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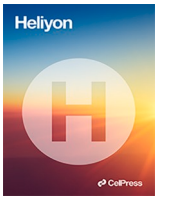

Association of vitamin D levels and VDR variant (rs2228570) with allergic rhinitis: A meta-analysis and trial sequential analysis

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ABSTRACT

Background: Allergic rhinitis (AR) is a most common allergic condition characterised by cough, sneezing and flu-like symptoms. The aetiology of AR is not known. A deficiency of vitamin D has been associated with various allergic diseases. The role of vitamin D in allergic rhinitis has been explored in different populations, but the results remained inconsistent. Furthermore, vitamin D exerts its effect through the vitamin D receptor (VDR), and genetic variations in the VDR gene significantly alter vitamin D. We performed a meta-analysis to investigate the role of vitamin D levels and VDR polymorphisms with a predisposition to the development of AR.

Materials and methods: All published articles were searched using databases such as PubMed, Google Scholar, and Science Direct. Based on rigorous inclusion and exclusion, appropriate studies were identified. Vitamin D levels, VDR genotype and allele frequencies were extracted from the eligible reports. The meta-analysis was performed by comprehensive meta-analysis software v3.3.

Results: The present meta-analysis comprised 14 reports with 1504 AR patients and 1435 healthy controls. Compared to healthy controls, AR had significantly lower levels of vitamin D ($P = 0.000$, standard difference of means $= -1.287$, 95% CI $= -1.921$ to -0.652). The meta-analysis of two separate investigations, which included 917 cases and 847 controls, showed no predisposition to allergic rhinitis. The trial sequential analysis also demonstrated the need for future case-control studies of VDR polymorphism to examine their involvement in AR.

Conclusions: Lower vitamin D levels are associated with allergic rhinitis, and vitamin D supplementation might be advantageous in addition to standard treatment. The connection of VDR polymorphism (rs2228570) remained equivocal, and additional research is needed.

Summary: Vitamin D exerct its beneficial effect through the vitamin D receptor (VDR) and role of vitamin D and VDR variant in the allergic rhinitis has been contradictories. We performed a meta-analysis to draw a definitive conclusion of importance of vitamin D and VDR polymorphisms in predisposition to development of allergic rhinitis. The observations of the meta-analysis revealed a significant association of lower vitamin D with allergic rhinitis. In addition the VDR rs2228570 variant predisposed subject to develop rhinitis. Collectively, the results of the present investigation redirect requirement of individualized vitamin D supplementation in the management of allergic rhinitis.

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1. Introduction

Allergic rhinitis (AR) is characterised by cough, sneezing, nasal itching, snoring, nasal discharge, nasal congestion and flu-like symptoms due to the mucosal inflammation mediated by immunoglobulin E after exposure of nasal mucosa to allergens [1]. Allergic rhinitis is a worldwide health issue, impairing the quality of life of those affected [2]. A recent study revealed that the median prevalence of AR is 18.1% of the global population, and the incidence of AR increases with time [3]. The aetiology of AR is unknown; however, environmental factors, genetic factors and interactions among them attributed to the risk factors for its pathogenesis [4].

Vitamin D is a crucial immunomodulator that has been shown to play a significant role in different allergic conditions [5]. Vitamin D deficiency has been associated with an increase in the occurrence of allergies in western countries [6], and vitamin D deficiency has been associated with atopy, asthma, and food allergies [7–9]. Several investigations have been carried out in different populations to explore the possible link between vitamin D and AR; however, the results remained contradictory. Although vitamin D deficiency has been related to susceptibility to AR in a wide range of populations [10–19], there are reports highlighting the absence of a link between vitamin D and allergic rhinitis [20,21]. Furthermore, another study in Pakistanis [10] found that 10% of AR had adequate vitamin D levels compared to 26% of healthy controls, but the difference was not statistically significant.

Vitamin D exhibits its immunomodulatory effects by signalling through the vitamin D receptor (VDR). Genetic variations in the VDR gene influenced vitamin D signalling by altering the expression of the VDR gene or structural changes of the VDR protein [22]. In the VDR gene, four common genetic variants (rs731236, rs1544410, rs7975232, and rs2228570) have been widely investigated for their association with different allergic conditions [23]. However, studies on the role of VDR polymorphisms in AR are limited. A hospital-based case-control study investigated the association of four common VDR variants (rs9729, rs2228570, rs1544410, and rs731236) with a predisposition to allergic rhinitis and noticed a protective role of VDR rs2228570 (GA and GA + AA genotypes) against AR in the Chinese population [24]. In contrast, another study in a similar population revealed increased susceptibility of the AA genotype for AR [25].

