

BMJ Open Association between periodontal disease and osteoporosis in postmenopausal women: a protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Periodontal disease and osteoporosis are common chronic diseases, especially for the postmenopausal women. Several original studies explore the association, but there still controversial. Therefore, we will conduct this systematic review and meta-analysis to assess the association between periodontal disease and osteoporosis in postmenopausal women.

Methods and analysis This study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses for Protocols. We will systematically search Medline/PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science and Scopus from inception to August 2021 to collect all relevant publications, with no restrictions on publication date or languages. Study selection, data extraction and risk of bias assessment will be conducted independently by two trained reviewers independently. The Cochrane's tool for assessing risk of bias, Newcastle-Ottawa Scale and Agency for Healthcare Research and Quality will be used for the risk of bias assessment. OR, HR and risk ratio with 95% CI were considered as the effect size for dichotomous outcomes, weighted mean difference with 95% CI were calculated as the effect size for continuous outcomes. Random-effects models will be used. Heterogeneity between studies will be assessed via the forest plot and I^2 . Publication bias will detected by funnel plots, Begg's test and Egger's test. The subgroup analyses and sensitivity analyses will also be used to explore and interpret the heterogeneity.

Ethics and dissemination This study does not require ethical approval. We will disseminate our findings by publishing results in a peer-reviewed journal.

PROSPERO registration number CRD42021225746.

INTRODUCTION

Osteoporosis is a systemic skeletal disease and the most prevalent bone disease affecting millions of people worldwide.¹ It is characterised by a decreased bone mineral density (BMD) and decreased bone microarchitecture,^{2 3} and results in an increase in bone fragility and fracture risk. The osteoporotic fractures cause significant mortality rate,

Strengths and limitations of this study

- This study will be the first systematic review and meta-analysis to synthetically investigate the association between periodontal disease and osteoporosis in postmenopausal women.
- This research will be conducted in strict accordance with the relevant methodological guidelines of systematic review and meta-analysis to minimise bias.
- The majority of included studies may be retrospectively designed, which may compromise the results of our study.
- The results of this study may be influenced by grey literature bias and heterogeneity in the case definitions of periodontitis.

high medical expenditures and substantial morbidity with low quality of life.⁴ Reducing the growing burden of osteoporosis is one of the aims of Expert Report on diet and chronic disease that WHO/Food and Agriculture Organization (FAO) released.⁵ Osteoporosis affects men and women of all race, especially for the older postmenopausal women, for risk factors differ in age, sex and level of hormones.^{4 6}

Periodontitis is a chronic inflammatory disease that results from the accumulation of dental plaque biofilm, microbial dysbiosis leads to a chronic, non-resolving and destructive inflammatory response,⁷ the tissue destruction that occurs is largely irreversible.⁸ The disease may begin in childhood or adolescence but usually debuts in early adulthood and occasionally in later years.⁹ In 2010, severe periodontitis was the sixth most prevalent condition and that it affected 743 million (10.8%) people aged 15–99 worldwide.¹⁰ The global prevalence of severe periodontitis increased steadily until individuals reached approximately 40 years of age and plateaued thereafter.¹¹

Although periodontal disease is confined locally and osteoporosis is a systemic process, bone loss is characteristic in both case.¹² Because their main feature influenced by common risk factors, including age, hormonal changes, the presence of cytokines, smoking habit, nutritional intake, educational level and so on.^{3 6 13 14} Additionally, postmenopausal women with osteoporosis are susceptible to an excessive response to dental plaque.¹⁵ Therefore, a hypothesis was proposed that periodontitis is associated with osteoporosis in postmenopausal women, although the biological mechanism underlying this association has not been fully elucidated. Several original studies explore the association,^{16 17} but there still controversial.¹⁸

High-quality systematic review and meta-analysis has been regarded as one of the key tools for achieving evidence. The previous systematic review and meta-analysis, published in 2017, explored the association of periodontal attachment loss with low BMD in postmenopausal women.¹⁹ The meta-analysis focused on the periodontal attachment loss and the clinical attachment level (CAL) is the only outcome. However, loss of alveolar crestal height (ACH), oral hygiene index simplified (OHI-S), probing depth (PD) and percentage of sites with bleeding on probing (BOP) are still the important outcomes for the clinical parameters of periodontal status. In addition, several new evidence published in recent years.^{18 20–22} Therefore, we will conduct this systematic review and meta-analysis to assess the impact of osteoporosis on the periodontal status of postmenopausal women with periodontal disease.

