A meta-analysis of the risk of osteoporotic fractures in inflammatory bowel disease

*Liansheng Hao[1,B,C], *Shengkai Mu[1,C,D], Junyan Yin[2,B,D], Jun Liu[3,4,A,E,F]

[1] 2nd Department of Trauma, Liaocheng Hospital of Traditional Chinese Medicine, China
[2] Department of Chinese Traditional Medicine, Liaocheng People's Hospital, China
[3] Department of Geriatric Medicine, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Shandong Province Hospital of Traditional Chinese Medicine, Jinan, China
[4] Postdoctoral Research Station, Shandong University of Traditional Chinese Medicine, Jinan, China

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online) *Adv Clin Exp Med*. 2024;33(4):327–333

Address for correspondence
Jun Liu
E-mail: sliujun2022@126.com

Funding sources
None declared

Conflict of interest
None declared

*Liansheng Hao and Shengkai Mu contributed equally to this work.

Received on October 24, 2022
Reviewed on March 23, 2023
Accepted on June 22, 2023

Published online on August 7, 2023

Abstract

Background. There are a variety of perspectives on the risk of osteoporotic fractures in inflammatory bowel disease (IBD), and few thorough assessments that are pertinent.

Objectives. We conducted a meta-analysis to assess the risk of osteoporotic fractures in IBD.

Materials and methods. A systematic literature search up to September 2022 was performed, and 1,158,982 subjects participated in the baseline trials of the selected studies. A total of 261,829 patients had IBD, while 897,153 were controls. Odds ratio (OR) and mean difference (MD) with 95% confidence intervals (95% CIs) were calculated to measure the risk of osteoporotic fractures in IBD patients using contentious and dichotomous approaches with a random or fixed influence model.

Results. The presence of IBD resulted in significantly higher frequency of osteoporotic fractures (OR: 1.42, 95% CI: 1.21–1.66, $p < 0.001$) compared to controls. Nevertheless, no significant differences in terms of osteoporotic fractures were found between ulcerative colitis (OR: 2.79, 95% CI: 0.88–8.87, $p = 0.08$) and Crohn's disease (OR: 1.84, 95% CI: 0.81–4.18, $p = 0.14$) compared to controls.

Conclusions. This study found a strong correlation between the risk of osteoporotic fractures and inflammatory bowel disease. The small number of studies in certain comparisons requires care when analyzing the results.

Key words: inflammatory bowel disease, osteoporotic fractures, Crohn's disease, ulcerative colitis

Cite as
Hao L, Mu S, Yin J, Liu J. A meta-analysis of the risk of osteoporotic fractures in inflammatory bowel disease. *Adv Clin Exp Med*. 2024;33(4):327–333. doi:10.17219/acem/168684

DOI
10.17219/acem/168684

Introduction

The development of osteoporosis and osteoporotic fractures is significantly influenced by inflammatory bowel disease (IBD), particularly ulcerative colitis and Crohn's disease.[1] The probability of developing osteoporosis varies from 17% to 41%.[2] Patients with IBD have higher rates of peripheral cortical and spinal trabecular osteoporosis. Young, amenorrheic women have clinical osteoporosis that is more severe.[3] Patients are more likely to sustain osteoporotic fractures due to the increased chance of developing osteoporosis. When compared to the general population, IBD patients may have a 40% higher incidence of fractures, which lowers their quality of life and increases their morbidity.[4] The mechanism by which IBD increases a patient's risk of osteoporosis and osteoporotic fractures is complex. Numerous studies examining glucocorticoid use have not found a statistically significant increase in osteoporosis in patients taking this medication.[4] Patients with IBD are frequently prescribed steroids, and this can predispose them to osteoporosis. Moreover, there seems to be a process affecting bone metabolism in IBD patients, such as a chronic inflammatory state that causes bone loss by activating the tumor necrosis factor alpha (TNF-α)-mediated RANK/RANKL/osteoprotegerin pathway, which encourages osteoclastogenesis.[4] Secondary hyperparathyroidism, which is frequently prevalent due to the decreased absorption of vital nutrients including calcium and vitamin D, is another cause of osteoporosis.[5] The goal of this study was to compile the most reliable data comparing IBD patients with control patients in terms of likelihood of developing osteoporotic fractures.

