Vitamin D deficiency associated with Crohn’s disease and ulcerative colitis: a meta-analysis of 55 observational studies

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Abstract

Purpose: To investigate the association of serum levels of 25(OH)D and 1,25(OH)₂D₃ in healthy and non-healthy controls with Crohn’s disease (CD) and ulcerative colitis (UC).

Methods: Three electronic databases: PubMed, EMBase and EBSCOhost CINAHL, were searched for observational studies to measure the relationship between serum levels of vitamin D (VitD) and CD (or UC).

Results: Fifty-five studies were included in the meta-analysis. We found that mean serum 25(OH)D levels in patients with CD were significantly lower than those in healthy controls (MD: −3.17 ng/mL; 95% CI −4.42 to −1.93). Results from the meta-analysis examining 1,25(OH)₂D₃ levels in Crohn’s patients revealed higher levels in the CD group than in healthy (MD: 3.47 pg/mL; 95% CI −7.72 to 14.66) and UC group (MD: 5.05 pg/mL; 95% CI −2.42 to 12.52). Serum 25(OH)D levels were lower in the UC group than in the healthy control group (MD: −2.52 ng/mL; 95% CI −4.02 to −1.02). In studies investigating the level of 1,25(OH)₂D₃ in UC and healthy control groups, the level of 1,25(OH)₂D₃ in the UC groups were found to be higher than that in the control groups (MD: 3.76 pg/mL; 95% CI −8.36 to 15.57). However, the 1,25(OH)₂D₃ level in patients with UC was lower than that in CD groups (MD: −6.71 pg/mL; 95% CI −15.30 to 1.88). No significant difference was noted between CD patients and UC patients in terms of average serum 25(OH)D levels.

Conclusions: This study found that VitD levels were inversely related to CD and UC. Serum levels of 25(OH)D were lower in patients with CD and UC than in healthy people, and more than half of the patients had insufficient vitamin D levels. The serum level of 1,25(OH)₂D₃ in both the CD and UC groups was higher than that in healthy people.

Keywords: Inflammatory bowel disease, Crohn’s disease, Ulcerative colitis, Vitamin D deficiency, Meta-analysis

Introduction

Inflammatory bowel disease (IBD), including the two major forms: Crohn’s disease (CD) and ulcerative colitis (UC), is a chronic, relapsing–remitting systemic disease that typically begins in young adulthood and lasts throughout life. Although progress has been made in understanding these diseases, their etiology is unknown [1]. CD is a chronic inflammatory disease characterized by discontinuously affected areas with transmural, granulomatous inflammation and/or fistula, and can affect any region in the digestive tract, from the mouth to the anus, but is more likely to involve the small and large intestines (especially the ileocecum) and the perianal region. UC is a diffuse, non-specific inflammatory disease of unknown cause that continuously affects the proximal colonic mucosa from the rectum and often forms erosions and/or ulcers [2]. Since there is currently no cure for IBD, medical therapy remains the primary treatment for achieving and maintaining remission [3].

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Currently, there is general agreement that variations in a patient’s genetic make-up, broad changes in the surrounding environment, alterations in the composition of gut microbiota, and the reactivity of the intestinal mucosal immune response are at the foundation of IBD pathogenesis [4]. Vitamin D (VitD) is known to induce and maintain the alleviation of IBD through anti-bacterial and anti-inflammatory actions and repair of the intestinal mucosal barrier [5, 6]. VitD belongs to a family of fat-soluble secosteroid hormones and comprises two major forms: VitD2 (ergocalciferol) and VitD3 (cholecalciferol) [7]. VitD3 is hydroxylated in the liver into 25(OH)D and subsequently in the kidney into 1,25(OH)2D3 [8]. VitD has been shown to target the three major components of the gastrointestinal epithelial barrier, intestinal immunity and intestinal microflora and has multiple effects on intestinal health [9]. Through active intestinal signaling, which has immunomodulatory and immunosuppressive effects on inflammatory and inhibitory markers of IBD, VitD interferes with the immune response to bacterial activity, antigen presentation and adaptive and innate immune regulation. Therefore, VitD may affect the incidence and progression of UC and CD [10–12]. While attempting to rule out VitD deficiency in patients with IBD due to reduced physical activity, sunlight exposure, malnutrition, inadequate dietary intake of VitD, or lower bioavailability, some studies [3, 13, 14] have found that VitD deficiency is also common in newly diagnosed IBD patients. Thus, VitD deficiency may play a role in the development of IBD and its severity. Other studies, however, have taken the opposite view of the relationship [15] between VitD and IBD and have left the controversy unresolved for patients with CD [16] and UC [17, 18]. Therefore, to explore this controversy we performed a pooled meta-analysis to investigate and determine the status of VitD in the serum of healthy and non-healthy controls and to study the association between serum 25(OH)D and 1,25(OH)2D3 concentrations and an IBD diagnosis (both UC and CD).

Materials and methods

Search strategy
All studies were obtained by searching PubMed, EMbase and EBSCOhost CINAHL for articles that were published through April 8, 2019. Detailed search strategies are shown in Additional file 1: Method S1.

Inclusion and exclusion criteria
Studies were eligible for analysis if they met the following criteria: (1) all included studies were limited to observational investigations in English; (2) serum VitD levels were detected in CD or UC patients; (3) when several trials from the same authors were identified as duplicates, we only included the most recent trial with the largest number of patients or with a longer follow-up period. The healthy control group was defined as those without CD or UC, and the non-healthy control was defined as patients diagnosed with CD or UC, but it was different from the exposed group.

Exclusion criteria included: (1) studies conducted exclusively on patients with IBD diseases, but not CD or UC; (2) studies that did not present any distinct serum levels of VitD; (3) studies that did not include the standard deviation of mean serum levels of VitD, and attempts to get these values by contacting the authors through email were unsuccessful; (4) non-full-text English articles.

Data extraction
For each included study, two investigators independently extracted the following essential information: name of the first author, publication year, study design, disease type, country, age, sex, use of any matching or adjustment approach, maturity, VitD assessment tool, VitD deficiency definition, and VitD supplementation. Disagreements were resolved through discussion or from a third party.

Study quality assessment
The quality of each study from case–control and cohort study in the meta-analysis was assessed using the Newcastle–Ottawa Scale [19, 20], which ranges from 1 to 9 stars and judges each study according to three aspects: selection of the study groups; the comparability of the groups; and, the ascertainment of the outcome of interest. For the cross-sectional study, the quality assessment method from were employed by The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews [21].

Data analysis
For continuous data, the mean difference (MD) and 95% confidence interval (CI) were calculated [22]. If different measurement indices adopted different tools in the various studies, the standardized mean difference (SMD) was used [22]. A fixed-effects model was used when there was no significant heterogeneity ($P > 0.1$, $I^2 < 40$%), otherwise, a random-effect model was employed [23]. To further explore sources of heterogeneity, subgroup analyses were performed according to age, VitD measurement tools, VitD supplementation, and study design based on both healthy and non-healthy populations using 25(OH)D and 1,25(OH)2D3. Publication bias was assessed by visual inspection of funnel plots [24]. Sensitivity analysis was used to explore the extent to which extrapolation might depend on a particular study or group of studies.
excluding small sample studies (both groups < 30) and studies with low study scores (< 5) to discuss the sources of heterogeneity. R 3.4.4 software was performed for all statistical analyses.