METHOD

This protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Protocols guidelines.²³ This systematic review and meta-analysis will be conducted and reported following the reporting guidelines provided in the PRISMA.²⁴ No ethical approval and informed consent needed because this is a retrospective study.

Search

We will systematically search Medline/PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science and Scopus from inception to August 2021 to collect publications related to association between periodontal disease and osteoporosis in postmenopausal women. The search strategy will be conducted by medical subject headings with text words. The search terms in each database included (“periodontal diseases” or “parodontosis” or “parodontoses” or “pyorrhea alveolaris”) and (“osteoporosis, postmenopausa” or “perimenopausal bone loss*” or “post-menopausal osteoporoses” or “post-menopausal osteoporosis” or “postmenopausal osteoporosis” or “postmenopausal osteoporoses” or “perimenopausal bone loss”). Online supplemental table S1 describes the detailed full search strategies.

In addition, the reference lists of the included studies and relevant reviews will also be checked, so as to supplement possible relevant literatures. There will no restrictions on publication date or languages. The results of the search will be updated before the final analysis to further identify possible new studies.

Inclusion criteria

This systematic review and meta-analysis will included the studies evaluated the association between periodontal disease and osteoporosis in postmenopausal women.

Participants

The participants were postmenopausal women, with no ethnicity, or health status restrictions.

Exposure

The exposures were participants with osteoporosis and/or osteopenia.

Comparator

The comparator was participants with normal BMD.

Study designs

There are no restrictions on the types of study, and randomised controlled trials(RCTs), cohort studies, case–control studies, longitudinal observational studies, cross-sectional studies and other original studies will be included.

Outcomes

The outcomes will be clinical parameters of periodontal status, including CAL, PD, gingival recession (GR), percentage of sites with BOP,²⁵ the loss of ACH and OHI-S.²⁶ CAL was measured as the distance from the cement-enamel junction (CEJ) to the bottom of the pocket.^{27 28} The PD reduction, defined as the distance from the gingival margin to the bottom of the pocket.^{27 28} GR was distance from the gingival margin to the CEJ.^{27 28} ACH was the distance from the CEJ to the most coronal point of the alveolar crest immediately adjacent to the root surface, and in the case of a vertical defect, ACH was the distance from the CEJ to the point immediately adjacent to the root surface at the base of the defect.²⁹

Exclusion criteria

Studies will be excluded if one of the following conditions is met:

1. Qualitative studies, case reports, case series, reviews, letters, comments, notes, animal studies, editorials and conference abstracts.
2. The research data are not complete.
3. The study is not in Chinese or English.

Additionally, studies with the same sample, we will select the study with the longest follow-up time and the largest sample size.

Study selection

Two trained reviewers will independently select the included studies based on the eligibility criteria. The

Rayyan web (<https://rayyanai/>) will be applied. The titles and abstracts of the citations retrieved by the literature search will be screened for potential studies. The full text is then screened according to eligibility criteria. Any disagreement will be resolved through discussions. The selection process will be recorded in a PRISMA flow chart.

Data extraction

A standard form will be used to extract data from the included studies. Two trained reviewers will perform the data extraction independently. Discrepancies between the reviewers will be resolved either by discussion or by a third reviewer. To identify other relevant study data, we will contact the authors of published studies for incomplete data.

Information to be extracted include four domains: (1) study characteristics (first authors, year of publication, country of participants, duration of study, number of participants); (2) participants information (age, ethnicity, the status of periodontal disease); (3) methods (study design, measures of exposure, outcomes and the criteria of periodontal disease and osteoporosis) and (4) outcomes (clinical parameters of periodontal status, HR, OR, risk ratio (RR), 95% CI, mean and SD).

