INPLASY

Prevalence and Risk Factors of Osteoporosis and Reduced Bone Mineral Density in Patients with Systemic Lupus Erythematosus: A Global Multicenter Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

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 11 December 2025 and was last updated on 11 December 2025.

INTRODUCTION

Review question / Objective Population:
• Adult patients (≥18 years) diagnosed with SLE according to established criteria (ACR 1997 classification)
• No restrictions on gender, ethnicity, or geographical location
• Exclusion of patients with conditions affecting bone metabolism
Intervention/Exposure:
• Glucocorticoid therapy (dose, duration, cumulative dose)
• Disease-related factors (SLE duration, disease activity measured by SLEDAI)
• Demographic factors (age, gender, menopausal status)
• Laboratory parameters (vitamin D levels, inflammatory markers)
Comparison:
• Comparison groups based on exposure status (exposed vs. unexposed)
• Subgroup comparisons by demographic and clinical characteristics
Outcomes:
Primary Outcomes:
• Prevalence of osteoporosis (defined by DXA T-score ≤ -2.5)
• Prevalence of osteopenia (defined by -2.5 < T-score < -1.0)
Secondary Outcomes:
• Site-specific bone mineral density (lumbar spine, femoral neck, total hip)
• Risk factors assessed through odds ratios (ORs) with 95% confidence intervals
Study Design:
• Observational studies including cross-sectional, cohort, and case-control designs
• Studies employing multivariate analysis for risk factor assessment
• No language restrictions (Chinese and English literature)
Methodological Approach:
• Comprehensive literature search across multiple databases
• Rigorous quality assessment using standardized tools (NOS for cohort/case-control studies, AHRQ for cross-sectional studies)

• Planned subgroup analyses to explore heterogeneity sources
• Sensitivity analysis to test result robustness
Expected Outcomes:
This systematic review aims to provide quantitative estimates of bone health impairment in SLE patients and establish evidence-based understanding of risk factor contributions, ultimately supporting clinical decision-making for osteoporosis prevention and management in this vulnerable population.

Condition being studied Systemic Lupus Erythematosus and Its Skeletal Complications
Systemic Lupus Erythematosus (SLE) is a chronic multisystem autoimmune disease characterized by abnormal activation of the immune system leading to inflammatory damage in multiple organs. The disease predominantly affects women of reproductive age, with a female-to-male ratio of approximately 9:1 and a global prevalence of 20-150 per 100,000 population.
SLE presents with highly heterogeneous clinical manifestations, potentially involving the skin, joints, kidneys, hematological system, and nervous system. Active disease is accompanied by significant inflammatory responses, with various autoantibodies (such as ANA and anti-dsDNA) serving as serological markers.
This study focuses on skeletal complications in SLE patients, particularly osteoporosis and reduced bone mineral density. Osteoporosis is defined by the World Health Organization as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration, leading to increased bone fragility and fracture risk.
The pathogenesis of bone complications in SLE patients involves multiple interconnected mechanisms:
First, glucocorticoids (GCs), as cornerstone therapy for SLE, directly inhibit osteoblast function and promote osteoclast activity when used long-term, resulting in glucocorticoid-induced osteoporosis (GIOP). Second, the chronic inflammatory state in SLE disrupts bone remodeling balance through the release of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). Additionally, disease-related photosensitivity leads to reduced vitamin D synthesis, renal involvement affects calcium-phosphate metabolism, and disease activity limits physical activity - all contributing to accelerated bone loss.
Notably, SLE patients have a significantly higher risk of developing osteoporosis compared to the general population, which not only increases fracture incidence but also further reduces quality of life and increases healthcare burden. Therefore, understanding the epidemiological characteristics and risk factors of skeletal complications in SLE patients is crucial for developing effective prevention and management strategies.

