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Vitamin D with asthma and COPD: not a false hope? A systematic review and meta-analysis

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ABSTRACT. Vitamin D deficiency and insufficiency are increasingly being recognized in the general population over the last few decades. However, a number of other disorders have now been linked to vitamin D deficiency and insufficiency, including asthma and COPD. The aim of this study was to evaluate the evidence on the effect of vitamin D on asthma and COPD. We searched electronic databases including SCI, EMBASE, Ovid, and PubMed. Reviewers working independently and in duplicate extracted study characteristics, quality, and the outcomes. The weighted mean differences across trials and random-effect meta-analysis were used to pool the relative risks (RR). This is the first meta-analysis about the risk of vitamin D deficiency for asthma and COPD. Ten studies were available for this meta-analysis and systematic review. The prevalence of vitamin D deficiency was significantly greater among cases than control subjects [RR = 1.59, 95%CI = 1.07-2.36, 488/812 (60%) *vs* 278/875 (32%)] for asthma. However, vitamin D insufficiency was not significantly associated with asthma [RR = 1.09, 95%CI = 0.91-1.30, 702/996 (70%) *vs* 665/1016

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(65%)]. Moreover, studies failed to demonstrate that COPD patients had an increased risk for vitamin D deficiency or insufficiency compared to controls (RR = 0.89, 95%CI = 0.63-1.25). Vitamin D deficiency was associated with a significant decrease in lung function in asthmatic children. Vitamin D deficiency was highly prevalent in asthma patients, and vitamin D status was associated with lung function. COPD cannot be considered as completely free of vitamin D deficiency.

Key words: Systematic review; Meta-analysis; COPD; Asthma; Vitamin D deficiency; Vitamin D insufficiency

INTRODUCTION

As many as 300 million people of all ages, and all ethnic backgrounds suffer from asthma, and the burden of this disease to governments, health care systems, families, and patients is increasing worldwide (Masoli et al., 2004). Asthma and COPD (chronic obstructive pulmonary disease) in every stage of severity are very prevalent diseases and represent a substantial burden on health care resources in all countries so far studied (Masoli et al., 2004). The costs of asthma and COPD are largely due to uncontrolled disease, and are likely to rise as their prevalence and severity increase. Asthma and COPD are chronic respiratory diseases characterized by heightened airway inflammation, airway hyper-responsiveness and airflow obstruction to specific triggers (Contoli et al., 2010). In recent years, there has been growing evidence to suggest that vitamin D plays an important role in inflammation (Zasloff, 2006). Vitamin D can suppress Th2-mediated allergic airway disease and may modulate the suppressive activity of local regulatory cells (Gorman et al., 2010), and vitamin D also plays a key role in the regulation of immune function (Hewison, 2012; Ooi et al., 2012).

The role of vitamin D in calcium and bone homeostasis has been well described, and vitamin D's relation to infection, cancer, cardiovascular disease has been recognized in the last years (Garland et al., 1985; Schwartz and Hulka, 1990; McGrath, 1999; McGrath et al., 2004; Wang et al., 2008). The underlying mechanisms how vitamin D metabolism could be linked to the pathophysiology of asthma and COPD are often complex and not fully understood (Paul et al., 2012). Vitamin D deficiency and asthma are common conditions that share risk factors such as African American ethnicity, inner-city residence, and obesity.

However, whether COPD and asthma patients actually have a higher prevalence of vitamin D deficiency than controls is not yet well established. Some reviews and studies have not confirmed a positive association between blood vitamin D and asthma and COPD. Some have supported the notion that vitamin D is not associated with asthma or COPD (Schauber and Gallo, 2008; Camargo et al., 2011; Shaheen et al., 2011; Krobtrakulchai et al., 2012), but some have an opposite opinion (Li et al., 2011; Chinellato et al., 2011; Goleva et al., 2012).

MATERIAL AND METHODS

Definition of vitamin D level

We divided subjects into vitamin D deficiency (<20 ng/mL), insufficiency (<30 ng/mL), and sufficiency (>30 ng/mL) groups.

