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Genetic Susceptibility Variants of Vascular Dementia among Asians: A Systematic Review and Meta-Analysis

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Keywords
Asians · Methylenetetrahydrofolate · Genetic polymorphism · Single nucleotide polymorphisms · Vascular dementia

Abstract

Introduction: Vascular dementia (VaD), a neurocognitive impairment directly related to vascular injury, is the second most common cause of age-related dementia. Although numerous studies have investigated candidate genetic polymorphisms associated with VaD in Asia, the genetics of VaD remains unclear. ***Methods:*** This review provides an updated meta-analysis of genetic polymorphisms associated with VaD in Asians, using the PRISMA guidelines. Published literature up to May 2021 was extracted from the PubMed, Scopus, Ovid, and EBSCOhost databases. Meta-analysis was conducted using the Open Meta analyst, Review Manager, and MedCalc® Statistical Software. Trial sequential analysis (TSA) was performed using TSA viewer software. ***Results:*** A total of 46 eligible studies, comprising 23 genes and 35 single nucleotide polymorphisms, were retrieved. The meta-analysis was conducted on the following genetic polymorphisms, *APOE ε2/3/4*, *MTHFR* rs1801131, *ACE* rs4340 (I/D) gene polymorphism, and a *PSEN1* intron 8 variant. The pooled odds ratio (ORs) revealed a significant increase in the risk of VaD in the apolipoprotein E (*APOE*) ε4 allelic model (OR, 1.79, $p < 0.001$), and the methylenetetrahydrofolate reductase (*MTHFR*) rs1801133 polymorphism T allele in the allelic model (OR, 1.23, $p = 0.013$). ***Conclusion:*** Our findings provide evidence that genetic polymorphisms of the *APOE ε4 allele* and *MTHFR*

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rs1801133 T allele increase the risk of developing VaD in Asians. However, future large-scale investigations examining particularly on South-Eastern and West-Asian populations are highly recommended.

Introduction

Vascular dementia (VaD) is the second most prevalent subtype of dementia after Alzheimer's disease (AD), representing almost 20% of all dementia cases in Europe and 30% in Asia [1]. In Asia, developing countries such as China, Japan, and India have the highest prevalence of dementia, accounting for 60% of all dementia cases and the number of cases is expected to double by 2040 due to Asia's rapid population growth [2]. Despite the fact that VaD is the second most common form of dementia, the lack of a consensual definition for VaD creates challenges and the contributing genetic factors remain poorly understood [3]. To date research investigating the genetics of VaD has mainly focused on candidate genes previously implicated in other dementias or stroke, such as genetic polymorphisms in the apolipoprotein ε (*APOE*) [4, 5], methylenetetrahydrofolate reductase (*MTHFR*) [6], and interleukin (*IL*) [5, 7] genes, albeit with inconclusive results. For example, a previous meta-analysis of the angiotensin-converting enzyme (*ACE*) intron 16 insertion/deletion gene polymorphism (rs4340) found no evidence of an association between the variant in Europeans [8]. In contrast, Pandey et al. [9] suggested an increased risk of VaD among Indians carrying the deletion allele. This may be due to variations in the genetic make-up of Asians compared to Africans and Caucasians, which can lead to distinct interactions with exposures that are susceptible to VaD, regardless of the fact that the pathophysiology of VaD may be similar worldwide. The present systematic review was therefore conducted to summarize the current knowledge regarding the genetics of VaD, to more precisely identify genetic polymorphisms associated with VaD in the Asian population, and to gain a better understanding of the molecular mechanisms underlying VaD development, to assist in the development of more effective therapeutic interventions in the future.

Materials and Methods

Search Strategy

The present study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines for reporting systematic reviews and meta-analysis. We conducted a systematic review of published literature up to May 2021 using PubMed, Scopus, Ovid, and EBSCOhost (Medline, academic search complete, CINAHL, psychology and behavioral sciences collection) databases, combining the search terms "polymorphism" or "mutation" or "variant" and "vascular dementia" using Boolean operators. Relevant articles from the reference lists that were not included in the initial search were retrieved manually, and publications in languages other than English were excluded from the whole search. A detailed search strategy is available in the Supplementary Material (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000538864).

Study Inclusion/Exclusion Criteria

Studies meeting the following criteria were included in the review as follows: (1) case-control studies (2) genetic polymorphisms in VaD (3) Asian population; (4) VaD diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) [10], the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) [11], or any other recognized diagnostic criterion; (5) full-text articles; and (6) reported genotype or allele frequencies. Case reports, genome-wide association studies (GWAS), reviews, meta-analyses, conference abstracts, letters to editors, book chapters, animal model studies, and studies on underlying diseases were excluded (Fig. 1).

Data Extraction and Quality Assessment

Following the search, all articles were imported into the EndNote software, and duplicates were eliminated. After redacting the details, the full texts of eligible papers were retrieved, and data were extracted independently by the two reviewers. Each study's first author, publication year, country of origin, sample size, gender distribution, the mean age of group individuals, assessment tools, genotype frequency, allele frequency, and genotyping method were extracted. The data were recorded in tabular format according to the respective genes and polymorphisms.

The methodological quality of the included studies was assessed by two reviewers using the Newcastle-Ottawa Scale (NOS) for case-control studies [12]. The scale evaluates eight criteria divided into three sections: selection of study groups, comparability of study groups, and ascertainment of exposure, and outcome of interest. The NOS score ranges from 0 to 9, with studies scoring more than six considered as good quality. Any disagreements between the two reviewers were resolved through discussion until an agreement was reached.

Statistical Analysis

Hardy-Weinberg equilibrium (HWE) was assessed for each study using χ^2 analysis from the genotype frequencies of control groups. The effect of each genetic polymorphism on VaD reported in three or more studies was evaluated using pooled odds ratio (OR) with 95% confidence interval (CI) using three different genetic models; dominant, recessive, and allelic models. Additionally, a subgroup analysis was conducted, taking into account subregions, age groups, and NOS scores. The subregions were classified into East Asia and South Asia, as genetic variations might vary among different Asian populations. Age groups were categorized either as above or below 70 years old, which was chosen as the threshold, given that the studies included in this review had recruited subjects with a mean age ranging from 60 to 80 years. This is supported by a study that has reported a higher incidence of developing VaD among older groups of patients, aged 70 and above [13]. Heterogeneity between studies was analyzed using the

