Bone mineral density is negatively correlated with ulcerative colitis: a systematic review and meta-analysis

Tianyu Zhou1, Jiaqi Pan1, Bin Lai1,2, Li Cen1, Wenxi Jiang1, Chaohui Yu1 and Zhe Shen1*

Abstract

Background: Newer epidemiological studies suggest that the incidence of ulcerative colitis might be increasing rapidly. Furthermore, osteoporosis in ulcerative colitis patients has gained great attention, but the epidemiologic evidence remains controversial. Therefore, a meta‐analysis was performed to explore the association between bone density and ulcerative colitis.

Methods: Two investigators used PubMed, EMBASE and the Cochrane Library databases to identify all studies published before August 2019. Depending on the outcomes, investigators divided these studies into four groups (OR, SMD [BMD], SMD [z-score] and SMD [t-score]). To address the use of steroids, which is a major confounding factor in this analysis, another subgroup analysis of studies of steroid-free patients was conducted. Additionally, heterogeneity, sensitivity and stratified analyses were also performed.

Results: A total of 13 cross-sectional studies that involved 1154 participants were included in the present meta-analysis, and three of them were included in the steroid-free subgroup analysis. The pooled OR was 6.41 (95% CI 2.59–15.87) and the pooled SMD (BMD), SMD (t-score) and SMD (z-score) were −0.24 (95% CI −0.44 to −0.04), −0.55 (95% CI −0.72 to −0.37), and −0.38 (95% CI −0.56 and −0.19), respectively. Since steroids are a significant confounder, the pooled SMD of the steroid-free subgroup was −0.55 (−0.85 to −0.25), which revealed a strong negative relationship between bone density and ulcerative colitis in steroid-free patients. Additionally, other subgroup analyses also revealed a strong relationship.

Conclusions: This meta-analysis provides evidence for the potential association between ulcerative colitis and decreased bone density. It is essential for clinicians to consider bone mineral density in ulcerative colitis patients regardless of steroid-therapy.

Keywords: Bone mineral density, Inflammatory bowel disease, Ulcerative colitis, Meta-analysis

Background

Inflammatory bowel diseases, Crohn's disease and ulcerative colitis are chronic idiopathic disorders that cause inflammation of the gastrointestinal tract. More than a decade ago, inflammatory bowel disease was rare in Asia. However, newer epidemiological studies have suggested that its incidence might be rapidly increasing in South America, Eastern Europe, Asia and Africa. In the past few years, inflammatory bowel disease has become a public health challenge worldwide and is associated with morbidity, mortality and substantial costs to society [1, 2].

Osteoporosis is a skeletal disease characterized by low bone density and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [3]. Due to the systemic nature of osteoporosis, the associated increase in fracture...
risk affects virtually all skeletal sites, such as the hips and vertebra [4]. Osteoporosis remains a large burden worldwide. The challenges in the future include wider implementation of integrated systems of care, such as fracture liaison services, improvement of treatment adherence; and the establishment of effective and safe long-term treatment regimens in order to provide sustained reductions in fracture risk [5].

Recently, the association between inflammatory bowel diseases and bone mineral density (BMD) has gained great interest. However, the conclusions of these investigations have been contradictory, especially regarding the relationship between ulcerative colitis and BMD. Some studies have revealed that decreased BMD in individuals with inflammatory bowel disease is related to corticosteroid use but not the disease itself, and some studies concluded that BMD is reduced in patients with Crohn's disease but not in patients with ulcerative colitis [6–9]. Therefore, we performed a meta-analysis to review the data obtained from related studies to investigate the potential association between ulcerative colitis and BMD, especially in steroid-free patients.

Materials and methods
This systematic review and meta-analysis was performed following the meta-analysis of observational studies in epidemiology (MOOSE) statement guidelines [10].

(1) Search strategy
Electronic databases, including PubMed, EMBASE and the Cochrane Library, were searched for relevant studies, and this search was independently conducted by two authors. All studies on BMD in ulcerative colitis patients were searched from database inception to August 2019. Two researchers separately searched for articles using the following terms: ((bone densities) OR (density, bone) OR (bone mineral density) OR (bone mineral densities) OR (density, bone mineral) OR (bone mineral content) OR (bone mineral contents) OR (osseous density) OR (bone density)) AND ((colitis, ulcerative) OR (idiopathic proctocolitis) OR (ulcerative colitis) OR (colitis gravis) OR (inflammatory bowel disease, ulcerative colitis type) OR (chronic ulcerative colitis) OR (colitis ulcerativa) OR (colitis ulcerosa) OR (colitis ulcerosa chronica) OR (colitis, mucosal) OR (colitis, ulcerative) OR (colitis, ulcerous) OR (colon, chronic ulceration) OR (histiocytic ulcerative colitis) OR (mucosal colitis) OR (ulcerative colorectalis) OR (ulcerative procto colitis) OR (ulcerative proctocolitis) OR (ulcerous colitis)). The references of the reviewed articles were hand-searched for additional potentially applicable studies.

