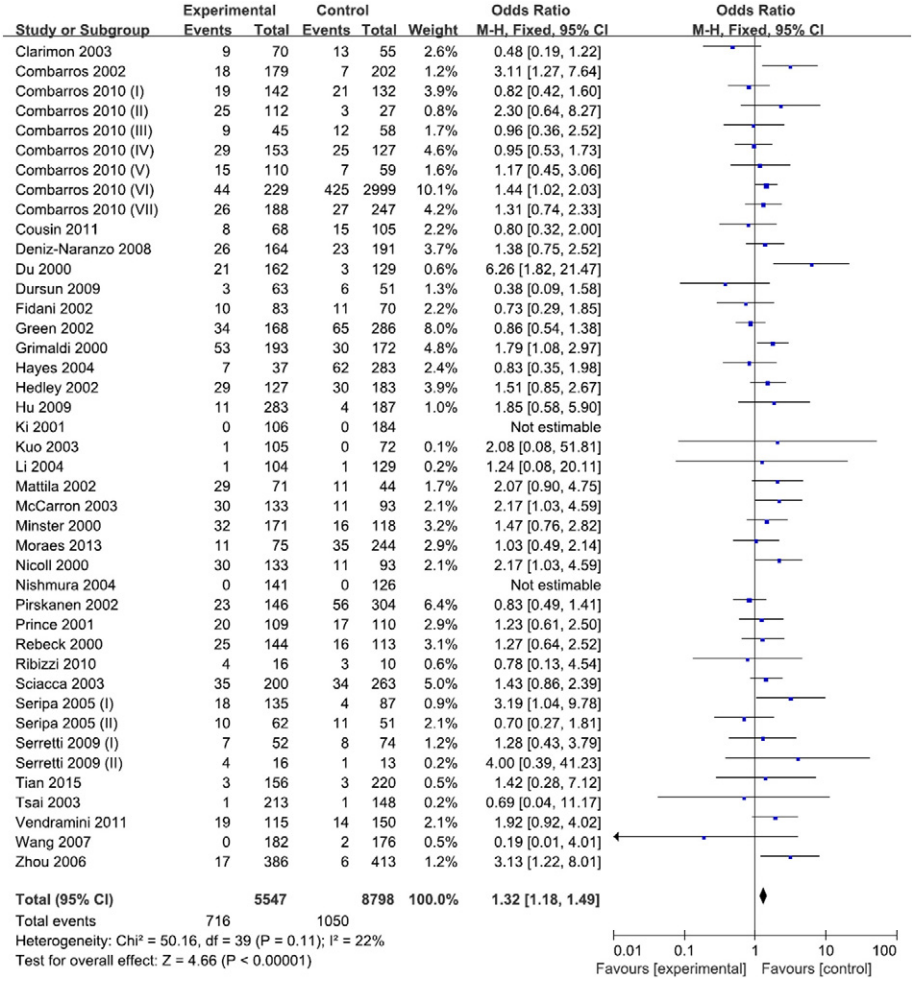

Fig. 2. Forest plot for the association between the homozygote model (CC vs. TT) of the −889C>T polymorphism of the IL-1α gene and risk of AD using a fixed-effects model.

Table 2
The associations between four polymorphisms of IL genes and AD risk.

