Vitamin D level in rheumatoid arthritis and its correlation with the disease activity: a meta-analysis

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Abstract

Objective

This study aimed to evaluate the relationship between the 25-hydroxyvitamin D [25(OH)D] level and rheumatoid arthritis (RA) and the correlation between serum vitamin D level and RA activity.

Methods

We searched the PUBMED, EMBASE, and Cochrane databases and performed a meta-analysis examining the vitamin D level and prevalence of vitamin D deficiency in patients with RA compared to healthy controls and the correlation coefficients between the vitamin D level and disease activity score 28 (DAS28) in RA patients.

Results

Fifteen studies that included a total of 1,143 RA patients and 963 controls were available for this meta-analysis. The meta-analysis showed that the serum vitamin D level in the RA group was significantly lower than that in the control group (SMD=–0.608, 95% CI=–1.105–[–0.017], p=0.017). In addition, the prevalence of vitamin D deficiency was significantly higher in the RA group than in the control group (55.2% vs. 33.2%; OR = 2.460, 95% CI = 1.135–5.332, p=0.023). Thirteen studies evaluated the correlation between the vitamin D level and its activity in 924 RA patients. Meta-analysis showed a significant inverse correlation between the vitamin D level and DAS28 (Correlation coefficient =–0.278, 95% CI =–0.393–[–0.153], p=1.8 x 10^{-5}).

Conclusion

Our meta-analysis demonstrates that serum vitamin D level is significantly low in patients with RA, vitamin D deficiency is prevalent in RA patients compared to controls, and the vitamin D level correlates inversely with RA activity. Our meta-analysis suggests that the vitamin D level is associated with susceptibility to RA and RA activity.

Key words

vitamin D, deficiency, rheumatoid arthritis, activity

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that predominantly affects the synovial joints, causing significant morbidity and shortened life expectancy (1). Although its cause is not fully understood, it has been established that genetic and environmental factors contribute to the pathogenesis of RA (2).

Vitamin D (25-hydroxyvitamin D [25(OH)D]) alters the expression of genes that affect cellular functions such as proliferation, differentiation, apoptosis, and angiogenesis (3). It is known that 1,25-dihydroxy vitamin D_3 [$1,25(OH)_2$ D_3] inhibits IFN-γ · secretion and negatively regulates IL-12 production by downregulating NF-kB (4). When administered *in vivo*, $1,25(OH)_2$ D_3 was found to have a preventative effect on autoimmune diseases (5), and other studies have revealed that vitamin D deficiency is linked to many autoimmune diseases (6, 7). The action of vitamin D is dependent on vitamin D receptor (VDR), and activation of VDR results in inhibition of pro-inflammatory T cells and DC differentiation. Furthermore, VDR agonists induce T regulator and natural killer cells and thus suppress autoimmunity (8), and the VDR polymorphism has been known to confer susceptibility to RA (9).

A low vitamin D level may increase the RA risk (10). However, studies on vitamin D level in RA patients compared to healthy controls and on the relationship between serum vitamin D levels and RA activity have shown mixed results (11-24). The reasons for this disparity may be small sample sizes, low statistical power, and/or clinical heterogeneity (25-27). Therefore, in order to overcome the limitations of individual studies, we turned to meta-analysis. The present study aimed to determine serum vitamin D concentrations and prevalence of vitamin D deficiency in RA patients compared to healthy controls as well as evaluate its correlation with disease activity using the meta-analysis approach.

