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Original Article

Relationship between the IL-18 gene polymorphisms and Alzheimer's disease: a meta-analysis

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Abstract: The aim of this meta-analysis was to evaluate the association between *IL-18* gene polymorphisms (-607 C/A and -137 G/C) and Alzheimer's disease (AD). PubMed, Embase, Cochrane Library, SinoMed, and the China Knowledge Resource Integrated Database were searched to identify eligible studies. Pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) were used to evaluate the strength of the association between *IL-18* gene polymorphisms and AD. Analysis of pooled data from five studies containing 781 AD patients and 876 controls suggested that the -607 C/A (rs1946518) polymorphism decreases the risk of AD. Similarly, collective analysis of five studies containing 862 AD patients and 713 controls showed that the -137 G/C (rs187238) polymorphism was associated with a decreased risk of AD. Stratification analyses indicated -607 C/A and -137 G/C were both more common in Asians and carriers of apolipoprotein-E ε4 (APOE4). Overall, our data indicate that *IL-18* gene polymorphisms may decrease the risk of AD, especially among Asians and those with the APOE4 allele. Due to the limited sample size, larger studies are required to validate the association between *IL-18* gene polymorphisms and AD.

Keywords: Interleukin-18, polymorphism, alzheimer's disease, meta-analysis, SNP

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive formation of amyloid senile plaques, neurofibrillary tangles, and selective neuronal death in the brain [1]. The aetiology of AD remains poorly understood, possibly because multifactorial causes, such as environmental factors and genetic predisposition, have been implicated. However, considerable evidence suggests that the innate immune response and neuroinflammation may play an important role in the pathogenesis of AD [2]. Moreover, inflammation reactions in the brain are a prominent pathological feature of AD [3, 4]. Previous studies indicate that the risk of AD is affected by genetic variation in cytokines, such as interleukin1-alpha (IL1-α), IL1-β, IL6, and tumor necrosis factor (TNF), which are found at higher levels in patients with AD [5, 6]. A large number of polymorphisms in cytokine genes associated with inflammation (proinflammatory cytokines) have been investigated in AD, such as IL-18.

IL-18, a pro-inflammatory member of the IL-1 superfamily, is produced by a variety of cell types in the brain, such as activated microglia and astrocytes [7]. The human *IL-18* gene is located on chromosome 11 (11q22.2-q22.3). Two different single nucleotide polymorphisms (SNPs), -607 C/A and -137 G/C, located in the promoter region have been confirmed to affect *IL-18* gene activity in previous studies [8, 9]. Several studies have investigated the relationship between the two SNPs and AD [10-15]. However, the results remain controversial, as some studies do not find an association between *IL-18* polymorphisms and AD. The inconsistency among different studies may be due to the differences between analyzed populations and small sample sizes, resulting in low statistical power.

Therefore, we conducted a meta-analysis to examine these inconsistent results and clarify the associations between -607 C/A or -137 G/C polymorphisms and AD.

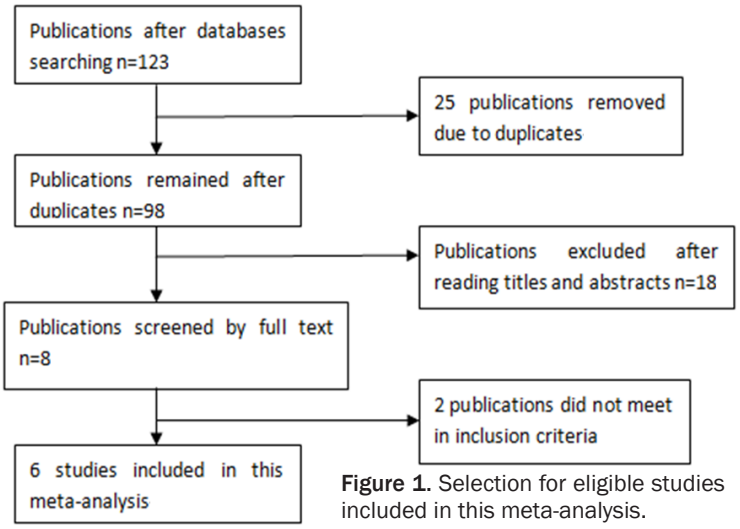

Figure 1. Selection for eligible studies included in this meta-analysis.