Studies and interventions and inclusion and exclusion criteria

We included studies with data on the study group of asthma and COPD and in a control group of non-asthmatics and non-COPD: 7 studies were in children (Brehm et al., 2010; Freishtat et al., 2010; Rothers et al., 2011; Alyasin et al., 2011; Bener et al., 2012; Brehm et al., 2012; Goleva et al., 2012); 3 studies were with adults (Li et al., 2011; Persson et al., 2012; Zhou et al., 2012); 2 studies were on COPD (Persson et al., 2012; Zhou et al., 2012), and 8 studies on asthma. Studies without a control group were excluded. Studies including different outcome (e.g., both asthma and COPD) were also excluded, if the outcomes were not reported separately.

Retrieval of studies and data extraction

A systematic search was performed from 1989 until June 2013 in PubMed, EMBASE and Cochrane Collaboration containing the following key words: chronic obstructive pulmonary disease, COPD, asthma, and vitamin D.

Statistical analysis

We used a random-effect model to pool relative risk (RR). A P value less than 0.05 was considered to be statistically significant. We assessed heterogeneity between studies with the Cochrane I^2 test and evaluated the percentage of total variation across studies caused by heterogeneity with the groups for studies that contributed data for multiple procedures. I^2 is the proportion of total variation contributed by between-study variation. In general, I^2 values greater than 60-70% indicate the presence of substantial heterogeneity. We assessed potential publication bias using formal tests, namely funnel's plot and the Egger test (Egger et al., 1997). As outcomes are rare (for instance, the incidence is less than 1% and several studies have no events in one of the comparison groups), the pooled RR can be unstable and influenced by the chosen continuity correction and pooling method (DerSimonian and Laird, 1986; Higgins et al., 2003). To test robustness, we applied several alternative methods for pooling (fixed- and random-effect models), weighting of the study estimates (Mantel-Haenszel, reciprocal of the variance), and continuity correction values. We used Review Manager 5 for statistical evaluation.

RESULTS

Study characteristics

The electronic database searches identified 3153 citations. After evaluating these citations, review articles, and the bibliographies of included studies, we included 10 trials (Figure 1).

Table 1 describes the characteristics of the studies included ranked by year of publication, asthma in 8 studies, COPD in 2 studies. Most included studies concerning retrospective cohorts; only one study (Rothers et al., 2011) included a prospective cohort. Other studies selected a control population after matching/adjusting each asthma patient for several potential confounding factors such as age, gender, race, ethnicity, seasonality, and BMI (Table 1).