Materials and methods

Identification of eligible studies and data extraction

We performed a literature search for studies that examined vitamin D status in RA patients and controls and the relationship between serum vitamin D levels and RA activity. The PUBMED, EMBASE, and Cochrane databases were searched to identify all available articles (up to July 2015). The following key words and subject terms were used in the search: "vitamin D," "level," "deficiency", "rheumatoid arthritis," and "RA." All references cited were also reviewed to identify additional studies not indexed by the electronic databases. Studies were considered eligible if: (1) they were case-control studies with patients with RA diagnosed on the basis of diagnosed according to ACR 1987 or ACR/EULAR classification criteria; (2) they provided data on vitamin D levels and/or vitamin D deficiency in case and control groups; or (3) they provided data on the correlation efficient between serum vitamin D levels and RA activity based on disease activity score 28 (DAS28). Disease activity is classified based on the DAS28 value as remission (<2.6), low (2.6 to <3.2), moderate (≥3.2 to 5.1), and high (≥5.1) (28). Course of disease, whether or not being new patients, immunosuppression, hormone or calcium treatment maybe have effect on the relationship between vitamin D level and RA, and may cause heterogeneity to affect the authenticity of testing results. However, for inclusion criteria, we did not limit studies based on this information in order to include as many studies as we can to examine a generalised finding. We excluded studies if: (1) they contained overlapping or insufficient data; or (2) they were reviews or case reports. The following information was extracted from each study: first author, year of publication, country, ethnicity, number of participants, age, vitamin D level, vitamin D deficiency, cut-off level, and correlation coefficients between the vitamin D level and DAS28. We scored the quality of each included study based on the Newcastle-Ottawa Scale (29). The highest score was 9, and a score in the 6–9 range was considered to be of high methodological quality.

Evaluation of statistical associations

We performed meta-analyses examining the relationship between serum 25(OH)

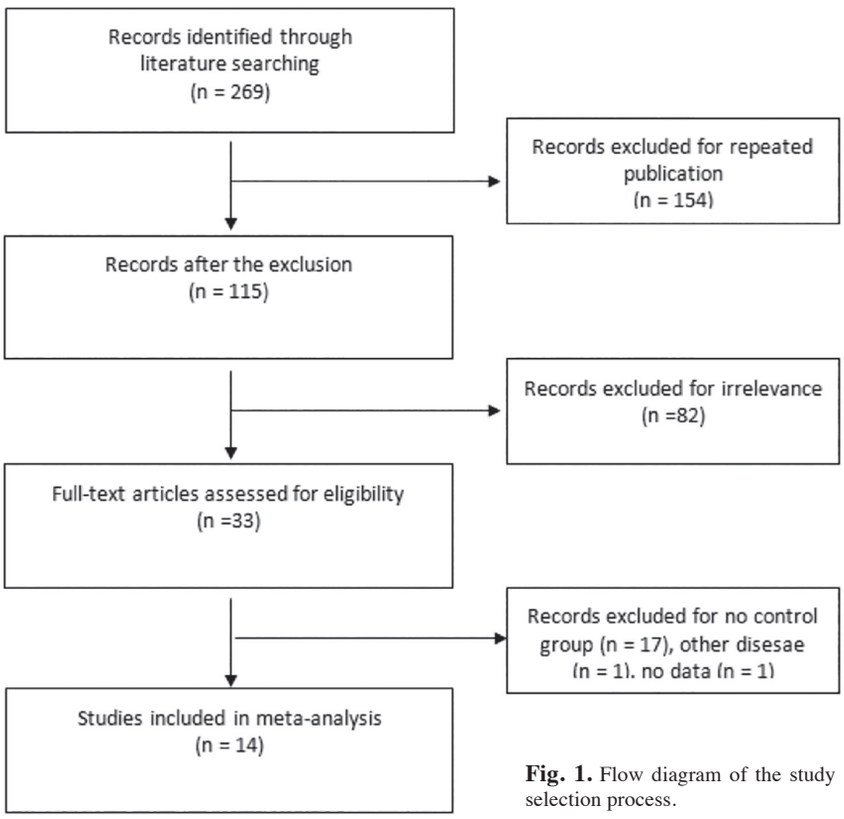

Fig. 1. Flow diagram of the study selection process.

D level level and RA, between vitamin D deficiency and RA, and correlation coefficient between vitamin D level and DAS28. The serum 25(OH)D level is a reliable indicator of vitamin D status. For continuous data, results were presented as standardised mean differences (SMDs) and 95% confidence intervals (CIs), and odds ratios (ORs) and 95% CIs were calculated for dichotomous data. We assessed within- and between-study variations and heterogeneities using Cochran's Q-statistics (30). When the significant Q-statistic (p<0.10) indicated heterogeneity across studies, the random effects model was used for the meta-analysis (31), and if not, the fixed effects model was used. The fixed effects model assumes that all studies estimate the same underlying effect and considers only within-study variation (30). We quantified the effect of heterogeneity using I^2 value, where I^2 measures the degree of inconsistency between (32). Statistical manipulations were undertaken using the Comprehensive Meta-Analysis computer programme (Biosta, Englewood, NJ).

