The impact of environmental factors on the immunopathogenesis of osteoporosis: A systematic review

Nurhasan Agung Prabowo[1,6*], Soetrisno[1,2], *Ida* Nurwati[1,3], *Tonang Dwi* Ardyanto[1,4], *Eti* Poncorini[1,5], *Arief* Nurudhin[1,6], *Paramasari* Dirgahayu[1,7]

[1] Doctoral Program of Medical Sciences, Faculty of Medicine, Universitas Sebelas Maret, 57126, Suarakarta, Indonesia
[2] Obstetrics and Gynecology Department, Faculty of Medicine, Universitas Sebelas Maret, 57126, Suarakarta, Indonesia
[3] Biochemistry Department, Faculty of Medicine, Universitas Sebelas Maret, 57126, Suarakarta, Indonesia
[4] Clinicopathologic Department, Faculty of Medicine, Universitas Sebelas Maret, 57126, Suarakarta, Indonesia
[5] Public Health Department, Faculty of Medicine, Universitas Sebelas Maret, 57126, Suarakarta, Indonesia
[6] Internal Medicine Department, Faculty of Medicine, Universitas Sebelas Maret, 57126, Suarakarta, Indonesia
[7] Parasitology Department, Faculty of Medicine, Universitas Sebelas Maret, 57126, Suarakarta, Indonesia

Abstract. Osteoporosis is a metabolic bone disease predominantly driven by environmental variables that damage bone microarchitecture and increase the risk of fractures. This systematic study analyzes environmental variables' impact on osteoporosis immunopathogenesis. We identified studies investigating the relationship between air pollution, heavy metal exposure, and chemical exposure with immune activity in osteoporosis through searches in PubMed databases. The review's findings indicate that exposure to environmental pollutants triggers systemic inflammation and oxidative stress, contributing to an imbalance between bone formation and resorption. Fine particulate matter (PM2.5) and nitrogen dioxide (NO2) pollutants are linked to reduced bone mineral density and a heightened risk of osteoporosis. This study underscores the importance of preventive strategies and public health policies that consider reducing environmental pollutant exposure to decrease osteoporosis risk. The results further emphasise the necessity for targeted interventions to safeguard at-risk individuals against the detrimental impacts of environmental variables on bone health.

* Corresponding author: dr.Nurhasan21@staff.uns.ac.id

1 Introduction

Osteoporosis is a worldwide severe problem defined as progressive bone loss and impaired microstructure of bones, making them more fragile and prone to fracture. Osteoporosis is affected by different environmental factors such as nutrition, physical activity and [1] osteoporosis is a metabolic bone disease characterized by low bone mass and increased fracture susceptibility [2]. More than 10 million Americans aged>50 years have osteoporosis. By the year 2010, an estimated 12 million non-institutionalized cases of osteoporosis and a further 40 million instances of osteopenia will occur in those aged >50 yr [3]. It is described as the sequelae of an accumulation of a deficit between osteoblastic resultant bone formation and osteoclastic resultant bone resorption [4].

Bone homeostasis is regulated by external environmental factors that can affect a rapid response in the skeletal system [5]. Nutrition, physical activity, and stress are significant ecological factors for bone health influencing osteoporotic development. Immunopathogenesis is how the immune system contributes to disease processes. In immunopathogenesis in osteoporosis, cellular immunity-induced inflammation leads to an imbalance in bone formation and resorption, which is the main reason for the fracture risk in persons with osteoporosis [6].

Coping with Osteoporosis, the role of immunity and environmental factors in the pathogenesis and prevention of environmental contaminants, including air pollutants, heavy metals and chemicals, are known to promote inflammation and oxidative stress, leading to bone metabolism disorders and an increased risk of fractures. This systematic review seeks to explore the modulating influences of environmental factors on immune processes leading to osteoporosis development, which can help in shaping prevention strategies and implementing public health policies.

2 Methods

The systematic review complied with the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses [7,8]. We systematically searched PubMed to identify peer-reviewed studies evaluating environmental factors' effects on osteoporosis's immunopathogenesis. The search strings used were ("Osteoporosis" AND "Immunopathogenesis" AND air pollution OR chemical). The research described in this review was published from 2012 to 2024. Observational studies included SLE patients and full papers; non-eligible publications are reviews, editorial content, letters and conference papers

After loading the search results into an Endnote library, two reviewers independently assessed them according to their titles and abstracts. To determine the inter-rater reliability for the review, both reviewers evaluated the papers based on the eligibility criteria. Search results were imported into an Endnote library, and two independent reviewers assessed the records against our inclusion criteria based on titles and abstracts. Both reviewers evaluated the papers according to the eligibility criteria for inter-rater reliability. We employed basic kappa analysis to assess the agreement, which was nearly flawless (kappa = 0.96). Two reviewers (NAP, TDA) evaluated the whole texts of each included paper, while a third reviewer (N) adjudicated any disputes over eligibility. Exclusion reasons were documented.