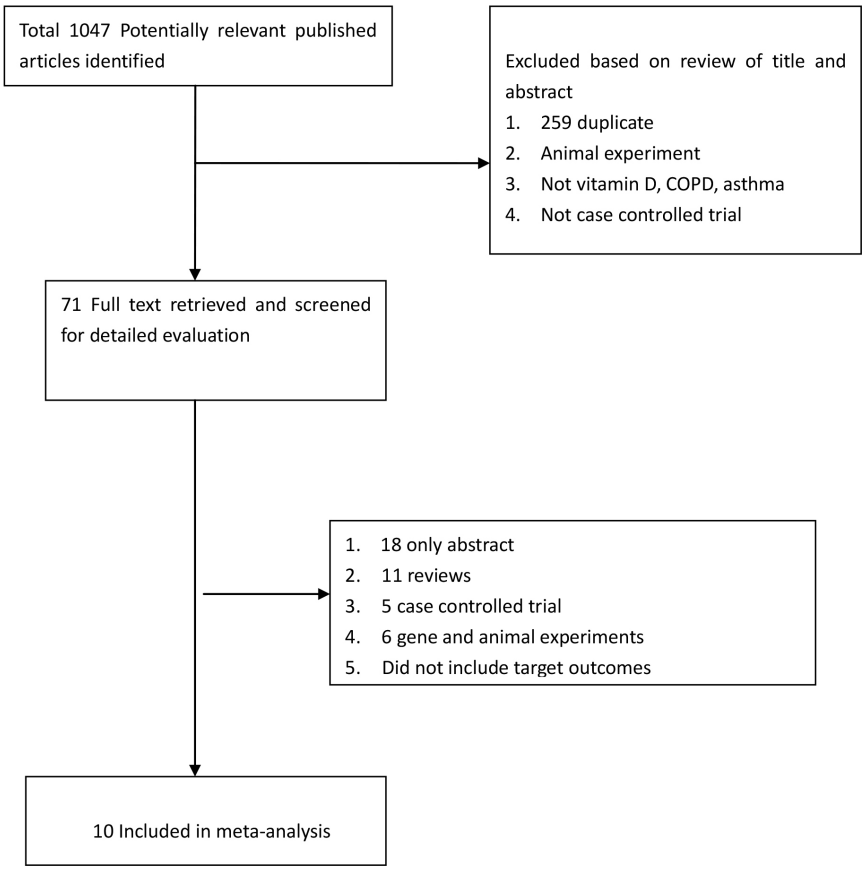

Figure 1. Flow of study selection.

Asthma

Figure 2A, B, C shows that the variation in RR for vitamin D <20 and <30 ng/mL in deficiency and insufficiency group and control group. Despite heterogeneity between procedures, we still showed an overall pooled RR.

Inter-study heterogeneity was seen for vitamin D <30 ng/mL (RR = 1.09, 95% confidence interval (CI) = 0.91-1.30; P = 0.34; I^2 = 71%). A study by Freishtat et al. (2010) showed huge increases (RR = 4.51, 95%CI = 1.86-10.93). Omission of this outlying study yielded a pooled RR that was not significantly different from unity (RR = 1.03, 95%CI = 0.93-1.15) (Figure 2A). The reason for this outlying result is not clear and could have been due to the study design mentioned earlier. The risk associated with vitamin D <20 ng/mL was RR = 1.59 with 95%CI = 1.07-2.36 (I^2 = 75%). A study by Rothers et al. (2011) showed no increase (0.63 [0.27-1.46]) and another showed a substantial increase and reach significance (1.59 [1.07-2.36]) (Figure 2B).

Vitamin D <10 ng/mL, described in only one study, was also followed by a significantly increased chance of asthma (2.40 [1.78-3.22]) (Figure 2C).

Table 1. Characteristics of our study population.

Source	Disease	Country	Study period	Population		Study type	Inclusion criteria	Outcome	Adjusted/matched
				Case group	Control group				
Zhou et al., 2012	COPD	China	2007-2010	193	181	Case-control study	Adult aged 40 years; FEV1/FVC ratio <0.7; No primary diagnosis of asthma	Vitamin D increased risk of COPD	Adjusted for age, gender, body mass index, season and smoking status, periodontal indexes
Persson et al., 2012	COPD	Norway	2006-2009	433	325	Cohort study	FEV1/FVC ratio <0.7 and FEV1 <80% predicted;a smoking history of ≥10 pack-years	COPD was increased risk of vitamin D deficiency	Adjusted for seasonality, age, smoking, and BMI
Goleva et al., 2012	Asthma	NA	NA	103	102	Case-control study	Children	In children, had a significant inverse correlation with ICS requirement with asthma	Matched for age, gender, race, and BMI
Brehm et al., 2012	Asthma	Puerto Rico	NA	287	273	Cross-sectional study	Children aged 6-14 years	Vitamin D insufficiency is associated with severe asthma exacerbations	Adjusted for African ancestry, time outdoors, atopy, and other covariates
Bener, et al., 2012	Asthma	Qatar	2009-July 2010	483	483	Case-control study	Children were below 16 years of age	Vitamin D deficiency was the major predictor of asthma in Qatari children	Matching the age, gender, and ethnicity
Rothers, et al., 2011	Asthma	USA	NA	50	144	Population-based birth cohort	Healthy children born to pregnant women	Low and high levels of vitamin D were associated with increased asthma	Adjusted maternal ethnicity, household smoking, and birth season
Li et al., 2011	Asthma	China	NA	435	None	Cross-sectional study	Chinese patients aged >18 years with newly diagnosed asthma	Vitamin D deficiency was prevalent in adults	Adjusted age, gender, BMI, smoking, season of blood collection, and symptom duration
Gupta et al 2011	Asthma	UK	NA	62	24	Cross-sectional study	Children aged 6-16 years	Lower vitamin D levels in children with worse asthma control and lung function	Adjusted age, gender, body mass index, FEV1, and ethnicity
Alyasin at al 2011	Asthma	Iran	2009	50	50	Cross-sectional study	Children aged 6-18 years	Serum vitamin D levels were inversely associated with asthma	Adjusted age, body mass index, and gender
Rothers et al., 2011	Asthma	USA	2008-2009	82	21	Cross-sectional case-control study	Healthy children aged 6 to 20 years	Vitamin D deficient or insufficient associated with asthma	Adjusted age, gender, BMI percentile, and season of sampling

COPD = chronic obstructive pulmonary disease; NA = not available; FEV1/FVC = forced expiratory volume in 1 s/forced vital capacity; ICS = inhaled corticosteroids; BMI = body mass index.

