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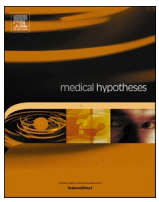

Traffic-derived metal bioaccumulation in bone tissue as a driver of osteoporosis

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ABSTRACT

Long-term air pollution exposures, particularly to fine particulate matter, have been linked to a wide range of health issues, including cardiovascular and respiratory diseases. Recent studies have expanded this scope to include skeletal disorders, such as osteoporosis and bone fragility. This is particularly concerning given the global burden of osteoporosis, which affects 500 million people worldwide and causes 13.5 million fractures annually. While traditional air pollution sources like exhaust emissions have been extensively studied, the role of non-exhaust sources, such as brake and tyre wear, remains largely unexplored. These non-exhaust sources are becoming a critical environmental concern, especially with the adoption of heavier electric vehicles. We hypothesize that lifetime accumulation of metals from non-exhaust traffic emissions contributes to the development of osteoporosis. This hypothesis is supported by several lines of evidence: epidemiological studies showing associations between air pollution exposures and increased fracture risk, particularly in populations living near busy roads; clinical studies demonstrating metal accumulation in the bone of individuals with osteoporosis and molecular studies showing the disruptive effects of metals on bone remodeling processes, including bone formation and resorption. To investigate this further, we propose a research approach combining *in vitro, in vivo*, *ex vivo* and computational modeling techniques. By studying the effects of metals on bone cells, analyzing the impact of metal exposure in animal models and simulating long-term exposure scenarios, we aim to elucidate the mechanisms underlying air pollution-induced bone damage. This research could inform urban planning policies, vehicle design and public health interventions protecting bone health.

Introduction

The evidence base linking airborne particulate matter (PM) with adverse cardiopulmonary health is both extensive and robust [1], but recently studies have emerged supporting associations with a more diverse range of health conditions, including impacts on brain [2] and bone heath [3]. These short and long-term health effects are strongest with the fraction of PM in the air with an average diameter of 2.5 μm and less ($PM_{2.5}$), however these associations do not frequently consider the composition, or the source contribution to this heterogeneous mixture. Where this has been done, studies have highlighted the contribution of traffic emissions to many of these health effects [4]. While extensive research has established links between tailpipe emissions (e.g., $PM_{2.5}$, NO_2) and osteoporosis, the role of non-exhaust traffic emissions (NEE)—such as brake, tyre, and road wear—remains critically underexplored despite constituting a growing proportion of ambient particulate matter. This knowledge gap is particularly concerning with the global shift toward electric vehicles (EVs), which, while reducing exhaust emissions, can exacerbate NEE due to their heavier weight [5,6]. Unlike combustion-derived pollutants, NEE-derived metals (e.g., Cd, Sb, Zn) persist in the environment and bioaccumulate in bone tissue over decades, potentially creating unique long-term risks that differ fundamentally from those posed by exhaust emissions. Our hypothesis uniquely addresses this intersection of changing vehicle technology, metal bioaccumulation kinetics and bone pathophysiology—areas that existing literature has not adequately integrated.

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NEE already account for a greater proportion of $PM_{2.5}$ and PM_{10} mass than exhaust-derived particles and yet they have received much less attention, despite their high metal content [6]. Recent evidence indicates that NEE contribute up to 85–90 % of traffic-related PM_{10} and 50–65 % of $PM_{2.5}$ in urban areas, with this proportion increasing as exhaust emissions decline due to stricter regulations [7]. These emissions contain a distinct metal signature including Cd, Sb and Ba [8] (indicative of brake wear), Zn [9] (tyre wear), Fe, Mo, Mn [10] (steel abrasion), and Al, Si [6] (road surface). Unlike gaseous pollutants from exhaust emissions, these metals persist in the environment, can be resuspended in air, and have the capacity to bioaccumulate in human tissues over decades. This persistence creates a unique exposure pattern where even low-dose chronic exposures may lead to significant health impacts through bioaccumulation, particularly in tissues with slow turnover rates such as bone. The expected increase in NEE from heavier electric vehicles (an additional 1.1 mg per vehicle kilometer for tyre wear and 1.4 mg/vkm for road wear per 280 kg weight increase) [11] makes understanding their specific health impacts increasingly urgent.

Given the tendency of NEE-derived metals to accumulate in bone, osteoporosis emerges as a plausible downstream health outcome of chronic exposure. Osteoporosis is a major global health concern, affecting 500 million people worldwide and causing 13.5 million fractures annually [12]. The economic burden is substantial, costing the global healthcare system $400 billion annually [13]. It is characterized by progressive decrease in bone mineral density and microarchitectural deterioration resulting in increased susceptibility to fragility fractures [14].

Recent studies have provided compelling evidence linking air pollution to changes in bone mineral density (BMD). In recent longitudinal cohort study on postmenopausal women long term exposure to pollutants NO and NO_2 over 1, 3 and 5 years was found to be negatively associated with various metabolites. In particular the metabolite C38:4 phosphatidylethanolamine was identified as partially mediating the effect of NO on lumbar spine BMD [15]. Complementing these findings, epidemiological and clinical studies have demonstrated an association between proximity to busy roads, an indicator of traffic related pollution, and increased risk of osteoporosis. For example, a retrospective cohort study of 529 elderly women (aged 65–91 years) in Beijing found that those residing within 50 m of busy roads exhibited a 5 % reduction in hip BMD and double the risk of hip fractures compared to individuals living more than 300 m away, with diagnoses confirmed via DEXA scans and imaging [16]. Similarly, a U.S.-based prospective cohort study of 1,175 Mexican-American adults (mean age 34 years; 72 % female) revealed that participants living within 500 m of major roads had significantly lower total body and pelvic BMD (measured by DEXA) and higher fracture risks than those residing beyond 1,500 m, using residence-specific air pollution monitoring data to estimate exposures [17,18]. These findings underscore a spatial gradient in osteoporosis risk tied to traffic pollution though they highlight associations rather than causation.

