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REVIEW ARTICLE **OPEN ACCESS**

VITAMIN D RECEPTOR GENE POLYMORPHISMS IN MULTIPLE SCLEROSIS SUSCEPTIBILITY: UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: The relationship between Vitamin D Receptor (VDR) gene polymorphisms and the risk of developing Multiple Sclerosis (MS) has been explored in numerous studies. However, the results were inconclusive. Therefore, this study aimed to investigate the relationship between VDR gene polymorphisms and susceptibility to MS.
Objective: This study aimed to systematically evaluate the association between Vitamin D Receptor (VDR) gene polymorphisms and susceptibility to Multiple Sclerosis (MS) through a meta-analysis of existing studies.
Methods: This study is a meta-analysis conducted in accordance with the PRISMA guideline. The literature search was conducted using the PubMed and Google Scholar databases from January 2014 to December 2024. Studies included in this meta-analysis were assessed using the Newcastle-Ottawa Scale (NOS). The association between VDR polymorphisms and the risk of MS was evaluated using pooled odds ratios (ORs) and 95% confidence intervals (CIs).
Results: Six studies (868 cases/982 controls) were included. The TaqI polymorphism showed that TT vs TC + CC was associated with reduced risk of MS (OR 95% CI = 0.43 [0.21 - 0.86], p = 0.02), while CC vs TT + TC was associated with an increased risk of MS (OR 95% CI = 1.89 [1.51 - 2.36], p < 0.00001). T vs C was associated with reduced risk of MS (OR 95% CI = 0.69 [0.49 - 0.98], p = 0.04) while C vs T was associated with an increased risk of MS (OR 95% CI = 1.45 [1.02 – 2.05], p < 0.04).
Conclusion: In summary, our meta-analysis revealed a significant association between VDR gene polymorphism and MS susceptibility in certain genetic models of the VDR gene.

Keywords: multiple sclerosis, single nucleotide polymorphism, Taq I, VDR gene

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disorder affecting the brain and spinal cord, primarily occurring in young individuals. Tissue damage in MS results from a dynamic and complex interaction between glial cells (oligodendrocytes and their precursors, astrocytes, and microglia), neurons, and the immune system[1,2]The most recent estimate of people living with MS worldwide was 2.2 million in 2016.[3] The prevalence of MS in Indonesia ranges from 0 to 5 per 100,000 people, with the highest incidence occurring in women aged 20 to 40.[4,5,6] The Global Burden of Disease Study (GBD) 2016 estimated that Indonesia had approximately 7,056 cases of MS in 2016. The incidence of MS in Indonesia has shown an upward trend, highlighting a growing disease burden within the population. MS, the most prevalent immune-mediated disorder, has a multifaceted pathophysiology that arises from a combination of genetic predisposition and environmental influences, but the exact cause of the disease remains unknown.[7]

Multiple pathological factors, such as vitamin D deficiency and its negative association with sunlight exposure, significantly contribute to the development of MS.[8] Vitamin D, a steroid hormone, exists in its bioactive form as 1,25(OH)$_2$D$_3$, which plays a key role in regulating immune responses.[9] Recent studies have shown that levels of 1,25(OH)$_2$D$_3$ may be involved in the pathological mechanisms underlying MS.[10,11,12]

Vitamin D is involved in several biological processes, such as bone metabolism, immune system modulation, and the regulation of cell growth and differentiation.[13,14] Vitamin D deficiency is associated with a higher risk of developing autoimmune diseases. It can contribute to the progression of existing conditions such as multiple sclerosis (MS), rheumatoid arthritis (RA), diabetes mellitus (DM), inflammatory bowel disease (IBD), and systemic lupus erythematosus (SLE). Additionally, it increases susceptibility to infectious diseases, including influenza, bacterial vaginosis, tuberculosis, and human immunodeficiency virus (HIV).[15]

Vitamin D interacts with the vitamin D receptor (VDR), which is an intracellular receptor for steroid hormones. This interaction leads to the formation of a complex in which vitamin D-bound VDR pairs with the retinoid X receptor (RXR) through a process known as heterodimerization. Once formed, this complex can bind to vitamin D response elements (VDRE) in the nucleus, acting as a transcription factor that regulates the expression of specific target genes. The VDR gene is situated on chromosome 12 (12q12-14) and contains around 200 single-nucleotide polymorphisms (SNPs). Among these, the most extensively studied SNPs are TaqI.[16] Numerous studies have explored the relationship between VDR polymorphisms and the risk of MS, but the findings have been inconsistent. To address this, the current systematic review seeks to evaluate the potential link between VDR polymorphisms and the risk of developing MS.

Methods

Research design

This research is a systematic review study to determine the relationship between VDR gene polymorphisms and the risk of multiple sclerosis. The article search was conducted from January 2014 to December 2024. Researchers collected various literature studies related to this topic, selected them based on the inclusion and exclusion criteria, and extracted the data. The inclusion criteria consisted of primary results in the form of an association between VDR polymorphisms and the risk of multiple sclerosis. The data were then analyzed using either a random or fixed model. We used PubMed and Google Scholar databases to search for relevant literature studies.

