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ORIGINAL ARTICLE

Association between rs10046, rs1143704, rs767199, rs727479, rs1065778, rs1062033, rs1008805, and rs700519 polymorphisms in aromatase (*CYP19A1*) gene and Alzheimer's disease risk: a systematic review and meta-analysis involving 11,051 subjects

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Abstract

Background CYP19A1 enzyme (aromatase) encoded by *CYP19A1* (*cytochrome p450 family 19 subfamily a member 1*) gene plays a key role in the biosynthesis of estrogen, which has been significantly associated with Alzheimer's disease (AD). To ascertain whether *CYP19A1* gene polymorphisms are correlated with the susceptibility to AD, we performed this systematic review and meta-analysis of currently available studies.

Materials and methods A comprehensive literature search was conducted by using PubMed, Embase, and Web of Science databases and the Cochrane Library. The association was evaluated by using odds ratios (ORs) and 95% confidence intervals (CIs) through Stata software (version 12.0).

Results A total of eight articles including 39 case–control studies with 11,051 subjects including 3215 AD cases and 7836 controls were involved in this meta-analysis. By pooling all eligible studies, we detected that rs10046, rs1143704, rs767199, and rs727479 polymorphisms in *CYP19A1* gene were significantly associated with AD risk. A significant association between rs10046 polymorphism and AD risk was found under allele contrast, homozygous (TT vs CC: OR = 1.17, 95%CI = 1.02–1.34, $I^2 = 0.0\%$, $P = 0.026$), and dominant genetic models. In addition, we observed an association between with rs1143704 polymorphism under heterozygous and dominant genetic models (TT+TA vs AA: OR = 1.36, 95%CI = 1.03–1.79, $I^2 = 0.0\%$, $P = 0.033$). Similar results were found in rs767199 and rs727479 polymorphisms, while null results were found for other polymorphisms.

Conclusions This systematic review and meta-analysis suggested that the rs10046, rs1143704, rs767199, and rs727479 polymorphisms in *CYP19A1* gene significantly increase AD susceptibility. In addition, our results demonstrated that homozygous TT genotype in rs10046, dominant AA and AG genotypes in rs767199, homozygous TT genotype in rs727479, and dominant TT and TA genotypes in rs1143704 might be the susceptibility genotypes for AD, while no associations were observed between rs1065778, rs1062033, rs1008805, and rs700519 polymorphisms and AD susceptibility.

Keywords Aromatase · Alzheimer's disease · Polymorphism · Systematic review · Meta-analysis

Introduction

Alzheimer's disease (AD) is a complex and progressive neurodegenerative disease in an aging population, characterized by a gradual but inexorable cognitive decline [1]. It is the most common form of dementia in the elder [1]. Current estimates suggest that about 44 million people live with AD worldwide nowadays [2]. This is predicted to more than triple by 2050 as the population ages [3, 4].

Various risk factors are established to contribute to AD risk. First, age was considered as a major risk factor, with a 3-fold higher risk at ages 75–84 compared to individuals at ages 65–74 [3]. In addition, a family history of AD was also reported as the second greatest risk factor to AD susceptibility. Individuals who have a parent, brother, or sister with AD are

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more likely to develop AD than those without a first-degree relative suffering from AD [5, 6].

However, only a few of the individuals exposed to the above risk factors finally develop AD in their lifetime. In addition, when Alzheimer's diseases run in families, heredity (genomics and genetics), lifestyle and shared environmental factors, or both, may play a role. This suggested that AD risk was not only associated with age and a family history of AD, genetic factors may also play an important role in AD susceptibility. Genetic studies of AD have found many loci that may contribute to the risk of AD, including *phosphatidylinositol-binding clathrin assembly protein* (PICALM), *clusterin* (CLU), *complement receptor type 1* (CR1), *bridging integrator 1* (BIN1), and *CD2-associated protein* (CD2AP) [7]. Among these loci, only the ε4-allele of the *apolipoprotein E* (*APOE*) gene has been confirmed as a dominant genetic risk factor for AD, and this allele is associated with about 40 to 70% of cases [7].

Recent advances have demonstrated that estrogen may have beneficial effects on the pathogenesis of AD. Estrogen promotes the growth and survival of cholinergic neurons [8, 9], increases cholinergic activity [10], and promotes the nonamyloidogenic metabolism of the amyloid precursor protein [11]. In addition, estrogen has neurogenerative [12], neuroprotective [13], antiexcitotoxic [14], antioxidative [15], and anti-inflammatory [12] functions, suggesting that an estrogen deficiency in the central nervous system may affect the pathogenesis of AD. Estrogens, containing estrone and estradiol, are formed from the conversion of androgens by CYP19A1 (cytochrome p450 family 19 subfamily a member 1), also known as aromatase, which is a cytochrome p450 enzyme encoded by the *CYP19A1* gene. CYP19A1 is abundantly expressed in several brain areas, including the prefrontal cortex astrocytes, limbic system, hypothalamus, and hippocampus [16]. The *CYP19A1* gene is located on 15q21.2 on the chromosome and consists of 10 exons, of which exons 2 to 10 are transcribed and translated to synthesize the aromatase enzyme [17].

Hence, we can assume that *CYP19A1* gene polymorphisms could influence the pathogenesis of AD through making differences in the activity and expression of CYP19A1 enzyme. Recently, many investigations on the association between *CYP19A1* gene polymorphisms and AD risk have been performed. Among these polymorphisms, rs10046, rs767199, rs727479, rs1143704, rs1065778, rs1062033, rs1008805, and rs700519 have been widely investigated for their potential effect on AD risk. However, previous studies reported inconsistent and conflicting results and the insufficient sample size of subjects with AD in these investigations weakens the strength of evidence.

Therefore, we performed this systematic review and meta-analysis of currently available articles to evaluate firstly the possible associations between *CYP19A1* gene polymorphisms with AD risk and secondly to evaluate the associations after stratification by ethnicity and *APOE* ε4-allele.

Material and methods

Results of this study were reported by following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [18].