(2) Study selection
Studies were included when they met the following inclusion criteria: (1) original cross-sectional studies and case-control or cohort studies about BMD and ulcerative colitis; (2) studies that provided sufficient information to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) or standardized mean differences (SMDs) and 95% CIs; (3) studies that diagnosed ulcerative colitis based on clinical, endoscopic, radiological, or histological data; (4) studies that measured BMD by dual-energy X-ray absorptiometry (DEXA), ultrasound bone density measurements, or other effective methods; and (5) studies published in English before August 2019. And studies exclusion criteria were as follows: (1) cell or animal studies, reviews, comments and letters; (2) duplicated studies; (3) research on irrelevant topics; (4) without necessary data or information. If the same samples were used in more than one study, the most complete and informative study was included.

(3) Data extraction and quality assessment
Two investigators extracted the data from each study independently. The extracted information included the study type, first author’s name, publication year, geographical location, disease duration, study population and demographic data (age and sex), BMD measurement (site, imaging location, disease duration, study population and study type, first author's name, publication year, geographical location), and diagnosis of ulcerative colitis.

The quality of these case-control studies was assessed using the Newcastle-Ottawa scale (NOS) by two authors separately: studies with ≥6 stars were defined as high-quality studies. In addition, cross-sectional studies were assessed using the Agency for Healthcare Research and Quality (AHRQ). These studies were categorized as follows: high quality, 8–11; moderate quality, 4–7; and low quality, 0–3. Discrepancies were resolved by consensus.

(4) Statistical analysis
The analyses were conducted using Stata Statistical Software (version 12.0; College Station; Texas 77845, USA) by two authors independently. According to the different types of data, the ORs or SMDs and their 95% CIs were calculated. If the outcome of the study was the number of low bone density patients, the ORs and 95% CIs were summarized, while if the outcome of the study was BMD, z-score, or t-score, the SMDs and 95% CIs were calculated. Depending on the outcomes, all the studies were divided into four groups: (OR, SMD [BMD], SMD [z-score] and SMD [t-score]). In light of the possible between-study variance due to the different study designs, methodologies and populations, random-effects models were used for high-heterogeneity groups, while fixed-effects models were used for low-heterogeneity groups.

Corticosteroid therapy can contribute to low BMD [26]. Glucocorticoids are conventional treatments for
inflammatory bowel disease and are a potential factor contributing to osteoporosis in ulcerative colitis patients. Some studies have concluded that decreased BMD in inflammatory bowel disease patients is related to corticosteroid use but not the disease itself. To take this confounding factor into consideration, a subgroup analysis of studies of steroid-free patients was conducted.

Other subgroup analyses were also performed for studies, especially for high-heterogeneity groups, to identify the possible sources of heterogeneity. The statistical heterogeneity between studies was assessed using the Chi-square statistic, which was quantified by $I^2$. This figure represents the percentage of the total variation accounted for by the between-study variation. For the $I^2$-value, $0$–$25\%$ represents insignificant heterogeneity, $>25\%$ but $\leq 50\%$ represents low heterogeneity, $>50\%$ but $\leq 75\%$ represents moderate heterogeneity, and $>75\%$ represents high heterogeneity [11]. Furthermore, a sensitivity analysis was carried out to investigate the influence of individual studies and the stability of the results by omitting one study at a time. Publication bias was assessed using Begg’s regression asymmetry test. $P < 0.05$ was considered representative of statistically significant publication bias [12, 13].

Results

(1) Study selection and study characteristics

The search strategy for the meta-analysis on BMD and ulcerative colitis yielded 734 publications from PubMed, EMBASE and the Cochrane Library. Among these records, 121 publications were excluded due to duplication, and 588 articles were excluded after the screening of the titles and abstracts. Then, the full text versions of 25 articles were reviewed, and 13 articles were finally included in the present meta-analysis (Fig. 1); all of the included studies were cross-sectional studies [8, 14–25].
The main characteristics and quality assessment of all studies are listed in Table 1. The 13 selected studies included a total of 1154 participants. Among these participants, there were 570 participants in the case group and 584 participants in the control group. Among the 13 included articles, nine articles were from Europe, one article was from China, and three articles were from Brazil. In addition, 11 studies measured bone density by DEXA, while another study measured bone density by ultrasound. Of all 13 of these studies, 11 detected BMD at the lumbar spine, and six studies detected BMD at the femoral neck. Moreover, five studies calculated the number participants with low bone density, eight studies calculated the BMD (g/cm²), five studies calculated the t-score, and four studies calculated the z-score. Regarding the quality of these 13 cross-sectional studies, four studies were of high quality, while eight studies were of moderate quality based on the AHRQ evaluation checklist (See Appendix).