Results

Study characteristics

The literature search identified 1385 individual studies. After removing 298 duplicates, 1087 potentially relevant studies were selected on the basis of the abstract, and of these, 119 full texts were assessed for eligibility. In total, 55 publications [16, 18, 25–77] were included in the meta-analysis (Fig. 1).

A total of 19 cohort studies [18, 34, 38, 41, 50–56, 64, 67, 68, 71, 73, 74, 76, 77], 22 case–control studies [16, 25–29, 31–33, 35, 42, 43, 46, 49, 59–63, 66, 69, 70] and 14 cross-sectional studies [30, 36, 37, 39, 40, 44, 45, 47, 48, 57, 58, 65, 72, 75] were included in the analysis. The total number of participants was 5123 patients and 3033 healthy controls. Different studies investigated a range of VitD deficiency values: some used 20 ng/mL [16, 18, 35, 36, 40, 42, 48, 51, 54, 55, 64, 65, 67, 68, 72–75] (50 nmol/L) (n = 18); Other studies used 15 ng/mL [31, 37, 46, 49, 57] (n = 5), 10 ng/mL [32, 41, 50, 62] (n = 4), 12 ng/mL [59–61] (n = 3) or 30 ng/mL [56, 65] (n = 2).

The mean difference in 25(OH)D concentrations among patients with CD compared with healthy controls ranged between −16.58 and 8.19 ng/mL and between −8.98 and 7.50 ng/mL for non-healthy controls. The values for 1,25(OH)2D ranged between −11.50 and 34.79 pg/mL.

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**Fig. 1** Meta-analyses (PRISMA) flow diagram depicting the process of identification and inclusion of selected studies
The significance. Both the presence and absence of VitD supplementation was statistically significant (MD: 2.12 ng/mL; 95% CI 3.22 to 0.90). The discussion between CD and UC about serum 25(OH)D levels were identified in thirty-seven studies [16, 18, 27–30, 32, 34, 36–42, 44–48, 50–52, 54, 56, 58, 61, 62, 64, 66–68, 71, 73, 75–77], which included a total of 2494 CD patients and 2017 non-healthy controls. The analysis revealed no significant difference in average serum 25(OH)D levels between the two groups (MD: −0.58 pg/mL; 95% CI −1.74 to 0.59) (Fig. 3). There was significant heterogeneity among the studies ($I^2 = 84\%$, P < 0.01). Subgroup analysis showed that only ECLIA (MD: 1.34 pg/mL; 95% CI 0.17–2.52) and the use of VitD supplementation (MD: 2.36 pg/mL; 95% CI 1.46–3.25) were statistically significant (Table 2). In sensitivity results, the residual results were unchanged after excluding small sample studies (MD: −0.51 ng/mL; 95% CI −1.69 to 0.66) or excluding studies with lower quality score (MD: −0.90 ng/mL; 95% CI −2.12 to 0.31).

Findings from the meta-analysis of 1,25(OH) 2 D3 levels in Crohn's patients
Eight studies [26, 29, 32, 34, 46, 55, 59, 70] reported average serum 1,25(OH) 2 D3 concentrations in Crohn's patients, and these were higher in the CD group in comparison with the healthy control group (MD: 3.47 pg/mL; 95% CI −7.72 to 14.66) (Fig. 4). There was significant heterogeneity among the studies ($I^2 = 98\%$, P < 0.01). Subgroup analysis showed that the CPBA (MD: 15.70 ng/mL; 95% CI 15.20–16.20) was the only statistically significant variable (Table 2).

In sensitivity results, the residual results were unchanged after excluding small sample studies (MD: 5.02 ng/mL; 95% CI −6.86 to 16.90) or excluding studies with lower quality score (MD: 3.46 ng/mL; 95% CI −9.58 to 16.49).

In 9 included studies [26, 28–30, 32, 34, 38, 46, 59], the combined effect of the 1,25(OH) 2 D3 concentration on the comparison between CD patients and UC group was 5.05 pg/mL (95% CI −2.42 to 12.52) (Fig. 5). There was significant heterogeneity among the studies ($I^2 = 97\%$, P < 0.01). Subgroup analysis showed that only the cohort study design (MD: 16.57 ng/mL; 95% CI 15.47–17.66) was statistically significant (Table 2). Sensitivity analysis results remained unchanged after the removing studies of lower quality score (MD: 3.56 ng/mL; 95% CI 4.78 to 11.91).

Findings from a meta-analysis of serum 25(OH)D levels in UC patients
A meta-analysis of 15 studies [16, 29, 34, 36, 46, 54, 61, 62, 64, 66, 68, 71, 74, 76, 77] on serum 25(OH)D levels in both UC and healthy controls showed that patients with UC had lower levels of serum 25(OH)D than did the controls (MD: −2.52 ng/mL; 95% CI −4.02 to −1.02) (Fig. 6).

Findings of the meta-analysis for serum 25(OH)D levels in Crohn's patients
A total of 31 studies [16, 25, 29, 31–36, 43, 44, 46, 49, 53–55, 57, 60–66, 68–72, 76, 77] were conducted on serum 25(OH)D levels in CD and healthy controls, and we conducted a meta-analysis of 29 effect values. We found mean serum 25(OH)D levels in patients with CD were significantly lower than in healthy controls (MD: −3.17 ng/mL; 95% CI −4.42 to −1.93) (Fig. 2). There was significant heterogeneity among the studies ($I^2 = 88\%$, P < 0.01). Subgroup analysis (Table 2) showed that the mean serum 25(OH)D levels in adult CD patients was statistically significant compared to the control group (MD: −3.22 ng/mL; 95% CI −4.75 to −1.70) and children (MD: −3.16 ng/mL; 95% CI −5.54 to −0.77).

Compared with the control group, CLIA (MD: −1.32 ng/mL; 95% CI −8.89 to 6.26), ELISA (MD: −8.29 ng/mL; 95% CI −13.83 to −2.76) and RIA (MD: −3.22 ng/mL; 95% CI −4.46 to −0.13) were statistically significant, while CPBA, HPLC and LC–MS showed no statistical significance. Both the presence and absence of VitD supplementation was statistically significant (MD: −1.49 ng/mL; 95% CI −4.40 to 1.42) and (MD: −3.46 ng/mL; 95% CI −4.90 to −2.03), respectively. In regards to study design, case–control studies (MD: −4.95 ng/mL; 95% CI −7.18 to −2.72) and cohort studies (MD: −2.11 ng/mL; 95% CI −3.69 to −0.53) reported statistically significant results to the control group, but the cross-sectional studies did not find statistically significant differences. In sensitivity results, the residual results were unchanged after excluding small sample studies (MD: −3.48 ng/mL; 95% CI −4.78 to −2.17) or excluding studies with lower quality score (MD: −2.12 ng/mL; 95% CI −3.34 to −0.90).

