REVIEW

Vitamin D Receptor Gene Polymorphisms and Risk of Alzheimer Disease and Mild Cognitive Impairment: A Systematic Review and Meta-Analysis

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ABSTRACT

The results from epidemiologic studies suggest that vitamin D receptor (*VDR*) gene polymorphisms are potentially associated with Alzheimer disease (AD) and mild cognitive impairment (MCI), but this association has yet to be confirmed. Here, we conducted a meta-analysis based on a larger sample size to clarify the contribution of *VDR* gene polymorphisms to MCI and AD susceptibility. The PubMed, Embase, Cochrane Library, and China National Knowledge Infrastructure databases were searched to obtain studies published before 30 October, 2020. The case group includes MCI and AD patients, and the matched controls were without any cognitive complaints. ORs and 95% CIs were used to assess the strength of the association. Ten case–control studies with 3573 participants and 4 loci of *ApaI* rs7975232, *BsmI* rs1544410, *FokI* rs10735810, and *TaqI* rs731236 were included in the meta-analysis. The global assessment indicated an association between the *BsmI* polymorphism and increased odds of MCI in the allelic model (b compared with B; OR: 1.77; 95% CI: 1.24, 2.54), the dominant model (bb + Bb compared with BB; OR: 2.04; 95% CI: 1.32, 3.16), and the heterozygote model (Bb compared with BB; OR: 1.97; 95% CI: 1.26, 3.09). In contrast, the *ApaI* polymorphism was protective against MCI in all models. The dominant model (tt + Tt compared with TT; OR: 1.44; 95% CI: 1.17, 1.79) and the homozygous model (tt compared with TT; OR: 1.43; 95% CI: 1.02, 2.00) revealed an association between the *TaqI* polymorphism of the *VDR* gene and increased odds of AD, particularly for Caucasian subjects. Egger's linear regression test found no publication bias. This meta-analysis indicated that *VDR ApaI* and *BsmI*, and *TaqI* gene polymorphisms may be important predictors of MCI and AD, respectively, with population discrepancies. More research is needed to further confirm these associations, especially considering gene–gene interactions, gene–environment interactions, and other confounding factors. *Adv Nutr* 2021;12:2255–2264.

Statement of Significance: Compared with previous studies on the same subject, this study included more data and found that the dominant and homozygous gene models of a *TaqI* gene polymorphism may increase the risk of Alzheimer disease. This study investigated the association between vitamin D receptor gene polymorphisms and mild cognitive impairment and for the first time indicated that the allele, dominant, and heterozygous gene models of *BsmI* polymorphisms are related to an increased risk of mild cognitive impairment.

Keywords: Alzheimer disease, mild cognitive impairment, polymorphisms, single nucleotide polymorphisms, vitamin D receptor

Introduction

Alzheimer disease (AD) is characterized by cognitive decline and memory loss, with insidious onset and a long incubation period (1), before which mild cognitive impairment (MCI) constitutes a typical prodromal stage. With the aging of the population, incidence has gradually increased and has become a public health issue of general concern. Patients with MCI have biomarker evidence of Alzheimer brain changes (e.g., abnormal amounts of amyloid-β) and subtle problems with memory and thinking, but these deficits do not interfere with the individual's ability to perform daily activities (2). In particular, they have a higher risk of developing AD over time than older adults with normal cognition (3). The 2019 World Alzheimer's Disease Report shows that 50 million people worldwide suffer from dementia, and this number is expected to reach 152 million by 2050 (4). Unfortunately, the specific pathogenesis is still ambiguous despite many explorations.

It has been hypothesized that early identification of genetic risk factors may contribute to the prevention and treatment of cognitive decline. Recently, genome-wide association analysis has been used to screen out numerous candidate genes associated with the risk of MCI and AD, including β-amyloid precursor protein (5), presenilin 1/2, and apoE (6). The vitamin D receptor (*VDR*) gene has been extensively investigated in recent years. Vitamin D is a fat-soluble steroid hormone that exerts biological effects by combining with VDRs. Epidemiologic investigations have shown that low serum vitamin D concentrations increase the risk of cognitive decline, and that the elderly with vitamin D deficiency have a higher risk of AD (7). There is increasing evidence that vitamin D prevents the progression of AD by removing β-amyloid deposits, inhibiting hyperphosphorylation τ protein, alleviating inflammation, regulating Ca^{2+} homeostasis, and reducing antioxidative stress (8, 9). In addition, vitamin D deficiency increases the risk of cardiovascular disease (10), which is considered a risk factor for AD. Because serum 25-hydroxyvitamin D deficiency has been reported to be associated with an increased risk of cognitive decline, the hypothesis exists that allelic variation in the *VDR* gene might contribute to cognitive impairment.

Genetic variation indicates a link between genes and diseases. Among several types of genetic variation, single-nucleotide polymorphisms (SNPs) are prominent in $\geq$1% of the population. Polymorphisms in gene-regulatory regions may affect gene expression levels and protein functions (11). The biological function of active vitamin D benefits from binding to VDR, which is a ligand-dependent nuclear transcription factor expressed in multiple system organs and tissues throughout the body. The *VDR* gene is located on chromosome 12 (12q13-14) and consists of 9 exons and 8 introns, exceeding 100 kb (12–14) in length. Among the *VDR* SNPs, *ApaI* rs7975232, *BsmI* rs1544410, *FokI* rs10735810, and *TaqI* rs731236 are the most concerning (15). The *BsmI* and *ApaI* restriction sites are located in the 8th intron, the *TaqI* restriction sites are in the 9th exon, and the *FokI* restriction sites are situated in the 5'-end 16 of the gene (16).

