Clinical Nutrition xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Meta-analyses

Risk of osteopaenia, osteoporosis and osteoporotic fractures in patients with chronic pancreatitis: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 14 February 2023
Accepted 25 May 2023

Keywords:
Bone mineral density
Chronic pancreatitis
Fractures
Osteopaenia
Osteoporosis
Systematic review

SUMMARY

Background & aims: Chronic pancreatitis results in irreversible pancreatic dysfunction and malnutrition which, alongside excess alcohol intake, can increase the risk of low bone density. Osteoporosis increases the risk of fractures and chronic bone pain, reduces quality of life, and poses considerable costs to healthcare. Despite this, there remains a paucity of literature evaluating bone health in this patient population. This systematic review and meta-analysis evaluated the prevalences of osteopaenia, osteoporosis and fractures in patients with chronic pancreatitis.

Methods: A comprehensive search of Medline, Embase, ClinicalTrials.gov, and CENTRAL databases was undertaken to identify eligible studies from January 2000 to May 2022. The prevalences of osteopenia, osteoporosis and fragility fractures were extracted from the included studies. Where available, a subgroup analysis was performed to compare the likelihood of developing osteoporosis in patients with chronic pancreatitis compared with control.

Results: Nineteen studies reporting on 2,027,764 participants (20,460 with chronic pancreatitis and 2,007,304 controls) were included. The pooled prevalence of osteoporosis was 19% (95% CI 13 to 26%; $I^2 = 94\%$). Patients with chronic pancreatitis were more likely to have osteoporosis when compared with those in the control group (OR 2.80, 95% CI 1.86 to 4.21; $I^2 = 21\%$). The prevalences of osteopaenia and fractures in patients with chronic pancreatitis were 37% (95% CI 31 to 44%; $I^2 = 81\%$) and 14% (95% CI 7 to 22%; $I^2 = 99\%$) respectively.

Conclusion: The prevalences of osteopenia and osteoporosis are significant in patients with chronic pancreatitis and can increase the risk of developing fractures. Further population-based studies are required to evaluate the disease burden of osteoporotic fractures and associated morbidity and mortality in chronic pancreatitis.

1. Introduction

Chronic pancreatitis is a chronic progressive fibro-inflammatory disorder of the pancreas. Over time, this can lead to irreversible fibrosis and loss of pancreatic exocrine and endocrine function [1]. Loss of pancreatic function leading to malabsorption, coupled with symptoms of chronic abdominal pain, reduced appetite, poor diet, persistent alcohol intake in some, and diabetes mellitus, put these patients at a high risk of malnutrition [2,3]. Nutrient and vitamin deficiencies, including that of vitamin D, increases the risk of low bone mineral density (BMD), and subsequently osteopenia and osteoporosis [4,5].

Abbreviations: BMD, bone mineral density; CI, confidence intervals; DXA, dual-energy X-ray absorptiometry; ESPEN, European Society for Clinical Nutrition and Metabolism; MOOSE, Meta-analysis Of Observational Studies in Epidemiology; NICE, National Institute for Health and Care Excellence; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; WHO, World Health Organisation.

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https://doi.org/10.1016/j.clnu.2023.05.019

Osteoporosis is a preventable disease characterised by low bone density and structural deterioration of bone tissue, with a consequent increase in bone fragility and risk of fractures [6]. Such fractures lead to severe pain, disability, reduction in quality of life, and significant costs to healthcare systems. A recent report produced by the National Osteoporosis Guideline Group [7] estimated that the cost of fragility fractures exceeds £4.7 billion annually in the United Kingdom.

Conditions such as inflammatory bowel disease and chronic liver disease, have been shown to increase the risk of osteopaenia and osteoporosis [8]. Progressive pancreatic exocrine and endocrine dysfunction in patients with chronic pancreatitis leads to an increased risk of bone disease. A systematic review of 10 studies published nearly a decade ago concluded that 23.4% of patients diagnosed with chronic pancreatitis developed osteoporosis [9]. This review, however, did not include data on the prevalence of fractures in this patient population due to the paucity of data at the time. Furthermore, the UK National Institute for Health and Care Excellence (NICE) has since published guidance that patients with chronic pancreatitis should be offered BMD assessments every 2 years [10]. The World Health Organisation (WHO) [11] and the European Society for Clinical Nutrition and Metabolism (ESPEN) [2] recommend that a dual-energy X-ray absorptiometry (DXA) scan is the investigation of choice to identify osteoporosis. Despite this, current literature suggests that the assessment and monitoring of bone health remains overlooked in patients with chronic pancreatitis [12–14].

This systematic review and meta-analysis aimed to evaluate current literature and estimate the prevalences of osteopaenia, osteoporosis and osteoporotic fractures in patients with chronic pancreatitis.