Search strategy

We performed a comprehensive electronic search in the databases Cochrane Library, PubMed, Embase, and Web of Science (up to March 20, 2019) to retrieve all eligible articles on the correlation between *CYP19A1* gene polymorphisms and AD risk. The main search strategy conducted in PubMed was as follows: (((((“Aromatase”[Mesh]) OR ((((((((((((Estrogen Synthetase) OR Estrogen Synthase) OR Cytochrome P450 19) OR CYP19 Protein) OR Protein, CYP19) OR Cytochrome P-450(AROM)) OR CYP 19) OR Cytochrome P-450 CYP19) OR Cytochrome P 450 CYP19) OR P450AROM) OR Androstenedione Aromatase) OR Aromatase, Androstenedione) OR CYP19))) AND ((polymorphism) OR variant)) AND ((“Alzheimer Disease”[Mesh]) OR “Dementia”[Mesh]). This strategy was also adapted in search of other databases. The language of eligible articles was restricted to English and no restriction was set for sample size limitation. In addition, the reference search was performed to identify additional eligible studies by scanning references.

Inclusion and exclusion criteria

All eligible articles included in this meta-analysis followed these criteria: (1) case–control studies evaluated the association between AD risk and the polymorphisms in *CYP19A1* gene; (2) control subjects matched with case patients for age and gender; (3) all the cases and controls are adults; (4) sufficient data to calculate an odds ratio (OR) with 95% confidence interval (CI); and (5) the distribution of genotypes among controls is in Hardy–Weinberg equilibrium (HWE). Besides, the exclusive criteria were as follows: (1) case-only studies, or reviews; (2) duplicates; and (3) genotype frequency not provided or unavailable data.

Data extraction

All eligible articles and available data from the enrolled studies were extracted respectively by two independent reviewers (Yuxuan Song and Yongjiao Yang) and then checked by each other. If any disagreement appeared, a third reviewer (Xiaoqiang Liu) would join in and discuss it with them to

reach a consensus. For each enrolled study, the following information was collected: first author, publication year, the area of origin, ethnic group, the number of subjects (containing both the number of cases with AD and the number of controls), the allelic/genotypic distribution, their distribution by *APOE* ε4-allele, and genotyping methods.

Quality assessment of included studies

Newcastle–Ottawa Scale (NOS) was adopted to assess the quality of the included case–control studies [19]. The 9-point scale assesses the biases from three aspects, including subject selection (a total of four points), group comparability (a total of two points), and ascertainment of exposure or outcome (a total of three points). A total score of ≤ 3 was considered low quality, 4–6 moderate, and ≥ 7 high.

Statistical analysis

ORs with their 95%CIs were calculated to evaluate the strength of the correlation between *CYP19A1* gene polymorphisms and AD risk, based on the genotype frequencies in the cases and controls. We applied the fixed effects model and the random effects model to assess the pooled ORs. The

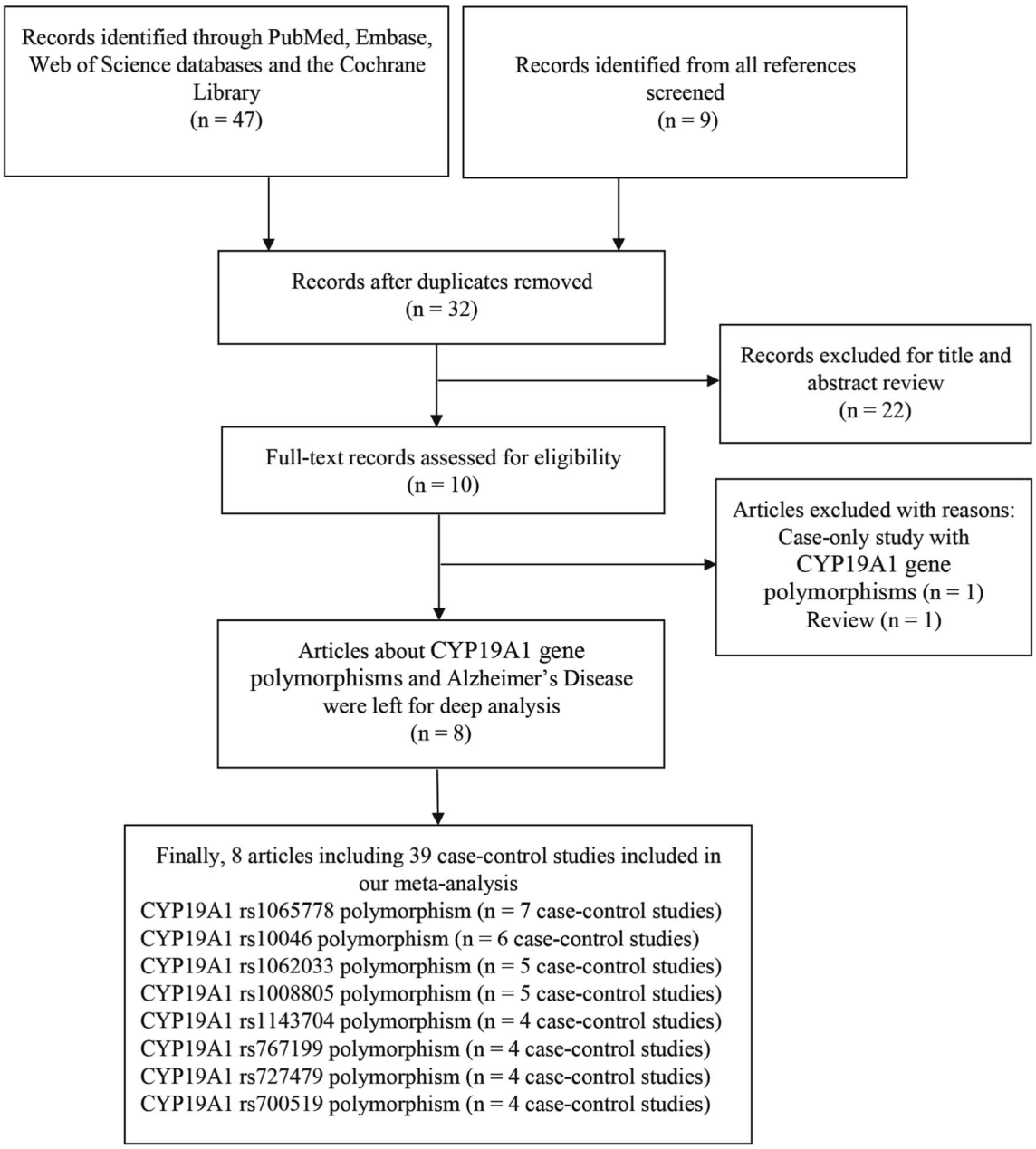

Fig. 1 Flow diagram illustrating the search strategy for CYP19A1 gene polymorphisms and the risk of Alzheimer's disease

