Particulate Air Pollution and Osteoporosis: A Systematic Review

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Abstract: Air pollution is associated with inflammation and oxidative stress, which predispose to several chronic diseases in human. Emerging evidence suggests that the severity and progression of osteoporosis are directly associated with inflammation induced by air pollutants like particulate matter (PM). This systematic review examined the relationship between PM and bone health or fractures. A comprehensive literature search was conducted from January until February 2021 using the PubMed, Scopus, Web of Science, Google Scholar and Cochrane Library databases. Human cross-sectional, cohort and case–control studies were considered. Of the 1500 papers identified, 14 articles were included based on the inclusion and exclusion criteria. The air pollution index investigated by most studies were PM$_{10}$ and PM$_{2.5}$. Current studies demonstrated inconsistent associations between PM and osteoporosis risk or fractures, which may partly due to the heterogeneity in subjects’ characteristics, study design and analysis. In conclusion, there is an inconclusive relationship between osteoporosis risk and fracture and PM exposures which require further validation.

Keywords: particulate matter, PM$_1$, PM$_{2.5}$, PM$_{10}$, bone mineral density, fracture

Introduction
Air pollution is a critical environmental and health issue in both developing and developed countries. According to the World Health Organization (WHO) statistics in 2016, around 91% of the world’s population was living with poor air quality.$^1$ Air pollution is closely associated with the incidence of pulmonary and non-pulmonary diseases, including metabolic disorders, cardiovascular diseases, central nervous system diseases and cancer.$^2$–$^7$ Recently studies also showed that air pollution predisposed the public to a higher risk of breast cancer and childhood leukaemia, apart from lung cancer.$^8$–$^9$ Besides, air pollution is estimated to contribute to 7 million deaths worldwide in 2016.$^1$

Air pollutants can be categorised into gaseous or solid type. The common examples of gaseous pollutant are ammonia, nitrogen dioxide (NO$_2$), carbon monoxide (CO), sulphur dioxide (SO$_2$), tropospheric or ground-level ozone (O$_3$) and volatile organic compounds.$^7$,$^{10}$,$^{11}$ Particulate matter (PM) is the sum of heterogeneous solid air pollutants, comprising water, dust and particles. The composition of PM is highly diverse, which is usually made up of acids, water droplets, elemental carbon (black carbon), organic carbon, polycyclic aromatic hydrocarbons (PAHs), metal dust, geographical mineral dust, and nitrate or sulphate compounds.$^{10}$,$^{12}$–$^{14}$ The classification of PM is based on its aerodynamic diameter but not its composition, wherein the particles with diameter <10 μm are grouped as PM$_{10}$, <2.5 μm as PM$_{2.5}$.
and <1 μm as PM_{10}. Ultrafine particles with aerodynamic diameter <0.2 μm or ≤0.1 μm are also being investigated but not as common as other PM species, probably due to the limitation in detection technology. These PMs are produced mainly from human activities, such as vehicle emission, coal or biomass combustion and high-temperature industrial works (manufacturing, mining, and agricultural activities).10,11,20

The negative effects of air pollution are partly attributed to PM.21 Short-term exposure to PM could lead to respiratory discomfort, airway inflammation, lung damages and cardiovascular disorders.22–24 Chronic exposure to PM is strongly associated with cardiopulmonary diseases, neurological disorders, cancer formation and increased mortality.25–28 PM_{10} is deposited mainly on the head or nose area, with a slight deposition in the upper respiratory tracts. PM_{1} and PM_{2.5} can reach the deeper lung area, including alveoli and terminal bronchioles.15,29–31 Subsequently, these fine particles could cross the alveolar barrier, enter the systemic circulation and reach several extrapulmonary organs.15 Mechanistically, PM could induce oxidative and inflammatory damages on respiratory tracts via mitogen-activated protein kinase and Toll-like receptor signalling pathway.32–34 Additionally, PM_{2.5} and its component, PAHs, also possess genotoxic, mutagenic and clastogenic effects, contributing to its cancer induction properties.35–37