To establish cause and effect it is necessary to identify the mechanism(s) connecting traffic emissions to osteoporosis and bone fragility fractures. The mechanism remains unclear, but mounting evidence suggests that the presence of metals in roadside dust may play a crucial role.

The hypothesis

Considering the adoption of heavier EVs on roads, their potential for higher non-exhaust emissions and mounting evidence linking traffic-related pollution to osteoporosis risk, we propose the following hypothesis:

Lifetime bioaccumulation of exogenous metals from non-exhaust traffic emissions increases the risk of osteoporosis and sustaining a fragility fracture.

This hypothesis predicts that the chronic exposure to and subsequent bioaccumulation of metals from traffic pollution in bone tissue leads to structural and metabolic changes that increase the risk of osteoporosis and related fractures over an individual's lifetime.

Evolution of the hypothesis

Collectively epidemiological, toxicological, clinical and observational studies suggest a potential link between traffic-related metal emissions, their bioaccumulation in bone tissue and the development of osteoporosis. Epidemiological evidence shows a correlation between proximity to busy roads and increased risk of osteoporosis and fractures. A *meta*-analysis in 2023 of 19 studies found indications of increased risk of osteoporosis related outcomes according to different pollution exposures [3]. Each 1 ug/m^3 increase in $PM_{2.5}$ (mainly attributed to traffic pollution) was associated with a 5 % increase in prevalence of osteoporosis in all participants [19]. This data was supported by a prospective observational study reporting that PM_{10}, NO, NO_2 and SO_2 were all negatively associated with whole-body, total hip, femoral neck and lumbar spine BMD [20].

Metal containing particulates ($PM_{2.5}$ and PM_{10}), primarily from non-exhaust traffic emissions such as the abrasion of tyres, brake pads and road surfaces, are inhaled and can bioaccumulate in bone tissue over time [5]. Metal deposition in bone tissue follows distinct toxicokinetic patterns that vary significantly by element. Lead demonstrates particularly high skeletal affinity, with studies revealing that over 90 % of the total body burden in adults resides in bone tissue, with more than 70 % concentrated in dense cortical bone [21]. This accumulation exhibits a biological half-life of 10–30 years, creating a persistent endogenous exposure source long after environmental contact ceases. Cadmium, though primarily stored in kidney and liver, accumulates in bone with a half-life exceeding 15 years [22], while aluminium deposits preferentially at the mineralization front.

The molecular mechanisms driving metal sequestration include both ionic substitution and protein binding. Metals such as Pb^{2+}, Al^{3+} and Fe^{3+} can directly substitute Ca^{2+} in hydroxyapatite crystals due to their similar ionic radii but stronger electronegativity [23]. At the protein level, binding studies by [24] demonstrated that Pb^{2+} binds to osteocalcin at concentrations 4 orders of magnitude lower than Ca^{2+}, explaining its exceptionally high affinity for bone tissue. This substitution not only alters mineral composition but significantly impacts protein conformation, with circular dichroism studies showing that metal binding induces conformational changes in bone matrix proteins that affect hydroxyapatite binding capacity.

Different metals exhibit selective deposition patterns within bone microarchitecture. Previous work has reported that lead preferentially incorporates into metabolically active trabecular bone, with concentrations ranging from 1-40 μg/g in human bone biopsies, while cadmium shows greater accumulation in cortical bone (0.5–3.0 μg/g) [25]. These distribution patterns may help explain the site-specific bone loss observed in epidemiological studies of pollution exposure.

A recent clinical observational study showed evidence of this metal bioaccumulation. Metal concentrations in bone biopsies from aging people with osteoporosis were compared to people with osteopenia and normal controls. Not all metals were deposited to the same extent in bone tissue. Quantitative analyses revealed that osteoporotic bone contained significantly higher concentrations of aluminium (8.7 ± 2.1 vs. 0.9 ± 0.4 mg/kg, $p < 0.001$), cadmium (0.27 ± 0.09 vs. 0.08 ± 0.03 mg/kg, $p < 0.001$), and lead (1.8 ± 0.5 vs. 0.6 ± 0.2 mg/kg, $p < 0.001$) compared to controls. While arsenic, cobalt, chromium, copper, manganese, nickel and zinc were also elevated in osteoporotic bone, the magnitude of difference was smaller (typically 1.5–2.0 fold increases versus 3–10 fold for the primary bone-seeking metals), suggesting differential affinity and persistence patterns that may influence their potential toxicity [26]. This accumulation of metals is also associated with changes in bone turnover markers (BTM) such as P1NP and CTX as well as decreases in trabecular number, width and bone volume fraction

[27]. For this reason, inhaled airborne metals are thought to be a risk factor in the development of osteoporosis [14].

The association between exposure to metals and increased risk of osteoporosis is not unique to traffic pollution. Studies on smokers and individuals with occupational exposure to metals have shown comparable increases in osteoporosis risk. A study comparing smokers and nonsmokers diagnosed with osteoporosis provides compelling evidence for this. In people who smoked the levels of metals (cadmium, lead, arsenate) in hip, femoral neck and lumbar spine bone were significantly higher which was associated with a significantly lower total and ionized calcium levels [28]. A larger *meta*-analysis which pooled data from 86 studies and 40,753 subjects found that smokers had significantly reduced bone mass compared to the nonsmokers at all bone sites [29]. Exposure to metals such as cadmium and lead from tobacco in cigarettes is a potential contributing mechanism for reduced BMD with mainstream smoke varying from 0.18-0.78 μg and 0.97–2.64 μg for different brands on cigarette [30].