Recent evidence supports the contention that *VDR* gene polymorphisms play a key role in AD and MCI by maintaining the biological function of vitamin D. However, those results are contradictory and uncertain owing to small sample sizes and limited statistical power. Although a previous meta-analysis established the association between *VDR TaqI* and *ApaI* polymorphisms and AD susceptibility (17), the results were limited to only 2 studies at the time. Notably, the role of *VDR* polymorphisms in MCI has yet to be investigated. Based on the aforementioned background, the present meta-analysis provides an overview of current knowledge to accurately assess the contribution of *VDR* gene polymorphisms to AD and MCI susceptibility.

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Abbreviations used: AD, Alzheimer disease; MCI, mild cognitive impairment; NOS, Newcastle-Ottawa Scale; SNP, single nucleotide polymorphism; *VDR*, vitamin D receptor; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D.

Methods

Search strategy

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (18). Two independent reviewers searched the China National Knowledge Infrastructure, PubMed, Embase, and Cochrane Library databases from inception to 20 November, 2020. The following combination of keywords was used and adjusted according to the characteristics of the database: (vitamin D receptor or *VDR* or *FokI* or rs10735810 or *BsmI* or rs1544410 or *ApaI* or rs7975232 or *TaqI* or rs731236) and (polymorphism or variant or mutation) and (mild cognitive impairment or Alzheimer's disease). We limited the search languages to English and Chinese. The reference lists of the retrieved articles were also searched to identify other potentially relevant studies.

Inclusion and exclusion criteria

All studies were strictly screened following the inclusion/exclusion criteria to minimize heterogeneity: *1*) case–control studies were included; *2*) the relation between *VDR* gene polymorphisms and the risk of MCI or AD was reported; *3*) the *VDR* gene polymorphisms and genotype distribution data were reported; and *4*) ORs and corresponding 95% CIs were used to assess the frequency of genotypes between cases and controls. Studies that met the following conditions were not included: *1*) commentary articles, editorials, conference abstracts, case reports, and duplicate studies; *2*) studies that did not report the genotype and frequency of the 2 comparative populations; and *3*) studies that did not report complete data.

Data extraction and quality assessment

Standardized data collection tables were used to extract the following information: first author, publication year, country, ethnicity, genotyping method, control source, numbers of cases and controls, population characteristics, and primary observed results. "A" and "a" were used to indicate the wild-type allele and mutant alleles of *ApaI* loci, respectively (A > a); "B" and "b" were used to indicate the wild-type allele and mutant alleles of *BsmI* loci, respectively (B > b). The same applies to the *FokI* and *TaqI* loci. The quality of each study was assessed through the Newcastle-Ottawa Scale (NOS) (19), which uses a "star" classification system, ranging from 0 (worst) to 9 (best). Studies with a score $\geq$7 are considered high-quality studies, whereas studies with a score $\leq$6 are considered of moderate quality or low quality. Two researchers independently completed the data

extraction and quality assessment. Any disagreements were resolved through discussion or consultation with a third researcher.

Statistical analysis

All statistical analyses were performed using Stata 15.1 software (StataCorp). Pooled ORs and 95% CIs were used to assess the strength of the relations between *VDR* gene polymorphisms and the risk of MCI and AD. The chi-square test was used to evaluate the genotype frequency of the control group in relation to the Hardy–Weinberg equilibrium ($P < 0.05$ was considered significant imbalance). Five genetic models were used for analysis: the allelic, dominant, recessive, heterozygous, and homozygous models. For the *ApaI* variant, the 5 models are represented by a compared with A, aa + Aa compared with AA, aa compared with Aa + AA, Aa compared with AA, and aa compared with AA. For the *BsmI* variant, the 5 models are represented by b compared with B, bb + Bb compared with BB, bb compared with Bb + BB, Bb compared with BB, and bb compared with BB. For the *FokI* variant, the 5 models are represented by f compared with F, ff + Ff compared with FF, ff compared with Ff + FF, Ff compared with FF, and ff compared with FF. For the *TaqI* variant, the 5 models are represented by t compared with T, tt + Tt compared with TT, tt compared with Tt + TT, Tt compared with TT, and tt compared with TT. Heterogeneity between the included studies was assessed through the I^2 statistic and P values (20); $I^2 \leq 50\%$ was considered to indicate low heterogeneity (the fixed-effects model was used), whereas $I^2 > 50\%$ was considered to indicate substantial heterogeneity (the random-effects model was used). A sensitivity analysis evaluated the stability of the results by removing each study in turn. Further subgroup analysis was carried out by stratification by ethnicity (Caucasian and Asian). Publication bias was evaluated using a visual funnel plot and Egger's linear regression test. A 2-sided $P < 0.05$ was considered significant.

Results

Literature search

Eighty-six potentially relevant studies were retrieved from 4 databases, 7 records were identified through other sources, 31 of which were excluded owing to duplication. The remaining 62 records were filtered based on titles and abstracts, of which 33 were excluded because they were irrelevant to the subject. We reviewed the full texts of the remaining 29 studies and determined 10 case–control studies that met the inclusion criteria (21–30). Two of them reported MCI (29, 30), 7 reported AD (22–28), and 1 reported both MCI and AD (21). **Figure 1** summarizes the detailed search process.

