Association Between Inflammatory Bowel Disease and Vitamin D Deficiency: A Systematic Review and Meta-analysis

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Background: Vitamin D plays a role in several immune-mediated diseases, but its association with inflammatory bowel disease (IBD) is unclear. We conducted a systematic review and meta-analysis to assess the association between IBD and vitamin D deficiency.

Methods: We searched electronic databases from inception to December 2014 for observational studies reporting the presence of vitamin D deficiency (defined as serum 25-hydroxycholecalciferol [25(OH)D] level of ≤20 ng/mL) in IBD patients and having a control group without IBD. Odds ratios (ORs) were combined using a random-effects model. Meta-regression was performed using latitude as a moderator. Study quality was assessed using the Newcastle–Ottawa scale.

Results: Out of 816 citations, 14 eligible studies were identified, comprising 1891 participants (938 IBD cases and 953 controls). Meta-analysis showed that patients with IBD had 64% higher odds of vitamin D deficiency when compared with controls (OR = 1.64; 95% confidence interval, 1.30–2.08; $I^2 = 7\%$; $P < 0.0001$). Patients with ulcerative colitis had more than double the odds of vitamin D deficiency when compared with normal controls (OR = 2.28; 95% confidence interval, 1.18–4.41; $I^2 = 41\%$; $P = 0.01$). Latitude did not influence the association between IBD and vitamin D deficiency ($P = 0.34$). Generalizability of our results might be limited as we summarized unadjusted ORs, because of nonavailability of adjusted ORs in individual studies.

Conclusions: IBD is significantly associated with having higher odds of vitamin D deficiency. Well-designed randomized controlled trials and longitudinal studies are needed to further explain the role of vitamin D in IBD pathogenesis and its therapy.

(Inflamm Bowel Dis 2015;21:2708–2717)

Key Words: meta-analysis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, vitamin D

Inflammatory bowel disease (IBD) is a chronic relapsing–remitting systemic disease that includes 2 major forms, Crohn's disease (CD) and ulcerative colitis (UC). CD primarily involves the ileum and colon, but it may affect any region of the gastrointestinal tract, whereas UC is mostly limited to the colon and/or rectum. The prevalence of IBD is increasing worldwide, with approximately 3 million people affected in Europe and 1.5 million in the United States and rapidly increasing trends observed in the Asia-Pacific regions.[1–4] IBD has a significant impact on health-related quality of life.[5] It poses a significant economic burden, with estimated annual direct medical costs of nearly 3 billion U.S. dollars.[6,7]

The exact etiology of IBD has not been fully elucidated; however, it is thought to result from an inappropriate and ongoing activation of the immune system against environmental triggers in genetically predisposed individuals.[8,9] Risk factors associated with IBD include altered intestinal flora,[9,10] a diet rich in carbohydrates and fats,[11] oral contraceptives,[12] and living in urban areas.[13] A stressful lifestyle is considered to exacerbate the disease.[14] In this setting, an aberrant innate immune response to gut luminal agents, possibly facilitated by an impaired mucosal barrier function, results in the stimulation of dendritic cells and subsequent activation of the inflammatory cascade, leading to intestinal inflammation.[15,16]

Vitamin D is a pleiotropic hormone with a diverse range of effects ranging from immune modulation to cell differentiation and intercellular adhesion. Several in vivo and in vitro studies have examined the role of vitamin D in immune-mediated diseases like IBD.[17–19] The consequences of vitamin D deficiency on the gastrointestinal tract include, but are not limited to, decreased colonic bacterial clearance,[20] reduced expression of tight junctions in the intestinal epithelium,[21] and elevated Th1-driven inflammation at the gut level.[22] Hypovitaminosis D is reported to be as high as 60% in IBD patients,[23] although it is not clear whether it results from IBD-related malabsorption because of intestinal mucosal damage,[24] or whether it is a possible contributor to disease onset and

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ibdjournal.org).

Received for publication April 26, 2015; Accepted June 17, 2015.

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The authors acknowledge continued support from the National Institutes of Health: DK 042191, DK 055812, and DK 091222 to F. Cominelli.

The authors have no conflict of interest to disclose.

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DOI 10.1097/MIB.0000000000000546

Published online 12 August 2015.

progression.[25,26] Evidence from observational studies remains questionable, as some studies report lower circulating vitamin D levels in IBD,[27–43] while others[44–53] do not. Given the lack of clarity regarding the association of vitamin D deficiency with IBD, we decided to conduct a systematic review and meta-analysis of observational studies looking at the association of IBD and its subtypes with vitamin D deficiency.

MATERIALS AND METHODS

Study Protocol

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines.[54] A comprehensive search of major electronic databases was conducted for articles from inception through December 2014. The following databases were included: (1) PubMed, (2), the COCHRANE library, (3) EMBASE, and (4) CINAHL. The search used the terms "Vitamin D," "ergocalciferol," "Inflammatory bowel disease," "Crohn's disease," and "Ulcerative colitis" in several combinations. The detailed search strategy is presented in Data, Supplemental Digital Content 1, http://links.lww.com/IBD/B42. In addition, review articles on the topic were searched for eligible articles. The search strategy was not limited by language. We did not attempt to contact the authors of the articles for retrieving additional information or clarifications.