A similar relationship also exists in those with occupational exposure to metals. A study investigating occupational exposure to Pb compared a control group of office faculty to an exposure group of battery plant workers for more than one year. Urinary Pb was significantly higher in the exposed vs control group and BMD significantly lower. The study concluded that increases in urinary Pb significantly increase the prevalence of osteoporosis in a linear manner [31]. Another study reported that occupational exposure to Cd in a radiator factory was associated with osteoporosis and fracture risk in 83 male workers. After adjusting for age and current smoking the study concluded that for each doubling of urinary Cd concentration was associated with a 1.47-fold (95 % CI 1.03–2.10) increase in the risk of osteoporosis and there is a dose-dependent relationship between exposure to cadmium in the factory workers and risk of osteoporosis [32].

Proposed mechanisms of toxicity

Taken together, the epidemiological, cohort and clinical observational studies above provide strong evidence of a link between metal exposure and osteoporosis, but the evidence is not strong enough to establish case and effect. A mechanism or mechanisms of toxicity must be identified and many potential pathways have been proposed. The potential mechanisms by which metals might increase the risk of osteoporosis and bone fragility fractures can be categorized into effects on bone chemistry and structure and effects on bone cell metabolism.

Metal such as Pb^{2+}, Al^{3+} and Fe^{3+} accumulate in bone hydroxyapatite by substituting divalent cations such as calcium (Ca^{2+}) due to stronger electronegative affinity for mineral phosphate. Hydroxyapatite bind assays show that Pb^{2+} binds to osteocalcin (a non-collagenous protein) at a concentration 4 orders of magnitude lower than Ca^{2+} [24]. This direct substitution not only weakens the matrix but also disrupts bone remodeling promoting osteoclastogenesis and inhibiting osteoblastogenesis [27].

Metals also indirectly affect bone through disruption of several pathways, the most critical being the Wnt/β-catenin signaling cascade (Fig. 1). This pathway regulates bone homeostasis by promoting osteoblast-mediated bone formation and suppressing osteoclast-driven resorption [23]. Metals such as lead and cadmium generate reactive oxygen species (ROS), which impair Wnt/β-catenin signaling, thereby reducing osteoprotegerin (OPG) production. OPG normally inhibits the receptor activator of nuclear factor kappa-B ligand (RANKL), a key driver of osteoclast activation. By downregulating OPG, metals tilt the RANK/RANKL/OPG axis toward excessive bone resorption, accelerating osteoporotic bone loss [23].

Metals can also indirectly affect bone via endocrine and renal disruption. Under normal conditions estrogen has a protective effect on bone downregulating RANKL production. However, exposure to metal upregulates inflammatory mediators (cytochrome P450) which increases estrogen metabolism and promotes osteoclastogenesis [34,35]. The kidneys are responsible for reabsorption of calcium into the blood and maintenance of the body's acid-base balance. Metals damage the kidneys which through various cellular mechanisms resulting in high PTH (parathyroid hormone) and metabolic acidosis [27]. These result in

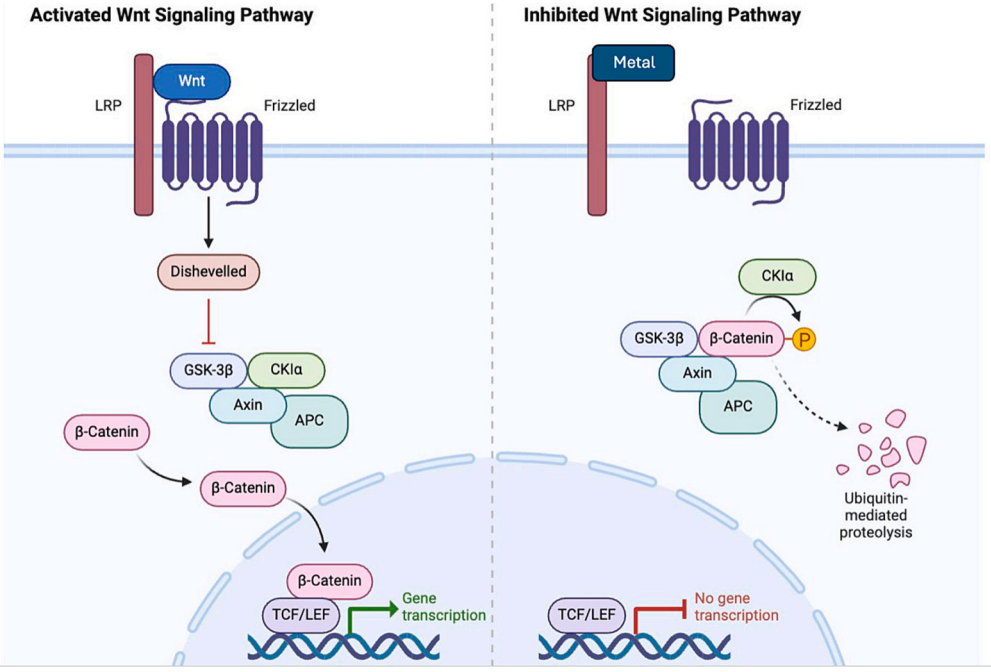

Fig. 1. The Wnt/ β-catenin signaling pathway in bone remodeling. Wnt proteins bind to cell surface receptors (LRP/Frizzled), stabilizing β-catenin translocates to the nucleus to activate genes promoting osteoblast activity and OPG synthesis. Metals disrupt this process via ROS generation, reducing OPG and exacerbating osteoclastogenesis. Abbreviations: APC = adenomatous polyposis coli; CK1α = casein kinase 1 alpha; GSK3β = glycogen synthase kinase 3 beta; LRP = low-density lipoprotein receptor protein; P = phosphate. []
Adapted from Sølling et al. 33.

increased bone resorption.

