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The Association Between Alzheimer's Disease and Bone Health: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Risk of bias assessment.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 March 2026 and was last updated on 24 March 2026.

INTRODUCTION

Review question / Objective • Primary Question: Is AD associated with lower mean BMD or an accelerated rate of BMD loss in adult populations compared to cognitively healthy controls?
• Secondary Question: Is AD associated with a higher prevalence or incidence of Osteopenia and Osteoporosis in adult populations compared to cognitively healthy controls?

• Primary Objective: Determine the association between AD and Bone Mineral Density (BMD).
• Secondary Objective: Evaluate the association between AD and the risk of Osteopenia and Osteoporosis.

Rationale To evaluate the potential association between Alzheimer's Disease (AD) and bone health by synthesizing evidence from observational studies in adult populations.

Condition being studied Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by continuous cognitive decline, memory loss, and behavioral changes, primarily affecting the aging population. Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD) and microarchitectural deterioration of bone tissue, leading to bone fragility and a significantly increased risk of fractures; osteopenia serves as a precursor clinical stage to this condition. Given that both conditions are highly prevalent in older adults and may share underlying systemic or metabolic pathways, this study aims to evaluate the potential association between AD and compromised bone health. Specifically, we focus on understanding whether adults with AD exhibit lower mean BMD, an accelerated rate of BMD loss, or a higher risk of developing osteopenia and osteoporosis compared to cognitively healthy controls.

METHODS

Search strategy The systematic search will be conducted across three primary databases: PubMed, Embase, and Web of Science.
The end date of the search range is 2026-03-18.
The Language is limited to English.
The search syntax is as follows:
1. PubMed: ("Alzheimer Disease"[MeSH Terms] OR "Alzheimer" OR "Alzheimer's" OR "Dementia") AND ("Bone Density"[MeSH Terms] OR "Bone Density" OR "Bone Mineral Density" OR "BMD" OR "Bone Loss" OR "Osteoporosis"[MeSH Terms] OR "Osteoporosis" OR "Osteopenia" OR "Bone Diseases, Metabolic"[MeSH Terms]) AND ("Cohort Studies"[MeSH Terms] OR "Case-Control Studies"[MeSH Terms] OR "Cross-Sectional Studies"[MeSH Terms] OR "Observational Study"[Publication Type] OR "Observational Studies as Topic"[MeSH Terms] OR "case control" OR "cross sectional" OR "prevalence study" OR "longitudinal" OR "prospective" OR "retrospective" OR "follow-up")

2. Embase: ('alzheimer disease'/exp OR 'alzheimer' OR 'alzheimers' OR 'dementia'/exp) AND ('bone density'/exp OR 'bone mineral density' OR 'bmd' OR 'bone loss' OR 'osteoporosis'/exp OR 'osteopenia'/exp OR 'metabolic bone disease'/exp) AND ('cohort analysis'/exp OR 'case control study'/exp OR 'cross-sectional study'/exp OR 'observational study'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR 'follow up'/exp)

3. Web of Science: TS=(Alzheimer* OR Dementia) AND TS=("Bone Density" OR "Bone Mineral Density" OR "BMD" OR "Bone Loss" OR Osteoporosis OR Osteopenia OR "Bone Disease*") AND TS=("Cohort Stud*" OR "Case-Control" OR "Cross-Sectional" OR "Observational Stud*" OR Longitudinal OR Prospective OR Retrospective OR "Follow-up").

Participant or population Population:
1) Adults (aged >= 18 years) with a formal diagnosis of AD.
2) AD Diagnostic Criteria: Diagnosis must be based on validated clinical criteria, such as the NIA-AA criteria, DSM IV or V, or ICD codes.

Intervention
Exposure:
1) Participants must have a primary diagnosis of AD;
2) Mixed Dementia: Studies involving "mixed dementia" will only be included if data for the Alzheimer's subgroup can be independently extracted.

Comparator Control Group: Comparison groups must consist of individuals without a diagnosis of AD or cognitive impairment at baseline.

Study designs to be included Peer-reviewed observational studies, including cross-sectional, case-control, and cohort studies.

Eligibility criteria Inclusion Criteria
• Population: 1) Adults (aged >= 18 years) with a formal diagnosis of AD; 2) AD Diagnostic Criteria: Diagnosis must be based on validated clinical criteria, such as the NIA-AA criteria, DSM IV or V, or ICD codes.
• Exposure: 1) Participants must have a primary diagnosis of AD; 2) Mixed Dementia: Studies involving "mixed dementia" will only be included if data for the Alzheimer's subgroup can be independently extracted.
• Control Group: Comparison groups must consist of individuals without a diagnosis of AD or cognitive impairment at baseline.
• Outcomes: 1) Primary Outcome: BMD measured via DXA, QCT, or QUS, etc; 2) Secondary Outcomes: Clinical diagnosis of Osteoporosis or Osteopenia based on T-scores or ICD-coded medical records.
• Study Design: 1) Peer-reviewed observational studies, including cross-sectional, case-control, and cohort studies; 2) For cohort studies, the mean/median follow-up period is a minimum of 12 months.
• Setting: Studies from all settings (community-based, hospital-based, or residential care/nursing homes) will be included.