Previous research on the impact of vitamin D levels and VDR polymorphisms in AR has been inconsistent. The conflicting results among the studies have been attributed to smaller sample sizes, varying ethnicity or inclusion of inappropriate clinically defined patients and controls. A meta-analysis is a valuable tool for increasing the power of the study by statistically combining similar reports' data [26]. We performed a meta-analysis of eligible published articles in the current study to establish a valid conclusion on the connection of vitamin D levels and VDR polymorphisms with the risk of AR.

2. Materials and methods

2.1. Literature search

All authors independently searched multiple databases, including PubMed, ScienceDirect, Scopus, and Google Scholar, for relevant articles to include in the present meta-analysis. Various keywords such as "vitamin D", "vitamin D3", "VDR", "vitamin D receptor", "polymorphism", "rhinitis", "allergic rhinitis", "case-control study", "rs2228570", "rs731236", "rs1544410", and "rs7975232" were used to explore various databases. The most recent database search was conducted on November 28, 2022.

2.2. Inclusion and exclusion criteria for the current meta-analysis

Before conducting the meta-analysis, the following inclusion and exclusion criteria were fixed to ensure the rigour of the analysis. The inclusion criteria were: (1) a case-control study that included information on vitamin D levels in individuals with rhinitis and healthy controls; (2) well-defined clinical rhinitis and healthy controls; (3) data on the prevalence of VDR polymorphisms (rs2228570, rs731236, rs1544410, and rs7975232) in patients and controls for genetic association investigations; (4) the genotype distribution of VDR polymorphisms in controls must adhere to the Hardy-Weinberg equilibrium (HWE); (5) articles must be published in English. The exclusion criteria were as follows: (1) reviews and case studies; (2) reports lacking information on healthy controls; (3) studies using human or animal cell lines; (4) publications lacking genotype or allele information; (5) the genotype distribution in healthy controls deviating from HWE; and (6) papers published in languages other than English.

2.3. Extraction of data

Two authors separately retrieved data from the relevant papers. The first author's name, the year the study was published, the vitamin D levels in rhinitis patients and controls, expressed as mean ± standard deviation or median (interquartile range), the genotype and allele frequency of the VDR polymorphism, the name of the country, and the total number of rhinitis patients and controls, were all noted from each qualifying study.

2.4. Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess each article's quality based on the subjects chosen for enrollment, comparability, and study findings [27]. Two authors independently reviewed the papers to determine the NOS score. The clinical outcome was given a score of 0–3 stars, the subject comparison was assigned a score of 0–2 stars, and the subject selection was given a score of 0–4 stars. A study that received five stars or more was deemed moderate or good quality [27].

2.5. Statistical analysis

The individual included study's power was measured using GPower v3.1 software [28]. The meta-analysis was carried out using the Comprehensive meta-analysis v3.3.070 programme. Data on median and interquartile range numbers were transformed into mean ± SD format. For each comparison model, a funnel plot and Egger's regression analysis were carried out to examine the publishing bias [29]. The Q statistics, P heterogeneity value, and I^2 value calculations were used to investigate heterogeneity among the included studies [30]. Heterogeneity is shown by substantial P values ($P < 0.05$) and I^2 values of more than 50%. A random (heterogeneous) or fixed (homogeneous) model was used for the meta-analysis in accordance with the findings of the heterogeneity study. Using the continuous variable structure of the Trial sequential Analysis (TSA) software, the impact of vitamin D levels on rhinitis was investigated. Probability values, 95% confidence intervals, and standard differences in mean were computed. Dichotomous data analysis was used to investigate the relationship between the VDR polymorphism and the likelihood of developing rhinitis. The odds ratio, probability value, and 95% confidence interval (CI) were obtained. Sensitivity analysis was performed by omitting one study at a time while doing the meta-analysis to examine the strength of the meta-analysis. All tests with probability values less than 0.05 were considered significant. An in-house Microsoft Excel application reviewed the distribution of VDR genotypes in the healthy controls for the Hardy-Weinberg equilibrium.