The discussion between CD and UC about serum 25(OH)D levels were identified in thirty-seven studies [16, 18, 27–30, 32, 34, 36–42, 44–48, 50–52, 54, 56, 58, 61, 62, 64, 66–68, 71, 73, 75–77], which included a total of 2494 CD patients and 2017 non-healthy controls. The analysis revealed no significant difference in average serum 25(OH)D levels between the two groups (MD: −0.58 pg/mL; 95% CI −1.74 to 0.59) (Fig. 3). There was significant heterogeneity among the studies ($I^2 = 84\%$, P < 0.01). Subgroup analysis showed that only ECLIA (MD: 1.34 pg/mL; 95% CI 0.17–2.52) and the use of VitD supplementation (MD: 2.36 pg/mL; 95% CI 1.46–3.25) were statistically significant (Table 2). In sensitivity results, the residual results were unchanged after excluding small sample studies (MD: −0.51 ng/mL; 95% CI −1.69 to 0.66) or excluding studies with lower quality score (MD: −0.90 ng/mL; 95% CI −2.12 to 0.31).
Table 1 Characteristics of studies included in the meta-analysis

| Study         | Year | Study design | Country | Disease | Total, CD/UC/control | Female, CD/UC/control | Matching or adjustment | Maturity (CD/UC/control) | Vitamin D assessment | Vitamin D deficiency definition (ng/mL for 25(OH)D, pg/mL for 1,25(OH)(2)D) | Vitamin D supplementation | Quality score |
|---------------|------|--------------|---------|---------|----------------------|-----------------------|-----------------------|------------------------|-----------------------|-----------------------------------------------------------------------------|-----------------------------|---------------|
| Driscoll [25] | 1982 | Case–control | US      | CD      | 82/–/40              | NR/–/NR               | NR                    | >18                    | CPBA                  | Normal: 15.1–27.9                                                        | Yes                         | 5             |
| Harries [26]  | 1985 | Case–control | Wales   | CD and UC | 40/20/9              | 21/9/6                | NR                    | 38.75±15.42/45±17.5   | RIA                   | NR                                                                     | No                          | 5             |
| Westarp [69]  | 1987 | Case–control | Canada  | CD      | 3/–/64               | 25/–/37               | NR                    | 9.3±0.3                | CPBA                  | NR                                                                     | No                          | 5             |
| Martin [70]   | 1994 | Case–control | Italy   | CD      | 20/–/12              | 0/–/0                 | Age                   | 38.8±9.94/–/43±14     | HPLC                  | NR                                                                     | No                          | 6             |
| Pollak [27]   | 1998 | Case–control | Israel  | CD and UC | 63/41/–              | 23/21/–               | Age, sex              | 37.7±14.5 (IBD)/34.6±11.2 | RIA                  | Normal: 10–45                                                        | No                          | 4             |
| Gokhale [28]  | 1998 | Case–control | US      | CD and UC | 58/37/–              | 22/17/–               | NR                    | 14.3±2.9/13.7±3.5/–    | CPBA                  | NR                                                                 | No                          | 5             |
| Anticzone [29]| 2000 | Case–control | Italy   | CD and UC | 5/140/30             | 30/15/16              | Age, sex              | 38.7±13.2/34.4±12.5/3 | RIA                   | 25(OH)DNormal: 10–40; 1,25(OH)(2)DNormal: (2–12 years): 10.8–90.2   | No                          | 7             |
| Jahnsen [30]  | 2002 | Cross-sectional | Norway | CD and UC | 6/60/–               | 36/36/–               | Age, sex              | 36±16.5/38±13.5/–     | HPLC + RIA            | 25(OH)DNormal: 12–44; 1,25(OH)(2)DNormal: 19–56                      | No                          | 7             |
| Haderslev [31]| 2003 | Case–control | Denmark | CD and UC | 42/–/384             | 24/–/NR               | NR                    | 50.3±12.3              | RIA                   | Deficiency: < 15                                                       | No                          | 4             |
| Tajika [32]   | 2004 | Case–control | Japan   | CD and UC | 33/11/55             | 8/5/7                 | Age, sex              | 37.6±7.5/47.6±12.4/37 | CPBA + RIA            | 25(OH)DNormal: 10–55; deficiency: ≤ 10; 1,25(OH)(2)DNormal: 20–60    | No                          | 6             |
| Duggan [33]   | 2004 | Case–control | Ireland | CD      | 44/–/44              | 29/–/29               | NR                    | 36.9±11.1/–/36.7±11.0  | ELISA                 | ELSA + 25(OH)DNormal: 10–55; deficiency: ≤ 10; 1,25(OH)(2)DNormal: 20–60 | No                          | 6             |
| Abreu [34]    | 2004 | Cohort       | US      | CD and UC | 138/29/96            | 63/12/29              | NR                    | 37.7±1.1/38±1.3/40±1.0 | CPBA                 | Elevated 1,25(OH)(2)D: > 60; normal: 1,25(OH)(2)D: < 60              | No                          | 6             |
| McCarthy [35] | 2005 | Case–control | Ireland | CD      | 44/–/44              | 29/–/29               | Age, sex              | 36.9±11.1/–/36.7±11.1  | ELISA                 | Insufficiency: < 32; sufficiency: > 32; replete: > 20; mild deficiency: 10–20; moderate deficiency: 5–10; severe deficiency: < 5 | 2.5–20 μg/day | 6             |
| Gilman [36]   | 2006 | Cross-sectional | Ireland | CD and UC | 47/26/73             | NR/NR/NR              | Age, sex              | >18                    | ELISA                 | Deficiency: < 20                                                       | No                          | 5             |
| Pappa [37]    | 2006 | Cross-sectional | US      | CD and UC | 94/36/–              | 43/20/–               | NR                    | 15±3/14±4/–            | NR                   | Deficiency: ≤ 15; severe deficiency: ≤ 8                                | Yes                         | 3             |
| Sinnott [38]  | 2006 | Cohort       | US      | CD and UC | 30/18/–              | 14/9/–                | Age, sex              | 48.0±12.0/48.9±15.7/–  | NR                   | NR                                                                     | No                          | 4             |
| Vagianos [39] | 2007 | Cross-sectional | Canada  | CD and UC | 84/42/–              | 52/25/–               | NR                    | 37.6±14.3/36.6±12.9/–  | CPBA                  | Normal: 14–80; deficiency: 20–30                                      | Yes                         | 4             |
| Kuwabara [40] | 2008 | Cross-sectional | Japan   | CD and UC | 29/41/–              | 9/17/–                | NR                    | 32.2±6.7/39.3±14.6/–   | RIA                   | Deficiency: < 20; insufficiency: 21–29                                  | No                          | 3             |
### Table 1 (continued)