Exclusion Criteria
• Non-AD Dementia: Studies focusing on vascular dementia, Lewy body dementia, or frontotemporal dementia without a distinct AD subgroup.
• Overlaping Population: When multiple reports using the same participant data, the most comprehensive or relevant report will be included.
• Publication Type: Animal studies, editorials, conference abstracts without full text, case reports, and review articles.
• Data Integrity: Studies with insufficient data to calculate effect sizes where the authors do not respond to data requests.

Information sources Systematic searches will be conducted in the following electronic databases: PubMed, Embase, and Web of Science.

The search will cover all records from the inception of each database up to March 2026. To ensure a comprehensive search, the reference lists of all included studies and relevant systematic reviews will be manually screened to identify any additional eligible studies (backward snowballing).
Additionally, we will search for grey literature via Google Scholar (the first 100 records) to minimize potential publication bias.

Main outcome(s) Primary Outcome: There is no significant difference in mean BMD between adults with Alzheimer's Disease and cognitively healthy controls in cross-sectional or case-control evidence. AD is not associated with an accelerated rate of BMD loss over time in longitudinal cohort evidence.

Effective Measures:
Primary Outcome (BMD): the WMD will be used as the primary effect measure if scales are consistent (g/cm2); otherwise, the Standardized Mean Difference (SMD) will be used.
Secondary Outcomes (Osteoporosis/Osteopenia): OR for case-control/cross-sectional studies and RR or HR for longitudinal cohort studies.

Additional outcome(s) Secondary Outcome: AD is not associated with increased odds of Osteoporosis or Osteopenia in cross-sectional or case-control evidence. AD is not associated with an increased incidence of Osteoporosis or Osteopenia over time in cohort evidence.

Protocol Registration and Amendments
This protocol has been prepared in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines.

Certainty of Evidence (GRADE)
The certainty of the evidence for the association between AD and bone health outcomes (BMD, Osteoporosis) will be assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) framework.
• Initial Rating: Evidence from observational studies (cohort, case-control, and cross-section) will start at a "Low" certainty rating.
• Downgrading: Certainty will be downgraded based on five factors: (1) Risk of Bias (using NOS), (2) Inconsistency (I2 > 50%), (3) Indirectness, (4) Imprecision (wide confidence intervals), and (5) Publication Bias.
• Upgrading: Certainty may be upgraded if there is a large effect size (HR/ RR/ OR > 2 or < 0.5).
• Final Conclusion: Evidence will be categorized as High, Moderate, Low, or Very Low.

Ethics
As this study involves the synthesis of previously published data, formal ethical approval is not required.

Data management Data Extraction:

• Piloting: The standardized data extraction form will be piloted using five included studies. • Missing Data: If essential data for the meta-analysis are missing, the corresponding authors of the primary studies will be contacted via email. If the data cannot be obtained, standard converting formulas will be used where possible; otherwise, the study will be excluded from the quantitative synthesis.

• Overlaping Population: If multiple publications report data from the same study population, the following hierarchy will be used to select the primary report: 1) The study reporting the largest sample size and the most comprehensive set of outcomes will be prioritized; 2) The study with the longest follow-up period will be selected; 3) The most recent publication will be used; 4) The adjusted report will be prioritized.

Extracted data will be structured into a standardized format with the following columns:
1. Study Characteristics: First Author (Publication Year), Location, Setting (hospital-based, community-based, nursing house, etc.), Study Design, Study Population, Recruitment Period, and Mean/Median Follow-Up Years.
2. Demographic & Anthropometric Data: Total N, Mean Age (SD), Sex (% Female), and BMI (Mean/SD).
3. Methodology & Diagnostic Criteria: Exposure, Outcome, Exposure Measurement/Diagnostic Criteria, Outcome Measurement/Diagnostic Criteria, and Bone Site.
4. Outcomes & Statistical Findings: Exposure (Mean/SD, unit, or cases num/controls num), Type of Estimate, Adjusted Effect Estimate (Weighted Mean Difference (WMD), Odds Ratios (OR), Risk Ratios).

Quality assessment / Risk of bias analysis The methodological quality and risk of bias for all included cohort and case-control studies will be evaluated using the original Newcastle-Ottawa Scale (NOS). Cross-sectional studies will be evaluated using the modified NOS. A study will be considered as "high quality" if its NOS scores >=5, any domain score >=1, and adjusted for at least age and sex.

Strategy of data synthesis Data synthesis will be performed using R language (R studio) with the 'meta' and 'metafor' packages.

Effect Measures:
• Primary Outcome (BMD): the WMD will be used as the primary effect measure if scales are consistent (g/cm2); otherwise, the Standardized Mean Difference (SMD) will be used.
• Secondary Outcomes (Osteoporosis/Osteopenia): OR for case-control/cross-sectional studies and RR or HR for longitudinal cohort studies.
Primary Analysis:
• Analysis by Study Design: Data will be stratified into distinct pools: 1) Cross-sectional/Case-Control studies (to assess association and prevalence); 2) Cohort studies (to assess the rate of BMD loss or disease incidence).
• Analysis by Outcome Type: BMD results and Osteoporosis/Osteopenia outcomes will be reported, respectively.