Table 1 Main characters of case–control studies included in this meta-analysis

First author	Year	Country	Ethnicity	Control source	Sample size cases/controls	Allelic distribution				Genotype methods	HWE	NOS
						Cases		Controls				
rs1065778						G	A	G	A			
Jiaqiang Zheng [24]	2016	China	Asian	HB	207/239	174	240	212	266	PCR	Yes	8
S. Iivonen [30]	2004	USA	Caucasian	PB	394/469	397	391	422	516	PCR	Yes	8
Christopher Medway [25]	2014	UK	Caucasian	PB	1685/6250	1677	1693	6136	6364	PCR	Yes	9
R Huang [29]	2006	USA	Caucasian	PB	227/131	214	240	139	123	PCR	Yes	8
Lu Hua Chen [23]	2017	China	Asian	PB	213/175	187	239	151	199	MassARRAY	Yes	7
Helen T. Butler [27]	2010	UK	Caucasian	PB	191/222	155[a]	36[b]	153[a]	AA[b]	PCR	Yes	8
Constance Chace [26]	2012	USA	Caucasian	PB	67/156	69	65	157	155	PCR-RFLP	Yes	9
rs10046						T	C	T	C			
S. Iivonen [30]	2004	USA	Caucasian	PB	414/469	437	391	464	474	PCR	Yes	8
Christopher Medway [25]	2014	UK	Caucasian	PB	1681/6237	1767	1595	6334	6140	PCR	Yes	9
R Huang [29]	2006	USA	Caucasian	PB	227/131	223	231	143	119	PCR	Yes	8
Lu Hua Chen [23]	2017	China	Asian	PB	213/175	222	204	178	172	MassARRAY	Yes	7
Helen T. Butler [27]	2010	UK	Caucasian	PB	166/171	138[c]	28[d]	126[c]	45[d]	PCR	Yes	8
Constance Chace [26]	2012	USA	Caucasian	PB	67/158	73	61	168	148	PCR-RFLP	Yes	9
rs1062033						C	G	C	G			
Christopher Medway [25]	2014	UK	Caucasian	PB	1594/6197	1793	1395	6982	5412	PCR	Yes	9
O. Combarros [28]	2008	Spain	Caucasian	PB	231/194	283	179	222	166	PCR	Yes	8
R Huang [29]	2006	USA	Caucasian	PB	227/131	199	255	125	137	PCR	Yes	8
Lu Hua Chen [23]	2017	China	Asian	PB	213/175	183	243	151	199	MassARRAY	Yes	7
Constance Chace [26]	2012	USA	Caucasian	PB	68/158	59	77	142	174	PCR-RFLP	Yes	9
rs1008805						C	T	C	T			
S. Iivonen [30]	2004	USA	Caucasian	PB	394/469	327	461	427	511	PCR	Yes	8
R Huang [29]	2006	USA	Caucasian	PB	227/131	197	257	99	163	PCR	Yes	8
Lu Hua Chen [23]	2017	China	Asian	PB	213/175	136	290	112	238	MassARRAY	Yes	7
Helen T. Butler [27]	2010	UK	Caucasian	PB	194/223	126[e]	68[f]	157[e]	66[f]	PCR	Yes	8
Constance Chace [26]	2012	USA	Caucasian	PB	66/157	58	74	119	195	PCR-RFLP	Yes	9
rs1143704						T	A	T	A			
S. Iivonen [30]	2004	USA	Caucasian	PB	394/469	397	391	432	506	PCR	Yes	8
R Huang [29]	2006	USA	Caucasian	PB	227/131	219	235	144	118	PCR	Yes	8
Lu Hua Chen [23]	2017	China	Asian	PB	213/175	222	204	182	168	MassARRAY	Yes	7
Constance Chace [26]	2012	USA	Caucasian	PB	65/154	72	58	162	146	PCR-RFLP	Yes	9
rs767199						A	G	A	G			

Table 1 (continued)

First author	Year	Country	Ethnicity	Control source	Sample size cases/controls	Allelic distribution				Genotype methods	HWE	NOS
						Cases		Controls				
S. Iivonen [30]	2004	USA	Caucasian	PB	394/469	391	397	422	516	PCR	Yes	8
R Huang [29]	2006	USA	Caucasian	PB	227/131	214	240	135	127	PCR	Yes	8
Helen T. Butler [27]	2010	UK	Caucasian	PB	198/220	154[g]	44[h]	155[g]	65[h]	PCR	Yes	8
Constance Chace [26]	2012	USA	Caucasian	PB	68/157	67	69	153	161	PCR-RFLP	Yes	9
rs727479						T	G	T	G			
S. Iivonen [30]	2004	USA	Caucasian	PB	394/469	556	232	610	328	PCR	Yes	8
R Huang [29]	2006	USA	Caucasian	PB	227/131	286	168	175	87	PCR	Yes	8
Lu Hua Chen [23]	2017	China	Asian	PB	213/175	290	136	241	109	MassARRAY	Yes	7
Constance Chace [26]	2012	USA	Caucasian	PB	69/158	31[i]	38 [j]	64[i]	94[j]	PCR-RFLP	Yes	9
rs700519						C	T	C	T			
Christopher Medway [25]	2014	UK	Caucasian	PB	1681/6236	3270	92	12,035	437	PCR	Yes	9
R Huang [29]	2006	USA	Caucasian	PB	227/131	431	23	252	10	PCR	Yes	8
Helen T. Butler [27]	2010	UK	Caucasian	PB	179/163	346	12	316	10	PCR	Yes	8
Constance Chace [26]	2012	USA	Caucasian	PB	228/161	432	24	312	10	PCR-RFLP	Yes	9

HB hospital-based, *PB* population-based, *PCR* polymerase chain reaction, *RFLP* restriction fragment length polymorphism, *HWE* Hardy–Weinberg equilibrium, *NOS* Newcastle–Ottawa Scale

[a] GG+GA

[b] AA

[c] TT+TC

[d] CC

[e] CC+CT

[f] TT

[g] AA+AG

[h] GG

[i] TT

[j] GG+GT

heterogeneity among these articles was tested by chi-square-based Q test and Higgins I^2 statistic. The fixed effects model (Mantel–Haenszel method) [20] was performed if the heterogeneity was acceptable ($I^2 < 50\%$) and the random effects model (DerSimonian and Laird method) [21] was conducted if the heterogeneity was unacceptable ($I^2 < 50\%$). Moreover, stratified analysis was further conducted by ethnicity and *APOE* ε4-allele to consider possible diversity in *APOE polymorphism* and different ethnic backgrounds.