Risk of bias assessment

Two researchers will independently assess the risk of bias (RoB) of all included studies. Any question will be solved through discussion or by a third reviewer. The Cochrane's tool for assessing RoB³⁰ will be used to evaluate the RoB for RCTs. The RoB tool covers six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. The Newcastle-Ottawa Scale will be used to assess the RoB for cohort studies and case-control studies.³¹ It comprises eight questions grouped under three broad dimensions: selection of groups under study, comparability of groups under study, and outcome ascertainment. The scale is given a score of 0–9 based on selection, comparability and outcome. We will represent 'low', 'medium' and 'high' quality research with scores of 0–3, 4–6 and 7–9, respectively. An 11-item checklist is recommended by Agency for Healthcare Research and Quality (available from: <https://www.ncbi.nlm.nih.gov/books/NBK35156/>) to evaluate the cross-sectional studies. The quality is assessed as 'low', 'medium' and 'high' quality with scores of 0–3, 4–7 and 8–11, respectively.

Data synthesis and statistical analysis

The available evidence will be synthesised in a meta-analysis on the basis of enough relevant studies. Statistical analysis was performed with STATA software, V.15.0 (StataCorp).

In this systematic review and meta-analysis, HR, OR or RR with 95% CI were considered as the effect size for dichotomous outcomes, weighted mean differences with 95% CI were calculated as the effect size for continuous outcomes.

Forest plots were produced to visually assess the effect size and corresponding 95% CI using random-effects models of DerSimonian and Laird. Heterogeneity between studies will be assessed via the forest plot and the Cochran Q test ($p < 0.05$ considered statistically significant), while I^2 values described the total variation between studies. I^2 values of $< 25\%$, $25\%–50\%$ and $> 50\%$ indicated low, moderate and high heterogeneity, respectively.

Publication bias

We will assess the publication bias of included studies when there are at least 10 studies reporting the primary outcomes. Visual inspection of funnel plots, and statistical assessments using the Begg-Mazumdar rank correlation³² and Egger's regression test³³ will be used to detect publication bias.

Additional analysis

Subgroup analyses will be used to explore and interpret the sources of heterogeneity, and to evaluate whether there are different. If data available, the subgroup analyses will be based on (1) study designs, (2) $CAL \geq 4$ mm and ≥ 6 mm, (3) definitions of periodontitis, (4) the BMD evaluations (dual energy X-ray absorptiometry (DXA) of lumbar spine, DXA of proximal femur, DXA of forearm, ultrasound and lateral radiographs) and (5) other characteristics of participants and exposure, which have influence on the periodontal disease and periodontal disease for postmenopausal women.

We will adopt sensitivity analyses to explore the sources of high heterogeneity and to evaluate the stability of the results by excluding studies with high/medium RoB or other special characteristics. We will also conduct sensitivity analyses by serially excluding one study at a time to determine the influence of individual studies on the overall estimates and to explore whether the results were robust.

Patient and public involvement

Patients and/or the public involved.

Current study status

Preliminary searches.

ETHICS AND DISSEMINATION

This systematic review and meta-analysis involves no patient contact and no interaction with healthcare providers or systems. We will disseminate the findings of this study through the presentation at scientific publication in a peer-reviewed journal.

DISCUSSION

Periodontal disease and osteoporosis are common chronic diseases, especially for the women in postmenopause. A hypothesis was proposed that periodontitis is associated with periodontitis in postmenopausal women, because bone loss is their common characteristic and

their main feature influenced by common risk factors (eg, age, hormonal changes, etc). Therefore, we will conduct this systematic review and meta-analysis, which is the first to synthetically investigate the association between periodontal disease and osteoporosis in postmenopausal women with more comprehensive outcomes. The findings may fill the gap in this field.

There may be several limitations for this systematic review and meta-analysis. First, the quality of included studies have impact on the quality of evidence for this meta-analysis, and the quality of evidence for this meta-analysis may not high for lack of prospective original studies, although these retrospective studies presented good scientific qualities. Second, case definitions of periodontitis maybe different,¹⁸ which may result in high heterogeneity. Third, the measurements of ACH, OHIS, PD and BOP are dependent, to a large extent, on the skills of the dental examiners, which may cause high heterogeneity.³⁴ The results may be influent by grey literature bias, since no additional searches are performed for unpublished studies and literature in this study.

The results of this study hope to provide high-quality evidence for the related research. And the final report of this systematic review and meta-analysis in the form of scientific paper will be published in peer-reviewed journals.

