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Prevalence of Osteopathy in Chronic Pancreatitis: A Systematic Review and Meta-Analysis

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INTRODUCTION: **Individuals with chronic pancreatitis (CP) are at increased risk for nutritional complications during their clinical course. We appraised the literature to provide updated estimates of the prevalence and predictors of osteoporosis, osteopenia, and osteopathy in CP using a systematic review and meta-analysis.**

METHODS: **Search strategies were developed for major databases from inception through October 2021. Outcomes of interest included rates of osteopenia and osteoporosis based on dual-energy X-ray absorptiometry scans and risk factors. A random-effects model was used for analysis, and results were expressed as pooled cumulative rates along with 95% confidence interval (CI).**

RESULTS: **From an initial total of 1,704 identified articles, we ultimately selected 17 studies that involved 1,659 subjects (n = 1,067 men) with CP. The pooled rate of osteopathy was 58% (95% CI: 49%–67%; $P < 0.001$; $I^2 = 91.8\%$). The pooled rate of osteoporosis was 18% (95% CI: 12%–23%; $P < 0.001$; $I^2 = 86.3\%$), and the pooled rate of osteopenia was 39% (95% CI: 31%–48%; $P < 0.001$; $I^2 = 91.53\%$). In the systematic review, factors associated with decreased bone mineral density included smoking, alcohol consumption, older age, female sex, low body mass index, decreased vitamins D and K, and fecal elastase levels.**

DISCUSSION: **Patients with CP have high rates of osteopathy when assessed with dual-energy X-ray absorptiometry imaging. Additional studies with longitudinal follow-up are needed to understand the observed heterogeneity, the cumulative burden of disease, and rate of bone loss in CP.**

KEYWORDS: bone density; osteoporosis; osteopenia; DXA

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A982

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INTRODUCTION

Chronic pancreatitis (CP) is a progressive inflammatory disorder that leads to morphological and functional changes including endocrine and/or exocrine insufficiency (1). CP occurs in the setting of repeated environmental insults, particularly in patients with an increased genetic or anatomical predisposition. CP-related complications are generally irreversible and contribute to a complex state of nutritional imbalance (2). To this end, patients can develop osteopenia and osteoporosis (collectively referred to as osteopathy) (3). Osteopathy is described by the sequential deterioration in the structural integrity of bone tissue and mass which may ultimately lead to bone fragility and pathological fractures (4,5).

The pathophysiology of bone disease in CP is multifactorial and may be related to age, low weight due to decreased dietary intake, maldigestion due to exocrine pancreatic insufficiency (EPI), vitamin D deficiency, and smoking and alcohol abuse (3–5). A previous meta-analysis (2014) involving approximately

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500 subjects with CP reported a pooled prevalence rate of osteopathy of 65% (95% confidence interval [CI]: 54.7–74.0) (6). Since this publication there have been additional large, single and multicenter studies, so a reappraisal of the literature is warranted to determine a more precise estimate of the prevalence of osteopathy in CP.

In the current study, we aimed to determine the point prevalence and predictors of osteoporosis, osteopenia, and osteopathy in CP using a systematic review and meta-analysis and to determine associated factors.

METHODS

Search strategy

PubMed, EMBASE, and Cochrane Library databases were searched from their date of inception through October 2021. A health sciences librarian created each database-specific search using a combination of keywords and controlled vocabulary. Keyword alternatives and variations were developed from the terms: CP, pancreatitis, osteopathy, osteoporosis, osteopenia, and bone loss. No filters or limits were applied to this initial search. Records were added to and deduplicated through Covidence (https://www.covidence.org/). Once deduplication was completed, unique results were assessed for eligibility.