| Study     | Year   | Study design | Country     | Disease | Total, CD/UC/control | Female, CD/UC/control | Matching or adjustment | Maturity (CD/UC/control) | Vitamin D assessment tool | Vitamin D deficiency definition (ng/mL for 25(OH)D, pg/mL 1,25(OH)2D) | Vitamin D supplementation | Quality score |
|-----------|--------|--------------|-------------|---------|----------------------|-----------------------|------------------------|--------------------------|----------------------------|----------------------------|---------------------------|---------------|
| Leslie [41] | 2008   | Cohort       | Canada      | CD and UC | 56/45/–              | NR/NR/–                | NR                     | > 18                      | RIA                        | Optimal: > 30; marginally deficient: 20–30; insufficiency: 10–19; deficiency: < 10 | No            | 6             |
| Souza [71] | 2008   | Cohort       | Brazil      | CD and UC | 39/37/40             | 18/25/24               | NR                     | 32.1 ± 8.7/35.0 ± 8.5/34 0 ± 7.0 | RIA                        | No            | 6             |
| Joseph [42] | 2009   | Case–control | India       | CD and UC | 34/34/–              | 10/10/–                | Age, sex               | 39.2 ± 12.9/38.9 ± 13.4 (IBS) | RIA                        | Deficiency: < 20; insufficiency: 20–32; adequate: > 32 | No            | 6             |
| Kumari [43] | 2010   | Prospective case–control | Georgia | CD | 4/–/4 | 0/–/0 | Age | 35.5 ± 9.75/–/42.40± 5.13 | ELISA                        | Optimum: ≥ 32 | No            | 3             |
| El-Matary [54] | 2011   | Cross-sectional | Canada      | CD and UC | 39/21/56             | 20/11/31               | Age, sex, ethnicity    | 12.2 ± 3.2/12.4 ± 3.7/11 3 ± 4.2 | CPBA                        | Optimum ≥ 32 | No            | 3             |
| Levin [45] | 2011   | Cross-sectional | Australia  | CD and UC | 70/8/–              | NR/NR/–                | NR                     | 12.6 ± 3.5               | CLIA                        | NR            | No            | 3             |
| Pappa [47] | 2011   | Cross-sectional | US         | CD and UC | 288/143/–            | 12/7/8/–               | Age, sex, ethnicity    | 15.9 ± 3.1/15.4 ± 3.3/– | CLIA                        | Optimum: ≥ 32 | Yes           | 4             |
| Atia [48] | 2011   | Cross-sectional | US         | CD and UC | 43/80/–              | 3/7/–                  | NR                     | 61.4 ± 14.7/66.5 ± 11.5/– | CLIA                        | Deficiency: | No            | 2             |
| EI-Hodhod [46] | 2012   | Case–control | Egypt       | CD and UC | 20/27/50             | 2/13/9                 | Age, sex               | 10.49 ± 3.3/4/12.77 ± 1.7 1/12.8 ± 3.77 | RIA                        | Deficiency: < 15; severe deficiency: < 8 | No            | 6             |
| Suibhne [49] | 2012   | Case–control | Ireland     | CD        | 81/–/70              | 48/–/42                | Age, sexsocio-economic status. | 36.43 ± 11.00/–/36.34 ± 9.53 | RIA                        | 2cut-points (1) deficiency: < 20; (2) deficiency: < 32 | No            | 5             |
| Hassan [50] | 2012   | Cohort       | Iran        | CD and UC | 26/3/4/–             | 7/10/–                 | NR                     | 34 ± 18/30 ± 11/–          | RIA                        | Sufficient: ≥ 30; insufficiency: 11–29; deficiency: ≤ 10 ng/mL | No            | 7             |
| Chatu [51] | 2012   | Retrospective cohort | UK        | CD and UC | 107/61/–             | NR/NR/–                | NR                     | 34.98 ± 14.36 (BD)/– | CPBA                        | Normal: ≥ 20; deficiency: ≤ 20; severe: < 10 | No            | 4             |
| Fu [52]    | 2012   | Cohort       | Canada      | CD and UC | 40/60/–              | 18/32/–                | NR                     | 40 ± 13.2/42.1 ± 13.9/– | RIA                        | Hypovitaminosis: ≤ 20 | No            | 5             |
| Salcincinski [53] | 2012 | Cohort | US          | CD        | 19/–/19              | 10/–/10                | Age, sex               | 44.16 ± 10.28/–/41.68 ± 11.19 | HPLC                        | Low 25(OH)D levels: < 20 ng/mL; insufficient 20–32 ng/mL | No            | 3             |
| Gang [54]  | 2013   | Cohort       | Australia   | CD and UC | 40/3/1/23            | 18/14/13               | Sunlight exposure      | 41 ± 13.2/4/15.4/11.5 ± 11.5 | CLIA                        | Sufficient: ≥ 30; insufficiency: 20–30; deficiency: < 20 | 795/927/473/UI | 6             |
| Study          | Year | Study design | Country     | Disease          | Total, CD/UC/control | Female, CD/UC/control | Matching or adjustment | Maturity (CD/UC/control) | Vitamin D assessment tool | Vitamin D deficiency definition (ng/mL for 25(OH)D, pg/mL for 1,25(OH)2D) | Vitamin D supplementation | Quality score |
|---------------|------|--------------|-------------|------------------|----------------------|-----------------------|------------------------|------------------------|--------------------------|------------------------------------------------------------------------|-----------------------------|---------------|
| Prosnitz [55] | 2013 | Cohort       | US          | CD               | 78/–/221             | 34/–/109              | Anthropometry, body composition, pubertal development, weight, height | 12.7 ± 2.8/–/13.5 ± 4.4 | RIA                      | Deficiency: < 20           | No                        | 7               |
| Manerova [56] | 2013 | Cohort       | Slovakia    | CD and UC        | 46/30/–              | 25/15/–               | NR                     | 36 ± 12.7/5/47 ± 13.5/– | ECLIA                    | Deficiency: < 30; very low: < 10 | No                        | 4              |
| Grunbaum [57] | 2013 | Case–control | Canada      | CD and UC        | 34/21/48             | 21/13/38              | Age, sex, ethnicity, weight | 39.9 ± 12.3/44.2 ± 13.7/3 | RIA                      | Replete ≥ 30; insufficiency: 20–29; deficiency: < 20; severely deficiency: < 10 | 932.4/1020.8 (IU)          | 6              |
| Jorgensen [72] | 2013 | Cross-sectional | Denmark    | CD               | 182/–/62             | 57/–/52               | NR                     | 36 ± 10.2/–/32 ± 11 | LC–MS                    | Deficiency: < 20           | Yes                        | 5              |
| Middleton [57] | 2013 | Cross-sectional | US         | CD               | 52/–/40              | 20/–/25               | Age, sex, ethnicity, weight | 17.0 ± 0.9/–/11.0 ± 2.5 | CLIA + LC–MS | Deficiency: ≤ 15; insufficiency: < 15 | No                        | 5              |
| Lorinczy [58] | 2013 | Cross-sectional | Hungary    | CD and UC        | 128/41/–             | NR/ NR/–              | Age, sex, ethnicity, weight | 35.8 ± 12.0 | CLIA | Deficiency: < 15; insufficiency: < 15 | No                        | 5              |
| Alkhour [59] | 2013 | Case–control | US          | CD and UC        | 46/12/61             | 14/6/31               | Age, sex, ethnicity, weight | 12.1 ± 4.1/12.3 ± 3.5/12 | NR | Deficiency: < 12; severely deficiency: < 4 | No                        | 4              |
| Bruyn [60]    | 2014 | Prospective case–control | Netherlands | CD               | 98/–/43              | 68/–/NR               | NR                     | 36 ± 10.2/–/32 ± 7.3 | CLIA | Normal: ≥ 30; insufficiency: 20–30; deficiency: < 20 | Yes                        | 5              |
| Dumitrescu [61] | 2014 | Prospective case–control | Romania | CD and UC        | 14/33/94             | 6/16/44               | Age, sex, ethnicity, weight | 36 ± 9/42 ± 14/42 ± 12 | HPLC | Sufficient ≥ 30; insufficiency: 20–30; deficiency: < 20 | No                        | 7              |
| Tan [62]      | 2014 | Case–control | China       | CD and UC        | 107/124/122          | 61/39/55              | Age, sex, ethnicity, weight | 38.0 ± 15.3/39.6 ± 14.4/3 9.43 ± 12.7 | ELISA | Sufficient ≥ 20; insufficiency: 10–20; deficiency: < 10 | No                        | 7              |
| Okonomou [63] | 2014 | Case–control | Greece      | CD               | 44/–/20              | 22/–/14               | NR                     | 31 ± 8/–/30 ± 6.75 | CLIA | Sufficient ≥ 20; insufficiency: 10–20; deficiency: < 10 | No                        | 4              |
| Veit [64]     | 2014 | Cohort       | US          | CD and UC        | 40/18/116            | 16/11/67              | Age                     | 16.61 ± 2.2/16.13 ± 1.9 9/145 ± 4.35 | CPBA | Sufficient ≥ 30 ng/mL; insufficiency: 20–29; deficiency: < 20 ng/mL | No                        | 7              |
| Basson [65]   | 2015 | Cross-sectional | South Africa | CD               | 186/–/199            | NR/ NR/ NR            | NR                     | 47.35 ± 14.20/–/34.11 ± 15.16 | CLIA | Deficiency: ≤ 20 or 29 ng/mL | No                        | 7              |
| Thorsen [66]  | 2016 | Case–control | Danish      | CD and UC        | 155/20/384           | 69/114/196            | NR                     | 1365/24/430 ± 448/NS | LC–MS | Deficiency: < 50 nmol/mL; insufficiency: < 75 nmol; normal: ≥ 75 nmol | No                        | 4              |
| Schaffer [67] | 2017 | Cohort       | Germany     | CD and UC        | 123/85/–             | NR/ NR/ NR            | NR                     | NR                     | NR | Deficiency: < 50 nmol/mL; insufficiency: < 75 nmol; normal: ≥ 75 nmol | No                        | 4              |
| Study | Year | Study design | Country | Disease | Total, CD/UC/control | Female, CD/UC/control | Matching or adjustment | Maturity (CD/UC/control) | Vitamin D assessment tool | Vitamin D deficiency definition (ng/mL for 25(OH)D, pg/mL 1,25(OH)(2)D) | Vitamin D supplementation | Quality score |
|-------|------|--------------|---------|---------|----------------------|-----------------------|-----------------------|------------------------|--------------------------|---------------------------------------------------------------------|-----------------------------|---------------|
| Opstelten [68] | 2018 | Multicenter cohort | UK | CD and UC | 72/169/144 38 | 56/82/112 164 | Age, sex | 49.55±6.2/51.63±2.19/48.94±3.37; 51.61±1.96 | LCMS | Deficiency: ≤50 nmol/mL; insufficiency: 50–75 nmol/mL; sufficiency: ≥75 nmol/mL | No | 5 |
| Scotti [73] | 2018 | Cohort | Italy | CD and UC | 126/174/– | 56/76/– | Age, sex | 51 ±16.7/51 ±17.9/– | ELISA | Severe deficiency: ≤10 ng/mL; deficiency: 11–20 ng/mL; insufficient levels 21–30 ng/mL; adequate levels >30 ng/mL | No | 6 |
| Garg [74] | 2018 | Cohort | Australia | UC | –/17/8 | –/7/3 | Age, sex | 49.26±115/50.75±8.95 | LCMS | Deficiency: <50 nmol/mL; NO | 40000 IU/week | 7 |
| Caviezel [75] | 2018 | Cross-sectional | Switzerland | CD and UC | 99/57/– | 48/31/– | Age, sex | 41.2±14.5/41.5±13.6/– | CPBA | Deficiency: <50 nmol/mL | NO | 7 |
| Kyoung [18] | 2018 | Retrospective cohort | Korea | CD and UC | 42/45/– | 17/13/– | Age, sex | 40.9 ±15.6/48.5 ±13.7/– | CLIA | Deficiency: <20 ng/mL | No | 6 |
| Strisciuglio [76] | 2018 | Cohort | Italy | CD and UC | 12/21/18 | 17/8 | Age, sex | 11 ±3.25/9.8/9.2 ±2.5 | ELISA | NR | NR | 7 |
| Grag [77] | 2019 | Cohort | Australia | CD and UC | 20/15/14 | 8/5/7 | Age, sex | 43.75 ±11.7/42.75 ±11.75/48.25 ±13.56 | NR | NR | Yes | 8 |

