

Role of vitamin D in chronic rhinosinusitis: a systematic review and meta-analysis study

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Background

Chronic rhinosinusitis (CRS) is one of the most common diseases with no specific long-term treatment. CRS can present in two phenotypes: chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP). Vitamin D (VD) is considered to have an immunomodulatory role, especially in allergic diseases. Recent studies have found that patients with CRS have VD level lower than normal, especially patients with CRSwNP.

Aim

The aim of this study was to systematically evaluate and find out whether there is a relationship between serum VD level and CRS and its phenotypes.

Materials and methods

Using Medline database, we conducted a systematic search to find all related articles published up to 31 August 2016 using the keywords Vitamin D, allergic rhinitis, CRSwNP, and CRSsNP and applying certain inclusion and exclusion criteria.

Results

Six articles were included with a total number of participants of 309 with serum VD level. Four comparisons were made. The first comparison showed no statistically significant difference in VD level between the CRSsNP and the control group. The second comparison showed a statistically significantly lower VD level in the CRSwNP group than in the control group. The third comparison showed a statistically significantly lower VD level in the CRSwNP than in the CRSsNP group. The last comparison showed no statistically significant difference in VD level between CRS with or without nasal polyps and controls.

Conclusion

VD level was significantly low in patients with CRSwNP, which might have a causative relationship. However, there was no relation between VD level and CRSsNP.

Keywords:

allergic rhinitis, chronic rhinosinusitis, nasal polyps, vitamin D

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Introduction

Chronic rhinosinusitis (CRS) is one of the most common diseases affecting people all over the world due to inflammation of the mucosal lining of the nose and paranasal sinuses. There is no specific long-term treatment for CRS, but different drugs and modalities are used to control the disease and decrease the attacks. Recent guidelines defined CRS on the basis symptoms, endoscopic examination, and radiological finding [1,2]. Pathological explanations of CRS are still unclear but most of the theories refer CRS to the interaction between host (human body) and the surrounding environment interaction [3,4]. CRS can be presented in two forms or phenotypes: chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP) [5].

Vitamin D (VD) was usually linked with bone mineralization, calcium level in plasma, and deposition

in bone, but now VD is considered to have an immunomodulatory role, especially in allergic diseases [6]. Low serum VD₃ level in the body is now considered as a risk factor for many immune-linked diseases such as allergic diseases – for example, asthma and recurrent upper respiratory tract infection [7]. VD₃ is initially generated in the skin through the nonenzymatic conversion of pro-VD₃ to pre-VD₃ [8]. The liver contains 25-hydroxylase enzyme, which is responsible for the conversion of pre-VD₃ to 25-hydroxy-vitamin D₃, the form that most accurately relates to skin and dietary exposure [9]. In the kidneys, 25-hydroxy-vitamin D₃ is converted to the active form of VD, which is 1,25-dihydroxy-vitamin D₃ [10]. Recent studies indicate that VD₃ has an important

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role in maintaining the skin healthy, reducing colonization of pathogens, and reducing sensitization in atopic dermatitis [11].

In a recent studies on CRS, Mostafa *et al.* [12] found that patients with CRS have VD level lower than normal, especially patients with CRSwNP and allergic fungal rhinosinusitis. Moreover, Stokes and Rimmer [13] showed that there is a significant relationship between low serum VD₃ and CRS with polyps.

Materials and methods

Using Medline database (<http://www.pubmed.com>), we conducted a systematic search to find all related articles published up to 31 August 2016 using the following keywords: vitamin D, allergic rhinitis, chronic rhinosinusitis with nasal polyps, and chronic rhinosinusitis without nasal polyps. All included articles were published in English language, conducted on humans, and measured serum VD₃ level in patients with CRS in two groups (CRSwNP and CRSsNP) and in the control group. Patients in the included studies were diagnosed with CRS based on symptomatology and/or computed tomography imaging, and did not receive any VD₃ supplementation. The control group was free of any otolaryngological diseases. Articles that did not fulfill one or more of the mentioned inclusion criteria and duplicated studies or studies that provided insufficient data were excluded. The following data were extracted from each included article in this study: author(s), number of participants, inclusion and exclusion criteria, method of VD₃ measurement, stated outcome measures, and results such as serum VD level in the CRSwNP, CRSsNP, and control groups.