The search was limited to studies performed on human subjects and published in the English language in peer-reviewed journals. Two authors (D.R. and A.F.) independently reviewed the titles and abstract of studies identified in the primary search and excluded studies that did not address the research question, based on prespecified eligibility criteria. The full text of the remaining articles was reviewed to determine whether it contained relevant information. Any discrepancy in article selection was resolved by consensus and discussion with a third investigator (P.A.H.). The bibliographic section of the selected articles and systematic and narrative articles on the topic were manually searched for additional relevant articles. The methodology of the study was developed and reviewed with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Study selection

We included studies that reported osteopathy outcomes in subjects with CP. Studies irrespective of the sample size, inpatient/outpatient setting, and geography were included if they provided data needed for the analysis. Inclusion criteria were (i) subjects diagnosed with CP based on patient history (abdominal pain typical of pancreatitis), functional deficits (such as endocrine and/or exocrine insufficiency), and/or findings on imaging studies (cross-sectional imaging and/or endoscopic ultrasonography) and (ii) studies reporting the prevalence of osteoporosis and/or osteopenia using dual-energy X-ray absorptiometry (DXA) scans. Exclusion criteria included (i) pediatric (age $<$ 18 years) studies, (ii) studies not published in the English language, and (iii) case reports or case series with $<$11 subjects with CP. In the event of multiple publications from the same cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were retained.

Data abstraction and quality assessment

Study references and citations were collected in Covidence. The full text of each selected article was reviewed to verify that it contained relevant information. Data on study-related outcomes in the individual studies were abstracted by 2 authors (D.R. and A.F.) who completed the quality scoring independently. Studies were assessed using the Newcastle-Ottawa Scale (7).

Study outcomes

Outcomes of interest included pooled rates of osteopenia, osteoporosis, and osteopathy (defined as either osteopenia or osteoporosis). Factors associated with decreased bone mineral density were assessed. We also analyzed pooled rates of EPI and vitamin D insufficiency as secondary outcomes.

Statistical analysis

We used meta-analysis techniques to calculate the pooled estimates in each case following the methods suggested by DerSimonian and Laird using the random-effects model (8,9). According to the Cochrane Handbook for Systematic Reviews, the choice between fixed and random-effects model should be based on an expectation of whether the intervention effects are truly identical, preferring the fixed-effect model if this is likely and a random-effects model if this is unlikely (10). Because it is generally considered to be implausible that intervention effects across studies are identical, this leads to the prevalent use (as in this case) of the random-effects model.

Heterogeneity between study-specific estimates was assessed using the inconsistency index (I^2) and cutoff points of $<$30%, 30%–59%, 60%–75%, and $>$75% were considered to suggest low, moderate, substantial, and considerable heterogeneities, respectively (11–16).

We developed the following *a priori* hypotheses that would explain heterogeneity and planned subgroup analyses for (i) study design (cohort or case control) and (ii) area of origin (e.g., Asia, Europe, or America).

Publication bias was assessed, qualitatively, by visual inspection of funnel plot and quantitatively by the Kendall Tau test (17,18). For all analyses, a P value of $<$ 0.05 was considered statistically significant. The analyses were performed using R packages (version 4.0) [computer software]. Retrieved from https://cran.r-project.org (R packages retrieved from MRAN snapshot 2021-04-01).

RESULTS

Search results and characteristics

From an initial 1,704 identified articles, 1,485 titles were screened after removal of duplicates. The study selection process is detailed in Figure 1. The final analysis included 17 studies (Table 1) (5,19–34). Twelve studies used a cohort design while 5 studies used case-control study designs. Two studies were multicenter and the remaining studies were single center. Most studies were conducted in Europe (n = 7), Asia (n = 5), and North America (n = 4). From the above studies, 1,659 subjects were diagnosed with CP of which 64.3% (n = 1,067) were men. Active smoking was reported in 525 subjects (31.6%) while alcohol use was reported in 535 subjects (32.2%). Population characteristics are further detailed in Table 1.

Study quality

Overall, all studies were considered of medium to high quality (Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A982). There were no low-quality studies.