Objectives

The aim of the study was to determine the risk of osteoporotic fractures in patients with IBD.

Materials and methods

Information sources

The main goal of the current meta-analysis was to appraise the risk of osteoporotic fractures in IBD. Every selected study involved human research. Inclusion was unaffected by study size or language. Commentaries, review papers and papers that did not that did not provide a measure of a relationship were excluded from the study. The complete course of the study is presented in Fig. 1. The following inclusion criteria had to be met for the publications to be selected for the meta-analysis:

1. The study was either a controlled trial, observational, prospective, or retrospective study;
2. Subjects with osteoporotic fractures make up the intended selected subjects for the meta-analysis;
3. The intervention program included IBD;
4. The study was about the risk of osteoporotic fractures in IBD.

Studies that had no comparison of outcomes within its protocol, research that did not examine IBD in subjects with osteoporotic fractures, and studies in subjects without osteoporotic fractures or without IBD were excluded from the study.[6]

Search strategy

A protocol of search strategy followed the Population, Intervention, Comparison, Outcomes and Study (PICOS) concept, and was characterized as follows: "population" comprised patients with osteoporotic fractures "intervention" or "exposure" concerned IBD treatment, whereas the "comparison" pertained IBD patients compared to controls, osteoporotic fractures were the "outcomes", and there were no restrictions regarding the study's design.[7]

We conducted a thorough search of the OVID, Embase, Cochrane Library, PubMed, and Google Scholar databases up until September 2022, using an arrangement of keywords and terms correlated with IBD, Crohn's disease, osteoporotic fractures, and ulcerative colitis (cf. Table 1). To identify studies that did not show a relationship between

Table 1. Search strategy for each database

Database	Search strategy
PubMed	#1 "inflammatory bowel disease" (MeSH terms) OR "osteoporotic fractures" (all fields) #2 "ulcerative colitis" (MeSH terms) OR "Crohn's disease new" (all fields) #3 #1 AND #2
Embase	#1 "inflammatory bowel disease"/exp OR "osteoporotic fractures" #2 "ulcerative colitis"/exp OR "Crohn's disease" #3 #1 AND #2
Cochrane Library	#1 "inflammatory bowel disease": ti,ab,kw OR "osteoporotic fractures": ti,ab,kw (word variations have been searched) #2 "ulcerative colitis": ti,ab,kw OR "Crohn's disease": ti,ab,kw (word variations have been searched) #3 #1 AND #2

MeSH – medical subject headings; ti,ab,kw – terms in either title or abstract or keyword fields; exp – exploded indexing term.

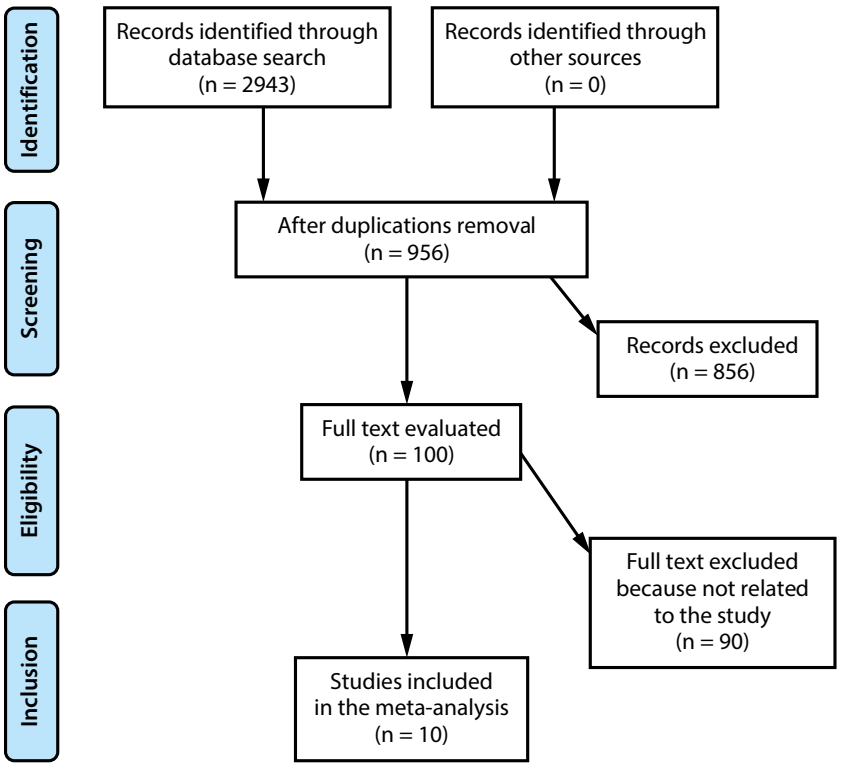

Fig. 1. Flowchart of the study process

IBD patients and the controls regarding the risk of osteoporotic fractures, all retrieved papers were joined into an EndNote file, duplicates were eliminated, and the titles and abstracts were reviewed.