Materials and methods

Literature search

We performed a comprehensive search in PubMed, Embase, Cochrane Library, SinoMed, and the China Knowledge Resource Integrated Database to identify studies through April 1, 2015 examining *IL-18* gene polymorphisms and AD. The following search terms were used: "Alzheimer's disease", "Alzheimer's dementia", "AD", ''IL-18", "Interleukin 18", 'Interleukin-18", "IL18", "SNP", and ''polymorphism". Two independent investigators conducted the search. No language or other restrictions were placed on the search. We also searched the reference lists of all related studies to identify other initially omitted studies. Any disagreements were resolved by consensus.

Inclusion and exclusion criteria

Inclusion criteria included studies that (1) evaluated the association between *IL-18* gene polymorphisms (-607 C/A and -137 G/C) and AD, (2) included human subjects, (3) provided sufficient data to calculate the odds ratios (ORs), 95% confidence intervals (CIs), and *P* value, and (4) were case-control studies.

Exclusion criteria included (1) duplication of previous publications; (2) review, editorial, or other non-original studies; (3) family-based studies of pedigrees; (4) studies without detailed genotype data; (5) inclusion of subjects with other disorders that may influence the results.

Data extraction

For all eligible studies, the extracted information included the name of the first author, publication year, numbers of cases and controls, country of origin, ethnicity, genotyping method, *P*-value for Hardy-Weinberg equilibrium (HWE), and *IL-18* gene genotype frequency in cases and controls. Data were independently extracted by two authors who agreed on all values; disagreements were resolved by discussion.

Quality assessment

Two reviewers independently evaluated each study's quality based on the Newcastle-Ottawa Scale (NOS) [16]. The NOS criteria includes three aspects: (1) subject selection: 0-4; (2) comparability of subjects: 0-2; and (3) clinical outcome: 0-3. Total NOS scores ranged from 0 to 9. A score ranging from 5 to 9 is considered to indicate generally high methodological quality, whereas a score ranging from 0 to 4 signifies relatively poor quality [17]. Any disagreements on the NOS score of included studies wereaddressedthroughacomprehensivereassessment by the latter authors until reaching a consensus.

Statistical analysis

All statistical analyses were performed using Stata 11.0 software (StataCorp, College Station, TX, USA). Pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to evaluate the strength of the association between the *IL-18* gene polymorphisms (-607 C/A and -137 G/C) and AD. The statistical significance of the summary OR was determined by the Z-test. Heterogeneity was evaluated by the Q statistic (significant at $P<0.1$) and I^2 statistic (where >50% indicates significant heterogeneity) [18]. A fixed-effects model was used to compare trials of low heterogeneity, whereas a random effect model was selected for comparing trials showing significant heterogeneity. Pooled ORs were calculated for each model: allele contrast, dominant, recessive, homozygous, and heterozygous. We performed sensitivity analyses by omitting each study in turn to explore its effect on heterogeneity and the stability of the

Table 1. Characteristics of included studies

Author and year	Country	Ethnicity	Case			Control			Allele		HWE	Genotyping method	QAS
									Case/control	Case/control			
rs1946518 (-607 C/A)			CC	CA	AA	CC	CA	AA	C	A			
Moraes_2013	Brazil	Caucasian	39	59	22	121	210	81	137/452	103/472	0.619	PCR	7
Wang_2012	China	Asian	17	24	10	8	26	17	58/42	44/60	0.781	PCR	7
Segat_2010	Italy	Caucasian	50	72	43	50	84	31	172/184	158/146	0.753	PCR	7
Yu_2009	China	Asian	34	62	13	21	64	24	130/106	88/112	0.086	SSP-PCR	7
Bossu_2007	Italy	Caucasian	124	170	42	38	71	30	418/147	254/131	0.865	PCR	8
rs187238 (-137 G/C)			GG	GC	CC	GG	GC	CC	G	C			
Tian_2015	China	Asian	158	40	3	185	68	4	356/438	46/76	0.619	PCR	7
Wang_2012	China	Asian	35	15	1	22	26	3	85/70	17/32	0.327	PCR	7
Segat_2010	Italy	Caucasian	79	76	10	86	64	15	234/236	96/94	0.567	PCR	7
Yu_2009	China	Asian	87	21	1	73	33	3	195/179	23/39	1.000	SSP-PCR	7
Bossu_2007	Italy	Caucasian	179	145	12	65	57	9	503/187	169/75	0.528	PCR	8

QAS: Quality assessment score. HWE: Hardy-Weinberg equilibrium. Na: Not available.