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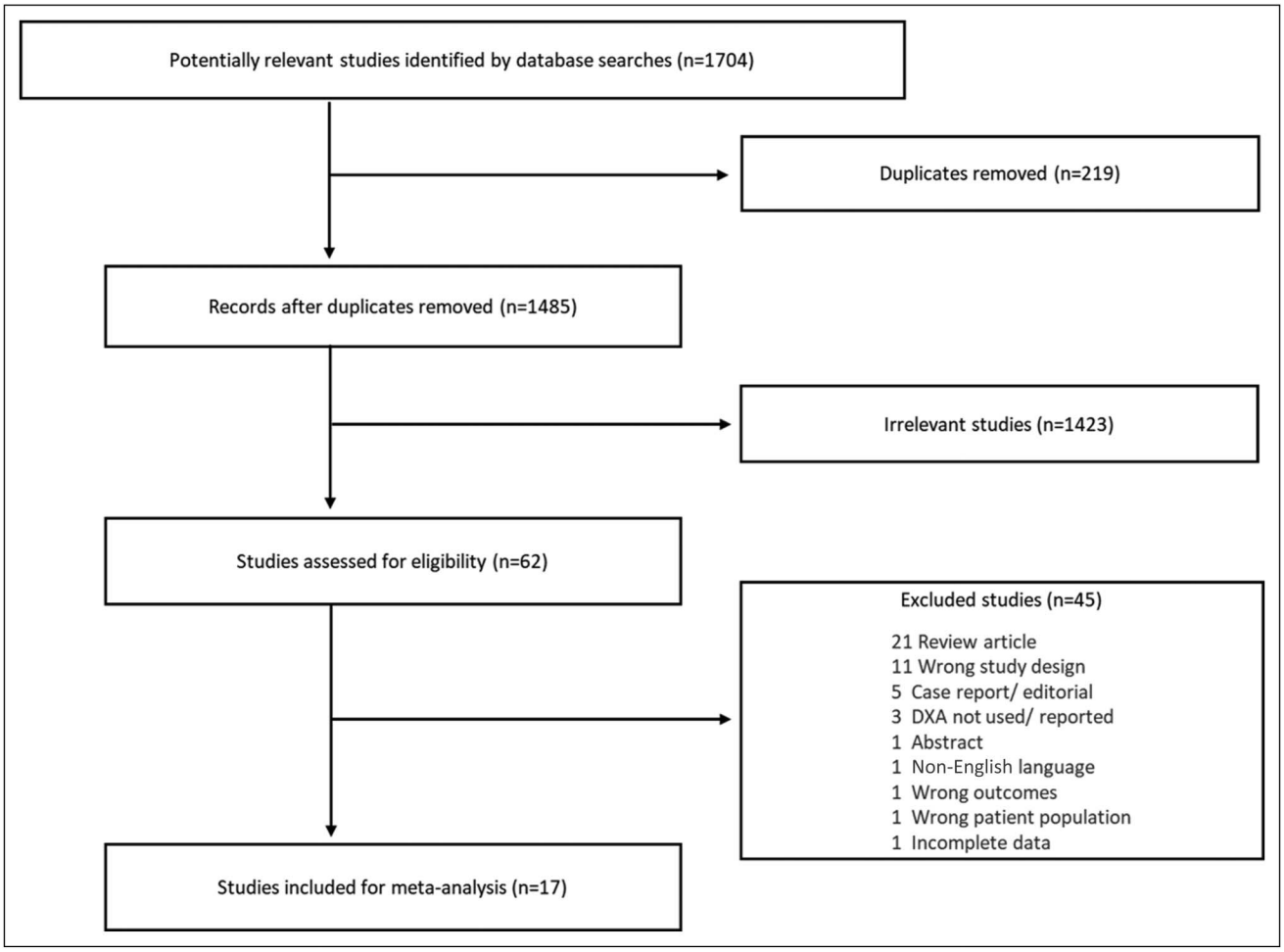

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses study chart. DXA, dual-energy X-ray absorptiometry.