Study characteristics and quality assessment

Ten studies published from 2003 to 2019 were included in the meta-analysis, involving 3573 participants. Four studies were conducted in Asia (22, 24, 29, 30), 2 in the Americas (21, 28), and 4 in Europe (23, 25–27). All participants were >60 y old. Most of the control participants were healthy subjects or without cognitive impairment. The association of the *VDR* gene *ApaI* polymorphism was examined in 8 case–control studies (21–26, 29, 30), the association of the *BsmI* polymorphism was examined in 7 studies (21–23, 25, 27, 29, 30), the association of the *FokI* polymorphism was examined in 6 studies (21–23, 25, 27, 28), and the association of the *TaqI* polymorphism was examined in 6 studies (21–24, 26, 27). **Table 1–3** summarize the characteristics and genotype frequencies of the included studies. With regard to the NOS, 2 studies were classified as high quality (21, 24), and the remaining studies were of moderate quality, with a mean score of 5.7 (Table 1). The evidence that contributes to these analyses is considered to be of moderate quality.

Meta-analysis results of *VDR* gene polymorphisms and MCI susceptibility

Three studies reported the associations between *VDR* gene polymorphisms and MCI risk (21, 29, 30). Two studies were conducted in Asia and 1 was conducted in the Americas. The fixed-effects model of the Mantel–Haenszel method was used because there was no heterogeneity. Overall, our meta-analysis indicated that the allelic model (OR: 1.77; 95% CI: 1.24, 2.54) (**Figure 2**B), the dominant model (OR: 2.04; 95% CI: 1.32, 3.16), and the heterozygote model (OR: 1.97; 95% CI: 1.26, 3.09) of the *VDR BsmI* polymorphism were associated with an increased risk of MCI (**Figure 3**A–D). In contrast, the *VDR ApaI* polymorphism was protective against MCI (allelic model: OR: 0.60; 95% CI: 0.46, 0.77; dominant model: OR: 0.50; 95% CI: 0.32, 0.80; recessive model: OR: 0.53; 95% CI: 0.37, 0.77; homozygote model: OR: 0.36; 95% CI: 0.21, 0.62; heterozygous model: OR: 0.62; 95% CI: 0.38, 1.01) (Figures 2A, **4**A–D).

Meta-analysis results of *VDR* gene polymorphisms and AD susceptibility

Pooled ORs were calculated to determine the association between *VDR* gene polymorphisms and the odds of AD. The random-effects model of the DerSimonian–Laird method was used in some comparative groups with significant heterogeneity. Our analysis revealed no altered odds of AD based on the *ApaI*, *BsmI*, and *FokI* polymorphisms of the *VDR* gene in any genetic model. In contrast, the dominant model (OR: 1.44; 95% CI: 1.17, 1.79) and the homozygous model (OR: 1.43; 95% CI: 1.02, 2.00) revealed an association between the *TaqI* polymorphism of the *VDR* gene and increased odds of AD, with no heterogeneity found (**Table 4**).

Subgroup analysis based on stratification by ethnicity showed that the dominant model (OR: 1.60; 95% CI: 1.22, 2.08) and the homozygous model (OR: 1.61; 95% CI: 1.10, 2.35) of the *TaqI* polymorphism were associated with an increased risk of AD in Caucasians but not in Asians. Moreover, the recessive model (OR: 4.33; 95% CI: 2.39, 7.87) of the *BsmI* polymorphism and the heterozygous model

TABLE 1 Summary characteristics of the studies included in the meta-analysis[1]

Authors	Country	Ethnicity	Study design	Disease	Age, y		Sample size, *n*		Sex, % female	Control source	Genotyping methods	SNPs	NOS
					Case	Control	Case	Control					
de Oliveira et al. (21)	Brazil	Caucasian	Case–control	MCI, AD	74.60 ± 4.94	74.09 ± 7.17	15	24	24 (61.5)	Healthy elderly	PCR	*ApaI, BsmI, FokI, TaqI*	7
Keyimu et al. (30)	China	Asian	Case–control	MCI	65.63 ± 7.46	64.44 ± 6.20	124	124	109 (44.0)	Patients who were without MCI, but have the same or similar life background, age, and gender as selected MCI patients	PCR	*ApaI, BsmI*	6
Abriz et al. (29)	China	Asian	Case–control	MCI	77. 22 ± 6.59	76. 72 ± 5.71	100	145	127 (51.8)	Patients who were without MCI, but have the same or similar life background, age, and gender as selected MCI patients	PCR	*ApaI, BsmI*	6
Gezen-Ak et al. (27)	Turkey	Caucasian	Case–control	AD	75.1 ± 5.7	73.6 ± 7.3	104	109	NA	Age-matched controls without any neurodegenerative diseases	PCR	*ApaI, BsmI, FokI, TaqI*	4
Gezen-Ak et al. (25)	Turkey	Caucasian	Case–control	AD	74 ± 4.2	75.2 ± 6.8	108	115	NA	Controls without any neurodegenerative diseases	PCR	*BsmI, FokI*	4
Khorram et al. (24)	Iran	Asian	Case–control	AD	78.5 ± 7.8	77.4 ± 7.0	145	162	190 (61.9)	Age-matched unrelated healthy controls	PCR	*ApaI, TaqI*	8
Lehmann et al. (26)	United Kingdom	Caucasian	Case–control	AD	NA	NA	255	260	265 (51.5)	Elderly controls from the longitudinal cohort of the Oxford Project to Investigate Memory and Ageing	PCR	*ApaI, TaqI*	5
Łaczmański et al. (23)	Poland	Caucasian	Case–control	AD	73.7 ± 8.6	64.5 ± 7.8	108	77	167 (90.3)	Healthy volunteers	PCR	*ApaI, BsmI, FokI, TaqI*	6
Luedecking-Zimmer et al. (28)	United States	Caucasian	Case–control	AD	77.3 ± 6.4	76.8 ± 6.3	564	523	NA	Controls were obtained from the same geographical area from which the patients were derived, and were found cognitively intact	PCR	*FokI*	5
Mun et al. (22)	South Korea	Asian	Case–control	AD	79.82 ± 7.02	68.94 ± 6.10	144	335	285 (59.5)	Healthy elderly	PCR	*ApaI, BsmI, FokI, TaqI*	6

