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Systematic review with meta-analysis: association of vitamin D status with clinical outcomes in adult patients with inflammatory bowel disease

John Gubatan[1,2] | Naomi D. Chou[1] | Ole Haagen Nielsen[3] | Alan C. Moss[1]

[1]Division of Gastroenterology and Hepatology, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA

[2]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA, USA

[3]Department of Gastroenterology, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark

Correspondence
Alan C. Moss, MD, Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Boston, MA 02215.
Email: amoss@bidmc.harvard.edu

Summary

Background: Vitamin D deficiency is highly prevalent among patients with IBD, however, data on its association with clinical outcomes are conflicting.

Aim: To perform a systematic review and meta-analysis to explore the association of low vitamin D status with clinical outcomes in patients with IBD.

Methods: We searched PubMed, Embase, Scopus and Web of Science from inception to February 2018 for observational studies evaluating the association of low 25(OH)D status on IBD disease activity, mucosal inflammation, clinical relapse and quality of life. Odds ratios (ORs) were pooled and analysed using a random effects model.

Results: Twenty-seven studies were eligible for inclusion comprising 8316 IBD patients (3115 ulcerative colitis, 5201 Crohn's disease). Among IBD patients, low 25(OH)D status was associated with increased odds of disease activity (OR 1.53, 95% CI 1.32-1.77, I^2 = 0%), mucosal inflammation (OR 1.25, 95% CI 1.06-1.47, I^2 = 0%), low quality of life (QOL) scores (OR 1.30, 95% CI 1.06-1.60, I^2 = 0%) and future clinical relapse (OR 1.23, 95% CI 1.03-1.47, I^2 = 0%). In subgroup analysis, low vitamin D status was associated with Crohn's disease activity (OR 1.66, 95% CI 1.36-2.03, I^2 = 0%), mucosal inflammation (OR 1.39, 95% CI 1.03-1.85, I^2 = 0%), clinical relapse (OR 1.35, 95% CI 1.14-1.59, I^2 = 0%), and low QOL scores (OR 1.25, 95% CI 1.04-1.50, I^2 = 0%) and ulcerative colitis disease activity (OR 1.47, 95% CI 1.03-2.09, I^2 = 0%) and clinical relapse (OR 1.20, 95% 1.01-1.43, I^2 = 0%).

Conclusions: Low 25(OH)D status is a biomarker for disease activity and predictor of poor clinical outcomes in IBD patients.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan. The Handling Editor for this article was Professor Jonathan Rhodes, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, inflammatory disorder of the gastrointestinal tract. The incidence and prevalence of IBD is increasing worldwide[1] and is associated with significant healthcare utilisation in the United States.[2] Although the exact aetiology of IBD remains unclear, IBD is speculated to arise from a complex interaction between genetic susceptibility, derangements in immune homeostasis, inappropriate responses to gut microflora and various environmental triggers.[3-7] Increasing evidence has proposed that vitamin D plays a protective role in the pathogenesis of inflammatory bowel disease.[8,9] Vitamin D has been shown to maintain gut epithelial barrier integrity against inflammatory and pathogenic stimuli.[10,11] Previous studies have demonstrated that vitamin D has anti-inflammatory effects on immune responses [12-15] and plays a role in regulating the gut microbiome.[16-18]

Vitamin D deficiency is highly prevalent among patients with inflammatory bowel disease. In one systematic review and meta-analysis[19] comprising of over 900 IBD patients, vitamin D deficiency (defined as serum 25(OH)D levels ≤25 ng/mL) was prevalent in 38.1% of patients with Crohn's disease and 31.6% in patients with ulcerative colitis. The same study demonstrated that IBD patients also had increased odds of lower vitamin D levels compared to matched controls. Due to the potential mechanistic link between vitamin D and colitis and the high prevalence of vitamin D deficiency in IBD patients, many groups have sought to examine the impact of vitamin D levels on IBD clinical outcomes,[20-46] often with conflicting results. Many of these previous studies were limited by their small sample size and inability to detect differences in clinical outcomes between low and high vitamin D groups. Differences in definitions of low vitamin D status, heterogeneity in disease characteristics among IBD cohorts and outcomes and measures evaluated have resulted in conflicting results between vitamin D and IBD clinical outcomes. There remains an unmet need for an understanding of vitamin D thresholds for beneficial outcomes in IBD, particularly in light of controversies over the impact of vitamin D thresholds on bone health in the general population. Given the conflicting results from previous studies and need for clarification, we performed a systematic review and meta-analysis to explore the association of low vitamin D status on IBD clinical outcomes (disease activity, mucosal inflammation, clinical relapse and quality of life).

2 | MATERIALS AND METHODS

2.1 | Study protocol

Our systematic review and meta-analysis was conducted according to PRISMA and MOOSE guidelines (MOOSE checklist summarised as Table S6).[47,48] We performed a search of major electronic databases from inception to February 2018. The following databases were included: (1) Medline (Pubmed), (2) EMBASE, (3) Scopus and (4) Web of Science. Our search strategy included the following combinations: (1) 'Vitamin D' [and] 'Inflammatory Bowel Disease', (2) 'Vitamin D' [and] 'Ulcerative Colitis' and (3) 'Vitamin D' [and] 'Crohn's Disease'. Our search strategy was limited to the English language. We contacted authors of studies for additional data/information and clarification. Only studies where authors provided missing information/clarifications were included in our final review.

2.2 | Definition of low vitamin D status

The measure of vitamin D status in our systematic review and meta-analysis used only serum 25-hydroxyvitamin D [25(OH)D]. Low vitamin D status was defined by vitamin D deficiency thresholds set by individuals studies. Most of our included studies defined low 25(OH)D with a serum level < 20 ng/mL (19 studies[21,23-28,32-39,41,42,44,45]). Five studies[22,30,40,43,46] defined low 25(OH)D as <30 ng/mL. Other low serum 25(OH)D thresholds included were <10 ng/mL (1 study[31]), <12 ng/mL (1 study[20]) and <35 ng/mL (1 study[29]).

2.3 | Definition of clinical outcomes

Clinical outcomes evaluated in our study included (a) clinically active disease (b) mucosal inflammation, (c) clinical relapse and (d) low quality of life scores. We accepted definitions defined by individual studies. Clinically active disease was defined by disease activity scores (Partial Mayo Index, Truelove and Witts Score, Simple Colitis Disease Activity Index (SCDAI), Simple Clinical Colitis Activity Index (SCCAI), Crohn's Disease Activity Index (CDAI), Ulcerative Colitis Disease Index (UCDI), Harvey Bradshaw Index (HBI), Ulcerative Colitis Activity Index (UCAI)) above set thresholds determined by individual studies. Mucosal inflammation was defined by faecal calprotectin, endoscopic scores (simple endoscopic score, Mayo endoscopic score) or histological scores (Geboes score) above set thresholds determined by individual studies. Clinical relapse was defined by individual studies and includes any of the following: longitudinal increase in disease activity/inflammation score, failure of TNF-α inhibitors, need for medication intensification, any IBD-related hospitalisations, surgeries or healthcare utilisation. 'Low' quality of life was defined as a short IBD questionnaire (sIBDQ) score <50 in all included studies that evaluated IBD quality of life.