Statistical analysis

Statistical analysis was performed using Comprehensive Meta-Analysis (version 2; Biostat, New Jersey, USA). The included studies were tested for heterogeneity of the estimates using the Cochran Q χ^2 -test and the I^2 index. In addition, effect size for continuous outcome measures was expressed as standardized mean difference (SMD) with its standard error and 95% confidence interval (95% CI) limits. Estimates from included studies were pooled using both the Mantel-Haenszel fixed-effects method and the DerSimonian Laird random-effects method. Publication bias was assessed through the examination of funnel plots. A two-sided P -value less than 0.05 denoted statistical significance.

Results

Over 100 000 articles were found using the search keywords. Of these articles; after screening the abstract; the full texts of 25 articles that were related to our study were reviewed by applying all inclusion and exclusion criteria. Only six articles matched our study design (Table 1) with a total of 309 participants; and the other studies were excluded.

The method of measuring serum VD₃ concentration varied among the studies, but all results were in ng/ml, except for the study by Mostafa *et al.* [12], which measured VD in nmol/l. An appropriate conversion method was used to unify all results in ng/ml. Mulligan *et al.* [16] divided the patients into two groups (cigarette smokers and noncigarette smokers). An appropriate statistical method was used for summation of the two groups to one group to match our study design. In our study, we extracted data from the included six studies measuring VD₃ levels in the three groups: the CRSwNP, CRSsNP, and control groups. A fourth group was made, the CRS group, from the summation of data of CRSwNP and CRSsNP using an appropriate statistical method. On the basis of these data, we made four comparisons: comparison of CRSsNP versus the control group; comparison of CRSwNP versus the control group; comparison of CRSwNP versus the CRSsNP group; and comparison of CRS with or without polyps versus the control group.

Results of comparison of the chronic rhinosinusitis without nasal polyps group versus the control group as regards vitamin D level

The comparison of the CRSsNP group versus the control group as regards VD level (Table 2) shows an evidence of substantial heterogeneity (Cochrane $Q=41.081$, $P<0.0001$, and $I^2=90.26\%$). Pooling of estimates using random-effects model (REF) shows a SMD of -0.156 (95% CI, $-1.129-0.816$), which was not statistically significant ($P=0.752$) (Fig. 1).

Table 1 Included articles in this study

References	Number of controls	Number of CRSsNP patients	Number of CRSwNP patients
Mulligan <i>et al.</i> [14]	14	20	9
Mulligan <i>et al.</i> [15]	14	17	5
Mulligan <i>et al.</i> [16]	21	40	45
Sansoni <i>et al.</i> [17]	12	30	14
Carroll <i>et al.</i> [18]	6	–	13
Mostafa <i>et al.</i> [12]	19	15	15
Total	86	122	101

CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.

The funnel plot for comparison of the CRSsNP group versus the control group as regards VD level shows that there is no evidence for publication bias (Fig. 2).

Results of comparison of the chronic rhinosinusitis with nasal polyps group versus the control group as regards vitamin D level

The comparison of the CRSwNP group versus the control group as regards VD level (Table 3) shows an evidence of

substantial heterogeneity (Cochrane $Q=76.330$, $P<0.0001$, and $I^2=93.45\%$). Pooling of estimates using REF shows a SMD of -1.645 (95% CI, -3.088 to -0.201), which is statistically significant ($P=0.026$) (Fig. 3).

The funnel plot for comparison of the CRSwNP group versus the control group as regards VD level shows that there is evidence for possible publication bias (Fig. 4).

Figure 1

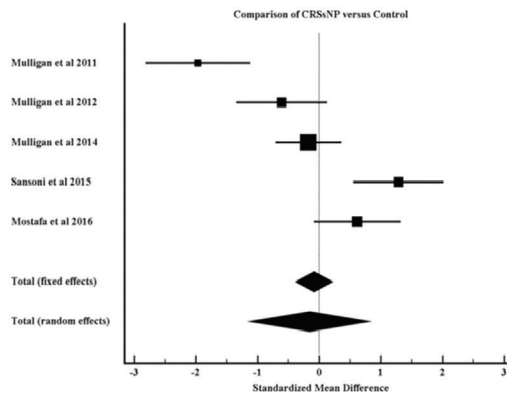


Figure (1): Forest plot for comparison of CRSsNP versus control regards vitamin D level.