[1] Values are means ± SDs unless otherwise indicated. AD, Alzheimer disease; MCI, mild cognitive impairment; NA, not available; NOS, Newcastle-Ottawa Scale; SNP, single nucleotide polymorphism.

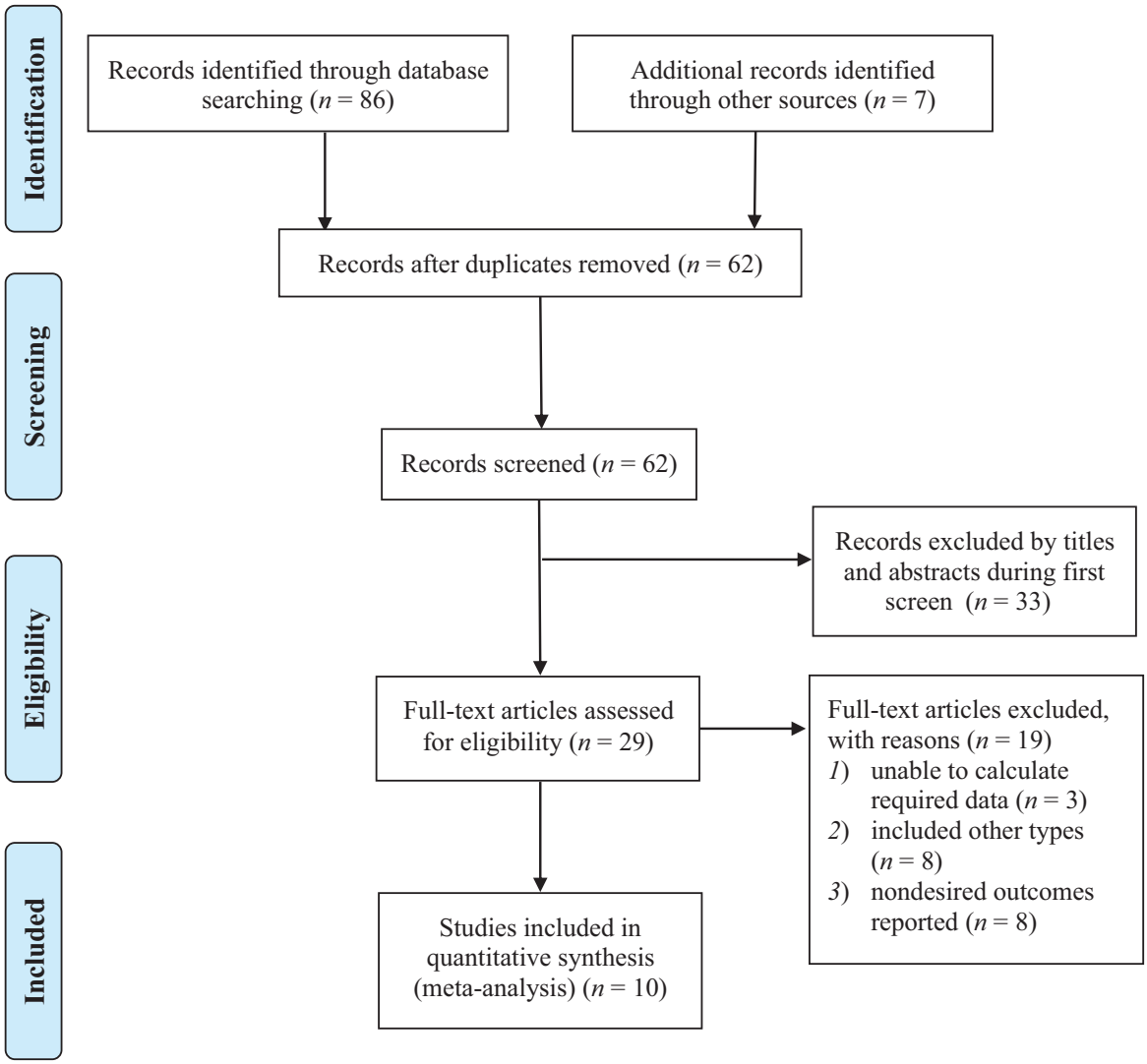

FIGURE 1 Flowchart of the literature retrieval and selection process.

(OR: 1.56; 95% CI: 1.00, 2.43) of the *FokI* polymorphism were associated with increased susceptibility to AD in Asians (**Table 5**).