2.4 | Inclusion and exclusion criteria

Two authors (JG and NC) independently reviewed abstracts and manuscripts for eligibility. Conflicts were resolved with consultation of a senior author (ACM) Our inclusion and exclusion criteria are outlined below:

2.4.1 | Inclusion criteria

1. Human studies including patients 18 years or older with known diagnosis of inflammatory bowel disease (ulcerative colitis or Crohn' disease)

2. Observational study design (cross-sectional, retrospective, prospective)
3. Measured serum 25(OH)D levels (exposure)
4. Vitamin D groups dichotomised into 'low' or 'normal/high group'
5. Study evaluated association of serum 25(OH)D on IBD clinical outcomes (disease activity, inflammation, clinical relapse, quality of life)

2.4.2 | Exclusion criteria

1. Review articles and other systematic reviews or meta-analyses
2. Non-Human Studies (cell culture, animal models)
3. Non-English study or studies without English translated versions
4. Paediatric cohorts (patients less than 18 years of age)
5. No measure of vitamin D available
6. Clinical outcomes not reported
7. Association between 25(OH)D and clinical outcomes not measured
8. Incomplete data on clinical outcome statistical measures (Odds ratios, 95% CIs), unable to calculate outcome measures with available data (number of IBD patients with low and high 25(OH)D with specified clinical outcomes not provided), or studies with authors not responding when contacted with provide additional data/clarification

We chose to include only observational studies in our systematic review and meta-analysis as we sought to evaluate the natural history of the association of low vitamin D status on clinical outcomes in IBD. We excluded interventional studies with vitamin D as our exposure of interest was low vitamin D status and not vitamin D treatment. Furthermore, we did not want to combine the results from observational studies with interventional studies given the significant risk of bias and heterogeneity inherent in the different study designs. While the effect of vitamin D supplementation on IBD clinical outcomes is an important question, we felt a separate meta-analysis should address this question.

The following data were extracted/determined (Table 1):

1. Study characteristics: primary author, year of publication, type of study design, location of study, latitude (in degrees) of study location
2. Patient characteristics: IBD cohort mean age, proportion of male patients, race (reported as percentage of Caucasian patients), total number of IBD patients, number of ulcerative colitis patients, number of Crohn's disease patients,
3. Type of 25(OH)D assay used
4. 25(OH)D concentration (ng/mL) cut-off for low/25(OH)D status group, IBD cohort mean 25(OH)D concentration (ng/mL)
5. Type of clinical outcomes (disease activity, mucosal inflammation, clinical relapse, quality of life scores), measures of clinical outcomes (disease activity scores, faecal calprotectin levels, endoscopic/histological scores, rates of clinical relapse, sIBDQ scores) and scores/thresholds used to define outcomes, statistical measure of outcome (RR, OR, 95% CIs) or number of IBD patients dichotomised into low and normal/high 25(OH)D groups with each specific clinical outcome

2.5 | Assessment of study quality

Two authors (JG and NC) independently assessed the quality of included studies using the Newcastle-Ottawa scale for case-control studies or cohort studies.[49] Significant conflicts between Newcastle-Ottawa scores were resolved with consultation of a senior author (ACM), otherwise scores were averaged between the two reviewers. The following criteria were evaluated: selection (case definition of IBD and low 25(OH)D), representativeness of cases, definition of controls (normal/high 25(OH)D groups), comparability (of cases and controls), ascertainment of exposure (25(OH)D measurements), assessment of outcomes. Newcastle-Ottawa scores were defined as high (score 7-9), moderate (score 4-6) or low (score 0-3).

2.6 | Statistical analyses

Adjusted odds ratios (OR) from individual studies were extracted when available otherwise unadjusted OR were calculated using dichotomous data (low vs normal/high 25(OH)D IBD groups) for each available clinical outcome (disease activity, inflammation, clinical relapse, quality of life). Review Manager v5.3 was used via a random-effects model to calculate the pooled odds (and 95% CI and *P*-values) of clinically active disease, mucosal inflammation, clinical relapse and quality of life among IBD patients with low versus normal/high 25(OH)D levels, generate forest plots and calculate the I^2 statistic. Heterogeneity was assessed using the I^2 statistic defined by the Cochrane Handbook for Systematic Reviews.[50] Either Chi^2 test $P < .10$ or I^2 value > 50% indicated substantial heterogeneity. We used the STATA/IC v15.1 (2017, College Station, TX) 'metafunnel' and 'metabias' functions to generate funnel plots and test for funnel plot asymmetry using Egger's test respectively. We performed the following subgroup analyses for each clinical outcome (when feasible based on number of available studies available in each subgroup):

1. IBD subtype (Ulcerative colitis vs Crohn's disease)
2. Study design (Prospective vs Retrospective studies)
3. 25(OH)D deficiency Cut-off Concentration (<20 ng/mL vs other cut-off values)
4. Adjusted vs Unadjusted OR
5. For mucosal inflammation: Faecal Calprotectin vs Endoscopic/Histological Scores

Since baseline differences in IBD cohort characteristics may mediate the association between low 25(OH)D and IBD clinical outcomes, we further performed meta-regression analyses to identify potential moderator variables. We performed meta-regression analyses for clinical outcomes that included ten or more studies (disease activity and clinical relapse) using the STATA/IC 'metareg' function. We performed the following meta-regression analyses:

1. Study Location Latitude (Absolute Degrees from Equator)
2. IBD Cohort 25(OH)D Deficiency Cut-off Concentration (ng/mL)
3. IBD Cohort Mean 25(OH)2D Concentration (ng/mL)

