

Estrogen receptor α gene polymorphisms and risk of Alzheimer's disease: evidence from a meta-analysis

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Objective: Human *estrogen receptor α* (*ESRI*), a member of the nuclear receptor superfamily of ligand-activated transcription factors, is one of the key mediators of hormonal response in estrogen-sensitive tissues. Accumulating evidence has demonstrated that two of the most widely studied single-nucleotide polymorphisms in *ESRI* – *PvuII* (T/C, rs223493) and *XbaI* (A/G, rs9340799) – are possibly associated with Alzheimer's disease (AD). However, individual study results are still controversial.

Materials and methods: We searched PubMed, Embase, Web of Science, Science Direct, SpringerLink, and the Chinese National Knowledge Infrastructure databases for eligible studies assessing the association of *ESRI* polymorphisms and AD risk (last search performed in November 2013). Thereafter, a meta-analysis of 13,192 subjects from 18 individual studies was conducted to evaluate the association between *ESRI* polymorphisms and susceptibility to AD.

Results: The results indicated that a significant association was found between the *ESRI PvuII* polymorphism and AD risk in Caucasian populations (CC + CT versus TT, odds ratio [OR] 1.14, 95% confidence interval [CI] 1.02–1.28, $P=0.03$; CT versus TT, OR 1.16, 95% CI 1.02–1.31, $P=0.02$), whereas no evidence of association was found in Asian populations. Nevertheless, we did not find any significant association between the *ESRI XbaI* polymorphism and AD risk for any model in Caucasian and Asian populations (all $P>0.05$).

Conclusion: Based on this meta-analysis, we conclude that the *ESRI PvuII* polymorphism might be a risk factor in AD development in Caucasian populations, not in Asian populations. Further confirmation is needed from better-designed and larger studies.

Keywords: Alzheimer's disease, estrogen receptor, polymorphism, meta-analysis

Introduction

Alzheimer's disease (AD) is one of the main causes of dementia among elderly individuals, and is characterized by memory impairments and loss of cognitive functions, which eventually leads to complete incapacity and death of patients within 3–9 years after diagnosis.¹ As the elderly population continues to grow, the prevalence of AD has increased remarkably worldwide. At present, AD is one of the leading causes of disability and death among the elderly.^{2–4} AD has emerged as a serious public health concern, affecting patients' quality of life and placing an immense burden on the individual, family, and community. Therefore, elucidating the pathogenesis and risk factors of AD is of great significance for early detection, prevention, and control of the susceptible population.

Genetic, metabolic, and environmental factors play a role in the development and progression of AD.⁵ Recent genome-wide association studies have identified many genetic variances and single-nucleotide polymorphisms (SNPs) that are associated with

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AD risk.⁶ Estrogen-receptor gene polymorphisms are possible candidates for AD susceptibility. In women, estrogen loss associated with menopause status has been suggested to contribute to the development of AD.^{7,8} Estrogen has been shown to act as a neuroprotectant and a neurotrophic agent.⁹ Estrogen promotes neuronal cell survival, reduces neuronal injury, protects against neurotoxins, facilitates axonal sprouting and neuronal repair, and enhances synaptic transmission and neurogenesis.¹⁰ Recently, estrogen-replacement therapy has been proposed as a therapeutic approach to reduce the risk of developing AD and help patients with AD maintain their cognitive function.¹¹ Estrogen exerts most of its effects through at least two major classes of receptors – estrogen receptor α (ESR1) and estrogen receptor β (ESR2).¹² Human *ESR1*, a member of the nuclear receptor superfamily of ligand-activated transcription factors, is located on human chromosome 6q25, and is one of the key mediators of hormonal response in estrogen-sensitive tissues. After binding to estrogen, ESR1 acts as a transcriptional factor that regulates gene expression and function by interacting with regulatory regions of target genes.¹³ Many studies have demonstrated that *ESR1* polymorphisms might influence *ESR1* expression and affect estrogen function. To date, associations between *ESR1* polymorphisms and cancer,^{14,15} coronary artery disease,¹⁶ hip fracture,¹⁷ and bone mineral density¹⁸ have been identified.