Table 2. Meta-analysis of the association between *IL-18* gene polymorphisms and AD susceptibility

Genetic contrasts	Random/Fixed effect mode	OR (95% CI)	*P*	I-squared	*P* for heterogeneity
-607 C/A					
A vs. C	Random	0.79 (0.61, 1.01)	0.063	63.5%	0.027
AA+CA vs. CC	Fixed	**0.73 (0.58, 0.92)**	**0.007***	28.5%	0.232
AA vs. CC+CA	Random	0.74 (0.46, 1.18)	0.201	66.0%	0.019
AA vs. CC	Random	0.59 (0.33, 1.05)	0.072	69.3%	0.011
CA vs. CC	Fixed	**0.75 (0.59, 0.96)**	**0.021***	0.0%	0.683
-137 G/C					
C vs. G	Fixed	**0.79 (0.66, 0.94)**	**0.009***	45.9%	0.116
CC+GC vs. GG	Random	0.72 (0.51, 1.03)	0.073	58.8%	0.045
CC vs. GG+GC	Fixed	**0.57 (0.34, 0.97)**	**0.040***	0.0%	0.896
CC vs. GG	Fixed	**0.57 (0.33, 0.97)**	**0.039***	0.0%	0.767
GC vs. GG	Random	0.75 (0.42, 1.10)	0.137	61.2%	0.036

*Bold values are statistically significant ($P<0.05$).

overall results. Potential publication bias was investigated using Begger's and Egger's linear regression test [19]. HWE was assessed in the controls using using the Pearson's chi-square test. *P* values of less than 0.05 were considered to indicate significant publication bias.

Results

Characteristics of the published studies

We identified six eligible studies in this meta-analysis [10-15]. The selection process is presented in **Figure 1** and the characteristics of the six studies are summarized in **Table 1** [10-15]. Four studies investigated both -607 C/A and -137 G/C polymorphisms [10-12, 15]. Included studies were published from 2007 to 2015. Genotype distributions of the controls in these studies all conformed to HWE. The NOS scores of all included studies ranged from 7 to 8, indicating that they were of high methodological quality. Genomic DNA was extracted from peripheral blood samples in all six studies [10-15]. One study used sequence-specific primers (SSP)-polymerase chain reaction (PCR) polymorphism analysis for genotyping [10] and five used PCR [11-15]. For the -607 C/A polymorphism, five studies with 781 AD patients and 876 normal controls were included [10-12, 14, 15]. Three studies were performed in Caucasian populations [11, 12, 14] and two in Asian populations [10, 15]. For the -137 G/C polymorphism, five studies with 862 AD patients and 713 normal controls were analyzed [10-13, 15]. Two studies were conducted in Caucasians [11, 12] and three in Asian populations [10, 13, 15].