CPBA competitive protein binding assay, RIA radioimmunoassay, ECLIA electrochemiluminescence immunoassay, ELISA enzyme-linked immunosorbent assay, CLIA chemiluminescence, HPLC high performance liquid chromatography, LC–MS liquid chromatograph mass spectrometer, NR not reported
These studies had high heterogeneity ($I^2 = 83\%$, $P < 0.01$). Subgroup analysis showed that the following variables were statistically significant: adults (MD: $-2.38$ ng/mL; 95% CI: $-4.20$ to $-0.56$), HPLC (MD: $-7.00$ ng/mL; 95% CI: $-11.58$ to $-2.42$), lack of VitD supplementation (MD: $-3.29$ ng/mL; 95% CI: $-4.99$ to $-1.60$), and cross-sectional study design (MD: $-18.07$ ng/mL; 95% CI: $-26.50$ to $-9.64$) (Table 2). Sensitivity analysis results was stabilization after small sample studies were removed (MD: $-2.94$ ng/mL; 95% CI: $-4.55$ to $1.33$).

There was almost no difference between UC and CD in 34 studies [16, 18, 27, 29–31, 34, 36–41, 46–48, 50–52, 54, 56, 58, 61, 62, 64, 66–68, 71, 73, 75–77] investigating VitD levels (MD: $0.75$ ng/mL; 95% CI: $-0.44$ to $1.94$) (Fig. 7). These studies had high heterogeneity ($I^2 = 84\%$, $P < 0.01$). Subgroup analysis showed that ECLI (MD: $-1.34$ ng/mL; 95% CI: $-2.52$ to $-0.17$), HPLC (MD: $3.69$ ng/mL; 95% CI: $0.34$–$7.04$), lack of VitD supplementation (MD: $-2.11$ ng/mL; 95% CI: $-3.69$ to $-0.53$), and the use of VitD supplementation (MD: $0.71$ ng/mL; 95% CI: $-0.63$ to $2.05$) were statistically significant (Table 2). Sensitivity analysis results remained stable after the removal of small samples (MD: $-0.88$ ng/mL; 95% CI: $-0.34$ to $2.10$) or lower quality score (MD: $0.72$ ng/mL; 95% CI: $-0.52$ to $1.96$).