TABLE 1 Baseline characteristics of included studies

Study (y)	Study design	Location of study	25(OH)D Def. Cut-Off (ng/mL)	Mean 25(OH) D (ng/mL)	Age (y)	Proportion Male	Caucasian race (%)	UC	CD	Clinical outcomes
Alrefai *et al* (2017)[20]	Retrospective cohort	Saskatoon, SK, Canada	12	23.2	40.2	0.413	Not given	0	201	DA
Anathakrishnan *et al* (2013)[21]	Retrospective cohort	Boston, MA, USA	20	26.0	48.0	0.393	87	1454	1763	CL
Blanck *et al* (2013)[22]	Retrospective CS	Philidelphia, PA, USA	30	26.0	45.7	0.471	79.4	34	0	DA
Bours *et al* (2018)[23]	Retrospective CS	Amersfoort, Netherlands	20	22.0	48.5	0.744	Not given	185	131	DA
Castro *et al* (2015)[24]	Retrospective CS	Guimarães, Portugal	20	26.0	33.8	0.276	Not given	19	57	DA, QOL
Dolatshahi *et al* (2016)[25]	Retrospective CS	Tehran, Iran	20	19.1	37.0	0.400	Not given	50	0	DA
Frigdstad *et al* (2017)[26]	Prospective Cohort	Gralum, Norway	20	20.4	39.8	0.510	Not given	178	230	DA, MI, CL
Garg et al (2013)[27]	Retrospective CS	Melbourne, Australia	20	28.0	42.5	0.549	97.2	31	40	MI
Ghaly *et al* (2016)[28]	Prospective Cohort	Murdoch, Australia	20	27.2	40.0	0.463	92	0	309	CL
Gubatan *et al* (2017)[29]	Prospective Cohort	Boston, MA, USA	35	44.0	48.6	0.214	92.9	70	0	MI, CL
Ham *et al* (2015)[30]	Prospective Cohort	Boston, MA, USA	30	32.0	32.2	0.514	Not given	0	37	DA
Hassan *et al* (2013)[31]	Retrospective CS	Mashad, Iran	10	13.2	32.0	0.283	Not given	34	26	DA
Hlavaty *et al* (2014)[32]	Retrospective CS	Bratislava, Slovakia	20	28.2	42.8	0.507	Not given	70	141	QOL
Jorgensen *et al* (2013)[33]	Retrospective CS	Aarhus, Denmark	20	24.4	36.0	0.687	Not given	0	182	DA
Kabbani et al (2016)[34]	Prospective Cohort	Pittsburgh, PA, USA	20	35.4	44	0.477	Not given	367	598	DA, CL, QOL
Meckel *et al* (2016)[35]	Retrospective CS	Chicago, IL, USA	20	21.8	45.8	0.535	90.4	230	0	MI
Raffner-Basson *et al* (2015)[36]	Retrospective CS	Bellville, South Africa	20	26.0	47.0	0.274	19	0	186	DA
Rafteryet *al* (2015)[37]	Retrospective CS	Dublin, Ireland	20	24	44.8	0.479	99.2	0	119	MI
Santos-Antunes *etal* (2016)[38]	Prospective Cohort	Porto, Portugal	20	19.0	41.9	0.485	Not given	12	56	CL
Schaffler *et al* (2017)[39]	Retrospective CS	Rostock, Germany	20	22.8	47.6	0.409	Not given	85	123	DA
Scolaro *et al* (2018)[40]	Retrospective CS	Santa Catarina, Brazil	30	27.9	49.3	0.350	Not given	26	34	DA, MI
Torki *et al* (2015)[41]	Retrospective CS	Isfahan, Iran	20	30.8	42.0	0.459	Not given	85	48	DA
Ulitsky *et al* (2011)[42]	Retrospective cohort	Milwaukee, WI, USA	20	23.6	43.1	0.550	Not given	101	403	DA, QOL
Venkata *et al* (2017)[43]	Retrospective cohort	Montgomery, AL, USA	30	26.9	49.1	0.342	75.5	0	196	CL
Winter *et al* (2017)[44]	Retrospective cohort	Boston, MA, USA	20	22.0	38.3	0.324	Not given	57	116	CL
Ye *et al* (2017)[45]	Retropsective CS	Hangzhou, China	20	21.1	27.0	0.733	Not given	0	131	DA, MI
Zator *et al* (2014)[46]	Retrospective cohort	Boston, MA, USA	30	27.0	30.0	0.495	95	27	74	CL

Abbreviations: CD, Crohn's disease; CL, clinical relapse; CS, cross-sectional; DA, disease activity; Def, deficiency; MI, mucosal inflammation; QOL, quality of life; UC, ulcerative colitis.