Table 1 presents the factors used to characterise this review's various studies. Three independent reviewers (NAP, TDA, and AN) extracted data on pertinent clinical outcomes, trial characteristics, and patient demographics. We evaluated the evidence following the Grading of Recommendations Assessment, Development, and Evaluation methodology. Each study was assessed for quality and risk of bias using the ROBINS-I tool evaluating seven domains (confounding; selection of participants, classification of exposure, deviations

from intervention, missing data, measurement of outcome, and selection report). Due to heterogeneity in study designs, populations, exposure assessment methods and outcomes, a meta-analysis was impossible; therefore, we provided a narrative synthesis. With this review, we aim to underline the influence of environmental & lifestyle factors—namely air pollution and smoking on osteoporosis. This work will inform public health initiatives and future osteoporosis prevention by identifying modifiable risks.

3 Results

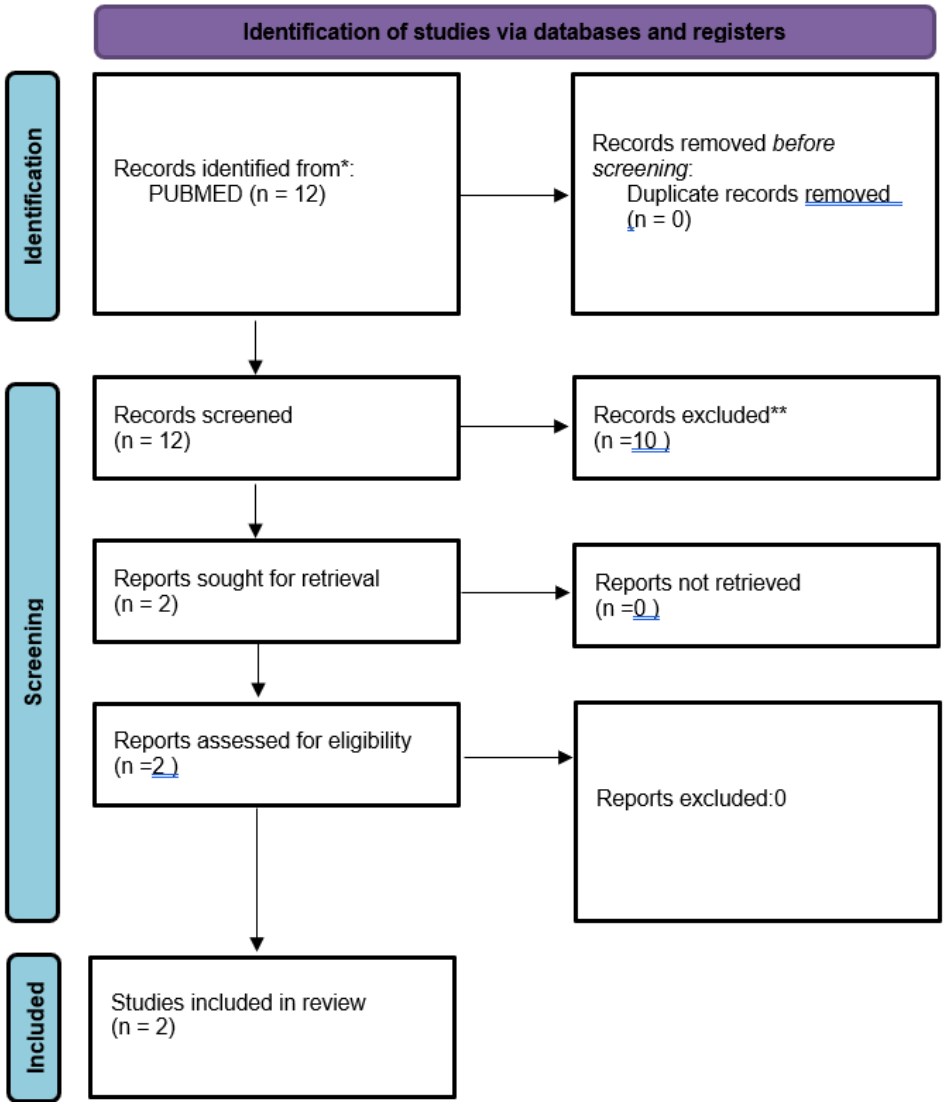

Figure 1. PRISMA Flow Diagram

A complete description of the studies included in this systematic review is given in table 1, (Table 1: Study Characteristics and Quality Assessment) presenting important information from each study. This table outlines relevant clinical outcomes, characteristics of the trials,

and patients in the studies, along with our quality assessments based on the Newcastle-Ottawa Scale. This accompanying summary aids in comprehending the variables and evidence base, which provide input into our analysis.