For these polymorphisms in *CYP19A1* gene, we used allele contrast (B vs. A), homozygous (BB vs. AA), heterozygous (BA vs. AA), recessive (BB vs. BA+AA), and dominant (BA+BB vs. AA) genetic models to analyze each polymorphism. A-allele means the wild allele, and B-allele means mutated allele.

Furthermore, sensitivity analysis was adopted to determine the stability and effect of the pooled results by consecutively deleting each one study once a time. In addition, Begg's funnel plots and Egger's test [22] were used to assess the publication bias, and a significant bias was established when the P value was less than 0.05. Stata 12.0 statistical software (STATA Corporation, College Station, TX) was used to conduct all statistical tests of this meta-analysis.

Results

Eligible studies

We identified 56 potentially relevant articles based on the literature search strategy including 47 references through searching databases and 9 references through checking reference lists. Among these relevant investigations, 32 different articles were obtained without duplication. Afterwards, based on abovementioned inclusion and exclusion criteria, 22 articles were excluded for their titles or abstracts. The remaining 10 studies were analyzed for their full texts. After these analyses, two articles were removed and there were eight articles containing 39 case–control studies remained [23–30]. Detailed literature searching and screening steps process were listed in Fig. 1.

Generally, 11,051 subjects containing 3215 patients with AD and 7836 controls are ultimately included in our meta-analysis for further evaluation. Seven studies including 2984 cases and 7642 controls studied the association between rs1065778 polymorphism and AD risk [23–27, 29, 30]. Five studies containing 2333 cases and 6855 controls evaluated the correlation with rs1062033 polymorphism [23, 25, 26, 28, 29]. For rs1008805 polymorphism, five studies involving 1094 cases and 1155 controls were included [23, 26, 27, 29, 30]. As to rs10046 polymorphism, six studies with a total number of 2768 cases and 7341 controls were involved [23, 25–27, 29, 30]. For the rs767199 polymorphism, three studies with 887 cases and 977 controls were included [26, 27, 29, 30]. With regard to rs727479 polymorphism, four studies with a total number of 903 cases and 933 controls were involved [23, 26, 29, 30]. For rs700519 polymorphism, four studies involving 2315 cases and 6691 controls were included [25–27, 29]. As to rs1143704 polymorphism, four studies with a total number of 899 cases and 929 controls were involved [23, 26, 29, 30]. Of these 8 articles, 6 [25–30] studied subjects of

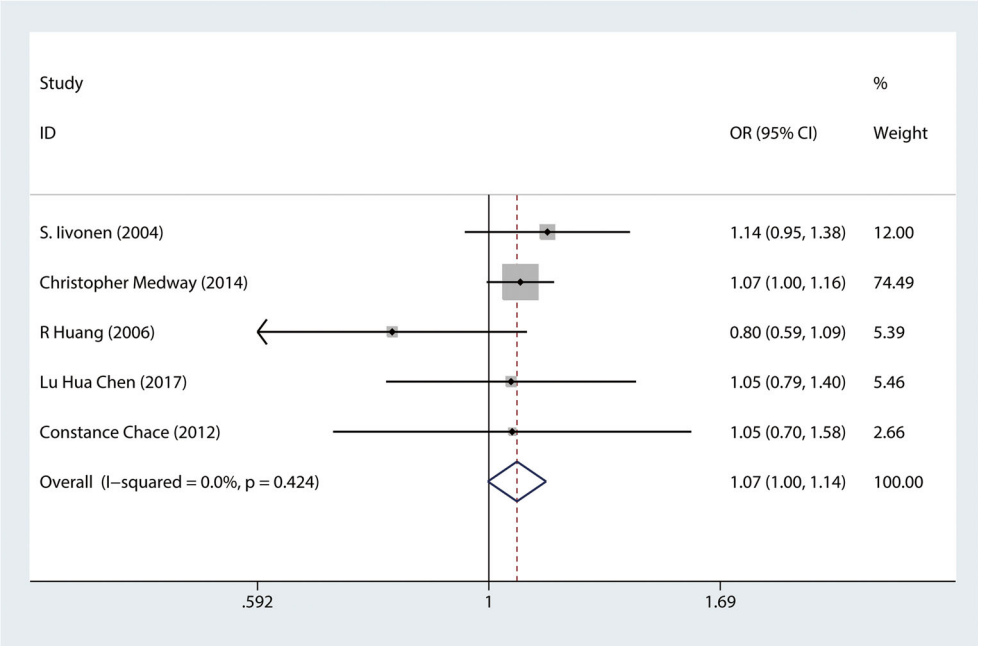

Fig. 2 Forest plot of rs10046 polymorphism and AD susceptibility (allele contrast genetic model T vs C)