Accumulating evidence has demonstrated that two of the most widely studied SNPs in *ESR1* – *PvuII* (T/C, rs223493) and *XbaI* (A/G, rs9340799) – are possibly associated with AD. However, the results of studies seeking associations of *ESR1* with AD risk have not always been consistent in different population analyses.¹⁹ Therefore, we performed a meta-analysis of all eligible studies to provide a more comprehensive and reliable conclusion by evaluating the association between *ESR1* gene polymorphisms and susceptibility to AD.

Materials and methods

Search strategy

We searched PubMed, Embase, Web of Science, Science Direct, SpringerLink, and the Chinese National Knowledge Infrastructure databases for eligible studies assessing the association of *ESR1* polymorphisms and AD risk (last search updated to November, 2013). The search terms were “Alzheimer’s disease (AD) or dementia” in combination with “estrogen receptor or oestrogen receptor or estrogen” in combination with “polymorphism or variant or mutation”. There was no restriction on time period, sample size,

population, language, or type of report in order to minimize potential publication bias.

Inclusion and exclusion criteria

Studies included in this meta-analysis had to meet the following criteria: 1) case-control studies or cohort studies, 2) studies investigating the association between *ESR1* gene polymorphisms and AD risk, 3) sufficient data available to calculate an odds ratio (OR) with 95% confidence interval (CI), and 4) clinical diagnosis of AD based on standards of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association. The exclusion criteria of the meta-analysis were: 1) case-control studies not focusing on the correlation between *ESR1* polymorphisms and AD risk; 2) insufficient original data was available for data extraction; and 3) meta-analyses, letters, reviews, and editorial articles. If more than one study was published by the same author using the same patient population, the study with the largest size of samples was included.

Data extraction

Two authors (DC and BL) independently extracted the data from all eligible publications based on the inclusion criteria. The following information was recorded: name of first author, year of publication, country, ethnicity, number of cases and controls, the source of control, genotype method, distribution of genotypes, and Hardy–Weinberg equilibrium in controls. According to the source of control, eligible studies were defined as hospital-based and population-based. Ethnicity was simply categorized as Asian or Caucasian. Discrepancies were resolved by consensus and by consulting a third author.

Statistical analysis

Crude ORs with their corresponding 95% CIs were used to assess the strength of association between *ESR1* polymorphisms and AD risk. The statistical significance of pooled ORs was assessed by the *Z*-test. Statistical heterogeneity across studies included in the meta-analysis was assessed by Cochran’s *Q* statistic and the *I*² test.²⁰ $P < 0.10$ and $I^2 > 50\%$ were considered to be statistically significant heterogeneity, and the random-effects model or the fixed-effects model were used. Sensitivity analysis was performed using the leave-one-out method to test the reliability of the overall pooled results.²¹ Publication bias was evaluated by funnel plot²² and further assessed by Egger’s linear regression test,²³ and $P < 0.05$ was considered representative of statistically

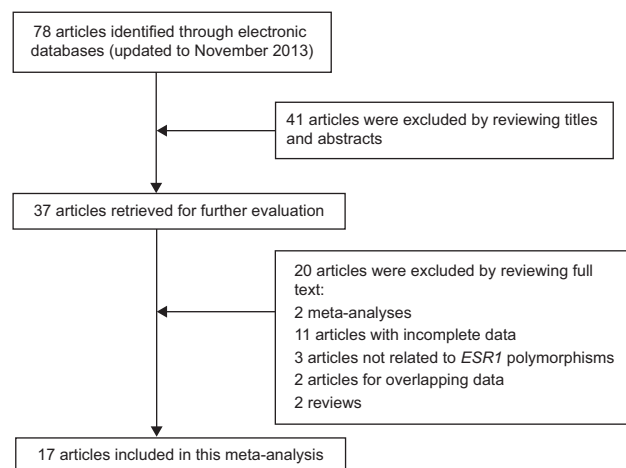


Figure 1 Flowchart of study selection.