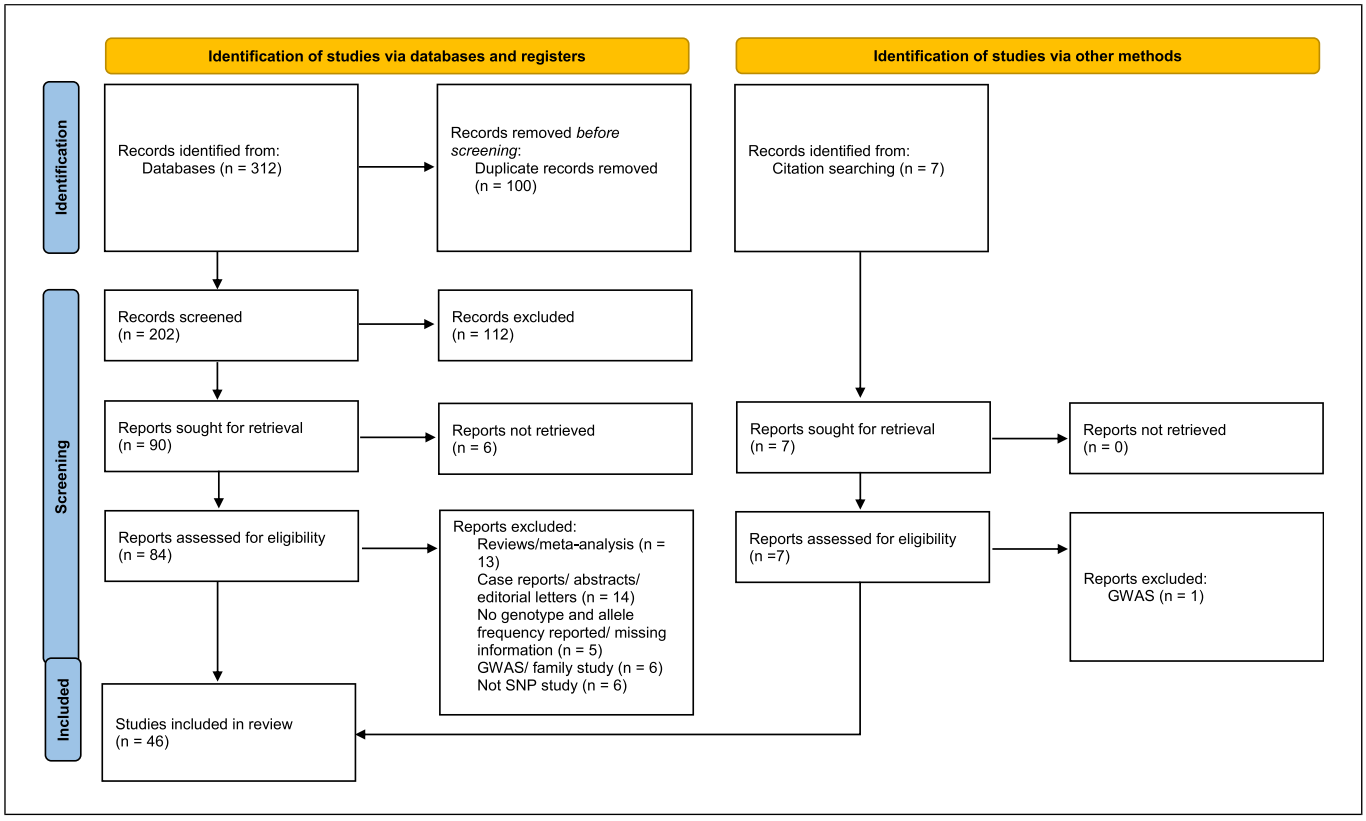

Fig. 1. Selection of included studies based on PRISMA guideline.

I^2 statistic and Q-test, whereby $p < 0.10$ and $I^2 > 50\%$ indicated high heterogeneity, and a random-effect model was applied for the meta-analysis. Otherwise, studies with low to moderate heterogeneity used a fixed-effect model. Sensitivity analysis was conducted using leave-one-out meta-analysis. Further analysis was performed on the following subgroups: subregion, age groups, and study quality to minimize heterogeneity. Publication bias was visually identified using funnel plots and estimated using Egger's test. All data analysis was performed using the Open Meta (Analyst) software (http://www.cebm.brown.edu/openmeta), Review Manager (RevMan) (Computer program) (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), and MedCalc® Statistical Software version 22.001 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023). Statistical significance was defined as a p value of less than 0.05. A Bonferroni correction was applied for adjustments of multiple testing.

Trial Sequential Analysis

Trial sequential analysis (TSA) is a method for evaluating the validity of a meta-analysis and determining whether additional studies are required. Therefore, a TSA was conducted to reduce type I and type II errors in the present meta-analysis and increase the robustness of the findings by using TSA viewer software (version 0.9.5.10 beta, the Copenhagen Trial Unit, Center for Clinical Intervention Research, Denmark) [14]. A significance of 5% type I error and 20% type II error (a power of 80%) was applied to calculate the TSA plot and required sample size.

Results

Study Characteristics

The initial systemic search yielded 319 publications, including 7 additional manual search records. From the initial search, 110 duplicates were removed, and 163 studies were excluded after screening based on the inclusion and exclusion criteria. A total of 46 eligible studies, consisting of 5,832 cases and 11,615 controls, were included in the meta-analysis. Among the studies, 33 studies were conducted on the East-Asian population (China, Korea, Taiwan, and Japan), 10 studies on the South-Asian population (India) and 3 studies on the West-Asian population (Israel). A total of 23 genes and 35 SNPs were investigated, with the *APOE* (rs429358 and rs7412) genetic polymorphisms receiving the most attention. The majority of studies diagnosed VaD using the DSM-IV and NINDS-AIREN criteria. Twenty studies scored NOS greater than six indicates that are good in quality (Table 1; online suppl. Table 2 [7, 16, 21, 34, 35, 39–55]).

Table 2 summarizes the genotype and allele frequencies of the *APOE* (rs429358 and rs7412) genetic polymorphisms. Most studies were conducted in East Asia, and

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Table 1. Study characteristics of the selected studies for meta-analysis of *APOE*, *MTHFR* and *ACE* genes

Gene	SNPs	First author, year	Country	Subregion (Asia)	Sample size		Gender (M/F)		Age (mean±SD), years		VaD assessment tool	Quality score*
					case	control	case	control	case	control		
APOE	rs429358 & rs7412	Chen et al. [15] (2016)	China	East	40	1,149	26/14	530/619	67.9±9.11	69.4±7.36	NINDS-AIREN	8
		Mou et al. [16] (2015)	China	East	255	234	151/104	139/95	73.1±8.3	73.1±9.1	DSM-IV and NINCDS-ADRDA	6
		Ryu et al. [4] (2012)	Korea	East	61	284	17/44	97/187	75.05±5.46	73.35±5.28	DSM-IV and NINDS-AIREN	8
		Hong et al. [17] (2011)	Korea	East	64	152	21/43	34/118	74.09±7.79	65.93±8.87	DSM-IV	8
		Bharath et al. [18] (2010)	India	South	31	195	19/12	120/75	68.5±9.7	64.8±7.7	CDR	7
		Mansoori et al. [5] (2010)	India	South	46	113	34/12	72/41	66.1±8.8	64.0±8.4	DSM-IV and NINDS-AIREN	7
		Pandey et al. [9] (2009)	India	South	80	170	NM	NM	64.16±10.02	60.60±8.48	DSM-IV. NINDS-AIREN	6
		Kim et al. [19] (2008)	Korea	East	100	200	55/45	110/90	73.55±7.64	73.55±7.64	CDR and NINDS-AIREN	8
		Baum et al. [20] (2006)	China	East	144	251	56/88	95/156	78.0±8.7	78.0±7.4	CDR, and NINDS-AIREN	8
		Wang et al. [21] (2006)	Taiwan	East	54	161	28/26	85/76	74.9±5.8	62.5±8.7	DSM-IV and NINDS-AIREN	5
		Lin et al. [22] (2004)	Taiwan	East	49	112	35/14	54/58	68.67±7.6	71.9±10.82	NINDS-AIREN	8
		Luthra et al. [23] (2004)	India	South	25	76	NM	NM	65.3±9.0	63.2±9.6	CDR, BDR, and NINDS-AIREN	8
		Lai et al. [24] (2004)	Taiwan	East	30	112	20/10	63/49	66.2±8.2	71.0±10.6	DSM-IV and NINDS-AIREN	5
		Huang et al. [25] (2002)	Taiwan	East	70	96	NM	NM	74.7±7.5	72.2±6.9	CDR and DSM-IV	5
		Yang et al. [26] (2001)	China	East	124	218	NM	NM	71±9.0	74.1±10.0	DSM-IV and NINCDS-AIREN	4
		Nishiyama et al. [27] (2000)	Japan	East	35	33	NM	NM	81.3±6.41	73.0±9.90	DSM-III-R	4
		Nakayama et al. [28] (1999)	Japan	East	45	1,090	22/23	314/776	75.4±8.0	51.2±12.6	DMS-III-R and NINDS-AIREN	4
		Ji et al. [29] (1998)	Japan	East	87	117	NM	NM	75.5±8.0	71.5±7.5	DSM-III-R	5
		Igata-Yi et al. [30] (1997)	Japan	East	20	31	5/15	17/16	75.9±6.9	53.2±15.7	DSM-IV	6
		Katzman et al. [31] (1997)	China	East	27	363	9/128	128/235	NM	NM	DSM-III	7
		Higuchi et al. [32] (1996)	Japan	East	55	75	20/35	30/45	78±8	77±10	DSM-III-R and NINDS-AIREN	6
		Kawamata et al. [33] (1994)	Japan	East	19	49	NM	NM	74.5±6.9	57.1±18.4	NINDS-AIREN	5