2. Methods

This systematic review and meta-analysis was performed in accordance with the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [16] statements and the protocol was registered with the PROSPERO database (Registration number: CRD42022360606, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=360606).

2.1. Search strategy

A comprehensive and systematic search of Medline, Embase, CENTRAL, and ClinicalTrials.gov databases was undertaken to identify the relevant studies from 1 January 2000 to 31 May 2022. Relevant MeSH terms and keywords relating to osteoporosis were combined with terms relating to chronic pancreatitis, ["osteoporosis" OR "osteopenia" OR "metabolic bone disease" OR "fracture"] AND ["chronic pancreatitis"]. The bibliographies of all studies that met the inclusion criteria were hand-searched for any additional suitable articles to ensure comprehensive study inclusion. The detailed search strategy can be found in Supplementary Table 1.

2.2. Eligibility criteria

Eligible study types were observational studies evaluating the risk of osteoporosis in patients with chronic pancreatitis. Studies which combined data for acute and chronic pancreatitis were excluded. Letters, case reports, case series with less than 20 participants, studies published in only abstract form and systematic reviews were excluded. Studies that did not report the desired outcome measures were also excluded. The studies had to be in human subjects 18 years of age or older. There was no limitation according to language of publication, sex, geographic location, or publication status.

2.3. Study selection and data extraction

Studies identified from the database search were screened based on their titles and abstracts by two reviewers independently (AK and OO), and the full texts of studies meeting the eligibility criteria were read. Duplicate studies were removed. This screening was undertaken using the Covidence screening tool (Covidence Systematic Review Software, Veritas Health Innovation, Melbourne, Australia, https://www.covidence.org). Any discordance was resolved by consensus with the other authors. Where multiple reports describing the same study were identified, data from all reports were used if required, ensuring no double counting of study participants.

A standardised data extraction form was used to document study characteristics and outcomes. This included information regarding the study design, patient population, age of participants, country of origin, and the aetiology of chronic pancreatitis.

The primary outcome of interest was the prevalence of osteoporosis based on bone density measurements investigated with DXA scans. Where available, a subgroup analysis was performed to compare the likelihood of developing osteoporosis in both chronic pancreatitis and control. The secondary outcomes included the prevalence of osteopenia and the risk of fragility fractures.

2.4. Risk of bias assessment

The risk of bias for each study was assessed using the Newcastle–Ottawa scale [17] for cohort studies. An overall risk of bias score was given to each study: low, moderate, and high risk of bias.

2.5. Statistical analysis

Meta-analyses of the pooled data and creation of forest plots were performed using StataMP version 14.1 (Stata Corp., College Station, TX, USA, https://www.stata.com/news/14-1/). Data were presented as prevalence rates with their respective 95% confidence intervals (CI). A pooled estimation was computed using a random-effects model to allow for variation between studies. Effects summary of the outcome comparing osteoporosis in both chronic pancreatitis and control groups were presented as odds ratio (OR) with their respective 95% CI. Publication bias was assessed as per the methods described by Egger et al. [18] using the visual inspection for asymmetry of the funnel plot. We assessed for statistical heterogeneity using the I^2 statistic with the following interpretation of values as outlined in the Cochrane Handbook [19]:

- 0%–40% might not be important,
- 30%–60% may represent moderate heterogeneity,
- 50%–90% may represent substantial heterogeneity,
- 75%–100% considerable heterogeneity.

3. Results

3.1. Study selection

A total of 1863 studies were retrieved from the database search (Fig. 1). After excluding duplicates, 1546 abstracts were screened, and 199 full-text articles were identified as being potentially eligible for analysis. After a critical appraisal of the full-texts, 180 were excluded from this review. Supplementary Table 2 lists potentially eligible studies that were excluded along with reasons.