Sensitivity analysis

Sensitivity analysis was performed to assess the impact of individual studies on the overall effect estimate. Deleting each study 1 at a time and reanalyzing the data set did not lead to significant changes in the pooled OR estimate, indicating the statistical stability of the results.

Publication bias

Egger's linear regression test and a visual funnel plot were used to estimate the publication bias between the studies involved in the meta-analysis (Table 4). These 2 testing methods showed that there was no evidence of publication bias in any of the genetic models that were compared.

Discussion

We comprehensively evaluated the correlations of 4 candidate SNPs (*ApaI*, *BsmI*, *FokI*, *TaqI*) of the *VDR* gene with susceptibility to MCI and AD from 10 selected studies. Our results are somewhat inconsistent with the previous study by Lee et al. (17). The *ApaI* and *TaqI* polymorphisms were demonstrated to be associated with a high risk of AD in the allelic, recessive, and homozygous gene models in Caucasians in their study, but the results were limited to only 2 studies. Regarding our results, 6 trials including Caucasians and Asians found that dominant genes and a homozygous gene model of the *TaqI* gene polymorphism may increase the risk of AD. This is the first meta-analysis that we know of to assess the relation between *VDR* gene polymorphisms and MCI susceptibility. The allele, dominant, and heterozygous gene models of the *BsmI* polymorphism are related to an increased risk of MCI. Conversely, the *ApaI* polymorphism may be protective. These results indicate

TABLE 2 Genotype frequencies of vitamin D receptor gene polymorphisms in AD patients and matched controls[1]

SNP	Authors	Genotype						HWE *P* value
		AD patients			Controls			
ApaI		AA	Aa	aa	AA	Aa	aa	
	Gezen-Ak et al. (27)	35	63	6	55	43	11	0.55
	de Oliveira et al. (21)	14	15	3	9	13	2	0.37
	Lehmann et al. (26)	86	132	37	64	140	56	0.21
	Łaczmański et al. (23)	26	59	23	17	41	12	0.14
	Mun et al. (22)	3	62	79	12	129	188	0.07
	Khorram et al. (24)	29	65	51	28	78	56	0.93
BsmI		BB	Bb	bb	BB	Bb	bb	
	Gezen-Ak et al. (25)	30	38	39	34	32	48	0.58
	de Oliveira et al. (21)	9	11	12	2	12	10	0.54
	Łaczmański et al. (23)	12	61	35	10	44	23	0.12
	Mun et al. (22)	0	19	125	1	34	294	0.99
FokI		FF	Ff	ff	FF	Ff	ff	
	Gezen-Ak et al. (25)	52	46	10	51	51	10	0.58
	de Oliveira et al. (21)	15	14	3	12	11	1	0.43
	Luedecking-Zimmer et al. (28)	233	225	78	198	229	65	0.92
	Łaczmański et al. (23)	36	53	19	27	36	14	0.74
	Mun et al. (22)	43	77	24	129	148	53	0.53
TaqI		TT	Tt	tt	TT	Tt	tt	
	Gezen-Ak et al. (27)	38	50	16	53	39	17	0.03
	de Oliveira et al. (21)	10	11	11	13	6	5	0.93
	Lehmann et al. (26)	68	136	51	101	117	42	0.41
	Łaczmański et al. (23)	42	55	11	31	38	8	0.46
	Mun et al. (22)	125	19	0	296	32	1	0.89
	Khorram et al. (24)	64	64	17	76	65	21	0.24

[1] AD, Alzheimer disease; HWE, Hardy–Weinberg equilibrium; SNP, single nucleotide polymorphism.

that functional polymorphisms of *VDR* located near the 3' untranslated region may affect the function of vitamin D by regulating gene stability and protein translation, thereby interfering with the effect of vitamin D on cognitive function.

SNPs describe the DNA sequence polymorphism caused by single-nucleotide variation at the genomic level, affecting the transcription, translation, expression, and function of proteins to define discrepancies in individual genetic polymorphisms (31). Confounding factors and reverse causality lead to relatively limited observational research results (32). Genetic genes are used as an instrumental variable to reveal the relation between exposure and outcome while avoiding confounding factors and reverse causality because genetic genes are rarely affected by environmental factors (8, 33). 1,25-Dihydroxyvitamin D [1,25$(OH)_2$D], the most active metabolic form of vitamin D, not only plays a vital role in bone metabolism and calcium homeostasis but also participates in nonendocrine effects, such as cardiovascular disease, immune function, diabetes, and cancer (34). The current view on the use of vitamin D in managing cognitive impairment is based on the hypothesis that low serum vitamin D concentration is associated with the prevalence and severity of cognitive decline. Therefore, the evaluation of serum vitamin D concentrations is part of the clinical management of cognitive impairment. Detecting its deficiency in a target population and replenishing it in a timely manner may help prevent or improve cognitive

TABLE 3 Genotype frequencies of vitamin D receptor gene polymorphisms in MCI patients and matched controls[1]

SNP	Authors	Genotype										HWE *P* value
		MCI patients					Controls					
ApaI		A	a	AA	Aa	aa	A	a	AA	Aa	aa	
	de Oliveira et al. (21)	20	10	6	8	1	31	17	9	13	2	0.37
	Keyimu et al. (30)	121	127	29	63	32	92	156	17	58	49	0.98
	Abriz et al. (29)	79	121	20	39	41	75	215	13	49	83	0.15
BsmI		B	b	BB	Bb	bb	B	b	BB	Bb	bb	
	de Oliveira et al. (21)	11	19	2	7	6	16	32	2	12	10	0.54
	Keyimu et al. (30)	185	63	69	47	8	211	37	89	33	2	0.59
	Abriz et al. (29)	184	16	84	16	0	279	11	135	9	1	0.07

[1] HWE, Hardy–Weinberg equilibrium; MCI, mild cognitive impairment; SNP, single nucleotide polymorphism.