(2) Association between BMD and ulcerative colitis
Among the four groups, ulcerative colitis patients had significantly lower BMD than healthy controls. Among the four groups, the pooled OR of low BMD was 6.41 (95% CI 2.59 to 15.87; I² = 56.8%), and the pooled SMD (BMD) group had moderate heterogeneity, sub-

(3) BMD in steroid-free ulcerative colitis patients
Among the 13 studies included in this meta-analysis, four studies [18, 20–22] analyzed BMD in steroid-free patients. In these four studies, patients have never been introduced to steroid therapy before and all of them showed a negative relationship between BMD and ulcerative colitis. The SMD depending on the t-score and its CI were calculated from three studies [20–22] because of their different outcomes. The SMD and its 95% CI was −0.55 (−0.85 to −0.25; I² = 0.0%), which indicated a correlation between ulcerative colitis and decreased BMD. The result is shown in Fig. 3.

(4) Subgroup analyses
To identify the sources of heterogeneity, subgroup analyses were conducted based on detection sites, regions, ages and body mass index (BMI). The results are shown in Tables 2 and 3. Since the OR group and the SMD (BMD) group had moderate heterogeneity, subgroup analyses were conducted. When the OR group was divided into two subgroups based on the detection sites, both exhibited low heterogeneity. The ORs (95% CIs) for lumbar spine and femoral neck studies were 6.84 (95% CI 2.03 to 23.08; I² = 21.3%) and 15.22 (95% CI 4.06 to 57.04; I² = 0), respectively. The ORs (95% CIs) for BMI < 25 and BMI ≥ 25 studies were 37.44 (95% CI 5.10 to 274.74; I² = 0) and 4.13 (95% CI 1.35 to 12.65; I² = 54.3%), respectively. The SMD (BMD) group was also divided into two subgroups based on detection sites. The SMDs (95% CIs) for the lumbar spine and femoral neck were −0.17 (95% CI −0.35 to 0.02; I² = 26.3%) and −0.38 (95% CI −0.91 to 0.16; I² = 84%), respectively. The two subgroups based on detection sites in the OR group both exhibited low heterogeneity, which may explain the possible bias in the OR group. In all the other subgroups, the correlation between BMD and ulcerative colitis was significant, but the I² of each was > 50%, which represented significant heterogeneity.

The subgroup analyses also revealed a negative relationship between BMD and ulcerative colitis. Moreover, the femoral neck was more susceptible to low BMD than the lumbar spine. The results of subgroup analyses based on detection sites are shown in Fig. 4. The SMDs (95% CIs) for the bone mineral density of European people and American people were −0.25 (−0.47, −0.04) and −0.03 (−0.64, 0.58), respectively. Among the group(BMD), the SMDs (95% CIs) for average age < 45 years old and ≥ 45 years old were −0.16 (−0.39, 0.07) and −0.52 (−0.83, −0.22), respectively. And the SMDs (95% CIs) for BMI < 25 kg/m² and ≥ 25 kg/m² were −0.24 (−0.56, 0.08) and −0.08 (−0.31, 0.14). It is revealed that the incidence of osteoporosis in European ulcerative colitis patients was higher than that of patients in other regions, and thin or older patients were more susceptible to osteoporosis. The results are shown in Tables 2 and 3.

(5) Assessment of bias
Publication bias was assessed using Begg’s method. All of the results suggested that there was no evidence of significant publication bias (P = 0.466, 0.200, 0.548 and 0.060).
Table 1 Main characteristics of the included studies in this meta-analysis