Osteoporosis is a chronic age-related disease of the skeletal system associated with changes in endocrine, metabolic and mechanical factors.38,39 According to the National Health and Nutrition Examination Survey 2013–2014, nearly 6–11% of adults age ≥50 years in the United States were osteoporotic.40,41 Osteoporosis affects mainly the elderly in both sexes, but women have a 4-time higher risk due to lower peak bone mass and the rapid decline of bone mass during menopause.42 Fragility or atraumatic fractures are the major contributors to osteoporosis-related comorbidity and mortality.43 Bone mass, measured as bone mineral content (BMC) or bone mineral density (BMD), is the surrogate indicators of bone strength. Osteoporosis is defined as a BMD value 2.5 standard deviations or more below the average value for young adult (T-score ≤ −2.5) at the spine, hip or mid-radius.44,45 WHO45 and the International Osteoporosis Foundation46 recommended using dual-energy X-ray absorptiometry (DXA) to measure the BMD for the diagnosis of osteoporosis. Quantitative ultrasound (QUS) is an alternative bone health screening technology. It is non-invasive, radiation-free and highly portable, and correlated well with DXA measurement.47,48

Some of the fixed and modifiable risk factors of osteoporosis include sex (female), old age, ethnicity, low body mass index (BMI), menopause, low physical activity, malnutrition, use of glucocorticoid, smoking, alcohol consumption and chronic diseases like diabetes and chronic kidney disease (CKD).49 The previously neglected role of pollution, like air pollution, as a risk factor of osteoporosis, is gaining attention in the recent 5 years.50,51 Several molecular mechanisms were postulated in explaining the association between PM and osteoporosis risk/fracture (reviewed in Prada et al.52). Several preclinical and epidemiological studies reported the pro-inflammatory properties of PM by increasing the inflammatory cells and acute response protein level and inducing inflammatory-related diseases like airway inflammation, cardiovascular diseases and arthritis.5,53–62 The upregulated inflammatory cytokines, including tumour necrosis factor-α, interleukin-1β, interleukin-6 and granulocyte-macrophage colony-stimulating factor, are osteoclastogenic and could stimulate bone resorption.63–66 Moreover, PM_{2.5} and PM_{10} exposures were significantly associated with serum receptor activator of nuclear factor-kappa B ligand level, suggesting their osteoclastogenic properties.53

Furthermore, PM exposure has been linked with vitamin D deficiency (reviewed in Afsar et al.67). PM exposure was positively associated with kidney diseases and negatively associated with kidney function in converting the inactive 25-hydroxyvitamin D to biologically active 1,25-dihydroxyvitamin D.68–70 Additionally, PM components like metal dust are nephrotoxic.52 Moreover, PM also reduces the cutaneous vitamin D biosynthesis in populations with normal kidney function71 by reducing the surface solar72 and ultraviolet radiation.73 Epidemiology studies reported lower serum vitamin D levels among healthy women, adolescents and children from the polluted area.74–76 Additionally, PM components like PAHs were also reported to increase vitamin D catabolism.77 Nevertheless, the causal relationship between PM and vitamin D level is not yet confirmed.

To the best of our knowledge, a systematic review that summarises the relationship between PM and bone health or fractures is not available. Therefore, this systematic review aims to summarise the relationship between PM and bone health or fracture in the human population.
Materials and Methods

Literature Search Strategies

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and checklist. We conducted an electronic search using five databases, including PubMed, Scopus, Web of Science, Google Scholar and Cochrane Library from January to February 2021. The following search string was used: (1) (osteo-porosis OR bone OR fracture OR "X-ray absorptiometry") AND (2) (“air pollution” OR “particulate matter” OR PM2.5 OR PM10). A manual search was performed to retrieve additional records from the reference list of included studies or review papers. The detailed search strategy is provided in Supplementary Table S2. The PRISMA checklist is included as Supplementary Table S1.