Evaluation of heterogeneity, sensitivity test, and publication bias

To examine potential sources of heterogeneity observed in the meta-analysis, meta-regression analysis was performed using the following variables: ethnicity, publication year, age, sample size, DAS28, and study quality. A sensitivity test was performed by comparing the random and fixed effects models. Sensitivity analysis was also performed to assess the influence of each individual study on the pooled OR by omitting each study individually. While funnel plots are often used to detect publication bias, they require diverse study types of varying sample sizes, and the interpretation of the plots involves subjective judgment. Considering this, we evaluated publication bias using Egger's linear regression test (33), which measures funnel plot asymmetry using a natural logarithm scale of ORs.

Results

Studies included in the meta-analysis

We identified 269 studies using electronic and manual searching methods,

Table I. Characteristics of individual studies included in the meta-analysis.

Authors	Country	Number of patients		Age (SD)		Vitamin D level (nmol/l or ng/ml)		Vitamin D deficiency		Cut-off (ng/ml)	Correlation coefficient	DAS28	Quality
		RA	Control	RA	Control	RA	Control	RA	Control				
Wen, 2015 (24)	China	132	100	39 (13.27)	37 (10.17)	15.32	40.53	na	na	na	–0.323	4.7 (1.23)	5
Grazio, 2015 (11)	Croatia	53	29	62.0 (9.9)	68.2 (6.6)	36.18	32.99	21	11	10	na	5.1 (1.2)	5
Brance, 2015 (12)	Argentina	34	41	52.2 (1.9)*	54.8 (1.7)*	20.40	26.30	12	17	20	na	4.0 (0.2)	9
Sharma, 2014 (13)	India	80	80	40.97 (12.52)	42.63 (12.66)	17.20	23.39	na	na	na	–0.604	5.06 (1.61)	9
Hong, 2014 (14)	China	130	80	54 (14)	54 (13)	43.12	57.93	85	26	20	–0.43	4.95 (2.11)	9
Chen, 2014 (15)	China	110	110	59.48 (11.41)	56.92 (10.51)	14.27	20.85	na	na	na	–0.325	4.43 (0.74)	9
Gheita, 2014 (16)	Egypt	63	62	41.59 (9.69)	39.66 (9.77)	23.11	32.59	32	8	20	–0.34	4.91 (0.71)	9
Sahebari, 2014 (17)	India	99	68	43.94 (14.31)	39.87 (13.41)	83.74	46.53	na	na	na	0.11	4.45 (1.67)	6
Atwa, 2013 (18)	Saudi Arabia	55	40	45.60 (12.41)	45.00 (7.99)	15.45	24.55	47	16	20	–0.104	4.76 (1.29)	7
Yazmalar, 2013 (19)	Turkey	71	70	45.30 (10.55)	41.39 (4.21)	27.85	22.62	na	na	na	–0.099	na	6
Baykal, 2012 (20)	Turkey	55	45	na	na	12.20	19.30	na	na	na	–0.15	5.4 (3.2)	9
Kostoglou, 2012 (21)	Greece	44	44	na	na	15.26	25.80	na	na	na	–0.084	4.26 (0.26)	9
Attar, 2012 (22)	Saudi Arabia	100	100	47 (13)	47 (15)	32.30	31.40	43	39	10	–0.42	4.6 (2)	9
Cutolo-1, 2006 (23)	Italy	53	64	58.5 (1.1)*	59.9 (0.98)*	65.20	68.90	na	na	na	–0.57	3.48 (0.25)	8
Cutolo-2, 2006 (23)	Estonia	64	30	56.3 (2.3)*	40.6 (3.8)*	54.50	43.30	na	na	na	–0.04	4.19 (1.24)	8

SD: Standard deviation; *: Standard error; DAS: Disease activity score; na: Not available.