Table 2 Meta-analysis results

Gene polymorphism	Inherited model	I^2 (%)	Analysis model	Pooled OR (95%CI)	*P* value	Begg's test
rs10046	Allele contrast (T vs C)	0.0%	Fixed-effects model	1.07 (1.00, 1.14)	0.058	0.462
	Homozygous (TT vs CC)	0.0%	Fixed-effects model	1.17 (1.02, 1.34)	0.026	0.602
	Heterozygous (TC vs CC)	31.5%	Fixed-effects model	1.10 (0.97, 1.25)	0.121	0.602
	Dominant (TT+TC vs CC)	36.6%	Fixed-effects model	1.15 (1.03, 1.29)	0.016	0.734
	Recessive (TT vs TC+CC)	0.0%	Fixed-effects model	1.10 (0.98, 1.22)	0.103	0.602
rs767199	Allele Contrast (A vs G)	49.8%	Fixed-effects model	1.08 (0.93, 1.25)	0.320	0.602
	Homozygous (AA vs GG)	0.0%	Fixed-effects model	1.33 (0.95, 1.87)	0.096	0.317
	Heterozygous (AG vs GG)	45.1%	Fixed-effects model	1.30 (0.97, 1.73)	0.076	0.317
	Dominant (AA+AG vs GG)	0.0%	Fixed-effects model	1.35 (1.07, 1.70)	0.010	0.296
	Recessive (AA vs AG+GG)	0.0%	Fixed-effects model	1.01 (0.76, 1.35)	0.944	0.317
rs727479	Allele Contrast (T vs G)	64.4%	Random-effects model	1.04 (0.80, 1.36)	0.765	0.296
	Homozygous (TT vs GG)	–	–	1.60 (1.00, 2.55)	0.048	–
	Heterozygous (TG vs GG)	–	–	1.20 (0.75, 1.92)	0.446	–
	Dominant (TT+TG vs GG)	–	–	1.39 (0.89, 2.17)	0.147	–
	Recessive (TT vs TG+GG)	0.0%	Fixed-effects model	1.35 (1.05, 1.72)	0.017	0.317
rs1143704	Allele Contrast (T vs A)	50.2%	Random-effects model	1.02 (0.83, 1.24)	0.869	0.497
	Homozygous (TT vs AA)	0.0%	Fixed-effects model	1.36 (0.96, 1.92)	0.08	0.317
	Heterozygous (TA vs AA)	0.0%	Fixed-effects model	1.35 (1.00, 1.82)	0.048	0.317
	Dominant (TT+TA vs AA)	0.0%	Fixed-effects model	1.36 (1.03, 1.79)	0.033	0.317
	Recessive (TT vs TA+AA)	0.0%	Fixed-effects model	1.13 (0.85, 1.50)	0.400	0.317
rs1065778	Allele Contrast (G vs A)	33.40%	Fixed-effects model	1.03 (0.97, 1.10)	0.351	0.851
	Homozygous (GG vs AA)	34.30%	Fixed-effects model	1.08 (0.95, 1.24)	0.242	1.000
	Heterozygous (GA vs AA)	30.00%	Fixed-effects model	1.08 (0.96, 1.21)	0.190	1.000
	Dominant (GG+GA vs AA)	62.40%	Random-effects model	1.24 (0.97, 1.58)	0.089	0.462
	Recessive (GG vs GA+AA)	1.70%	Fixed-effects model	1.04 (0.93, 1.16)	0.539	1.000
rs1062033	Allele Contrast (C vs G)	0.0%	Fixed-effects model	1.00 (0.93, 1.07)	0.941	0.462
	Homozygous (CC vs GG)	0.0%	Fixed-effects model	1.01 (0.87, 1.17)	0.900	0.602
	Heterozygous (CG vs GG)	0.0%	Fixed-effects model	0.97 (0.84, 1.11)	0.668	0.602
	Dominant (CC+CG vs GG)	0.0%	Fixed-effects model	0.98 (0.86, 1.12)	0.813	0.602
	Recessive (CC vs CG+GG)	0.0%	Fixed-effects model	1.03 (0.92, 1.15)	0.638	0.602
rs1008805	Allele Contrast (C vs T)	52.8%	Random-effects model	1.04 (0.84, 1.29)	0.710	0.710
	Homozygous (CC vs TT)	77.7%	Random-effects model	1.06 (0.42, 2.64)	0.905	0.317
	Heterozygous (CT vs TT)	0.0%	Fixed-effects model	0.92 (0.70, 1.21)	0.543	0.317
	Dominant (CC+CT vs TT)	0.0%	Fixed-effects model	0.86 (0.69, 1.07)	0.187	0.602
	Recessive (CC vs CT+TT)	84.6%	Random-effects model	1.16 (0.43, 3.13)	0.776	0.317
rs700519	Allele Contrast (C vs T)	48.0%	Fixed-effects model	1.15 (0.94, 1.40)	0.177	1
	Homozygous (CC vs TT)	–	–	3.01 (0.39, 23.33)	0.292	–
	Heterozygous (CT vs TT)	–	–	2.39 (0.30, 18.71)	0.408	–
	Dominant (CC+CT vs TT)	–	–	2.97 (0.38, 23.01)	0.298	–
	Recessive (CC vs CT+TT)	0.0%	Fixed-effects model	1.23 (0.98, 1.53)	0.069	0.296

Caucasian population and 2 [23, 24] studied subjects of Asian population. Moreover, all the 39 case–control studies suggested that the distribution of genotypes in the controls was in agreement with HWE. All the included case–control studies were of high quality by using the NOS quality score. The main characteristics of the enrolled articles are displayed in Table 1.

Meta-analysis results

Association between rs10046 polymorphism and AD risk

When it came to rs10046 polymorphism, a significant association was uncovered under allele contrast, homozygous, and dominant genetic models (TT vs CC: OR = 1.17, 95%CI =

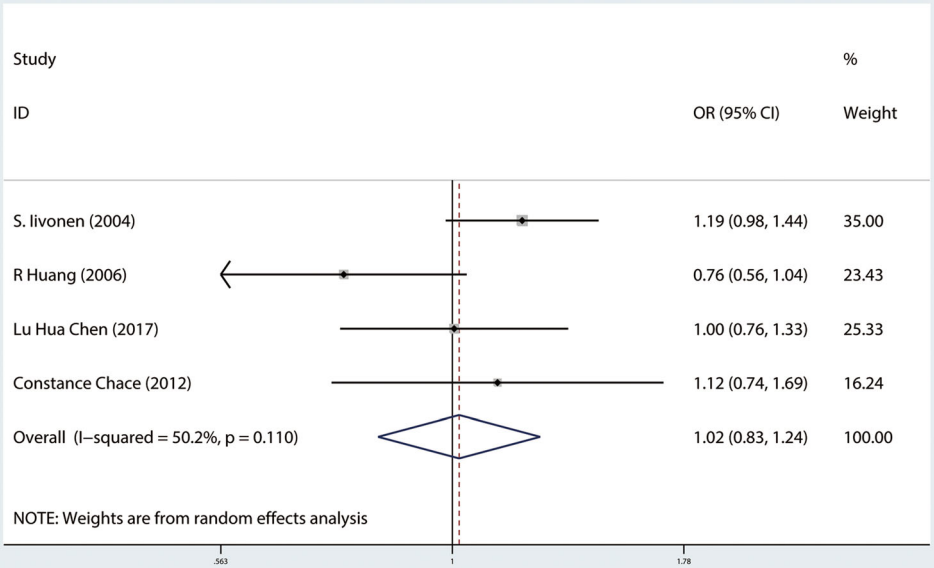

Fig. 3 Forest plot of rs1143704 polymorphism and AD susceptibility (allele contrast genetic model T vs A)

1.02–1.34, $I^2 = 0.0\%$, $P = 0.026$, Fig. 2 and Table 2). While null results were detected in recessive and heterozygous genetic models.

Association between rs1143704 polymorphism and AD risk

In respect of rs1143704 polymorphism, we observed a significant association with AD risk under heterozygous and dominant genetic models (TT+TA vs AA: OR = 1.36, 95%CI = 1.03–1.79, $I^2 = 0.0\%$, $P = 0.033$, Fig. 3 and Table 2). While null results were detected in the other three genetic models.