Meta-analysis primary outcomes

A total of 1,347 subjects had a DXA scan completed, which was used to calculate estimates of the osteopathy end points (Supplementary Table 2, Supplementary Digital Content 1, http://links.lww.com/CTG/A982). The pooled rate of osteopathy was 58% (95% CI: 49%–67%; $P < 0.001$; $I^2 = 91.8\%$) (Figure 2). The pooled rate of osteoporosis was 18% (95% CI: 12%–23%; $P < 0.001$; $I^2 = 86.3\%$) (Figure 3), while the pooled rate of osteopenia was 39% (95% CI: 31%–48%; $P < 0.001$; $I^2 = 91.53\%$) (Figure 4).

In the systematic review, factors associated with decreased bone mineral density included smoking, alcohol consumption, older age, female sex, low body mass index (BMI), low vitamins D and K, and decreased fecal elastase levels (Table 2).

Subgroup analysis

Subgroup analysis was performed according to the study design showing a similar prevalence of osteopathy in case-control (55% [95% CI: 34%–76%; $P < 0.001$; $I^2 = 90.4\%$]) and cohort studies (59% [95% CI: 50%–69%; $P < 0.001$; $I^2 = 91.2\%$]). A subgroup analysis was also performed to assess the prevalence of osteopathy according to the geographic area. There were similar and not statistically significant differences in the estimates of osteopathy for studies conducted in North America, Europe, and Asia.

Meta-analysis secondary outcomes

Eight studies reported on EPI. The pooled rate of EPI in the selected study populations was 57% (95% CI: 41%–72%; $P < 0.001$; $I^2 = 95.9\%$). Similarly, 9 studies reported on vitamin D insufficiency. The pooled rate of vitamin D deficiency was 69% (95% CI: 57%–82%; $P < 0.001$; $I^2 = 95.8\%$).

Validation of meta-analysis results

There was considerable heterogeneity in the primary and secondary outcomes and both subgroup comparisons. There was no qualitative or quantitative evidence of publication bias (data not shown).

DISCUSSION

The current systematic review and meta-analysis provides a contemporary estimate of the point prevalence of osteopathy in CP, demonstrating it as a common (>50%) complication in this patient population. Our study adds to the literature by providing a more precise estimate and includes recent data from North American studies (6). There was considerable heterogeneity between studies, which may reflect variations in study design, geographic variability, and/or unaccounted variables in individual participants. Further studies are needed to understand

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Table 1. Study characteristics from systematic review of osteopathy in chronic pancreatitis

Author	Year	Study design	Study design	Continent	CP subjects (n)	Mean age (SD)	Male sex	Active smoking	Ever smoker	Alcohol use
Moran et al (19)	1997	Cohort	Single center	South America	14	55.6 (13.1)	100%	NR	NR	71%
Dujsikova et al (20)	2008	Cohort	Single center	Europe	73	46.61 (13.23)	77%	NR	NR	11%
Joshi et al (21)	2011	Case control	Single center	Asia	72	31.1 (10.3)	53%	NR	NR	0%
Sudeep et al (22)	2011	Case control	Single center	Asia	31	35.8 (9.0)	100%	NR	NR	0%
Duggan et al (23)	2012	Case control	Single center	Europe	62	48.7 (12.5)	76%	60%	74%	94%
Sikkens et al (24)	2013	Cohort	Single center	Europe	40	52 (11)	58%	68%	NR	3%
Prabhakaran et al (25)	2014	Case control	Single center	Asia	103	36.7 (20.7)	100%	NR	NR	70%
Duggan et al (5)	2015	Case control	Single center	Europe	29	44.3 (12.3)	59%	69%	79%	93%
Haas et al (26)	2015	Cohort	Single center	Europe	50	45.2 (8.36) median	100%	84%	NR	72%
Kumar et al (27)	2017	Cohort	Single center	Asia	102	40.8 (12.6)	83%	NR	NR	66%
Min et al (28)	2018	Cohort	Single center	North America	91	48.6 (10.4)	37%	68%	NR	NR
Stigliano et al (29)	2018	Cohort	Multicenter	Europe	211	60 (NR)	67%	NR	69%	60%
Gupta et al (30)	2019	Cohort	Single center	North America	38	44 (10.7)	50%	47%	NR	11%
Kanakis et al (31)	2020	Cohort	Single center	North America	239	56 (16.4)	54%	55%	NR	8%
Tang et al (32)	2020	Cohort	Single center	Asia	104	46.1 (14.43)	70%	43%	NR	50%
Hart et al (33)	2021	Cohort	Multicenter	North America	282	56 (12.7)	49%	35%	68%	NR
Vujasinovic et al (34)	2021	Cohort	Single center	Europe	118	53.1 (16.3)	58%	36%	64%	45%