3. Results

3.1. Literature search and eligible studies

Various databases were searched for published articles on the role of vitamin D levels and VDR variants with allergic rhinitis. Details are shown in the PRISMA flow chart (Fig. 1). A total of 39,242 articles were found for vitamin D levels, and 10,238 reports were available on the role of VDR polymorphism with rhinitis. Based on inclusion and exclusion criteria, a total of 14 studies were included in the present meta-analysis to study the role of vitamin D in rhinitis (case: 1504 and controls: 1435) (Table 1), and only two reports (cases: 917, controls: 847) for investigation on the genetic association of VDR polymorphism with susceptibility to rhinitis development (Table 2). All included reports were under power to detect a possible link between vitamin D levels and rhinitis. The power analysis of the individual study was performed by a post hoc analysis with a minimal effect size of 0.20 and an alpha error probability

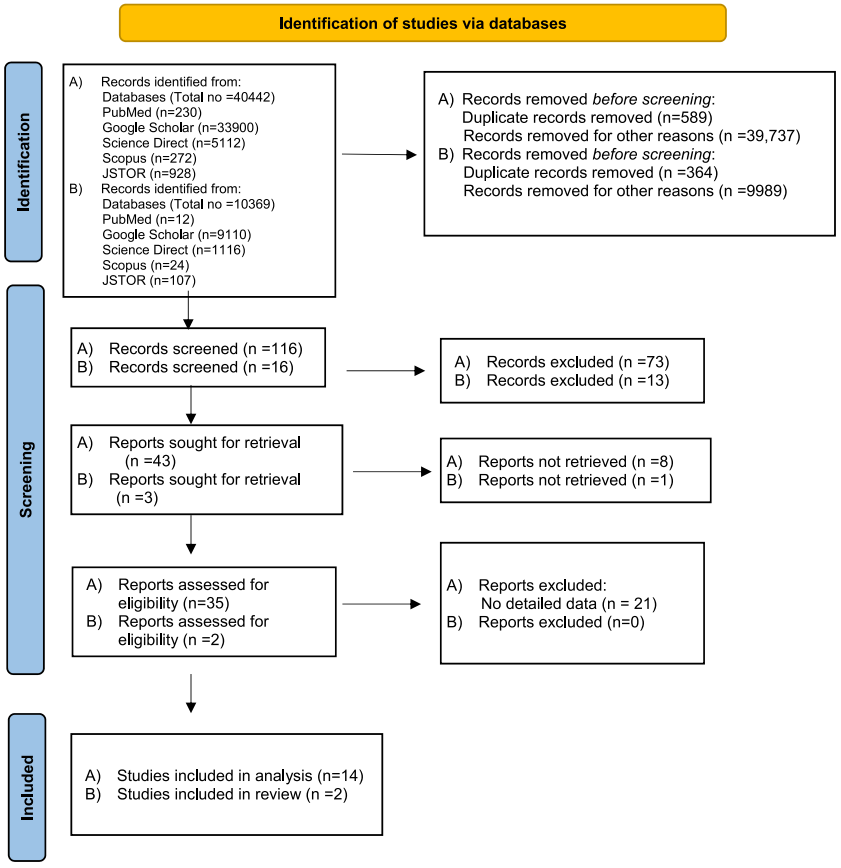

Fig. 1. Studies inclusions and exclusions flow of the present meta-analysis. Note: A) mean vitamin D levels, B) VDR polymorphisms.

Table 1
Details of the eligible studies on the role of vitamin D and allergic rhinitis.