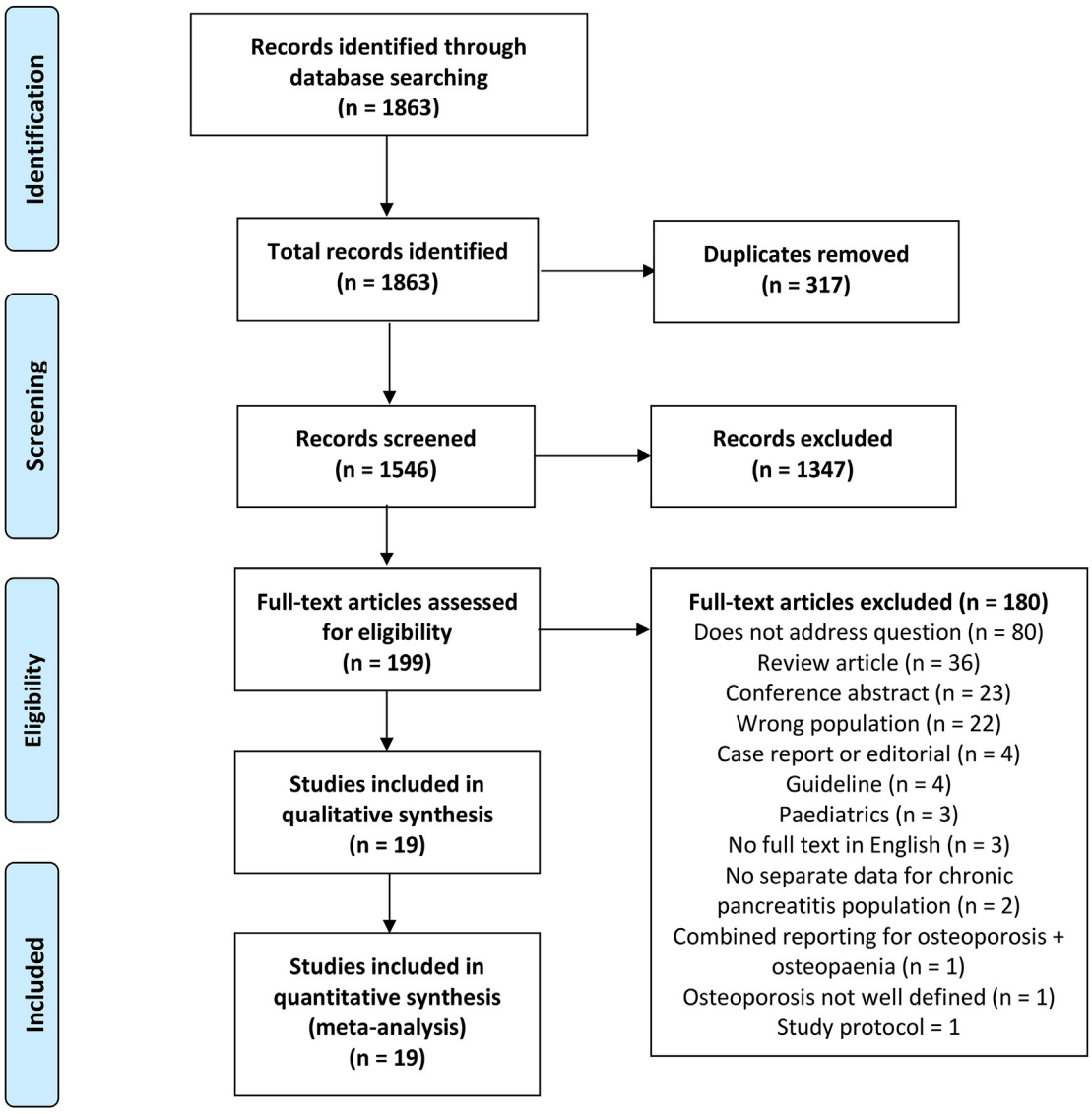


Fig. 1. PRISMA diagram.

Finally, 19 studies [8,14,20–36] with a total of 2,027,764 participants met the eligibility criteria and were assessed quantitatively and qualitatively. There were 20,460 participants with chronic pancreatitis and 2,007,304 in the control group.

3.2. Study characteristics

The included studies were published between 2000 and 2022 (Table 1). Ten studies were from Europe [20–22,25–29,33,36], five from the United States [8,14,30,32,34], and four from Asia [23,24,31,35]. Fifteen of the studies were single-centre studies, and four were population-based studies. The underlying aetiology for chronic pancreatitis was mixed; however, 41% were reportedly secondary to alcohol. Eleven [14,20–22,26,28–31,33,36] of the 19 studies reported alcohol as the leading underlying aetiology for chronic pancreatitis. Three [33,35,36] of the 11 studies reported on the correlation between chronic pancreatitis secondary to alcohol and low BMD (either osteopenia or osteoporosis). There was no association between excess alcohol intake and low BMD (OR 1.18, 95% CI 0.47 to 2.96, p = 0.72, I^2 = 79%).

The mean ages of patients in the studies ranged from 31 to 59 years. The majority of the studies used T-score from various locations to define osteoporosis (T-score < −2.5 standard deviations) and osteopenia (T-score between −1.0 and −2.5 standard deviations) [14,21,22,24–26,28,29,32–36]. Three studies defined osteoporosis and osteopenia using Z-scores (Z-score <−2: osteoporosis and <−1: osteopaenia) [20,23,31] while one used clinical and hospital coding to define osteoporosis and osteopaenia [27].

3.3. Meta-analysis

3.3.1. Prevalence of osteopenia

Fifteen studies [14,20–23,25,26,28,29,31–36] reported on the prevalence of osteopaenia in 2011 patients with chronic pancreatitis (Fig. 2). The pooled prevalence for this was 37% (95% CI 31 to 44%). There was considerable heterogeneity across studies (I^2 = 81%).

Table 1
Characteristics of included studies.