Abbreviation: ESR1, estrogen receptor α .

significant publication bias. Data analyses were performed using Stata 11.0 (StataCorp, College Station, TX, USA) and RevMan 5.0 (Cochrane, Oxford, UK).

Results

Eligible studies

A flowchart of the process of study selection is shown in Figure 1. Based on the inclusion and exclusion criteria, a total of 17 articles were included in the meta-analysis after full-text review.^{9,24–39} The main characteristics of included studies are presented in Table 1. Of the 18 case-control studies included in the 17 articles, 18 studies investigated the

ESR1 PvuII polymorphism (3,902 cases and 9,290 controls) and 17 studies investigated the *ESR1 XbaI* polymorphism (2,841 cases and 8,094 controls). Eight studies were performed in Caucasian populations,^{9,24,25,29–31,36,37} and ten studies were performed in Asian populations.^{26–28,32–35,37–39} The genotype distributions among the controls of all studies were in agreement with the Hardy–Weinberg equilibrium, except for one study for the *ESR1 PvuII* polymorphism²⁵ and one study for the *ESR1 XbaI* polymorphism.³⁴

Quantitative data synthesis

The results of this meta-analysis are presented in Table 2. The heterogeneity was significantly observed under all models ($P < 0.05$) for the *ESR1 PvuII* and *XbaI* polymorphisms, which might have resulted from differences in ethnicity, country, source of controls, and genotype methods, so the random-effects model was used.

For the *ESR1 PvuII* polymorphism, a total of 18 studies including 3,902 cases and 9,290 controls were included in the meta-analysis. In the overall analysis, we did not find any significant association between the *ESR1 PvuII* polymorphism and AD risk in any comparison model (C allele versus T allele, OR 1.05, 95% CI 0.95–1.17, $P = 0.35$; CC + CT versus TT, OR 1.13, 95% CI 0.98–1.32, $P = 0.10$; CC versus CT + TT, OR 0.95, 95% CI 0.80–1.13, $P = 0.60$; CC versus TT, OR 1.03, 95% CI 0.84–1.28, $P = 0.75$; CT versus TT, OR 1.15, 95% CI 1.00–1.33, $P = 0.05$). Subgroup analysis stratified by ethnicity showed a significant association between the *ESR1 PvuII*

Table 1 Characteristics of the 18 eligible studies included in the meta-analysis

Study	Year	Country	Ethnicity	Source of controls	Sample size, (cases/controls)	SNP studied	Genotyping method	HWE
Brandi et al ²⁴	1999	Italy	Caucasian	PB	193/202	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.827, 0.364
Boada et al ²⁵	2012	Spain	Caucasian	PB	1,069/1,215	<i>PvuII</i>	Real-time PCR	0.024
Lambert et al ⁹	2001	UK	Caucasian	PB	186/405	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.943, 0.159
Lin et al ²⁶	2003	People's Republic of China	Asian	PB	30/125	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.841, 0.051
Ji et al ²⁷	2000	Japan	Asian	PB	234/134	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.659, 0.679
Usui et al ²⁸	2006	Japan	Asian	PB	205/92	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.385, 0.150
Corbo et al ²⁹	2006	Italy	Caucasian	PB	277/212	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.193, 0.512
Monastero et al ³⁰	2006	Italy	Caucasian	PB	172/172	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.445, 0.062
Porrello et al ³¹	2006	Italy	Caucasian	PB	131/109	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.103, 0.751
Li et al ³²	2004	People's Republic of China	Asian	PB	66/143	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.288, 0.867
Xu and Jia ³³	2002	People's Republic of China	Asian	PB	49/55	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.736, 0.869
Hou ³⁴	2009	People's Republic of China	Asian	PB	203/138	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.798, 0.036
Deng et al ³⁵	2013	People's Republic of China	Asian	HB	236/236	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.240, 0.475
den Heijer et al ³⁶	2004	Netherlands	Caucasian	PB	230/5,514	<i>PvuII</i> , <i>XbaI</i>	Taqman	0.802, 0.627
Maruyama et al ³⁷	2000	Japan	Asian	PB	183/133	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.068, 0.061
Maruyama et al ³⁷	2000	UK	Caucasian	PB	156/120	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.903, 0.661
Ma et al ³⁸	2009	People's Republic of China	Asian	PB	219/215	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.424, 0.962
Zhou et al ³⁹	2008	People's Republic of China	Asian	PB	63/70	<i>PvuII</i> , <i>XbaI</i>	PCR-RFLP	0.858, 0.142