Table II. Meta-analysis of vitamin D level (A) and vitamin D deficiency (B) in RA patients and the correlation coefficient between vitamin D level and RA activity (C).

A.Vitamin D level in RA

Comparison	No. of studies	No. of patients		Test of association			Test of heterogeneity			Publication bias *p*-value
		RA	Control	SMD	95% CI	*p*-value	Model	*p*-value	I^2	
Vitamin D level	15	1,143	963	–0.608	–1.105–(–0.017)	0.017	R	0.000	96.5	0.310

SMD: Standard mean difference; CI: Confidence interval; R: Random effects model; DAS: Disease activity score.

B. Vitamin D deficiency in RA

Comparison	No. of studies	No. of patients		Test of association			Test of heterogeneity			Publication bias *p*-value
		RA	Control	OR	95% CI	*p*-value	Model	*p*-value	I^2	
Vitamin D deficiency	6	435	352	2.460	1.135–5.332	0.023	R	0.000	83.0	0.744

OR: Odds ratio; CI: Confidence interval; R: Random effects model.

C. Inverse correlation between the vitamin D level and DAS28

Comparison	No. of studies	No. of RA patients	Test of association			Test of heterogeneity			Publication bias p-value
			Correlation coefficient	95% CI	*p*-value	Model	*p*-value	I^2	
Correlation coefficient	13	1,056	–0.278	–0.393–(–0.153)	1.8×10^{-5}	R	0.000	77.0	0.475

CI: Confidence interval; R: Random effects model; DAS: Disease activity score.

and 33 of these were selected for full-text review based on the title and abstract. Nineteen of these were excluded, because they had data on other diseases, no control group, or no vitamin D data. Thus, 14 articles met the inclusion criteria (11-24). One of the eligible studies contained data on two different groups (23), and these were treated independently. Thus, 15 comparisons were considered in the meta-analysis, which consisted of 1,143 patients and 963 controls (Table I). Fifteen of these studies examined the vitamin D level in the RA and control groups; 13 studies provided correlation coefficients between the vitamin D level and DAS28, and six of these studies provided the frequency of vitamin D deficiency in the RA and control groups. The quality assessment score of each study ranged from 5 to 9. Table I shows the characteristic features of the studies' participants as well as the studies' reported quality assessments.

Meta-analysis of vitamin D level and deficiency prevalence in RA patients

Serum vitamin D level was found to be inversely associated with RA. It was significantly lower in the RA group than in the control group [SMD = -0.608, 95% CI = -1.105–(-0.017), p=0.017] (Table II, Fig. 2). In addition, the prevalence of vitamin D deficiency was significantly higher in the RA group than in the control group (55.2% *vs*. 33.2%; OR = 2.460, 95% CI = 1.135–5.332, p=0.023) (Table II, Fig. 2).

Meta-analysis of the correlation between vitamin D levels and RA activity

Meta-analysis of correlation coefficients showed a significant negative correlation between vitamin D level and DAS28 [Correlation coefficient = -0.278, 95% CI = -0.393–(-0.153), p=1.8x10^{-5}] (Table II, Fig. 2). The meta-analysis revealed that vitamin D levels were inversely associated with RA activity based on DAS28.

Heterogeneity, sensitivity test, and publication bias

Between-study heterogeneity was identified during the meta-analyses of the vitamin D levels in RA patients (Table II). Meta-regression analysis showed that sample size (p<0.001), ethnicity (p<0.001), and publication year (p<0.001), but not age, study quality, and DAS28, had a significant impact on the heterogeneity in the meta-analysis of the vitamin D levels in RA patients (Table III). Sensitivity analysis showed that random and fixed effects model results provided the same interpretation, and no individual study significantly affected the pooled OR, indicating that the results of this meta-analysis are robust (Table III). Funnel plots to detect publication bias showed symmetry, and Egger's regression analysis showed no evidence of publication bias for the meta-analyses of vitamin D addressed (Egger's regression test p-values >0.1) (Fig. 3, Table II).