Together, these proposed mechanisms suggest that chronic, low-dose exposure to complex metal mixtures from traffic-related emissions could impact bone health through pathways that differ in important ways from those documented in occupational metal exposures. While occupational studies typically examine higher-dose exposures to specific metals in workplace settings (such as cadmium in battery plants or lead in radiator factories), traffic-derived exposure presents a distinct challenge characterized by: 1) Complex metal mixtures rather than single-metal exposures, creating potential synergistic or antagonistic effects not observed in occupational settings; 2) Lifelong, continuous exposure patterns affecting all age groups versus time-limited workplace exposures in adults; 3) Highly variable exposure concentrations that fluctuate with traffic patterns, weather conditions, and urban microenvironments; and 4) Co-exposure to other traffic-related pollutants that may modify metal toxicity.

Furthermore, while occupational exposures typically affect specific worker populations with relatively uniform exposure parameters, traffic-derived metals affect diverse populations including children, the elderly, and those with pre-existing conditions who may exhibit different susceptibilities to metal-induced bone damage. These distinctive aspects of traffic-derived metal exposure may trigger bone remodeling disruptions through multiple simultaneous pathways, affecting both the structural integrity of bone and the cellular processes involved in bone remodeling, potentially creating cumulative effects not observed in higher-dose but more time-limited occupational exposures.

The combination of these direct and indirect effects may explain the observed association between traffic pollution exposure and increased risk of osteoporosis and fragility fractures. The interplay of these mechanisms—direct substitution, Wnt pathway inhibition, RANKL/OPG imbalance and systemic hormonal/renal disruptions—creates a self-reinforcing cycle of bone degradation (Fig. 1). Over time, chronic metal exposure reduces trabecular thickness, connectivity and bone volume fraction, culminating in osteoporosis and fragility fractures [27].

Hypothesis testing and limitations

To test this hypothesis, we propose a structured, multi-phase research approach with clear prioritization and staged validation logic. Our framework begins with cell culture studies to identify the most relevant metals and mechanisms for further investigation. These findings will directly inform the second phase, where animal studies and computational modeling will proceed concurrently to validate cellular observations at the organism level and simulate long-term exposure effects. Finally, human studies will address systemic interactions not captured in earlier phases, completing the translational pathway from cellular mechanisms to clinical relevance. This sequential approach ensures each phase builds upon previous findings, creating a robust validation framework while maximizing resource efficiency. The specific methodologies for each phase are detailed below.

Cell culture studies

To investigate the impact of metals on bone cell function *in vitro* approaches utilizing pre-osteoblasts and osteoclasts could be used, with cells exposed to sterilized metals solutions, simulating metallic particle exposures, or source specific PM reflecting various NEE sources. Key parameters to examine would include cell proliferation, differentiation and viability, including alkaline phosphatase (ALP) [36], and tartrate-resistant acid phosphatase (TRAP) staining [37]. This experimental design would also allow the evaluation of bone cell activity including matrix production: collagen mineralization using alizarin red staining and the measurement of bone resorption on dentin slices [38]. Cell culture studies could also be used to test the effect of metals in combination with one another. Evidence suggests that metals such as As and Cd have opposing effects on bone metabolism and can interact with each other in the environment [2]. To investigate this a phased approach is required, first testing the effect of individual metals (Pb, Cd) on cells, then synergistic combinations. The outcome here could help identify the most appropriate metal(s) to test in animal and computational studies.

Animal studies

The causal mechanism between traffic pollution and bone health could be investigated using mouse models [39] allowing the bioaccumulation of metals from traffic emissions to mirror the lifetime exposure of human populations. Mice could be kept in isolated ventilated cages (IVC) and exposed to PM from traffic pollution as it occurs in real time [40] simulating how humans are continuously exposed to traffic pollution. To strengthen translational relevance, the PM dose for mice would closely mirror human exposure levels, expressed in $\mu g/m^3$. Alternatively, traffic pollutants could be delivered directly into the trachea of the mouse via intratracheal instillation ensuring precise dosing of pollutant without relying on breathing mechanisms [41]. Mouse models have already been successfully used to test the effect of lifetime exposure to metal emissions on brain and lung health [42]. Investigations using this model have reported that short term exposure caused lung inflammation, with chronic exposure causing airway fibrosis and emphysema [42,43]. These effects are transgenerational, with exposure in pregnancy resulting in altered lung, kidney, liver and brain function in offspring. The same models could be used to study the effect of traffic exposure in bone and bone health across a lifetime and across generations.

Computational modelling

Concurrently with animal studies mathematical models iteratively designed by Lemaire, Pivonka and Scheiner could be further developed to simulate the effects of metal accumulation on bone remodeling. The models could be modified to incorporate parameters for metal induced changes such as reduced differentiation rate or increased apoptosis rate of osteoblasts to determine structural changes in bone due to metal accumulation [44,45]. This would be a low-cost method to test the mechanisms proposed of metal toxicity. Predictions from these in silico models could be bench-marked and validated using human bone, under stress in a bioreactor [46]. This approach would not allow modelling of systemic interactions, such as the hormonal response, to metal toxicity. This would be investigated in human studies.