| Author   | Country   | Year  | Sex | M/F | Age mean age ± SD (range age) years | Disease duration mean duration ± SD | BMD measurement | Ulcerative colitis diagnosis | Detection site | Outcome | Cases | Controls | Total | Quality scores |
|----------|-----------|-------|-----|-----|-------------------------------------|------------------------------------|-----------------|-------------------------------|----------------|---------|-------|----------|-------|----------------|
| Krela    | Poland    | 2018  | 49/56 | 39.6 ±15.0 | 7.48 ±7.0 years | DXA | Endoscopic, histopathologic and radiologic criteria | Lumber spine, femoral neck | BMD (g/cm²), T score, Z score, number of low bone density | 105 | 41 | 146 | 7 |
| Lima     | Brazil    | 2017  | 26/42 | 38.2 ±9.0 | None | DXA | Clinical, endoscopic, histopathologic and radiologic data | Lumber spine and femoral neck | Number of low bone density | 68 | 67 | 135 | 7 |
| Bastos   | Brazil    | 2012  | None | 41.7 ±14.3 | None | DXA | None | Lumber spine, hip | BMD (g/cm²), number of low bone density | 14 | 40 | 54 | 4 |
| Zanetti  | Brazil    | 2011  | None | (20–50) | None | DXA | None | Lumbar spine, proximal femoral neck and total hip | Number of low bone density | 20 | 44 | 64 | 4 |
| Kaya     | Turkey    | 2011  | 27/13 | 41.53 ±11.93 | 38.6±36.1 months | DXA | Clinical, endoscopic and histopathologic data | Lumber spine, femoral neck | Number of low bone density | 40 | 29 | 69 | 6 |
| Pluskiewicz | Poland | 2009  | 20/27 | 47.64 ±14.83 | 8.6 ±7.2 years | DXA | None | Lumber spine | BMD (g/cm²), T score, Z score | 47 | 47 | 94 | 7 |
| Liu      | China     | 2009  | None | (20–50) | None | DXA | None | None | T score | 43 | 37 | 80 | 3 |
| Sakellariou | Greece | 2006  | Male | 25.8 ±4.6 | 50±44 months | None | None | Histological finding | Right calcaneous | 14 | 28 | 42 | 6 |
| Lamb     | UK        | 2002  | 15/8 | 45 | <3 months | DXA | None | Lumbar spine, femoral neck | BMD (g/cm²), T score, Z score | 23 | 18 | 41 | 9 |
| Ulivieri | Italy     | 2001  | 21/22 | Male 36.5±8.4, Female 35.3±6.2 | 8 years | DXA | Radiologic, endoscopic and histopathologic data | Lumber spine | BMD (g/cm²) | 43 | 111 | 154 | 7 |
| Schoon   | The Netherlands | 2000 | 24/20 | 38.4 ±14.4 | 3.4 ±7.7 months | DXA | Radiologic, endoscopic and histopathologic data | Lumber spine, femoral neck | BMD (g/cm²) | 44 | 44 | 88 | 9 |
| Dinca    | Italy     | 1999  | 33/16 | 38 | 8 ±1 years | DXA | Radiologic, endoscopic and histopathologic data | Lumber spine | BMD (g/cm²), T score | 49 | 18 | 67 | 8 |
| Jahnssen | Norway    | 1999  | 24/36 | 38 | 7 years | DXA | Radiologic, endoscopic and histopathologic data | Lumber spine, femoral neck | BMD (g/cm²) | 60 | 60 | 120 | 8 |

*BMD* bone mineral density, *DXA* dual energy X-ray absorptiometry
Discussion

Newer epidemiological studies have suggested that the incidence of ulcerative colitis might be increasing rapidly in places other than Europe [1, 2], and low BMD in ulcerative colitis patients has gained increasing attention. It has been stated that BMD is reduced in patients with Crohn’s disease but not in patients with ulcerative colitis [8]. The possible reason might be as follows: Crohn’s disease is a systemic disease with a long premorbid phase, while ulcerative colitis is a mucosal disease with an acute onset and is often limited to distal colonic tracts. In addition, Crohn’s disease also has important immunological differences when compared to ulcerative colitis [26, 27]. The localization of Crohn’s disease is in the small intestine, and intestinal resection may cause malnutrition and estrogen deficiency [28], which may contribute to low BMD. Due to these conflicting results, the present meta-analysis was conducted to identify the possible correlation between BMD and ulcerative colitis.

Four groups (OR, SMD [BMD], SMD [z-score] and SMD [t-score]) were assessed, and all of them revealed that BMD has a negative correlation with ulcerative colitis.

Several potential mechanisms may account for the association between BMD and ulcerative colitis. One of the possible mechanisms is vitamin D deficiency and secondary hyperparathyroidism. Vitamin D has been shown to have anti-inflammatory, anticancer and immune-regulatory effects, in addition to its traditional role in regulating calcium and phosphorus metabolism [29–33]. It has been reported that vitamin D deficiency is commonly observed in inflammatory bowel disease patients and is independently correlated with disease activity [34, 35]. Biochemical data from three studies [22, 24, 25] included in the present meta-analysis also demonstrated this trend: ulcerative colitis patients had lower concentrations of serum 25-hydroxy vitamin D and higher concentrations of serum parathyroid hormone. Bone metabolism is unbalanced in inflammatory bowel disease patients, with increased bone resorption but no evident variations in bone formation [36]. Another mechanism is the high circulating levels of cytokines [37]. The prevailing
theory of the pathogenesis of bone loss in inflammatory bowel disease patients suggests that the increase in T-cell activity in the state of intestinal inflammation leads to an increase in the systemic release of numerous pro-inflammatory cytokines, such as interleukin-1, tumor necrosis factor, transforming growth factor-α, interleukin-6 and interleukin-4 [38–40]. These inflammatory factors stimulate osteoclast function, an effector of bone resorption, and could inhibit osteoblasts, a mediator of bone formation, with potential deleterious effects on BMD [41–44].

One study included in this meta-analysis [19] divided patients into three forms (mild, moderate and severe) based on the severity of disease and detected the bone mineral density respectively. And it also shown that the bone mineral density in severe patients was much lower than mild patients. This concept may explain the bone loss in ulcerative colitis patients. Moreover, other factors, such as malnutrition and malabsorption, which lead to secondary hypogonadism; corticosteroid treatment; decreased physical activity; and diminished sun exposure, may also contribute to low bone density in ulcerative colitis patients [19].