Discussion

Given the immunosuppressive effects of vitamin D and the potential link between vitamin D deficiency and autoimmune diseases (34), vitamin D has been studied as a potential player in the pathogeneses of autoimmune diseases including RA (10). Our previous meta-analysis has shown that individu-

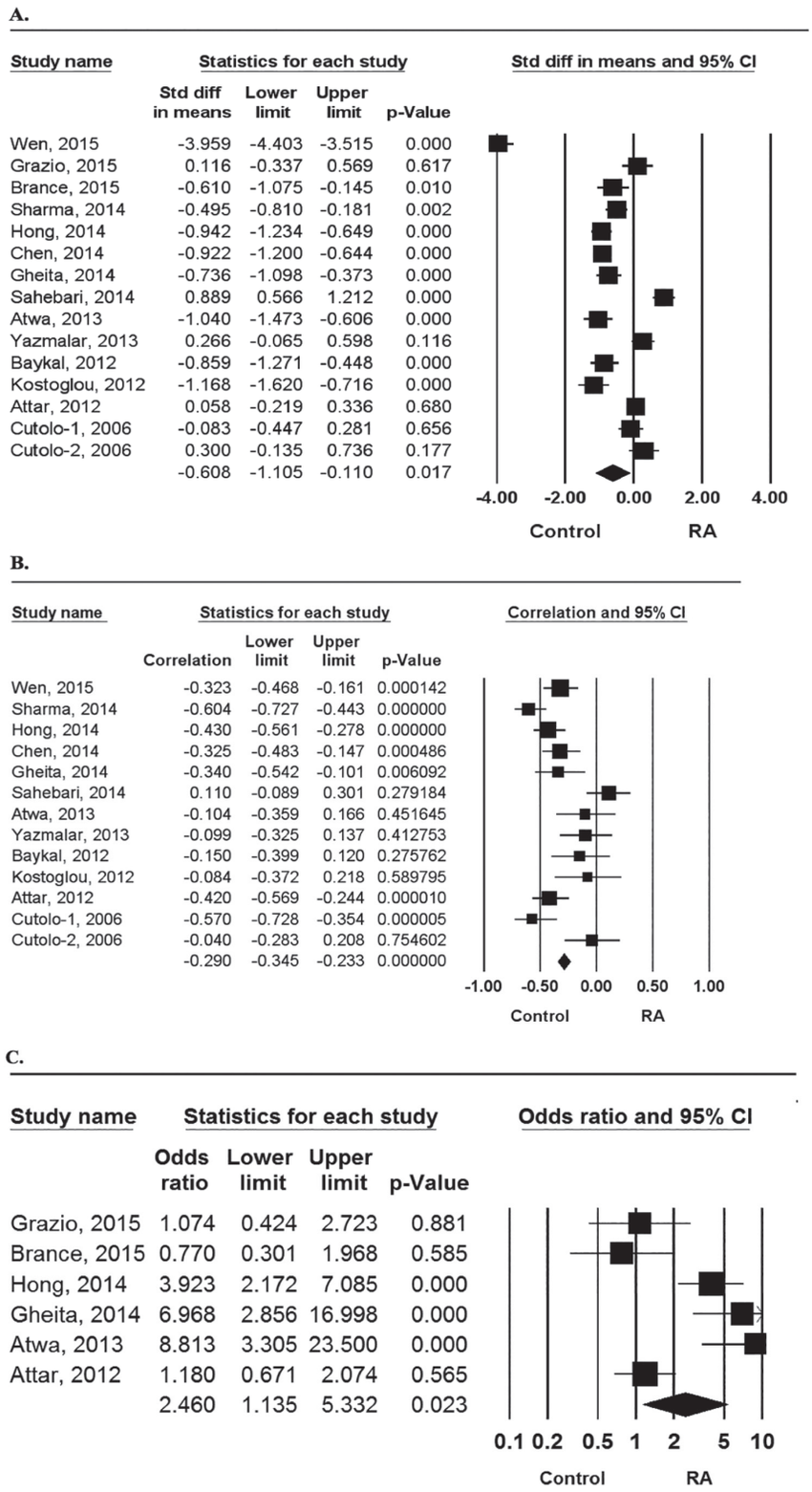

Fig. 2. Meta-analysis of the relationship between vitamin D level and RA (A), linear regression on correlation coefficient between vitamin D level and RA activity (B), and vitamin D deficiency and RA (C).

als in the highest total vitamin D intake group were found to have a 24.2% lower risk of developing RA than those in the lowest group, supporting the notion that low vitamin D intake is associated with the risk of RA (35). In addition, we revealed a significant association between VDR polymorphism and RA, suggesting that the VDR FokI F allele may be a risk factor for RA (36).