Inclusion and Exclusion Criteria

Two authors (R.D.P. and D.P.) independently reviewed abstracts and articles for eligibility. Conflicts were resolved in consultation with a senior author (F.C.).[55] Inclusion of studies was limited to case–control, cohort, and cross-sectional studies with a control group that reported dichotomous outcomes of vitamin D deficiency in adult or pediatric subjects. Vitamin D deficiency was defined as circulating 25(OH)D ≤20 ng/mL (≤50 nmol/L), according to the Endocrine Society Guidelines.[56] We did not exclude studies on the basis of disease parameters (IBD activity, severity, duration of disease, or region/extent of involvement), previous or current IBD therapy (including use of corticosteroids, salicylates, and biologics), history of IBD-related surgery, and vitamin D supplementation.

The following data were extracted (Table 1):

1. Study characteristics: primary author, year of publication, time period of study, country, latitude of the area where the study was conducted, seasonality data, and number of patients with IBD and in the control group
2. Patient characteristics: age, sex, race/ethnicity, BMI, smoking status, serum vitamin D levels, current IBD-related therapy, prior IBD-related surgery, vitamin D supplementation, and tanning habits
3. Disease characteristics: distribution of IBD subtypes (CD versus UC), disease activity, site/s and extent of involvement, and disease duration
4. Assay characteristics: type of assay used for circulating vitamin D assessment (such as radioimmunoassay or enzyme-linked immunosorbent assay) and inter/intra-assay coefficients of variability
5. Outcome measures: prevalence of vitamin D deficiency in participants with and without IBD, as defined by the number or percentage of participants with circulating vitamin D levels ≤20 ng/mL or adjusted ORs, and a measure of variability such as 95% confidence interval (CI) or standard error (SE).

Assessment of Study Quality

Quality of included articles was assessed using the Newcastle–Ottawa Scale for case–control studies.[57] The following items were assessed:

1. Adequacy of definition of cases: IBD cases had to be confirmed by clinical, histological, and radiographic confirmation
2. Representativeness of the defined cases
3. Criteria used for selection of controls
4. Comparability of cases and controls. Age and sex were considered the most important matching factors, and an additional star was awarded if the study controlled for at least one additional confounder such as race, BMI, sun exposure, vitamin D supplementation, smoking, socioeconomic status, or absence of bone pathology
5. Method of ascertainment of exposure, i.e., assessment of vitamin D levels in cases and controls.

Statistical Analysis

Using a random-effects model, studies were pooled to calculate the odds of vitamin D deficiency in the IBD group in comparison with the control group. We used adjusted ORs whenever available, otherwise dichotomous data were used to calculate unadjusted ORs. Heterogeneity between studies was assessed by the I^2 statistic as defined by the *Cochrane Handbook for Systematic Reviews*.[58] Accordingly, an I^2 value of 50% or more was considered to represent a substantial heterogeneity. Review manager 5 was used to generate forest plots, and generated funnel plots were used to test for publication bias.[58] Since studies reported the prevalence of vitamin D deficiency by specific groups, namely adults or children, we conducted stratified meta-analyses based on these groups. We also conducted stratified analysis based on the 2 IBD subtypes, CD and UC. Because latitude affects sunlight exposure and thereby serum vitamin D levels as well, we decided to perform meta-regression using latitude as a moderator. The "metafor" package[59] in R software was used to perform random-effects meta-regression and plot the graph.[60] We also performed sensitivity analysis based on 2 different cutoffs for vitamin D deficiency (i.e., ≤20 ng/mL and <15 ng/mL).

RESULTS

Out of 816 citations, 14 articles with a total of 1891 patients met our predefined inclusion and exclusion criteria. The study flow is presented in Figure 1. The descriptive characteristics of the included studies are presented in Table 1. Women comprised