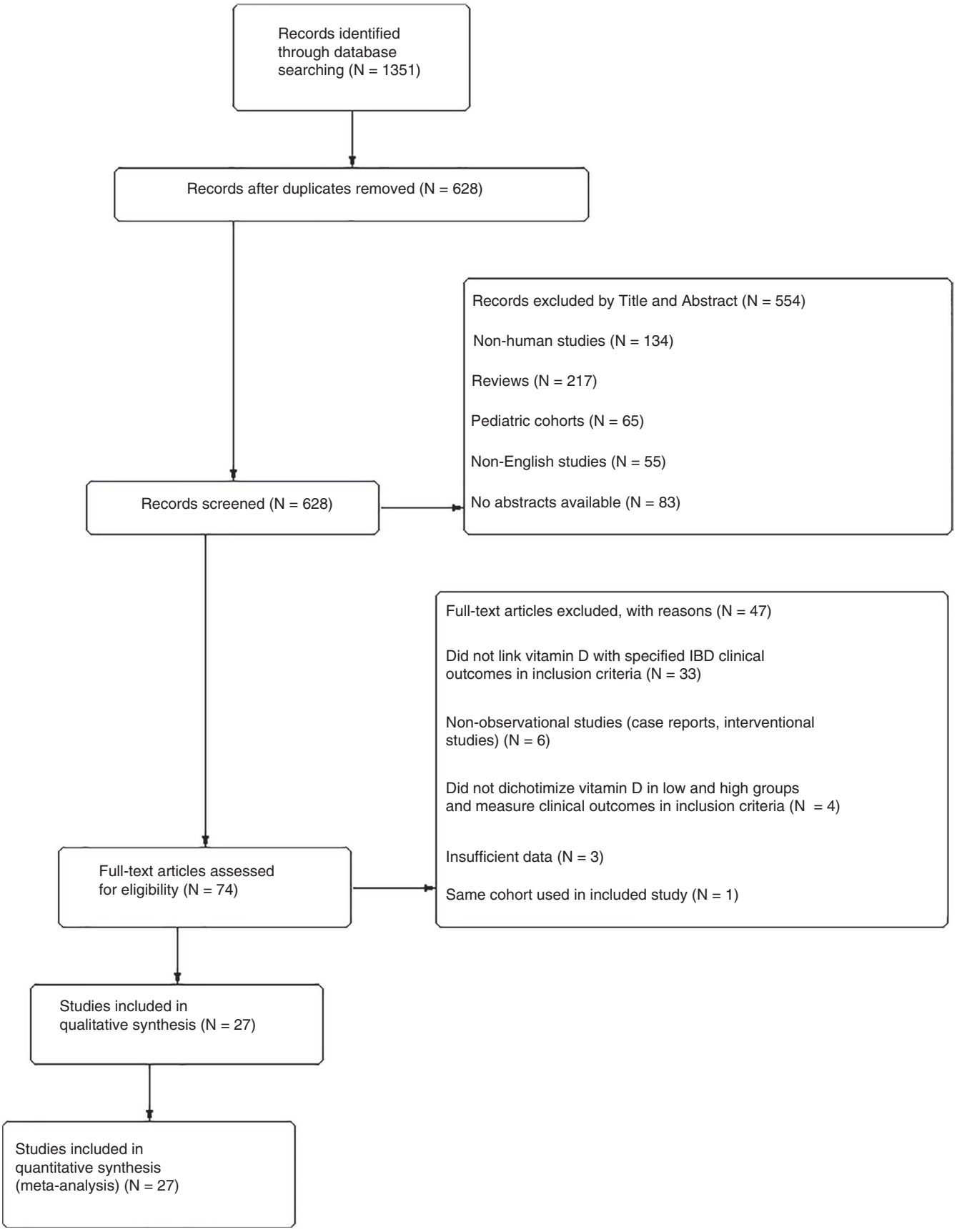

FIGURE 1 PRISMA flow diagram

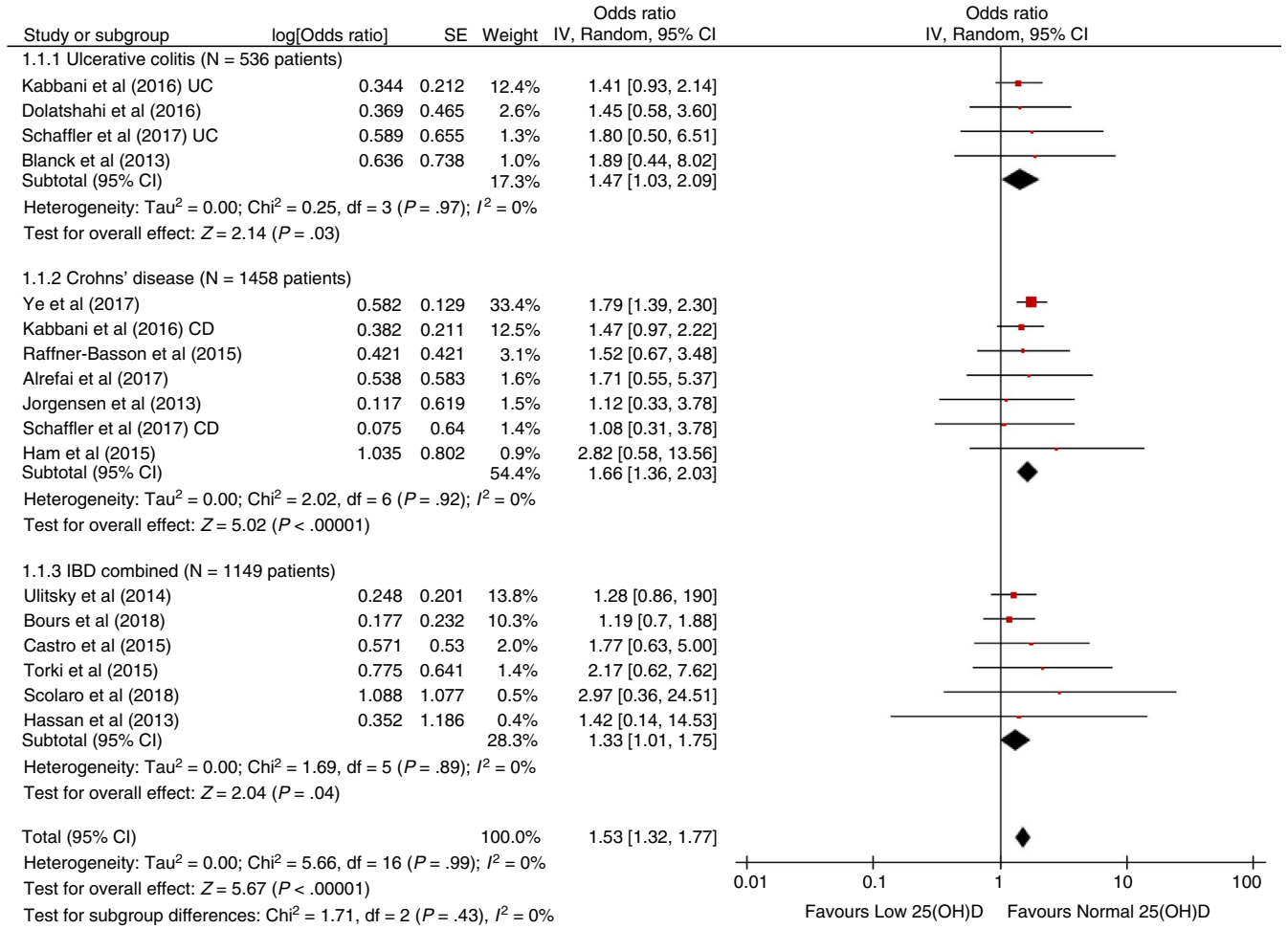

FIGURE 2 Low 25(OH)D status and clinically active disease

4. IBD Cohort Mean Age (years)
5. IBD Cohort Proportion of Males
6. IBD Cohort Proportion of Crohn's Disease Patients

3 | RESULTS

Out of 1351 citations, 27 articles[20-46] comprising of 8316 IBD patients met our predefined inclusion and exclusion criteria. The PRISMA flow diagram is presented in Figure 1. The description of baseline characteristics of included studies is presented in Table 1. The patients included in the systematic review and meta-analysis come from 6 continents and 14 countries (Australia, Brazil, Canada, China, Denmark, Germany, Iran, Ireland, The Netherlands, Norway, Portugal, Slovakia, South Africa, United States of America). The cohort consisted of 3115 patients with ulcerative colitis, and 5201 patients with Crohn's disease. The mean age was 41.4 years and mean proportion of male patients was 0.457. The mean IBD cohort 25(OH)D concentration was 25.5 ng/mL. Data regarding specific IBD clinical characteristics (disease duration, disease location, extent), history of IBD-related surgeries, medications, vitamin D supplementation or diet were not readily available from all studies and ultimately not included in the data extraction process. Table S1 summarises definitions of clinical outcome measures set by individual studies. Table S2 summarises which studies provided adjusted OR and factors adjusted. Table S3 summarises the clinical outcome statistical measures extracted or calculated used in this meta-analysis.

The quality of included studies assessed by the Newcastle-Ottawa scale is summarised in Table S4. The mean Newcastle-Ottawa score among the 27 studies included was 7. Among included studies, 22 studies had high quality (score 7-9), whereas five studies had a moderate quality (score 4-6).

3.1 | Description of excluded studies

Table S5 summarises a list of studies that were excluded with reason for exclusion. Among these studies, 33 did not link vitamin D with IBD clinical outcomes specified in the inclusion criteria. Six studies were non-observational studies. Four studies did not dichotomise IBD patients to low and normal/high 25(OH)D groups. Three studies had insufficient data (authors contacted via email but did not respond) to calculate clinical outcome statistical measures. One study was excluded because it consisted of an IBD cohort already included in the review.