Association between rs767199 polymorphism and AD risk

As for rs767199 polymorphism, we observed a significant association with increased AD risk under dominant genetic model (AA+AG vs GG: OR = 1.35, 95%CI = 1.07–1.70, $I^2 = 0.0\%$, $P = 0.010$, Table 2). And no differences were observed in the other four genetic models.

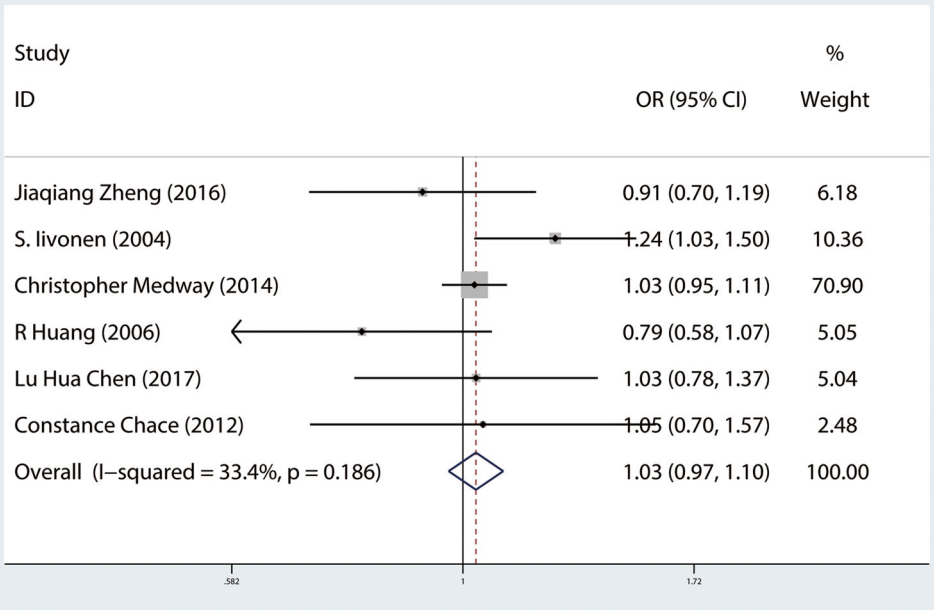

Fig. 4 Forest plot of rs1065778 polymorphism and AD susceptibility (allele contrast genetic model G vs A)

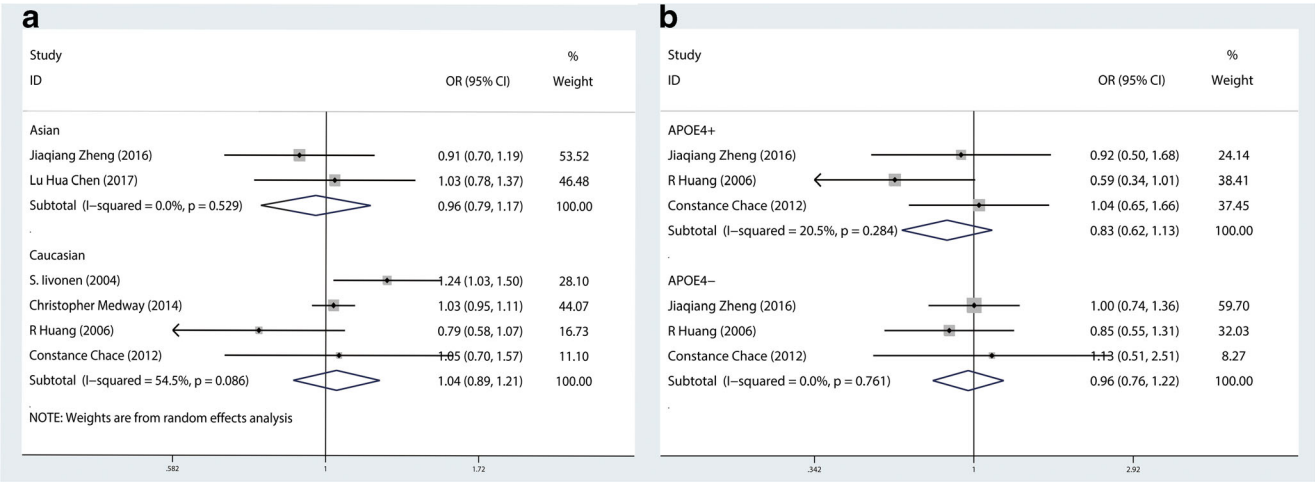

Fig. 5 Subgroup meta-analysis for the association between rs1065778 polymorphism and AD susceptibility (allele contrast genetic model G vs A). **a** By ethnicity. **b** By APOE ε4-allele

Association between rs727479 polymorphism and AD risk

In terms of rs727479 polymorphism, an intimate association was found in homozygous and recessive genetic models (TT vs GG: OR = 1.60, 95%CI = 1.00–2.55, $P = 0.048$, Table 2). But no correlations were observed in allele contrast, heterozygous and dominant genetic models.

Association between rs1065778 polymorphism and AD risk

Based on the pooled OR value, no association was demonstrated between rs1065778 polymorphism and increased AD risk under the five genetic models (G vs A: OR = 1.03, 95%CI = 0.97–1.10, $I^2 = 33.4\%$, $P = 0.351$, Fig. 4 and Table 2). To further investigate the association in different ethnicities, we