METHODS

Participant or population This systematic review will focus on patients with a confirmed diagnosis of Systemic Lupus Erythematosus (SLE). Specifically, the population of interest consists of patients meeting the American College of Rheumatology (ACR) 1997 revised classification criteria for SLE.
Inclusion criteria encompass patients with the following characteristics:
Diagnostic criteria: All participants must fulfill the ACR 1997 classification criteria for SLE
Age range: Adult patients (≥18 years) with no upper age limit
Gender distribution: Both male and female patients, with particular attention to female patients in different menopausal status subgroups
Disease status: Patients with varying disease activity levels, disease duration, and treatment backgrounds
Geographical distribution: Patients from multiple global regions, including Asia, Europe, and North America
Exclusion criteria clearly define the following conditions:
Patients with history of using medications affecting bone metabolism (e.g., estrogens, androgens, anticoagulants)
Patients with severe hepatic or renal dysfunction, Cushing's syndrome, thyroid or parathyroid diseases
Patients with history of oophorectomy or other comorbidities potentially affecting bone metabolism
Subjects from animal studies or studies with unavailable full-text
Special considerations for the study population:
We will pay particular attention to the characteristics of different patient subgroups, including premenopausal versus postmenopausal women, patients across different age stages (especially those over 50 years), and patients with varying glucocorticoid usage patterns. This stratified analysis will facilitate a deeper understanding of the distribution characteristics of skeletal complications in SLE patients across different populations.
By strictly adhering to these inclusion and exclusion criteria, we will ensure the homogeneity of the study population and the reliability of data, thereby providing a high-quality evidence base for subsequent prevalence and risk factor analyses.

Intervention This review will evaluate a group of exposure factors potentially associated with the development of osteoporosis (OP) and reduced bone mineral density (BMD) in patients with Systemic Lupus Erythematosus (SLE). As this is a meta-analysis of observational studies, the primary "interventions" of interest are the naturally occurring exposures and patient characteristics that may modify bone health risk.
The key exposure factors to be investigated include:
Pharmacological Exposures:
Glucocorticoid Therapy: This is a primary exposure of interest. We will evaluate the use of glucocorticoids (GCs), including aspects such as average daily dose (e.g., ≤10 mg/day vs. >10 mg/day prednisone equivalent), cumulative dose, and duration of therapy, which are critical for assessing the risk of glucocorticoid-induced osteoporosis (GIOP)
.
Disease-Related Characteristics:
Disease Duration: The length of time since SLE diagnosis.
Disease Activity: Measured by indices such as the SLE Disease Activity Index (SLEDAI).
Organ Involvement: Particularly the presence of lupus nephritis, which can affect calcium and vitamin D metabolism.
Demographic and Clinical Factors:
Age: Categorized, with a specific focus on patients over 50 years old.
Menopausal Status: Comparing postmenopausal women with premenopausal women.
Gender: Assessing risk differences between male and female patients.
Comparison Groups:
The effect of these exposures will be assessed by comparing groups of SLE patients with and without the specific exposure. For example:
SLE patients exposed to GCs will be compared to SLE patients not exposed to GCs.
Postmenopausal SLE patients will be compared to premenopausal SLE patients.
Analyses will also involve comparisons based on different levels or categories of the exposures (e.g., low-dose vs. high-dose GCs).
Outcome Measurement:
The impact of these exposures will be measured by their association with the primary outcomes: the prevalence of osteoporosis (T-score ≤ -2.5) and osteopenia (-2.5 < T-score < -1.0), as measured by Dual-Energy X-ray Absorptiometry (DXA). The strength of association will be quantified using odds ratios (ORs) or risk ratios (RRs) with 95% confidence intervals, as extracted from multivariate analyses in the included studies.

Comparator In this systematic review, the "Comparator" refers to the reference groups used for comparison with the target exposed population. Given the observational nature of the included studies, the term "Comparator" more accurately denotes "Reference groups" rather than active interventions in RCTs.
Primary comparator groups are defined as follows:
Based on Glucocorticoid Use
Target population: SLE patients using glucocorticoids
Comparator: SLE patients not using glucocorticoids
Subgroup comparisons: Between different dosage groups (≤10 mg/day vs >10 mg/day) and duration categories
Based on Demographic Characteristics
Target population: Postmenopausal female SLE patients
Comparator: Premenopausal female SLE patients
Target population: SLE patients aged >50 years
Comparator: SLE patients aged ≤50 years
Based on Disease Characteristics
Target population: SLE patients with long disease duration (e.g., >5 years)
Comparator: SLE patients with short disease duration (e.g., ≤5 years)
Target population: Patients with high disease activity (e.g., high SLEDAI scores)
Comparator: Patients with low disease activity
Based on Geographical Region
Target population: SLE patients from Asian regions
Comparator: SLE patients from European or North American regions
Purpose of Comparison: These comparator groups enable the assessment of the independent effect of specific exposures (e.g., GCs use, menopausal status) on osteoporosis prevalence, allowing for the calculation of relative risks or odds ratios.