	SNP	Genetic models	Pooled OR (95% CI)		Heterogeneity		Publication bias
			Fixed effect model	Random effect model	I^2 value	*p*-Value	*p*-Value
Overall	rs1800587 (IL-1α; −889C>T)	Homozygote model (TT vs. CC)	**1.32 (1.18–1.49)***	1.31 (1.13–1.51)	22%	0.110	0.900
		Heterozygote model (CT vs. CC)	1.05 (0.98–1.12)	1.04 (0.97–1.13)	24%	0.080	0.174
		Dominant model (TT/CT vs. CC)	**1.09 (1.03–1.16)***	1.08 (1.00–1.17)	31%	0.030	0.164
		Recessive model (TT vs. CC/CT)	**1.32 (1.18–1.45)***	1.30 (1.14–1.49)	18%	0.160	0.897
	rs16944 (IL-1β; −511C>T)	Homozygote model (TT vs. CC)	0.95 (0.82–1.11)	0.94 (0.77–1.16)	37%	0.050	0.381
		Heterozygote model (CT vs. CC)	0.93 (0.83–1.03)	0.92 (0.81–1.04)	24%	0.160	0.323
		Dominant model (TT/CT vs. CC)	0.94 (0.85–1.04)	0.93 (0.82–1.05)	27%	0.140	0.223
		Recessive model (TT vs. CC/CT)	0.97 (0.84–1.11)	0.98 (0.77–1.25)	61%	<0.001	0.735
	rs1800795 (IL-6; −174C>G)	Homozygote model (GG vs. CC)	0.79 (0.71–0.88)	0.83 (0.65–1.06)	74%	<0.001	0.579
		Heterozygote model (GG vs. GC)	0.95 (0.88–1.02)	0.96 (0.84–1.10)	62%	<0.001	0.546
		Dominant model (CC/GC vs. GG)	0.92 (0.85–0.99)	0.92 (0.79–1.07)	72%	<0.001	0.831
		Recessive model (CC vs. GG/GC)	0.80 (0.72–0.88)	0.83 (0.68–1.005)	68%	<0.001	0.690
	rs1800896 (IL-10; −1082G>A)	Homozygote model (AA vs. GG)	0.99 (0.88–1.13)	1.06 (0.87–1.29)	49%	0.005	0.146
		Heterozygote model (GA vs. GG)	1.11 (1.00–1.23)	1.16 (0.98–1.37)	50%	0.004	0.517
		Dominant model (AA/GA vs. GG)	1.08 (0.97–1.19)	1.13 (0.96–1.33)	51%	0.002	0.331
		Recessive model (AA vs. GG/GA)	0.93 (0.85–1.03)	0.97 (0.83–1.13)	49%	0.005	0.177
Caucasian	rs1800587 (IL-1α; −889C>T)	Homozygote model (TT vs. CC)	**1.30 (1.15–1.47)***	1.28 (1.10–1.50)	28%	0.070	0.796
		Heterozygote model (CT vs. CC)	1.03 (0.96–1.10)	1.03 (0.95–1.11)	12%	0.280	0.435
		Dominant model (TT/CT vs. CC)	**1.07 (1.00–1.15)***	1.07 (0.99–1.16)	21%	0.150	0.490
		Recessive model (TT vs. CC/CT)	**1.30 (1.16–1.46)***	1.28 (1.11–1.48)	26%	0.090	0.780
	rs16944 (IL-1β; −511C>T)	Homozygote model (TT vs. CC)	1.04 (0.87–1.26)	1.02 (0.77–1.35)	47%	0.030	0.438
		Heterozygote model (CT vs. CC)	0.96 (0.85–1.09)	0.96 (0.83–1.11)	25%	0.190	0.378
		Dominant model (TT/CT vs. CC)	0.98 (0.88–1.11)	0.098 (0.85–1.13)	32%	0.130	0.284
		Recessive model (TT vs. CC/CT)	1.02 (0.86–1.21)	1.01 (0.73–1.40)	66%	<0.001	0.873
	rs1800795 (IL-6; −174C>G)	Homozygote model (GG vs. CC)	0.78 (0.70–0.88)	0.82 (0.64–1.05)	75%	<0.001	0.521
		Heterozygote model (GG vs. GC)	0.94 (0.87–1.02)	0.94 (0.83–1.08)	60%	<0.001	0.433
		Dominant model (CC/GC vs. GG)	0.91 (0.85–0.98)	0.91 (0.78–1.06)	73%	<0.001	0.652
		Recessive model (CC vs. GG/GC)	0.82 (0.74–0.91)	0.86 (0.71–1.04)	66%	<0.001	0.652
	rs1800896 (IL-10; −1082G>A)	Homozygote model (AA vs. GG)	0.99 (0.87–1.13)	1.06 (0.87–1.29)	51%	0.004	0.229
		Heterozygote model (GA vs. GG)	1.11 (1.00–1.23)	1.15 (0.97–1.36)	52%	0.003	0.628
		Dominant model (AA/GA vs. GG)	1.11 (1.00–1.23)	1.15 (0.97–1.36)	52%	0.003	0.334
		Recessive model (AA vs. GG/GA)	0.93 (0.85–1.03)	0.97 (0.83–1.14)	52%	0.003	0.172