Table 3 Subgroup analyses results of meta-analysis

rs1065778 polymorphism	Inherited model	I^2 (%)	Analysis model	Pooled OR (95% CI)	*P* value	Begg's test
Ethnicity						
Asian	Allele Contrast (G vs A)	0.00%	Fixed-effects model	0.96 (0.79, 1.17)	0.714	0.851
	Homozygous (GG vs AA)	–	–	0.76 (0.43, 1.33)	0.331	1.000
	Heterozygous (GA vs AA)	–	–	1.13 (0.74, 1.73)	0.567	1.000
	Dominant (GG+GA vs AA)	–	–	1.02 (0.68, 1.53)	0.916	0.462
	Recessive (GG vs GA+AA)	–	–	0.70 (0.43, 1.15)	0.160	1.000
Caucasian	Allele Contrast (G vs A)	54.50%	Random-effects model	1.04 (0.89, 1.21)	0.625	0.851
	Homozygous (GG vs AA)	31.00%	Fixed-effects model	1.11 (0.96, 1.27)	0.148	1.000
	Heterozygous (GA vs AA)	52.80%	Random-effects model	1.15 (0.88, 1.50)	0.311	1.000
	Dominant (GG+GA vs AA)	71.20%	Random-effects model	1.30 (0.96, 1.77)	0.093	0.462
	Recessive (GG vs GA+AA)	0.00%	Fixed-effects model	1.06 (0.94, 1.19)	0.335	1.000
APOE4						
APOE ε4+	Allele Contrast (G vs A)	20.50%	Fixed-effects model	0.83 (0.62, 1.13)	0.245	0.851
	Homozygous (GG vs AA)	–	–	1.07 (0.42, 2.76)	0.881	–
	Heterozygous (GA vs AA)	–	–	1.09 (0.47, 2.52)	0.839	–
	Dominant (GG+GA vs AA)	0.00%	Fixed-effects model	1.15 (0.65, 2.04)	0.633	0.734
	Recessive (GG vs GA+AA)	–	–	1.01 (0.48, 2.15)	0.973	–
APOE ε4–	Allele Contrast (G vs A)	0.00%	Fixed-effects model	0.96 (0.76, 1.22)	0.756	0.851
	Homozygous (GG vs AA)	–	–	1.25 (0.29, 5.41)	0.765	–
	Heterozygous (GA vs AA)	–	–	0.78 (0.20, 3.01)	0.716	–
	Dominant (GG+GA vs AA)	0.00%	Fixed-effects model	1.10 (0.70, 1.73)	0.670	0.734
	Recessive (GG vs GA+AA)	–	–	1.44 (0.41, 5.05)	0.567	–

APOE ε4+ apolipoprotein E gene ε4-allele carriers, *APOE ε4–* apolipoprotein E gene ε4-allele non-carriers

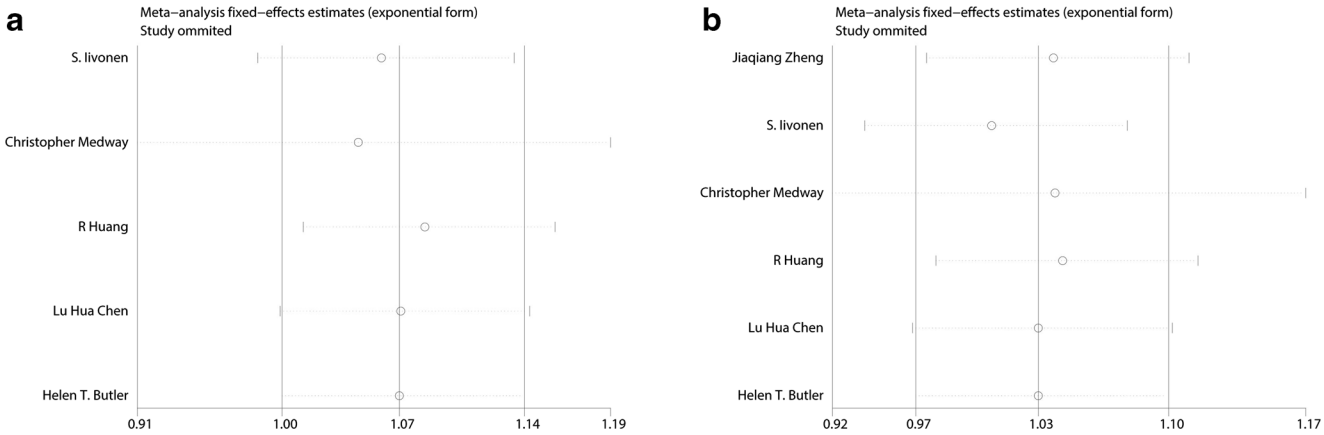

Fig. 6 Sensitivity analysis. Each point represents a separate study for the indicated association. **a** rs10046 polymorphism (allele contrast genetic model T vs C). **b** rs1065778 polymorphism (allele contrast genetic model G vs A)

conducted a subgroup analysis and pooled results showed no differences were found in both Asians and Caucasians (Fig. 5a and Table 3). Moreover, we also performed stratified analysis by APOE ε4-allele and we observed no correlation in both APOE ε4-allele carriers and non-carriers (APOE ε4-allele carrier, G vs A: OR = 0.83, 95%CI = 0.62–1.13, I^2 = 20.5%, P = 0.245; non-carriers, G vs A: OR = 0.96, 95%CI = 0.76–1.22, I^2 = 0.0%, P = 0.756, Fig. 5b and Table 3).

Association between rs1062033, rs1008805, and rs700519 polymorphisms and AD risk

As for rs1062033, rs1008805, and rs700519 polymorphisms, overall results revealed a null association between the three polymorphisms and AD risk under the five genetic models ($P > 0.05$, Table 2).

Sensitivity analyses

Sensitivity analysis was performed to evaluate the stability of the meta-analysis and to assess the effect of individual article on the pooled results by removing each enrolled single study in turn. As it was shown in Fig. 6, the combined results of our study are reliable and no individual data significantly influenced the pooled ORs.

Publication bias

The Begg's and Egger's tests were conducted to evaluate the publication bias of this meta-analysis. The results indicated that no publication bias was identified and the pooled results were stable ($P > 0.05$) (Tables 2 and 3 and Fig. 7).

Discussion

Genetic susceptibility has been generally considered as one of the vital risk factors in AD patients [31]. There is sufficient evidence that *CYP1A1* gene polymorphisms are gradually considered to be critical risk factors for many diseases such as lung cancer [32], endometriosis [33], coronary heart disease [34], essential hypertension [35], and breast cancer [36].