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Table 1 (continued)

Gene	SNPs	First author, year	Country	Subregion (Asia)	Sample size		Gender (M/F)		Age (mean±SD), years		VaD assessment tool	Quality score*
					case	control	case	control	case	control		
MTHFR	**rs1801133**	Jin et al. [6] (2013)	China	East	304	300	182/122	179/121	66.3±6.7	67.1±6.9	DSM-IV and NINDS-AIREN	8
		Mansoori et al. [7] (2012)	India	South	50	120	37/13	75/45	65.4±9.1	63.8±8.2	DSM-IV and NINDS-AIREN	8
		Pandey et al. [9] (2009)	India	South	80	170	NM	NM	64.16±10.02	60.60±8.48	DSM-IV, NINDS-AIREN	6
		Nishiyama et al. [27] (2000)	Japan	East	35	33	NM	NM	81.3±6.41	73.0±9.90	DSM-III-R	4
		Pollak et al. [36] (2000)	Israel	West	85	82	33/52	21/61	84±6.3	82±8.2	DSM-IV	7
		Yoo et al. [37] (2000)	Korea	East	143	217	42/69	87/130	75.6±8.6	72.2±6.5	NINDS-AIREN	7
		Chapman et al. [38] (1998)	Israel	West	41	40	NM	NM	74.3±7.2	72.7±7.8	NINDS-AIREN	5
ACE	**rs4340**	Pandey et al. [9] (2009)	India	South	80	170	NM	NM	64.16±10.02	60.60±8.48	DSM-IV, NINDS-AIREN	6
		Kim et al. [42] (2006)	Korea	East	207	207	112/95	112/95	66.7±10.4	67.1±10.5	DSM-IV and NINDS-AIREN	8
		Wang et al. [21] (2006)	Taiwan	East	54	161	28/26	85/76	74.9±5.8	62.5±8.7	DSM-IV, NINDS-AIREN	5
		Chapman et al. [38] (1998)	Israel	West	41	40	NM	NM	74.3±7.2	72.7±7.8	NINDS-AIREN	5

ADDTC, Alzheimer's Disease Diagnostic and Treatment Centers; BDR, blessed dementia rating scale; CDR, Clinical Dementia Rating; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; F, female; M, male; NINDS-AIREN, National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences; NM, not mentioned; SD, standard deviation; SNPs, single nucleotide polymorphisms. *Quality score was determined using the Newcastle-Ottawa quality assessment scale.

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Table 2. Genotype and allele frequencies of *APOE* gene polymorphisms among the selected studies

First author, year	Cases/controls									Genotyping method	HWE*
	ε2ε2	ε2ε3	ε2ε4	ε3ε3	ε3ε4	ε4ε4	ε2	ε3	ε4		
Chen et al. [15] (2016)	0/8	8/154	0/21	22/802	6/156	4/8	0.1/0.08	0.73/0.83	0.18/0.08	TaqMan assay	0.600
Mou et al. [16] (2015)	0/0	22/38	18/8	148/160	53/21	14/7	0.08/0.09	0.73/0.81	0.19/0.09	PCR-RFLP	<0.001
Ryu et al. [4] (2012)	0/2	6/31	0/3	42/209	12/39	1/0	0.05/0.07	0.84/0.86	0.12/0.07	PCR, fluorogenic probes	0.512
Hong et al. [17] (2011)	0/1	10/17	1/2	37/107	15/22	1/3	0.09/0.07	0.77/0.83	0.14/0.10	PCR	0.560
Bharath et al. [18] (2010)	0/1	1/24	2/5	20/141	7/22	1/2	0.48/0.08	0.77/0.84	0.18/0.08	PCR-RFLP	0.261
Mansoori et al. [5] (2010)	0/0	1/6	0/1	31/92	12/14	2/1	0.01/0.03	0.82/0.90	0.17/0.07	PCR-RFLP	0.833
Pandey et al. [9] (2009)	0/0	7/23	0/1	56/133	16/13	1/0	0.04/0.07	0.84/0.89	0.11/0.04	PCR-RFLP	0.728
Kim et al. [19] (2008)	0/0	10/18	2/2	69/146	18/32	1/2	0.06/0.05	0.83/0.86	0.11/0.09	One-stage PCR	0.901
Baum et al. [20] (2006)	2/3	23/33	1/3	84/174	32/37	2/1	0.10/0.08	0.77/0.83	0.13/0.08	PCR-RFLP	0.680
Wang et al. [21] (2006)	0/1	2/11	1/2	39/120	11/27	1/0	0.03/0.05	0.84/0.86	0.13/0.09	PCR-RFLP	0.351
Lin et al. [22] (2004)	0/4	3/5	0/5	36/78	10/19	0/1	0.03/0.08	0.87/0.80	0.10/0.12	PCR-RFLP	<0.001
Luthra et al. [23] (2004)	0/6	4/9	0/1	10/1	5/11	6/1	0.08/0.15	0.58/0.14	0.34/0.09	PCR-RFLP	0.004
Lai et al. [24] (2003)	0/4	1/5	0/5	23/78	6/19	0/1	0.02/0.08	0.88/0.80	0.1/0.12	PCR-RFLP	<0.001
Huang et al. [25] (2002)	3/3	4/12	2/1	51/66	9/15	1/1	0.09/0.09	0.82/0.83	0.09/0.08	PCR-RFLP	0.119
Yang et al. [26] (2001)	2/2	10/32	3/8	76/139	31/36	2/1	0.07/0.10	0.78/0.79	0.15/0.11	PCR-RFLP	0.313
Nishiyama et al. [27] (2000)	0/0	1/2	1/0	26/27	7/4	0/0	0.03/0.03	0.86/0.91	0.11/0.06	PCR-RFLP	0.954
Nakayama et al. [28] (1999)	0/3	1/90	0/15	33/803	11/173	0/6	0.01/0.05	0.87/0.86	0.12/0.09	IEF	0.298
Ji et al. [29] (1998)	0/0	3/4	2/4	50/95	29/14	3/1	0.03/0.03	0.76/0.89	0.21/0.08	PCR-RFLP	0.000
Igata-Yi et al. [30] (1997)	0/0	2/3	0/1	10/21	8/7	0/1	0.05/0.06	0.75/0.84	0.2/0.16	PCR-RFLP	0.903
Katzman et al. [31] (1997)	0/3	2/36	2/4	16/250	4/70	3/0	0.07/0.06	0.70/0.84	0.22/0.10	PCR	0.079
Higuchi et al. [32] (1996)	0/0	3/6	0/0	38/54	13/12	1/3	0.03/0.04	0.84/0.84	0.14/0.12	PCR-RFLP	0.165
Kawamata et al. [33] (1994)	0/0	2/9	0/1	13/31	3/8	1/1	0.05/0.10	0.82/0.81	0.13/0.11	PCR-RFLP	0.807