Abbreviations: PB, population-based; HB, hospital-based; HWE, Hardy–Weinberg equilibrium; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SNP, single-nucleotide polymorphism.

Table 2 Association between *ESR1* polymorphisms and Alzheimer's disease risk

	Allele model		Dominant model		Recessive model		Homozygous comparison		Heterozygous comparison	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
<i>PvuII</i> (T/C)	C allele versus T allele		CC + CT versus TT		CC versus CT + TT		CC versus TT		CT versus TT	
Overall	1.05 (0.95–1.17)	0.35	1.13 (0.98–1.32)	0.10	0.95 (0.80–1.13)	0.60	1.03 (0.84–1.28)	0.75	1.15 (1.00–1.33)	0.05
Caucasian	1.06 (0.98–1.15)	0.12	1.14 (1.02–1.28)	0.03	1.01 (0.88–1.15)	0.89	1.10 (0.94–1.28)	0.23	1.16 (1.02–1.31)	0.02
Asian	1.06 (0.87–1.30)	0.55	1.23 (0.91–1.67)	0.18	0.84 (0.61–1.17)	0.31	0.98 (0.65–1.47)	0.91	1.28 (0.95–1.72)	0.10
<i>XbaI</i> (A/G)	G allele versus A allele		GG + GA versus AA		GG versus GA + AA		GG versus AA		GA versus AA	
Overall	1.05 (0.90–1.23)	0.53	1.07 (0.89–1.30)	0.47	1.00 (0.75–1.34)	0.99	1.04 (0.74–1.45)	0.84	1.04 (0.93–1.16)	0.50
Caucasian	1.02 (0.85–1.22)	0.84	1.03 (0.83–1.28)	0.78	1.00 (0.70–1.42)	0.99	1.01 (0.67–1.53)	0.97	1.03 (0.88–1.20)	0.71
Asian	1.10 (0.84–1.43)	0.50	1.14 (0.82–1.57)	0.44	1.03 (0.62–1.70)	0.92	1.09 (0.62–1.91)	0.78	1.13 (0.83–1.55)	0.44

Abbreviations: *ESR1*, estrogen receptor α ; OR, odds ratio; CI, confidence interval.

polymorphism and AD risk under the dominant model (CC + CT versus TT, OR 1.14, 95% CI 1.02–1.28, $P=0.03$; Figure 2) and heterozygous comparison (CT versus TT, OR 1.16, 95% CI 1.02–1.31, $P=0.02$), whereas no evidence of association

was found under the allele model (C allele versus T allele, OR 1.06, 95% CI 0.98–1.15, $P=0.12$), recessive model (CC versus CT + TT, OR 1.01, 95% CI 0.88–1.15, $P=0.89$), or homozygous comparison (CC versus TT, OR 1.10, 95% CI