Selection process

The present study followed the meta-analysis of studies in the epidemiology statement, which was performed following an established protocol.

Data collection process

The criteria used to gather the data included the last name of the first author, country, population, the quantitative and qualitative assessment technique, the information source, the assessment of the results, and statistical analysis.[8]

Data items

When there were disparate findings from a single study on the risk of osteoporotic fractures in IBD, such data were collected independently.

Risk of bias assessment

Two authors individually evaluated the methodology of the designated articles to ascertain the possibility of bias in each study. The procedural quality was assessed using the "risk of bias instrument" from the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (https://handbook-5-1.cochrane.org/). Each study was classified according to the appraisal criteria and was assigned with one of the 3 levels of the bias. A study was rated as having a low risk of bias if all the quality standards were met; if one or more requirements were not met or were not taken into account in a given study, such study was rated as having a moderate risk of bias. The study was considered to have a high risk of bias when one or more quality criteria were not met at all or were only partially met. Any discrepancies were addressed through a reassessment of a given analyzed article.

Effect measures

Only studies that reported and assessed the influence of IBD in comparison to controls on the risk of osteoporotic fractures were subjected to sensitivity studies. A sensitivity and subclass analysis was utilized to compare the risk of osteoporotic fractures in IBD.

Synthesis methods

The current meta-analysis used a random-effects model with dichotomous and continuous techniques to calculate the odds ratio (OR) with a 95% confidence interval (95% CI). Additionally, we decided to evaluate the I^2 index, with a range of 0–100%. Meta-analyses use either a fixed-effect or a random-effects statistical model. A fixed-effect meta-analysis assumes that all studies are estimating the same (fixed) treatment effect, whereas a random-effects

meta-analysis allows for the differences in the treatment effect from study to study. The choice of method affects the interpretation of the summary estimates.[9]

Reporting bias assessment

Publication bias was measured both qualitatively and statistically using funnel plots and the Egger's regression test that displays the logarithm of ORs or mean differences (MDs) compared to their standard errors (publication bias existed if the p-value was <0.05), if the number of selected studies was bigger than 4. However, if the number of selected studies for the comparison was 4 or less, the Begg's rank correlation test was used.[10]

Certainty assessment

Two-tailed tests were used to analyze all p-values. The graphs and statistical analysis were created using Reviewer Manager v. 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

From the total of 2943 related research studies, 10 articles published between 2000 and 2022 met the requirements and were included in the meta-analysis.[11–20] Table 2 presents the findings from these studies. A total of 1,158,982 subjects participated in the baseline trials of the selected studies, of which 261,829 had IBD, while 897,153 were controls. The number of controls ranged from 105 to 463,576. Ten studies presented data related to IBD, 3 studies presented data organized by ulcerative colitis, and 4 studies presented data organized by Crohn's disease.

The presence of IBD resulted in significantly higher number of osteoporotic fractures (OR: 1.42, 95% CI: 1.21–1.66, p < 0.001) with high heterogeneity (I^2 = 81%) compared to controls, as shown in Fig. 2. Nevertheless, no significant differences were found amongst ulcerative colitis patients (OR: 2.79, 95% CI: 0.88–8.87, p = 0.08) with high heterogeneity (I^2 = 99%), and Crohn's disease patients (OR: 1.84, 95% CI: 0.81–4.18, p = 0.14) with high heterogeneity (I^2 = 97%) compared to the control group for osteoporotic fractures, as shown in Fig. 3 and Fig. 4.