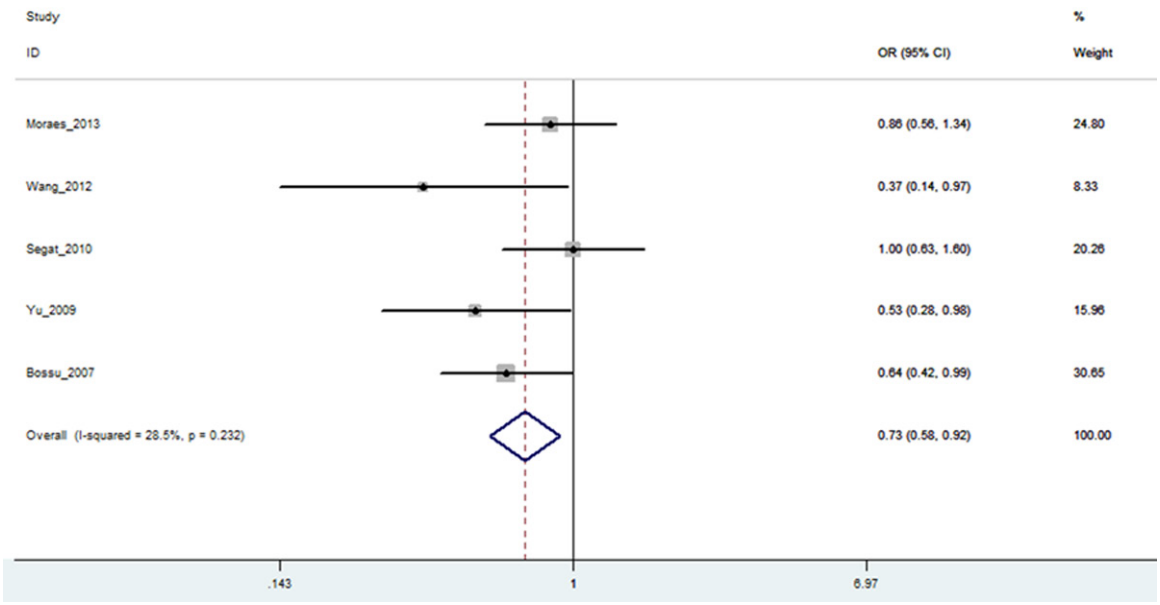

Figure 2. Forest plot shows odds ratio for the association between the *IL-18* gene -670 C/A polymorphism and risk of AD with dominant model (AA+CA *vs.* CC).

Meta-analysis: IL-18 -607 C/A polymorphism

Fixed effects were assumed for the dominant model (AA+CA *vs*. CC) and heterozygous model (CA *vs*. CC), as these did not display significant heterogeneity, whereas random-effects models were used for the allele model (A *vs*. C), recessive model (AA *vs*. CC+CA), and homozygous model (AA *vs*. CC), which were significantly heterogeneous.

As shown in **Table 2**, the *IL-18* gene -670 C/A polymorphism was associated with AD in the dominant and heterozygous models (AA+CA *vs*. CC: OR, 0.73; 95% CI, 0.58-0.92, *P*=0.007, **Figure 2**; CA *vs*. CC: OR, 0.75; 95% CI, 0.59-0.96, *P*=0.021). Stratification analyses according to ethnicity and apolipoprotein-E ε4 (APOE4) status (**Table 3**). The results indicated that *IL-18* gene -670 C/A polymorphism was significantly associated with AD in Asian populations. Furthermore, we found that the *IL-18* gene -670 C/A polymorphism may decrease the risk of AD in those carrying the APOE4 allele in the allele model, dominant model, recessive model, and the homozygous model. We assessed sensitivity by omitting each study one at a time in each genetic model. Upon exclusion of the study of Segat *et al*., [11], the pooled estimates of the remaining four studies [10, 12, 14, 15] showed that the -670 C/A polymorphism may decrease the risk of AD in the allele model (A *vs*. C, **Figure 3**), recessive model, and homozygous model. Both Egger's and Begg's tests suggested that there was no obvious publication bias in the overall analysis for the -670 C/A polymorphism.

Meta-analysis: IL-18 -137 G/C polymorphism

Fixed effects models were applied for the allele model (C *vs*. G), recessive model (CC *vs*. GG+GC), and homozygous model (CC *vs*. GG), while random effects models were used for the dominant model (CC+GC *vs*. GG) and heterozygous model (GC *vs*. GG). Our data indicated that the *IL-18* -137 G/C polymorphism may be protective against AD (C *vs*. G: OR, 0.79; 95% CI, 0.66-0.94, *P*=0.009, **Figure 4**; CC *vs*. GG+GC: OR, 0.57; 95% CI, 0.34-0.97, *P*=0.040; CC *vs*. GG: OR, 0.57; 95% CI, 0.33-0.97, *P*= 0.039) (**Table 2**). Stratification analyses also suggested that the *IL18* gene -137 G/C polymorphism decreases the risk of AD, especially in Asians and APOE4 carriers. Sensitivity analysis indicated that -137 G/C polymorphism may protect against AD in the dominant model (CC+GC vs. GG, **Figure 5**) and heterozygous model by exclusion of the Segat *et al*. study [11]. For the -137 G/C polymorphism, the *p* value of Egger's and Begg's tests indicated that there was no evident publication bias.