Literature search strategy

This systematic review and meta-analysis were carried out following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guideline.[18] Review authors (ISP and BER) independently selected and assessed the literature. Literature searches were conducted in the following databases: PubMed and Google Scholar. The search strategy used a combination of several words: (Multiple sclerosis or MS) AND (VDR gene or vitamin D receptor gene) AND (polymorphisms or single nucleotide polymorphisms or SNP). The language was restricted to English. The study was limited to publications from the past decade. The searching process was done from January 2014 to December 2024. If more than one article was published using the same study data, only the most recent study was included. Reviews on longevity were also hand-searched to identify additional potentially relevant studies. In addition to electronic database searches, the researchers manually examined review articles on longevity to identify original studies that may not have been retrieved through standard search queries. This step served as a supplementary strategy to reduce the risk of overlooking relevant literature. Where necessary, authors were contacted directly for any additional data required.

Eligibility criteria

The eligibility criteria consisted of inclusion and exclusion criteria. Studies were included in the analysis if they met the following inclusion criteria. The inclusion criteria consisted of: 1) Individuals in the "case" group are patients diagnosed with multiple sclerosis, 2) polymorphisms occur in the VDR genes TaqI, 3) individuals in the control group are healthy individuals, 4) primary results in the form of an association between VDR polymorphisms and the risk of multiple sclerosis and data available to calculate the 95% odds ratio (OR), and 5) studies in the form of case control, cohort, comparative studies. Exclusion criteria consist of: 1) Articles with no control group or genotype data to calculate the odds ratio (OR) and corresponding 95% CI, 2) irrelevant titles and/or abstracts, 3) case reports or case series, 4) literature reviews, 5) review articles, 6) in vitro studies, 7) literature with uncommon and incomplete data, 8) duplication of existing literature, and 9) deviation from Hardy-Weinberg equilibrium (HWE). If a study had incomplete data or only an abstract, we contacted the corresponding author via e-mail. If there was no response within three days, the study was excluded.

Quality assessment

We assess the quality of included studies using the New-Ottawa Scale (NOS). This scale contains eight items under the three categories (selection, comparability, and outcome). We considered a study to be of high quality if it had a score > 6. Studies with scores of 4–6 were deemed to have moderate quality, and those with a score < 4 were deemed to have low quality.

Data extraction

Literature was collected, and the researcher conducted a screening to collect literature that met the criteria. Then, data extraction will be conducted. The data from the literature that will be extracted to calculate the 95% OR consists of: 1) the first author's name, 2) year of study, 3) country of study, 4) sample size in the case and placebo groups, 5) number of each genotype and allele, and 6) genotyping method.

Research variables

The population consisted of patients diagnosed with multiple sclerosis (MS) as the case group and healthy individuals as the control group, with the exposure of interest being the Vitamin D Receptor (VDR) gene polymorphism, specifically the TaqI (rs731236) variant with the T allele, compared with individuals carrying the C allele or CC/TC genotypes. The outcome assessed was the risk of developing MS, measured as either an increased or decreased susceptibility depending on genotype or allele distribution. The VDR itself belongs to the nuclear steroid hormone receptor superfamily and regulates gene transcription through interactions with response elements in gene promoters. The human VDR gene is located on chromosome 12q12–14, with TaqI (rs731236) being the most common single nucleotide polymorphism (SNP), positioned at the 3′-end of the gene, where it may cause silent mutations that increase the stability of VDR mRNA. Measurement results for this variable were expressed as T and C alleles, obtained through a systematic search strategy, with the scale used being nominal. Multiple sclerosis, on the other hand, is a chronic demyelinating disease of the central nervous system (CNS) characterized as an inflammatory neurodegenerative disorder associated with motor and sensory loss as well as significant clinical disabilities. As the most common immune-mediated disorder, MS has a complex pathophysiology involving both genetic susceptibility and environmental factors, with the measurement results in this variable expressed as an increase or decrease in MS risk, also obtained through search strategies, and assessed on a nominal scale.

Statistical Analysis

The association between VDR gene polymorphisms and the risk of developing multiple sclerosis was estimated by calculating the pooled OR and 95% CI. The pooled OR value was obtained from the Z test results ($p < 0.05$ was statistically significant). A Q test was performed to evaluate heterogeneity. If $p < 0.05$, the data were heterogeneous, and a random effect model was applied. If the data is homogeneous ($p \geq 0.05$), then proceed with the fixed model. The Funnel Plot determines the bias value. Researchers used Review Manager 5.4 software to analyze the data.

Critical appraisal

A critical review was conducted using the Oxford Centre for Evidence-Based Medicine21, which assessed the validity, importance, and applicability of the selected journals.

Results

Study identification

A total of 40 relevant literature were identified based on the search strategy. Of these, five studies were excluded due to duplicates. After our search, 23 studies were excluded due to irrelevant titles and abstracts. After screening the full text of the literature, four were excluded because they were systematic reviews, one was excluded because it did not provide sufficient data for OR and 95% CI calculation, and one was excluded because it had irrelevant results. A chart showing the inclusion or exclusion of studies is shown in Figure 1.