Forest plot for comparison of the chronic rhinosinusitis without nasal polyps (CRSsNP) group versus the control group as regards vitamin D level

Figure 2

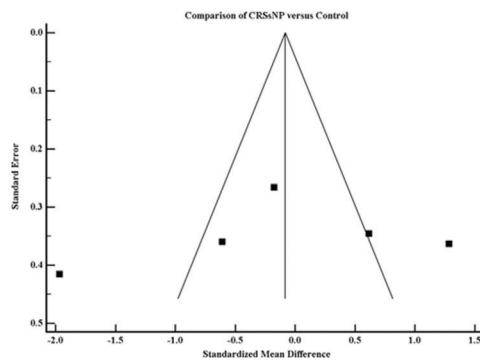


Figure (2): Funnel plot for comparison of CRSsNP versus control regards vitamin D level.

Funnel plot for comparison of the chronic rhinosinusitis without nasal polyps (CRSsNP) group versus the control group as regards vitamin D level

Table 2 Comparison of the chronic rhinosinusitis without nasal polyps group versus the control group as regards vitamin D level

References	CRSsNP	Control	Total	SMD	SE	95% CI	<i>t</i>	<i>P</i> -value
Mulligan <i>et al.</i> [14]	20	14	34	-1.966	0.415	-2.813 to -1.120		
Mulligan <i>et al.</i> [15]	17	14	31	-0.607	0.360	-1.343-0.129		
Mulligan <i>et al.</i> [16]	40	21	61	-0.175	0.267	-0.708-0.358		
Sansoni <i>et al.</i> [17]	30	12	42	1.284	0.363	0.550-2.019		
Mostafa <i>et al.</i> [12]	15	19	34	0.618	0.345	-0.086-1.322		
Total FEM	122	80	202	-0.083	0.152	-0.382-0.215	-0.550	0.583
Total REM	122	80	202	-0.156	0.493	-1.129-0.816	-0.317	0.752
Test for heterogeneity								
<i>Q</i>	41.081							
<i>d.f.</i>	4							
<i>P</i> -value	<0.0001							
<i>I</i> ² (inconsistency)	90.26%							
95% CI for <i>I</i> ²	80.17-95.22							

CI, confidence interval; CRSsNP, chronic rhinosinusitis without nasal polyps; FEM, fixed-effects method; REM, random-effects method; SMD, standardized mean difference.

Table 3 Comparison of the chronic rhinosinusitis with nasal polyps group versus the control as regards vitamin D level

References	CRSwNP	Control	Total	SMD	SE	95% CI	<i>t</i>	<i>P</i> -value
Mulligan <i>et al.</i> [14]	9	14	23	-7.951	1.243	-10.535 to -5.367		
Mulligan <i>et al.</i> [15]	5	14	19	-4.865	0.933	-6.834 to -2.897		
Mulligan <i>et al.</i> [16]	45	21	66	-0.916	0.273	-1.461 to -0.370		
Carroll <i>et al.</i> [18]	13	6	19	0.708	0.485	-0.316-1.731		
Sansoni <i>et al.</i> [17]	14	12	26	0.664	0.392	-0.145-1.473		
Mostafa <i>et al.</i> [12]	15	19	34	-0.137	0.338	-0.825-0.551		
Total FEM	101	86	187	-0.486	0.170	-0.821 to -0.152	-2.866	0.005
Total REM	101	86	187	-1.645	0.732	-3.088 to -0.201	-2.247	0.026
Test for heterogeneity								
<i>Q</i>	76.330							
<i>d.f.</i>	5							
<i>P</i> -value	<0.0001							
<i>I</i> ² (inconsistency)	93.45%							
95% CI for <i>I</i> ²	88.41-96.30							

CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; FEM, fixed-effects method; REM, random-effects method; SMD, standardized mean difference.