Model Choice:
• Heterogeneity Assessment: Inconsistency across studies will be quantified using the I2 statistic, where I2 > 50% indicates substantial heterogeneity.
• Model Selection: A Random-Effects Model will be the default approach. Fixed-effects models will be conducted only as sensitivity analyses.
• Meta-Regression (Optional): If I2 is high, a random-effects meta-regression will be performed using mean age, sex and study quality score as independent covariates.

The Synthesis Groups and Corresponding Clinical Estimator will be as follows:
Format: Primary Synthesis Group – Subgroup (Study Design) – Clinical Estimator
1. BMD Mean Difference – Case-Control – Difference in BMD between AD patients and healthy controls
BMD Mean Difference – Cross-Sectional – The association between AD and bone density in the general population

2. Osteoporosis Prevalence – Case-Control – The Odds ratios of having Osteoporosis
Osteoporosis Prevalence – Cross-Sectional – The Odds ratios of having Osteoporosis

3. Rate of Bone Loss – Cohort – The annual change in BMD (g/cm2 per year) in AD vs. controls

4. Osteoporosis Risk – Cohort – The Risk (RR/HR) of developing Osteoporosis.

Subgroup analysis Clinical and Methodological Subgroup Analyses: To address the clinical complexity of the association between AD and bone health, the following factors will be used across all outcomes to explore specific biological and environmental variations:
• Bone Measurement Site: Separate analyses for different bone sites, including the Femoral Neck, Lumbar Spine, Hip, etc.
• Bone Health: Separate analyses for populations with/without conditions primarily affecting bone metabolism or those on long-term corticosteroid therapy.
• Study Setting: Separate analyses for hospital-based, community-based, and nursing home populations.
• Disease Severity: Separate analyses for AD severity (Mild, Moderate, or Severe) based on MMSE scores or clinical staging where data are available.

Heterogeneity-Driven Subgroup Analysis (I2 > 50%): If substantial heterogeneity is detected, the following factors will be used as grouping variables to identify the source of inconsistency:
• Study Quality: 1) Separate analysis excluding studies with a high risk of bias (NOS scores <5 or any domain score <1). 2) Separate analysis excluding studies without adjusting for age and sex.
• Diagnostic Criteria: Separate analyses for studies using different Alzheimer's diagnostic frameworks (NIA-AA, DSM-IV/V, or ICD codes).
• Geographic Region: Separate analysis by region.

Sensitivity analysis Leave-One-Out: Using the "leave-one-out" approach and perform a separate analysis excluding studies with a high risk of bias (NOS scores <5 or any domain score = 10 studies. For groups with fewer than 10 studies, a qualitative assessment will be performed (The consistency of results across small and large studies, and checking for outcome reporting bias within the included papers). If significant asymmetry is detected ($p < 0.1$), the trim-and-fill method will be applied to estimate the impact of potential missing studies.

Language restriction English.

Country(ies) involved United States.

Other relevant information Screening:
• Piloting: Prior to the formal screening, a pilot test will be conducted on a random sample of 50 titles and abstracts. The two independent reviewers will compare their results to refine the eligibility criteria and ensure high inter-rater reliability.

• Independent Review: Two reviewers will independently screen all titles and abstracts identified in the search against the pre-specified inclusion criteria. Potentially relevant studies will then undergo an independent full-text review.

• Adjudication of Disagreements: Any discrepancies between the two reviewers at either the screening stages will be resolved through discussion. If a consensus cannot be reached, a third senior reviewer (Prof. Wu) will act as an adjudicator to make the final decision.

Keywords Alzheimer's disease; Bone mineral density; Meta-analysis; Osteoporosis.

Dissemination plans The findings of this systematic review and meta-analysis will be submitted to a peer-reviewed journal for publication. Additionally, the results may be presented at relevant academic conferences (such as neurodegeneration or osteoporosis research forums). We also plan to make the final dataset available upon reasonable request to ensure transparency and data sharing.

Contributions of each author

Author 1 - Liangwei He - Liangwei He refined the study concept and developed the detailed methodology; established the research questions and PICO framework; led the protocol development; executed the multi-stage systematic search and screening process; coordinated the overall project workflow; and will be responsible for data synthesis, statistical analysis, and drafting the final manuscript.
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Author 2 - Yinhe Chai - Yinhe Chai will contribute to: (1) drafting and revising the protocol; (2) designing and executing the systematic literature search; (3) screening titles, abstracts, and full texts; (4) conducting data extraction; (5) conducting quality assessment.
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Author 3 - Qing Wu - Professor Qing Wu conceived the original research theme and provided overall scientific supervision; contributed to the refinement of the study design and methodology; provided critical revisions of the protocol for important intellectual content; and will oversee the data analysis and final manuscript preparation.
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