Author	Study design	Country and year(s) of study	Population	Subjects (CP)	Subjects (Control)	Age, CP *Years (SD)*	Age, Control *Years (SD)*	Aetiology of CP
Hart et al. 2022 [34]	Prospective cohort	United States, 2017–2020	Population-based study from 9 centres	282	–	56 (47, 64)[a]	–	41.6% alcohol 58.4% other
Tang et al. 2021 [35]	Prospective cohort	China, 2017–2018	Single centre	104	–	46 (14.4)	–	31.7% alcohol 68.3% other
Vujasinovic et al. 2021 [36]	Retrospective cohort	Sweden, 1999–2020	Single centre	495	–	53.1 (16.3)	–	33.9% alcohol + smoking 14.4% immunological 13% smoking 11.8% hereditary 9.3% obstructive 7% alcohol 6.7% other
Kanakis et al. 2020 [14]	Retrospective cohort	United States, 2000–2014	Single centre (database)	239	–	55 (45, 67)[a]		54% alcohol 46% other
Min et al. 2018 [32]	Retrospective cohort	United States, 2014–2016	Single centre	91	–	48.6 (10.4)		59.% toxic/metabolic 18.7% idiopathic 14.3% genetic 5.8% autoimmune 2.2% obstructive
Stigliano et al. 2018 [33]	Prospective cohort	Europe, 2015–2016	Population-based study from 7 centres	211	–	59.3 (12.6)	–	43.6% alcohol 19% idiopathic 4.3% hereditary 5.7% obstructive 27.5% other
Kumar et al. 2017 [31]	Cross-sectional	India	Single centre (armed forces tertiary hospital)	102	–	40.8 (12.6)	–	65.7% alcohol 34.3% TCP
Munigala et al. 2016 [30]	Cross-sectional	United States veterans, 1998–2007	Single centre (veterans database)	3257	450,655	54.2 (11.1)	53.6 (13.9)	32% alcohol + smoking 24.2% smoking 7.3% alcohol
Duggan et al. 2015 [28]	Prospective case–control	Ireland, 2012–2013	Population-based study from 2 centres	29	29	44.3 (12.3)	45.8 (9.8)	62.1% alcohol 27.6% idiopathic 10.3% other
Haas et al. 2015 [29]	Prospective cohort	Sweden	Single centre	50	–	45.2 (8.38)	–	72% alcohol 28% other
Bang et al. 2014 [27]	Retrospective cohort	Denmark, 1977–2010	Population-based study (nationwide register)	11,972	119,720	54.4 (14)	54.4 (14)	Not specified
Sikkens et al. 2013 [26]	Prospective cohort	Netherlands, 2011	Single centre	40	–	52 (11)	–	50% alcohol 43% idiopathic 7% other
Duggan et al. 2012 [25]	Cross-sectional	Ireland, 2007–2011	Single centre	62	66	47.9 (12.5)	47.7 (11)	38.7% alcohol 41% idiopathic 7% other
Joshi et al. 2011 [23]	Case-control	India, 2006–2008	Single centre	72	100	31 (10)	32.6 (9.6)	100% TCP
Sudeep et al. 2011 [24]	Case-control	India	Single centre	31	35	35.8 (9)	38.6 (5.2)	65% TCP 35% idiopathic
Drozdov et al. [22]	Cross-sectional	Russia	Single centre	100	–	51 (10.2)	–	62% alcohol 48% gallstones
Tignor et al. 2010 [8]	Retrospective cohort	United States, 1998–2008	Single centre	3192	1,436,699	Not specified	Not specified	Not specified
Dujsikova et al. 2008 [21]	Cross-sectional	Czech Republic	Single centre	73	–	46.6 (13.2)	–	89% idiopathic 11% alcohol
Haaber et al. 2000 [20]	Cross-sectional	Denmark	Single centre	58	–	55 (11)	–	79% alcohol 21% other

CP, chronic pancreatitis.
[a] Value presented as median (IQR).