Human studies

Ex vivo studies with human bone samples offer a robust method to investigate how metals affect bone health. Samples can be categorized into two groups: normal bones (e.g., collected from trauma patients) and exposed bones (e.g., from patients undergoing joint replacements in high-pollution areas). Inductively Coupled Plasma Mass Spectrometry (ICP-MS) provides precise quantification of metals such as cadmium, lead and aluminum, which are known to bioaccumulate in bone tissue by substituting calcium ions in hydroxyapatite. This substitution compromises bone strength and microarchitecture [47]. Advanced imaging techniques like micro-CT can reveal microstructural deterioration, such as reduced trabecular thickness and connectivity, associated with metal accumulation [14]. Although human studies would provide the most efficacious results, they also come with limitations. Using air quality data or proximity to roads as a proxy for measuring individual exposure to metal pollution may not be accurate due to personal protective measures and time spent indoors. Achieving a sufficiently diverse sample population to test these mechanisms would also be challenging.

Overlapping theories of bone damage

Alternative environmental health theories could overlap with our metal bioaccumulation hypothesis. Traffic emissions contain a complex mixture of pollutants including dust, particulates, soot, and various hydrocarbons [11], making it challenging to isolate the effects of metals alone. Two prominent competing mechanisms could explain similar bone damage patterns observed in populations exposed to traffic pollution.

Systemic inflammation pathway

Non-metal components of traffic pollution might trigger inflammatory responses that indirectly damage bone through cytokine signalling cascades. Exposure to air pollutants such as nitrogen dioxide and particulate matter can induce production of pro-inflammatory cytokines including tumour necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, and IL-17, which affect osteoblast and osteoclast differentiation and function, potentially disrupting bone homeostasis [48]. These inflammatory processes are established mechanisms for bone demineralization and osteoporosis [49]. The systemic inflammation pathway suggests that airborne particulates may not need to contain metals to cause bone damage; rather, their ability to trigger inflammatory cascades throughout the body could be sufficient to disrupt normal bone remodelling processes regardless of composition.

Endocrine disruption pathway

Many environmental pollutants in traffic emissions possess the ability to interfere with the functioning of the endocrine system and are classified as endocrine disrupting chemicals (EDCs) [50]. Polycyclic aromatic hydrocarbons (PAHs), produced by incomplete combustion of organic substances and present in vehicle emissions including diesel exhaust, are known endocrine disruptors that can affect oestrogen receptors and aryl hydrocarbon receptors [51]. These organic compounds may alter bone remodelling independently of metal toxicity through disruption of hormonal signalling that regulates bone metabolism. Environmental EDCs can interfere with oestrogen signalling, vitamin D metabolism, or parathyroid hormone function, all of which play crucial roles in maintaining bone homeostasis. This disruption could potentially mimic the effects of metal-induced bone damage, creating similar clinical presentations through entirely different mechanistic pathways.

Distinguishing mechanisms through testable predictions

To differentiate our metal-specific hypothesis from these alternative mechanisms, we propose several testable predictions across different experimental models. In cell culture studies, exposure of osteoblasts and osteoclasts to sterilized metal solutions will reduce cell proliferation and alter differentiation to an equal or greater extent than exposure to non-metal PM fractions from NEE sources. Additionally, these effects will persist even when inflammatory pathways are blocked using cytokine inhibitors, which would indicate direct effects of metals rather than inflammation-mediated damage.

In animal studies, instillation of metal-rich PM in comparison to metal-poor PM with equivalent inflammatory potential will induce more severe trabecular bone loss. Furthermore, this bone loss will correlate specifically with bone metal content rather than with systemic inflammatory markers, which would support metal bioaccumulation as the primary driver of bone damage.

In human studies, bone samples from individuals exposed to high traffic areas will show significantly higher levels of specific metals, and these levels will correlate more strongly with bone microarchitectural deterioration than markers of systemic inflammation or hormonal disruption. Such findings would provide compelling evidence that metal bioaccumulation, rather than alternative pathways, represents the predominant mechanism linking traffic pollution to osteoporosis risk.

Fulfilling these predictions would help distinguish our proposed metal bioaccumulation mechanism from overlapping pathways of bone damage and establish it as the primary driver of pollution-induced osteoporosis. The systematic testing of these predictions across multiple experimental systems would provide robust evidence for determining the relative contributions of these distinct but potentially coexisting mechanistic pathways.

Mitigating metal toxicity of bone

There is scope to investigate and develop interventions aimed at mitigating against the potentially harmful effects of metal accumulation on bone health. Reducing exposure to metals is the first step. Regulations for metal emissions in occupational settings, such as factories and public health initiatives should warn against the dangers of prolonged metal exposure on bone health and attempt to reduce exposures. Any subsequent bioaccumulation of metal could be negated by pharmacological approaches. Anti-resorptive agents such as bisphosphonates and denosumab can inhibit bone resorption to preserve bone mass. Anabolic agents such as romosozumab or abalaoparatide enhance osteoblast activity to stimulate bone formation [27]. Chelation therapy with deferoxamine or with EDTA (ethylenediaminetetraacetic acid) to facilitate removal and excretion of metals [52]. However, this is less effective in reducing metal that has already sequestered in bone making the timing of treatment important [27].

For this reason, there is a need to develop biomarkers for early detection of metal induced changes in bone, specifically in those who live in close proximity to main roads. A potential protocol is regular monitoring of blood and urine metals as well as bone turnover markers regularly used in clinical practice; serum osteocalcin for bone formation, c-terminal telopeptide (CTX) for bone resorption [53]. Supplementary DEXA and micro-CT scans could assess trabecular thickness, trabecular number, trabecular separation in ‘at risk’ individuals [27]. Other markers to investigate as elevated amino acids (lysine, taurine, proline, glutamine, threonine, tyrosine) or lipids (11,14-eicosadienoic acid, oleic acid, linoleic acid, and arachidonic acid) both associated with reduced BMD [54]. An area of emerging research incorporating these concepts involves the use of multiscale models. By combining patient-specific genetic and lifestyle data these models could enhance fracture risk prediction beyond DEXA based measurements. For instance, individuals identified as ‘high risk’ due to their proximity to roads could receive prophylactic treatments to improve their bone strength before changes to bone are detected on traditional scans. Additionally, models integrating patient-specific bone microarchitecture and collagen-mineral interactions could inform the development of therapeutics that act on aspects of bone fragility specific to each patient. Personalised prevention protocols such as these could reduce incidence of bone fractures improving patient’s quality of life [55].