TABLE 1. Characteristics of the Included Studies

Study	Country, Latitude, degrees[a]	Time Period of Study	25(OH) D Assay	IBD/Control	N	Sex (M/F)	Race/Ethnicity, %	Age (SD), yr	Mean 25(OH)D (SD or CI)[bc]
Grunbaum et al[48]	Canada, Montréal, 45.46	March 2009 to April 2011	RIA	IBD (CD/UC)	55 (34/21)	21/34	Caucasian: 95%; Jewish: 51%	CD: 39.9 (12.3); UC: 44.2 (13.7)	71.2 (32.8)[b]
				Non-IBD	48	10/38	Caucasian: 79%; Jewish: 42%	39.6 (13.8)	68.3 (26.2)[b]
Souza et al[31]	Brazil, Curitiba, 25.42	N/A	RIA	IBD (CD/UC)	76 (39/37)	33/43	N/A	CD: 32.1 (8.7); UC: 35.0 (8.5)	CD: 25.9 (8.2)[c]; UC: 21.8 (8.0)[c]
				Non-IBD	40	16/24	N/A	34 (7)	34.4 (12.8)[c]
Silvennoinen[35]	Finland, Oulu 65.01	April to May 1993	RIA	IBD (CD/UC)	150 (76/67)	79/71	N/A	40 (9.3)	28.4 (12.0)[b]
				Non-IBD	73	35/38	N/A	40.8 (9.3)	36.1 (16.7)[b]
Suibhne et al[45]	Ireland, Dublin, 53.34	All seasons	RIA	IBD (CD/UC)	81 (81/-)	33/48	Caucasian: 100%	36.4 (11)	47.76 (27.27)[b]
				Non-IBD	70	28/42	Caucasian: 100%	36.3 (9.5)	51.86 (24.53)[b]
Garg et al[37]	Australia, Melbourne, 37.86	All seasons	ECLA	IBD (CD/UC)	71 (40/31)	39/32	Australian/New Zealander: 72%; European: 18%; Other: 8%	CD: 41 (23–76); UC: 44 (22–82)	CD: 70 (61–78)[b]; UC: 70 (58–81)[b]
				Non-IBD	23	10/13	Australian/New Zealander: 70%; European: 9%; Other: 26%	39 (22–68)	66 (55–76)[b]
Gilman et al[27]	Ireland, Cork, 51.89	All seasons	ELISA	IBD (CD/UC)	73 (47/26)	NS	N/A	CD: 36.0 (11.6); UC: 40.5 (11.0)	CD: 71.6 (33)[b]; UC: 63.9 (20.5)[b]
				Non-IBD	73	NS	N/A	CD ctr: 35.9 (11.5); UC ctr: 40.3 (11.2)	CD ctr: 133 (69.2)[b]; UC ctr: 109 (50.8)[b]
Duggan et al[40]	Ireland, Cork, 51.89	September to October 2002	ELISA	IBD (CD/UC)	44 (44/-)	15/29	N/A	36.9 (11)	75 (28.7)[b]
				Non-IBD	44	15/29	N/A	36.7 (11)	105.3 (55.5)[b]
Prosnitz et al[39]	Pennsylvania, Philadelphia, 40.00	All seasons	RIA	IBD (CD/UC)	78 (78/-)	44/34	Black: 10%; Non-Black: 90%	12.7 (2.8)	Black: 10.5 (4.6)[c]; Non-Black: 23.5 (9.2)[c]
				Non-IBD	221	112/109	Black: 28%; Non-Black: 72%	13.5 (4.4)	Black: 15.8 (7.9)[c]; Non-Black: 25.3 (8.7)[c]
Laakso et al[50,d]	Finland, Helsinki, 60.17	June 2004 to December 2005	HPLC	IBD (CD/UC)	80 (49/28)	37/43	N/A	14.9 (5.1–20.1)	N/A
				Non-IBD	80	37/43	N/A	14.4 (7.4–18.8)	N/A
Tajika et al[46]	Japan, Nagoya, 35.16	December 2001 to January 2002	CPBA	IBD (CD/UC)	44 (33/11)	31/13	Asian: 100%	CD: 37.6 (7.5); UC: 47.6 (12.4)	CD: 15.2 (6.5)[c]; UC: 17.6 (4.7)[c]
				Non-IBD	15	8/7	Asian: 100%	37.7 (10)	16.9 (5.2)[c]
de Bruyn et al[34]	Netherlands, Amsterdam, 52.37	September to December 2012	CLIA	IBD (CD/UC)	101 (101/-)	31/70	Caucasian: 83%	41 (30–50)	51.6 (26.6)[b]
				Non-IBD	41	8/33	Caucasian: 88%	28 (24–39)	60.8 (27.6)[b]

TABLE 1 (*Continued*)

Study	Country, Latitude, degrees[a]	Time Period of Study	25(OH) D Assay	IBD/Control	N	Sex (M/F)	Race/Ethnicity, %	Age (SD), yr	Mean 25(OH)D (SD or CI)[bc]
Veit et al[53]	Massachusetts, Worcester, 42.27	January 2007 to June 2013	CLIA	IBD (CD/UC)	58 (40/18)	31/27	White: 88%; Black: 3%; Multiethnicity: 3%; Unknown: 5%	CD: 16.6 (2.2); UC: 16.1 (1.9)	CD: 61.69 (24.43)[b]; UC: 53.26 (25.51)[b]
				Non-IBD	116	49/67	White: 80%; Black: 8%; Multiethnicity: 5%; Unknown: 4%	14.5 (4.3)	65.32 (27.97)[b]
Dumitrescu et al[41]	Romania, Iasi, 47.13	March 2011 to June 2012	HPLC	IBD (CD/UC)	47 (14/33)	25/22	N/A	CD: 36 (9); UC: 42 (14)	24 (10)[e]
				Non-IBD	94	50/44	N/A	42 (12)	31 (13)[e]
Salacinski et al[52]	Pennsylvania, Pittsburgh, 41.94	October to November	HPLC	IBD (CD/UC)	19 (19/-)	9/10	N/A	44.16 (10.28)	32.0 (9.1)[e]
				Non-IBD	19	9/10	N/A	41.68 (11.19)	35.3 (11.1)[e]

[a]Degrees of latitude as reported by the included studies or, if data not available, derived from the region where research was conducted (see text).
[b]Circulating 25(OH)D expressed as nanomole per liter.
[c]Circulating 25(OH)D expressed as nanogram per milliliter.
[d]Winter values were used (IBD: n = 41; non-IBD: n = 76).
[e]Circulating 25(OH)D expressed as microgram per liter.
CPBA, competitive protein-binding assay; ctr, control subjects; ECLA, electrochemiluminescence assay; ELISA, enzyme-linked immunosorbent assay; HPLC, high-performance liquid chromatography; N/A, not available; NS, not specified; RIA, radioimmunoassay.