Figure 3

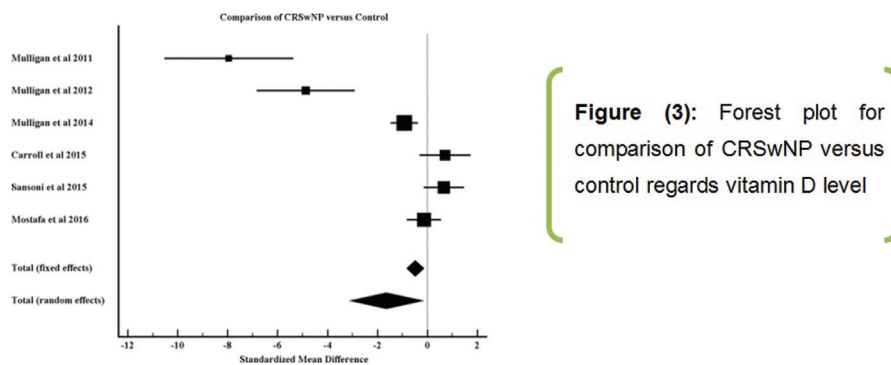


Figure (3): Forest plot for comparison of CRSwNP versus control regards vitamin D level

Forest plot for comparison of the chronic rhinosinusitis with nasal polyps (CRSwNP) group versus the control group as regards vitamin D level

Figure 4

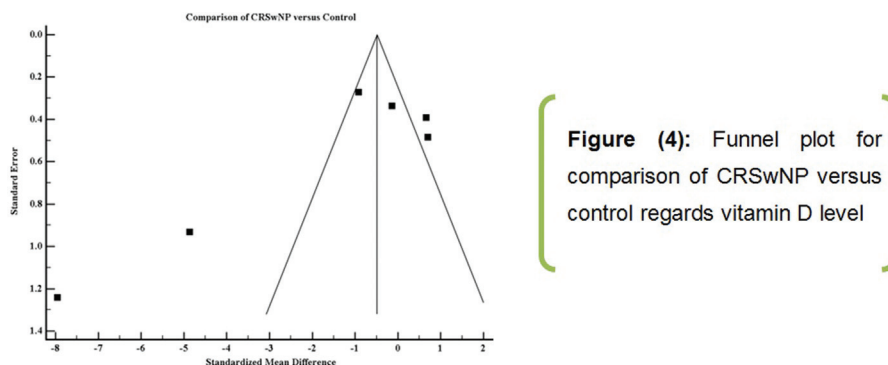


Figure (4): Funnel plot for comparison of CRSwNP versus control regards vitamin D level

Funnel plot for comparison of the chronic rhinosinusitis with nasal polyps (CRSwNP) group versus the control group as regards vitamin D level

Results of comparison of the chronic rhinosinusitis with nasal polyps group versus the chronic rhinosinusitis without nasal polyps group as regards vitamin D level

The comparison of the CRSwNP group versus the CRSsNP group as regards VD level (Table 4) shows an evidence of substantial heterogeneity (Cochrane $Q=60.4427$, $P<0.0001$, and $I^2=93.38\%$). Pooling of estimates using REF

shows a SMD of -2.485 (95% CI, -3.918 to -1.051), which is statistically significant ($P=0.001$) (Fig. 5).

The funnel plot for comparison of the CRSwNP group versus the CRSsNP group regards VD level shows that there is evidence for possible publication bias (Fig. 6).

Results of comparison of the chronic rhinosinusitis group with or without nasal polyps versus the control group

The comparison of the CRS group with or without nasal polyps versus the control group as regards VD level (Table 5) shows an evidence of substantial heterogeneity (Cochrane $Q=88.073$, $P<0.0001$, and $I^2=94.32\%$). Pooling of estimates using REF shows a SMD of -0.709 (95% CI, $-1.904-0.486$), which is not statistically significant ($P=0.244$) (Fig. 7).

The funnel plot for comparison of the CRS group with or without nasal polyps versus the control group as regards VD level shows that there is no evidence for publication bias (Fig. 8).

Discussion

CRS is mainly a medical disease. Surgery plays an adjuvant treatment when maximal medical treatment fails [19]. New advanced options in drugs and surgery reduce morbidity and also upgrade the lifestyle of the

patient [19]. VD is used now as one of the new drugs for the treatment of allergic diseases besides its role in calcium homeostasis and bone mineralization [20]. Stokes and Rimmer [13] said that most of the studies supported a role for VD_3 in the development of CRS, but the exact explanation of this remains mysterious. In this meta-analysis, we included studies with homogenous natural data. We excluded studies with different parameters or with no control group. The included studies are six in number with a total of 309 patients arranged in three groups (control=86, CRSsNP=122, and CRSwNP=101) (Table 1), and all studies were published between 2011 and 2016. Using appropriate statistically methods, we made four comparisons as regards CRS and its phenotypes versus VD level: comparison of the CRSsNP group versus the control group; comparison of the CRSwNP group versus the control group; comparison of the CRSwNP group versus the CRSsNP group; and comparison of the CRS group with or without polyps versus the control group.