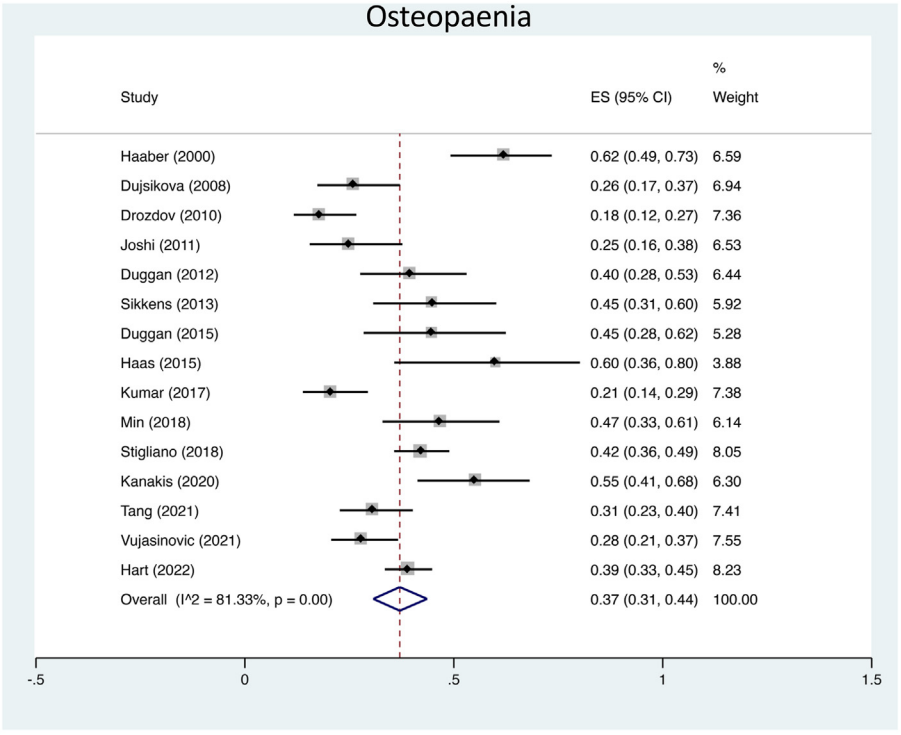
3.3.2. Prevalence of osteoporosis

Seventeen studies [14,20–29,31–36] reported on the prevalence of osteoporosis in 14,014 patients with chronic pancreatitis (Fig. 2). The pooled prevalence of osteoporosis was 19% (95% CI 13 to 26%). Similar to the data for osteopaenia, there was considerable statistical heterogeneity ($I^2 = 94\%$).

Of the 17 studies, four [24,25,27,28] compared outcomes between patients with chronic pancreatitis and controls (Fig. 3). Patients with chronic pancreatitis were more likely to have osteoporosis (OR 2.80, 95% CI 1.86 to 4.21, $I^2 = 21\%$).

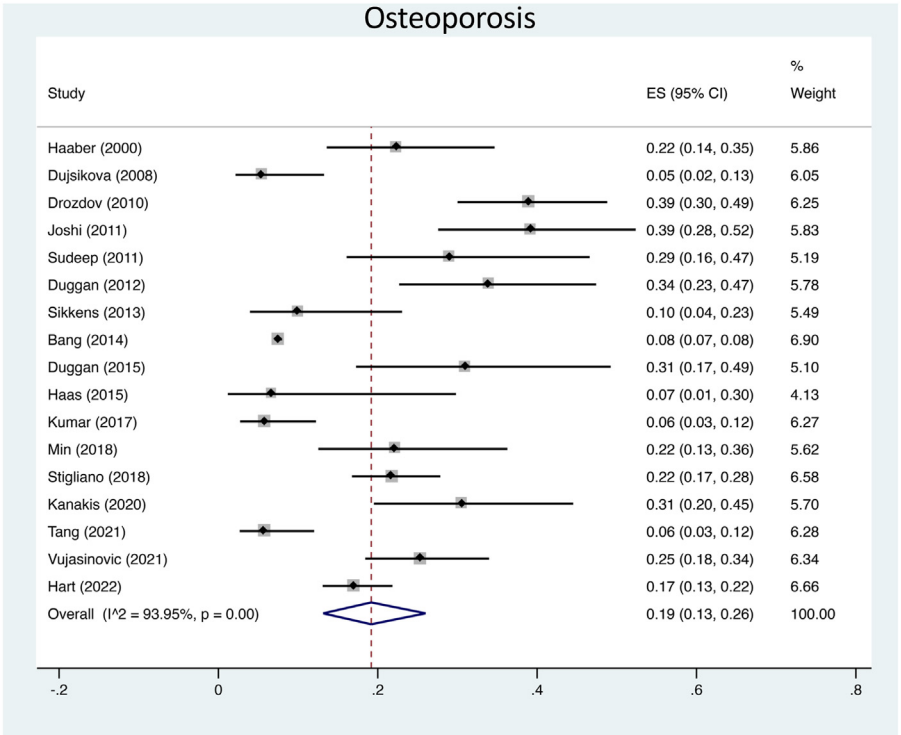
3.3.4. Prevalence of fractures

Eleven studies [8,14,21,26,27,29,30,33–36] reported on fractures as an outcome (Fig. 4). The pooled prevalence across 19,915 patients with chronic pancreatitis was 14% (95% CI 7 to 22%).