* Statistically significant ($p < 0.05$).

models (homozygote, heterozygote, dominant and recessive) were 1.04, 1.12, 1.10 and 0.97, respectively, using a random-effects model (95% CIs: 0.85–1.28, 0.94–1.33, 0.93–1.29 and 0.83–1.14, respectively). The results of the meta-analysis are summarized in Tables 2 and 3.

3.3. Publication bias

Publication bias is shown graphically with a funnel plot (Fig. 3). We confirmed publication bias using Egger's linear regression test, as the funnel plot shapes did not indicate distinct symmetry in all of the genetic models. We did not find any evidence of publication bias in most of the genetic models.

3.4. Heterogeneity and sensitivity

No significant heterogeneity was found among the studies of the −889C>T polymorphism. However, significant heterogeneity was found in the recessive model for the −511C>T polymorphism, all genetic models (homozygote, heterozygote, dominant and recessive) for the −174C>G polymorphism and all genetic models for the −1082G>A polymorphism. Therefore, we applied fixed-effects and random-effects models in the meta-analysis (Tables 2 and 3). We also performed a sensitivity test to assess the stability and reliability of the results by sequentially deleting each subgroup study from the meta-analysis. The sensitivity test results indicated that none of the subgroup studies altered the pooled OR, suggesting that our meta-analysis was stable and reliable.

4. Discussion

Our meta-analysis summarizes the evidence to date regarding the association between four polymorphisms (−889C>T, −511C>T, −172G>C and −1082G>A) and the risk of AD. The results indicate that −889C>T was significantly associated with an increased risk of AD. However, three polymorphisms (−511C>T, −172G>C and −1082G>A) were statistically not related to the risk of AD.

Over the past decades, many genetic studies and meta-analyses have been performed to investigate the relationship between IL gene polymorphisms and the risk of AD. The most recent meta-analyses of the association between the four IL gene polymorphisms (−889C>T, −511C>T, 174G>C and −1082G>A) and the risk of AD were reported in 2012 and 2013 (Dai et al., 2012; Di Bona et al., 2012; Hua et al., 2012; Qi et al., 2012; Li et al., 2013; Yuan et al., 2013). A previous meta-analysis of −889C>T polymorphism had included twenty-eight studies and a total 12,817 subjects (Li et al., 2013). They results indicated that −889C>T polymorphism was significantly associated with increased risk of AD. Furthermore, Caucasian studies revealed that this polymorphism was associated with increased risk of AD. However, most of genetic models (dominant, recessive and T allele vs. C allele) showed that −889C>T polymorphism was not associated with risk of AD in Asian. Similarly, our results showed that −889C>T polymorphism was associated with increased risk of AD in overall and Caucasian subgroup studies. In −511C>T polymorphisms, Yuan et al. reported that −511C>T polymorphism was not associated with risk of AD. Furthermore, subgroup studies demonstrated that −511C>T polymorphism was not related with AD in Europe, non-Europe, Caucasian and non-Caucasian. In addition, many genetic models showed that heterogeneity (Yuan et al., 2013). Similar to previous meta-analysis, our results indicated that −511C>T polymorphism was not associated with risk of AD in overall and Caucasian subgroup studies. In 2012, Bona et al. suggested that GG vs. AG/AA model of −1082G>A polymorphism was modestly associated with risk of AD (OR: 0.82, 95% CI: 0.65–1.02). In addition, results of meta-analysis showed that moderate degree of heterogeneity between studies (Di Bona et al., 2012). In contrast, our

Table 3
Associations between four polymorphisms of IL genes and AD risk in studies in Hardy–Weinberg equilibrium (HWE).