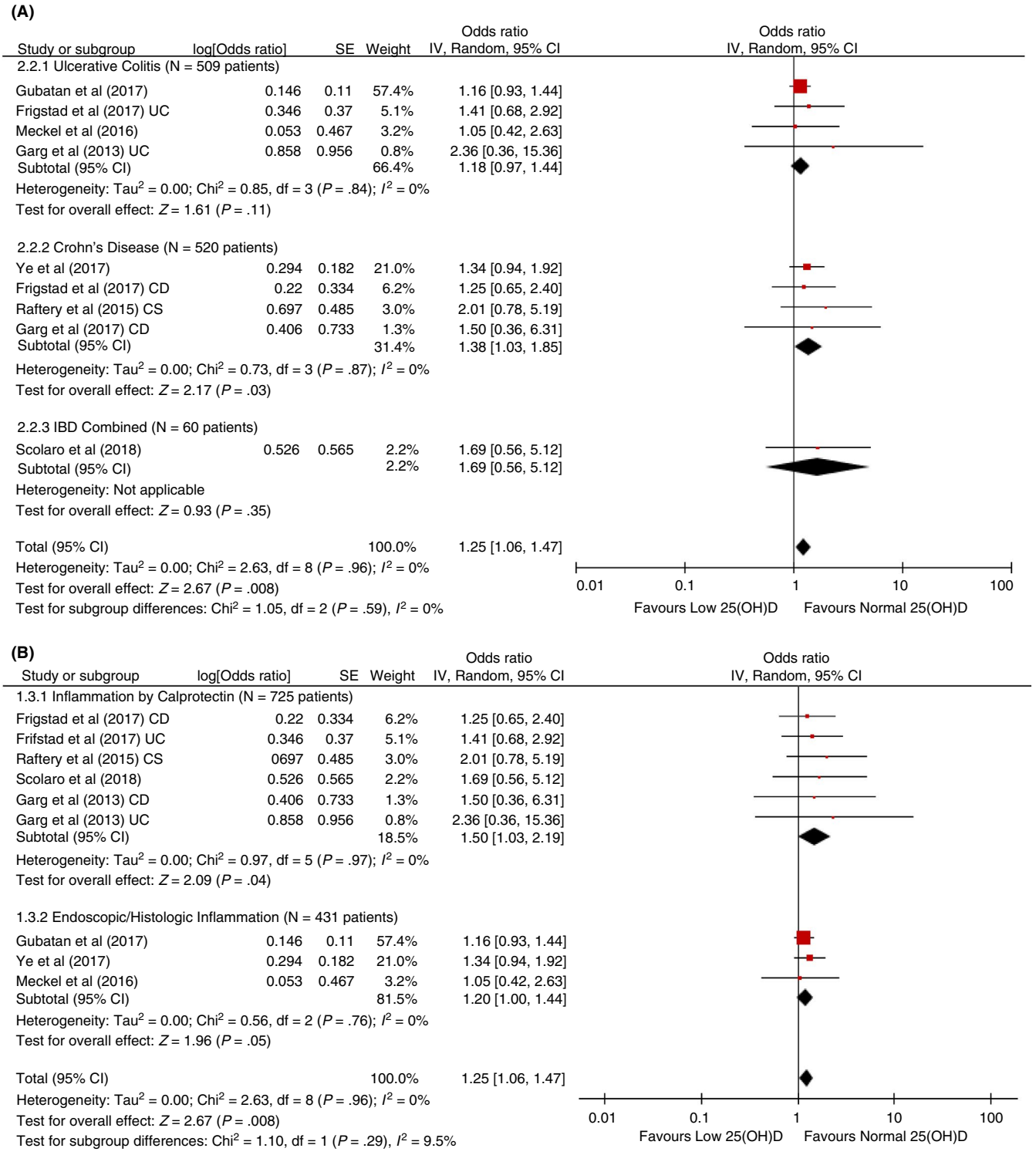

FIGURE 3 A, Low 25(OH)D status and mucosal inflammation by IBD type. B, Low 25(OH)D status and mucosal inflammation by biomarker

3.2 | Low vitamin D status and risk of clinically active disease

Figure 2 shows the forest plot of low 25(OH)D status and risk of clinically active disease. For the outcome of clinically active disease, 17 studies[20,22-25,30,31,33,36,39-42,45] met inclusion criteria and included a total of 3143 patients. There was no evidence of publication bias based on funnel plot asymmetry (Figure S1A, Egger's Test $P = .768$). Among all IBD patients, low 25(OH)D status was associated with increased odds of clinically active disease (pooled OR 1.53, 95% CI 1.32-1.77, $P < .00001$, $I^2 = 0\%$). Low 25(OH)D status was associated with increased odds of clinically active disease in both