HWE, Hardy-Weinberg equilibrium; IEF, isoelectric focusing and immunoblotting; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR, polymerase chain reaction. *$p < 0.05$ shows significant deviation from HWE.

Table 3. Genotypic and allelic frequencies of *MTHFR* and *ACE* genetic polymorphisms for meta-analysis

Gene	SNPs	First author, year	Cases/controls					Genotyping method	HWE*
			CC	CT	TT	C	T		
MTHFR	rs1801133	Jin et al. [6] (2013)	132/152	99/96	73/52	0.60/0.67	0.40/0.33	PCR-RFLP	<0.001
		Mansoori et al. [7] (2012)	35/89	14/29	1/2	0.84/0.86	0.16/0.14	PCR-RFLP	0.836
		Pandey et al. [9] (2009)	49/118	29/45	2/7	0.79/0.83	0.21/0.17	PCR-RFLP	0.314
		Nishiyama et al. [27] (2000)	9/13	17/15	9/5	0.50/0.62	0.50/0.38	PCR-RFLP	0.844
		Pollack et al. [36] (2000)	34/29	41/37	10/16	0.64/0.58	0.40/0.42	PCR-RFLP	0.501
		Yoo et al. [37] (2000)	49/77	58/114	36/26	0.55/0.62	0.45/0.38	PCR-RFLP	0.099
		Chapman et al. [38] (1998)	14/15	20/16	7/9	0.59/0.57	0.41/0.43	PCR-RFLP	0.251
		Mansoori et al. [7] (2012)	17/44	27/59	6/17	0.61/0.61	0.39/0.39	PCR-RFLP	0.695
			II	ID	DD	I	D		
ACE	rs4340	Pandey et al. [9] (2009)	24/62	36/89	20/19	0.53/0.63	0.48/0.37	PCR	0.122
		Wang et al. [21] (2006)	25/93	17/59	12/9	0.62/0.76	0.38/0.24	PCR-RFLP	0.929
		Kim et al. [42] (2006)	79/75	95/100	33/32	0.61/0.60	0.39/0.40	PCR	0.888
		Chapman et al. [38] (1998)	3/5	20/17	18/18	0.32/0.34	0.68/0.66	PCR	0.754

HWE, Hardy-Weinberg equilibrium; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR, polymerase chain reaction; SNPs, single nucleotide polymorphisms. *$p < 0.05$ shows significant deviation from HWE.

PCR-RFLP was the preferred genotyping method, followed by *Taqman* assay, fluorogenic probes, and isoelectric focusing immunoblotting. Out of the 22 case-control studies, 17 were in HWE, while the remaining 5 were not consistent (Table 2). Two *MTHFR* gene polymorphisms are studied among Asians, the rs1801133 and rs1801131. There was only one study in India on the *MTHFR* rs1801131, and 7 studies on the *MTHFR* rs1801133 polymorphism, with one study from China inconsistent with HWE. The *ACE* insertion or deletion polymorphism (*ACE I/D*, rs4340) is an extensively studied polymorphism of the *ACE* gene, a major component of the renin-angiotensin system (RAS), followed by *ACE* rs4291. All studies on the *ACE* gene were consistent with HWE and PCR was the most common genotyping method, followed by PCR-RFLP. The genotypic and allelic frequencies, genotyping methods and HWE of *MTHFR*, *ACE*, and other gene polymorphisms studied among Asians are presented in Table 3 and online supplementary Table 3.