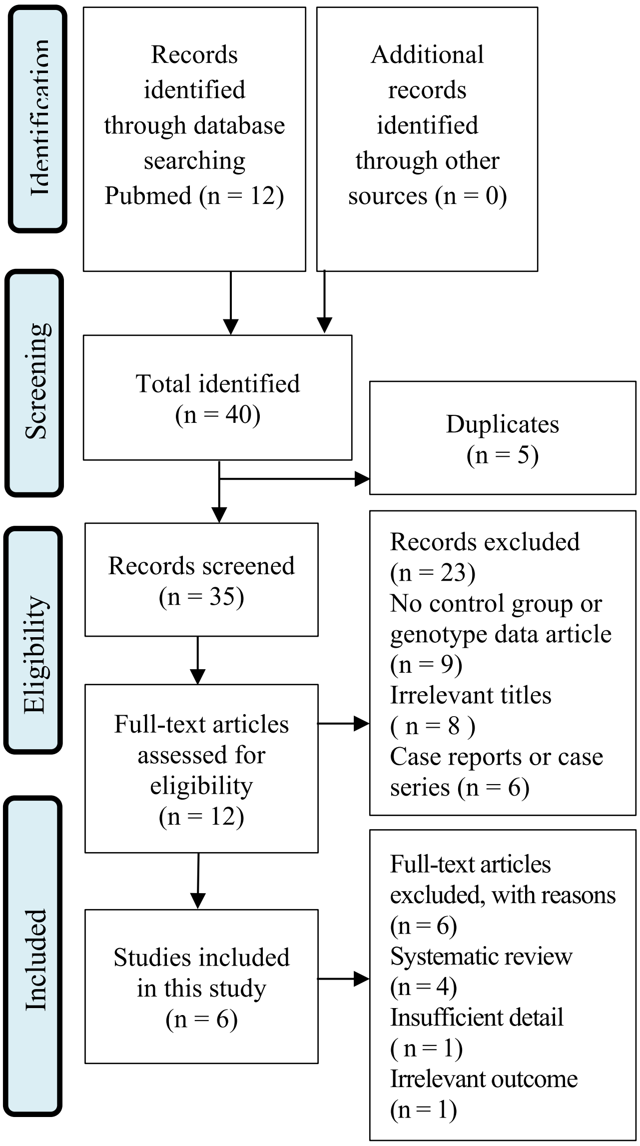


Figure 1. PRISMA chart

Study quality characteristics and assessment

Six studies (868 cases/982 controls) were included in this study. Table 1 describes the characteristics of the studies included in this meta-analysis. The quality of the literature included in this meta-analysis was assessed with the New-Ottawa Scale, where literature is considered to be of good quality if the score is >7. Table 2 describes the quality assessment of the literature included in this study.

Quantitative data synthesis

Overall, several results showed an association between VDR gene polymorphisms and MS risk in TaqI genetic models. Significant heterogeneity was shown in several genotypes and alleles. In the TaqI polymorphism, TT vs TC + CC genotype was associated with a decreased risk of MS (OR 95% CI = 0.43 [0.21 - 0.86], p = 0.02), and T vs C allele also associated with a decreased risk of MS (OR 95% CI = 0.69 [0.49 - 0.98], p = 0.04), whereas CC vs TC + TT genotype was associated with an increased risk of MS (OR 95% CI = 1.80 [1.26 - 2.56], p = 0.001) and C vs T allele also associated with a increased risk of MS (OR 95% CI = 1.45 [1.02 - 2.05], p = 0.04). More in-depth data are presented in Table 3**,** and the forest plots are presented in Figures 2-5**.**

Potential publication bias

The funnel plot showed varying degrees of publication bias. Publication bias was detected in the TaqI polymorphism of CC vs CT + TT; TT vs CC + CT genotypes, and T vs C allele (asymmetrical funnel plot). No publication bias was detected in the TaqI gene polymorphism TC vs TT + CC genotype and C vs T allele (symmetrical funnel plot). The funnel plot illustrating the association between VDR gene polymorphisms and the risk of multiple sclerosis is provided in Figures 6 and 7**.**

Table 1. Characteristics of studies included in this meta-analysis

Name	Year	Country	Ethnicity	Sample Size		Case							Control							Genotyping	HWE
				Case	Control	CC	CT	TT	N	C	T	n	CC	CT	TT	N	C	T	n		
Abdollahzadeh et al	2016	Iran	Iranian	160	150	79	80	38	197	238	156	394	42	80	63	185	164	206	370	PCR-RFLP	2,837
Abdollahzadeh et al	2017	Iran	Iranian	118	124	24	61	33	118	109	127	236	13	49	62	124	75	173	248	PCR-RFLP	0,498
Arani et al	2022	Iran	Iranian	101	101	8	40	53	101	56	146	202	16	45	40	101	42	68	110	PCR-RFLP	0.312
Bulan et al	2022	Turkey	Turkish	271	203	72	110	89	271	254	288	542	34	93	76	203	161	245	406	PCR	0,371
Nejad et al	2014	Iran	Iranian	113	122	60	44	9	113	164	62	226	60	27	94	181	164	62	226	PCR-RFLP	86,36
Pistono et al	2022	Italy	Italian	105	282	20	53	32	105	93	117	210	20	53	121	194	93	295	388	PCR-RFLP	12,168

HWE: Hardy-Weinberg Equilibrium; N: Sum of Genotype (TT, TC, CC); n : Sum of Allele (T, C)

Table 2. Quality assessment of included studies using the Newcastle Ottawa Scale (NOS)