50.7% of the total IBD population. Thirteen studies reported on previous surgery and 22% of 788 IBD patients had had a history of bowel resection. Thirteen studies reported on vitamin D supplementation and 24.3% of 862 IBD cases and 14.3% of 913 controls were on vitamin D supplements (see Table, Supplemental Digital Content 2, http://links.lww.com/IBD/B43). Data on disease location and extent and seasonality are reported in Table, Supplemental Digital Content 3, http://links.lww.com/IBD/B44.

The methodological quality of these studies based on the Newcastle–Ottawa scale is described in Table, Supplemental Digital Content 4, http://links.lww.com/IBD/B45. Three studies matched for age/sex and at least one other a priori defined confounding variable, whereas 8 studies only matched for age/sex. Studies had a quality score between 6 and 9 stars.

Description of Excluded Studies

The study by Alkhouri et al[47] was excluded as a higher cutoff for vitamin D deficiency was used (30 ng/mL). The study by McCarthy et al[29] was excluded as the prevalence of vitamin D deficiency was examined in 2 different seasons resulting in unit-of-analysis errors when combined. The study by Sylvester et al[32] was excluded, as events were not observed in the examined groups. Two studies[42,43] where the control group participants comprised persons with functional gastrointestinal disorders were excluded. Three other studies[30,33,51] that reported extractable data for only 1 of the 2 groups, i.e., either for cases or controls only, were also excluded.

Results of the Meta-analysis

Vitamin D Deficiency in IBD Cases Versus Non-IBD Controls

Meta-analysis of 14 studies including 1891 patients (938 IBD cases and 953 controls) showed that patients with IBD had 64% higher odds of vitamin D deficiency when compared with controls (OR = 1.64; 95% CI, 1.30–2.08; $P < 0.0001$) (Fig. 2). Heterogeneity between studies was low ($I^2 = 7\%$). We did not assess for publication bias using funnel plots because of the lack of sufficient studies.

Stratified Analysis Based on Adult Versus Pediatric Participants

Of the 14 included studies, 11 reported on adult participants, whereas 3 were on pediatric participants. Therefore, we conducted a stratified meta-analysis based on age (adult versus pediatric). Meta-analysis of the 11 studies reporting on adults showed that 761 adult participants with IBD had nearly double the odds of vitamin D deficiency when compared with 540 controls (OR = 1.81; 95% CI, 1.37–2.40; $I^2 = 1\%$; $P < 0.0001$). Meta-analysis of the 3 studies reporting on children showed that 177 pediatric cases with IBD had a higher, although not significant, odds of vitamin D deficiency compared with 413 non-IBD controls (OR = 1.36; 95% CI, 0.91–2.04; $I^2 = 18\%$; $P = 0.14$) (Fig. 2).