SNP	Genetic models	Pooled OR (95% CI)		Heterogeneity		Publication bias	Departed from the HWE
		Fixed effect model	Random effect model	I^2 value	*P*-value	*P*-value	
rs1800587 (IL-1α; −889C>T)	Homozygote model (TT vs. CC)	**1.32 (1.18–1.49)***	1.31 (1.13–1.51)	22%	0.110	0.900	/
	Heterozygote model (CT vs. CC)	1.05 (0.98–1.12)	1.04 (0.97–1.13)	24%	0.080	0.174	
	Dominant model (TT/CT vs. CC)	**1.09 (1.03–1.16)***	1.08 (1.00–1.17)	31%	0.030	0.164	
	Recessive model (TT vs. CC/CT)	**1.32 (1.18–1.45)***	1.30 (1.14–1.49)	18%	0.160	0.897	
rs16944 (IL-1β; −511C>T)	Homozygote model (TT vs. CC)	0.95 (0.81–1.12)	0.94 (0.75–1.18)	42%	0.040	0.284	Ma et al. (2003) and Minster et al. (2000)
	Heterozygote model (CT vs. CC)	0.94 (0.84–1.06)	0.94 (0.82–1.08)	29%	0.130	0.924	
	Dominant model (TT/CT vs. CC)	0.95 (0.86–1.06)	0.94 (0.82–1.08)	32%	0.100	0.528	
	Recessive model (TT vs. CC/CT)	0.96 (0.82–1.11)	0.98 (0.75–1.28)	63%	<0.001	0.475	
rs1800795 (IL-6; −174C>G)	Homozygote model (GG vs. CC)	0.79 (0.70–0.88)	0.85 (0.64–1.13)	78%	<0.001	0.670	Bagli et al. (2000), Combarros et al. (2010) (I), Combarros et al. (2010) (IV), Depboylu et al. (2004) and Toral-Rios et al. (2015)
	Heterozygote model (GG vs. GC)	0.97 (0.89–1.05)	0.99 (0.85–1.15)	64%	<0.001	0.953	
	Dominant model (CC/GC vs. GG)	0.93 (0.86–1.01)	0.95 (0.80–1.13)	76%	<0.001	0.917	
	Recessive model (CC vs. GG/GC)	0.79 (0.71–0.88)	0.83 (0.67–1.03)	70%	<0.001	0.616	
rs1800896 (IL-10; −1082G>A)	Homozygote model (AA vs. GG)	0.98 (0.86–1.12)	1.04 (0.85–1.28)	51%	0.005	0.158	Heun et al. (2012) (III), Lio et al. (2003), Ma et al. (2005) and Toral-Rios et al. (2015)
	Heterozygote model (GA vs. GG)	1.07 (0.96–1.20)	1.12 (0.94–1.33)	51%	0.006	0.631	
	Dominant model (AA/GA vs. GG)	1.04 (0.94–1.16)	1.10 (0.93–1.29)	51%	0.005	0.353	
	Recessive model (AA vs. GG/GA)	0.93 (0.84–1.03)	0.97 (0.83–1.14)	55%	0.002	0.144	

Combarros et al. (2010) (I), Bonn, Ethics Review Board of the University of Bonn; Combarros et al. (2010) (IV), OPTIMA, Central Oxford Ethics Committee No 1656; Heun et al. (2012), Nottingham, Nottingham Research Committee 2 (NHS).
−889C>T polymorphism of IL-1α studies were not departed from HWE.
* Statistically significant ($p < 0.05$).