Eligibility Criteria and Study Selection

We included cross-sectional, case-control, longitudinal/prospective and retrospective cohorts that reported the relationship between air pollutants, primarily particulate matter, and bone health, osteoporotic risk or fractures published within 30 years, from 1990 to 2021. We excluded studies that were (1) only available in abstract form; (2) not written in English; (3) books, book chapters, reviews, meta-analysis, conference/proceeding papers, letter to editor, and commentary; (4) pollutants or PM from smoking, cigarette smoke and tobacco; (5) no PM measurement; or (6) without bone mass assessment. The PRISMA flow chart that summarises the records identification, screening, eligibility, and inclusion of articles, are shown in Figure 1.

Study Extraction

Two reviewers (K.-L.P. and S.O.E) independently extracted the data from each article into an extraction table, firstly by referring to the title and abstract, followed by a full-text screening. Discussions with the third reviewer (K.-Y.C.) were held if there was any disagreement in the inclusion of an article. Table 1 shows the data retrieve from the articles, including the name of the first author, year of publication, year of subject recruitment/study period, study location, study design, number of subjects, PM assessment, bone health, osteoporosis or fracture assessment and outcomes.
| Author | Study Period | Study Location | Study Design | Sample Size | PM Assessment | Bone Health, Osteoporosis or Fracture Assessment | Outcomes | JBI Score |
|--------|--------------|----------------|--------------|-------------|---------------|-------------------------------------------------|----------|-----------|
| Alvær et al, 2007<sup>8</sup> | 2000–2001 | Oslo, Norway | Cross-sectional study | 590 men aged 75–76 years old | Annual mean PM<sub>2.5</sub> and PM<sub>10</sub> levels from the Norwegian Institute of Air Research, AirQUIS system | Total body BMD by DXA Low BMD = BMD Z-score ≤ −1 | Total body BMD was negatively associated with PM<sub>2.5</sub> (β = −47, 95% CI = (−77, −17)) and PM<sub>10</sub> (β = −28, 95% CI = (−48, −8)) after BMI, smoking, physical activity and education adjustment. Risk of low total body BMD was positively associated with PM<sub>2.5</sub> [OR= 1.33, 95% CI= (1.05, 1.70)] and PM<sub>10</sub> levels [OR= 1.28, 95% CI= (1.00, 1.63)] after multivariate adjustment | 8 |
| Alver et al, 2010<sup>9</sup> | 2000–2001 | Oslo, Norway | Cross-sectional study | 5976 subjects with men (n= 2674) and women (n=3302) aged 59–60 or 75–76 years old | Annual mean PM<sub>2.5</sub> and PM<sub>10</sub> levels from outdoor air pollution exposure estimated by EPISODE dispersion model, the Norwegian Institute of Air Research | Mean distal forearm BMD by DXA Self-reported forearm (wrist/lower arm) fracture | The forearm fracture was not significantly associated with PM<sub>2.5</sub> and PM<sub>10</sub> regardless of age and sex (all p>0.05). Distal forearm BMD was not associated with PM<sub>2.5</sub> and PM<sub>10</sub> among subjects aged 59–60 years old and 75–76 years old regardless of sex after adjustment of education, smoking, years of smoking, physical activity and years after menopause (all p>0.05) | 7 |
| Cevei and Stoicanescu, 2010<sup>10</sup> | Jan – Dec 2009 | Oradea, Romania | Cross-sectional study | 105 subjects aged 62.2 ± 3.98 years old | Annual mean PM<sub>10</sub> from EPA Bihor | BMDs of total body, lumbar spine or femoral neck by DXA | The total body BMD (but not hip BMD) was negatively associated with PM<sub>10</sub> without covariate adjustment | 6 |
| Lee et al, 2014<sup>11</sup> | 1 Jan 2010–31 Dec 2012 | New Taipei City, Taiwan | Cross-sectional study | 70 retired workers with men (n=68) and women (n=2) aged: 75.2 ± 5.5 years old | An annual mean concentration of PM<sub>10</sub> calculated from the daily data from monitoring stations operated by the Taiwan Environmental Protection Administration | The hip, femoral neck and lumbar spine BMD by DXA Followed WHO definition of osteopenia and osteoporosis | Osteoporosis risk was not significantly associated with PM<sub>10</sub> level [OR= 1.012, 95% CI= (0.949, 1.079)], after adjusted for age, sex, BMI current smoking, drinking, inhaled corticosteroids usage, 6-minute walk distance, COPD severity and smooth functions of visit date and yearly temperature | 8 |
| Study | Year | Location | Design | Participants | Exposure | Outcome | Findings |
|-------|------|----------|--------|--------------|----------|---------|----------|
| Chen et al 2015<sup>8</sup> | 2002–2008 | California, United State | Cross-sectional study | 1173 Mexican American with men (n=324) and women (n=849) aged 34.4 years old | Annual mean ambient PM<sub>2.5</sub> level from the US Environmental Protection Agency’s Air Quality System | Total body and pelvic BMD by DXA | PM<sub>2.5</sub> was not associated with the total body (β = −0.09, p=0.75) and pelvic BMD (β = −0.13, p=0.76) after adjusting for age, sex, weight, and height. Total body and pelvic BMD were negatively associated with residential distance from the nearest freeways (≤ 500 m; all p< 0.05) after adjusting for age, sex, weight, height, body fat percentage, menopausal status, gestational diabetes, physical activity, ambient pollutants, contextual variables, daily calcium and vitamin D intakes. Total body BMD (but not pelvic BMD) was negatively associated with residential distance from a major road (75–150 m; all p< 0.05) after multivariate adjustment. |
| Lin et al 2020<sup>7</sup> | 2012 -April 2014 | Taiwan | Cross-sectional study | 4595 subjects with men (n=2118) and women (n=2477) aged 49.7 ± 10.7 years old | Annual mean concentrations of PM<sub>2.5</sub> and PM<sub>10</sub> levels from the Taiwan Air Quality Monitoring Database | Bone health of the non-dominant foot by calcaneal QUS followed WHO definition of osteopenia and osteoporosis | PM<sub>2.5</sub> and PM<sub>10</sub> exposures were significantly higher among subjects with normal BMD (all p<0.05). NS association between BMD T-score and PM<sub>2.5</sub> [β = −0.002; 95% CI (−0.006, 0.002); p=0.311] and PM<sub>10</sub> [β = 0.001; 95% CI (−0.002, 0.004); p= 0.491] after adjusting for age, sex, smoking history, diabetes, hypertension, BMI, systolic blood pressure, diastolic blood pressure, fasting glucose, triglyceride, total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, haemoglobin, estimated glomerular filtration rate, uric acid, and regular exercise. |