CP, chronic pancreatitis; NR, not reported; SD, standard deviation.

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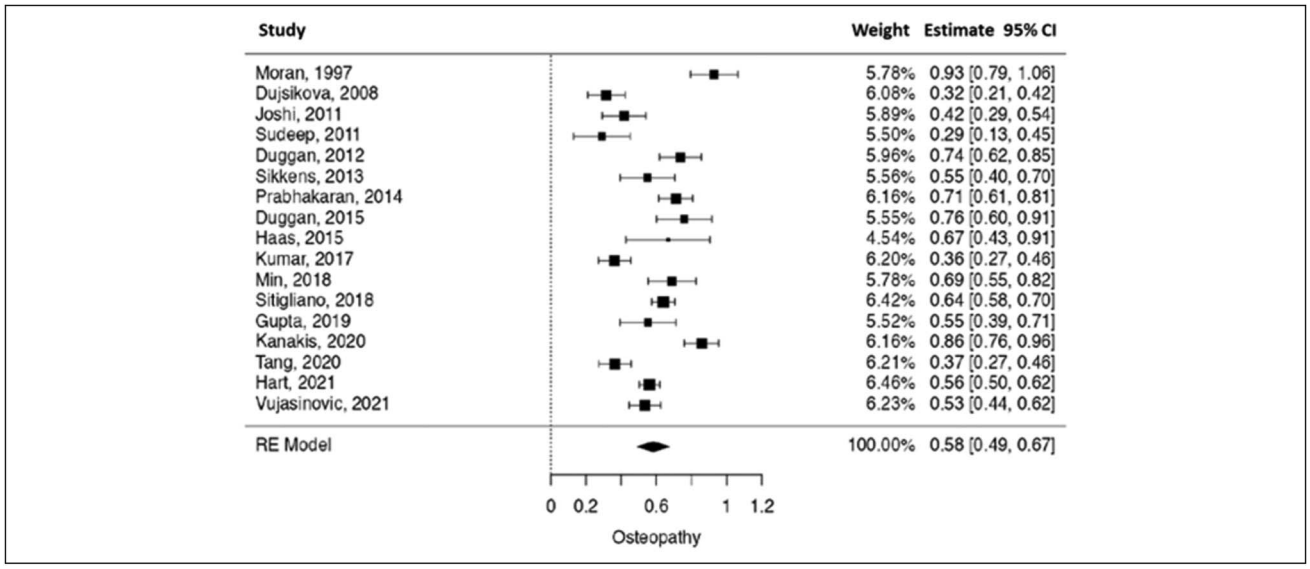

Figure 2. Forest plot of pooled prevalence rates of osteopathy in chronic pancreatitis. CI, confidence interval; RE, random effects.

the underlying mechanisms of disease and identify options for tailored screening and management.