Table 3. Stratified analyses between the *IL-18* gene polymorphisms and risk of AD

Variable	-607 C/A (case/control)			OR (95% CI); P				
	CC	CA	AA	A vs. C	AA+CA vs. CC	AA vs. CC+CA	AA vs. CC	CA vs. CC
Ethnicity								
Caucasian	213/209	301/365	107/142	0.89 (0.66, 1.20); 0.457	0.81 (0.63, 1.05); 0.108	0.90 (0.49, 1.65); 0.729	0.79 (0.41, 1.54); 0.494	0.82 (0.62, 1.07); 0.141
Asian	51/29	86/90	23/41	**0.60 (0.44, 0.83); 0.002***	**0.47 (0.28, 080); 0.005***	**0.48 (0.27, 0.85); 0.012***	**0.31 (0.16, 0.62); 0.001***	**0.54 (0.32, 0.94); 0.028***
APOE4								
Positive	29/6	38/13	12/17	**0.34 (0.19, 0.61); 0.001***	**0.35 (0.13, 0.93); 0.036***	**0.19 (0.08, 0.48); 0.001***	**0.14 (0.04, 0.44); 0.001***	0.61 (0.21, 1.81); 0.373
Negative	22/23	48/77	11/24	0.76 (0.51, 1.13); 0.176	0.62 (0.32, 1.21); 0.160	0.67 (0.31, 1.47); 0.323	0.51 (0.20, 1.30); 0.161	0.65 (0.33, 1.30); 0.226
	-137 G/C (case/control)							
	GG	GC	CC	C vs. G	CC+GC vs. GG	CC vs. GG+GC	CC vs. GG	GC vs. GG
Ethnicity								
Caucasian	258/151	221/121	22/24	0.93 (0.73, 1.17); 0.509	1.00 (0.74, 1.37); 0.989	0.58 (0.31, 1.06); 0.078	0.61 (0.32, 1.14); 0.119	1.08 (0.78, 1.50); 0.645
Asian	280/280	76/127	5/10	**0.62 (0.46, 0.82); 0.001***	**0.56 (0.39, 0.81); 0.002***	0.56 (0.19, 1.64); 0.288	0.47 (0.16, 1.37); 0.166	**0.58 (0.42, 0.81); 0.001***
APOE4								
Positive	64/18	15/17	0/1	**0.29 (0.14, 0.61); 0.001***	**0.23 (0.10, 0.55); 0.001***	Na	Na	**0.24 (0.10, 0.59); 0.002***
Negative	58/78	21/41	2/5	0.74 (0.43, 1.26); 0.264	0.70 (0.38, 1.32); 0.270	Na	Na	0.73 (0.38, 1.39); 0.331

*Bold values are statistically significant ($P<0.05$). Na: Not available.

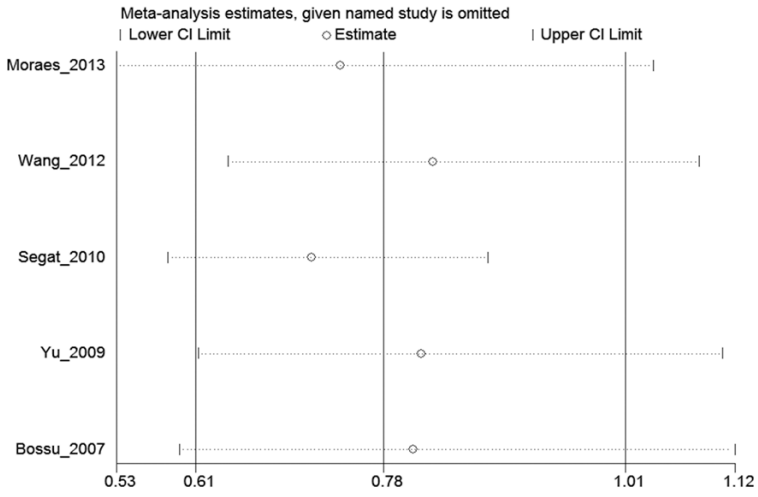

Figure 3. Sensitivity analysis shows odds ratio for the association between the *IL-18* gene -670 C/A polymorphism and risk of AD with allele model (A *vs.* C).

Discussion

This is the first meta-analysis to summarize the evidence to date regarding the association between *IL-18* gene polymorphisms and the risk of AD. Based on our results, *IL-18* gene polymorphisms may decrease the risk of AD, especially among Asian and APOE4-positive AD patients.