Due to the high heterogeneity in the two groups (OR and SMD [BMD]), subgroup analyses were also
conducted. These analyses revealed that the femoral neck had lower BMD than the lumbar spine in ulcerative colitis patients. Additionally, thinner or older ulcerative colitis patients were more susceptible to osteoporosis, which may lead to more positive prevention in these patients. When the OR group was further divided into two subgroups based on detection sites, both subgroups exhibited low heterogeneity. This finding may explain the possible bias in the OR group. However, none of the subgroups of the SMD (BMD) group exhibited lower heterogeneity. Hence, it is possible that certain kinds of biases may not have been found. Some studies have shown that inflammatory bowel disease patients have a genetic predisposition to osteoporosis [45], such as variations in the IL-6 and IL-1 genes, which may explain the unknown bias in the detection of BMD in ulcerative colitis patients.

| Table 3 Subgroup analyses of group [SMD (BMD)], group [SMD (t-score)] and group [SMD (z-score)] |
|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
| Group (SMD [BMD])                                   | No. of studies | SMD (95% CI)       | P   | P heterogeneous | I² (%) |
| Place                                               |               |                    |     |                 |       |
| Lumber spine                                       | 9             | −0.17 (−0.35, 0.02)| 0.072 | 0.021            | 26.3 |
| Femoral neck                                       | 4             | −0.38 (−0.91, 0.16)| 0.169 | <0.001           | 84   |
| Region                                              |               |                    |     |                 |       |
| Europe                                              | 12            | −0.25 (−0.47, −0.04)| 0.021 | 0.001            | 64.5 |
| America                                             | 1             | −0.03 (−0.64, 0.58)| 0.918 |                 |       |
| Average age (years old)                             |               |                    |     |                 |       |
| < 45                                                | 10            | −0.16 (−0.39, 0.07)| 0.173 | 0.002            | 64.7 |
| ≥ 45                                                | 3             | −0.52 (−0.83, −0.22)| 0.001 | 0.627            | 0    |
| BMI (kg/m²)                                         |               |                    |     |                 |       |
| < 25                                                | 7             | −0.24 (−0.56, 0.08)| 0.139 | 0.001            | 72.4 |
| ≥ 25                                                | 4             | −0.08 (−0.31, 0.14)| 0.47  | 0.297            | 18.6 |
| Group (SMD [T-score])                               |               |                    |     |                 |       |
| Place                                               |               |                    |     |                 |       |
| Lumber spine                                       | 4             | −0.50 (−0.72, −0.28)| <0.001 | 0.827           | 0    |
| Femoral neck                                       | 2             | −0.67 (−0.99, −0.35)| <0.001 | 0.494           | 0    |
| Region                                              |               |                    |     |                 |       |
| Europe                                              | 6             | −0.53 (−0.72, −0.34)| <0.001 | 0.842           | 0    |
| Asia                                                | 1             | −0.63 (−1.08, −0.18)| 0.006 |                 | 0    |
| Average age (years old)                             |               |                    |     |                 |       |
| < 45                                                | 4             | −0.55 (−0.76, −0.34)| <0.001 | 0.915           | 0    |
| ≥ 45                                                | 3             | −0.55 (−0.85, −0.24)| <0.001 | 0.43            | 0    |
| BMI (kg/m²)                                         |               |                    |     |                 |       |
| < 25                                                | 3             | −0.53 (−0.77, −0.28)| <0.001 | 0.838           | 0    |
| ≥ 25                                                | 1             | −0.38 (−0.79, 0.03)| 0.069 |                 | 0    |
| Group (SMD [Z-score])                               |               |                    |     |                 |       |
| Place                                               |               |                    |     |                 |       |
| Lumber spine                                       | 4             | −0.36 (−0.59, −0.14)| 0.002 | 0.353            | 8.1  |
| Femoral neck                                       | 2             | −0.40 (−0.72, −0.09)| 0.012 | 0.169            | 47.2 |
| Average age (years old)                             |               |                    |     |                 |       |
| < 45                                                | 3             | −0.33 (−0.56, −0.09)| 0.006 | 0.226            | 32.8 |
| ≥ 45                                                | 3             | −0.46 (−0.76, −0.16)| 0.003 | 0.422            | 0    |
| BMI (kg/m²)                                         |               |                    |     |                 |       |
| < 25                                                | 3             | −0.33 (−0.56, −0.09)| 0.006 | 0.226            | 32.8 |
| ≥ 25                                                | 1             | −0.30 (−0.70, 0.11)| 0.151 |                 | 32.8 |
[46, 47]. Second, steroids have been shown to contribute to low BMD in ulcerative colitis patients, and various patients in these studies had taken glucocorticoids as a normal treatment for ulcerative colitis before the detection of BMD, and the doses received by these patients varied.