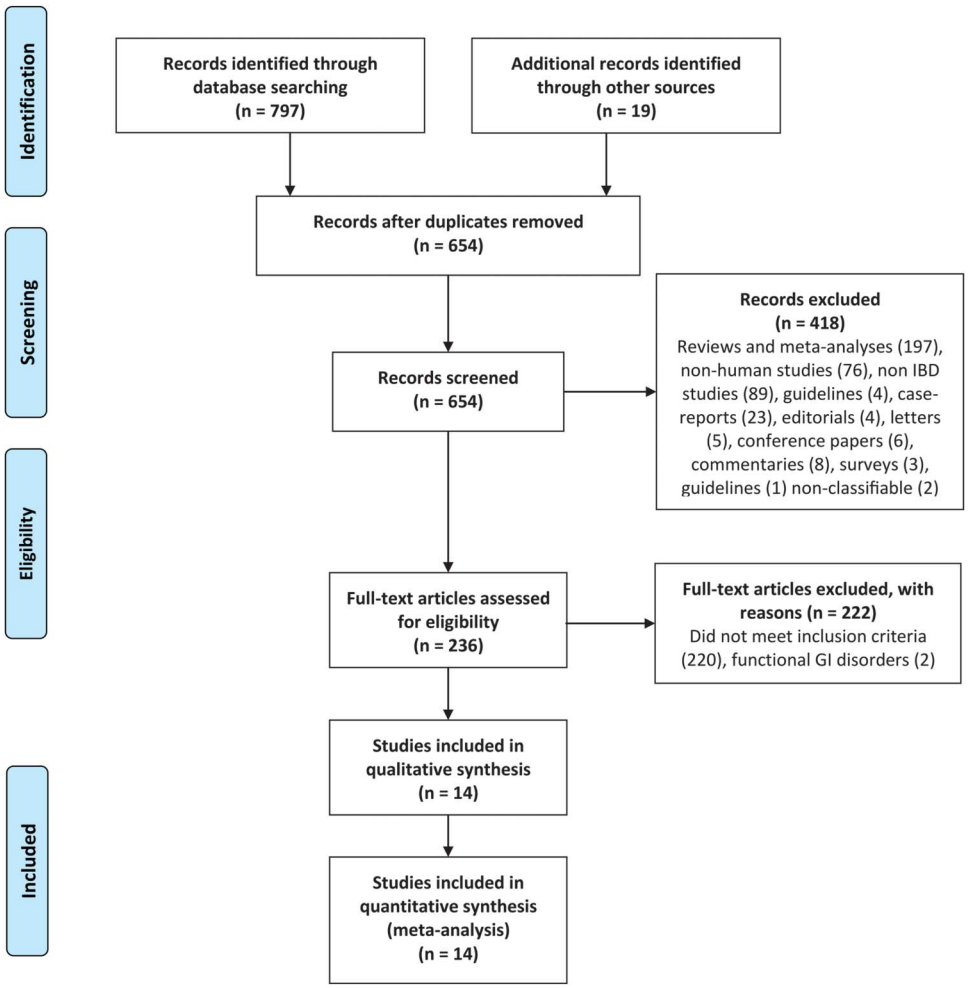

FIGURE 1. PRISMA flow diagram.

Vitamin D Deficiency in CD and UC Cases Versus Controls

We also conducted meta-analysis of studies that reported vitamin D deficiency by type of IBD. Meta-analysis of 12 studies reporting on vitamin D deficiency in CD showed that 570 participants with CD had a significantly higher odds of vitamin D deficiency compared with 778 controls (OR = 1.63; 95% CI, 1.24–2.13; $P = 0.0004$) (Fig. 3). Heterogeneity between studies was not detected ($I^2 = 0\%$). Meta-analysis of 7 studies reporting on prevalence of vitamin D deficiency in UC showed that 177 participants with UC had more than double the odds of vitamin D deficiency compared with 362 controls (OR = 2.28; 95% CI, 1.18–4.41; $P = 0.01$) (Fig. 4). Heterogeneity between studies was moderate ($I^2 = 41\%$).

Meta-regression Using Latitude as a Moderator

Whenever latitude data were available in studies, we extracted this information. When studies did not provide latitude data, we used the region of the hospital where the study was conducted (or using the region of the source of cases and controls) to obtain the latitude as we felt that this would be a reasonable approximation of the true latitude. We performed meta-regression analysis on the main meta-analysis (IBD versus controls), which showed that latitude had no effect on the association between IBD and serum vitamin D status ($P = 0.34$) (see Fig., Supplemental Digital Content 5, http://links.lww.com/IBD/B46).

Sensitivity Analysis Based on Vitamin D Deficiency Cutoffs

Out of the 14 studies, 5 studies[27,35,40,46,50] reported on vitamin D deficiency using a more stringent cutoff of 15 ng/mL.[61] Therefore, we conducted sensitivity analyses to check if the exclusion of these studies would change the effect estimate. Exclusion of these 5 studies from the meta-analysis did not substantially influence the summary estimate (OR = 1.65; 95% CI, 1.25–2.19; $I^2 = 11\%$; $P = 0.0004$).

DISCUSSION

Our meta-analysis shows that vitamin D deficiency is significantly higher in IBD patients, and its subtypes, when