The role of inflammation in the pathogenesis of AD has been investigated by several studies focusing on production of cytokines such as IL-1, IL-6, and TNF, which are associated with neuroinflammation [20]. IL-18 is a member of the IL-1 superfamily of pro-inflammatory cytokines produced in the brain. The involvement of IL-18 in mediating neuroinflammation and neurodegeneration among brain diseases has recently been reported [21, 22]. Several studies found that IL-18 plasma level was significantly increased in AD patients [23-25]. Bossù *et al*. found significantly increased production of IL-18 in stimulated blood mononuclear cells from AD patients, which was associated with cognitive impairment [26]. Furthermore, a previous meta-analysis reported significantly higher concentrations of the proinflammatory cytokines IL-18 in the peripheral blood of AD subjects compared with control subjects [27]. The above studies indicate that IL-18 may be a risk factor for AD patients. It is possible that *IL-18* promoter polymorphisms may be useful to predict the risk and outcome of AD. However, our data indicate that *IL-18* gene polymorphisms (-607 C/A and -137 G/C) decrease the risk of AD. Stratification analyses suggested these two SNPs were both related to AD, especially in Asian and APOE4-positive patients.

The two earliest studies, in Italian populations, investigated the relationship between *IL-18* polymorphisms (-607 C/A and -137 G/C) and AD, with conflicting results [11, 12]. Bossù *et al*. found that these two SNPs were genetic risk factors for AD [12], whereas Segat *et al*. suggested that they were not associated with AD [11]. The distribution of *IL-18* functional polymorphisms and the relationship between *IL-18* and AD among different races [11, 12] cannot be evaluated in this study since the populations analyzed were both Italian. As noted by Segat *et al*. [11], the significance of the results of Bossu *et al*. [12] may diminish after multiple test corrections. They only considered *p* values for -607 C/A and -137 G/C polymorphisms, but ignored the interference of confounding factors, such as age. Another significant difference between these two studies was that Segat *et al*. [11] enrolled patients at the onset of Alzheimer's disease (EOAD) (age ≤65 years), while Bossu *et al*. [12] recruited patients with late onset Alzheimer's disease (LOAD) (age >65 years). Thus, we interpreted these results with caution [11, 12]. Two studies conducted by Yu *et al*. and Wang *et al*. in Chinese Han populations demonstrated an association between 137 G/C polymorphism and the risk of AD [10, 15]. However, Yu *et al*. found that these associations were influenced by the presence of ApoE4 alleles, and -137 G alleles were shown to closely interact with ApoE4 [10]. Furthermore, a previous study demonstrated that the APOE4 gene was a genetic risk factor for AD patients [28]. Therefore, this effect may be due largely to the concomitant presence of APOE ε4, but not -137 G/C polymorphisms.

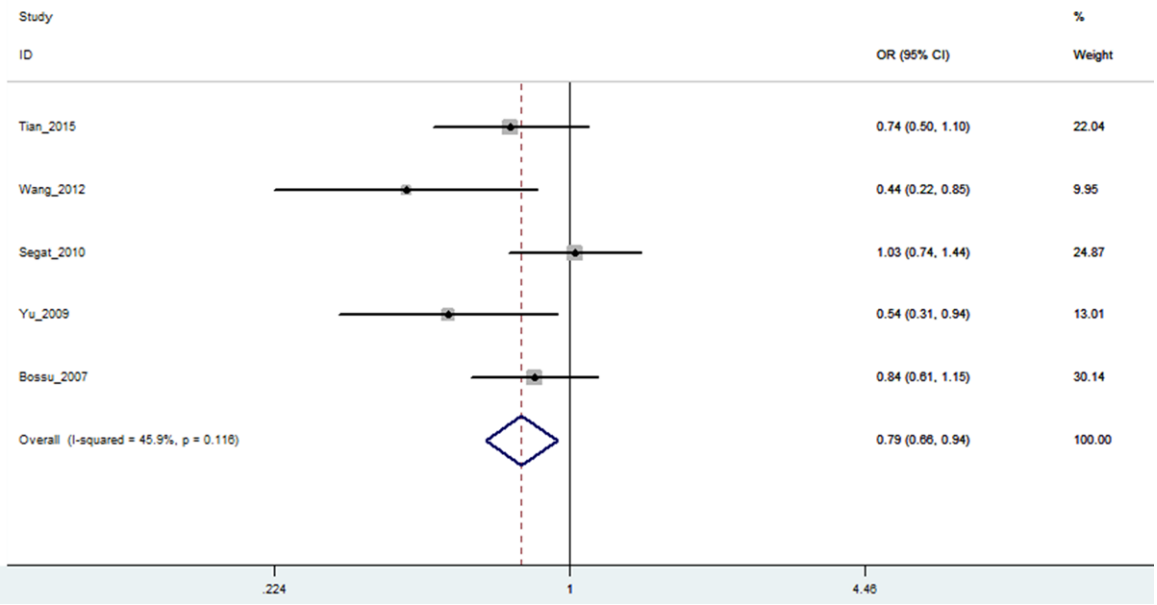

Figure 4. Forest plot shows odds ratio for the association between the *IL-18* gene -137 G/C polymorphism and risk of AD with allele model (C *vs.* G).