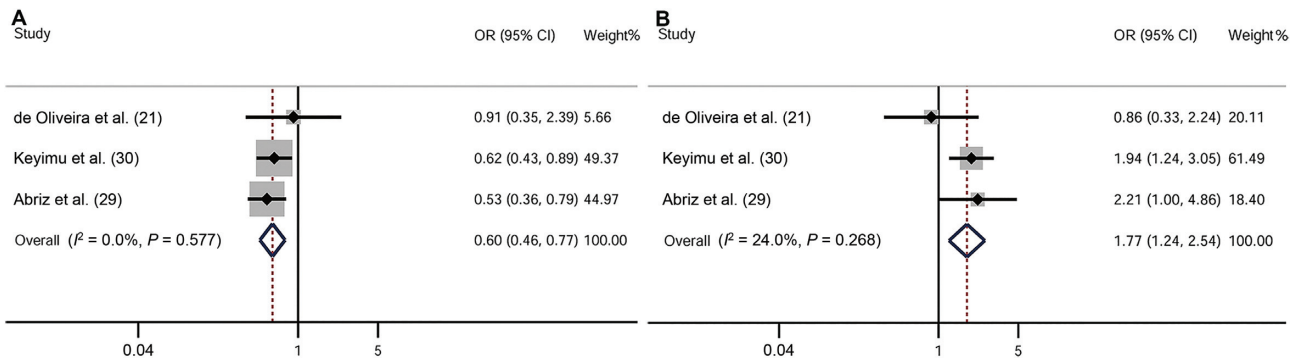

FIGURE 2 ORs and 95% CIs of individual studies and pooled data for the allele associations between the vitamin D receptor *ApaI* (A) and *BsmI* (B) polymorphisms and mild cognitive impairment.

decline. In fact, vitamin D supplementation might play a critical role in the pathophysiology of neurodegenerative disease, including AD, multiple sclerosis, Parkinson disease, amyotrophic lateral sclerosis, and Huntington disease (35–39). *VDR* expression and nuclear activation are necessary for $1,25(OH)_2D$ function, although the vitamin D needs to be metabolized in the liver and kidneys first (40). Therefore, genetic alteration of *VDR* genes may lead to abnormal gene activation, which could influence the biological effects of vitamin D. Multiple studies have reported the relation between *VDR* polymorphism and susceptibility to MCI and AD, but which SNPs are protective or dangerous has not been determined. Our results may provide clear evidence for this controversy.

The results of the stratified analysis showed that the dominant and homozygous models of the *TaqI* polymorphism were associated with an increased risk of AD in Caucasians, and the recessive model of the *BsmI* polymorphism and the heterozygous model of the *FokI* polymorphism were associated with increased susceptibility to AD in Asians. These results can be explained by ethnic differences because SNPs play a multifunctional role in cognitive impairment and vary between different ethnic groups, which indicates the influence of genetic and environmental factors. It is worth