Stratified models could not be utilized to examine the influence of some factors on comparison outcomes, such as gender, age and ethnicity, due to no available data for these parameters. Quantitative evaluations using the Egger's regression test for the 1st comparison and Begg's rank correlation test for the 2nd and 3rd comparisons, as well as visual inspection of the funnel plot were conducted (Fig. 5–7). There was no evidence of publication bias (p = 0.86). However, most of the included randomized controlled trials were found to have subpar methodological quality, no bias in selective reporting and scant outcome data.

Discussion

A total of 1,158,982 subjects participated in the baseline trials of the studies selected for this meta-analysis, of which 261,829 had IBD and 897,153 were controls.[11–20] Inflammatory bowel disease resulted in significantly higher number of osteoporotic fractures compared to controls. Nevertheless, no significant differences regarding osteoporotic fractures were found between ulcerative colitis and Crohn's disease patients compared to controls. Particular attention should be paid when evaluating the results due to the small number of studies included in some comparisons, e.g., ulcerative colitis and Crohn's disease.

Numerous pieces of information have been gathered to evaluate the connection between IBD and osteoporosis; the latter is characterized by decreased bone mineral density. The only related outcome that has considerable morbidity, mortality and healthcare expense is the probability of suffering bone fractures.[11] These findings demonstrate

Table 2. Characteristics of the studies selected for the meta-analysis

Study, year, reference	Country	Total	Inflammatory bowel disease	Control
Bernstein et al. (2000)[11]	Canada	66,297	6027	60,270
Loftus et al. (2002)[12]	USA	476	238	238
van Staa et al. (2003)[13]	UK	463,576	231,788	231,788
Targownik et al. (2013)[14]	Canada	46,404	1230	45,174
Tsai et al. (2015)[15]	China	15,705	3141	12,564
Bartko et al. (2020)[16]	Austria	350,078	531	349,547
Lo et al. (2020)[17]	Denmark	11,080	513	10,567
Soare et al. (2021)[18]	Romania	162	81	81
Soare et al. (2022)[19]	Romania	105	52	53
Ahn et al. (2022)[20]	South Korea	205,099	18,228	186,871
Total		1,158,982	261,829	897,153

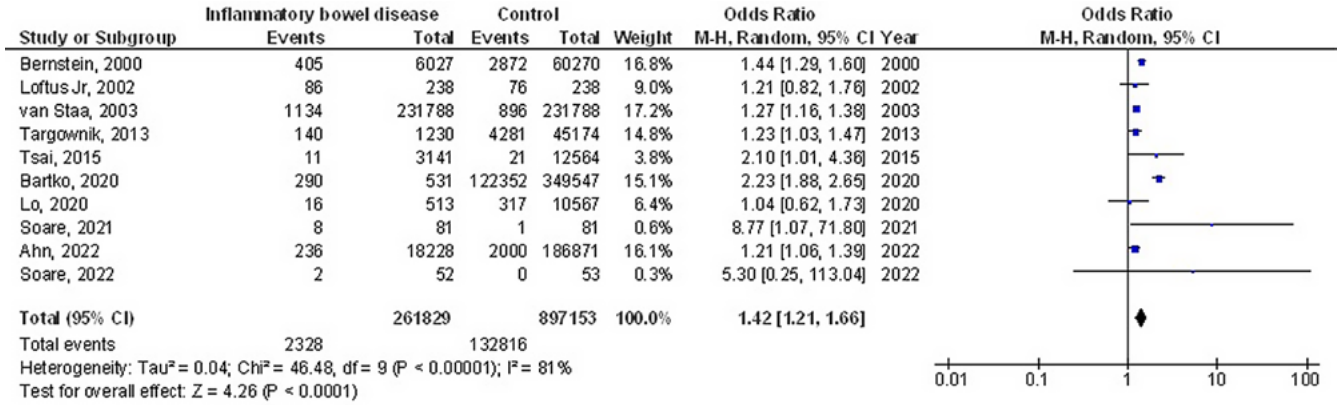

Fig. 2. Forest plot showing the impact of inflammatory bowel disease compared to controls on osteoporotic fractures

95% CI – 95% confidence interval; df – degrees of freedom.