Findings from the meta-analysis of $1,25$(OH)$_2$D$_3$ levels in UC patients

Five studies [26, 29, 34, 46, 59] reporting on levels of $1,25$(OH)$_2$D$_3$ in UC and healthy control groups found higher levels of $1,25$(OH)$_2$D$_3$ in the UC group than in the control group (MD: $3.76$ pg/mL; 95% CI: $-8.36$ to $15.57$) (Fig. 8). There was significant heterogeneity among the studies ($I^2 = 96\%$, $P < 0.01$). None of the results of the subgroup analyses from these studies were statistically significant (Table 2). Sensitivity analysis results remained unchanged after small samples were removed (MD: $3.40$ ng/mL; 95% CI: $-10.26$ to $17.06$).
### Table 2 Results of subgroup analysis

| Subgroup analyses                          | Crohn disease | Ulcerative colitis |
|--------------------------------------------|---------------|--------------------|
|                                            | No. of effect sizes | Mean (95% CI) | P for mean | I² (%) | No. of effect sizes | Mean (95% CI) | P for mean | I² (%) |
| **25(OH)D among disease patients and healthy controls** |               |                   |           |        |                   |           |           |        |
| Maturity                                   |               |                   |           |        |                   |           |           |        |
| Adults (> 18 years old)                    | 24            | -3.22 (-4.75 to -1.70) | <0.01   | 90     | 11                | -2.38 (-4.20 to -0.56) | <0.01   | 85     |
| Children (< 18 years old)                  | 8             | -3.61 (-4.89 to -2.32) | <0.01   | 90     | 4                 | -4.45 (-9.42 to 0.53)  | <0.01   | 78     |
| **Vitamin D assessment tool**              |               |                   |           |        |                   |           |           |        |
| CLIA                                       | 5             | -1.32 (-8.89 to 6.26)  | <0.01   | 95     | 2                 | -3.10 (-7.50 to 1.30)  | 0.2     | 38     |
| CLIA + LC–MS                               | 1             | -0.20 (-2.90 to 2.50)  | NR      | NR     | 0                 | -1.10 (-2.31 to 0.11)  | NR      | NR     |
| CPBA                                       | 5             | -4.28 (-6.40 to -2.16) | 0.06    | 55     | 1                 | -1.09 (-2.21 to 0.11)  | NR      | NR     |
| ELISA                                      | 6             | -8.29 (-13.83 to -2.76) | <0.01   | 85     | 3                 | -8.22 (-16.62 to 0.19) | <0.01   | 86     |
| HPLC                                       | 3             | -2.33 (-9.40 to 2.93)  | 0.09    | 58     | 1                 | -7.00 (-11.58 to -2.42) | NR      | NR     |
| LC–MS                                      | 3             | -0.35 (-0.99 to 0.29)  | 0.25    | 27     | 2                 | -0.15 (-0.57 to 0.27)  | 0.77    | 0      |
| RIA                                        | 8             | -4.46 (-9.05 to 0.13)  | <0.01   | 90     | 4                 | -4.52 (-12.89 to 3.85) | <0.01   | 89     |
| NR                                         | 1             | 3.11 (-3.37 to 9.59)   | NR      | NR     |                   |                     |          |        |
| **Vitamin D supplementation**              |               |                   |           |        |                   |           |           |        |
| No                                         | 24            | -3.46 (-4.90 to -2.03) | <0.01   | 91     | 12                | -3.29 (-4.99 to -1.60) | <0.01   | 87     |
| Yes                                        | 7             | -1.49 (-4.40 to 1.42)  | <0.01   | 66     | 3                 | 0.72 (-1.98 to 3.41)   | 0.95    | 0      |
| NR                                         | 1             | -12.14 (-19.54 to -4.74) | NR      | NR     | 0                 | -12.24 (-25.05 to -9.44) | NR      | NR     |
| **Study design**                           |               |                   |           |        |                   |           |           |        |
| Case–control study                         | 19            | -4.95 (-7.85 to -3.11) | <0.01   | 89     | 7                 | -2.24 (-4.39 to 0.11)  | <0.01   | 79     |
| Cohort study                               | 9             | -2.11 (-3.69 to -0.53) | <0.01   | 82     | 4                 | -2.58 (-5.29 to 0.13)  | <0.01   | 89     |
| Cross-sectional study                      | 4             | -0.44 (-6.76 to 5.87)  | <0.01   | 93     | 1                 | -18.07 (-26.50 to -9.64) | NR      | NR     |
| **25(OH)D among disease patients and non-healthy controls** |               |                   |           |        |                   |           |           |        |
| Maturity                                   |               |                   |           |        |                   |           |           |        |
| Adults (> 18 years old)                    | 28            | -0.84 (-2.12 to 0.44)  | <0.01   | 85     | 26                | 0.65 (-0.65 to 1.95)   | <0.01   | 86     |
| Children (< 18 years old)                  | 9             | 0.53 (-2.16 to 3.22)   | <0.01   | 78     | 8                 | 0.92 (-2.05 to 3.90)   | <0.01   | 79     |
| NR                                         | 1             | -1.88 (-5.52 to 1.76)  | NR      | NR     | 1                 | 1.88 (-1.76 to 5.52)   | NR      | NR     |
| **Vitamin D assessment tool**              |               |                   |           |        |                   |           |           |        |
| CLIA                                       | 7             | 1.66 (-1.36 to 4.68)   | <0.01   | 73     | 6                 | -0.81 (-3.96 to 2.43)  | <0.01   | 73     |
| CPBA                                       | 7             | -0.80 (-2.79 to 1.20)  | <0.01   | 76     | 6                 | 1.94 (-0.03 to 3.91)   | <0.01   | 78     |
| ELISA                                      | 2             | 1.34 (0.17 to 2.52)    | 0.62    | 0      | 0                 | -1.34 (-2.52 to -0.17) | 0.23    | 31     |
| HPLC                                       | 4             | 1.60 (-5.26 to 2.07)   | <0.01   | 84     | 1                 | 0.18 (-3.65 to 4.01)   | NR      | NR     |
| LC–MS                                      | 2             | -3.27 (-6.35 to 0.19)  | 0.53    | 0      | 1                 | 3.69 (0.34 to 7.04)    | NR      | NR     |
| RIA                                        | 10            | -1.65 (-5.16 to 1.86)  | <0.01   | 85     | 9                 | 1.18 (-2.61 to 4.98)   | <0.01   | 87     |
| NR                                         | 4             | -2.35 (-4.91 to -0.20) | 0.67    | 0      | 2                 | 2.33 (-0.20 to 4.91)   | 0.45    | 0      |
| **Vitamin D supplementation**              |               |                   |           |        |                   |           |           |        |
| No                                         | 34            | -0.48 (-1.70 to 0.74)  | <0.01   | 84     | 31                | -0.71 (-0.63 to -2.05) | <0.01   | 85     |
| Yes                                        | 4             | -2.36 (-3.25 to -1.46) | 0.45    | 0      | 3                 | 2.36 (1.46 to 3.25)    | 0.45    | 19     |
| **Study design**                           |               |                   |           |        |                   |           |           |        |
| Case–control study                         | 12            | -0.07 (-1.77 to 1.64)  | <0.01   | 58     | 9                 | 0.91 (-1.09 to 2.91)   | 0.37    | 68     |
| Cohort study                               | 10            | 0.46 (-1.28 to 2.20)   | <0.01   | 74     | 16                | 0.09 (-1.52 to 1.69)   | 0.92    | 78     |
| Cross-sectional study                      | 10            | -0.56 (-4.21 to 3.10)  | <0.01   | 91     | 9                 | 1.47 (-1.56 to 4.50)   | 0.34    | 91     |
| **1,25(OH)2D3 among disease patients and healthy controls** |               |                   |           |        |                   |           |           |        |
| Maturity                                   |               |                   |           |        |                   |           |           |        |
| Adults (> 18 years old)                    | 5             | 0.31 (-12.88 to 13.50) | <0.01   | 96     | 3                 | -2.94 (-7.25 to 1.38)  | 0.11    | 55     |
Overall, when all seven eligible studies [26, 29, 30, 34, 38, 46, 59] were analyzed using a random-effects model, the results showed that VitD levels were lower in patients with UC than in CD (MD: −6.71 pg/mL; 95% CI −15.30 to 1.88) (Fig. 9). There was significant heterogeneity among the studies (I² = 94%, P < 0.01). Subgroup analysis showed that only the cohort studies (MD: −16.57 ng/mL; 95% CI −17.66 to −15.47) were statistically significant (Table 2). Sensitivity analysis results remained unchanged after small samples were removed (MD: −5.09 ng/mL; 95% CI −15.28 to 5.10).