Author details and year of publication	Country	Sample size (n)		serum 25(OH)D level (ng/mL)				Power of the study (%)
		Case	Control	Case		Control		
				Mean	SD	Mean	SD	
Ansari et al., 2019 [10]	Pakistan	50	50	14.8	7.4	19.1	6.6	16.7
Awan et al., 2021 [11]	Pakistan	112	112	16.24	6.7	26.92	3.5	31.9
Bavi et al., 2019 [12]	Iran	186	172	12.11	1.43	35.9	3.87	47
Agarwal et al., 2019 [18]	India	38	40	20.15	10.26	27.94	13.38	14
Coban et al., 2019 [19]	Turkey	86	43	19.33	21.86	28.36	52.38	18.6
Demir et al., 2018 [13]	Turkey	125	131	25.5	3.74	31.58	3.85	35.7
Dogru et al., 2016 [14]	Turkey	76	65	18.07	6.1	24.03	9.43	21.7
Lee et al., 2015 [15]	Korea	59	63	19	8.5	26.9	10.7	19.4
Ma et al., 2020 (a) [16]	China	160	158	17.5	6.47	19.4	7.82	42.7
Ma et al., 2020 (b) [16]	China	136	142	16.64	6.68	19.28	8.91	38.2
Ma et al., 2020 (c) [16]	China	359	382	16.89	6.38	18.47	8.03	77.5
Wu et al., 2017 [21]	China	32	25	24.25	31.06	34.18	49.9	11.4
Wang et al., 2019 [20]	China	25	21	48.94	12.1	54.1	17.1	10.1
Thakur et al., 2020 [17]	India	60	31	14.6	7.68	29.36	7.49	14.5

Table 2
Details of studies included for investigating the role of VDR (rs2228570) polymorphism with allergic rhinitis.

First author and year	Country	Healthy Control (n)	GG	GA	AA	HWE (P-value)	Rhinitis cases (n)	GG	GA	AA	Power of the study (%)
Tian et al., 2015 [24]	China	447	115	226	106	0.806	517	147	261	109	80
Zhang et al., 2020 [25]	China	400	216	150	34	0.278	400	167	147	86	71.7

Note: HWE: Hardy-Weinberg equilibrium.

of 0.05. However, after the inclusion of all studies for meta-analysis, the study's power was increased to 99.97%. Similarly, for the VDR polymorphism, the minimal effect size was fixed at 0.10, and the alpha error probability was 0.05. The power analysis revealed that the reports by Tian et al. [24] and Zhang et al. [25] had 80% and 71.7% power to detect possible association of VDR polymorphism (rs2228570), respectively, with rhinitis and it became 96.66% after compiling data of both studies for the meta-analysis (Table 1).

3.2. Publication bias

Begg's funnel plot and Egger's regression analysis were performed to investigate the publication bias in the included reports. In the funnel plot, the log odds ratio was plotted against the standard error of individual studies. The funnel plots analysis revealed no publication bias in investigating vitamin D levels with rhinitis (data not shown). In addition, Egger's regression investigation for vitamin D levels revealed an absence of publication bias (intercept: −9.19, 95% confidence interval: −18.60 to 0.20, P value: 0.054). However, a publication bias investigation for the association of VDR polymorphisms with rhinitis could not be performed as only two eligible studies were enrolled in the present meta-analysis.

3.3. Heterogeneity investigation

The Cochrane Q and I^2 statistics were used to assess heterogeneity among the included reports. A fixed (homogeneous) or random (heterogeneous) model was used for the meta-analysis based on the heterogeneity test results. Significant heterogeneity was observed while investigating the association of vitamin D levels with rhinitis (Q = 738.83, $P_{heterogeneity}$ = 0.000, I^2 = 96.240); thus random model was employed for the meta-analysis. Similarly, for the association of VDR polymorphism (rs2228570), all genetic comparison models demonstrated significant heterogeneity (G vs A: Q = 23.13, $P_{heterogeneity}$ = 0.000, I^2 = 95.67; GG vs AA: Q = 22.94, $P_{heterogeneity}$ = 0.000, I^2 = 95.64; AG vs AA: Q = 8.85, $P_{heterogeneity}$ = 0.003, I^2 = 88.70; AG + GG vs AA: Q = 21.41, $P_{heterogeneity}$ = 0.000, I^2 = 95.33; GG vs AG + AA: Q = 9.56, $P_{heterogeneity}$ = 0.002, I^2 = 89.54) leading to use of the random model for the current meta-analysis.

3.4. Vitamin D levels and rhinitis

As per the inclusion and exclusion criteria, fourteen studies with a total of 1504 rhinitis patients and 1435 healthy controls were evaluated for the current meta-analysis to investigate the possible connection of vitamin D levels with the development of rhinitis. As shown in Fig. 2A, the rhinitis patients displayed significantly lower vitamin D levels than healthy controls (P = 0.000, the standard difference of means = −1.287, 95% CI = −1.921 to −0.652), indicating an essential role of vitamin D in the pathogenesis of rhinitis.