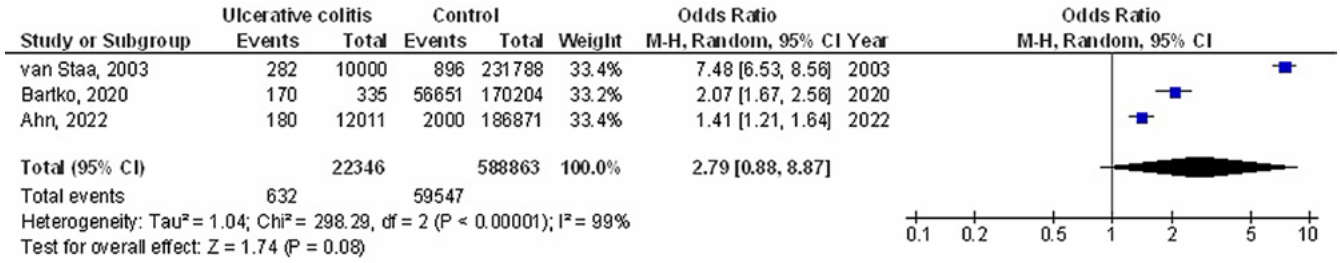

Fig. 3. Forest plot showing the impact of ulcerative colitis compared to controls on osteoporotic fractures

95% CI – 95% confidence interval; df – degrees of freedom.

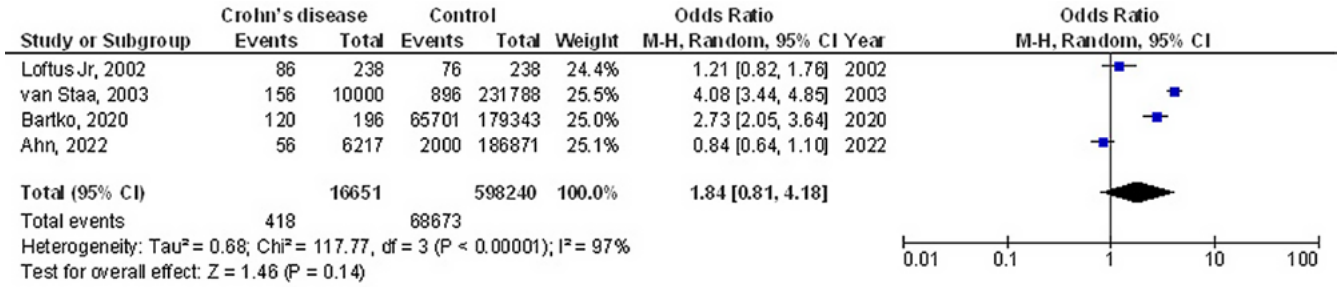

Fig. 4. Forest plot showing the impact of Crohn's disease compared to controls on osteoporotic fractures

95% CI – 95% confidence interval; df – degrees of freedom.

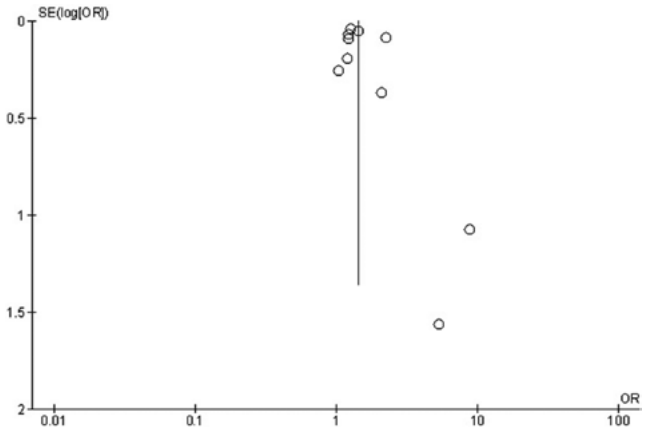

Fig. 5. Funnel plot showing the impact of inflammatory bowel disease compared to controls on osteoporotic fractures (Egger's test p-value = 0.88)

SE – standard error; OR – odds ratio.