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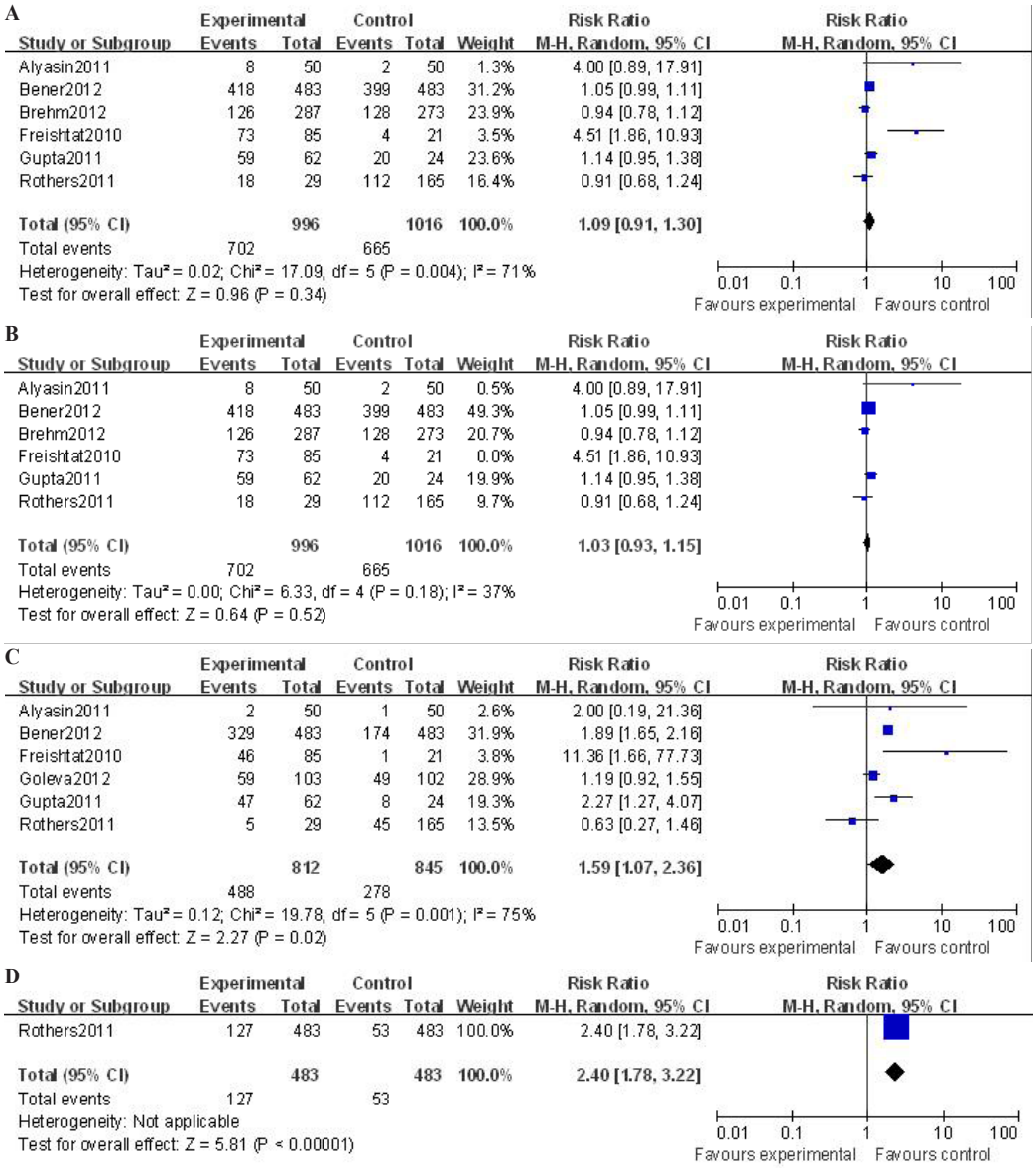

Figure 2. Relative risk for vitamin D <20 and <30 ng/mL in deficiency and insufficiency group and control group. **A.** Vitamin D <30 ng/mL. **B.** Omission of one study. **C.** Vitamin D <20 ng/mL. **D.** Vitamin D <10 ng/mL.