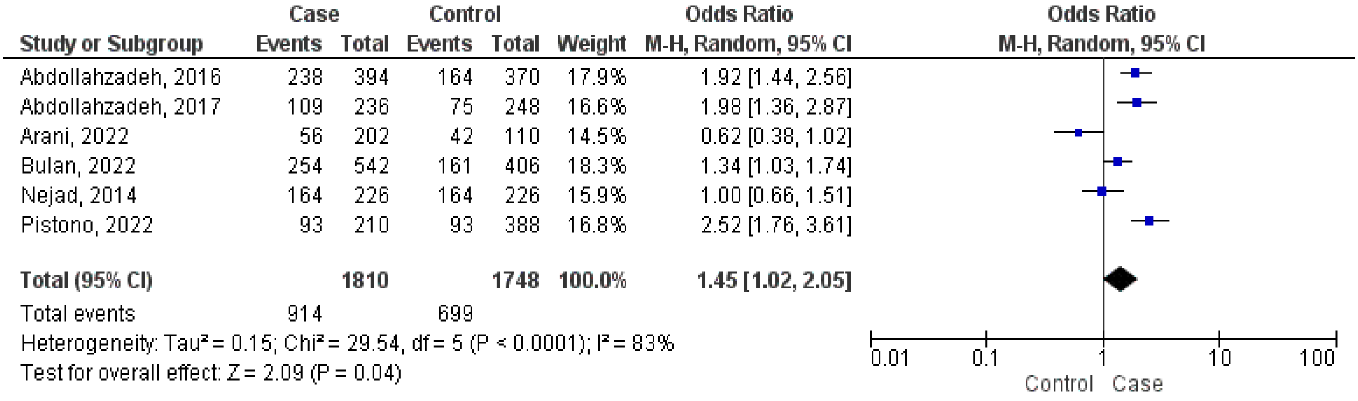
Study	Year	Selection				Comparability	Exposure			Total
		Case definition	Representativeness of the cases	Selection of controls	Definition of controls		Ascertainment of Exposure	Same method of ascertainment for all subjects	Non-Response Rate	
Abdollahzadeh et al	2016	*	-	-	*	*	*	*	*	6
Abdollahzadeh et al	2017	*	-	-	*	*	*	*	*	6
Arani et al	2022	*	-	-	*	**	*	*	*	7
Bulan et al	2022	*	-	-	*	**	*	*	*	7
Nejad et al	2014	*	-	-	*	*	*	*	*	6
Pistono et al	2022	*	-	-	*	**	*	*	*	7

(*) means one point

Table 3. Summary of association between Vitamin D receptor gene polymorphisms and Multiple Sclerosis susceptibility

Group	Numbef of Study	Genetic Model	Model	Test of Association			Test of Heterogeneity	
				OR	95% CI	*p*	I^2	*p*
TaqI	6	T vs C	Random	0.69	0.49 - 0.98	0.04	83%	<0.00001
		C vs T	Random	1.45	1.02 - 2.05	0.04	83%	<0.00001
		TT vs TC+CC	Random	0.43	0.21 - 0.86	0.02	91%	<0.00001
		TC vs TT+CC	Random	1.44	0.07 - 2.39	0.16	86%	<0.00001
		CC vs TT+TC	Random	1.80	1.26 - 2.56	0.0001	55%	0.05

Notes : OR = odds ratio, CI = confidence interval, p = p value based on a between-study Z test

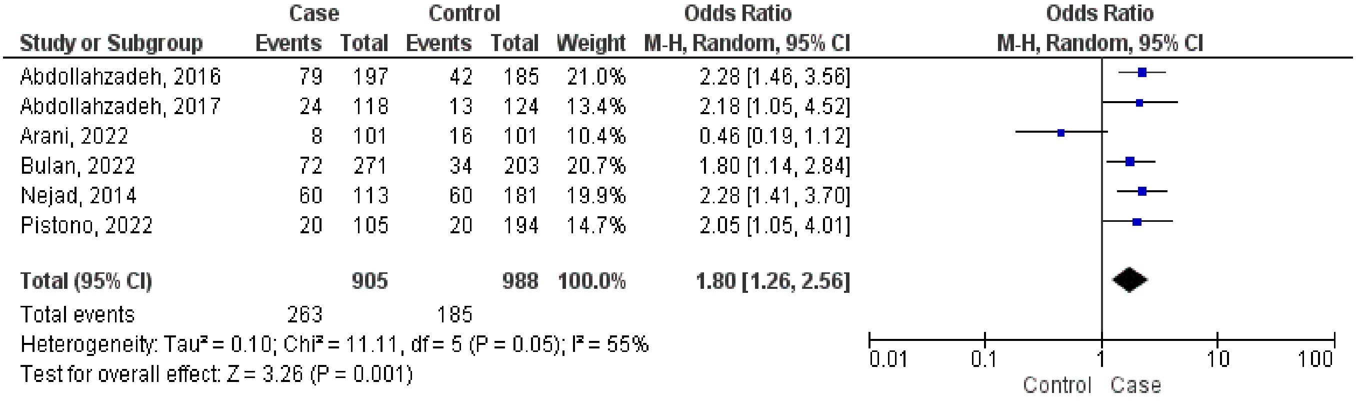


Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdollahzadeh, 2016	238	394	164	370	17.9%	1.92 [1.44, 2.56]
Abdollahzadeh, 2017	109	236	75	248	16.6%	1.98 [1.36, 2.87]
Arani, 2022	56	202	42	110	14.5%	0.62 [0.38, 1.02]
Bulan, 2022	254	542	161	406	18.3%	1.34 [1.03, 1.74]
Nejad, 2014	164	226	164	226	15.9%	1.00 [0.66, 1.51]
Pistono, 2022	93	210	93	388	16.8%	2.52 [1.76, 3.61]
Total (95% CI)		**1810**		**1748**	**100.0%**	**1.45 [1.02, 2.05]**
Total events	914		699			