Conclusions

The proposed hypothesis linking bioaccumulation of exogenous metals from NEE to increased risk of osteoporosis and fragility fractures represents a critical intersection of environmental pollution and public health. Our synthesis of current evidence reveals a compelling pattern: epidemiological studies show increased fracture risk near high-traffic areas, clinical observations demonstrate elevated metal concentrations in osteoporotic bone and molecular studies illuminate mechanisms by which metals disrupt bone homeostasis.

The implications of this hypothesis extend beyond academic interest. As urban populations grow and electric vehicle adoption accelerates, non-exhaust traffic emissions are likely to increase. If validated, our hypothesis would necessitate significant policy responses, including:

- Revised vehicle emissions standards that consider non-exhaust emissions, particularly for heavier electric vehicles
- Wider adoption of redesigned cars meeting Euro 7 emissions standards [56].
- Urban planning strategies to minimize population exposure to traffic-related metals
- Enhanced monitoring of bone health in populations living near high-traffic areas
- Development of targeted interventions such as chelation therapies for at-risk individuals

The proposed multi-faceted testing approach, combining *in vitro* studies, animal models, computational simulations and human tissue analysis, provides a roadmap for establishing causation and quantifying risk. Moreover, understanding the mechanisms of metal-induced bone damage could lead to novel therapeutic strategies, such as targeted chelation therapy or pathway-specific interventions to protect bone health.

Looking ahead, this work may help bridge the gap between environmental science and clinical medicine, potentially transforming our approach to both traffic pollution management and osteoporosis prevention. The global burden of osteoporotic fractures demands such innovative perspectives, particularly as urbanization and vehicle emissions continue to rise worldwide.

Ethics Statement.

This article is a hypothetical work. Ethical approval was not needed for this article. Manuscript does not need ethics statement.

CRediT authorship contribution statement

Meeran Hamawandi: Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **Xing Zhou:** Writing – original draft. **Ian Mudway:** Writing – review & editing, Conceptualization. **Ulrich Hansen:** Conceptualization. **Suk-Yu Yau:** Writing – review & editing. **Richard L. Abel:** Writing – review & editing, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Fuller, G., Freidman S., Mudway I., (2023). Impacts of air pollution across the life course – evidence highlight note. Avaliable at [https://www.london.gov.uk/sites/default/files/2023-04/Imperial%20College%20London%20Projects%20-%20impacts%20of%20air%20pollution%20across%20the%20life%20course%20%E2%80%93%20evidence%20highlight%20note.pdf].

[2] Delgado-Saborit JM, Guercio V, Gowers AM, Shaddick G, Fox NC, Love S. A critical review of the epidemiological evidence of effects of air pollution on dementia, cognitive function and cognitive decline in adult population. Sci Total Environ 2021;757:143734. https://doi.org/10.1016/j.scitotenv.2020.143734.

[3] Mousavibaygei SR, Bisadi A, ZareSakhvidi F. Outdoor air pollution exposure, bone mineral density, osteoporosis, and osteoporotic fractures: a systematic review and meta-analysis. Sci Total Environ 2023;865:161117.

[4] Boogaard H, Patton AP, Atkinson RW, Brook JR, Chang HH, Crouse DL, et al. Long-term exposure to traffic-related air pollution and selected health outcomes: a systematic review and meta-analysis. Environ Int 2022;164:107262.

[5] Timmers VRJH, Achten PAJ. Non-exhaust PM emissions from electric vehicles. Atmos Environ 2016;134:10–7. https://doi.org/10.1016/j.atmosenv.2016.03.017.

[6] Fussell JC, Franklin M, Green DC, Gustafsson M, Harrison RM, Hicks W, et al. A review of road traffic-derived non-exhaust particles: emissions, physicochemical characteristics, health risks, and mitigation measures. EnvironSci Technol 2022;56(11):6813–35.

[7] Air Quality Expert Group (2019). *Non-Exhaust Emissions from Road Traffic*. [online] Availableat:https://ukair.defra.gov.uk/assets/documents/reports/cat09/1907101151_20190709_Non_Exhaust_Emissions_typeset_Final.pdf.

[8] Selley L, Schuster L, Marbach H, Forsthuber T, Forbes B, Gant TW, et al. Brake dust exposure exacerbates inflammation and transiently compromises phagocytosis in macrophages. Metallomics 2020;12(3):371–86.

[9] O'Loughlin DP, Haugen MJ, Day J, Brown AS, Braysher EC, Molden N, et al. Multi-element analysis of tyre rubber for metal tracers. Environ Int 2023;178:108047.

[10] Kelly F, Armstrong B, Atkinson R, Anderson HR, Barratt B, Beevers S, et al. HEI health review committee. The London low emission zone baseline study. Res Rep Health Eff Inst 2011;163:3–79.

[11] Jin HJ, Bae YK, Kim M, Kwon S-J, Jeon HB, Choi SJ, et al. Comparative analysis of human mesenchymal stem cells from bone marrow, adipose tissue, and umbilical cord blood as sources of cell therapy. Int J Molecular Sciences 2013;14(9):17986–8001. https://doi.org/10.3390/ijms140917986.

[12] Javaid MK, Pinedo-Villanueva R, Shah A, Mohsin Z, Hiligsmann M, Motek-Soulié A, et al. The Capture the Fracture® Partnership: an overview of a global initiative to increase the secondary fracture prevention care for patient benefit. Osteoporos Int 2023;34(11):1827–35. https://doi.org/10.1007/s00198-023-06759-x.