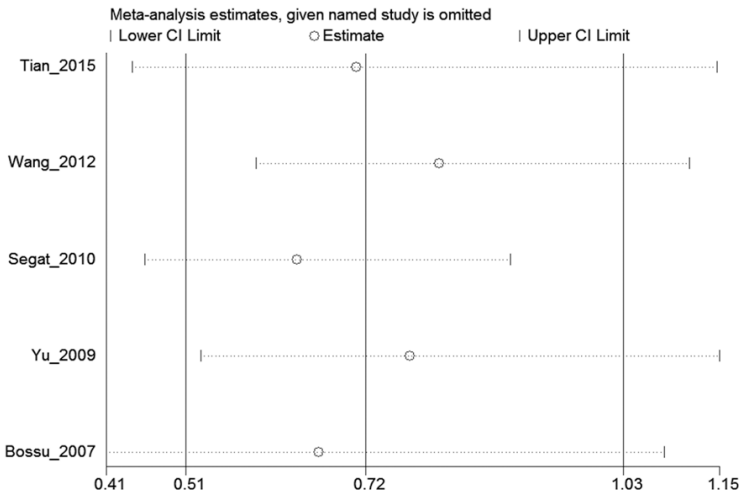

Figure 5. Sensitivity analysis shows odds ratio for the association between the *IL-18* gene -137 C/A polymorphism and risk of AD with dominant model (CC+GC vs. GG).

In this meta-analysis, our results indicated that *IL-18* gene polymorphisms (-607 C/A and -137 G/C) may decrease the risk of AD. However, positive results were obtained when the fixed-effects model was used (see **Table 2**). The fixed-effects model is prone to false positives, which may result in publication bias. Therefore, we used the more conservative random-effects model to reanalyze the data. The results still indicated that *IL-18* gene polymorphisms were protective against AD, supporting our previous results. Studies from Bossu et al., 2007 [12] and Bossu *et al*., 2008 [26] presented a partially overlapping population; therefore, we did not include the latter study [26]. Bossu *et al*. showed a significant correlation between IL-18 production and cognitive decline in AD patients [26]. However, they could not verify whether the association was due to *IL-18* gene polymorphisms (-607 C/A and -137 G/C). Sensitivity analysis identified the study conducted by Segat *et al*. [11] as largely responsible for the heterogeneity of results of -607 C/A and -137 G/C in this meta-analysis. Moreover, removing the study of Segat *et al*. [11] from the overall analysis led to a statistically significant association between *IL-18* gene polymorphisms (-607 C/A and -137 G/C) and reduced risk of AD.

Several potential limitations should be taken into consideration. First, the number of studies included was small, and the sample sizes were not large. Second, our analysis is subject to

publication bias; any unpublished trials would have been missed. Third, our results were based on unadjusted estimates, without considering other confounders (such as age, gender, and environmental factors); as a result, more precise analysis should be conducted if individual data are available. Fourth, only Caucasian and Asian populations were included in this meta-analysis, and further studies on other ethnic groups should be pursued because the incidence of these polymorphisms may vary among ethnicities.

In conclusion, this meta-analysis suggests that *IL-18* gene polymorphisms may decrease the risk of AD. Stratification analyses revealed that *IL-18* gene polymorphisms are also associated with AD, especially in Asian and APOE4-positive AD patients. Further larger-scale studies are required to investigate the association between -607 C/A and -137 G/C polymorphisms and AD to confirm our results.

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Disclosure of conflict of interest

None.

Abbreviations

CI, confidence interval; OR, odds ratio; AD, Alzheimer's disease; EOAD, onset of Alzheimer's disease; LOAD, late onset of Alzheimer's disease; TNF, tumor necrosis factor; SNPs, single nucleotide polymorphisms; HWE, Hardy-Weinberg equilibrium; APOE4, apolipoprotein-E ε4; NOS, Newcastle-Ottawa Scale.

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