Meta-Analysis

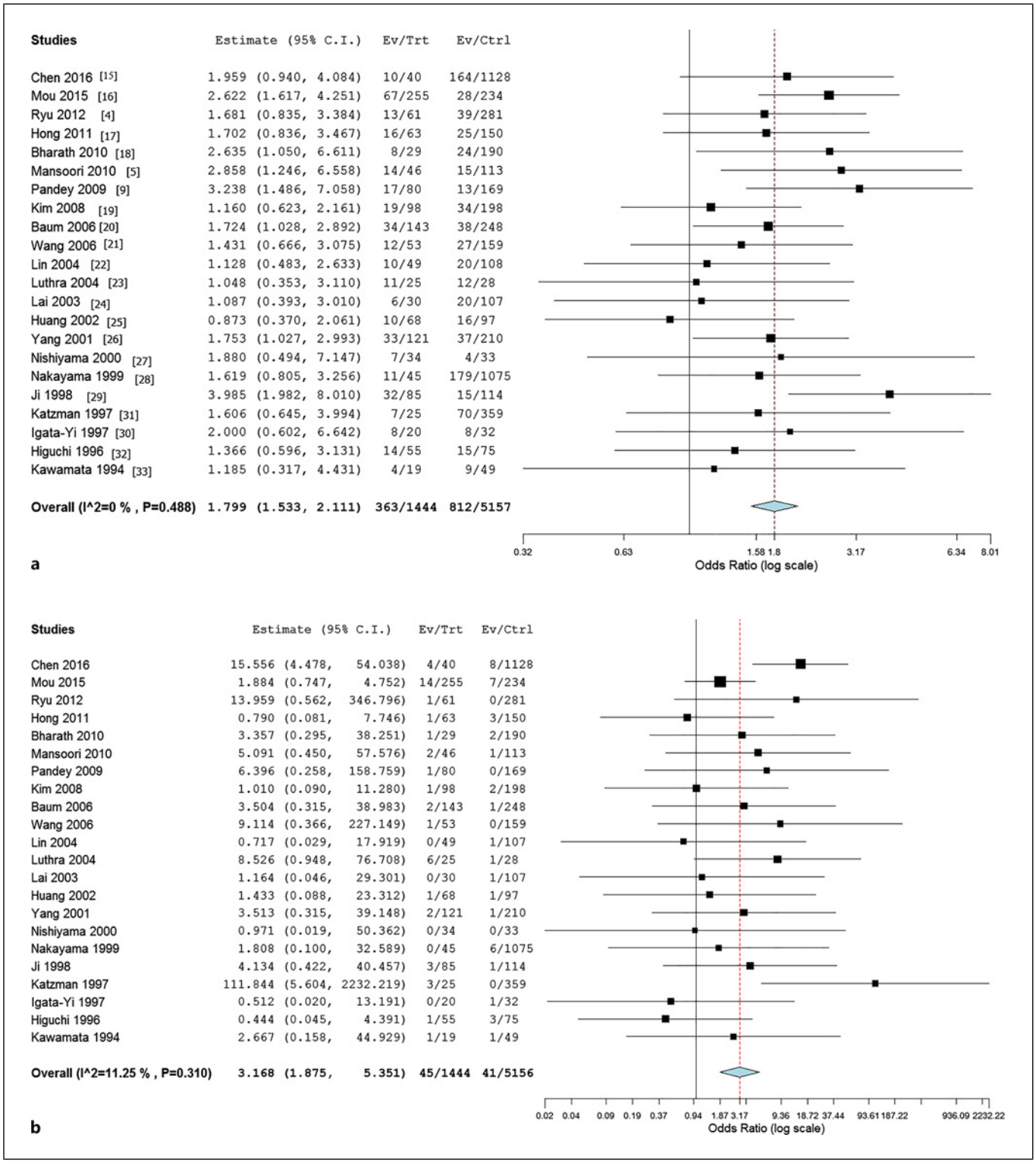
APOE ε2/3/4 Gene Polymorphism

There were 22 studies on the *APOE ε rs429358* and *rs7412* gene polymorphisms among Asians [4, 5, 9, 15–33], which were included for meta-analysis. The pooled results of a fixed-effect model analysis showed significant associations with an increased risk of VaD for ε4 in all genetic models (dominant model: OR = 1.80, CI = 1.53–2.11, $p < 0.001$); recessive model: OR = 3.17, CI = 1.88–5.35, $p < 0.001$; *APOE ε4* allelic model: OR = 1.79, CI = 1.53–2.08, $p < 0.001$). An allelic model of ε2 allele when compared to ε3 and ε4 alleles also showed a significant pooled result (*APOE ε2* allelic model: OR = 0.72, CI = 0.55–0.94, $p < 0.001$) (Fig. 2; Table 4). Furthermore, carriers of the ε4 allele showed an increased risk of developing VaD when compared within Asian subregions and age groups ($p < 0.01$) (Table 4). A funnel plot of publication bias indicated that the studies were nearly symmetrically distributed across genetic models (online suppl. Fig. 1). However, a publication bias was detected for the *APOE ε2* allelic model ($p = 0.031$) using the Egger's test (online suppl. Table 4). A leave-one-out analysis showed that the significance value did not change when each study was removed, indicating that the results of this meta-analysis are robust (online suppl. Fig. 2).

MTHFR rs1801131 Gene Polymorphism

A total of 7 publications [6, 7, 9, 26, 35–37] of *MTHFR* rs1801131 revealed no significant association of the overall ORs in both dominant (OR = 1.22, CI = 1.00–1.50, $p = 0.051$) and recessive (OR = 1.26, CI = 0.79–2.01, $p = 0.338$) genetic models. However, carriers of the T variant allele showed an increased risk of VaD compared to C allele carriers in an allelic genetic model (OR = 1.23, CI = 1.04–1.43, $p = 0.013$) (Table 5; Fig. 3).

All the pooled ORs were calculated using a random-effect model analysis. Subgroup analysis by subregions



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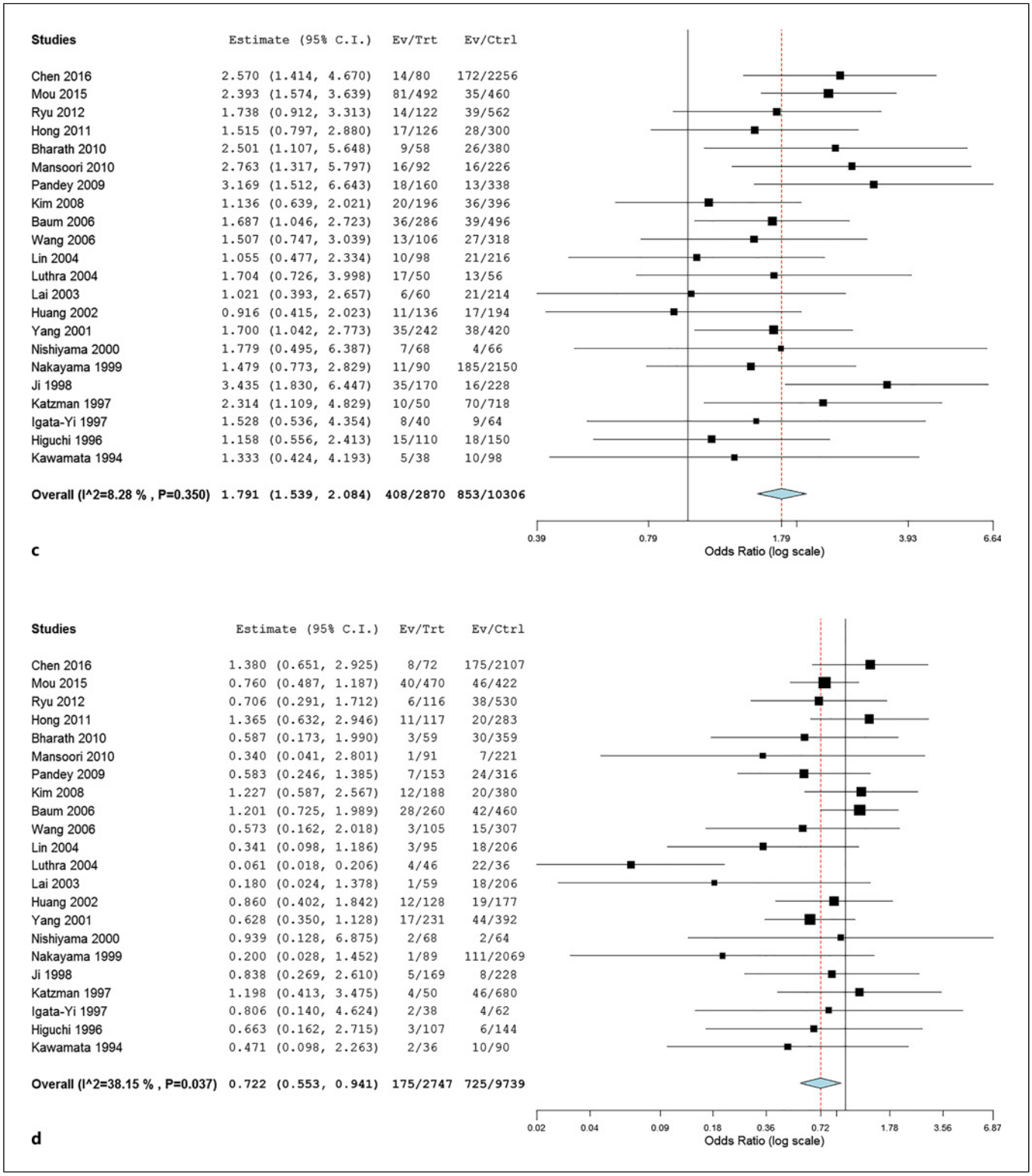

Fig. 2. Forest plots of the associations between *APOE* gene polymorphisms and VaD for *APOE ε4* in dominant (**a**), recessive (**b**), and allelic models (**c**), and an *APOE ε2* allelic genetic model (**d**).