Table 4 Comparison of the chronic rhinosinusitis with nasal polyps group versus the chronic rhinosinusitis without nasal polyps group as regards vitamin D level

References	CRSwNP	CRSsNP	Total	SMD	SE	95% CI	t	P-value
Mulligan et al. [14]	9	20	29	-9.547	1.313	-12.241 to -6.853		
Mulligan et al. [15]	5	17	22	-3.968	0.773	-5.581 to -2.356		
Mulligan et al. [16]	45	40	85	-0.730	0.222	-1.172 to -0.287		
Sansoni et al. [17]	14	30	44	-0.648	0.325	-1.304-0.00836		
Mostafa et al. [12]	15	15	30	-0.693	0.366	-1.444-0.0572		
Total FEM	88	122	210	-0.971	0.159	-1.285 to -0.657	-6.092	<0.001
Total REM	88	122	210	-2.485	0.727	-3.918 to -1.051	-3.417	0.001
Test for heterogeneity								
Q	60.4427							
d.f.	4							
P-value	<0.0001							
I^2 (inconsistency)	93.38%							
95% CI for I^2	87.48-96.50							

CI, confidence interval; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; FEM, fixed-effects method; REM, random-effects method; SMD, standardized mean difference.

Figure 5

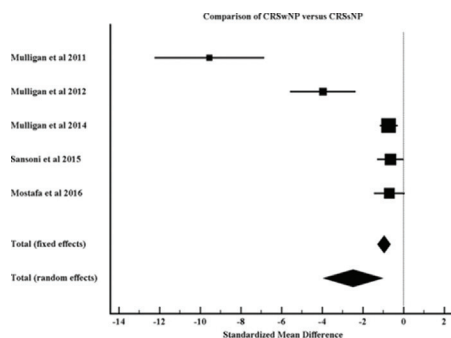


Figure (5): Forest plot for comparison of CRSwNP versus CRSsNP regards vitamin D level

Forest plot for comparison of the chronic rhinosinusitis with nasal polyps (CRSwNP) group versus the chronic rhinosinusitis without nasal polyps (CRSsNP) group as regards vitamin D level

Figure 6

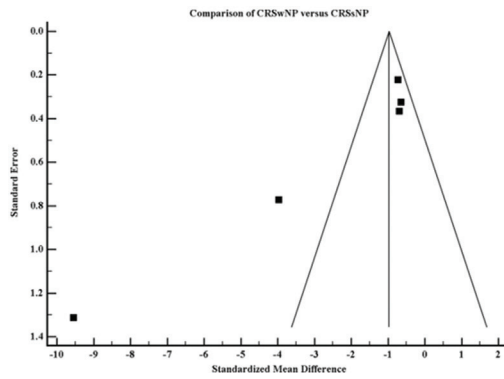


Figure (6): Funnel plot for comparison of CRSwNP versus CRSsNP regards vitamin D level

Funnel plot for comparison of the chronic rhinosinusitis with nasal polyps (CRSwNP) group versus the chronic rhinosinusitis without nasal polyps (CRSsNP) group as regards vitamin D level

Table 5 Comparison of the chronic rhinosinusitis group with or without nasal polyps versus the control group

References	CRS	Control	Total	SMD	SE	95% CI	t	P-value
Mulligan <i>et al.</i> [14]	29	14	43	-4.452	0.577	-5.616 to -3.287		
Mulligan <i>et al.</i> [15]	22	14	36	-1.554	0.381	-2.329 to -0.780		
Mulligan <i>et al.</i> [16]	85	21	106	-0.559	0.245	-1.045 to -0.0735		
Carroll <i>et al.</i> [18]	13	6	19	0.708	0.485	-0.316-1.731		
Sansoni <i>et al.</i> [17]	44	12	56	1.084	0.337	0.408-1.760		
Mostafa <i>et al.</i> [12]	30	19	49	0.222	0.289	-0.360-0.804		
Total FEM	223	86	309	-0.353	0.139	-0.627 to -0.0791	-2.536	0.012
Total REM	223	86	309	-0.709	0.607	-1.904-0.486	-1.168	0.244
Test for heterogeneity								
Q	88.073							
d.f.	5							
P-value	<0.0001							
I ² (inconsistency)	94.32%							
95% CI for I ²	90.19-96.72							