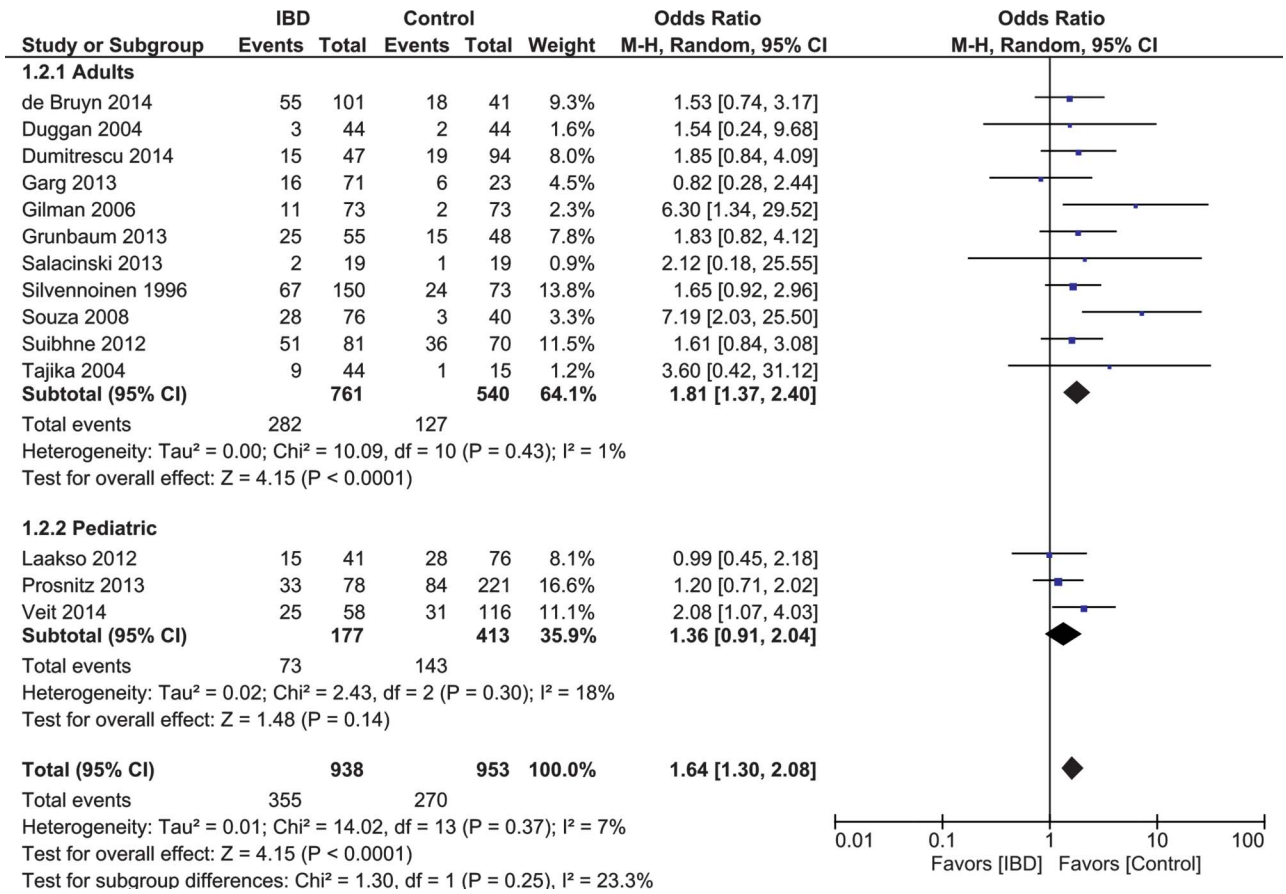

FIGURE 2. Meta-analysis of vitamin D deficiency in IBD cases compared with non-IBD controls. Stratified analysis based on adult versus pediatric participants.

compared with non-IBD subjects. UC, in particular, was found to be associated with more than double the odds of vitamin D deficiency compared with the absence of the disease. Stratified analysis based on age showed that adult IBD patients had nearly twice the odds of vitamin D deficiency when compared with healthy adult controls, whereas a similar comparison in the pediatric population showed higher odds of vitamin D deficiency in the presence of IBD, but did not reach statistical significance, likely

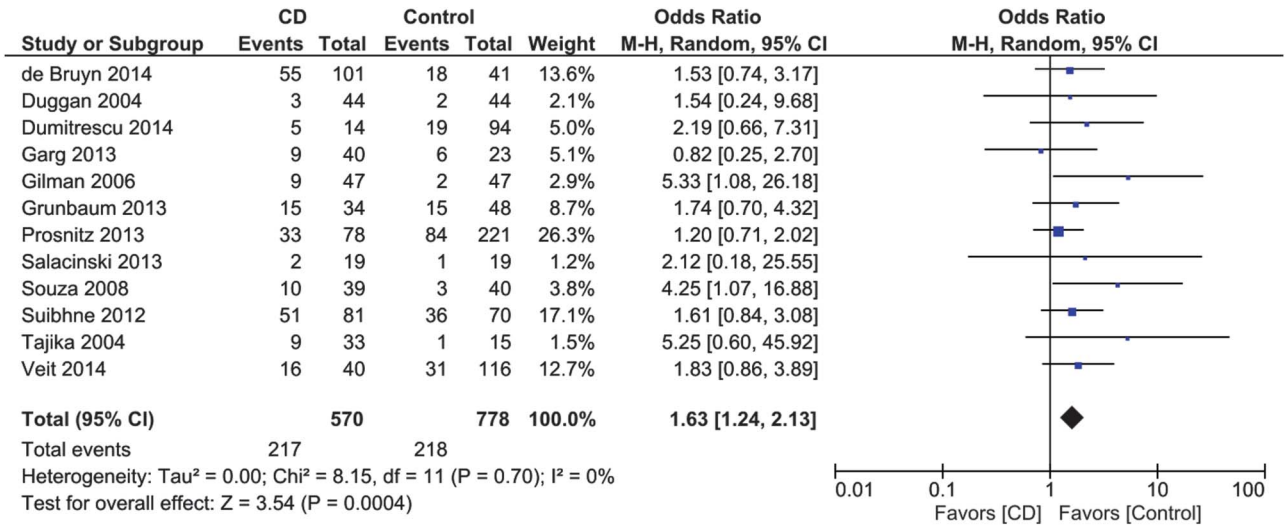

FIGURE 3. Stratified meta-analysis of vitamin D deficiency in CD cases compared with controls.