Table 4. Meta-analysis results of *APOE* genetic models

Genetic models	Subgroup	*n*	OR (95% CI)	*p* value*	I^2 (%)	pHET**[a]
Dominant model (ε4/ε4 + ε4/ε3 vs. ε2/ε3 +ε2/ε2 + ε3/ε3)						
Overall		22	1.80 (1.53–2.11)	<0.001	0	0.488
Subregion	East Asia	18	1.72 (1.46–2.04)	<0.001	0	0.578
	South Asia	4	2.43 (1.57–3.79)	<0.001	0	0.393
Age group, years	<70	6	1.69 (1.18–2.42)	0.005	0	0.425
	>70	14	1.78 (1.48–2.14)	<0.001	2.1	0.426
NOS score	Good	10	1.64 (1.30–2.07)	<0.001	0	0.778
	Others	12	1.95 (1.57–2.41)	<0.001	21.6	0.231
Recessive model (ε4/ε4 vs. ε2/ε2+ε2/ε3+ε3/ε3+ε3/ε4						
Overall		22	3.17 (1.88–5.35)	<0.001	11.3	0.310
Subregion	East Asia	18	2.35 (1.42–3.89)	<0.001	24.2	0.117
	South Asia	4	6.74 (1.81–25.0)	0.004	0	0.938
Age group, years	<70	6	5.48 (2.20–13.7)	<0.001	2.7	0.366
	>70	14	1.79 (1.01–3.18)	0.047	0	0.890
NOS score	Good	10	4.61 (2.33–9.14)	<0.001	33.4	0.122
	Others	12	1.82 (0.96–3.46)	0.066	0	0.919
APOE4 allelic model (ε4 vs. ε2+ε3)						
Overall		22	1.79 (1.53–2.08)	<0.001	8.3	0.350
Subregion	East Asia	18	1.70 (1.46–1.98)	<0.001	6.9	0.373
	South Asia	4	2.52 (1.70–3.73)	<0.001	0	0.744
Age group, years	<70	6	1.86 (1.36–2.54)	<0.001	19.1	0.283
	>70	14	1.70 (1.44–2.01)	<0.001	1.91	0.428
NOS score	Good	10	1.73 (1.40–2.13)	<0.001	0	0.502
	Others	12	1.84 (1.52–2.23)	<0.001	24.6	0.202
APOE2 allelic model (ε2 vs. ε3+ε4)						
Overall		22	0.72 (0.55–0.94)	<0.001	38.2	0.037
Subregion	East Asia	18	0.82 (0.67–1.00)	0.046	0	0.574
	South Asia	4	0.29 (0.09–0.93)	0.037	69.6	0.020++
Age group, years	<70	6	0.34 (0.12–0.99)	0.047	74.9	0.001++
	>70	14	0.83 (0.67–1.03)	0.087	0	0.786
NOS score	Good	10	0.73 (0.44–1.22)	0.233	66.8	0.001[b]
	Others	12	0.65 (0.50–0.84)	<0.001	0	0.950

n, number of studies; OR, odds ratio; 95% CI, 95% confidence interval; pHET, *p* value of heterogeneity; I^2, value of I^2 statistic for heterogeneity; NOS, Newcastle-Ottawa Scale. *$p < 0.02$ are statistically significant after Bonferroni correction (0.05/3 for 3 subgroups). **$p < 0.10$ are statistically significant. [a]Fixed-effect model analysis method. [b]Random-effect model analysis method.

revealed a significant association between East Asians who are T allele carriers as presented in both recessive and allelic genetic models ($p < 0.001$) (Table 5). A symmetry funnel plot and Egger's test of the included studies in all three genetic models showed no presence of publication bias (online suppl. Table 4; Fig. 3). Additionally, the ORs of this meta-analysis were consistent as shown in a leave-one-out analysis (online suppl. Fig. 4).

ACE rs4340 (I/D) Gene Polymorphism

The pooled ORs of four Asian population studies on *ACE I/D* gene polymorphism [9, 21, 36, 38], revealed no significant association in all three genetic models (dominant model, $p = 0.671$; recessive model, $p = 0.101$; allelic model, $p = 0.109$) (online suppl. Fig. 5). Heterogeneity was present in both the recessive and allelic genetic models with I^2 values of 73.5% ($p = 0.01$) and 61.5% ($p = 0.05$), respectively. Stratified analysis based on age group <70 years demonstrated a significant difference among D allele carriers in both recessive (OR = 3.26, CI = 1.87–5.67, $p < 0.001$) and allelic (OR = 1.67, CI = 1.25–2.25, $p < 0.001$) genetic models (online suppl. Table 5). No publication bias was observed based on the visually symmetrical funnel plot (online suppl. Fig. 6), and Egger's test (online suppl. Table 4). The findings of the meta-analysis were consistent in a leave-one-out analysis (online suppl. Fig. 7).

Table 5. Meta-analysis results of *MTHFR* rs1801133 genetic models

Genetic models	Subgroup	*n*	OR (95% CI)	*p* value*	I^2 (%)	pHET**[a]
Dominant model (TT + CT vs. CC)						
Overall		7	1.22 (1.00–1.50)	0.051	0	0.773
Subregion	East Asia	3	1.27 (0.98–1.63)	0.067	0	0.515
	South Asia	2	1.36 (0.87–2.11)	0.176	0	0.742
	West Asia	2	0.92 (0.55–1.54)	0.742	0	0.542
Age group, years	<70	3	1.34 (1.04–1.74)	0.025	0	0.946
	>70	4	1.06 (0.77–1.45)	0.731	0	0.602
NOS score	Good	4	1.17 (0.93–1.47)	0.181	0	0.546
	Others	3	1.43 (0.93–2.21)	0.101	0	0.788
Recessive model (TT vs. CT + CC)						
Overall		7	1.26 (0.79–2.01)	0.338	47.9	0.074
Subregion	East Asia	3	1.79 (1.31–2.45)	<0.001	1.0	0.364
	South Asia	2	0.74 (0.20–2.80)	0.655	0	0.636
	West Asia	2	0.61 (0.31–1.19)	0.146	0	0.721
Age group, years	<70	3	1.42 (0.97–2.08)	0.071	0	0.539
	>70	4	1.20 (0.53–2.75)	0.661	70.8	0.016
NOS score	Good	4	1.37 (0.74–2.54)	0.311	64.2	0.039
	Others	3	0.98 (0.47–2.03)	0.956	0	0.385
Allelic model (T vs. C)						
Overall		7	1.23 (1.04–1.44)	0.013	8.61	0.363
Subregion	East Asia	3	1.37 (1.14–1.63)	<0.001	0	0.863
	South Asia	2	1.22 (0.83–1.79)	0.304	0	0.932
	West Asia	2	0.83 (0.58–1.19)	0.306	0	0.576
Age group, years	<70	3	1.31 (1.08–1.61)	0.007	0	0.907
	>70	4	1.15 (0.92–1.43)	0.222	46.1	0.135
NOS score	Good	4	1.19 (0.94–1.51)	0.157	43.1	0.153
	Others	3	1.23 (0.89–1.71)	0.219	0	0.523

n, number of studies; OR, odds ratio; 95% CI, 95% confidence interval; pHET, *p* value of heterogeneity; I^2, value of I^2 statistic for heterogeneity; NOS, Newcastle-Ottawa Scale. *$p < 0.02$ are statistically significant after Bonferroni correction (0.05/3 for 3 subgroups). **$p < 0.10$ are statistically significant. [a]Random-effect model analysis method.