Study designs to be included To comprehensively evaluate the prevalence and influencing factors of osteoporosis in SLE patients, this systematic review will include the following three main types of observational study designs:1. Cross-sectional StudiesRole: To quantitatively analyze the prevalence and distribution characteristics of osteoporosis and osteopeniaAdvantage: Provides snapshot data on disease burden at a specific time pointPlanned inclusion: 54 cross-sectional studies (based on preliminary search results)2. Cohort Studies Role: To analyze the causal relationship between exposure factors (e.g., gluc.

Eligibility criteria English Description
Eligibility Criteria

In addition to the criteria defined within the PICOS framework, the following additional inclusion and exclusion criteria are established to ensure the rigor of the review and the quality of the evidence.
Additional Inclusion Criteria:
Language Requirement
Only studies published in Chinese or English will be included to ensure accurate understanding and data extraction by the research team.
Data Accessibility
Studies must provide sufficient data to calculate prevalence or effect sizes (e.g., Odds Ratios with 95% Confidence Intervals). If data in the publication is incomplete but can be obtained by contacting the corresponding author, the study will be included.
Population Clarity
Studies must clearly report the source of the SLE patient population (e.g., rheumatology clinic, inpatients, community cohort) to ensure clear population definition.
Additional Exclusion Criteria:
Publication Type
Dissertations, conference abstracts, commentaries, editorials, and review articles that do not provide original data will be excluded to ensure the maturity and reliability of the included evidence.
Data Overlap or Duplicate Publication
If multiple studies are based on the same population or dataset, only the study with the largest sample size or the most comprehensive and recent data will be included to avoid double-counting.
Baseline Data from Intervention Studies
Although Randomized Controlled Trials (RCTs) are excluded, if baseline data from an RCT is reported in a cross-sectional manner regarding osteoporosis prevalence relevant to our objective and can be independently extracted, that specific data may be considered for inclusion.
Specific Comorbidities or Treatment History
As specified in the document, patients with the following histories will be explicitly excluded:
History of using estrogen, androgens, anticoagulants, and drugs affecting bone metabolism.
History of severe hepatic or renal dysfunction, Cushing's syndrome, thyroid and parathyroid diseases, or oophorectomy.
These additional criteria are designed to minimize bias and enhance the accuracy and applicability of the synthesized evidence.

Information sources PubMed;Embase;Cochrane Library；Web of Science；CNKI；WanFang Data.

Main outcome(s) Glucocorticoid Therapy
Long-term or high-dose GCs use (dose-response relationship)
Parameters: daily dose (≤10 mg vs. >10 mg/day), duration, cumulative dose
Primary mechanism for glucocorticoid-induced osteoporosis
Disease-Related Factors
Disease activity (SLEDAI scores) and chronic inflammation
Disease duration and organ involvement (particularly renal)
Vitamin D deficiency common in SLE patients
Key Patient Characteristics
Menopausal status (postmenopausal vs. premenopausal)
Age factors (>50 years as critical threshold)
Gender differences and genetic predisposition
Comparison Groups
GCs users vs. non-users
Different dosage stratifications
Menopausal status subgroups
Geographic variations (Asian vs. European populations)
Assessment Methods
Multivariate logistic regression for confounder control
Odds ratios with 95% confidence intervals
Dose-response and time-effect relationships
This structured approach enables comprehensive evaluation of osteoporosis risk factors in SLE, supporting targeted prevention strategies for this vulnerable population.