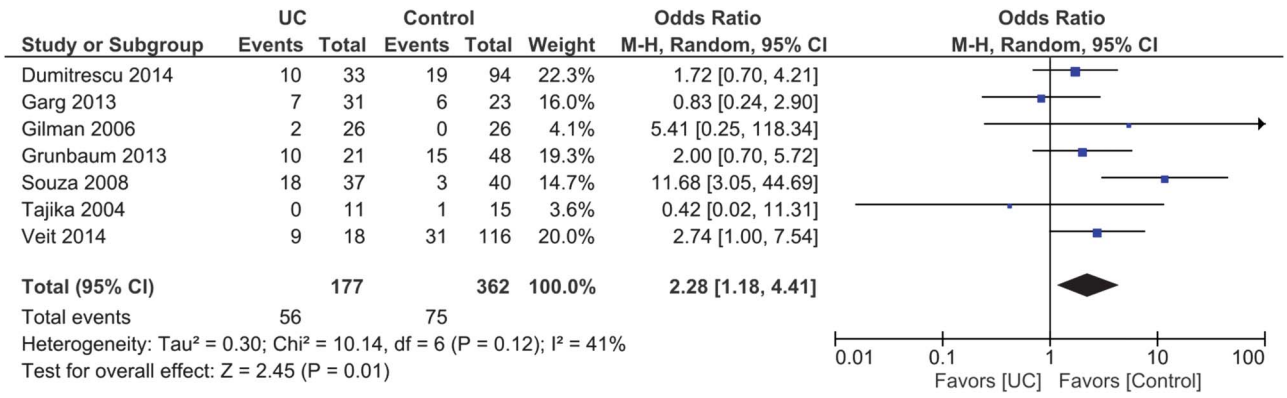

FIGURE 4. Stratified meta-analysis of vitamin D deficiency in UC cases compared with controls.

because of a small sample size. Latitude did not seem to moderate the association between IBD and serum vitamin D. Sensitivity analysis after excluding studies that used a lower cutoff of 15 ng/mL did not substantially influence the pooled effect estimate. All studies were of moderate to high quality as assessed by the Newcastle–Ottawa scale, with a rating between 6 and 9 stars.

Previous studies[62–64] have reviewed the scientific evidence regarding the role of vitamin D in IBD and concluded that crucial aspects of this relationship are still to be elucidated. In particular, whether effective preventive or therapeutic strategies with vitamin D supplementation can be adopted in IBD, and how they should be conducted to obtain meaningful clinical results, still remains an open question. Therefore, we believe that our meta-analysis evaluating vitamin D status in a relatively large cohort of 1891 patients might provide useful information for future investigations.

Hypovitaminosis D in IBD may have several explanations. It is of significance that both conditions are associated with common environmental factors such as air pollution, industrialization, high latitude, and seasonality.[13] Hypovitaminosis D in the context of IBD may be the consequence of malabsorption, due to bowel inflammation or surgical resection[24]; reduced outdoor activities with less UV exposure, as a consequence of IBD symptomatology[63]; or increased uptake of vitamin D by inflammatory cells in the affected sites.[44] Consistent with the latter point, enhanced 25(OH)D uptake has been demonstrated in peripheral monocyte/macrophages from HIV-infected patients with hypovitaminosis D after in vitro stimulation with the viral envelope protein gp120 or lipopolysaccharide.[65] Low vitamin D levels may also negatively affect the gut barrier and immune system functions, thus potentially affecting IBD onset and progression. In particular, vitamin D has been demonstrated to inhibit several proinflammatory pathways,[66,67] modulate autophagy,[67] decrease oxidative stress,[68] reduce white cells differentiation and activation,[67,69,70] and enhance expression of tight junctions in the intestinal epithelium, thereby influencing mucosal permeability and tissue integrity.[21] In vivo studies show that vitamin D receptor knockout mice are more susceptible to bowel inflammation,[71] and genetic studies have also linked vitamin D receptor and vitamin D-binding protein polymorphisms to IBD.[72,73]

The Nurses' Health Study, a large longitudinal study of 72,719 adult women in the United States followed from 1986 to 2008 showed that higher prediagnosis vitamin D levels were associated with a significant reduction in risk of incident CD and a nonsignificant reduction in risk of incident UC in the examined cohort.[26] A retrospective study of 504 IBD patients not only demonstrated the high prevalence of vitamin D deficiency (defined as serum vitamin D $<$20 ng/mL) in the study population ($\sim$50%) but also showed that vitamin D deficiency is independently associated with greater disease activity and lower quality of life in CD patients.[74] Low plasma 25(OH)D levels have been shown to be associated with an increased risk of IBD-related surgery and increased hospitalizations.[75] Vitamin D might also enhance the durability of anti-TNF therapy in IBD and its insufficiency has been found to be associated with earlier cessation of anti–TNF-α therapy, particularly in CD.[76] A recent randomized, double-blind placebo-controlled study on 94 CD patients with inactive disease, assigned to either 1200 IU vitamin D3 daily or placebo for 12 months, showed that the IBD relapse rate had a trend toward being lower in the treatment group ($P = 0.06$).[77] Other authors have observed a short-term beneficial effect on disease activity in CD patients treated with vitamin D, and this was particularly true for those patients receiving the active form of the vitamin.[78] Similarly, a recent prospective randomized controlled trial on 18 patients with UC and hypovitaminosis D showed that vitamin D3 supplementation improved quality of life and reduced UC disease activity, especially at higher doses (4000 IU daily versus 2000 IU daily).[79]