(Continued)
| Author          | Study Period | Study Location | Sample Size | Study Design     | Cross-Sectional Studies | PH Assessment | Bone Health, Osteoporosis or Fracture Assessment | Outcomes                                                                                          |
|-----------------|--------------|----------------|-------------|------------------|-------------------------|---------------|---------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Qiao et al      | 2020         | Henan province, China | 8033 subjects (men n=3001, women n=5032) aged 55.8 ± 10.8 years | Cross-sectional study  | 3-year average PM₁, PM₂.₅ and PM₁₀ levels were estimated using machine learning algorithms (random forests model) with satellite remote sensing, land use information, and meteorological data | Bone health of the non-dominant foot by QUS Followed WHO definition of osteoporosis | Osteoporosis risk were positively associated with PM₁ (5.5–57 mg/m³) OR=1.068, 95% CI= (1.357, 1.907); >57 mg/m³: OR= 2.075, 95% CI= (1.724, 2.497), PM₂.₅ (2.2–6.7 μg/m³) OR= 1.93, CI= (1.24, 2.97); PM₁₀ (1.26–2.68 μg/m³) OR= 1.39, CI= (0.95, 0.98) | PM₁, PM₂.₅ and PM₁₀ (for each 1 μg/m³ increase) were associated with a 14.9%, 14.6% and 7.3% higher risk of osteoporosis. An estimated 20.29% (PM₁), 23.20% (PM₂.₅) and 24.36% (PM₁₀) osteoporosis cases could be prevented by reducing the exposure to PM₁, PM₂.₅ and PM₁₀ below their respective first quartile limit. |
| Ranzani et al   | 2020         | Hyderabad, South India | 3717 subjects (men n=2006, women n=1711) aged 35.7 ± 14 years | Cross-sectional study  | Annual mean exposures of PM₂.₅ and PM₁₀ levels were estimated from sampling data and land use regression models | BMC, and BMD at left hip and lumbar spine L1-L4 were measured via DXA | PM₂.₅ (for every 3 μg/m³ increase) was negatively associated with lumbar spine BMC, mean difference=−0.57 g, 95% CI= (−1.06, −0.07) and lumbar spine BMD, mean difference=−0.57 g, 95% CI= (−1.09, 0.05) after adjusting for the bone area, percentage lean, percentage body mass, fruit intake, vegetable intake, calcium intake, physical activity, smoking, household cooking fuel, occupation, education and standard of living index. NS association between PM₂.₅ and lumbar spine BMD, hip BMC and hip BMD. Subgroup analysis revealed that PM₂.₅ was negatively associated with hip and spine BMC and hip (but not spine) BMD for those aged ≥40 years old. |
| Pang et al      | 2020         | Hyderabad, South India | 3717 subjects (men n=2006, women n=1711) aged 35.7 ± 14 years | Cross-sectional study  | Annual mean exposures of PM₂.₅ was estimated from sampling data and land use regression models | BMC, and BMD at left hip and lumbar spine L1-L4 were measured via DXA | PM₂.₅ (for every 3 μg/m³ increase) was negatively associated with lumbar spine BMC, mean difference=−0.57 g, 95% CI= (−1.06, −0.07) and lumbar spine BMD, mean difference=−0.57 g, 95% CI= (−1.09, 0.05) after adjusting for the bone area, percentage lean, percentage body mass, fruit intake, vegetable intake, calcium intake, physical activity, smoking, household cooking fuel, occupation, education and standard of living index. NS association between PM₂.₅ and lumbar spine BMD, hip BMC and hip BMD. Subgroup analysis revealed that PM₂.₅ was negatively associated with hip and spine BMC and hip (but not spine) BMD for those aged ≥40 years old. |