[13] Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. Arch Osteoporos 2013;8(1–2). https://doi.org/10.1007/s11657-013-0136-1.

[14] Battistini B, Greggi C, Visconti VV, Albanese M, Messina A, De Filippis P, et al. Metals accumulation affects bone and muscle in osteoporotic patients: a pilot study. Environ Res 2024:118514. https://doi.org/10.1016/j.envres.2024.118514.

[15] Prada D, Kalia V, Gao F, Rexrode K, Kooperberg C, Reiner A, et al. Metabolomic evaluation of air pollution-related bone damage and potential Mediation in Women's Health Initiative Participants. J Bone Miner Res 2025. https://doi.org/10.1093/jbmr/zjaf059.

[16] Ren Li, Chen L, Fan. Proximity to major roads and the incidence of osteoporotic fractures in elderly women: the BONE study in Beijing. Front Public Health 2022;10:1036534.

[17] Chen, et al. Living near a freeway is associated with lower bone mineral density among Mexican Americans. Osteoporos Int 2015;26:1713–21.

[18] Cooper, Fuggle, Javaid, Pinedo-Villanueva. Capture the fracture partnership: guidance for policy shaping. 10–15 (2020).

[19] Zhang F, Zhou F, Liu H, Zhang X, Zhu S, Zhang X, et al. Long-term exposure to air pollution might decrease bone mineral density T-score and increase the prevalence of osteoporosis in Hubei province: evidence from China Osteoporosis Prevalence Study. Osteoporos Int 2022;33(11):2357–68. https://doi.org/10.1007/s00198-022-06488-7.

[20] Prada D, Crandall CJ, Kupsco A, Kioumourtzoglou M-A, Stewart JD, Liao D, et al. Air pollution and decreased bone mineral density among Women's Health Initiative participants. eClinicalMedicine 2023. https://doi.org/10.1016/j.eclinm.2023.101864.

[21] Barry PS. A comparison of concentrations of lead in human tissues. Occup Environ Med 1975;32(2):119–39. https://doi.org/10.1136/oem.32.2.119.

[22] Engström A, Michaëlsson K, Suwazono Y, Wolk A, Vahter M, Åkesson A. Long-term cadmium exposure and the association with bone mineral density and fractures in a population-based study among women. J Bone Miner Res 2011;26(3):486–95. https://doi.org/10.1002/jbmr.224.

[23] Rodríguez J, Mandalunis PM. A review of metal exposure and its effects on bone health. J Toxicology 2018;2018:1–11. https://doi.org/10.1155/2018/4854152.

[24] Dowd TL, Rosen JF, Mints L, Gundberg CM. The effect of Pb2+ on the structure and hydroxyapatite binding properties of osteocalcin. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 2001;1535(2):153–63. https://doi.org/10.1016/S0925-4439(00)00094-6.

[25] Philip AT, Gerson B. Lead poisoning-part II: effects and assay. Clin. Lab. Med. 1994;14(3):651–70. https://doi.org/10.1016/s0272-2712(18)30373-1.

[26] Scimeca M, Feola M, Romano L, Rao C, Gasbarra E, Bonanno E, et al. Heavy metals accumulation affects bone microarchitecture in osteoporotic patients. Environ Toxicol 2016;32(4):1333–42. https://doi.org/10.1002/tox.22327.

[27] Ha T, Tien TV. Exploring the impact of chronic heavy metal accumulation in the kidneys on bone microarchitecture: mechanisms of mineral metabolism disruption, inflammation, and direct metal deposition leading to trabecular alterations. J Adv Analytics in Healthcare Management 2024;8(8):1–19.

[28] Banjabi AA, Kurunthachalam K, Kumosani TA, Abulnaja KO, Al-Malki AL, Moselhy SS. Serum heavy metals of passive smoker females and its correlation to bone biomarkers and risk of osteoporosis. Environ Sci and Pollution Res Int 2022;29(5):6943–8. https://doi.org/10.1007/s11356-021-16186-2.

[29] Ward KD, Klesges RC. A meta-analysis of the effects of cigarette smoking on bone mineral density. Calcif Tissue Int 2001;68(5):259–70. https://doi.org/10.1007/bf02390832.

[30] Ashraf MW. Levels of heavy metals in popular cigarette brands and exposure to these metals via smoking. The Scientific World J 2012:1–5. https://doi.org/10.1100/2012/729430.

[31] Sun Y, Sun D, Zhou Z, Zhu G, Zhang H, Chang X, et al. Osteoporosis in a chinese population due to occupational exposure to lead. American J Industrial Medicine 2008;51(6):436–42. https://doi.org/10.1002/ajim.20567.

[32] Nawrot T, Geusens P, Nulens TS, Nemery B. Occupational cadmium exposure and calcium excretion, bone density, and osteoporosis in men. J Bone Miner Res 2010;25(6):1441–5. https://doi.org/10.1002/jbmr.22.