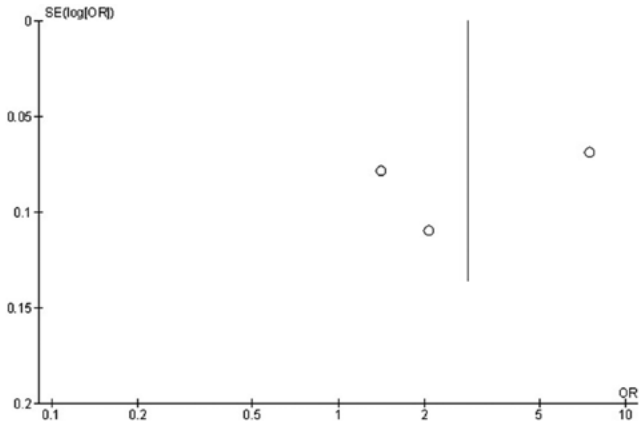

Fig. 6. Funnel plot showing the impact of ulcerative colitis compared to controls on osteoporotic fractures (Egger's test p-value = 0.85)

SE – standard error; OR – odds ratio.

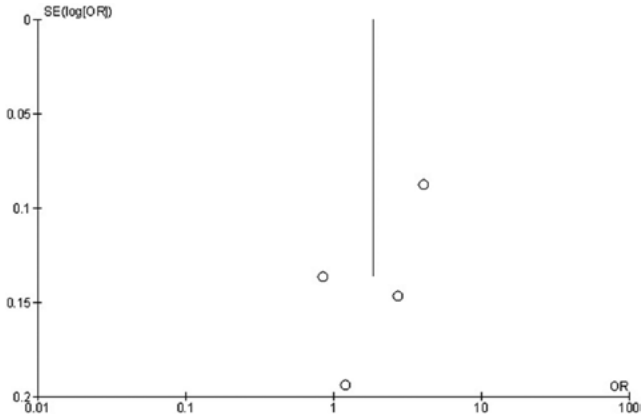

Fig. 7. Funnel plot showing the impact of Crohn's disease compared to controls on osteoporotic fractures (Egger's test p-value = 0.83)

SE – standard error; OR – odds ratio.

that the risk of osteoporotic fractures increases with age and that even people with IBD often do not exhibit accelerated bone disease symptoms until the disease has significantly advanced.[21] The use of corticosteroids in the data utilized for this meta-analysis was matched. Patients who took steroids alone were more likely to suffer from fractures. The biggest impact of steroids on bone health is the reduction of osteoblastic activity, which decreases bone growth. The reduction in osteoblast production is a result of both a decline in the generation of new osteoblasts and an increase in the mortality of mature osteoblasts. Glucocorticoids also suppress the production of insulin-like growth factor 1, which reduces the function of the remaining osteoblasts, both directly and indirectly.[22] Since most IBD patients are currently using or have previously used steroids, this could be a confounding issue. For this confounder, direct standardization was utilized as an adjustment. After accounting for the usage of this medicine, the decrease in bone mass and the increased number of bone fractures confirmed that an inflammatory condition is sufficient to alter bone metabolism. Since early detection, risk factor modification and treatment can reduce the risk of bone mass loss and improve morbidity in this particular demographic, further research is needed to determine the risk of developing fractures in the pediatric population.

This meta-analysis assesses the risk of osteoporotic fractures in IBD. More investigation is needed to clarify probable associations of the consequences under discussion. Larger and more homogeneous samples are obligatory for this investigation.[23–28] This was likewise emphasized in a previous work that employed a related meta-analysis technique and reported similar advantageous outcomes for IBD on osteoporotic fractures.[29–32] Since our meta-analysis was incapable of defining whether differences in gender, age and ethnicity are connected to the outcomes, well conducted randomized controlled trials are required to evaluate these factors and the mixture of variables such as gender, ethnicity, age, and other variants of subjects.

Limitations

Since several studies identified during this systemic review were not encompassed in the meta-analysis, there might have been a selection bias. The removed publications, nevertheless, did not meet the necessary inclusion criteria for this systemic review. Furthermore, we were incapable to determine whether factors such as age, gender or ethnicity affected the outcomes. The study aimed to compare the results regarding osteoporotic fractures between a control group and an IBD group. The incorporation of data from earlier studies could have added bias due to incomplete or inaccurate data. Potential sources of bias included the nutritional status of the participants as well as their age and gender characteristics. Regrettably, some unpublished papers and missing data can bias the study outcomes.

Conclusions

Inflammatory bowel disease resulted in significantly higher osteoporotic fractures compared to controls. Nevertheless, no significant differences regarding osteoporotic fractures were found between ulcerative colitis patients and Crohn's disease patients compared to controls. Particular attention should be paid when evaluating the results due to the small number of studies included in some comparisons, e.g., ulcerative colitis and Crohn's disease.