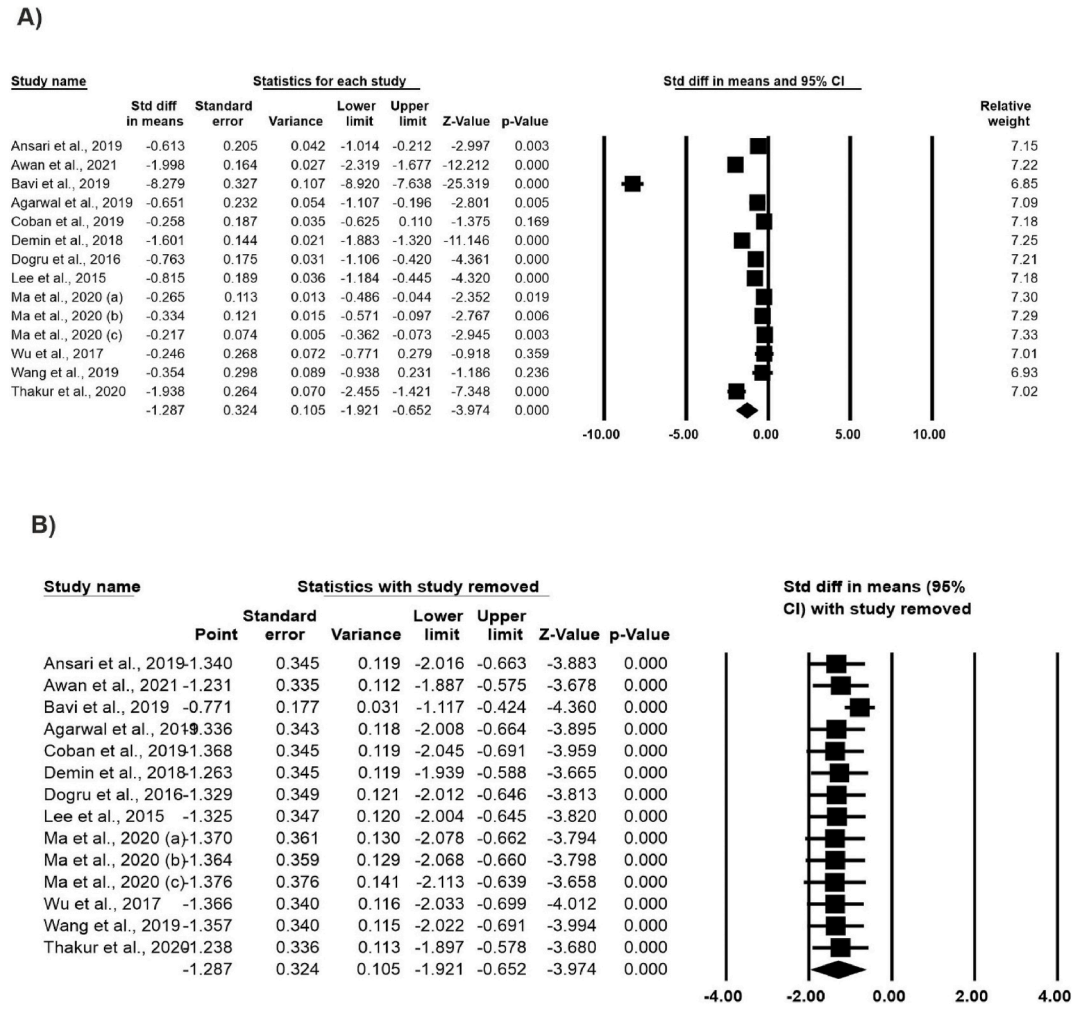

Fig. 2. Association of vitamin D levels with the development of allergic rhinitis. All eligible studies were analyzed in the present meta-analysis by comprehensive meta-analysis v3. (A) Forest plot showing significantly diminished vitamin D levels in AR cases compared to healthy controls. (B) Sensitivity analysis plot indicating the robustness of the meta-analysis.

Furthermore, we investigated the robustness of the present meta-analysis by sensitivity analysis. In sensitivity analysis, data from one study is omitted, and meta-analysis is performed, with the findings compared to the original meta-analysis. As shown in Fig. 2B, the sensitivity analysis revealed no significant variation in the meta-analysis results when one study was excluded at a time, indicating the robustness of the current meta-analysis.