[33] Sølling ASK, Harsløf T, Langdahl B. The clinical potential of romosozumab for the prevention of fractures in postmenopausal women with osteoporosis. Therapeutic

Adv Musculoskeletal Disease 2018;10(5–6):105–15. https://doi.org/10.1177/1759720x18775936.
[34] Kwon Y-J, Shin S, Chun Y-J. Biological roles of cytochrome P450 1A1, 1A2, and 1B1 enzymes. Archives of Pharmacal Res 2021;44(1):63–83. https://doi.org/10.1007/s12272-021-01306-w.
[35] Cheng C-H, Chen L-R, Chen K-H. Osteoporosis due to hormone imbalance: an overview of the effects of estrogen deficiency and glucocorticoid overuse on bone turnover. Int J Molecular Sci 2022;23(3):1376. https://doi.org/10.3390/ijms23031376.
[36] Ateş GB, Ak A, Garipcan B, Gülsoy M. Methylene blue mediated photobiomodulation on human osteoblast cells. Lasers Med Sci 2017;32(8):1847–55. https://doi.org/10.1007/s10103-017-2286-7.
[37] Edsall SC, Franz-Odendaal TA. A quick whole-mount staining protocol for bone deposition and resorption. Zebrafish 2010;7(3):275–80. https://doi.org/10.1089/zeb.2009.0641.
[38] Ariffin SHZ, Wahab A, Razak MA, Yazid MD, Shahidan MA, Miskon A, et al. Evaluation of *in vitro* osteoblast and osteoclast differentiation from stem cell: a systematic review of morphological assays and staining techniques. PeerJ 2024;12:e17790–. https://doi.org/10.7717/peerj.17790.
[39] Chen H, Oliver BG, Pant A, Olivera A, Poronnik P, Pollock CA, et al. Effects of air pollution on human health - mechanistic evidence suggested by in vitro and in vivo modelling. Environ Res 2022;212(Pt C):113378. https://doi.org/10.1016/j.envres.2022.113378.
[40] Li D, Chen S, Li Q, Chen L, Zhang H, Li H, et al. Caloric restriction attenuates C57BL/6 J mouse lung injury and extra-pulmonary toxicity induced by real ambient particulate matter exposure. Part Fibre Toxicol 2020;17(1). https://doi.org/10.1186/s12989-020-00354-2.
[41] Zeng Y, Jin H, Wang J, Guo C, Chen W, Tan Y, et al. An optimized method for intratracheal instillation in mice. J Pharmacol Toxicol Methods 2022;118:107230. https://doi.org/10.1016/j.vascn.2022.107230.
[42] Chan YL, Wang B, Chen H, Ho KF, Cao J, Hai G, et al. Pulmonary inflammation induced by low-dose particulate matter exposure in mice. Am J Physiol Lung Cell Mol Physiol 2019;317(3):L424–30. https://doi.org/10.1152/ajplung.00232.2019.
[43] Feng O, Bai, Hui. TSANZ abstracts. Respirology 2024;29:25–273.
[44] Scheiner S, Pivonka P, Hellmich C. Coupling systems biology with multiscale mechanics, for computer simulations of bone remodeling. Comput. Methods Appl. Mech. Eng. 2013;254:181–96. https://doi.org/10.1016/j.cma.2012.10.015.
[45] Lerebours C, Buenzli PR, Scheiner S, Pivonka P. A multiscale mechanobiological model of bone remodelling predicts site-specific bone loss in the femur during osteoporosis and mechanical disuse. Biomechanics and Modeling in Mechanobiology 2015;15(1):43–67. https://doi.org/10.1007/s10237-015-0705-x.
[46] Matziolis D. Osteogenic predifferentiation of human bone marrow-derived stem cells by short-term mechanical stimulation. The Open Orthopaedics J 2011;5(1):01–6. https://doi.org/10.2174/1874325001105010001.
[47] Shepherd JH, Shepherd DV, Best SM. Substituted hydroxyapatites for bone repair. J Mater Sci - Mater Med 2012;23(10):2335–47. https://doi.org/10.1007/s10856-012-4598-2.
[48] Yu X-H, Cao H-W, Bo L, Lei S-F, Deng F-Y. Air pollution, genetic factors and the risk of osteoporosis: a prospective study in the UK biobank. Front Public Health 2023;11. https://doi.org/10.3389/fpubh.2023.1119774.
[49] Prada D, Zhong J, Colicino E, Zanobetti A, Schwartz J, Dagincourt N, et al. Association of air particulate pollution with bone loss over time and bone fracture risk: analysis of data from two independent studies. The Lancet Planetary Health 2017;1(8):e337–47. https://doi.org/10.1016/s2542-5196(17)30136-5.
[50] Darbre PD. Overview of air pollution and endocrine disorders. Int J General Medicine 2018;11:191–207. https://doi.org/10.2147/IJGM.S102230.
[51] Plunk EC, Richards SM. Endocrine-disrupting air pollutants and their effects on the hypothalamus-pituitary-gonadal axis. Int J Mol Sci 2020;21(23):9191. https://doi.org/10.3390/ijms21239191.
[52] Zhang J, Zhao H, Yao G, Qiao P, Li L, Wu S. Therapeutic potential of iron chelators on osteoporosis and their cellular mechanisms. Biomed Pharmacother 2021;137:111380. https://doi.org/10.1016/j.biopha.2021.111380.
[53] Greenblatt MB, Tsai JN, Wein MN. Bone turnover markers in the diagnosis and monitoring of metabolic bone disease. Clinical chemistry 2017;63(2):464–74. https://doi.org/10.1373/clinchem.2016.259085.
[54] Panahi N, Arjmand B, Ostovar A, Kouhestani E, Heshmat R, Soltani, Larijani B. Metabolomic biomarkers of low BMD: a systematic review. Osteoporos Int 2021. https://doi.org/10.1007/s00198-021-06037-8.
[55] Rowe J, Shen S, de Alcântara ACS, Skaf MS, Dini D, Harrison NM, et al. Integrating computational and experimental advances in bone multiscale mechanics. Prog Mater Sci 2025;153:101474. https://doi.org/10.1016/j.pmatsci.2025.101474.
[56] International Council on Clean Transportation (ICCT), 2024. *Euro 7 standard: A comprehensive review of the new regulations*. [pdf] Available at: https://theicct.org/wp-content/uploads/2024/03/ID-116-%E2%80%93-Euro-7-standard_final.pdf [Accessed 28 February 2025].