CI, confidence interval; CRS, chronic rhinosinusitis; FEM, fixed-effects method; REM, random-effects method; SMD, standardized mean difference.

Figure 7

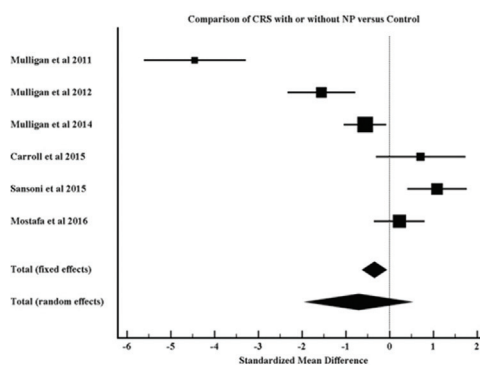


Figure (7): Forest plot for comparison of CRS with or without NP versus control regards vitamin D level

Forest plot for comparison of the chronic rhinosinusitis (CRS) group with or without nasal polyps (NP) versus the control group as regards vitamin D level

The comparison between the CRSsNP group versus the control group as regards VD level (Table 2 and Figs 1 and 2) showed an evidence of substantial heterogeneity (Cochrane $Q=41.081$, $P<0.0001$, and $I^2=90.26\%$). Pooling of estimates using REF showed a SMD of -0.006 with 95% CI $-1.129-0.816$, which indicates no statistically significant difference in VD level between the CRSsNP group and the control

group ($P=0.752$). Examination of the funnel plot (Fig. 2) shows no evidence for publication bias.

These results are augmented by those of Mulligan and colleagues, who found that there were no significant changes in VD level in the CRSsNP compared with the control group (45 ± 2 and 51 ± 4 ng/ml, respectively). Moreover, Mulligan and colleagues showed no

Figure 8

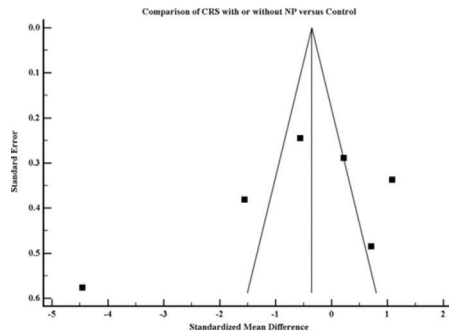


Figure (8): Funnel plot for comparison of CRS with or without NP versus control regards vitamin D level

Funnel plot for comparison of the chronic rhinosinusitis (CRS) group with or without nasal polyps (NP) versus the control group regards vitamin D level

significant change in VD level compared with the control group (36.3 ± 3.5 and 38.4 ± 3.2 ng/ml, respectively), and same results were reported in the study by Mulligan and colleagues. The results in the study by Mostafa *et al.* [12] are also in agreement with these results (125 nmol/l in the CRSsNP group and 129 nmol/l in the control group) [14–16].

However, the study by Sansoni *et al.* [17] was the only one to show a lower VD level in the control group than in the CRSsNP group (33.4 ± 11 ng/ml in the CRSsNP group and 19.7 ± 8.9 ng/ml in the control group); they attributed this to the control group not being healthy and having risk factors for hypovitaminosis D, such as obesity, tobacco use, and chronic diseases.

In the second comparison between the CRSwNP group versus the control group as regards VD level (Table 3 and Figs 3 and 4), there was an evidence of substantial heterogeneity (Cochrane $Q=76.330$, $P<0.0001$, and $I^2=93.45\%$). Pooling of estimates using REF showed an SMD of -1.646 with 95% CI -3.088 to -0.201 , which indicates a statistically significant difference in VD level between the CRSwNP group and the control group ($P=0.026$) (i.e. VD levels were very low in the CRSwNP group compared with the control group). Examination of the funnel plot (Fig. 4) shows an evidence for possible publication bias.