3.5. Association of VDR rs2228570 polymorphism with rhinitis

The association of VDR (rs2228570) polymorphism with susceptibility to the development of rhinitis was explored by including two eligible studies comprising 917 cases and 847 controls. As shown in the Fig. 3A–E, all genetic comparison models failed to demonstrate a possible association with susceptibility to rhinitis. Furthermore, to validate the robustness of the present meta-analysis, the exclusion of Tian et al. study revealed a significant association with the development of rhinitis in allele contrast, homozygous comparison, dominant and recessive genetic comparison models (Fig. 3F–J).

3.6. Trial sequential analysis

An efficient way to figure out whether a meta-analysis has enough studies with enough cases and controls to produce a conclusive result is the TSA. We performed the TSA in the data used for meta-analysis in the dominant genetic model. As shown in Fig. 4A, the cumulative z-curve for the VDR rs2228570 polymorphism neither passed the alpha monitoring boundary nor the futility boundary nor approached the requisite information size line, indicating that further studies are needed to make a firm conclusion.

In the TSA plot for the vitamin D levels in patients and controls, the cumulative z-curve crossed the monitoring boundary and

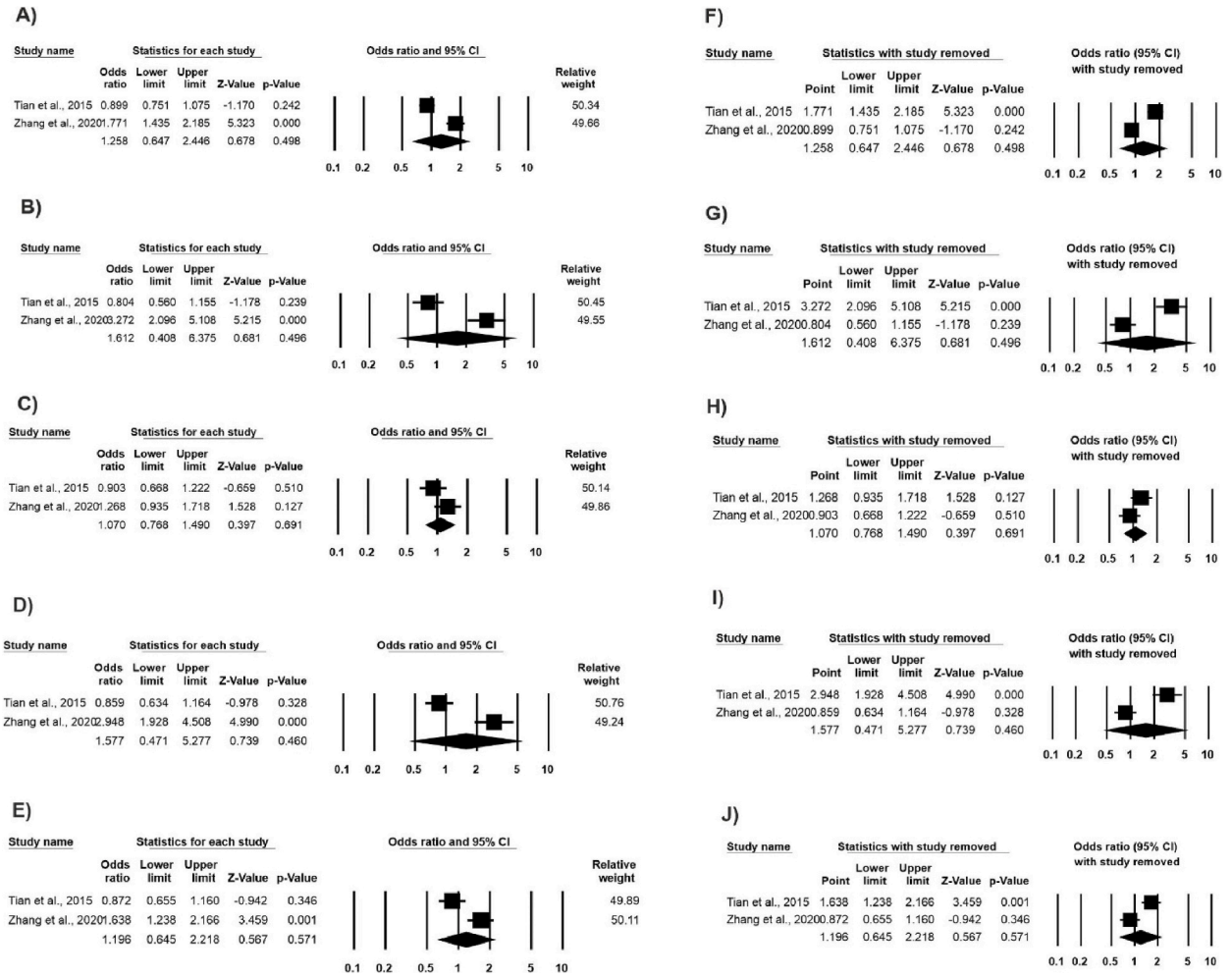

Fig. 3. Forest and sensitivity analysis plot for VDR polymorphism (rs2228570) association with allergic rhinitis. (A–E) The combined odds ratio, 95% confidence interval and p-values were calculated for all five genetic comparison models (A: allele contrast, B: homozygous comparison, C: heterozygous comparison, D: Dominant model, E: recessive comparison model). A p-value less than 0.05 was taken as significant. All analysis was performed in Comprehensive meta-analysis v3 software (Biostat Inc. USA). Sensitivity analysis was performed for all five genetic comparison models to test the meta-analysis's robustness (F: allele contrast, G: homozygous comparison, H: heterozygous comparison, I: Dominant model, J: recessive comparison model).