PSEN1 *(Intron 8) Gene Polymorphism*

Presenilin-1 (*PSEN1*) intron 8 variant demonstrated no significant association with VaD in any of the three genetic models ($p > 0.05$). Due to absence of heterogeneity, a fixed-effect model analysis was used to calculate the pooled OR for the gene polymorphisms (online suppl. Table 6). Additionally, no publication bias was detected from an Egger's test (online suppl. Table 4).

Trial Sequential Analysis

TSA was performed for dominant genetic models of *APOE* (rs429358 and rs7412) and allelic genetic models of *MTHFR rs1801131* gene polymorphisms (online suppl. Fig. 8). The cumulative z-curve for *APOE* gene polymorphisms crossed the TSA monitoring boundary before reaching the required sample size. The cumulative z-curve for *MTHFR rs1801131* also reached the required sample size, but only crossed the conventional boundary. These results indicate that our findings are robust and do not require further study.

Discussion

The present systematic review and meta-analysis demonstrated an association between genetic polymorphisms and VaD in Asian populations. Based on pooled OR from multiple genetic models and subgroup analysis, it was determined that the *APOE* ε4 allele and *MTHFR* rs1801133 polymorphism (T allele) were associated with an increased risk of VaD.

The *APOE* ε2/3/4 polymorphism is the most researched gene polymorphism among Asians in association with VaD and is determined by the rs7412 and

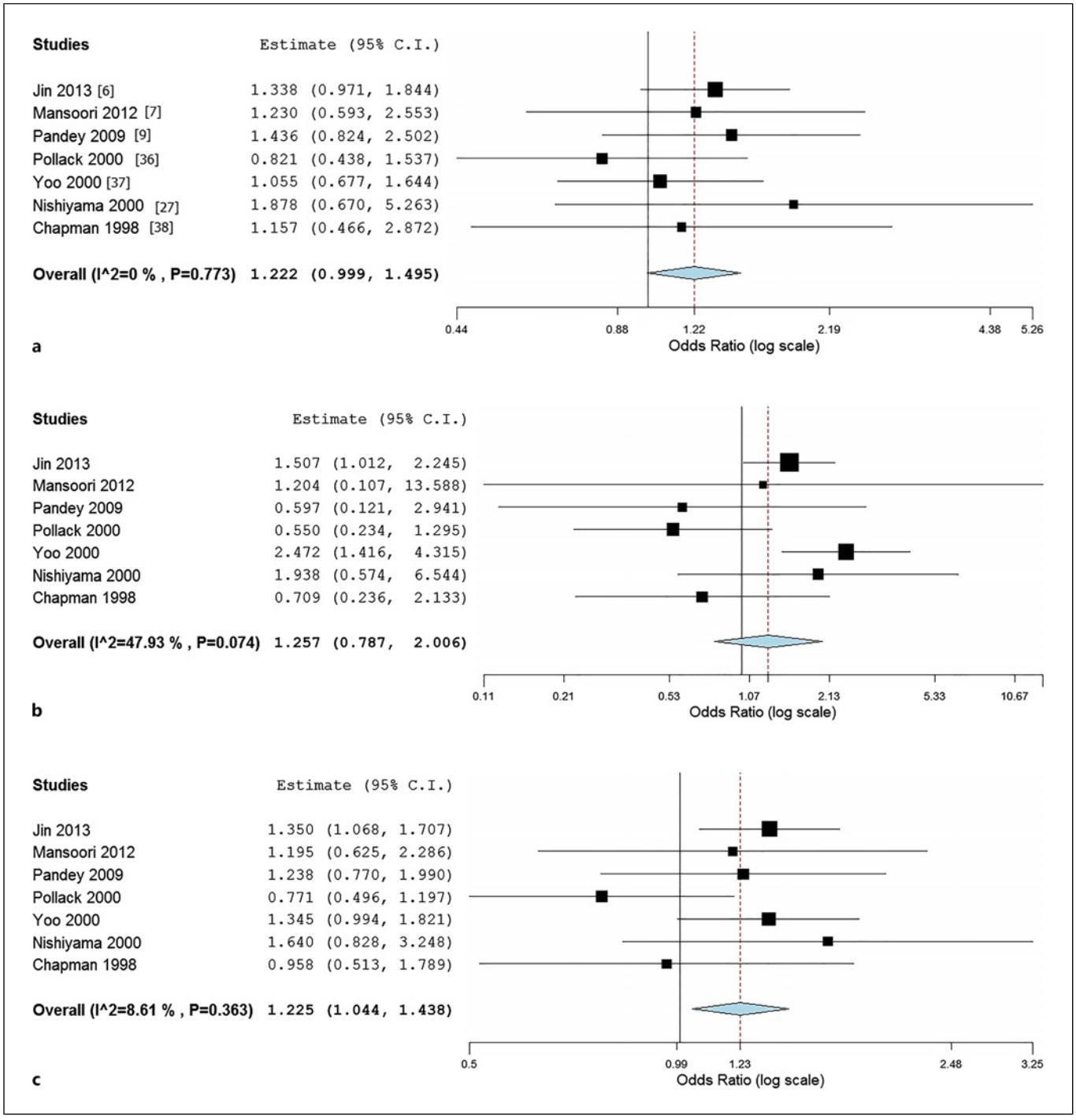

Fig. 3. Forest plots of the associations between *MTHFR* rs1801133 gene polymorphism and VaD in dominant (**a**), recessive (**b**) and allelic (**c**) genetic models.

rs429358 genetic variants. These variants have been extensively studied in relation to AD, and individuals with the ε4 allele are at an increased risk of developing the disease [56]. This was also demonstrated in AD human postmortem brains, when *APOE* RNA expression levels were found to be elevated [57], and *APOE* plasma levels in *APOE ε2* carriers were linked to increased risk of dementia and AD [58]. Additionally, it

has been observed that *APOE* levels are disrupted in the brain and CSF of AD patients, resulting in cerebrovascular effects, which may be related to impaired pericyte-mediated basement membrane development [59]. Several variants of the *APOE* gene have been validated as candidate biomarkers for AD by in silico analysis, with the aim of improving early detection and effective intervention [60, 61].

According to a previous meta-analysis, *APOE* ε4 homozygotes were associated with a 3.129-fold increased risk of VaD compared with *APOE* ε3 genotypes. This was based on an average observation across all populations, and the subgroup analysis revealed no statistically significant differences between Asians and Caucasians [62]. Similarly, the present review among Asians found a significant association between *APOE* ε4 in all genetic models, with no evidence of heterogeneity among the included studies.

Out of the 22 studies included in the present review, 10 (45.5%) studies indicated that the *APOE* ε4 allele might increase the risk of VaD [5, 9, 16, 18, 20, 23, 26, 29–31], with a report that VaD patients are more likely to carry the ε3ε4 (23.6%) or ε4ε4 (15.1%) genotypes than healthy individuals ($p = 0.036$) [20]. Lin et al. did not infer a significant effect for the *APOE* ε4 allele but reported that the *APOE* ε2 allele was protective against the development of VaD in individuals younger than 65 years of age [22]. In the present review, the *APOE* ε2 allele also showed a protective effect against VaD when compared to the other *APOE* variants. Despite compelling evidence that *APOE* ε2 confers protection against other neurological diseases, such as slower cognitive decline and less cortical thinning in patients with subcortical vascular mild cognitive impairment [63] and protection against AD [64], additional risk studies in VaD on both *APOE* ε2 and ε4 alleles among Asians are necessary. Furthermore, the presence of publication bias for the *APOE* ε2 allele model necessitates additional research.