Qualitative review of risk factors identified that smoking, alcohol consumption, older age, female sex, low BMI, low vitamin D and K levels, and decreased fecal elastase levels were associated with osteopathy in the selected studies. Given the vulnerable nutritional milieu created by CP, it is reasonable that these factors may exacerbate bone disease. Smoking has been broadly implicated in bone turnover imbalances, leading to lower bone mass and making bone vulnerable to osteoporosis and ultimately fractures (35). Tobacco smoking influences and directly contributes to loss of bone mass by altering osteogenesis and angiogenesis of bone (36–38). Alcohol-induced oxidative stress has been found to increase osteoclastogenesis activity while individuals with a low BMI have been found to have inverse relationship with BMD (39,40). Systematic inflammation affects bone mineral density by driving bone toward a resorptive state (41). Older age and female sex likely reflect a postmenopausal state for many individuals where estrogen deficiency would be a key contributing factor to osteopathy. However, a recent study demonstrates high rates of osteopathy in men and premenopausal women, suggesting alternate mechanisms are present (33).Therefore, there remains a need to systematically investigate the pathogenesis of osteopathy in CP.

Expert groups in the United States and European society guidelines recommend instituting proactive measures in identifying at-risk patients, with the goal of addressing modifiable risk factors to reduce the risk of fractures (42,43). European societal guidelines recommend that a baseline DXA scan should be extended to all patients with CP with follow-up scans every 2 years if evidence for osteopenia is found. In addition, initiation of vitamin D and calcium supplementation can help treat and prevent

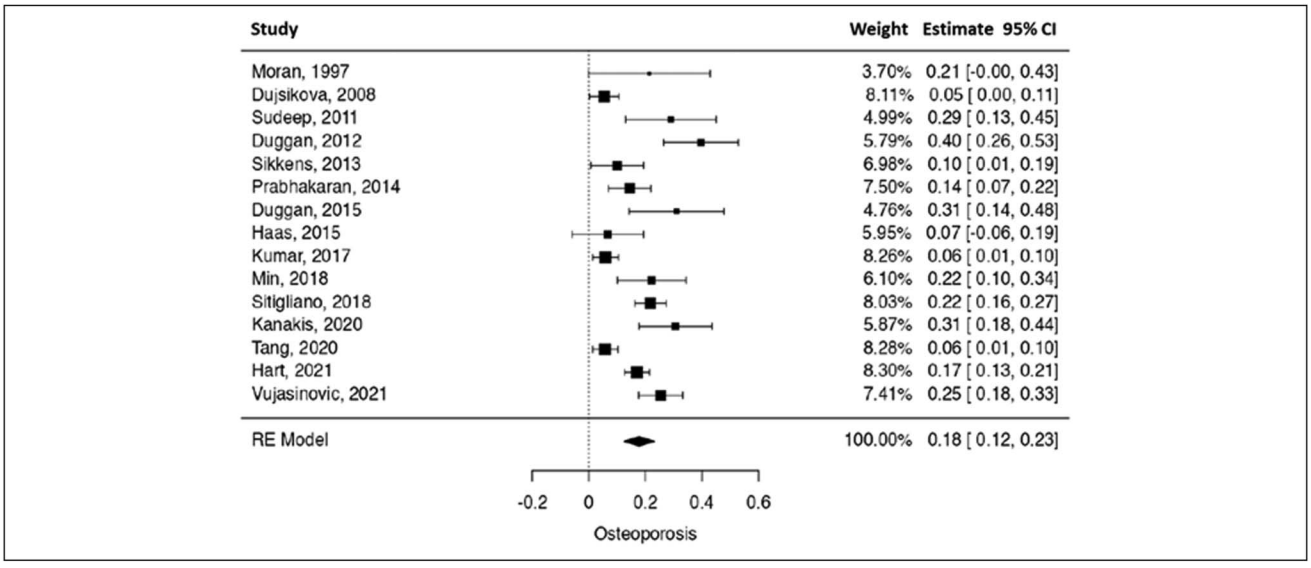

Figure 3. Forest plot of pooled prevalence rates of osteoporosis in chronic pancreatitis. CI, confidence interval; RE, random effects.