It is accepted that glucocorticoids can reduce BMD. Glucocorticoids not only inhibit osteoblast proliferation and the synthesis of type-I collagen and osteocalcin but also promote osteoblast apoptosis, osteoclast formation and activity, and bone resorption [49]. Moreover, glucocorticoids can also reduce intestinal calcium absorption, increase the renal excretion of calcium, and lead to an early increase in fracture risk prior to the loss of BMD [50–54]. And it is revealed that the bone mineral density of patients can significantly improve after discontinuation of glucocorticoids [55]. Glucocorticoids are conventional treatments for inflammatory bowel disease, and some patients in the studies included in the present study had taken glucocorticoids as a normal treatment for ulcerative colitis before the detection of BMD.
The present meta-analysis has several strengths. This meta-analysis was the first to assess the correlation between BMD and ulcerative colitis. All studies were divided into four groups. These groups were separately analyzed, and certain subgroup analyses were conducted. Two groups (the SMD [z-score] group and the SMD [t-score] group) had low heterogeneity, while the OR group had low heterogeneity after the subgroup analyses. Glucocorticoids are conventional treatments for inflammatory bowel disease. The subgroup analysis of studies of steroid-free patients addressed the use of steroids, which is a confounding factor of low BMD in ulcerative colitis patients. This subgroup analysis also revealed a significant negative relationship between BMD and ulcerative colitis. Last, the large number of participants provided high statistical power. In the sensitivity analysis, the overall estimates remained significant, which contributed to these robust results.

However, there were some limitations in the present meta-analysis. First, there was significant heterogeneity among studies in the SMD (BMD) group when the data was pooled together, and this could not be explained through the subgroup analyses. Multiple factors may have caused the heterogeneity but the majority of these factors could not be examined. For example, except for the potential factors included in the subgroup analyses, genetic predisposition may also contribute to heterogeneity. But the races of people included in this analysis varied and they were not mentioned in some studies included in this meta-analysis. At the same time, it could not be excluded that some medicines such as bisphosphonates might be introduced to some ulcerative colitis patients who had severe osteoporosis. But some studies did not clarify whether the patients included had taken bisphosphonates or not. It may have also contributed to heterogeneity. Second, since the included studies were all observational studies, the severity of the disease could not be balanced, and few studies divided patients based on disease severity. This situation may have contributed to some bias in the present analysis. More convincing experimental trials should be conducted to further investigate these relationships.

Conclusions
The present meta-analysis indicated that BMD negatively correlates with ulcerative colitis regardless of steroid therapy and that thinner or older ulcerative colitis patients are more susceptible to osteoporosis. This finding provides convincing positive implications for osteoporosis prevention in ulcerative colitis patients regardless of whether they are taking corticosteroids. More convincing studies should account for the confounding factors mentioned above to further evaluate the relationship between BMD and ulcerative colitis.

Abbreviations
BMD: Bone mineral density; DXA: Dual energy X-ray absorptiometry; MOOSE: Meta-analysis of observational studies in epidemiology; OR: Odds ratio; CI: Confidence interval; SMD: Standardized mean difference; NOS: Newcastle–Ottawa scale; AHRQ: Agency for Healthcare Research and Quality.

Acknowledgements
Not applicable.

Authors’ contributions
ZS acted as guarantors of the article. ZS and CY conceived and designed the study. TZ, JP, BL, LC and WJ collected the data. TZ and JP analyzed the data. TZ and JP wrote the article. All authors read and approved the final manuscript.

Funding
None.

Availability of data and materials
PubMed, EMBASE and the Cochrane Library databases.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Department of Gastroenterology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China. 2 People’s Hospital of Jianggan District, Hangzhou, China.
Appendix
MOOSE Checklist
Bone mineral density is negatively correlated with ulcerative colitis: a systematic review and meta-analysis.

| Criteria | Brief description of how the criteria were handled in the meta-analysis |
|----------------|--------------------------------------------------------------------------------|
| Reporting of background should include | |
| ✓ Problem definition | Newer epidemiological studies suggest that the incidence of ulcerative colitis might be increasing rapidly. Furthermore, osteoporosis in ulcerative colitis patients has gained great attention, but the epidemiologic evidence in ulcerative colitis decreasing bone mineral density remains controversial. |
| ✓ Hypothesis statement | Bone mineral density is negatively correlated with ulcerative colitis regardless of steroid therapy. |
| ✓ Description of study outcomes | Low bone mineral density |
| ✓ Type of exposure or intervention used | Ulcerative colitis |
| ✓ Type of study designs used | We included cross-sectional studies. We excluded studies of reverse association. |
| ✓ Study population | We placed no restriction |
| Reporting of search strategy should include | |
| ✓ Qualifications of searchers | The credentials of the two investigators Tianyu Zhou and Jiaqi Pan are indicated in the author list. |
| ✓ Search strategy, including time period included in the synthesis and keywords | PubMed from 1965—August 2019 | EMBASE from 1974—August 2019 | Cochrane library from 1999—August 2019 | See Fig. 1 in the article. |
| ✓ Databases and registries searched | PubMed, EMBASE and Cochrane library |
| ✓ Search software used, name and version, including special features | We did not employ a search software. EndNote was used to merge retrieved citations and eliminate duplications. |