Contributors H-QY and JQ conceived the idea and design the protocol. H-QY, JQ, EL and Y-FG drafted the manuscript. H-QY, JQ, EL, Y-FG, J-MH, Y-TL and GC critically revised the manuscript for methodology and intellectual content. H-QY, JQ and EL are the guarantors of the review. All authors approved the final version of this manuscript.

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Competing interests None declared.

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Table S1 Full search strategies

Databases	Strategies
Embase	1. Perimenopausal Bone Loss.ab,kw,ti. 2. Perimenopausal Bone Losses.ab,kw,ti. 3. Postmenopausal Bone Loss.ab,kw,ti. 4. Postmenopausal Bone Losses.ab,kw,ti. 5. Postmenopausal Osteoporoses.ab,kw,ti. 6. Post-Menopausal Osteoporoses.ab,kw,ti. 7. Postmenopausal Osteoporosis.ab,kw,ti. 8. Post-Menopausal Osteoporosis.ab,kw,ti. 9. Osteoporosis, Postmenopausal.ab,kw,ti. 10. exp postmenopause osteoporosis/ 11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 12. Parodontoses.ab,kw,ti. 13. Parodontosis.ab,kw,ti. 14. Periodontal Disease.ab,kw,ti. 15. Periodontal Diseases.ab,kw,ti. 16. Pyorrhea Alveolaris.ab,kw,ti. 17. exp periodontal disease/ 18. 12 or 13 or 14 or 15 or 16 or 17 19. 11 and 18
Medline/PubMed	1 "Periodontal Diseases"[Mesh] 2 (((((Parodontoses[Title/Abstract])) OR (Parodontosis[Title/Abstract])) OR (Periodontal Disease[Title/Abstract])) OR (Periodontal Diseases[Title/Abstract])) OR (Pyorrhea Alveolaris[Title/Abstract]) 3 ("Periodontal Diseases"[Mesh]) OR (((((Parodontoses[Title/Abstract])) OR (Parodontosis[Title/Abstract])) OR (Periodontal Disease[Title/Abstract])) OR (Periodontal Diseases[Title/Abstract])) OR (Pyorrhea Alveolaris[Title/Abstract])) 4 "Osteoporosis, Postmenopausal"[Mesh] 5 (((((((Perimenopausal Bone Loss[Title/Abstract]) OR (Perimenopausal Bone Losses[Title/Abstract])) OR (Postmenopausal Bone Loss[Title/Abstract])) OR (Postmenopausal Bone Losses[Title/Abstract])) OR (Postmenopausal Osteoporoses[Title/Abstract])) OR (Post-Menopausal Osteoporoses[Title/Abstract])) OR (Postmenopausal Osteoporosis[Title/Abstract])) OR (Post-Menopausal Osteoporosis[Title/Abstract]) 6 (((((((Perimenopausal Bone Loss[Title/Abstract]) OR (Perimenopausal Bone Losses[Title/Abstract])) OR (Postmenopausal Bone Loss[Title/Abstract])) OR (Postmenopausal Bone Losses[Title/Abstract])) OR (Postmenopausal Osteoporoses[Title/Abstract])) OR (Post-Menopausal Osteoporoses[Title/Abstract])) OR (Postmenopausal