Heterogeneity chi^2 = **74.97** (d.f. = **14**) p = **0.00**
I^2 (variation in ES attributable to heterogeneity) = **81.33%**
Estimate of between-study variance Tau^2 = **0.05**

Test of ES=0 : z= **17.60** p = **0.00**



Heterogeneity chi^2 = **264.54** (d.f. = **16**) p = **0.00**
I^2 (variation in ES attributable to heterogeneity) = **93.95%**
Estimate of between-study variance Tau^2 = **0.10**

Test of ES=0 : z= **9.65** p = **0.00**

Fig. 2. Meta-analysis of the prevalence of osteopenia (top) and osteoporosis (bottom) in patients with chronic pancreatitis. ES: effect size.

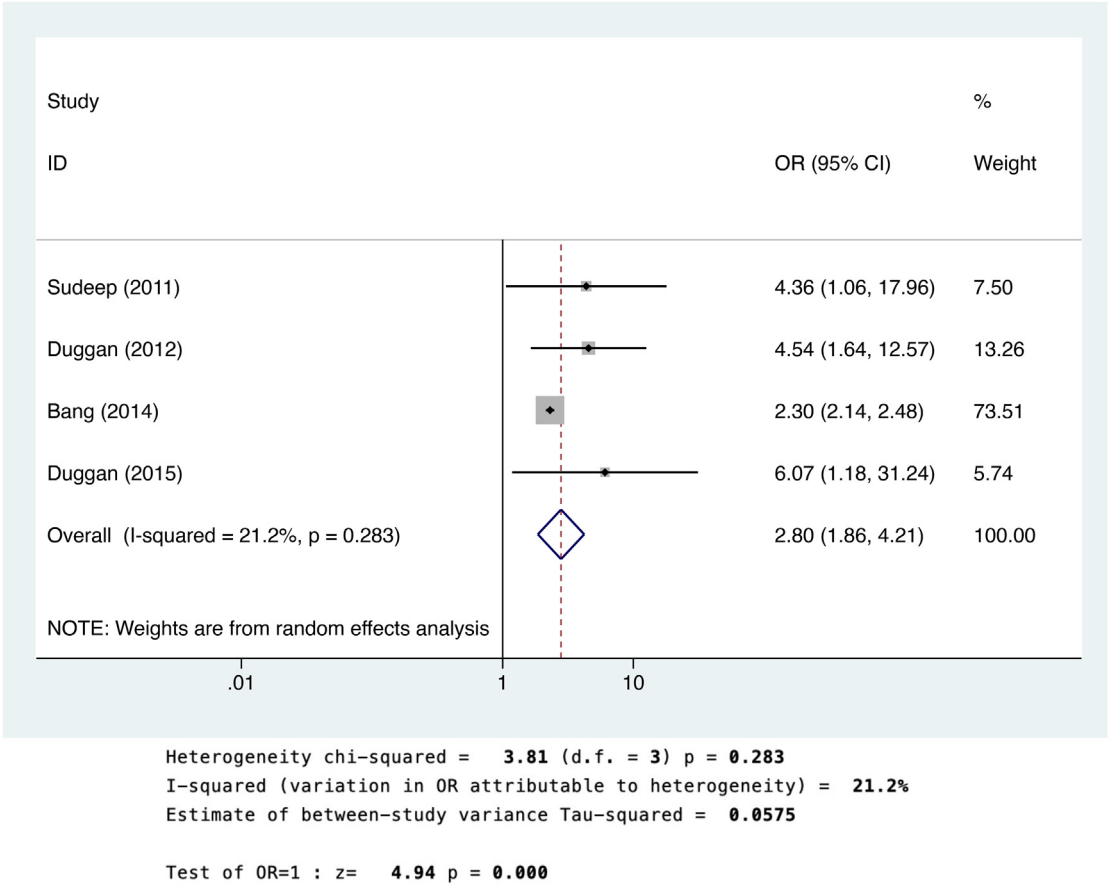


Fig. 3. Meta-analysis of the prevalence of osteoporosis in patients with chronic pancreatitis compared with controls. OR: odds ratio.

3.4. Risk of bias

The risk of bias was evaluated using the Newcastle–Ottawa Scale (Table 2). Overall, 8 studies had a high risk of bias [14,20–22,24,29,31,32], whilst 6 had a medium [23,26–28,30,33] and 5 had a low risk of bias [8,14,25,35,36].

4. Discussion

This meta-analysis of 19 studies found that there was an increased prevalence of osteoporosis in patients with chronic pancreatitis compared with controls. Of the patients diagnosed with chronic pancreatitis, 19% were found to be osteoporotic, which is substantial when compared with the estimated 5.6% in the general European population [37]. A further 37% had osteopaenia and 14% sustained fractures. When compared with the control group, patients with chronic pancreatitis were nearly thrice as likely to have osteoporosis. The reported aetiology of chronic pancreatitis in the studies included alcohol, smoking, gallstones, hereditary, autoimmune, and tropical. There was, however, significant statistical heterogeneity in the analysis of the prevalence of osteopaenia, osteoporosis and fractures. This was not unexpected as the population and methodology used varied greatly across the 19 studies.