ORCID iDs

Liansheng Hao https://orcid.org/0000-0001-5853-7642
Shengkai Mu https://orcid.org/0000-0003-0688-1534
Junyan Yin https://orcid.org/0009-0001-9813-2727
Jun Liu https://orcid.org/0000-0001-9515-3699

References

1. Lima CA, Lyra AC, Mendes CMC, et al. Bone mineral density and inflammatory bowel disease severity. *Braz J Med Biol Res*. 2017;50(12):e6374. doi:10.1590/1414-431x20176374
2. Ali T, Lam D, Bronze MS, Humphrey MB. Osteoporosis in inflammatory bowel disease. *Am J Med*. 2009;122(7):599–604. doi:10.1016/j.amjmed.2009.01.022
3. Mundy GR. Osteoporosis and inflammation. *Nutr Rev*. 2007;65(12 Pt 2):S147–S151. doi:10.1111/j.1753-4887.2007.tb00353.x
4. Madney YM, Laz NI, Elberry AA, Rabea H, Abdelrahim MEA. The influence of changing interfaces on aerosol delivery within high flow oxygen setting in adults: An in-vitro study. *J Drug Deliv Sci Technol*. 2020;55:101365. doi:10.1016/j.jddst.2019.101365
5. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. *J Clin Endocrinol Metab*. 2011;96(1):53–58. doi:10.1210/jc.2010-2704
6. Stroup DF, Berlin J, Morton S, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008–2012. doi:10.1001/jama.283.15.2008
7. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1–e34. doi:10.1016/j.jclinepi.2009.06.006