https://doi.org/10.2147/RMHP.S316429

Risk Management and Healthcare Policy 2021:14
### Cross-sectional study

- **Author:** Sung et al 2020
- **Study period:** 2002–2013
- **Study location:** Seoul, Incheon and Busan, South Korea
- **Sample size:** 44,602 women aged > 50 years old
- **PM assessment:** Annual mean PM$_{2.5}$, PM$_{2.5–10}$ and PM$_{10}$ levels from the Air Korea database based on residential address estimation
- **Bone health, osteoporosis and fracture assessment:** Osteoporotic fracture data from the National Health Insurance Service database, South Korea
- **Outcomes:** Osteoporotic fractures were positively associated with PM$_{2.5}$ [aHR= 1.10, 95% CI= (1.01, 1.23) for 26.8–29.2 μg/m$^3$; aHR= 1.13, 95% CI= (1.02, 1.24) for 29.2–34.6 μg/m$^3$] among women aged > 50 years, after adjusting for age, household income, Charlson Comorbidity Index and region. No significant association between osteoporotic fracture and PM$_{2.5–10}$ and PM$_{10}$
- **Similar associations:** Similar positive associations were found between PM$_{2.5}$ and osteoporotic spine fractures [aHR= 1.17, 95% CI= (1.00, 1.38) for 29.2–34.6 μg/m$^3$] and non-spine fractures [aHR= 1.16, 95% CI= (1.02, 1.33) for 26.8–29.2 μg/m$^3$; aHR= 1.16, 95% CI= (1.01, 1.33) for 29.2–34.6 μg/m$^3$]
- **Sensitivity analysis:** The sensitive analysis identified a similar positive association with PM$_{2.5}$ after excluding subjects diagnosed with osteoporotic fractures within 1 year and 2 years (all p ≤ 0.008).