| Criteria | Brief description of how the criteria were handled in the meta-analysis |
|----------------|--------------------------------------------------------------------------------|
| ✓ Use of hand searching | We hand-searched relevant studies of retrieved papers for additional references. |
| ✓ List of citations located and those excluded, including justifications | Details of the literature search process are outlined in the flow chart. The citation list is available upon request. |
| ✓ Method of addressing articles published in languages other than English | We include full papers published in English. |
| ✓ Method of handling abstracts and unpublished studies | We extracted information from abstracts and some abstracts which were lack of enough information were excluded. There was no unpublished study in the present analysis. |
| ✓ Description of any contact with authors | None |
| Reporting of methods should include | |
| ✓ Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | Detailed inclusion and exclusion criteria were described in "Materials and methods" section. |
| ✓ Rationale for the selection and coding of data | Data extracted from each of the studies were relevant to name of the first author, year of publication, country where the study was conducted, study population, method used to detect bone density as well as ulcerative colitis, and the number of events (or cases) and non-events (or controls). |
| ✓ Assessment of confounding | Restricted the analysis to method estimates. |
| ✓ Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results | Sensitivity analyses by several quality indicators such as methods to detect bone density and diagnose ulcerative colitis, control selection, potential duplicate data, and origin of samples. |
| Criteria | Brief description of how the criteria were handled in the meta-analysis |
|----------|---------------------------------------------------------------------|
| ✓        | Assessment of heterogeneity                                          |
| ✓        | Description of statistical methods in sufficient detail to be replicated |
| ✓        | Provision of appropriate tables and graphics                        |

**Reporting of results should include**

| ✓ | Graph summarizing individual study estimates and overall estimate |
| ✓ | Results of sensitivity testing                                     |
| ✓ | Table giving descriptive information for each study included       |

**Reporting of discussion should include**

| ✓ | Quantitative assessment of bias                                    |
| ✓ | Justification for exclusion                                       |
| ✓ | Assessment of quality of included studies                          |