reached the required information size (Fig. 4B) indicating enough studies have already been considered for the meta-analysis, and the conclusion drawn by the present study is robust.

4. Discussion

The current meta-analysis found a strong association between low vitamin D levels and rhinitis. However, a meta-analysis of VDR polymorphisms (rs2228570) found no significant connection between the mutation and rhinitis development. Furthermore, the TSA argued that the number of case-control studies for both VDR (rs2228570) polymorphism has been insufficient and that more research is needed to draw a definite conclusion on the significance of the VDR variants in rhinitis.

Although the exact aetiology of the development of AR is not clear, it is believed that environmental and host genetic factors play a major role in predisposition to the development of AR [31]. AR is characterised by the predominant type 2 immune response with the proliferation of $CD4^+$ T cells, which has been linked with the disease severity [32]. In addition, elevated Th17 and IL17 and lower Treg cells have been reported in the AR cases [33]. As the vitamin D effectively suppresses $CD4^+$ T cells proliferation [34], maintains optimum levels of Th17 cells [35] and increased Treg cells in circulation [36], several studies have been performed in different population to explore the role of vitamin D in AR, however, those remained contradictories. In the present meta-analysis, we observed significantly diminished plasma vitamin D levels in AR patients compared to healthy controls, indicating beneficial role of vitamin D against AR development. In line with the present observation, an earlier meta-analysis reported a lower prevalence of subjects with serum 25-(OH) D $\geq$ 75 nmol/L in AR compared to those with 25 (OH)D $<$ 50 nmol/L in men only [37]. However, mean vitamin D levels