In this meta-analysis, we showed that the serum vitamin D level was significantly low in the RA group compared to the control group, and the prevalence of vitamin D deficiency was significantly higher in the RA group than in the control group (55.2% *vs*. 33.2%). In addition, vitamin D had an inverse correlation with RA activity. These meta-analysis data suggest that vitamin D level is associated with the development and activity of RA.

Vitamin D deficiency has been linked to the pathogenesis of autoimmune diseases, and a low vitamin D level has been considered as a risk factor in the development of RA (10). Vitamin D inhibits the differentiation of monocytes to DCs, and therefore, reduces the number of antigen presenting cells available to stimulate T cells, which are believed to play a key role in RA (8). In addition, vitamin D inhibits B cell proliferation before differentiation to immunoglobulin-secreting cells and consequently reduces immunoglobulin production (37), and contributes to immune tolerance by affecting both the innate and adaptive immune responses (10). Vitamin D deficiency may be one of the several environmental factors for RA risk.

Current evidence may provide the rationale for vitamin D supplementation in the treatment of RA. However, little is known about how vitamin D intake modifies the risk and activity of RA, although increased vitamin D intake has been shown to be associated with a lower risk of contracting other autoimmune diseases (34). Vitamin D supplementation is known to prevent disease progression in mice with collagen-induced arthritis (38). More studies are needed to demonstrate the clinical benefits of vitamin D supplementation in the treatment of RA.

The present study has some shortcomings that should be considered. First, most of the studies included in this meta-analysis had small sample sizes, and only a small number of studies evaluated the prevalence of vitamin D deficiency in RA patients and controls. Thus, the meta-analysis of the prevalence of vitamin D deficiency may

Table III. Sensitivity analysis of the meta-analysis comparing the random and fixed models (**A**) and meta-regression analysis of potential sources of heterogeneity in the meta-analysis of vitamin D level (**B**).

A. Sensitivity analysis

Comparison	Random effects model			Fixed effects model		
	Effect size	95% CI	*p*-value	Effect size	95% CI	*p*-value
Vitamin D level	–0.608*	–1.105–(–0.017)	0.017	–0.507*	–0.599–(–0.414)	$<1.0 \times 10^{-8}$
Correlation coefficient	–0.278	–0.393–(–0.153)	1.8×10^{-5}	–0.292	–0.345–(–0.233)	$<1.0 \times 10^{-8}$
Vitamin D deficiency	2.460**	1.135–(–5.332)	0.023	2.321**	1.707–(–3.156)	7.0×10^{-8}

*: Standard mean difference; **: Odds ratio; CI: Confidence interval

B. Meta-regression analysis

Covariates	Coefficient	SE	95% CI	p-value
Sample size	–0.328	0.063	–0.452–(–0.204)	<0.001
Ethnicity	0.236	0.054	0.129–0.343	<0.001
Publication year	–0.109	0.018	–0.146–(–0.073)	<0.001
Age	–0.007	0.044	–0.095–0.080	0.869
Study quality	–0.021	0.032	–0.085–0.043	0.520
DAS28	0.001	0.045	–0.088–0.091	0.972

DAS28: Disease activity score 28; SE: Standard error; CI: Confidence interval.

be underpowered. Second, the studies included in the meta-analysis were heterogeneous in demographic characteristics and clinical features. The heterogeneity and confounding factors such as climate, season, sun exposure, and nutritional status may have affected our results, which may be compounded by the limited information provided on clinical status and disease activity in the populations involved. This limited data did not allow further analysis, although we performed a sensitivity test and a meta-regression analysis. Third, in relating vitamin D level to RA disease activity, the association between vitamin D level and medications for RA treatment (*e.g.* methotrexate, hydroxychloroquine, corticosteroids) may exist (39). However, we could not adjust treatment medications for RA in this analysis due to insufficient information. Nevertheless, this meta-analysis also has its strengths. The number of patients from individual studies ranged from 34 to 132, but our pooled analysis included more than 1,100 patients. Our study was able to provide more accurate data by increasing the statistical power and resolution through pooling of the results of independent analyses.