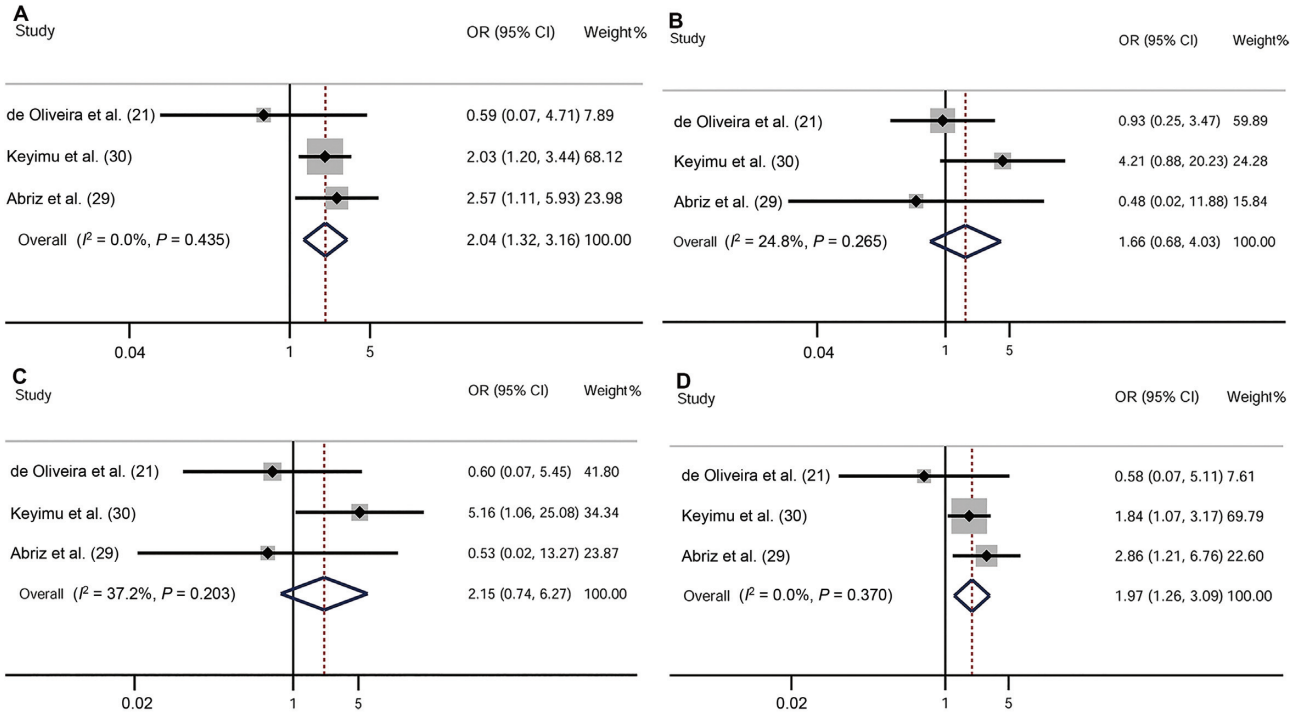

FIGURE 3 ORs and 95% CIs of individual studies and pooled data for the associations between the vitamin D receptor *BsmI* polymorphism and mild cognitive impairment. (A) Dominant model (bb + Bb compared with BB); (B) recessive model (bb compared with Bb + BB); (C) homozygous model (bb compared with BB); (D) heterozygous model (Bb compared with BB).

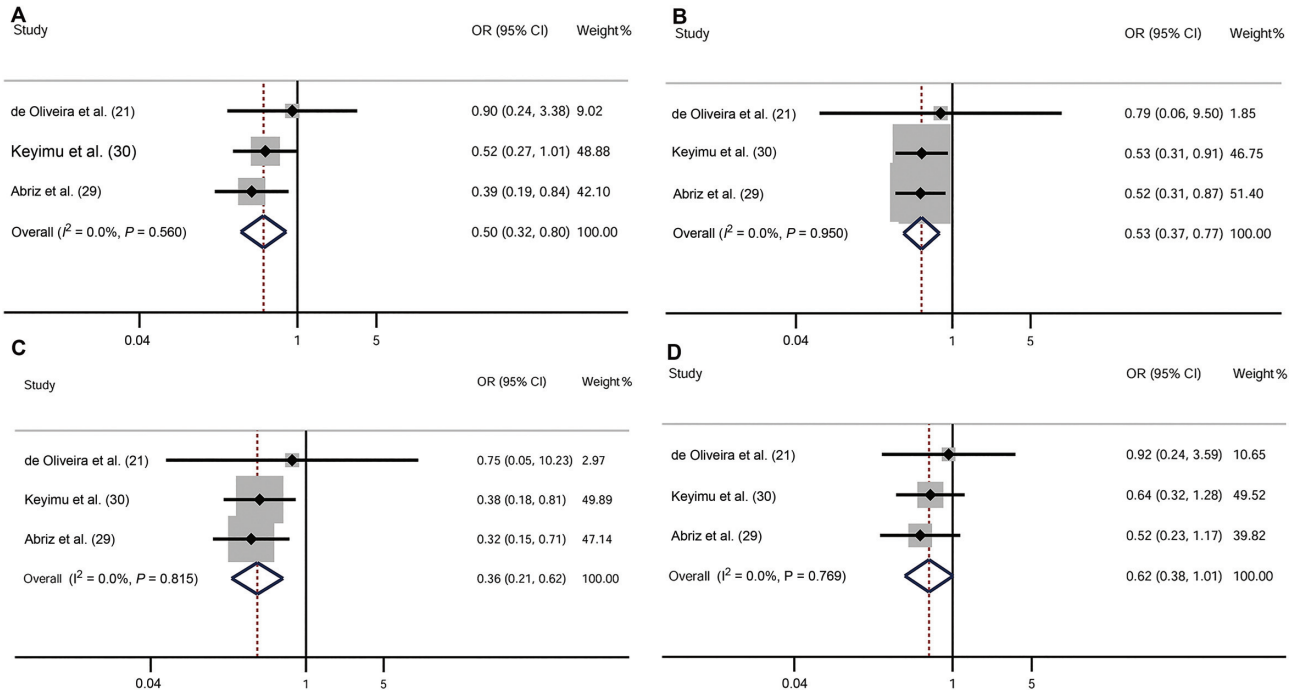

FIGURE 4 ORs and 95% CIs of individual studies and pooled data for the associations between the vitamin D receptor *ApaI* polymorphism and mild cognitive impairment. (A) Dominant model (aa + Aa compared with AA); (B) recessive model (aa compared with Aa + AA); (C) homozygous model (aa compared with AA); (D) heterozygous model (Aa compared with AA).

noting that the expression and effect of *VDR* are determined by not only genetics but also race and environment and involve complex interactions that can change the connection with disease.