More than half of the studies reported alcohol as the most common underlying aetiology for chronic pancreatitis. Alcohol consumption in excess is commonly associated with an increased risk of falls and consequently sustaining more severe injuries [38,39]. This, compounded with the symptoms of chronic abdominal pain and lack of appetite, malnutrition, and low bone density, inevitably leads to more severe injuries.

Bone mineral density is commonly assessed regularly in other chronic gastrointestinal diseases. One study reported that patients with chronic pancreatitis were 2.4 times more likely to sustain a fracture, with similar figures reported in patients with cirrhosis, coeliac disease, Crohn's disease, and those having undergone gastrectomy [8].

A previous systematic review of 10 studies published in 2014 also reported a slightly higher prevalence of osteoporosis and osteopenia in patients with chronic pancreatitis, with 23.4% and 39.8% reported as having osteoporosis and osteopaenia respectively [9]. This is in comparison with 19% and 37% found in this present analysis for osteoporosis and osteopaenia respectively. Due to the lack of available data at the time, the prevalence of fractures was not calculated in the published review [9]. Further subgroup analysis was performed to only include data from studies published after the previous systematic review [9], and found that 14% of patients with chronic pancreatitis had osteoporosis and 39% had osteopaenia (Supplementary Figs. 1 and 2). This suggests an improvement in screening and consequently treating patients with chronic pancreatitis having osteoporosis. Despite this, recent studies found that less than half of patients with chronic pancreatitis were evaluated with DXA scans [12–14,36]. The estimated prevalence of osteoporosis and osteopaenia in this present review is, therefore, likely to be an underestimation of actual figures.

The present analysis has some limitations. While this evaluation of the prevalence of low BMD and fractures included 19

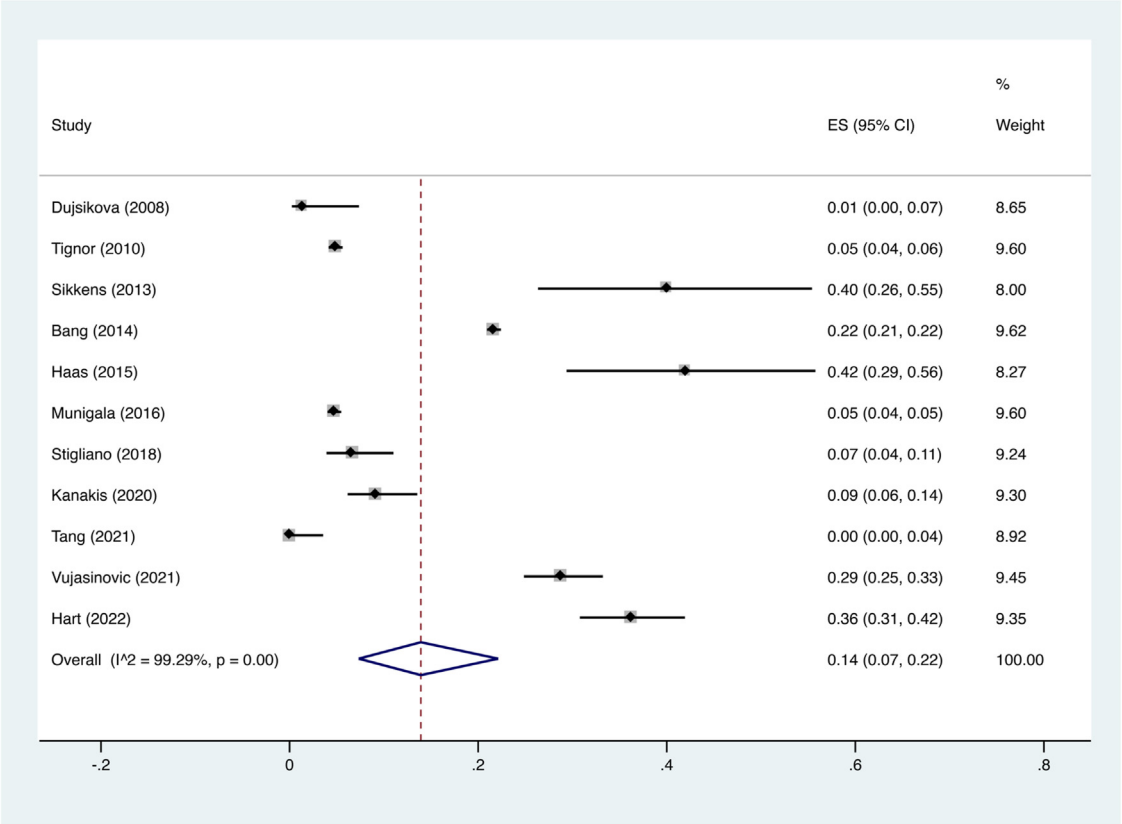


Fig. 4. Meta-analysis of the prevalence of fractures in patients with chronic pancreatitis. ES: effect size.