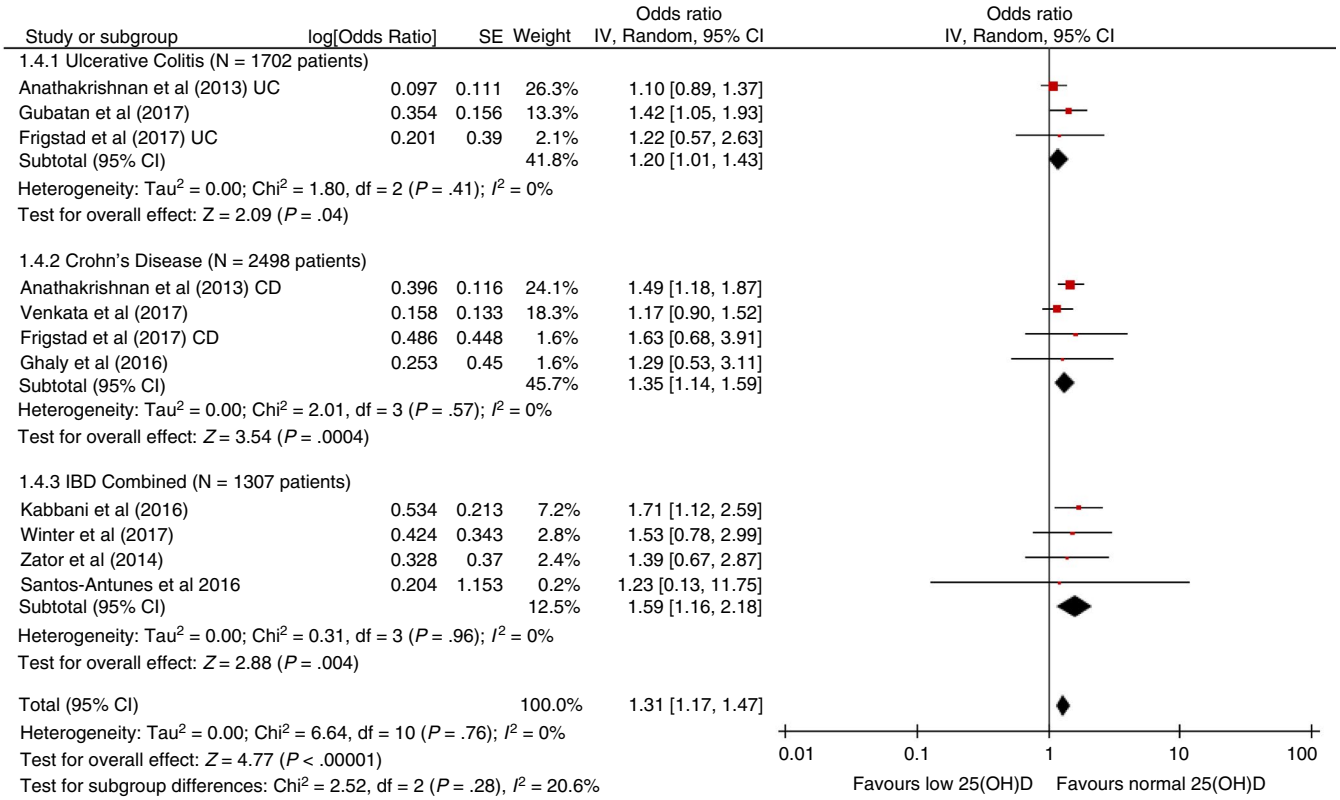

FIGURE 4 Low 25(OH)D status and clinical relapse

ulcerative colitis (pooled OR 1.47, 95% CI 1.03-2.09, P = .03, I^2 = 0%) and Crohn's disease (pooled OR 1.66, 95% CI 1.36-2.02, P < .00001, I^2 = 0%). Among studies that reported only combined IBD (ulcerative colitis and Crohn's disease) disease activity, low vitamin D status was associated with increased risk of clinically active disease (pooled OR 1.33, 95% CI 1.01-1.75, P = .04, I^2 = 0%). There was no difference between the ulcerative colitis only, Crohn's disease only and combined IBD subgroups (test for subgroup differences, P = .43, I^2 = 0%). Figure S2A-C summarises subgroup analyses based on A) study design (prospective vs retrospective), B) OR Adjustment (adjusted OR vs unadjusted OR) and C) 25(OH)D deficiency cut-off concentration (<20 ng/mL vs < 30 ng/mL). The increased odds of clinically active disease with low 25(OH)D was comparable (test for subgroup differences, P = .80, I^2 = 0%) between prospective studies (pooled OR 1.47, 95% CI 1.10-1.96, P = .009, I^2 = 0%) and retrospective studies (pooled OR 1.54, 95% CI 1.29-1.82, P < .00001, I^2 = 0%). The increased odds of clinically active disease with low 25(OH)D was comparable (test for subgroup differences, P = .61, I^2 = 0%) between studies with adjusted OR (pooled OR 1.51, 95% CI 1.30-1.76, P < .00001, I^2 = 0%) and unadjusted OR (pooled OR 1.75, 95% CI 1.01-3.04, P = .05, I^2 = 0%). There was also no subgroup difference (test for subgroup differences, P = .35, I^2 = 0%) between studies with a 25(OH)D deficiency cut-off concentration of < 20 ng/mL vs < 30 ng/mL with regards to low vitamin D status and disease activity. In meta-regression analysis, study location latitude, 25(OH)D deficiency cut-off concentration, mean 25(OH)D concentration and IBD cohort clinical characteristics (mean age, proportion of males, proportion of Crohn's disease patients) did not impact risk of clinically active disease (Figure S6).

3.3 | Low vitamin D status and risk of mucosal inflammation

For the outcome of mucosal inflammation, nine studies met inclusion criteria and included a total of 1089 patients.[26,27,29,35,37,40,45] Assessment for publication bias was not performed given less than 10 included studies. Figure 3A summarises the association of low 25(OH)D status and risk of mucosal inflammation. Among all IBD patients, low 25(OH)D status was associated with increased odds of mucosal inflammation (pooled OR 1.25, 95% CI 1.06-1.47, P = .008, I^2 = 0%). Low 25(OH)D status was associated with increased odds of mucosal inflammation in Crohn's disease (pooled OR 1.39, 95% CI 1.04-1.87, P = .03, I^2 = 0%). Association of low vitamin D status with mucosal inflammation was not statistically significant in ulcerative colitis patients (pooled OR 1.18, 95% CI 0.97-1.44, P = .11, I^2 = 0%) and in one study[40] which reported combined IBD mucosal inflammation risk with low vitamin D (P = .35). There was no statistical difference between subgroups (test for subgroup differences P = .59, I^2 = 0%). In subgroup analysis, there was no difference in association between low vitamin D status with risk of mucosal inflammation by biomarker measurement (Figure 3B, faecal calprotectin vs endoscopic/histological inflammation, test for subgroup differences, P = .29, I^2 = 9.5%), study design (Figure S3A, prospective vs retrospective, test for subgroup differences, P = .33, I^2 = 0%), OR