	<p>Osteoporosis[Title/Abstract])) OR (Post-Menopausal Osteoporosis[Title/Abstract])) OR ("Osteoporosis, Postmenopausal"[Mesh])</p> <p>7 (((((((((Perimenopausal Bone Loss[Title/Abstract]) OR (Perimenopausal Bone Losses[Title/Abstract])) OR (Postmenopausal Bone Loss[Title/Abstract])) OR (Postmenopausal Bone Losses[Title/Abstract])) OR (Postmenopausal Osteoporoses[Title/Abstract])) OR (Post-Menopausal Osteoporoses[Title/Abstract])) OR (Postmenopausal Osteoporosis[Title/Abstract])) OR (Post-Menopausal Osteoporosis[Title/Abstract])) OR ("Osteoporosis, Postmenopausal"[Mesh]))</p> <p>AND (("Periodontal Diseases"[Mesh]) OR ((((((Parodontoses[Title/Abstract])) OR (Parodontosis[Title/Abstract])) OR (Periodontal Disease[Title/Abstract])) OR (Periodontal Diseases[Title/Abstract])) OR (Pyorrhea Alveolaris[Title/Abstract]))))</p>
Cochrane Central Register of Controlled Trials (CENTRAL)	<p>#1 MeSH descriptor: [Osteoporosis, Postmenopausal] explode all trees</p> <p>#2 ("perimenopausal bone loss"):ti,ab,kw OR (Perimenopausal Bone Losses):ti,ab,kw OR (Postmenopausal Bone Loss):ti,ab,kw OR (Postmenopausal Bone Losses):ti,ab,kw OR (Postmenopausal Osteoporoses):ti,ab,kw (Word variations have been searched)</p> <p>#3 (Post-Menopausal Osteoporoses):ti,ab,kw OR (Postmenopausal Osteoporosis):ti,ab,kw OR (Post-Menopausal Osteoporosis):ti,ab,kw OR (Osteoporosis, Postmenopausal):ti,ab,kw (Word variations have been searched) 5163</p> <p>#4 #1 OR #2 OR #3</p> <p>#5 MeSH descriptor: [Periodontal Diseases] explode all trees</p> <p>#6 (Parodontoses):ti,ab,kw OR (Parodontosis):ti,ab,kw OR (Periodontal Disease):ti,ab,kw OR (Periodontal Diseases):ti,ab,kw OR (Pyorrhea Alveolaris):ti,ab,kw (Word variations have been searched)</p> <p>#7 #5 OR #6</p> <p>#8 #4 AND #7</p>
Web of Science (All Databases)	<p>1. Perimenopausal Bone Loss (Topic) or Perimenopausal Bone Losses (Topic) or Postmenopausal Bone Loss (Topic) or Postmenopausal Bone Losses (Topic) or Postmenopausal Osteoporoses (Topic) or Post-Menopausal Osteoporoses (Topic) or Postmenopausal Osteoporosis (Topic) or Post-Menopausal Osteoporosis (Topic) or Osteoporosis, Postmenopausal (Topic)</p> <p>2. Parodontoses (Topic) or Parodontosis (Topic) or Periodontal Disease (Topic) or Periodontal Diseases (Topic) or Pyorrhea Alveolaris (Topic)</p> <p>3. (#2) AND #1</p>
Scopus	<p>1. (TITLE-ABS-KEY (parodontoses) OR TITLE-ABS-KEY (parodontosis) OR TITLE-ABS-KEY (periodontal AND disease) OR TITLE-ABS-KEY (periodontal AND diseases) OR TITLE-ABS-KEY (pyorrhea AND alveolaris))</p> <p>2. (TITLE-ABS-KEY (perimenopausal AND bone AND loss) OR TITLE-ABS-KEY (perimenopausal AND bone AND losses) OR</p>

	<p> TITLE-ABS-KEY (postmenopausal AND bone AND loss) OR TITLE-ABS-KEY (postmenopausal AND bone AND losses) OR TITLE-ABS-KEY (postmenopausal AND osteoporoses) OR TITLE-ABS-KEY (post-menopausal AND osteoporoses) OR TITLE-ABS-KEY (postmenopausal AND osteoporosis) OR TITLE-ABS-KEY (post-menopausal AND osteoporosis) OR TITLE-ABS-KEY (osteoporosis, AND postmenopausal)) 3. ((TITLE-ABS-KEY (perimenopausal AND bone AND loss) OR TITLE-ABS-KEY (perimenopausal AND bone AND losses) OR TITLE-ABS-KEY (postmenopausal AND bone AND loss) OR TITLE-ABS-KEY (postmenopausal AND bone AND losses) OR TITLE-ABS-KEY (postmenopausal AND osteoporoses) OR TITLE-ABS-KEY (post-menopausal AND osteoporoses) OR TITLE-ABS-KEY (postmenopausal AND osteoporosis) OR TITLE-ABS-KEY (post-menopausal AND osteoporosis) OR TITLE-ABS-KEY (osteoporosis, AND postmenopausal))) AND ((TITLE-ABS-KEY (parodontoses) OR TITLE-ABS-KEY (parodontosis) OR TITLE-ABS-KEY (periodontal AND disease) OR TITLE-ABS-KEY (periodontal AND diseases) OR TITLE-ABS-KEY (pyorrhea AND alveolaris))) </p>
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