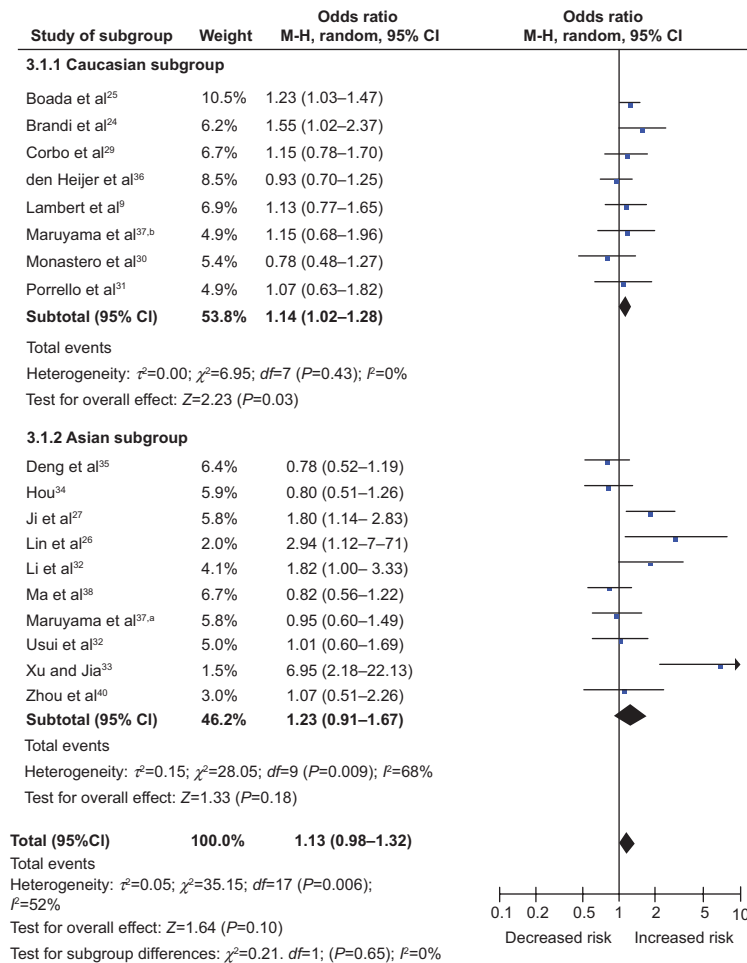


Figure 2 Forest plots of *ESR1 PvuII* polymorphism and Alzheimer's disease risk in Caucasian and Asian populations (dominant model, CC + CT versus TT).

Notes: A random model of meta-analysis was employed for calculation of the combined ORs and P -values. Caucasian population, OR 1.14, CI 1.02–1.28, $P=0.03$; Asian population, OR 1.23, CI 0.91–1.67, $P=0.18$. The study of Maruyama et al³⁷ was performed in Asian populations (a), and Caucasian populations (b).

Abbreviations: M-H, Mantel-Haenszel; OR, odds ratio; CI, confidence interval; *ESR1*, estrogen receptor α .

0.94–1.28, $P=0.23$) in Caucasian populations. Nevertheless, we did not find any significant association between the *ESR1 PvuII* polymorphism and AD risk under any model in the Asian population (all $P>0.05$).

For the *ESR1 XbaI* polymorphism, a total of 17 studies including 2,841 cases and 8,094 controls were included in the meta-analysis. Overall, there was no evidence of an association between the *ESR1 XbaI* polymorphism and AD risk in different genetic models when all the eligible studies were pooled into the meta-analysis (G allele versus A allele, OR 1.05, 95% CI 0.90–1.23, $P=0.53$; GG + GA versus AA, OR 1.07, 95% CI 0.89–1.30, $P=0.47$ [Figure 3]; GG versus

GA + AA, OR 1.00, 95% CI 0.75–1.34, $P=0.99$; GG versus AA, OR 1.04, 95% CI 0.74–1.45, $P=0.84$; GA versus AA, OR 1.04, 95% CI 0.93–1.16, $P=0.50$). The association of the *ESR1 XbaI* polymorphism with AD was further stratified by ethnicity. Neither Caucasian populations nor Asian populations showed a significant association between the *ESR1 XbaI* polymorphism and AD risk in any model (all $P>0.05$) (Figure 3).