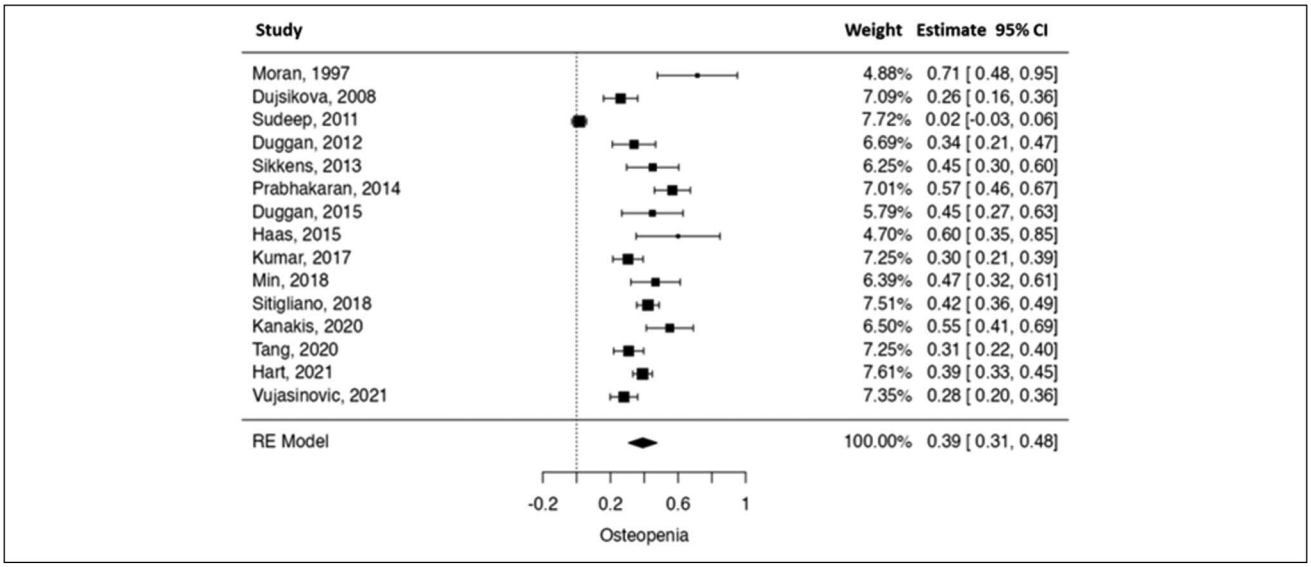

Figure 4. Forest plot of pooled prevalence rates of osteopenia in chronic pancreatitis. CI, confidence interval; RE, random effects.

osteopenia, osteoporosis, and lower the risk of fracture, and thus, patients with established bone disease should be thoroughly evaluated for appropriate therapies by an endocrinologist. The most recent guidelines on CP by the American College of Gastroenterology recommend the measurement of fat-soluble vitamin levels and bone density at baseline and periodically thereafter (44).

Unfortunately, although there is an increased risk of osteopathy in CP, DXA screening is often underutilized in this population. For example, 2 recent studies showed that less than half of the subjects with CP received a clinical DXA scan (45,46). This illustrates a risk for bias in studies reporting retrospective data because there are potentially differences in the patients who receive versus who do not receive a DXA scan. Interestingly, DXA screening rates were higher in a single center study for patients seen by a pancreas specialist (52%), in contrast to a primary care provider (28%) or gastroenterologist (29%) [476]. This difference suggests there is likely an opportunity for additional provider education; however, there are additional barriers to successful implementation. One innovative approach to overcome a number of these challenges is to estimate bone density from computed tomography scan images, which are ubiquitous in this patient population and would not require additional imaging. Large studies have demonstrated a high concordance of bone density on computed tomography imaging compared with DXA T scores in the general population, and a pilot study in CP suggests this warrants further investigation in this patient population (47,48).