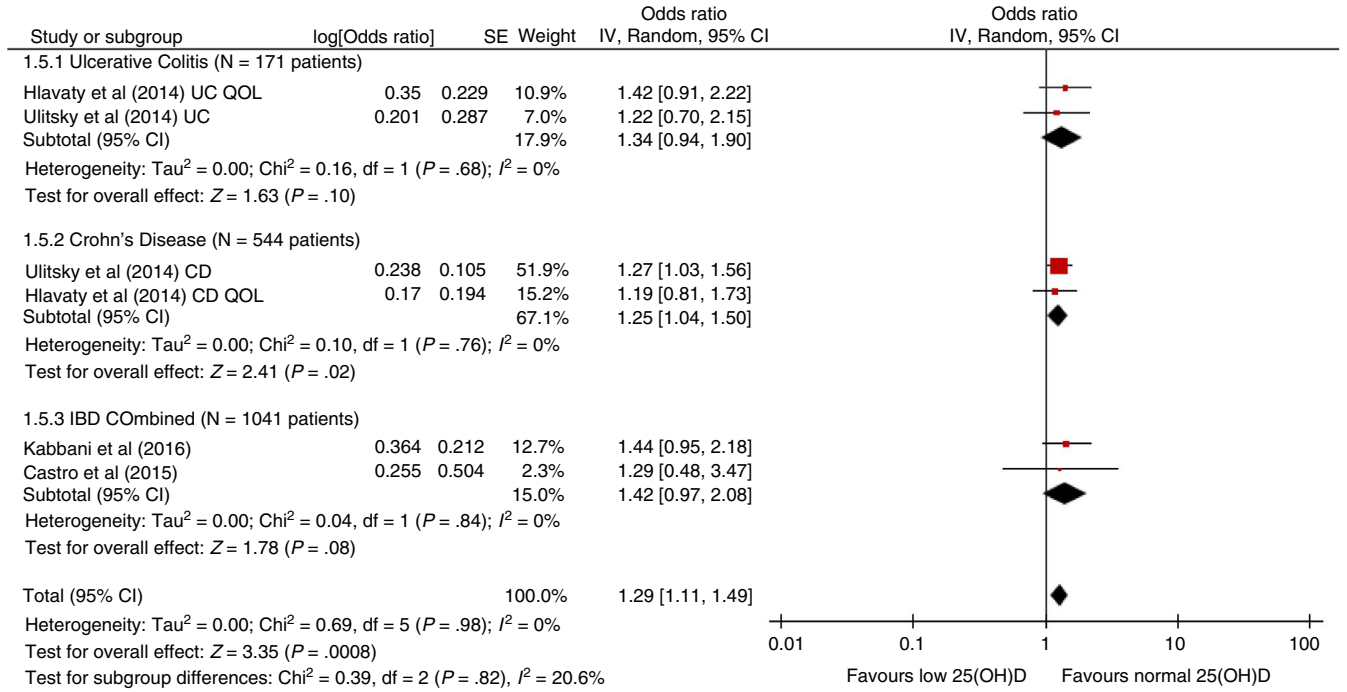

FIGURE 5 Low 25(OH)D status and low quality of scores

adjustment (Figure S3B, adjusted vs unadjusted OR, test for subgroup differences, $P = .59$, $I^2 = 0\%$), 25(OH)D deficiency cut-off concentration (Figure S3C, 20 ng/mL vs other cut-offs, test for subgroup differences, $P = .53$, $I^2 = 0\%$). In meta-regression analysis for the outcome of mucosal inflammation was not performed given less than 10 included studies.

3.4 | Low vitamin D status and risk of clinical relapse

For the outcome of clinical relapse, 11 studies met inclusion criteria and included a total of 5,507 patients.[21,26,28,29,34,38,43,44,46] There was no evidence of publication bias based on funnel plot asymmetry (Figure S1B, Egger's Test $P = .421$). Figure 4 summarises the association of low 25(OH)D status and risk of clinical relapse. Among all IBD patients, low 25(OH)D status was associated with increased odds of clinical relapse (pooled OR 1.31, 95% CI 1.17-1.47, $P < .00001$, $I^2 = 0\%$). Low 25(OH)D status was associated with increased odds of clinical relapse in ulcerative colitis (pooled OR 1.20, 95% CI 1.01-1.43, $P = .04$, $I^2 = 0\%$), Crohn's disease (pooled OR 1.35, 95% CI 1.14-1.59, $P = .0004$, $I^2 = 0\%$) and among studies reporting a combined IBD risk of relapse (pooled OR 1.59, 95% CI 1.16-2.18, $P = .004$, $I^2 = 0\%$). There was no statistical difference between subgroups (test for subgroup differences $P = .28$, $I^2 = 20.6\%$). The increased odds of clinical relapse with low 25(OH)D was comparable (Figure S4A, test for subgroup differences $P = .36$, $I^2 = 0\%$) between prospective studies (pooled OR 1.23, 95% CI 1.03-1.47, $P = .02$, $I^2 = 0\%$) and retrospective studies (pooled OR 1.37, 95% CI 1.19-1.58, $P < .0001$, $I^2 = 0\%$). All included studies with the outcome of clinical relapse included adjusted OR. In subgroup analysis stratified by 25(OH)D deficiency cut-off concentration (Figure S4B), a concentration of < 20 ng/mL was associated with risk of clinical relapse (pooled OR 1.48, 95% CI 1.27-1.73, $P < .00001$, $I^2 = 0\%$), whereas other cut-off concentrations (<30 ng/mL and < 35 ng/mL) were not statistically significant. There was increased heterogeneity and a trend towards a difference between subgroup by 25(OH)D deficiency cut-off concentrations (test for subgroup differences $P = .06$, $I^2 = 63.9\%$). In meta-regression analysis, a higher 25(OH)D deficiency cut-off concentration was associated with decreased risk of clinical relapse ($\beta = -0.020$, $P = .043$) (Figure S7B). In meta-regression, study location latitude, mean 25(OH)D concentration and IBD cohort clinical characteristics (mean age, proportion of male patients, proportion of Crohn's disease) did not impact the risk of clinical relapse (Figure S7).

3.5 | Low vitamin D status and risk of low quality of life scores

For the outcome of low quality of life scores, six studies met inclusion criteria and included a total of 1756 patients.[24,32,34,42] Assessment for publication bias was not performed given less than 10 included studies. Figure 5 summarises the association of low 25(OH)D and risk of low quality of life scores. Among all IBD patients, low 25(OH)D status was associated with increased odds of low quality of life scores (pooled OR 1.29, 95% CI 1.11-1.49, $P = .0008$, $I^2 = 0\%$). Low 25(OH)D was associated with increased odds of low quality of life scores in Crohn's disease (pooled OR 1.25, 95% CI 1.04-1.50, $P = .02$, $I^2 = 0\%$). There was a trend towards increased risk of low quality of life scores with low 25(OH)D status among ulcerative

colitis patients(pooled OR 1.34, 95% CI 0.94-1.90, P = .10, I^2 = 0%) and in studies that reported a combined IBD quality of life scores (pooled OR 1.42, 95% CI 0.97-2.08, P = .08, I^2 = 0%). There was no statistical difference between subgroups (test for subgroup differences P = .82, I^2 = 0%). Only one included study [34] for the outcome of quality of life was prospective. In subgroup analysis, there was no difference in risk of low quality of life scores with low vitamin D status between prospective and retrospective studies (Figure S5A, test for subgroup differences P = .58, I^2 = 0%). All included studies for the outcome of quality of life used a 25(OH)D deficiency cut-off concentration of < 20 ng/mL and provided adjusted OR. Meta-regression analyses were not performed given less than 10 included studies.

4 | DISCUSSION

This is the first meta-analysis, to our knowledge, to specifically quantify the association of low vitamin D levels with clinical outcomes in IBD. In this systematic review and meta-analysis of 27 observational studies comprising of 8316 IBD patients, we demonstrate that low vitamin D status is associated with increased risk of clinically active disease, mucosal inflammation, clinical relapse and low quality of life scores. We also show that a higher 25(OH)D deficiency concentration cut-off level is associated with decreased risk of clinical relapse.

Previous systematic reviews and meta-analyses have shown an association of between inflammatory bowel disease and vitamin D deficiency per se,[19,51-53] and concluded that patients with active Crohn's disease were more likely to have low D levels.[51,52] Whether this was cause or effect remains unclear.