Our meta-analysis demonstrated an association between IBD and low serum vitamin D levels only in adults, but not in the pediatric population. There could be several reasons for this, including, but not limited to, shorter disease duration, more frequent outdoor activities leading to increased sunlight exposure, and greater use of vitamin D fortified foods when compared with adults. Furthermore, a physiological decline in cutaneous levels of the vitamin D precursor, 7-dehydrocholesterol, associated with aging, may profoundly affect the skin's vitamin D production capability, particularly when sun exposure is limited, which might explain the significantly higher vitamin D deficiency in adults.[80]

Our meta-analysis produced an interesting finding in that UC patients had higher odds of vitamin D deficiency than CD patients. This is likely a sample size issue as there were fewer total patients and fewer events in the UC meta-analysis in comparison with the CD meta-analysis. However, there might be other pathophysiological mechanisms; particularly, alterations in the vitamin D metabolic pathway that could potentially explain our findings. These include vitamin D activation and deactivation processes mediated by cytochromes (CYP2R1 and CYP27B1 for activation and CYP24A1 for deactivation), its transportation in blood and across cell membranes mediated by proteins (vitamin D-binding protein, megalin/cubilin) and its genetic effects mediated by cellular complexes such as vitamin D receptor/RXR and transcriptional activators/repressors.[81] In addition, genetic polymorphisms[25,73,82] and disease-related impairments (altered protein turnover,[83] protein-losing enteropathies,[84,85] and dysbiosis[86,87]) might also modify the association between IBD and serum vitamin D levels.

Our meta-regression analysis seemed to indicate that latitude does not moderate the association between IBD and vitamin D levels. However, it would be simplistic to dismiss this association as the relationship between latitude, vitamin D levels, and IBD is likely more complex. Second, the effect of latitude also could not be measured precisely because most studies did not provide the latitude of the region where they conducted the study. Nevertheless, we felt that using the region of the hospital where the studies were conducted (or using the region of the source of cases and controls) was a reasonable approximation of the true latitude. Most importantly, because of the variable nature of seasonality data (as different studies were conducted in different seasons), the effect of latitude, if any, might have been suppressed. Finally, it should be noted that meta-regression itself typically has low power to detect statistically significant relationships,[88] and hence the lack of such a relationship should be interpreted with caution.

Despite considerable diagnostic and therapeutic achievements in recent years, IBD still represents a challenge in terms of treatment.[89] The available therapies are not curative and their side effects may considerably impact patients' general health. Current drug research is therefore highly oriented toward the study of novel therapies that target specific pathogenetic pathways.[90] In parallel with disease-modifying agents, there are promising results from other approaches aimed at modulating the gut environment. Intestinal microbiota and the innate immune system have therefore become interesting targets for complementary therapies, such as probiotic formulations. Vitamin D as a therapeutic agent, in particular, has also shown promise in lowering relapse rates and bettering quality of life in IBD, but larger well-designed randomized controlled trials investigating the long-term effectiveness of vitamin D in IBD are needed to substantiate these findings from early trials.

This meta-analysis had several strengths. First, the number of included studies (n = 14) provided a sufficiently large sample size. Second, study quality was systematically assessed using the Newcastle–Ottawa scale,[57] and the included studies were of reasonably high quality. Third, subgroup and sensitivity analyses were conducted, the results of which were congruent with our findings in the main meta-analysis. Finally, heterogeneity was moderate or not present in all the meta-analyses we conducted. Our study was not without limitations. The entire body of evidence was observational, which is often biased because of unmeasured confounders. Included studies, with the exception of one,[39] did not provide baseline adjusted data; therefore, in the absence of adjusted measures of risk, unadjusted measures (unadjusted ORs) were used, which limits the generalizability of our results. In that study, even after adjusting for several confounders like age, sex, race, season, and vitamin D supplementation, the odds of vitamin D deficiency was still twice as high in IBD cases in comparison to healthy controls. Few studies reported stratified results on vitamin D deficiency based on important parameters such as surgery, disease location, or disease activity, and hence, stratified meta-analyses based on these criteria were not possible. Different 25 (OH)D assays were also used in the studies (Table 1); consequently, inter-assay variability is possible because of the different sensitivities of each assay method to vitamin D2 or D3.

In summary, this meta-analysis shows that IBD is associated with higher odds of vitamin D deficiency compared with the absence of the disease. Further studies, particularly longitudinal studies in different settings, are needed for corroborating our findings. Well-designed, large randomized controlled trials using variable doses of vitamin D supplementation in different IBD statuses can help us better understand the therapeutic significance of vitamin D in IBD.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Shari Bolen and Dr. Kristen Arseneau for critical revision of the manuscript.

Author contributions: R. Del Pinto and D. Pietropaoli devised and designed the study. R. Del Pinto and D. Pietropaoli performed database searches and data extraction. A. K. Chandar. conducted the meta-analyses and sensitivity analyses. D. Pietropaoli conducted the meta-regression analysis. R. Del Pinto and A. K. Chandar performed the quality assessment and wrote the first draft. F. Cominelli and C. Ferri supervised the study selection and quality assessment, interpreted the results, and implemented the manuscript draft. All authors reviewed the study findings, and read and approved the final version before submission.

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