These results were augmented by Mulligan and colleagues, who found significant changes in VD level in the CRSwNP group compared with the control group (18 ± 4 and 51 ± 4 ng/ml, respectively). Moreover, Mulligan and colleagues showed a significant change in VD level compared with the control group (22.1 ± 3.2 ng/ml and 38.4 ± 3.2 ng/ml, respectively) and similar results were reported by Mulligan and colleagues. The results of Mostafa *et al.* [12] also are in agreement with these results

(32.5 nmol/l in the CRSsNP group and 129 nmol/l in the control group) [14–16].

However, Sansoni *et al.* [17] showed a lower VD level in the control group than in the CRSwNP group (26.3 ± 10.2 ng/ml in the CRSwNP group and 19.7 ± 8.9 ng/ml in the control group); they attributed it to the control group not being healthy and having risk factors for hypovitaminosis D, such as obesity, tobacco use, and chronic diseases. Carroll *et al.* [18] also showed a lower VD level in the control group than in the CRSwNP group (20.8 ± 9.7 ng/ml in the control group and 34.5 ± 21.2 ng/ml in the CRSwNP group) and attributed it to the insufficient number of cases.

In the third comparison between the CRSwNP group versus the CRSsNP group as regards VD level (Table 4 and Figs 5 and 6), there was an evidence of substantial heterogeneity (Cochrane $Q=60.4427$, $P<0.0001$, and $I^2=93.38\%$). Pooling of estimates using REF showed a SMD of -2.485 with 95% CI -3.918 to -1.051 , which indicates a statistically significant difference in VD level between the CRSwNP group and the control group ($P=0.001$) (i.e. VD levels were very low in the CRSwNP group in comparison with the CRSsNP group). Examination of the funnel plot (Fig. 6) showed an evidence for possible publication bias.

These results are supported by Mulligan and colleagues, who showed a lower VD level in the CRSwNP group than in the CRSsNP (18 ± 4 vs. 45 ± 2 ng/ml). Mulligan and colleagues reported VD levels of 22.1 ± 3.2 ng/ml in the CRSwNP group versus 36.3 ± 3.5 ng/ml in the CRSsNP group. Mulligan and colleagues also showed lower VD in the CRSwNP group compared with the CRSsNP group. The results by Sansoni *et al.* [17] augment this result (26.3 ± 10.2 ng/ml in the CRSwNP group and 33.4 ± 11 ng/ml in the CRSsNP group). Finally, Mostafa *et al.* [12] also supported this result

(32.5 nmol/l in the CRSwNP group and 129 nmol/l in the control group) [14–16].

In the last comparison, which was between the CRS group with or without nasal polyps versus the control group as regards VD level (Table 5 and Figs 7 and 8), there was an evidence of substantial heterogeneity (Cochrane $Q=88.073$, $P<0.0001$, and $I^2=94.32\%$). Pooling of estimates using REF showed a SMD of -0.709 with 95% CI -1.904 to 0.486 , which indicates no statistically significant difference in VD level between the CRS group with or without nasal polyps and the control group ($P=0.244$). Examination of the funnel plot (Fig. 8) showed no evidence of publication bias.

The CRS groups with or without nasal polyps were compared using an appropriate statistical method to summate the results of CRSsNP and CRSwNP, and then compared it with the control group.

Thus, our meta-analysis shows a statistically significantly low VD level in the CRSwNP group than in the control group and also in the CRSsNP group. However, no statistically significant difference was found in VD level in the CRSsNP group versus the control group and CRS as total versus the control group.

McCarty *et al.* [21] said that VD_3 was shown to inhibit the proliferation of nasal polyp fibroblasts that may confirm its anti-inflammatory effect [21].

In another study, Faruk *et al.* [22] suggests that, when using VD_3 in high therapeutic dose, it reduces the size of nasal polyp and facilitates the restoration of nearly normal sinonasal mucosa. Hence, normalization of VD_3 level may result in clinical improvement due to restoration of its anti-inflammatory role in the body. Moreover, it may provide a new, safe, and cheap drug for the treatment of CRS, especially with nasal polyps [15].

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Nil.

Conflicts of interest

There are no conflicts of interest.

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