MTHFR, an enzyme that regulates homocysteine metabolism levels in the body, has also been extensively studied in various populations [6, 7, 65]. Homocysteine elevation has been identified as an independent risk factor for VaD [66], with mutations in pathway-regulating genes such as *MTHFR* C677T (rs1801133) and rs1801131 may impair the enzyme's function. A study found that the flavin adenine dinucleotide binding ability of *MTHFR* bearing the rs1801133 mutation was significantly lowered, resulting in conformational changes to the protein's tertiary structure and hence reduced enzyme activity [67]. This may be related to the finding that individuals with *MTHFR* variants develop hyperhomocysteinemia, which has an effect on oxidative stress, DNA methylation and is a risk factor for AD [68, 69]. Additionally, an in silico analysis through four different bioinformatics tools identified the *MTHFR* C677T mutation as deleterious and correlated with homocysteine synthesis, making them potential candidate biomarkers for AD [70]. Among the Asian studies, the *MTHFR* rs1801133 variant T allele was significantly higher in VaD among Koreans [37], Japanese [27], and Chinese [6], which constitute the East-Asian region. The pooled results also indicated that *MTHFR* rs1801133 T allele was significantly associated with VaD in an allelic model. Further subgroup analysis revealed that T allele carriers of rs1801133 in East-Asian populations are at an increased risk of developing VaD in both the recessive and allelic models. Other subregions, including India [7, 9] and Israel [36, 38], demonstrated no association between *MTHFR* rs1801133 and VaD. Similarly, a previous meta-analysis reported an increased risk of rs1801133 T allele carriers developing VaD in an allelic model but no variation in the Caucasian population, implying that genetic diversity among different populations may also affect the risk of *MTHFR* rs1801133 in VaD [62].

The *ACE* insertion or deletion polymorphism (*ACE I/D*, rs4340) is an extensively studied variant of the *ACE* gene, a major component of the RAS. The RAS has been linked to the development of hypertension and has been implicated in the pathophysiology of dementia and cognitive impairment [71, 72]. In the present review, pooled analysis of *ACE I/D* polymorphism did not demonstrate a significant association with VaD in all genetic models. Significant genetic susceptibility of VaD to *ACE I/D* was observed in Indian and Taiwanese population studies [9, 21], contrary to findings in Korea and Israel [38, 42].

Significant higher frequency of the DD genotype ($p = 0.013$) and the D allele ($p = 0.032$) in VaD patients was reported in India compared to controls [9] and in a Taiwanese population [21]. According to the subgroup analysis, *ACE* D carriers within patients aged less than 70 years showed an increased risk of developing VaD. However, this may be attributable to the fact that there were greater sample sizes in the <70 years age group than in the >70 years age group. Other RAS gene polymorphisms, *PAI-1 46/5G*, *AT1R A1166C*, and *AGT T235M* were analyzed in a single study among Koreans [42], and thus were not eligible for meta-analysis in the present review.

Variation in the *PSEN1* gene was associated with amyloid plaque aggregation in AD and other degenerative dementias [46]. However, the present meta-analysis found no evidence of a significant association between the *PSEN1* intron 8 polymorphism and VaD [46–48]. Moreover, several other variants were investigated in association with VaD. However, due to the limited number of studies available, meta-analyses were not conducted for the remaining gene polymorphisms. This includes the paraoxonase 1 (*PON1*) rs662 polymorphism in Indians and the estrogen receptor-b (*ERb*) rs944050 polymorphism in Chinese, which demonstrated a significant association with VaD [39, 45]. According to Alam et al. [39] the presence of at least one variant allele of *PON1* rs662 increased the risk of developing VaD by 3.09-fold among Indians, whereas the *ERb* rs944050 was associated with an elevated risk of VaD in Chinese Han women over the age of 50 [45].

Studies have also shown that the levels of pro-inflammatory cytokines in dementia are altered and that inflammation plays a potential role in the pathophysiology of VaD which might be caused by many factors [73, 74]. The possible role of inflammation in VaD pathogenesis has led to genetic studies on various cytokines, including *IL*, tumor necrosis factor (*TNF*) and transforming growth factor-beta (*TGFB*) [50, 75]. Significant associations have been identified for *TNF rs1799964, IL-6 rs1800795*, *IL-1α rs1800587,* and *TGFB1 rs1800470 (C869T)* gene polymorphisms in Asian populations [40], but no meta-analysis was performed due to insufficient number of studies.

Despite the findings reported, this study has a few limitations. GWAS studies were not included; however, to date, only a single study has been performed among Korean population, which shows a significant association of an intronic variant rs290227 located in the spleen tyrosine kinase gene among VaD patients [76]. Second, the majority of candidate gene polymorphisms have been investigated in only a few studies and hence, were ineligible for meta-analysis and additional subgroup stratification. The evaluation of gene-gene, epigenetic and gene-environment interactions was limited by the lack of data on significant risk factors and gene interaction among the studies. Additionally, our research included only English-language articles, which implies that some data from publications in other languages may have been missing. Therefore, future research strategies should incorporate data from studies published in other languages, epigenetics, gene-environment interactions, and in silico analysis to predict the effect of gene polymorphisms.

Conclusion

The present meta-analysis demonstrated that the *APOE ε4* allele and *MTHFR* rs1801133 T allele significantly increased the risk of developing VaD in Asians. Nonetheless, there was insufficient data to validate the association of some of the other polymorphisms due to too few publications. Overall, there is limited data from Asian populations, including the Southeast – which has not examined any VaD mutations to date. Future research should incorporate other types of variants such as tandem repeats, copy number variations and to undertake GWAS, and functional characterization of the underlying mechanisms between candidate gene polymorphism and VaD pathology to extend this work.

Statement of Ethics

An ethics statement is not applicable because this study was based exclusively on published literature.

Conflict of Interest Statement

The authors declared that there is no potential conflict of interest.

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Author Contributions

Conceptualization: V.R, N.A.M., W.A.W.S., and M.H.M.; methodology: V.R., N.A.M., A.H.K.Y.K.and S.M.C.; validation: W.A.W.S., L.N.I., A.H.K.Y.K., S.M.C., and H.B.; formal analysis: V.R., N.A.M.; data curation, N.A.M.; investigation: V.R., N.A.M., and M.H.M.; writing-original draft: V.R., N.A.M.; writing-review and editing: V.R., N.A.M., M.N.S., W.A.W.S., M.H.M., L.N.I., A.H.K.Y.K., S.M.C., H.B., P.P., S.V., and N.J.; supervision: V.R. N.A.M. and H.B.; project administration: L.N.I. and M.H.M.; funding acquisition: Vasudevan R; revising manuscript: V.R. N.A.M., M.N.S., and N.J., All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data used to support the findings of this study are included within the article. Further inquiries can be directed to the corresponding author.

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