### Retrospective or prospective cohorts

| Author | Study period | Study location | Study type/design | Sample size | PM assessment | Bone health, osteoporosis and fracture assessment | Outcomes | JBI score |
|--------|--------------|----------------|-------------------|-------------|---------------|-----------------------------------------------|-----------|-----------|
| Mazzucchelli et al 2018 | 1 Jan 2000–31 Dec 2015 | Alcorcón, Spain | Retrospective cohort study | 4271 subjects with men (n=925) and women (n=3346) aged 83.8 ± 8.9 years old | Daily mean levels of PM$_{2.5}$ and PM$_{10}$ from the Air Pollution Monitoring Network, Community of Madrid Environmental Local Government and Regional Planning Department | Hip fracture record from the Hospital Universitario Fundación Alcorcón database | NS association between hip fracture and PM$_{2.5}$ [IRR= 1.01, 95% CI= (0.92–1.09), p = 0.955] and PM$_{10}$ [IRR= 1.01, 95% CI= (0.99–1.03), p = 0.144], regardless of sex or age group (> or ≤ 75 years old; all p> 0.05) after adjusting a natural spline function of time, season and mean air temperature | 8 |
| Ormeño Illanes and Quevedo Langenegger 2019 | 2017 | Chile | Retrospective cohort study | 8322 elderly aged > 65 years old | Annual mean concentration of PM$_{2.5}$ from the National Air Quality Information System, Chile | Osteoporotic hip fracture record from the Ministry of Health’s Department of Health Statistics and Information, Chile | NS association between osteoporotic hip fracture IRR and PM$_{2.5}$ [r= −0.114, p > 0.05] regardless of sex (all p> 0.05) without covariate adjustment | 6 |
| Oh et al 2020 | 2010–2015 | South Korea | Retrospective cohort study | 178,147 subjects with men (n= 98,749) and women (n=79,398) aged 49.5 ± 12 years old | Annual mean concentration per area of PM$_{10}$ from the National Ambient Air Information System, Korean Ministry of the Environment | Hip fracture record from National Health Insurance Service database, South Korea | PM$_{10}$ was positively associated with hip fracture incidence [OR= 1.02; 95% CI (1.01, 1.03); p<0.05] after adjusting with age, sex, BMI, annual income, residence area, smoking, alcohol drinking, exercise, Charlson Comorbidity Index and/or an underlying disease | 8 |

(Continued)
Table 1 (Continued).