results suggested that −1082G>A polymorphism was statistically not associated with risk of AD. However, degree of heterogeneity was similar to previous meta-analysis. As mentioned above, meta-analysis results of three polymorphisms (−889C>T, −511 C>T and −1082G>A) were similar to previous meta-analysis. However, the results of the −174G>C polymorphism were different. In 2012, Dai et al. reported an association between the −174G>C polymorphism and the risk of AD in a meta-analysis including 3101 cases and 3860 controls. The overall analysis showed that the −174G>C polymorphism was significantly associated with a decreased risk of AD using a recessive model (OR: 0.70, 95% CI: 0.54–0.90). In addition, the heterozygote model revealed that the −174G>C polymorphism was strongly associated with a decreased risk of AD (OR: 0.83, 95% CI: 0.60–0.96) (Dai et al., 2012). Similarly, Qi et al.'s meta-analysis (4280 cases and 8788 controls) suggested that the recessive model (CC vs. GC/GG) was significantly associated with a decreased risk of AD (OR: 0.65, 95% CI: 0.52–0.82) (Qi et al., 2012). However, our meta-analysis (5755 cases and 12,456 controls) shows that all genetic models (homozygote, CC vs. GG; heterozygote, GC vs. GG; dominant CC/GC vs. GG; recessive models, CC vs. GC/GG) were significantly not associated with the risk of AD. The conflicting results between Qi et al. and our meta-analysis may be due to the included studies. Our meta-analysis contains an additional eight studies (Ravaglia et al., 2006; Combarros et al., 2010; Shawkatova et al., 2010; Cousin et al., 2011; Moraes et al., 2013; Rasmussen et al., 2013; Flex et al., 2014; Toral-Rios et al., 2015). In addition, we deleted four studies (Infante et al., 2004; Combarros et al.,

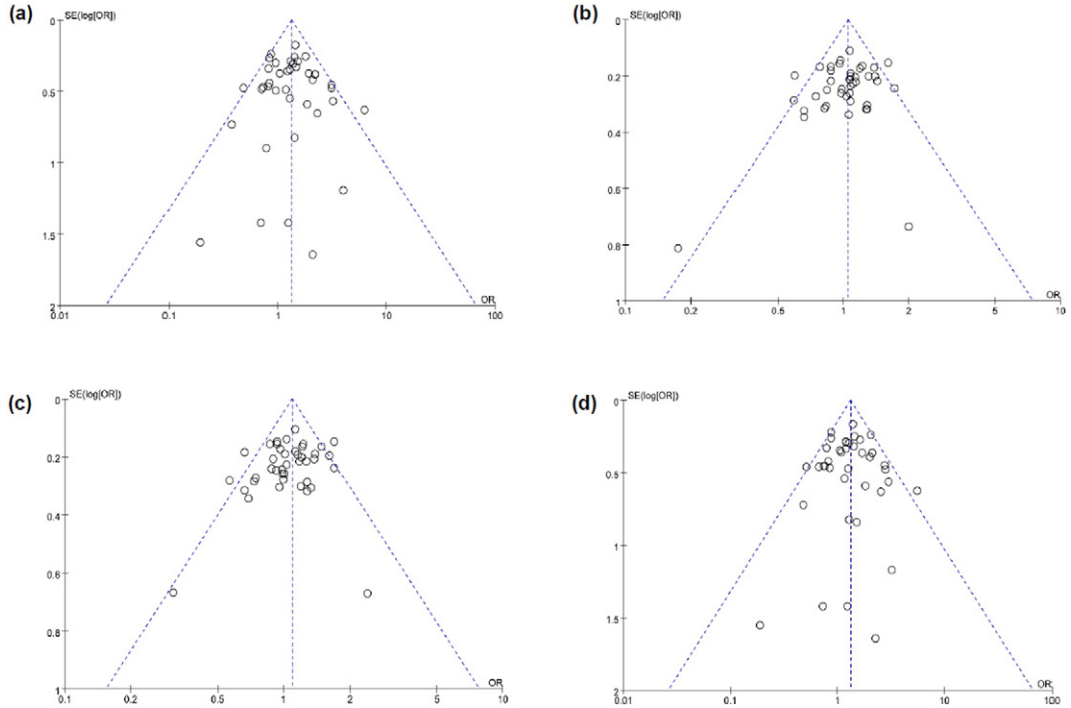

Fig. 3. Funnel plot for the association between the −889C>T polymorphism and Alzheimer's disease.