Table 1. Study Characteristics and Quality Assessment

Characteristic	**Taiwan Study (NHIRD)** [9]	**UK Biobank Study** [10]
Population	36,608 participants	430,120 participants
Study Design	Retrospective cohort	Prospective cohort
Average Age (SD)	62.3 years (±8.84)	56.54 years (±8.09)
Gender (%)	Male: 50.6%; Female: 49.4%	Male: 45.7%; Female: 54.3%
Pollutants Assessed	CO, NO2	PM2.5, PM10, NO2, NOx
Pollution Exposure (Average)	CO: 200.9–295.9 ppm; NO2: 6600.8–9825.1 ppb	PM2.5: 9.98 μg/m³; NO2: 29.12 μg/m³
Main Findings	Increased OP risk (HR NO2: 1.60)	Increased OP risk (HR PM2.5: 1.046)
Measurement Method	National Health Insurance Database (NHIRD), environmental exposure data from Taiwan EPA	Land Use Regression Model (ESCAPE), UK Biobank data
Covariate Adjustments	Age, gender, urbanization, comorbidities	Age, gender, Townsend deprivation index (TDI), genetics
Genetic Factors	Not assessed	Genetic risk scores (GRS) for osteoporosis
GRADE	Moderate-quality evidence	High-quality evidence

The Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool assesses the methodological quality of non-randomized studies. This tool evaluates seven key domains that may introduce bias into study results: confounding, participant selection, exposure classification, deviations from intended interventions, missing data, outcome measurement, and result selection. Each domain is rated to provide an overall risk of bias, categorized as low, moderate, severe, or critical. Two independent reviewers conducted the assessments for this review, with a third reviewer resolving any disagreements. The ROBINS-I assessment aids in determining the reliability and validity of findings by systematically addressing potential sources of bias.

Table 2. The Risk of Bias in Non-Randomized Studies of Interventions

study	Confounding	Selection Bias	Exposure Classification	Missing Data	Outcome Measurement	Overall Bias
Taiwan Study	Moderate	Low	Low	Moderate	Moderate	Moderate
UK Biobank Study	Low	Low	Low	Low	Low	Low

4 Discussion

Osteoporosis immunopathogenesis consists of an interaction between immune cells and bone cells, leading to an imbalance within the dynamics of bone remodelling [11]. Chronic, low-grade inflammation is an essential component of the pathogenesis, whereby pro-inflammatory cytokines (e.g., TNF-α, IL-1, and Il-6) induce osteoclast formation and activity, leading to an uptick in bone resorption that outstrips new-phase bone formation by osteoblasts. The RANKL/RANK/OPG pathway is central to this process; inflammatory cytokines increase the upregulation of RANKL expression and stimulate osteoclastogenesis [12]. T cells, especially Th17-type expression, play an essential role in this process via IL-17 to induce additional osteoclastogenesis. Antibody production and secretion of cytokines by B cells are also engaged. Oxidative stress, usually caused by environmental toxins, can directly damage bone cells and prevent the formation of new bones, preventing a balance between bone resorption and formation [9].

Indeed, the immunopathogenesis of osteoporosis can be altered due to environmental factors such as air pollution and heavy metal exposure [13]. Such exposures activate systemic inflammation and promote oxidative stress, disturbing the bone remodelling balance [14]. Air pollution is an important modifiable risk factor for the global burden of non-communicable diseases. Fine particulate matter (PM2. Airborne fine particles (PM2. This phenomenon contributes to pre-existing statuses such as cardiovascular disease and results in worsening risks of myocardial infarction, stroke and heart failure. In addition, long-term exposure to air pollution is associated with respiratory diseases, including asthma and chronic obstructive pulmonary disease (COPD), which reduce lung function and increase exacerbation [15]. Furthermore, emerging evidence suggests that air pollution adversely affects organ systems beyond the cardiorespiratory system, including the nervous, reproductive, and metabolic systems, underscoring the systemic nature of this hazard to human health [16].

Yu et al.'s study (N = 391,850) examines the association of air pollution with osteoporosis risk modification for genetic predisposition using data from the UK Biobank [9]. Combined effects of different air pollutants (PM2. 5, PM10, PM2. To evaluate the association of long-term exposure to nitrogen oxides and particulate matter (PM2. Capitalizing on a large sample, they used observational and genetic analyses (including construction of genetic risk scores) to evaluate single and joint impacts of pollutants. Establishing the joint effects of myriad air pollutants and genetic susceptibility on osteoporosis risk is particularly challenging, with prior studies limited by cross-sectional designs. Uncontrolled time-series analyses were conducted on data from 1642 women, which showed a positive association between air pollutant exposure to osteoporosis and fractures [9]. The negative association of air pollution exposure was stronger in those genetically at higher risk for osteoporosis. This implies that the detrimental effect of air pollution on bone health is amplified by genetic susceptibility (gene−environment interaction). Osteoporosis is a condition mostly associated with genetics. Still, the current research stressed that researchers should not neglect the environmental factors as well, and this was important in assessing osteoporosis risk among vulnerable populations while emphasising strategies to reduce exposure to air pollution that need adjuvant for people genetically at high bone fragility.