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 29.54$, df = 5 ($P < 0.0001$); $I^2 = 83\%$

Test for overall effect: Z = 2.09 (P = 0.04)

Figure 1. Forrest plot of association between VDR TaqI polymorphysm and MS susceptibility**.** CC vs TC + TT (Genotype) The pooled OR is 1.89 [1.51, 2.36], suggesting a statistically significant association (Z = 5.55, P < 0.00001). The heterogeneity statistic shows $I^2 = 55\%$, indicating moderate heterogeneity, meaning that some variability among studies exists but is not excessively high

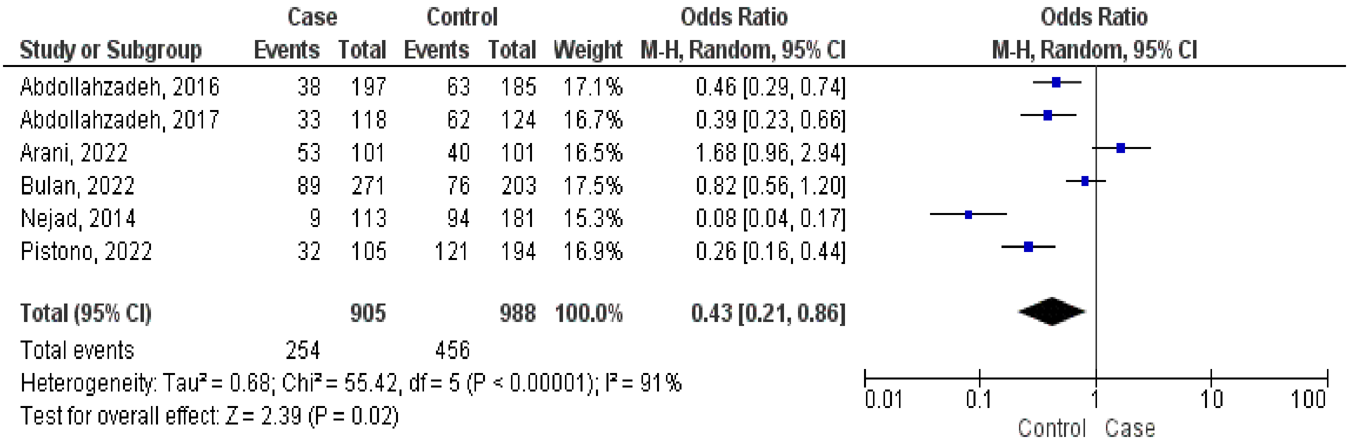


Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdollahzadeh, 2016	79	197	42	185	21.0%	2.28 [1.46, 3.56]
Abdollahzadeh, 2017	24	118	13	124	13.4%	2.18 [1.05, 4.52]
Arani, 2022	8	101	16	101	10.4%	0.46 [0.19, 1.12]
Bulan, 2022	72	271	34	203	20.7%	1.80 [1.14, 2.84]
Nejad, 2014	60	113	60	181	19.9%	2.28 [1.41, 3.70]
Pistono, 2022	20	105	20	194	14.7%	2.05 [1.05, 4.01]
Total (95% CI)		**905**		**988**	**100.0%**	**1.80 [1.26, 2.56]**
Total events	263		185			

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 11.11$, df = 5 ($P = 0.05$); $I^2 = 55\%$

Test for overall effect: Z = 3.26 (P = 0.001)

Figure 2. Forrest plot of association between VDR TaqI polymorphysm and MS susceptibility**.** C vs T (Allele) The pooled OR is 1.45 [1.02, 2.05], suggesting a statistically significant association (Z = 2.09, P = 0.04). However, the analysis shows considerable heterogeneity ($I^2 = 83\%$), indicating substantial variability among the included studies