### Discussion

There are several competing views on the link between VitD deficiency and IBD in the literature. For UC, Ulitsky et al. [17] reported that VitD deficiency is not associated with UC, but another study [78] reported a correlation. With regard to CD, Khalili et al. [79] reported that VitD deficiency was associated with CD, but the Grunbaum’s [16] study did not. To explore this controversy, we performed a pooled meta-analysis to determine the status of VitD in the serum of healthy and non-healthy controls.

Vitamin D is the only fat-soluble vitamin that may provide potential effects in treating IBD [7]. From our meta-analysis, we have concluded that VitD levels are strongly associated with IBD. Our meta-analysis found that patients with CD and UC had mean lower levels of VitD compared to healthy controls. This finding is consistent with previous studies that have reported a correlation between VitD deficiency and IBD.

### Publication bias

For the meta-analyses, publication bias was not assumed, as all funnel plots were essentially symmetrical.
**Fig. 3** Mean difference of serum 25(OH)D levels among patients with Crohn’s disease compared with non-healthy controls

**Fig. 4** Mean difference of serum 1,25(OH)2D levels among patients with Crohn’s disease compared with healthy controls
25(OH)D than did healthy populations; however, there was no significant difference in serum 25(OH)D levels between CD and UC patients. So VitD levels may be independent of disease type. This can be explained by insufficient intake, insufficient absorption or excessive loss of VitD in patients with IBD [13]. When comparing the mean levels of 1,25(OH)₂D₃ we found that patients with CD and UC did not lack 1,25(OH)₂D₃, and, in fact, patients with CD and UC had higher levels of VitD than healthy populations. Moreover, the average concentration of 1,25(OH)₂D₃ in CD patients was significantly higher than in patients with UC.

Current studies [80–82] have suggested that VitD plays a role in IBD-specific complications. The best indicator of VitD status is serum 25(OH)D because it closely reflects both dietary intake and the amount of sunlight exposure [83], and 25(OH)D has a half-life of 12 to 19 days [5, 13], however, 1,25(OH)₂D₃ has a short half-life of 4 to 20 h and is not a reliable indicator of the total amount of vitamin D in the body [84]. Although the serum 1,25(OH)₂D₃ content of IBD patients was higher than that of healthy populations, we cannot ignore the importance of 1,25(OH)₂D₃. In accordance with our findings, Abreu’s study [34] also demonstrated that IBD patients have high levels of 1,25(OH)₂D₃ especially in CD patients. It has been suggested that elevated 1,25(OH)₂D₃ may be a direct cause of bone loss or act as a surrogate marker for the type of intestinal inflammation that results in
ostoporosis. In addition, in the presence of intestinal inflammation, an increase in the number of lamina propria monocytes, combined with the availability of 25(\text{OH})D as a 1α-hydroxylase substrate, resulted in increased levels of 1,25(\text{OH})2D3 [34, 85]. In our study, we also found that the level of 1,25(\text{OH})2D3 in patients with CD was...
significantly higher than that in patients with UC. However, in some studies, we also found that the serum level of 1,25(OH)2D3 was lower in IBD patients than in healthy control groups. This may be due to improved BMD after remission of IBD, making 1,25(OH)2D3 normal.

Based on the subgroup analysis of age, VitD deficiency was more common in adults and children with IBD. Although, there was no significant difference in VitD levels between adults and children, whether they were in an IBD or a healthy control group. In children, El-Matary et al. [44] found that VitD levels were lower (though not statistically significant) in UC patients than in a CD group. However, in Veit’s study, 25(OH)D was significantly higher in children with CD than in children with UC [65]. In our subgroup analysis, we found no significant differences in vitamin D levels between CD and UC pediatric patients; and, we found the same results in adults. An association between IBD risk and pre-diagnosis predicted VitD status has been established in adult populations. There may be differences in genetic susceptibility and immunopathogenic pathways between childhood and adult onset IBD, because children with IBD seem to be a unique group with special characteristics that require highly skilled and specialized methods for diagnosis and treatment [76, 86, 87].

With VitD intake and foods meeting only 20% of total daily needs, it is important to educate people about the importance of introducing foods rich in vitamin D into their daily diet [88]. The RDA is 400 international units (IU) or 10 ng for male and female infants (i.e., less than 1 year old), 600 IU or 15 ng for all male and female individuals from 1 to 70 years old, and 800 IU or 20 ng for those over 70 years old [89]. Dietary supplements are generally considered to be a rapid form of VitD supplementation, and the total intake of VitD always reflects the combined contribution of the food source and the supplement to the diet. VitD can be found in VitD2 or VitD3; however, the former is rarely used as a fortifier in dietary supplements [90, 91]. Increasing VitD in foods may be the best way to increase intake, but it does not significantly increase serum 25(OH)D levels. We believe that VitD supplements should be used to increase serum VitD levels more quickly and directly. Of course, dietary supplements with high VitD content may help improve the low VitD levels in patients with IBD.