In our meta-analysis, there was no difference between the association of low vitamin D status with risk of clinically active disease and clinical relapse among patients with CD and UC. However, in subgroup analysis vitamin D status was not significantly associated (although there was a trend) with risk of mucosal inflammation and low quality of life scores in UC patients. The loss of association between low vitamin D and quality of life in UC patients may have been from underpowering due to a smaller sample size compared to CD patients (171 vs 544 patients). For the outcome of mucosal inflammation, there was a comparable number of patients in both subgroups thus differences in sample size for this outcome cannot account for the subgroup difference. Low vitamin D status may be a stronger biomarker for mucosal inflammation in CD because vitamin D malabsorption may be indicative of small bowel inflammation in CD which is not seen in UC. Furthermore, vitamin D may play a more specific and targeted role in the pathogenesis of CD compared to UC. For example previous studies have shown that the active form of vitamin D [1,25(OH)2D] induces the Crohn's susceptibility genes NOD2 and ATG16L1.[54,55]

The results of our study may have several explanations. First, low vitamin D may be an effect of increased disease activity among IBD patients. Our results indicate that a low vitamin D status is a marker of disease activity. IBD patients with active disease may have low vitamin D levels because of malnutrition and malabsorption in the setting of an acute inflammatory state. IBD patients who are flaring may also feel unwell and spend less time outdoors resulting in less sunlight exposure and thus less endogenous vitamin D production. Another explanation is that low vitamin D may be a cause of poor IBD clinical outcomes. Although our meta-analysis consisted of observational studies and cannot establish direct causality, our subgroup analyses restricting the meta-analysis to prospective studies suggest that a baseline low vitamin D status is associated with increased risk of future clinically active disease and clinical relapse in IBD patients. It is possible that low vitamin D status plays both a 'cause and effect' role in IBD clinical outcomes.

Given that low vitamin D status is associated with adverse clinical outcomes in IBD patients, should thresholds to define vitamin D deficiency be increased in patients with IBD? The traditional cut-off of vitamin D deficiency (<20 ng/mL) is based on skeletal health, but optimal vitamin D thresholds for immune function is still unknown. We performed a meta-regression analysis to evaluate the association of 25(OH)D deficiency thresholds on risk of IBD clinical outcomes. In our meta-regression analysis, higher 25(OH)D deficiency cut-off concentration was associated with a decreased risk of clinical relapse. How higher 25(OH)D deficiency cut-off concentration affects the risk of clinical relapse remains unknown. Given limited data reported by included studies, it remains unclear how higher 25(OH)D deficiency cut-off concentrations influenced vitamin D supplementation practices in the different IBD cohorts.

In a recent meta-analysis of 7 interventional studies involving 347 IBD patients with vitamin D supplementation, Li et al[56] showed that vitamin D supplementation increased baseline 25(OH)D levels and was associated with decreased risk of IBD clinical relapse compared to placebo controls. There was no difference in rates of clinical relapse among studies comparing high- and low-dose vitamin D supplementation. The same meta-analysis showed no effect of vitamin D supplementation on inflammatory markers (ESR and CRP). The outcomes of disease activity or quality of life were not evaluated. Subgroup analyses to evaluate the effects of vitamin D supplementation between CD and UC were not performed. The authors of the meta-analysis acknowledge that there was significant heterogeneity between studies with regards to IBD characteristics, vitamin D supplementation dose, duration and route of administration. In a systematic review involving 10 interventional studies with vitamin D supplementation in paediatric IBD patients,[57] authors conclude that most vitamin D regimens were insufficient in correcting vitamin D deficiency or maintaining adequate levels. Disease activity was reported in only a few studies and a meta-analysis could not be performed to assess the effect of vitamin D supplementation on this outcome.

Our study has several strengths. First, our meta-analysis examined clinical outcomes beyond symptoms scores as we also evaluated the association of low vitamin D with objective markers of mucosal inflammation, clinical relapse and quality of life in IBD patients. Second, our meta-analysis used multicentre-derived data and included IBD cohorts from diverse geographical and ethnic groups (14 countries represented in cohort) thus greatly expanding the external validity of our findings. Third, the large sample size of

our meta-analysis helps overcome some of the power limitations of previous studies. Fourth, the quality of included in our studies was high, the heterogeneity of our meta-analysis was low, and there was no evidence of publication bias. Fifth, we performed subgroup analyses restricting the definition of vitamin D deficiency to the traditional cut-off of <20 ng/mL with results consistent with our main findings. Finally, we performed meta-regression analyses and demonstrated that differences in study location latitude and baseline IBD cohort clinical characteristics were not mediating the association between low vitamin D status and IBD clinical outcomes.

Our meta-analysis has several limitations that warrant consideration. First, our meta-analysis included only observational studies and thus cannot account for residual confounders or establish causation. Second, our meta-analysis excluded paediatric patients and thus our results can only apply to adult patients. Third, our meta-analysis may have some selection bias as we excluded Non-English studies and studies with incomplete information. Finally, information regarding vitamin D supplementation, diet, or history of previous IBD-related surgeries was not available from all studies and not included in our meta-analysis, however, some of our included studies adjusted for these variables in the outcomes OR. Furthermore, subgroup analyses excluding studies with unadjusted OR had no significant impact on the association with low vitamin D status with our IBD clinical outcomes.

Our study has several clinical implications. First, our study suggests that vitamin D status is associated with clinical outcomes in IBD patients. At a minimum, it provides a rationale for the surveillance of vitamin D levels in IBD patients, even when in remission.[58] A low vitamin D status in an IBD patient may signify active disease at the clinical, biomarker, or histological level and may predict increased risk of clinical relapse. The recent meta-analysis by Li et al[56] complements our study and demonstrates that a low vitamin D status is modifiable and may be rectified with vitamin D supplementation and in turn decrease the risk of IBD clinical relapse. Second, our data show that higher 25(OH)D deficiency thresholds are associated with a decreased risk of clinical relapse in IBD patients. Specific 25(OH)D concentration thresholds that could be beneficial to outcomes in IBD warrants further evaluation.

In conclusion, our systematic review and meta-analysis provides evidence that a low vitamin D status in IBD patients is associated with increased risk of clinically flaring disease, mucosal inflammation, clinical relapse, and impaired quality of life. A low vitamin D status is a potential therapeutic target in IBD patients. The therapeutic benefit of increasing 25(OH)D levels through diet or supplementation to avoid these adverse clinical outcomes warrants further investigation.

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AUTHORSHIP

Guarantor of the article: Alan C. Moss.

Author contributions: John Gubatan and Alan Moss planned and designed the study and analysed the data; John Gubatan and Naomi Chou performed the systematic review and extracted data from manuscripts; John Gubatan and Naomi Chou performed the quality assessment of studies; John Gubatan performed the statistical analyses, Ole Haagen Nielsen provided critical review of the manuscript; John Gubatan drafted the manuscript; all authors interpreted the results and contributed to critical review of the manuscript; John Gubatan had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

ORCID

John Gubatan https://orcid.org/0000-0001-6037-2883

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section at the end of the article.

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