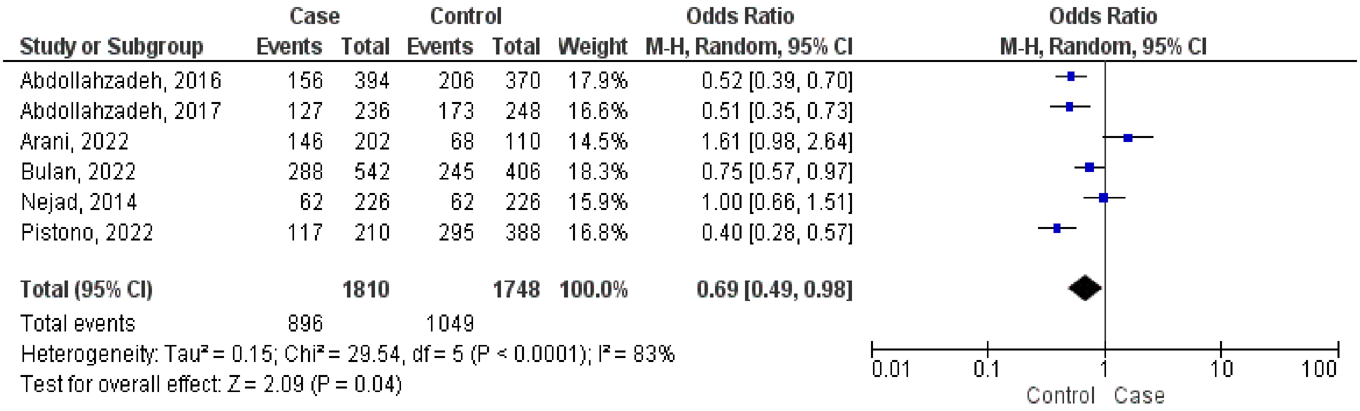


Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdollahzadeh, 2016	38	197	63	185	17.1%	0.46 [0.29, 0.74]
Abdollahzadeh, 2017	33	118	62	124	16.7%	0.39 [0.23, 0.66]
Arani, 2022	53	101	40	101	16.5%	1.68 [0.96, 2.94]
Bulan, 2022	89	271	76	203	17.5%	0.82 [0.56, 1.20]
Nejad, 2014	9	113	94	181	15.3%	0.08 [0.04, 0.17]
Pistono, 2022	32	105	121	194	16.9%	0.26 [0.16, 0.44]
Total (95% CI)		**905**		**988**	**100.0%**	**0.43 [0.21, 0.86]**
Total events	254		456			

Heterogeneity: $Tau^2 = 0.68$; $Chi^2 = 55.42$, df = 5 ($P < 0.00001$); $I^2 = 91\%$

Test for overall effect: Z = 2.39 (P = 0.02)

Figure 3. Forrest plot of association between VDR TaqI polymorphysm and MS susceptibility. TT vs TC + CC (Genotype) The pooled OR is 0.43 [0.21, 0.86], suggesting a statistically significant protective effect (Z = -2.39, P = 0.02). However, there is substantial heterogeneity among the studies ($Tau^2 = 0.68$, $Chi^2 = 55.42$, df = 5, $P < 0.00001$; $I^2 = 91\%$), indicating considerable variability in the results

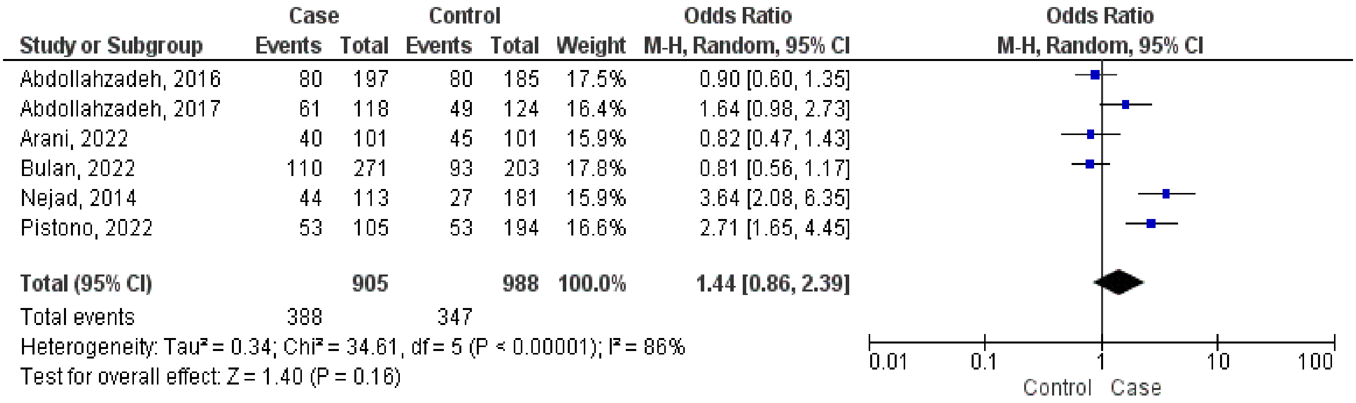


Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdollahzadeh, 2016	156	394	206	370	17.9%	0.52 [0.39, 0.70]
Abdollahzadeh, 2017	127	236	173	248	16.6%	0.51 [0.35, 0.73]
Arani, 2022	146	202	68	110	14.5%	1.61 [0.98, 2.64]
Bulan, 2022	288	542	245	406	18.3%	0.75 [0.57, 0.97]
Nejad, 2014	62	226	62	226	15.9%	1.00 [0.66, 1.51]
Pistono, 2022	117	210	295	388	16.8%	0.40 [0.28, 0.57]
Total (95% CI)		**1810**		**1748**	**100.0%**	**0.69 [0.49, 0.98]**
Total events	896		1049			

Heterogeneity: Tau² = 0.15; Chi² = 29.54, df = 5 (P < 0.0001); I² = 83%

Test for overall effect: Z = 2.09 (P = 0.04)

Figure 4. Forrest plot of association between VDR TaqI polymorphysm and MS susceptibility. T vs C (Allele) The pooled OR is 0.69 [0.49, 0.98], suggesting a statistically significant association (Z = 2.09, P = 0.04)



Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdollahzadeh, 2016	80	197	80	185	17.5%	0.90 [0.60, 1.35]
Abdollahzadeh, 2017	61	118	49	124	16.4%	1.64 [0.98, 2.73]
Arani, 2022	40	101	45	101	15.9%	0.82 [0.47, 1.43]
Bulan, 2022	110	271	93	203	17.8%	0.81 [0.56, 1.17]
Nejad, 2014	44	113	27	181	15.9%	3.64 [2.08, 6.35]
Pistono, 2022	53	105	53	194	16.6%	2.71 [1.65, 4.45]
Total (95% CI)		**905**		**988**	**100.0%**	**1.44 [0.86, 2.39]**
Total events	388		347			