**Reporting of conclusions should include**

This table details the criteria for conducting a meta-analysis and the handling of each criterion. The references section includes articles on inflammatory bowel disease and bone density, emphasizing the need for further research on the topic.
12. Egger M, Smith GD, Schneider M et al (1997) Bias in meta-analysis detected by a simple, graphical test. Br Med J 315:629–634
13. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50:1088–1101
14. Kleia-Kazmierczak Ivona, Michalak Michal, Szymczak-Tomczak Aleksandra et al (2018) Prevalence of osteoporosis and osteopenia in patients with inflammatory bowel diseases from Greater Poland Province. Pol Arch Intern Med 128:447–454
15. Lima CA, Lyra AC, Mendes CMC et al (2017) Bone mineral density and inflammatory bowel disease severity. Braz J Med Biol Res 50:1–8
16. Bastos C, Nogueira-Barbosa M, Salmon C et al (2012) The impact of low activity Crohn's disease (CD) and ulcerative colitis (UC) in calcium metabolism, bone mass and marrow adiposity. J Bone Miner Res 27:1
17. Zanetti GR, Farias MLF, Lacatina PGS et al (2011) Evaluation of bone turnover and bone mineral density in patients with inflammatory bowel disease. Clin Chem 57:187
18. Kaya G, Kocak E, Akbal E et al (2011) Comparison of the possible risk factors of bone mineral density in subjects with ulcerative colitis and healthy subjects. South Med J 104:747–751
19. Pluskiewicz Wojciech, Karasek Dariusz (2009) Spine bone mineral density and VDR polymorphism in subjects with ulcerative colitis. J Bone Miner Metab 27:567–573
20. Liu JB, Gao X, Zhang FB et al (2009) The risk factor for low bone mineral density in patients with inflammatory bowel disease. Zhonghua Nei Ke Za Zhi 48:833–836
21. Sakellariou GT, Moschos J, Berberidis C et al (2006) Bone density in young males with recently diagnosed inflammatory bowel disease. Joint Bone Spine 73:725–728
22. Lamb EJ, Wong T, Smith DJ et al (2002) Metabolic bone disease is present at diagnosis in patients with inflammatory bowel disease. Aliment Pharmacol Ther 15:1895–1902
23. Ullivieri FM, Piopi LP, Taroli E et al (2001) Bone mineral density and body composition in ulcerative colitis: a six-year follow-up. Osteoporo Int 12:343–348
24. Schoon EJ, Blok BM, Geerling BJ et al (2000) Bone mineral density in patients with recently diagnosed inflammatory bowel disease. Gastroenterology 119:1203–1208
25. Dinca M, Fries W, Lusietto G et al (1999) Evolution of osteopenia in inflammatory bowel disease. Am J Gastroenterol 94:1292–1297
26. Arzdzone S, Bollani S, Bettica P et al (2000) Altered bone metabolism in inflammatory bowel disease: there is a difference between Crohn's disease and ulcerative colitis. J Intern Med 247:63–70
27. Shanahan F (1993) Pathogenesis of ulcerative colitis. Lancet 342:407–411
28. Bernstein CN, Leslie WD (2003) The pathophysiology of bone disease in gastrointestinal disease. Eur J Gastroenterol Hepatol 15:857–864
29. Mora JR, Iwata m, von Andrian UH (2008) Vitamin effects on the immune system: vitamin A and D take centre stage. Nat Rev Immunol 8:685–698
30. Kimray AW, Feldman D (2011) Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin D. Annu Rev Pharmacol Toxicol 51:311–336
31. Raman M, Milestone AN, Walters JR et al (2011) Vitamin D and gastrointestinal diseases: inflammatory bowel disease and colorectal cancer. Therap Adv Gastroenterol 4:499–62
32. Holick MF (2007) Vitamin D deficiency. N Engl J Med 357:266–281
33. Raftery T, O'morain CA, O'Sullivan M (2012) Vitamin D: new roles and therapeutic potential in inflammatory bowel disease. Curr Drug Metab 13:1294–1302
34. Ullitsky A, Ananthakrishnan AN, Naik A et al (2011) Vitamin D deficiency in patients with inflammatory bowel disease: association with disease activity and quality of life. JPN J Parenter Enteral Nutr 35:308–316
35. Leslie WD, Miller N, Rogala L, Bernstein CN (2008) Vitamin D status and bone density in recently diagnosed inflammatory bowel disease: the Manitoba IBD Cohort Study. Am J Gastroenterol 103:1451–1459
36. Hadj ST, Kallel L, Feki M et al (2013) Unbalanced bone remodeling in Tunisian patients with inflammatory bowel diseases. Tunis Med 91:273–277
37. Madama MZ, Hodgson HF (1992) Peripheral blood monocyte cytokine production and acute phase response in inflammatory bowel disease. Gut 33:775–778
38. Theill LE, Boyle WJ, Penninger JM (2002) RANK-L and RANK: T cells, bone loss, and mammalian evolution. Annu Rev Immunol 20:795–823
39. Boyce BF, Xing L (2008) Functions of RANKL/RANK/OPG in bone modeling and remodeling. Arch Biochem Biophys 473:139–146
40. Pollak RD, Karmeli F, Elaiakim R et al (1998) Femoral neck osteopenia in patients with inflammatory bowel disease. Am J Gastroenterol 93:1483–1490
41. Raiz LG (1988) Local and systemic factors in the pathogenesis of osteoporosis. N Engl J Med 318:818–828
42. Macdonald BR, Gowen M (1992) Cytokines and bone. Br J Rheumatol 31:149–155
43. Nguyen L, Dewhirst FE, Haushka PV et al (1991) Interleukin-1 stimulates bone erosion and inhibits formation in vivo. Lymphocyte Cytokine Res 10:15–21
44. Bjarnason I, Macpherson A, Buxton-Thomas M et al (1993) High prevalence of osteoporosis in patients with inflammatory bowel disease and low lifetime intake of corticosteroids. Gastroenterology 105:541
45. Krela-Kazmierczak I, Kaczmarek-Rys M, Szymczak A et al (2016) Bone metabolism and the C-223C>T polymorphism in the 5′UTR region of the osteoprotegerin gene in patients with inflammatory bowel disease. Calcif Tissue Int 6:616–624
46. Schulte CMS, Dignass AU, Goebell H et al (2000) Genetic factors determine extent of bone loss in inflammatory bowel disease. Gastroenterology 119:909–920
47. Nemetz A, Toth M, Garcia-Gonzalez MA et al (2001) Allelic variation at the interleukin 1b gene is associated with decreased bone mass in patients with inflammatory bowel diseases. Gut 49:644–649
48. Szafiors P, Che H, Barnetche T et al (2018) Risk of fracture and low bone mineral density in adults with inflammatory bowel diseases. A systematic literature review with meta-analysis. Osteoporos Int 29:2389–2397
49. Etzel JP, Larson MF, Anawalt BD et al (2011) Assessment and management of low bone density in inflammatory bowel disease and performance of professional society guidelines. Inflamm Bowel Dis 17:2122–2129
50. Bernstein CN, Leslie WD (2003) The pathophysiology of bone disease in gastrointestinal disease. Eur J Gastroenterol Hepatol 8:857–864
51. American College of Rheumatology Task Force on Osteoporosis Guidelines (1996) Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheum 11:1791–1801
52. Whittier X, Saag KG (2016) Glucocorticoid-induced osteoporosis. Rheum Dis Clin North Am 1:177–189
53. Longui CA (2007) Glucocorticoid therapy minimizing side effects. J Pediatriatr Pharmacol Ther 11:1–17
54. Pereira RM, Carvalho JF, Paula AP, Committee for Osteoporosis and Bone Metabolic Disorders of the Brazilian Society of Rheumatology, Brazilian Medical Association, Brazilian Association of Physical Medicine and Rehabilitation et al (2012) Guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis. Rev Bras Reumatol 4580–593
55. Buckley L, Humphrey MB (2018) Glucocorticoid-induced osteoporosis. N Engl J Med 379:2547–2556

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.