Sensitivity analysis

A sensitivity analysis was performed to assess the influence of each individual study on the pooled ORs through omitting

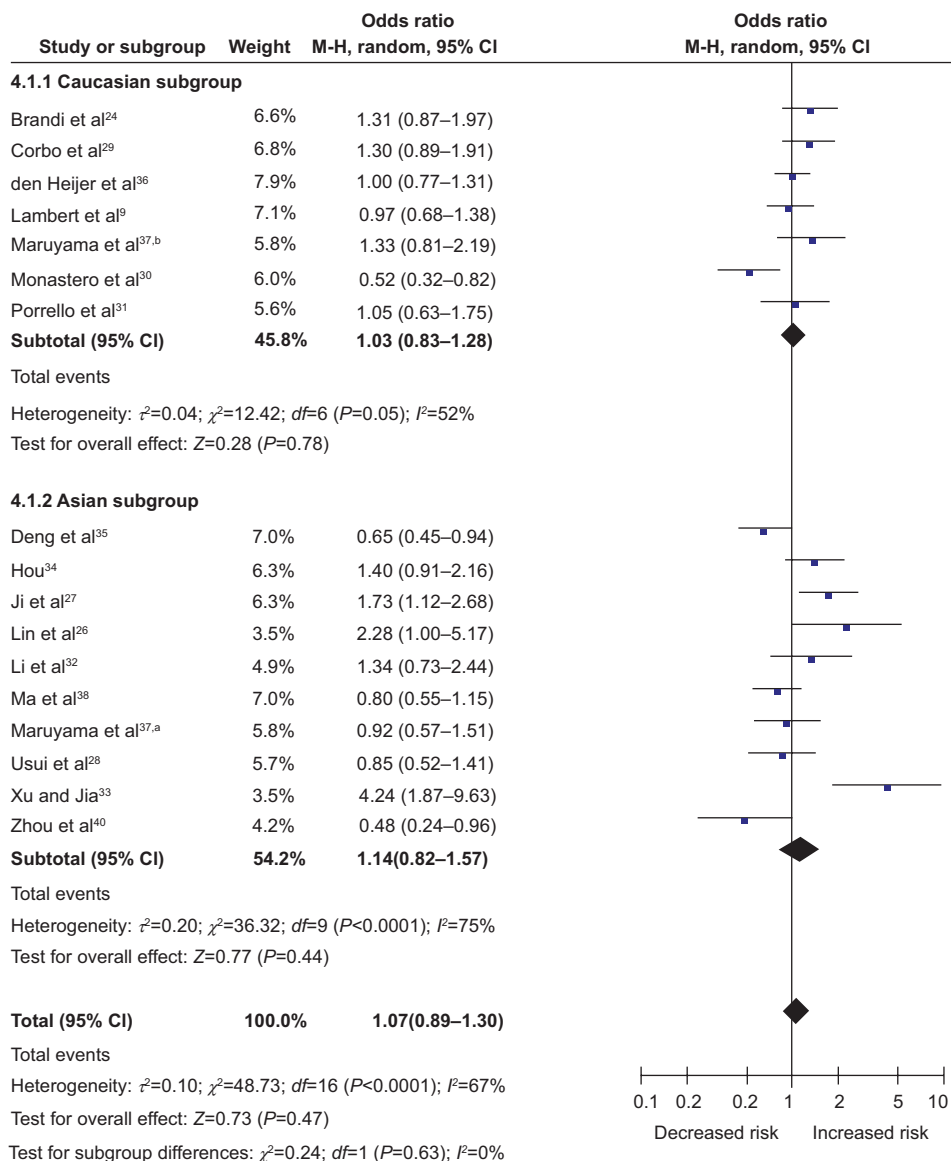


Figure 3 Forest plots of *ESR1 XbaI* polymorphism and Alzheimer's disease risk in Caucasian and Asian populations (dominant model, GG + GA versus AA). **Notes:** Random model of meta-analysis was employed for calculation of the combined ORs and P -values. Caucasian population, OR 1.03, CI 0.83–1.28, $P=0.78$; Asian population, OR 1.14, CI 0.82–1.57, $P=0.44$. The study of Maruyama et al³⁷ was performed in Asian populations (a), and Caucasian populations (b). **Abbreviations:** M-H, Mantel-Haenszel; CI, confidence interval; OR, odds ratio; *ESR1*, estrogen receptor α .

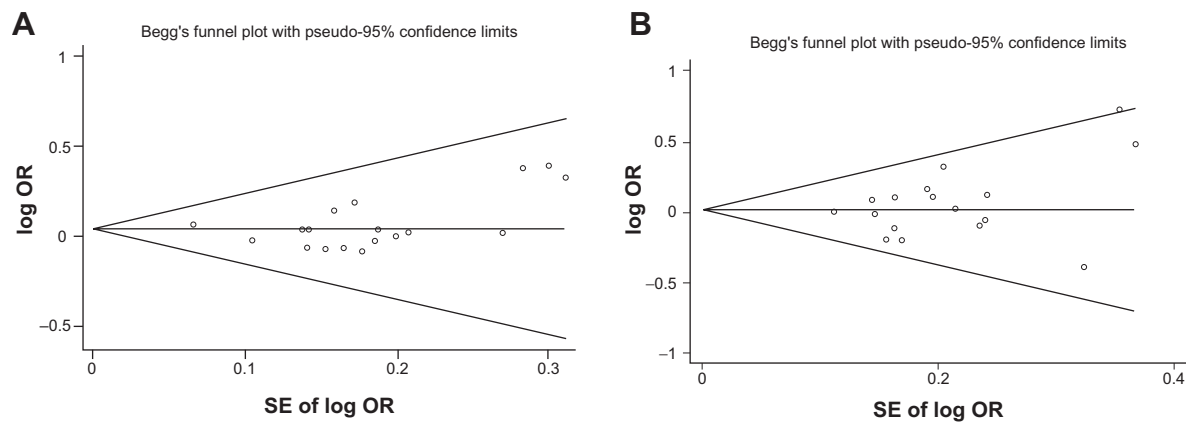


Figure 4 Egger's funnel plots of publication-bias analysis for the polymorphisms.

Notes: (A) *ESR1 PvuII* polymorphism; (B) *ESR1 XbaI* polymorphism.

Abbreviations: SE, standard error; OR, odds ratio; *ESR1*, estrogen receptor α .

individual studies. Statistically similar results were obtained after sequentially excluding each study, suggesting the stability of this meta-analysis.

Publication bias