2005; van Oijen et al., 2006; Fontalba et al., 2009). Three studies (Fontalba et al., 2009, Combarros et al., 2005 and Infante et al., 2004) provided deficient genotype data. Also, the genotype data presented by van Oijen et al.'s (2006) group may overlap with that of Combarros et al. 2010 (Rotterdam study). However, the Qi et al. meta-analysis included these four studies.

Three limitations of this meta-analysis should be mentioned. First, most of the cases and controls were Caucasians. Thus, the lack of studies involving Asian populations may limit the general application of our results. Second, the studies included in our meta-analysis were limited to published reports. Unpublished reports or those published in non-international journals could not be included in the analysis. These problems may have affected the stability of the meta-analysis data. Third, AD is a multifactorial disease. However, we did not consider gene–gene or gene–environmental interactions—such as age, smoking, alcohol status, and progression of AD—which may have influenced the associations between IL gene polymorphisms and AD risk. Nevertheless, this meta-analysis improves our understanding of the associations between four polymorphisms of IL genes and the risk of AD.

Many studies have reported the association between several gene polymorphisms and the risk of AD. Coon et al., suggested that ε2/ε4, ε3/ε4 and ε4/ε4 variant types of ApoE significantly increased the risk of AD (odds ratios: 3.49, 4.32 and 25.31, respectively) compared with ε3/ε3 (Coon et al., 2007). In addition, meta-analysis data suggested that ApoE e4/e4 type was significantly associated with the prevalence of AD. Interestingly, meta-analyses indicated that the highest estimates were in Northern Europe and the lowest estimates were in Asia (prevalence 14.1%, 95% CI: 12.2–16.0 in Northern Europe; prevalence: 7.70%, 95% CI: 5.84–9.55 in Asia) (Ward et al., 2012). In addition, it is known that mutations in the presenilin-1 (PSEN-1) and presenilin-2 (PSEN-2) genes are related to AD. Manotas-Rodriguez et al. reported that the PSEN-1 polymorphism (rs165932) was probably associated with the risk of AD in the European sub-group (fixed effect model. OR: 1.19, 95% CI: 1.02–1.37, p-value < 0.05) (Rodriguez-Manotas et al., 2007). In addition, a meta-analysis by Chen et al. suggested that the rs8383 polymorphism of PSEN-2 was associated with an increased risk of AD (C vs. T, OR: 1.16, 95% CI: 1.00–1.33, p-value: 0.043; CC vs. TT, OR: 1.37, 95% CI: 1.02–1.84, p-value: 0.037) (Chen et al., 2012). Furthermore, genome-wide association studies have provided several polymorphisms of candidate genes and loci for AD (Li et al., 2008; Harold et al., 2009). However, the associations between several polymorphisms of candidate genes and the risk of AD are still unclear. To better understand the genetic risk factors for AD, large scale studies are needed to validate the associations and further investigations should consider the effects of environmental factors and genetic interactions.

5. Conclusions

In summary, our updated meta-analysis of 93 studies showed that the results of −889C>T polymorphism was statistically associated with the risk of AD. In contrast, three other polymorphisms were not associated with the risk of AD. In addition, our results of three polymorphisms (−889C>T, −511C>T and 1082G>A) were similar to those of previous meta-analyses. However, our results for the −174G>C polymorphism differed from those of previous meta-analyses. Consequently, our results suggested that the −889C>T polymorphism may be a potential risk factor in AD. However, the other three polymorphisms may not be a risk factor for AD.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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