VitD supplementation has been shown to reduce the recurrence of some immune-mediated diseases [92, 93], and adverse events associated with VitD supplementation is relatively low. VitD supplementation reduced clinical recurrence from 29 to 13% (P = 0.06) [94]. We measured VitD supplementation in the analysis, which was found in 12 studies. Jorgensen [57] found that CD patients reported taking VitD supplements in winter, and their levels of 25(OH)D were significantly higher than non-users. This further confirms the views of Pappa [47] and Grunbaum [16] who suggested that higher doses may yield better results. Other studies have shown that VitD is more necessary in winter and that large amounts of it are more effective (even up to 10,000 IU/day) [95–97]. High doses of VitD3 supplements (10,000 IU/day) may significantly reduce clinical recurrence and significantly improve quality of life [94, 98–100]. VitD3 is formed by exposure of the skin to sunlight [101]. In winter, when sunlight is scarce, VitD should be taken. Notably, in several studies more IBD patients were found to be taking VitD supplements, and subsequently tended to have higher total daily oral intake of vitamin D [43, 54, 77]. Since there is not enough trial data investigating different doses of vitamin D supplements, large, well-designed randomized controlled trials using different doses of vitamin D supplements are needed to help better understand the therapeutic significance of vitamin D in IBD.

In addition, we found that different VitD measurement tools may affect the final results. After our analysis, VitD

### Table 1

| Study              | Ulcerative colitis | Non-healthy controls | Mean Difference | Weight (fixed) | Weight (random) |
|--------------------|--------------------|-----------------------|----------------|----------------|-----------------|
| Ardizzone 2000     | 40 28.70 9.40      | 51 28.70 8.60         | 0.00 [−3.75; 3.75] | 7.6% 16.8%     |
| El−Hodhod 2012     | 27 56.11 12.11     | 20 65.65 14.99        | −9.54 [−17.54; −1.54] | 1.7% 15.1%     |
| Abreu 2004         | 29 41.30 2.80      | 138 57.80 2.50        | −16.50 [−17.60; −15.40] | 87.8% 17.3%     |
| Gokhale 1998       | 37 42.20 27.80     | 58 36.50 23.30        | 5.70 [−5.08; 16.48] | 0.9% 13.6%     |
| Alkhouri 2013      | 12 32.00 25.80     | 46 29.90 12.70        | 2.10 [−12.95; 17.15] | 0.5% 11.3%     |
| Harries 1985       | 20 52.00 25.05     | 40 54.62 24.29        | −2.62 [−15.93; 10.69] | 0.6% 12.2%     |
| Sinnott 2006       | 18 29.60 17.00     | 30 52.40 20.40        | −22.80 [−33.52; −12.08] | 0.9% 13.7%     |

Fig. 9 Mean difference of serum 1,25(OH)2D3 levels among patients with ulcerative colitis compared with non-healthy controls

| Study | Ulcerative colitis | Non-healthy controls | Mean Difference | Weight (fixed) | Weight (random) |
|-------|--------------------|-----------------------|----------------|----------------|-----------------|
| Ardizzone 2000 | 40 28.70 9.40 | 51 28.70 8.60 | 0.00 [−3.75; 3.75] | 7.6% 16.8% |       |
| El−Hodhod 2012 | 27 56.11 12.11 | 20 65.65 14.99 | −9.54 [−17.54; −1.54] | 1.7% 15.1% |       |
| Abreu 2004 | 29 41.30 2.80 | 138 57.80 2.50 | −16.50 [−17.60; −15.40] | 87.8% 17.3% |       |
| Gokhale 1998 | 37 42.20 27.80 | 58 36.50 23.30 | 5.70 [−5.08; 16.48] | 0.9% 13.6% |       |
| Alkhouri 2013 | 12 32.00 25.80 | 46 29.90 12.70 | 2.10 [−12.95; 17.15] | 0.5% 11.3% |       |
| Harries 1985 | 20 52.00 25.05 | 40 54.62 24.29 | −2.62 [−15.93; 10.69] | 0.6% 12.2% |       |
| Sinnott 2006 | 18 29.60 17.00 | 30 52.40 20.40 | −22.80 [−33.52; −12.08] | 0.9% 13.7% |       |

Fig. 9 Mean difference of serum 1,25(OH)2D3 levels among patients with ulcerative colitis compared with non-healthy controls.

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Li et al. J Transl Med (2019) 17:323
deficiency in IBD patients measured by ELISA and HPLC was found to be more severe (though not statistically significant) in comparison to control groups. Therefore, different VitD measurements may affect the results. There are different methods for the determination of 25(OH)D, including competitive binding protein assays, immunosays (such as chemiluminescence immunoassays [CLIA]), high performance liquid chromatography (HPLC), and liquid chromatography-tandem mass spectrometry (LC-MS/MS) that are currently considered more accurate and accurate [102, 103]. A studies have shown that different methods of vitamin D measurement can affect the results of vitamin D measurement [104–107]. Therefore, I believe that the standardization of vitamin D measurement is helpful for the diagnosis and treatment of IBD. In addition, free 25(OH)D may reflect the status of biologically active vitamin D better than total 25(OH)D [108]. Recent studies have shown that patients with IBD have normal or even higher levels of free 25(OH)D, despite a total deficiency of 25(OH)D [76]. Measuring free 25(OH)D may establish a relationship between IBD and vitamin D.

In terms of study design, a significant difference was found in the cohort studies for 1,25(OH)2D3 between the diseased patients and non-healthy controls, but this result may have been caused by small sample sizes. There was no significant difference between study designs among the other groups. Therefore, different research designs did not affect the final results.

It is unclear whether VitD deficiency is a consequence of IBD or a contributing factor to its pathogenesis. However, VitD may be an important mediator in the pathogenesis of CD and possibly UC [109]. Though our research found a relationship between the VitD deficiency and IBD, the relationship with UC was not obvious in some respects. It is possible that VitD deficiency is more closely related to celiac disease, and that the disease activity of celiac disease promotes the process of UC.

One advantage of this meta-analysis was that it included a large number of subjects, including CD and UC subjects, which examined the associations between 25(OH)D and 1,25(OH)2D3 levels, and considered healthy and non-healthy controls in their analyses. Furthermore, it was possible to perform subgroup analyses according to age group, VitD assessment tools, VitD supplementation and study design. In our sensitivity analysis, we excluded small samples and low-scoring studies to see if the results were altered. However, this meta-analysis has some limitations. First, there was no subgroup analysis based on gender, season, race, or disease activity, as there was not enough data. Second, although funnel plots showed no significant publication bias, there may still be publication biases in the retrieved articles. Third, there was no unified diagnostic standard for IBD in the included studies, which may have greatly increased the false positive rate and affected the results of the included studies. Fourth, the relevant parties of RDA cannot do in-depth analysis due to various objective reasons.

Conclusions
In summary, we found that VitD levels were inversely related to CD and UC. Serum levels of 25(OH)D3 were lower in these patients than in healthy controls, and more than half of the patients had insufficient vitamin D levels; however, the serum level of 1,25(OH)2D3 was higher than that of healthy controls. Our analysis indicates that attention should be paid to VitD levels to prevent the occurrence of IBD. In clinical practice, IBD patients should supplement their diets with VitD and be aware of the effects different seasons have on VitD content. In follow-up studies, vitamin D may be used as a treatment for IBD, or as an adjunctive therapy. We believe our research can provide a reference point for other scholars; however, our results cannot clarify the pathogenesis or suggest a cure for IBD. Rather, these results should provide directions for future research, as more exploration is needed.

Supplementary information
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Additional file 1: Method S1 Search strategy.
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