8. Gupta S, Rout G, Patel AH, et al. Efficacy of generic oral directly acting agents in patients with hepatitis C virus infection. *J Viral Hepat*. 2018;25(7):771–778. doi:10.1111/jvh.12870
9. Sheikhbahaei S, Trahan TJ, Xiao J, et al. FDG-PET/CT and MRI for evaluation of pathologic response to neoadjuvant chemotherapy in patients with breast cancer: A meta-analysis of diagnostic accuracy studies. *Oncologist*. 2016;21(8):931–939. doi:10.1634/theoncologist.2015-0353
10. Higgins JPT, Thompson S, Deeks J, Altman D. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560. doi:10.1136/bmj.327.7414.557
11. Bernstein CN, Blanchard J, Leslie W, Wajda A, Yu B. The incidence of fracture among patients with inflammatory bowel disease: A population-based cohort study. *Ann Intern Med*. 2000;133(10):795–799. doi:10.7326/0003-4819-133-10-200011210-00012
12. Loftus EV, Crowson CS, Sandborn WJ, Tremaine WJ, O'Fallon WM, Melton LJ. Long-term fracture risk in patients with Crohn's disease: A population-based study in Olmsted County, Minnesota. *Gastroenterology*. 2002;123(2):468–475. doi:10.1053/gast.2002.34779
13. van Staa TP, Cooper C, Samuels Brusse L, Leufkens H, Javaid MK, Arden NK. Inflammatory bowel disease and the risk of fracture. *Gastroenterology*. 2003;125(6):1591–1597. doi:10.1053/j.gastro.2003.09.027
14. Targownik LE, Bernstein CN, Nugent Z, Leslie WD. Inflammatory bowel disease has a small effect on bone mineral density and risk for osteoporosis. *Clin Gastroenterol Hepatol*. 2013;11(3):278–285. doi:10.1016/j.cgh.2012.10.022
15. Tsai MS, Lin CL, Tu YK, Lee PH, Kao CH. Risks and predictors of osteoporosis in patients with inflammatory bowel diseases in an Asian population: A nationwide population-based cohort study. *Int J Clin Pract*. 2015;69(2):235–241. doi:10.1111/ijcp.12526
16. Bartko J, Reichardt B, Kocijan R, Klaushofer K, Zwerina J, Behanova M. Inflammatory bowel disease: A nationwide study of hip fracture and mortality risk after hip fracture. *J Crohns Colitis*. 2020;14(9):1256–1263. doi:10.1093/ecco-jcc/jjaa052
17. Lo B, Holm JP, Vester-Andersen MK, Bendtsen F, Vind I, Burisch J. Incidence, risk factors and evaluation of osteoporosis in patients with inflammatory bowel disease: A Danish population-based inception cohort with 10 years of follow-up. *J Crohns Colitis*. 2020;14(7):904–914. doi:10.1093/ecco-jcc/jjaa019
18. Soare I, Sirbu A, Martin S, et al. Assessment of bone quality with trabecular bone score in patients with inflammatory bowel disease. *Sci Rep*. 2021;11(1):20345. doi:10.1038/s41598-021-99669-z
19. Soare I, Sirbu A, Diculescu M, et al. Therapies and bone impairment in inflammatory bowel disease young adults. *Farmacia*. 2022;70(2):355–359. doi:10.31925/farmacia.2022.2.22
20. Ahn HJ, Kim YJ, Lee HS, et al. High risk of fractures within 7 years of diagnosis in Asian patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. 2022;20(5):e1022–e1039. doi:10.1016/j.cgh.2021.06.026
21. Sakellariou GT, Moschos J, Berberidis C, et al. Bone density in young males with recently diagnosed inflammatory bowel disease. *Joint Bone Spine*. 2006;73(6):725–728. doi:10.1016/j.jbspin.2006.01.017
22. Canalis E. Mechanisms of glucocorticoid-induced osteoporosis. *Curr Opin Rheumatol*. 2003;15(4):454–457. doi:10.1097/00002281-200307000-00013
23. Saeed H, Mohsen M, Salah Eldin A, et al. Effects of fill volume and humidification on aerosol delivery during single-limb noninvasive ventilation. *Respir Care*. 2018;63(11):1370–1378. doi:10.4187/respcare.06022
24. Nicola M, Elberry A, Sayed O, Hussein R, Saeed H, Abdelrahim M. The impact of adding a training device to familiar counselling on inhalation technique and pulmonary function of asthmatics. *Adv Ther*. 2018;35(7):1049–1058. doi:10.1007/s12325-018-0737-6
25. Rabea H, Ali AMA, Salah Eldin R, Abdelrahman MM, Said ASA, Abdelrahim ME. Modelling of in-vitro and in-vivo performance of aerosol emitted from different vibrating mesh nebulisers in non-invasive ventilation circuit. *Eur J Pharm Sci*. 2017;97:182–191. doi:10.1016/j.ejps.2016.11.018
26. Moustafa IOF, Ali MRAA, Al Hallag M, et al. Lung deposition and systemic bioavailability of different aerosol devices with and without humidification in mechanically ventilated patients. *Heart Lung*. 2017;46(6):464–467. doi:10.1016/j.hrtlng.2017.08.004
27. Madney YM, Fathy M, Elberry AA, Rabea H, Abdelrahim MEA. Nebulizers and spacers for aerosol delivery through adult nasal cannula at low oxygen flow rate: An in-vitro study. *J Drug Deliv Sci Technol*. 2017;39:260–265. doi:10.1016/j.jddst.2017.04.014
28. Elgendy MO, Abdelrahim ME, Salah Eldin R. Potential benefit of repeated MDI inhalation technique counselling for patients with asthma. *Eur J Hosp Pharm*. 2015;22(6):318–322. doi:10.1136/ejhpharm-2015-000648
29. Rajput S, Mehta P, Mittal M, Rajender S, Chattopadhyay N. Human relevance of preclinical studies on the skeletal impact of inflammatory bowel disease: A systematic review and meta-analysis. *Calcif Tissue Int*. 2021;108(6):708–724. doi:10.1007/s00223-021-00808-5
30. Shen X, Wan Q, Zhao R, et al. Inflammatory bowel diseases and the risk of adverse health outcomes: Umbrella review of meta-analyses of observational studies. *Dig Liver Dis*. 2021;53(7):809–816. doi:10.1016/j.dld.2021.01.018
31. Hidalgo DF, Boonpheng B, Phemister J, Hidalgo J, Young M. Inflammatory bowel disease and risk of osteoporotic fractures: A meta-analysis. *Cureus*. 2019;11(9):e5810. doi:10.7759/cureus.5810
32. Kärnsund S, Lo B, Bendtsen F, Holm J, Burisch J. Systematic review of the prevalence and development of osteoporosis or low bone mineral density and its risk factors in patients with inflammatory bowel disease. *World J Gastroenterol*. 2020;26(35):5362–5374. doi:10.3748/wjg.v26.i35.5362