Chang et al. conducted a study on the association between exposure to air pollution and osteoporosis risk [10]. Using data from the Taiwan National Health Insurance Research Database, researchers examined data on more than 480,000 adults with acute upper respiratory infections. Air pollution exposure was evaluated according to the population-weighted mean concentrations of PM10, SO2, NO2, CO and O3 based on the subjects' cities of residence. This study controlled for several potential confounding factors: age, sex,

urbanization and comorbidities. The findings [10] showed a significant association between exposure to air pollution and an increased risk of osteoporosis. The risk of osteoporosis in those exposed to higher levels of air pollution after other factors such as age, sex and smoking were taken into account (adjusted OR) for PM10 (1.18 [1.03-1.35]), SO2 (2.67 [0.88-8.21]), NO2 (1.32 [0.88-2,00]), CO (3 months average 24 hr mean) (5,17[0,79--33,62]) This association remained significant following adjustment for potential confounders. The present study indicates that air pollution should be ranked among the risk factors of OP, and therefore, efforts to decrease exposure to air pollution might play a role in OP prevention. For osteoporosis, ambient air pollution and environmental-level factors lead to systemic inflammation and oxidative stress, disrupting the balance between osteogenesis and osteoclast activity. Several studies have shown that exposure to particulate matter and other air pollutants is linked to lower bone mineral density and a greater risk of osteoporosis and fractures [11–14]. Such mechanisms include upregulation of inflammatory pathways, induction of oxidative stress and alteration in osteoblast and osteoclast function, culminating in net bone loss.

In Osteoporosis, there is a link between heavy metal pollution and immunopathogenesis. This is supported by several studies that proposed a link between heavy metals, such as lead, cadmium and mercury and osteoporosis risk [17]. Such toxic metals can disturb calcium metabolism, imbalance the cycle of new bone formation and resorption, and cause oxidative stress and inflammation, contributing to the development of osteoporosis [18,19]Exposure to specific industrial chemicals (such as persistent organic pollutants and endocrine-disrupting compounds) has been associated with a higher risk of osteoporosis. These substances interfere with hormone signalling, disrupt bone remodelling, and provoke inflammatory responses, decreasing bone mineral density and increasing fracture risk [20]. In addition, environmental influences like heavy metals, pesticide exposure, and endocrine-disrupting chemicals may cause hormonal changes, metabolic syndrome, and possible disruption of vitamin D metabolism. They can also directly affect bone cell function, ultimately leading to osteoporosis [9,10,21].

While covering several studies, this systematic review is still limited in some aspects. A significant limitation is the risk of study selection bias because we were most likely to have included studies indexed on large databases and published in English. The restriction can eliminate significant results from studies published in other languages or small journals, possibly biasing the collective conclusion. In addition, the heterogeneity of study designs, populations, and methods of measuring environmental exposures and osteoporosis outcomes in included studies may limit generalizability. The overwhelmingly observational nature of most included studies also limits causal inference, demonstrating the impact of residual confounding.

These limitations can be addressed in future work by enabling a more exhaustive extraction of studies, including published studies in other languages and from different geographic and cultural placements, that would improve the generalisability of the results. Further prospective longitudinal studies are required to determine whether a multitude of environmental exposures influences the development of osteoporosis. Moreover, at a minimum, utilizing standardized techniques to assess both environmental exposures and osteoporosis (except for specific site-effect associated clinical endpoints) will facilitate the comparability of results from different studies. Lastly, promoting research designs that could adequately control for the confounders will lead to more robust evidence to support broad public health and policy measures towards preventing osteoporosis across population groups.

5 Conclusion

Environmental exposure has a profound influence on the immunopathogenesis of osteoporosis, as confirmed by this systematic review. Environmental pollution and toxic exposure (air, heavy metals) can be potent stimulators of systemic inflammation and oxidative stress that may dysregulate the coupling of bone formation to bone resorption, enhancing the risk of osteoporosis and fractures.

We acknowledge funding from Lembaga Penelitian dan Pengabdian kepada Masyarakat (LPPM) Universitas Sebelas Maret (UNS), contract no 196.2/UN27. 22/PT.01. 03/2024.

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