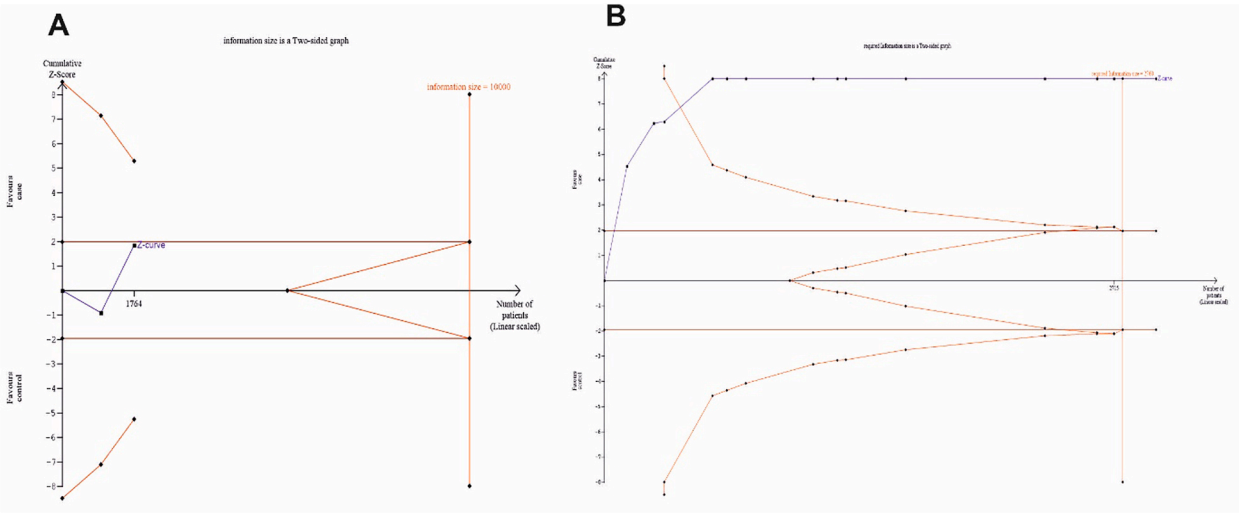

Fig. 4. Trial sequential analysis of the vitamin D levels and VDR (rs2228570) polymorphism association with rhinitis. (A) Assocaition of VDR polymorphisms with predisposition to development of rhinitis and (B) vitamin D levels in rhinitis versus healthy controls. The Z-value is the test statistic, and $|Z| = 1.96$ corresponds to a $P = 0.05$; the higher the Z-value, the lower the P-value. The trial sequential alpha monitoring borders are indicated on the left by the red, downward-sloping lines. The red, outward-sloping lines on the right represent the futility region. The cumulative z-curve is shown as a solid blue line. A horizontal red line indicates information size. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

in AR cases and healthy controls were available for three reports only [37]. Another independent meta-analysis failed to demonstrate the association between vitamin D and AR by comprising data from seven reports, including adults' and children's samples [38]. The present meta-analysis has several advantages over previous reports: 1) includes a larger number of cases and controls, and 2) considers only adults AR cases. The observation of the present study directs towards the execution of randomised placebo-controlled clinical trials of the role of vitamin D supplementation for the treatment of AR in larger cohorts. However, reports including a limited sample size (Bakhshaee et al., 2019; Liu et al., 2020) on vitamin D supplementation showed a positive role of vitamin D in improving clinical symptoms.

Variations in the vitamin D receptor gene have been linked with the differential immunomodulation effect of vitamin D [39]. However, reports on the genetic association between common VDR polymorphisms (rs2228570, rs731236, rs1544410, and rs7975232) with a predisposition to the development of AR are very limited. The present meta-analysis comprising data from two independent studies from the Chinese population revealed no significant contribution of VDR rs2228570 polymorphism with a predisposition to AR. However, the TSA demonstrated the consideration of a very limited number of samples and controls for the meta-analysis suggesting further studies are required to draw a definitive conclusion about the role of VDR in susceptibility to AR.

Although the current meta-analysis effectively proved the significance of vitamin D levels in the development of rhinitis and could not decode the link between the VDR (rs2228570) mutation and rhinitis susceptibility, it has several limitations. First, the literature search parameters were limited to English, which increased the likelihood that papers published in other languages would be excluded. Second, in the present meta-analysis, PubMed, Google Scholar, and Science Direct were used to search for eligible published articles, which enhances the likelihood of omitting studies indexed in other databases. Thirdly, there were very few investigations on VDR polymorphisms. Fourthly, meta-regression analysis was unable to be conducted in this inquiry due to the lack of baseline data in all included reports.

5. Conclusions

Low vitamin D levels are linked with rhinitis. VDR (rs2228570) polymorphism is not associated with susceptibility to develop rhinitis; nevertheless, the number of studies included in the present meta-analysis is insufficient to draw a valid conclusion; additional case-control studies are necessary.

Ethics approval statement

Not applicable for the present report.

Author contribution statement

Fei Ju: Performed the experiments, Analyzed and interpreted the data and wrote paper; Ruonan Zhu: Conceived and designed the experiments, Performed the experiments, Analyzed and interpreted the data and wrote paper.

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Data availability statement

All data are already provided in the manuscript. For further if any may put a request to the corresponding author.

Patient consent statement

Not applicable.

Permission to reproduce material from other sources

Not applicable.

Clinical trial registration

Not required for the present report.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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