The shapes of the funnel plots did not reveal any evidence of obvious asymmetry visually under the dominant model of *PvuII* and *XbaI* polymorphisms (Figure 4). Also, there was no statistical evidence of publication bias among studies using Egger's regression test for the *PvuII* ($P=0.296$) and *XbaI* ($P=0.206$) polymorphisms.

Discussion

The *ESR1* gene is critical for hormone binding, deoxyribonucleic acid binding, and activation of transcription, because it encodes an estrogen receptor that is key in the mediation of hormonal response in estrogen-sensitive tissues.⁴⁰ Given that the effect of a hormone is given by the interaction with its receptor, genetic changes in the *ESR1* gene may lead to differences in *ESR1* expression and estrogen metabolism, and thereby possibly explain interindividual differences in cognitive impairment or AD risk. Several SNPs have been identified in *ESR1*, and among these identified SNPs, *PvuII* (T/C, rs2234693) and *XbaI* (A/G, rs9340799), which are located in intron 1 of the *ESR1* gene, 397 and 351 base pairs upstream of exon 2, respectively, are the most studied. Many previous genetic studies have investigated the function of *ESR1 PvuII* and *XbaI* polymorphisms in the etiology of AD, but the results remain inconclusive. Bertram et al reported that *ESR1 PvuII* and *XbaI* polymorphisms were associated with AD risk, and the *ESR1* gene could be a candidate gene in the development of AD using a systematic meta-analysis.⁴¹ Another meta-analysis by Luckhaus and