This meta-analysis tested the strength of the association between 4 *VDR* gene polymorphisms and MCI or AD based on 5 gene models. The probability of random errors was reduced by grouping data from a single study. Most of the trials received ≥5 stars according to NOS criteria. Considering the sample size, inclusion criteria, and characteristics of patients and controls, our results may provide the strongest evidence to date. However, despite the strong statistical significance of these results, the current research still has some potential limitations. First, language and selection biases cannot be excluded without quantifying publication bias. Publications were limited to Chinese and English, and some research

TABLE 4 Meta-analysis results for the association between vitamin D receptor gene polymorphisms and Alzheimer disease[1]

SNP	Comparison	*n*	Model	Pooled estimate value			I^2, %	*P*-heterogeneity	Egger's *P* value
				OR (95% CI)	*Z*	*P* value			
ApaI	aa + Aa vs. AA	6	Random	1.01 (0.65, 1.55)	0.02	0.981	60.2	0.028	0.870
	aa vs. Aa + AA		Fixed	0.86 (0.68, 1.08)	1.31	0.187	0	0.468	0.140
	aa vs. AA		Fixed	0.77 (0.55, 1.06)	1.59	0.112	9.0	0.358	0.129
	Aa vs. AA		Random	1.06 (0.67, 1.67)	0.24	0.811	61.0	0.025	0.640
BsmI	bb + Bb vs. BB	4	Fixed	0.96 (0.61, 1.51)	0.18	0.858	9.8	0.344	0.536
	bb vs. Bb + BB		Random	1.14 (0.41, 3.12)	0.25	0.805	88.9	<0.001	0.663
	bb vs. BB		Fixed	0.89 (0.54, 1.48)	0.44	0.657	0	0.498	0.679
	Bb vs. BB		Fixed	1.05 (0.64, 1.74)	0.21	0.836	26.0	0.255	0.510
FokI	ff + Ff vs. FF	5	Fixed	1.01 (0.84, 1.21)	0.07	0.944	20.5	0.284	0.501
	ff vs. Ff + FF		Fixed	1.09 (0.84, 1.41)	0.62	0.533	0	0.964	0.548
	ff vs. FF		Fixed	1.10 (0.83, 1.46)	0.65	0.516	0	0.888	0.395
	Ff vs. FF		Fixed	0.98 (0.81, 1.20)	0.15	0.877	32.7	0.203	0.720
TaqI	tt + Tt vs. TT	6	Fixed	1.44 (1.17, 1.79)	3.37	0.001	0	0.463	0.803
	tt vs. Tt + TT		Fixed	1.14 (0.84, 1.55)	0.85	0.397	0	0.860	0.788
	tt vs. TT		Fixed	1.43 (1.02, 2.00)	2.09	0.037	0	0.609	0.704
	Tt vs. TT		Random	1.59 (0.84, 3.01)	1.43	0.152	86.0	<0.001	0.229

[1] SNP, single nucleotide polymorphism.

TABLE 5 Meta-analysis results for the association between vitamin D receptor gene polymorphisms and Alzheimer disease based on stratification by ethnicity[1]

SNP, ethnicity	*n*	OR (95% CI)	*P*-interaction	OR (95% CI)	*P*-interaction	OR (95% CI)	*P*-interaction	OR (95% CI)	*P*-interaction
ApaI	6	aa + Aa vs. AA		aa vs. Aa + AA		aa vs. AA		Aa vs. AA	
Asian	2	0.96 (0.47, 1.94)	0.915	0.96 (0.71, 1.30)	0.305	1.00 (0.56, 1.78)	0.269	1.02 (0.48, 2.20)	0.939
Caucasian	4	1.01 (0.55, 1.85)		0.74 (0.50, 1.10)		0.69 (0.43, 1.10)		1.06 (0.56, 1.98)	
BsmI	4	bb + Bb vs. BB		bb vs. Bb + BB		bb vs. BB		Bb vs. BB	
Asian	1	1.32 (0.59, 32.05)	0.722	4.33 (2.39, 7.87)*	0.036	1.28 (0.05, 31.60)	0.828	1.70 (0.07, 43.66)	0.580
Caucasian	3	0.90 (0.46, 1.78)		0.73 (0.39, 1.39)		0.89 (0.49, 1.60)		0.92 (0.41, 2.11)	
FokI	5	ff + Ff vs. FF		ff vs. Ff + FF		ff vs. FF		Ff vs. FF	
Asian	1	1.51 (0.99, 2.29)	0.034	1.05 (0.62, 1.77)	0.764	1.36 (0.75, 2.46)	0.419	1.56 (1.00, 2.43)*	0.023
Caucasian	4	0.91 (0.74, 1.12)		1.10 (0.81, 1.48)		1.03 (0.75, 1.42)		0.88 (0.70, 1.09)	
TaqI	6	tt + Tt vs. TT		tt vs. Tt + TT		tt vs. TT		Tt vs. TT	
Asian	2	1.20 (0.84, 1.72)	0.207	0.89 (0.45, 1.73)	0.413	0.95 (0.47, 1.92)	0.196	3.23 (0.42, 24.79)	0.265
Caucasian	4	1.60 (1.22, 2.08)*		1.22 (0.87, 1.72)		1.61 (1.10, 2.35)*		1.00 (0.74, 1.36)	

[1] SNP, single nucleotide polymorphism.
*Significant association with AD, *P* 0.05

published in other languages may have been omitted. Moreover, a limited number of electronic databases were reviewed, and related research indexed in other electronic databases may have been ignored. Second, most studies did not report on genetic–environment interactions, limiting the scope of this topic. Third, significant heterogeneity may weaken the validity of the conclusions. Fourth, data on stratification by ethnicity are limited; thus, a large-scale case–control study needs to be carried out to provide strong evidence to verify our findings.

In conclusion, the current meta-analysis provides statistical evidence that *VDR ApaI* and *BsmI* polymorphisms may be associated with the risk of MCI, and *TaqI* polymorphisms may be associated with the risk of AD. Further studies with larger sample sizes are essential to reach clear conclusions.

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