Lung function

Two investigators also described FEV1% with a positive association between lower vitamin D (<20 ng/mL) and higher vitamin D (>40 ng/mL) (WMD = -10.03 [-11.01 to -9.05]) (Figure 3A), and FEV1/FVC% (WMD = -5.31 [-5.65 to -4.96]) (Figure 3B). Both of them were associated with a significant decrease in lung function in asthmatic children. Although

our study did not have strong enough power to confirm or exclude a definite decrease in lung function, lung function was consistently decreased in the study group. According to Wu et al. (2012), vitamin D deficiency is associated with poorer lung function in children with vitamin D insufficiency or sufficiency. They corroborated the suggestion that vitamin D deficiency is a potential risk in some patients.

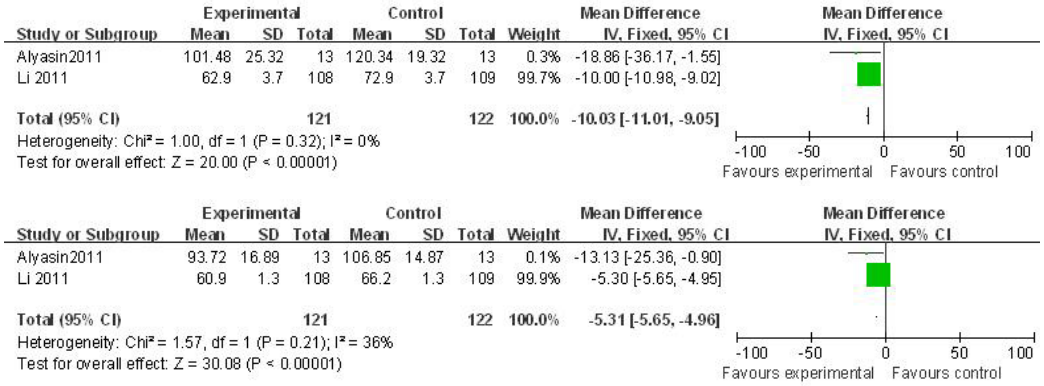

Figure 3. Association of FEV1 and FEV1/FVC between lower vitamin D (<20 ng/mL) and higher vitamin D (>40 ng/mL). **A.** FEV1 vitamin D <20 ng/mL compared with vitamin D >40 ng/mL. **B.** FEV1/FVC vitamin D <20 ng/mL compared with vitamin D >40 ng/mL.

Exacerbations

Children with vitamin D levels <30 ng/mL were more likely to have severe asthma exacerbations over the course of the 4-year trial (OR = 1.76 [1.01-3.09]) (Litonjua et al., 2008).

COPD

Two studies (Persson et al., 2012; Zhou et al., 2012) showed that the prevalence of vitamin D insufficiency and deficiency was not significantly different between cases and control subjects (RR = 0.89 [0.63-1.25], P = 0.5; I^2 = 25%) (Figure 4).

Figure 4. Chronic obstructive pulmonary disease <25 ng/mL.

Intervention

There were 2 randomized, placebo-controlled trials that showed the effects of vitamin D

on asthma and COPD (Schou et al., 2003; Lehouck et al., 2012) (Table 2). The exacerbations did not significantly differ between the groups (including the median time to first exacerbation, exacerbation rates), nor did FEV1 and PEF (peak expiratory flow). However, Lehouck et al. (2012) showed that a severe vitamin D deficiency (<10 ng/mL) at baseline displayed a significant reduction in exacerbations in the vitamin D group (RR = 0.57 [0.33-0.98], P < 0.042).

Table 2. Effects of vitamin D on asthma and chronic obstructive pulmonary disease (COPD).