In conclusion, our meta-analysis suggests that serum vitamin D level is low in RA, and vitamin D deficiency is frequent in RA patients compared to controls, and that an inverse relationship exists between serum vitamin D levels and RA activity. Our meta-analysis indicates that vitamin D plays a key role in the susceptibility and activity of RA. Further studies are necessary to elucidate that vitamin D status directly contributes to the pathogenesis of RA.

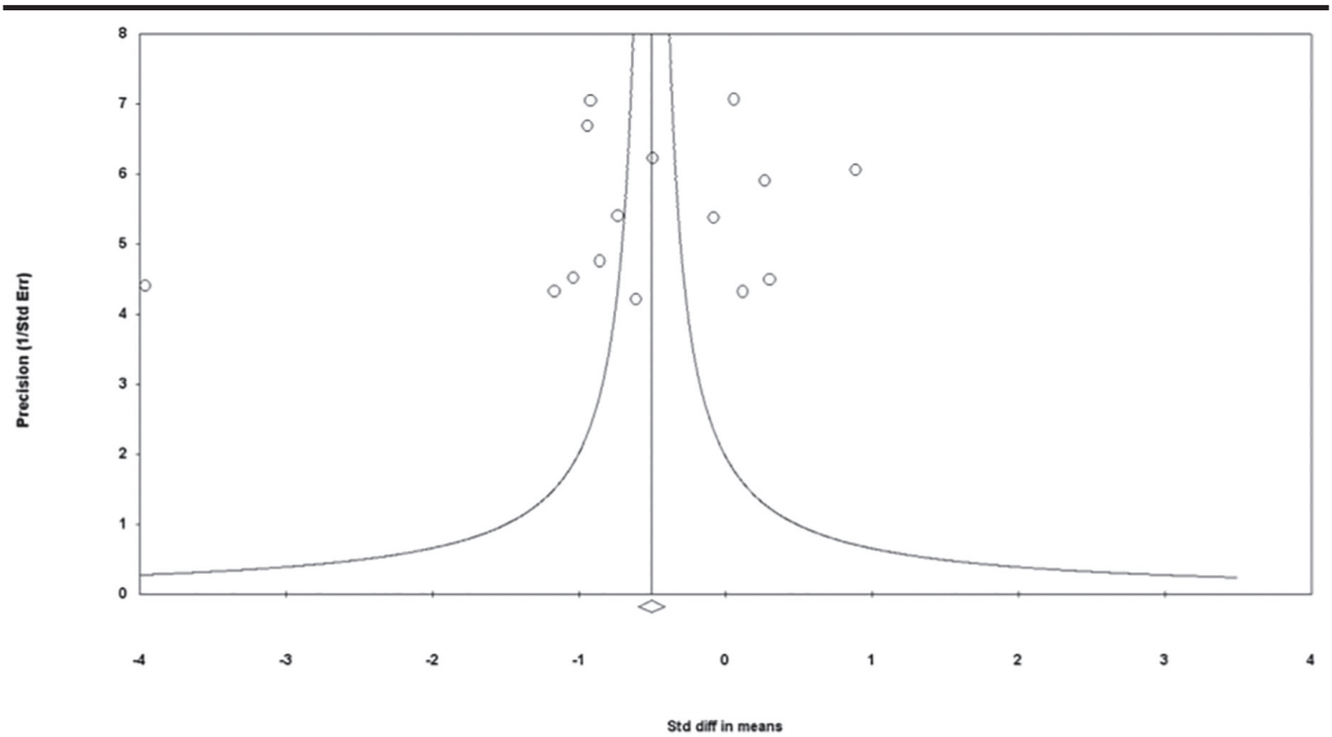

Fig. 3. Funnel plot of studies examining the relationship between vitamin D level and RA (Egger's regression *p*-values = 0.812).

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