Table 2
Risk of bias assessment.

Study	Risk of bias assessment			
	Selection	Comparability	Outcome/exposure	Overall score
Hart et al. 2022 [34]	★★★	★	★★	6
Tang et al. 2021 [35]	★★★	★	★★	6
Vujasinovic et al. 2021 [36]	★★★	★	★★	6
Kanakis et al. 2020 [14]	★★	–	★	3
Min et al. 2018 [32]	★★	–	–	2
Stigliano et al. 2018 [33]	★★★	–	★	4
Kumar et al. 2017 [31]	★★	–	★	3
Munigala et al. 2016 [30]	★★★	–	★★	5
Duggan et al. 2015 [28]	★★★	★	★	5
Haas et al. 2015 [29]	★	–	★	2
Bang et al. 2014 [27]	★★	★	★★	5
Sikkens et al. 2013 [26]	★★	–	★★	4
Duggan et al. 2012 [25]	★★★	★	★★	6
Joshi et al. 2011 [23]	★★	–	★★	4
Sudeep et al. 2011 [24]	★	–	★	2
Drozdov et al. 2010 [22]	★	–	★	2
Tignor et al. 2010 [8]	★★★	★	★★	6
Dujsikova et al. 2008 [21]	★★	–	★	3
Haaber et al. 2000 [20]	★	–	★	2

Risk of bias:
6 or above: low risk.
4 to 5: medium risk.
1 to 3: high risk.

studies and over two million patients, some studies had small sample sizes (four studies had 50 patients or less in each arm). There was significant heterogeneity in the data for the prevalences of osteopaenia, osteoporosis and fractures. This is likely due to the diversity in the population and methodology used across the 19 studies. The criteria for diagnosis of osteoporosis varied between the studies. Although most studies relied on T-scores, three reported Z-scores [20,23,31], and one relied on clinical/hospital coding which has a risk of inaccurate diagnosis [27]. The WHO [11] and ESPEN [2] have recommended that the non-invasive DXA scan should be used as the gold standard to measure BMD. DXA scans assess BMD by calculating a T-score and a Z-score. The T-score compares an individual's BMD against healthy young individuals of the same sex, whereas the Z-score calculates an individual's BMD against an age- and sex-matched control as a standard deviation score. Although the T-score is more widely used in practice, both calculations are accepted methods of estimating BMD and identifying patients with osteoporosis [40,41]. Bang et al. [27], however, relied on clinical coding to define osteoporosis. This has an inherent risk of incorrect diagnosis due to inaccurate coding. However, further subgroup analysis has been performed to exclude data from Bang et al. [27] and found no discernible differences in the outcome (Supplementary Fig. 3). The reported aetiology of chronic pancreatitis in the eligible studies varied greatly, including alcohol, smoking, gallstones, hereditary, autoimmune, and tropical pancreatitis. The patient demographics, therefore, invariably differed. Of note, tropical pancreatitis is often found mainly in the low- and middle-income countries in the tropics [42]. The prevalence of osteoporosis and fragility fractures in this cohort can potentially be confounded by the low socioeconomic status of the population who are often have pre-existing malnutrition.

5. Conclusion

The prevalences of osteopaenia and osteoporosis are significant in patients with chronic pancreatitis. Further large population-based studies need to be conducted to evaluate the disease burden of osteoporotic fractures including the associated mortality in patients with chronic pancreatitis.

Author contributions

Study design: AK, DJH, DNL.
Data collection: AK, OO.
Data-analysis: AK, DJH, DNL.
Data-interpretation: AK, OO, DJH, DNL.
Writing of the manuscript: AK, OO, DJH, DNL.
Critical review of the manuscript: AK, OO, DJH, DNL.
Final approval: AK, OO, DJH, DNL.
All authors had access to the data.

Funding

This work was supported by the Medical Research Council [grant number MR/K00414X/1]; and Arthritis Research UK [grant number 19891]. The funders had no involvement in the development of the protocol, conduct or writing up of this study, or the decision to submit for publication. This work does not represent the views of the funders.

Data sharing

No original data to share.

Ethical statement

As this was a systematic review and meta-analysis, ethical approval was not necessary.

Protocol registration

The protocol was registered with the PROSPERO database (Registration number: CRD42022360606, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=360606).

Conference presentation

This paper was presented to the Annual Meeting of the Surgical Research Society, Nottingham, March 2023 and has been published in abstract form – Br J Surg. 2023;110(Suppl 3):znad101.148.

Conflicts of interest

None of the authors has a direct conflict of interest to declare. DNL has received an unrestricted educational grant from B. Braun for unrelated work. He has also received speaker's honoraria for unrelated work from Abbott, Nestlé and Corza.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.05.019.

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