Heterogeneity: Tau² = 0.34; Chi² = 34.61, df = 5 (P < 0.00001); I² = 86%

Test for overall effect: Z = 1.40 (P = 0.16)

Figure 5. Forrest plot of association between VDR TaqI polymorphysm and MS susceptibility. TC vs TT + CC (Genotype) The pooled OR is 1.44 [0.86, 2.39], suggesting a possible association, but the result is not statistically significant (Z = 1.40, P = 0.16). Additionally, the analysis shows considerable heterogeneity (I² = 86%), indicating substantial variability among the included studies

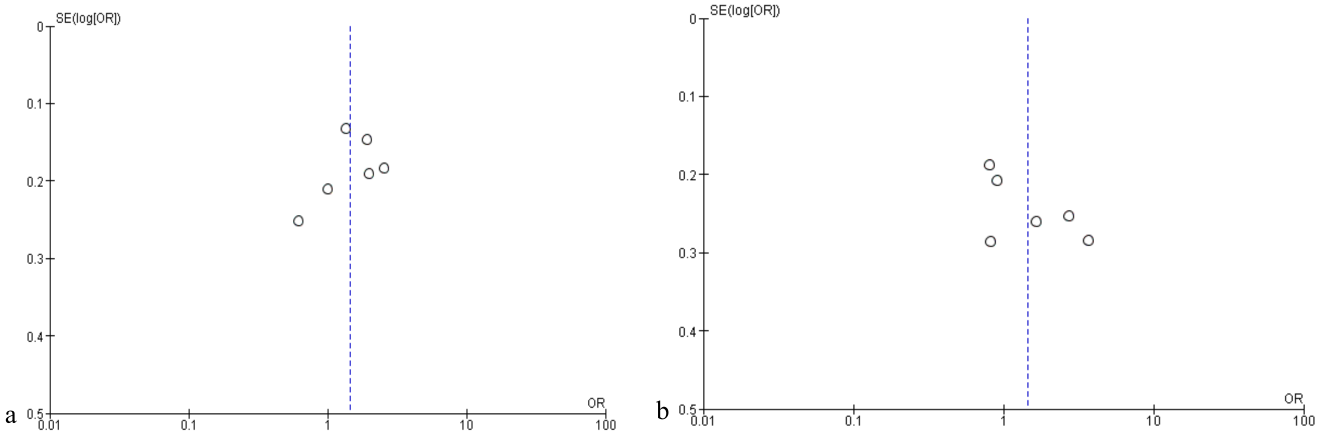


Figure 6. Funnel plot of association between TaqI gene polymorphisms and Multiple Sclerosis. a) C vs T funnel plot, used in meta-analysis to assess the presence of publication bias. The X-axis represents the Odds Ratio (OR) on a logarithmic scale (ranging from 0.01 to 100), indicating the effect size of different studies. The Y-axis represents the standard error of the log (OR), where smaller values indicate larger sample sizes and greater precision The dashed vertical line around OR = 1 represents the overall effect estimate in the meta-analysis. The distribution of the points appears symmetrical, no significant publication bias b) TC vs TT + CC symmetrically distributed, no substantial publication bias