Sand indicated that *ESR1 PvuII* and *XbaI* polymorphisms were confirmed to modulate susceptibility to AD in Asian individuals, but not in Europeans.⁴² However, only eleven studies and eight studies were included in Bertram et al's and Luckhaus and Sand's studies, respectively. Therefore, we performed a meta-analysis to update previous meta-analyses, and provide a more comprehensive and reliable analysis of the association between *ESR1 PvuII* and *XbaI* polymorphisms and AD risk.

This meta-analysis included 18 case-control studies with 3,902 cases and 9,290 controls for the *PvuII* polymorphism, and 17 case-control studies with 2,841 cases and 8,094 controls for the *XbaI* polymorphism. In the overall analysis, the *ESR1 PvuII* polymorphism was not associated with AD risk. In the analysis stratified by ethnicity, the *ESR1 PvuII* polymorphism was associated with AD susceptibility in Caucasian populations, while there was no evidence of an association between the *ESR1 PvuII* polymorphism and AD risk in Asian populations, which suggested that the differences in genetic background may affect AD susceptibility due to different ethnicities with different allele frequencies. Although the exact mechanism of the *PvuII* polymorphism in the development of AD is not yet clear, a possible reason could be that the *PvuII* polymorphism produces a binding site for a specific transcription factor that may affect gene expression,⁴³ while the presence of the C allele in the *PvuII* site was associated with decreased *ESR1* transcription and, consequently, a low number of receptors.⁴⁴ However, neither Caucasian populations nor Asian populations showed statistically significant associations between the *ESR1 XbaI* polymorphism and AD risk. Given that the *PvuII* and *XbaI* polymorphisms are in strong linkage disequilibrium,⁴⁵ it is difficult to determine which of the two polymorphic sites is driving the association.

In our meta-analysis, the results suggested that the *ESR1 PvuII* polymorphism may be of importance in AD risk in Caucasian populations. These findings are not consistent with previous meta-analyses;^{41,42} our results indicated that only the *ESR1 PvuII* polymorphism may alter the risk of AD in Caucasian populations, not in Asian populations, suggesting multiple and different genes are involved in the pathophysiological process of AD in different ethnicities.

Several limitations should not be ignored when interpreting the results. First, all eligible studies were from Caucasian and Asian populations; therefore, our results were limited to these two populations. More studies containing the full range of possible ethnic differences are needed to avoid selection bias. Second, AD is a multifactorial disease involving complex gene–gene or gene–environment interactions. In this study, we had insufficient data to evaluate such interactions for the independent role of *ESR1* polymorphisms in AD risk. Third, we did not perform subgroup analysis by sex, age, or different stage of AD, due to limited data in primary studies. Fourth, because only published studies were included in this study, publication bias may have occurred, even though no statistical test bias was found.

Conclusion

In summary, this meta-analysis indicates that the *ESR1 PvuII* polymorphism is associated with increased AD risk in Caucasian populations, but not in Asian populations. However, no significant association was observed for the *ESR1 XbaI* polymorphism and AD risk. This result should be interpreted cautiously. To confirm or refute this result, well-designed studies with larger sample sizes and more ethnic groups are required to elucidate this association further.

Acknowledgment

This study was supported by a grant from the National Natural Science Foundation of China (C120108).

Disclosure

The authors report no conflicts of interest in this work.

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