The current study represents a substantial increase in the sample size available for this meta-analysis, including representation of study populations with increased geographic diversity providing more precise and generalizable estimates, respectively. Nevertheless, our study has limitations. First, there were considerable heterogeneity observed between studies. Unfortunately, the reports did not provide sufficient detail to allow us to investigate the contribution of differences in study design, such as method of primary outcome ascertainment (i.e., the primary indication for obtaining the DXA scan such as high risk, universal screening, or based on research protocol). In addition, an individual patient data meta-analysis to better investigate the role of exposures, nutritional deficiency, and EPI was not possible. We hypothesize that some of the variability may relate to a number of

Table 2. Tabulation of independent risk factors associated with low BMD in chronic pancreatitis in the individual studies

Study	Year	Factor(s) associated with low BMD
Moran et al (19)	1997	NA
Dujsikova et al (20)	2008	NA
Joshi et al (21)	2011	Low BMI
Sudeep et al (22)	2011	Low BMI
Duggan et al (23)	2012	Heavy smoking, low BMI, increasing age
Sikkens et al (24)	2013	Low fat-soluble vitamins
Prabhakaran et al (25)	2014	NA
Duggan et al (5)	2015	Increasing age, low BMI, low serum 25-hydroxyvitamin D
Haas et al (26)	2015	Low fecal elastase
Kumar et al (27)	2017	NA
Min et al (28)	2018	Low ductal bicarbonate secretion, smoking
Stigliano et al (29)	2018	Increasing age, female sex, low BMI, low vitamin K
Gupta et al (30)	2019	Age, low BMI, alcohol use, smoking
Kanakis et al (31)	2020	NA
Tang et al (32)	2020	Increasing age, low BMI, PTH levels
Hart et al (33)	2021	Increasing age, female sex, low BMI, White race
Vujasinovic et al (34)	2021	NA

BMD, bone mineral density; BMI, body mass index; NA, multivariate analysis was not performed; PTH, parathyroid hormone.

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unmeasured variables in these studies, including chronic inflammation, alterations in the gut microbiome, and genomic changes, all of which have been implicated in the development of bone loss in the general population (49). Considering recent reports of marked gut microbiota dysbiosis and reduced diversity in CP, this is a potential area of high interest for future study (50).

Owing to limited data availability, quantitative analysis of risk factors contributing to decreased BMD was not feasible and was restricted to a qualitative assessment. Additional translational studies are needed to understand whether there are similar mechanisms in the patient population with CP, and if so, the magnitudes of the effect. Other limitations with this analysis include the lack of longitudinal data to accurately report a cumulative prevalence. Rather, the current estimates in our study represent a pooled estimate of the point prevalence from the selected studies. We believe these results are reliable and provide the best possible estimate of osteopathy in CP. Potential contributors to the heterogeneity in estimates may reflect differences in the duration of CP of individuals studied, different combinations of risk factors, and ultimately may reflect the complex pathogenesis of osteopathy. Because there may have been a bias toward only testing patients who were perceived to be at increased risk, it is likely that this value underestimates the true burden of disease.

In conclusion, there is a high point prevalence of osteoporosis and osteopenia for individuals with CP. Additional studies are needed to determine whether the observed heterogeneity between studies is potentially due to unique biological factors in this patient population. Further prospective studies will be meaningful to define the rate of bone loss, identify factors associated with accelerated loss, and address barriers to implementation of screening recommendations for this high-risk population.

CONFLICTS OF INTEREST

Guarantor of the article: Phil A. Hart, MD.

Specific author contributions: P.A.H. conceived the study; D.R. and A.F. collected the data; M.M. performed the analysis; D.R. drafted the manuscript; G.C., S.C., M.S., R.E.R., C.H., A.R., S.D., D.L.C., and P.A.H. edited the final version of the manuscript. All authors approved the final version of the manuscript.

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Potential competing interests: None to report.

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