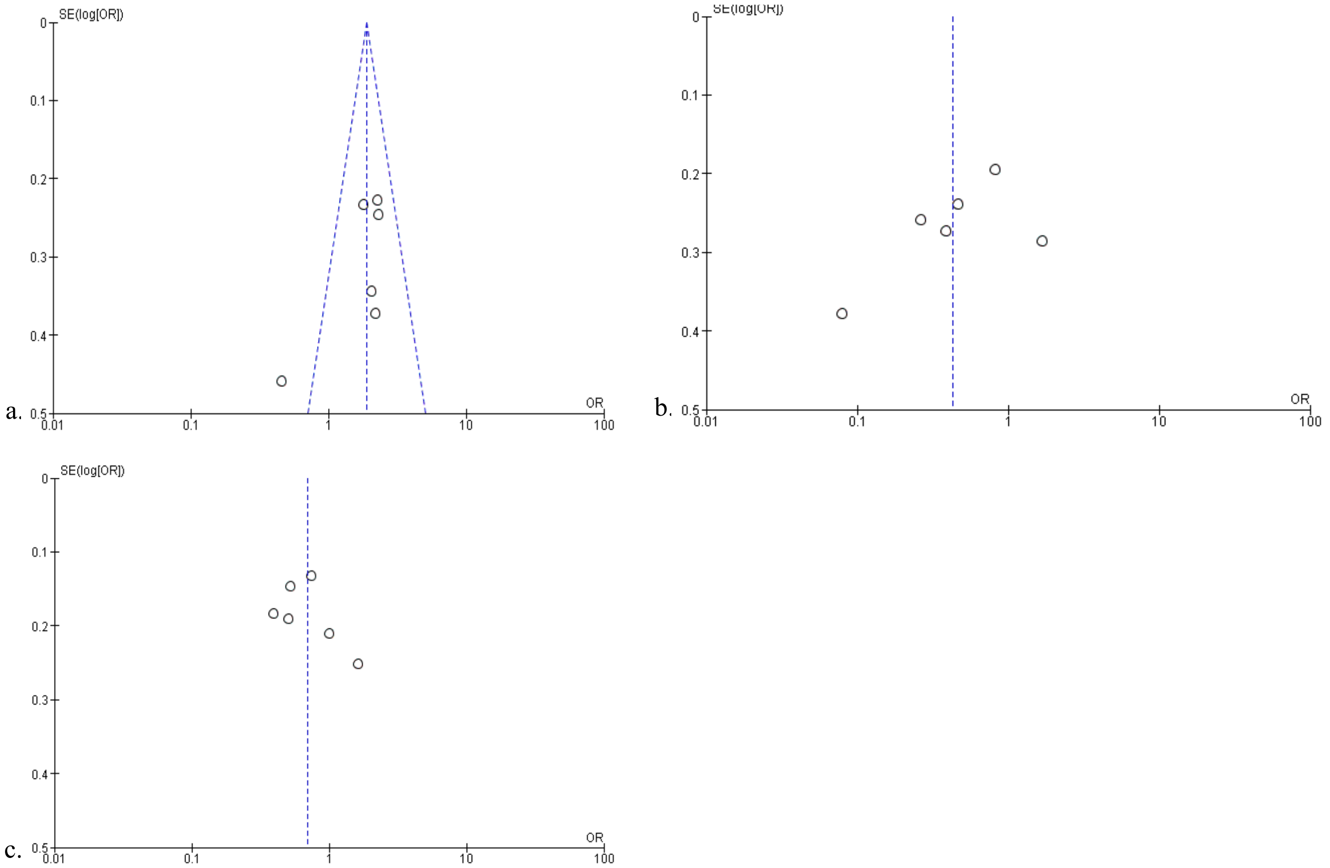


Figure 7. Funnel plot of association between TaqI gene polymorphisms and Multiple Sclerosis. a) CC vs TC + TT In this plot, one study appears to be an outlier on the left side, suggesting potential asymmetry. This could indicate possible publication bias or heterogeneity among the studies.; b) TT vs TC + CC The distribution of points appears asymmetrical, with more studies on the left side, which may suggest potential publication bias or heterogeneity among studies; c) T vs C The studies appear symmetrically distributed, suggesting no strong indication of publication bias

Discussion

This study is the first systematic review to assess the association of VDR polymorphisms with MS. We conducted a systematic review and meta-analysis of the available literature with the aim of evaluating the association between VDR gene polymorphisms and MS. A total of six studies were used in this study, which focused on the TaqI (rs731236) polymorphism. Pooled OR results from models showed a significant association between VDR polymorphisms and MS. The Funnel plot showed publication bias in some genotypes and alleles.

Pathogenesis of Multiple Sclerosis (MS) involves a complex interaction between the immune system and the central nervous system (CNS), leading to inflammation and demyelination.[20] The role of genetics in the pathogenesis of MS is well-documented, but environmental factors, such as vitamin D, also play an essential role in MS development. Vitamin D is known to have immunomodulatory effects, influencing autoimmune processes involved in MS. The VDR functions as a receptor for vitamin D, regulating the expression of genes involved in immune regulation, including T-cells, which are key players in immune responses to pathogens or damaged cells.[17] Polymorphisms in the VDR gene can alter the body's response to vitamin D, contributing to increased susceptibility to MS.

In this meta-analysis, we found that variations in the TaqI (rs731236) polymorphism in the VDR gene were significantly associated with an increased or decreased risk of MS. Specifically, the genotype TT vs TC + CC was associated with a reduced risk of MS, while CC vs TT + TC was associated with an increased risk of MS. These findings are consistent with earlier research indicating that the TaqI (rs731236) polymorphism can affect VDR function, thereby modulating immune activity and influencing MS development. The TaqI (rs731236) polymorphism impacts the stability of VDR mRNA, which in turn can affect the body's response to vitamin D.

Previous studies have shown that vitamin D deficiency plays a role in the development of various autoimmune diseases, including MS. For example, research by Li et al. (2018) demonstrated a significant association between the FokI polymorphism and the incidence of MS, as well as several types of cancer.[18] Moreover, a study by Imani et al. (2019) found that the TaqI polymorphism is linked to an increased risk of MS,[17] further supporting the role of vitamin D and VDR in MS susceptibility.[19] Additionally, variations in VDR can influence the immune system's response to vitamin D, impacting immune regulation and autoimmune disease progression.

This study demonstrates several strengths. It was designed as a systematic review and meta-analysis, which provides a higher level of evidence by synthesizing data across multiple studies. It adhered to the PRISMA 2020 guidelines to ensure methodological transparency and rigor. However, several limitations must be acknowledged. The number of included studies was relatively small (six studies, comprising 868 cases and 982 controls), which may limit the generalizability of the results. Significant heterogeneity was observed across studies, reducing the consistency of the conclusions.

In conclusion, this meta-analysis highlights the significant association between VDR gene polymorphisms and MS susceptibility across various genetic models, particularly the TaqI polymorphism. These findings suggest that vitamin D's role in immune regulation could be pivotal in MS development, and future studies considering gene-environment interactions could provide deeper insights into this relationship.

Conclusion

In conclusion, this meta-analysis identified a significant association between VDR gene polymorphisms and susceptibility to MS. Future studies incorporating gene-environment interactions are warranted to elucidate further the relationship between VDR gene polymorphisms and the risk of multiple sclerosis.

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