Quality assessment / Risk of bias analysis
Methodology:
We employed standardized tools to rigorously assess the quality and risk of bias in included primary studies:
Assessment Tools:
Cohort and case-control studies: Newcastle-Ottawa Scale (NOS)
Cross-sectional studies: Agency for Healthcare Research and Quality (AHRQ) scale
NOS Scale Criteria:
Evaluated through three domains (8 items):
Selection (4 stars): Case definition, representativeness, control selection, control definition
Comparability (2 stars): Control for confounding factors
Exposure/Outcome (3 stars): Exposure ascertainment, method, non-response rate
Scoring: 9-star system, ≥7 stars = high quality, 5-6 = medium, ≤4 = low quality
AHRQ Scale Criteria:
11 items rated as "yes"/"no"/"unclear":
"Yes" = 1 point, "no" or "unclear" = 0 points

Total score 11, ≥8 = high quality, 6-7 = medium, ≤5 = low quality.

Strategy of data synthesis A standardized extraction form will capture study characteristics, participant demographics, exposure details, and outcome measures. Dual independent extraction with consensus resolution will ensure accuracy.
Statistical Methods
Effect Measures: Pooled proportions with 95% CIs for prevalence; ORs with 95% CIs for risk factors
Model Selection: Random-effects models if $I^2 \geq 50\%$; fixed-effects if $I^2 < 50\%$
Heterogeneity: Quantified using I^2 statistic with thresholds: 25% (low), 50% (moderate), 75% (high)
Analytical Approach
Primary Analysis: Inverse variance method for continuous data; Mantel-Haenszel for dichotomous outcomes
Subgroup Analyses: By diagnostic criteria, geographical region, patient characteristics, and study design
Sensitivity Analysis: Excluding low-quality studies (NOS ≤4, AHRQ ≤5) and assessing outlier influence
Bias Assessment
Publication Bias: Funnel plots and Egger's test ($p<0.05$ indicating significance)
Quality Integration: Stratified analysis by study quality scores
Robustness Testing: Comparison across statistical models
Data Presentation
Forest plots for individual and pooled estimates
Summary tables of study characteristics
Quality assessment results integration
This comprehensive strategy ensures transparent, rigorous synthesis of SLE-related bone health outcomes through systematic data integration and robust statistical methodology.

Subgroup analysis This study plans to conduct comprehensive subgroup analyses to explore potential sources of heterogeneity and assess result robustness. Analyses will be stratified by:
Primary Subgroup Categories:
Diagnostic Criteria: WHO standard (T-score ≤ -2.5) vs other criteria
Geographical Regions: Asia, Europe, North America, etc.
Population Characteristics:
Gender (male, female, mixed populations)
Age groups (adults, premenopausal women, postmenopausal women)
Menopausal status (pre- vs post-menopausal)
Methodological Factors:
Study designs (cross-sectional, cohort, case-control)
Study quality (high, medium, low quality)
Clinical Features:
Glucocorticoid usage (users vs non-users)
Dose stratification (≤10mg/day vs >10mg/day)
Analytical Methods:
Random-effects models for each subgroup
Between-group heterogeneity tests to assess statistical significance
Meta-regression for continuous variables (e.g., mean age, disease duration).

Sensitivity analysis We will perform sensitivity analyses to evaluate the robustness of pooled results, identify influential individual studies, and explore sources of heterogeneity.
Primary Methods:
Leave-one-out analysis: Sequentially remove each included study and re-run the meta-analysis. Significant changes in the pooled effect size (e.g., prevalence, OR) or heterogeneity (e.g., I^2 reduction >50%) upon removal of a study will flag it as a potential source of heterogeneity.
Quality-stratified analysis: Conduct analysis using only high-quality studies (e.g., NOS≥7, AHRQ≥8) to assess the impact of lower-quality studies on the conclusions.
Model comparison: Compare results from fixed-effect and random-effects models to test the stability of conclusions against model selection.
Focus:
We will examine whether point estimates and confidence intervals for key outcomes (e.g., overall prevalence, OR for glucocorticoid use) change significantly after excluding studies with very small sample sizes, older publication dates, or low quality scores. This process verifies if main findings are robust and not driven by outliers.

Country(ies) involved China.

Keywords Systemic lupus erythematosus; Osteoporosis; Bone loss; Prevalence; Risk factors.

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