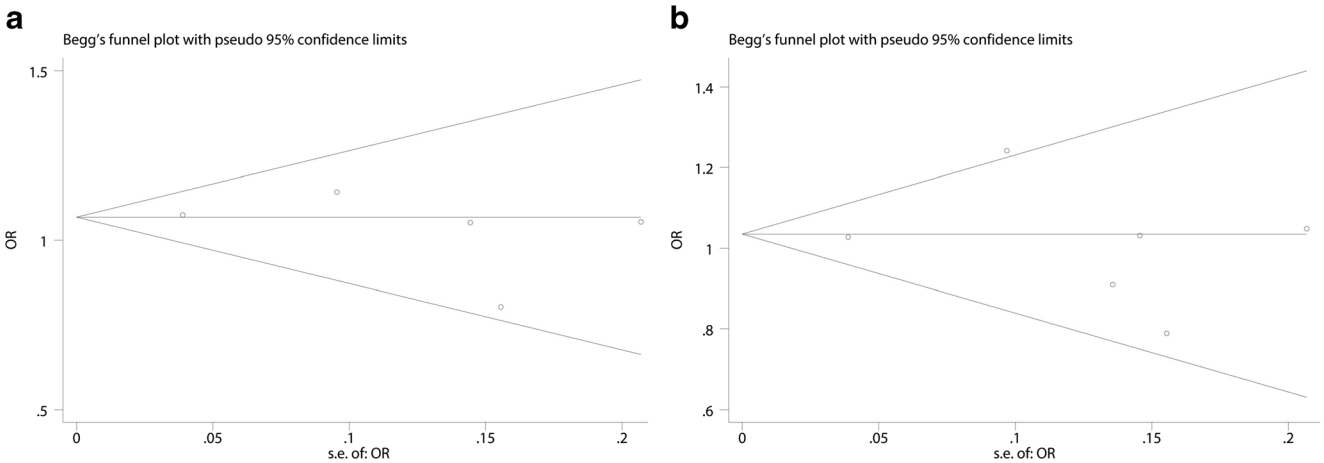

Fig. 7 Funnel plot of publication bias tests. Each point represents a separate study for the indicated association. **a** rs10046 polymorphism (allele contrast genetic model T vs C). **b** rs1065778 polymorphism (allele contrast genetic model G vs A)

Although accumulating data had been performed to explore *CYP1A1* polymorphisms and AD susceptibility, these perspectives were lack of persuasion due to small sample size and limited eligible studies. Furthermore, the definite role of these polymorphisms in different ethnicities has not been fully clarified. In addition, whether these polymorphisms can lead to AD between *APOE* ε4-allele carriers and non-carriers remained to be defined. Hence, this systematic review and updated meta-analysis was carried out with more enrolled studies and a larger sample size to reevaluate the relationship between *CYP1A1* polymorphisms and AD susceptibility and to clarify the abovementioned doubts.

To the best of our knowledge, this is the first and largest systematic review and meta-analysis to conduct an extensive analysis of all major *CYP19A1* polymorphisms and their contributions to AD risk. In this meta-analysis, based on the database of published articles with regard to all major *CYP19A1* polymorphisms, we included 8 articles with 39 case–control studies and 11,051 subjects including 3215 AD cases and 7836 controls. Quality assessment tool indicated that all the enrolled case–control studies were of high quality by NOS.

Overall, our study detected that rs10046, rs1143704, rs767199, and rs727479 polymorphisms were correlated with an increased susceptibility to AD. It is worth noting that the results of our study suggested that homozygous TT genotype (1.17-fold) in rs10046 is a risk factor for AD, indicating that the AD susceptibility of individuals with homozygous TT genotype was 1.17 times higher than those with CC genotype (TT vs CC: OR = 1.17, 95%CI = 1.02–1.34) and TT genotype might be the susceptibility genotype. In addition, dominant AA and AG genotypes (1.35-fold) in rs767199, homozygous TT genotype (1.60-fold) in rs727479, and dominant TT and TA genotypes (1.36-fold) in rs1143704 might also be the susceptibility genotypes for AD based on the pooled ORs. While for rs1065778, rs1062033, rs1008805, and rs700519 polymorphisms, null results were found. Furthermore, stratification analyses categorized by ethnicity and *APOE* ε4-allele identified no correlation between rs1065778 polymorphism and AD risk. The results of sensitivity analyses and publication bias demonstrated that our final results were persuasive and stable.

It is widely acknowledged that estrogen has beneficial effects on brain function; estrogen can increase cerebral blood flow, resist oxidation, have inhibiting effect on the pathological effect of AD and prevent the pathological process of AD [37, 38]. The rs10046, rs1143704, rs767199, and rs727479 polymorphisms in *CYP19A1* gene significantly influenced the expression levels of estrogen in the cerebral cortex and certain subcortical regions. Therefore, rs10046, rs1143704, rs767199, and rs727479 polymorphisms may increase AD susceptibility through reduction of estrogen formation and release, which may explain the negative effects of these polymorphisms on the susceptibility to AD in this study. A case–control study conducted by Butler et al. [27] showed rs767199, rs1065778, and rs10046 in *CYP19A1* gene polymorphisms were significantly associated with AD in Caucasian women and rs10046 was correlated with AD in Caucasian men. Due to the difference in the incidences of AD between different genders, we assume that these polymorphisms in *CYP19A1* gene might be a gender-related factor of susceptibility to AD.

Previous studies on the correlations between *CYP19A1* gene polymorphisms and AD gave varied results. The findings reported here were in agreement with some studies [23–25], while were different from others [29, 30]. By including a larger sample size and carrying out sensitivity analysis, our results proved to be stable and convincing.

There are some advantages in our systematic review and meta-analysis. Firstly, we have performed a comprehensive literature search and references screening to retrieve qualified articles enrolled as possible as we can for the purpose of making our study more reliable and stable. Secondly, compared with previous case–control studies, this meta-analysis contained a large sample size containing 11,051 subjects including 3215 AD cases and 7836 controls, which would be sufficient to draw a reliable conclusion. Thirdly, we performed various subgroup analyses on the basis of ethnicity and *APOE* ε4-allele to get more results. In addition, after sensitivity analysis and Begg's test, the pooled results and conclusions are proved to be credible and persuasive to evaluate the relationship between *CYP19A1* gene polymorphisms and AD risk.

Although our study provided strong evidence that rs10046, rs1143704, rs767199, and rs727479 polymorphisms are significantly associated with AD risk, there were some limitations. Firstly, in spite of strict inclusive and exclusive criteria, heterogeneity was still observed under a few genetic models. Thus, after stratification on the basis of ethnicity and *APOE* ε4-allele, we observed that the heterogeneity significantly decreased. In addition, in the results of some polymorphisms, the limited case number and insufficient case–control studies resulted in indefinite analyses. So, these results may require more studies to make it persuasive. Follow-up studies are needed to focus on this topic. Finally, AD is a complex disease affected by both genetic and environmental factors. However, lacking the original data confined our ability to assess the potential interactions among gene–gene and gene–environment.

In conclusion, to the best of our knowledge, this is the first and largest systematic review and meta-analysis to conduct an extensive analysis of all major CYP19A1 polymorphisms and their contributions to AD risk. The findings from this systematic review and meta-analysis of 39 case–control studies indicated that rs10046, rs1143704, rs767199, and rs727479 of *CYP19A1* gene polymorphisms increased the susceptibility to AD. No significant associations between rs1065778, rs1062033, rs1008805, and rs700519 polymorphisms and

AD risk were observed. Considering the limitations mentioned earlier, further studies with larger sample sizes that consider gene–gene and gene–environment interactions are warranted to validate our results.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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