Type	Asthma (Schou et al., 2003)	COPD (Lehouck et al., 2012)
Patients	Children with asthma treated with inhaled dry-powder budesonide 400 mg daily	182 patients with moderate to very severe COPD and a history of recent exacerbations
Interventions	15 mg (600 IU) 25-OH-vitamin D once daily in the morning with run-in and washout periods of 2 weeks and treatment periods of 4-week duration.	100,000 IU vitamin D supplementation or placebo every 4 weeks for 1 year
FEV1	P = 0.60	P = 0.95
PEF (morning)	P = 0.84	NA
PEF (evening)	P = 0.79	NA
exacerbations	NA	Annual rate of exacerbations 0.94 (CI = 0.76 to 1.16); P = 0.57
	NA	Time to first exacerbation: hazard ratio = 1.1 (CI = 0.82 to1.56); P = 0.41
	NA	Vitamin D levels <10 ng/mL exacerbation rate ratio = 0.57 (CI = 0.33 to 0.98); P < 0.042

FEV1 = forced expiratory volume in 1 s; PEF = peak expiratory flow; NA = not available.

DISCUSSION

This is the first meta-analysis covering the relationship of vitamin D to asthma and COPD. We compared serum vitamin D levels in asthmatic and COPD subjects with those in a healthy control group. Although we observed a higher prevalence of vitamin D insufficiency and deficiency in asthmatic children, this difference was not statistically significant. We also further demonstrated that vitamin D insufficiency at baseline is associated prospectively with increased odds of severe asthma exacerbations. In addition, children with insufficient vitamin D levels have a slightly lower mean FEV1 compared with children with sufficient levels. Moreover, COPD patients have an increased risk for having vitamin D deficiency. However, vitamin D in addition to regular therapy does not reduce exacerbation and increase lung function, such as FEV1 and PEF.

Our study has its limitations. Due to lack of data on exacerbations from all studies, our pooled results were likely underpowered to get a significant difference in exacerbations. Second, the choice of entry criteria could be perceived as a limitation of our study. Some early clinical trials of subjects showed deficiency consistent with substantial reductions in lung function or exacerbations, but failed to demonstrate significant clinical or functional improvement in pooled results.

Biological mechanisms

Several proposed mechanisms may be considered about vitamin D deficiency worsening COPD and asthma. The first is anti-microbial effects. There is evidence from epidemiological studies that vitamin D deficiency is a risk factor for respiratory infection (Urashima et al., 2010; Camargo et al., 2011). Vitamin D insufficiency may contribute to chronic respiratory infections and airway colonization (Zasloff, 2006). The second is lung tissue remodeling. Indirectly or directly, vitamin D regulates extracellular matrix homeostasis in tissues other than

bone, within particular lung and skin tissue via the control of transforming growth factor-b, matrix metalloproteinase and plasminogen activator systems (Boyan et al., 2007). Immune modulation and peripheral muscle function should also be considered. Periodontitis, which is an infectious disease correlated with vitamin D deficiency, may intensify the pathogenesis of COPD. Third, it is challenging to propound a unifying hypothesis to account for airway smooth muscle changes being the sole manifestation of vitamin D deficiency (Gupta et al., 2011). Fourth, the positive association between high levels of vitamin D at birth and total and inhalant allergen-specific IgE may be attributable to a different mechanism (Wittke et al., 2004).

Implications for practice

This study suggests the opportunity for early intervention in young children with vitamin D, especially those with vitamin D deficiency (<20 ng/mL). Interestingly, supplementation with vitamin D seems to lack therapeutic effect. Freishtat et al. (2010) found that participants with severe COPD cannot obtain any additional effect of vitamin D in addition to regular treatment. Thus, these findings may help guide the design and supplement dose in future trials. More studies in other chronic diseases and allergy diseases are needed to further explore the need and safety in recommending these higher doses of vitamin D to obtain potential beneficial effects.

CONCLUSION

The prevalence of vitamin D insufficiency and deficiency was different between cases and control subjects in asthma or COPD, although the quality of the available evidence was low to moderate at best. Due to the observational study design and the heterogeneity between the studies, the results remain difficult to interpret. More clinical trials are necessary to resolve the uncertainties about the association between vitamin D deficiency and COPD.

Conflicts of interest

The authors declare no conflict of interest.

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