| Author | Study Period | Study Location | Study Design | Sample Size | PM Assessment | Bone Health, Osteoporosis or Fracture Assessment | Outcomes | JBI Score |
|--------|--------------|----------------|--------------|-------------|---------------|-----------------------------------------------|----------|-----------|
| Prada et al 2017<sup>22</sup> | 2003–2010 | Northeast-mid-Atlantic US states | Retrospective cohort study | 763,630 subjects with men (n=314,525) and women (n=449,105) aged ≥ 65 years old | Annual mean PM<sub>2.5</sub> concentrations estimated using a validated spatio-temporal prediction model | Annual osteoporotic-related bone fractures data (hip, wrist, spine and pelvis) from hospital data | PM<sub>2.5</sub> was positively associated with bone fractures [RR = 1.041; 95% CI (1.030, 1.051); p = 0.0001] with a nearly linear relationship after adjusting for sociodemographic variables (age, sex, race, education and income), geographical characteristics, obesity, number of days with freezing temperatures and calendar year. A positive association between PM<sub>2.5</sub> and bone fracture was observed in women [RR = 1.046; 95% CI (1.036, 1.056); p = 0.0002] and men [RR = 1.037; 95% CI (1.027, 1.047); p = 0.0008] | 8 |
| Pang et al | Nov 2002-Oct 2012 | Greater Boston, MA, USA | Prospective cohort study | 692 African, Latin, and European American male residents aged 30–79 years old with 8 years of follow-up | Annual PM<sub>2.5</sub> concentrations estimated using a validated spatio-temporal prediction model | BMDs of the femoral neck, total hip, lumbar spine [L1–L4], distal radius and ultradistal radius by DXA (during baseline and follow-up) Serum parathyroid hormone, calcium (at baseline), and vitamin D (25(OH)D<sub>3</sub>) | PM<sub>2.5</sub> was not significantly associated with BMDs of the femoral neck, total hip, lumbar spine, ultradistal radius and one-third distal radius (all p < 0.05) after adjusting for age, race, height, weight, smoking, household income, physical activity, caffeine consumption, serum vitamin D levels and/or C-reactive protein. Serum parathyroid hormone (but not serum calcium and vitamin D) was negatively associated with PM<sub>2.5</sub> (β = −7.39; 95% CI (−14.17, −0.61); p < 0.05) after multivariate adjustment. | 8 |
| Wu et al 2020 | 3rd July 2007–21st Feb 2011 | Mexico City, Mexico | Prospective cohort study | 941 pregnant women aged 27.3 ± 5.5 years old with 3 years of follow-up | Daily mean ambient PM$_{2.5}$ was estimated from PM$_{2.5}$ monitoring stations data by using a spatial-temporal model | Bone health (SOS T-score) of radius (trabecular) and the proximal phalanx (cortical) of the middle finger by using QUS scan |
|---|---|---|---|---|---|---|
| Maternal trabecular bone health was negatively associated with PM$_{2.5}$ exposure (for each 10 $\mu$g/m$^3$ increase) during first trimester $[\beta = -0.18; 95\%$ CI ($-0.35$, $-0.01$); $p< 0.05]$ and third trimester exposure $[\beta = -0.18; 95\%$ CI ($-0.36$, $-0.01$); $p< 0.05]$ after adjusting for maternal age, BMI, socioeconomic status, education, parity, time since conception, natural trajectory of bone strength changes over time and PM$_{2.5}$ concentrations at other time periods. |
| Maternal cortical bone health was negatively associated with PM$_{2.5}$ exposure (for each 10 $\mu$g/m$^3$ increase) during the first month of post-partum $[\beta = -0.20; 95\%$ CI ($-0.39$, $-0.01$); $p< 0.05]$. |
| PM$_{2.5}$ exposure during the 60 days preconception was positively associated with the trabecular and cortical bone health, during the third trimester and first month post-partum (all $p<0.05$) after adjusting for maternal age, BMI, socioeconomic status, education, parity and PM$_{2.5}$ concentrations at other periods. |
| The first and second trimester PM$_{2.5}$ exposures were initially negatively associated with trabecular and cortical bone health during the second and third trimesters but positively associated with the bone health of 1 to 6 months post-partum (all $p<0.05$). |
| NS association for PM$_{2.5}$ exposure during the third trimester for both bone health ($p>0.05$). |
| PM$_{2.5}$ exposure during the first month post-partum was negatively associated with trabecular (but not cortical) bone health of 1 to 6 months post-partum ($p<0.001$). |

**Abbreviations:** aHR, adjusted hazard ratio; $\beta$, adjusted regression coefficient; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DXA, dual-energy X-ray absorptiometry; IRR, incidence rate ratio; JBI, Joanna Briggs Institute; L1, first lumbar spine; L4, fourth lumbar spine; NS, not significant; OR, odds ratio; PM$_i$, PM with aerodynamic diameter $< i$ $\mu$m; PM$_{2.5}$, PM with aerodynamic diameter $< 2.5$ $\mu$m; PM$_{2.5-10}$, PM with aerodynamic diameter between 2.5 and 10 $\mu$m; PM$_{10}$, PM with aerodynamic diameter $< 10$ $\mu$m; QUS, quantitative ultrasound; $r$, Pearson correlation coefficient; RR, risk ratio; SOS, speed-of-sound; WHO, World Health Organization.
Quality Assessment
Two reviewers (K.-L.P. and S.O.E.) independently evaluated the article quality using the Joanna Briggs Institute (JBI) critical appraisal checklist. Two different checklists were used for cross-sectional and cohort studies covering “Sampling”, “Exposure”, “Confounding factors”, “Outcomes” and “Statistical analysis” domains, with a maximum score of 8 (cross-sectional study) or 11 (cohort study). Every item was rated as Yes (score of 1), No or Unclear (score of 0). Non-applicable item is excluded from the overall scoring. Cross-sectional or retrospective cohort studies with an overall score ≥6 or prospective cohort studies with ≥8 were considered as high-quality articles. Any disagreement was resolved by discussion among three reviewers. The overall score was listed in the evidence table (Table 1) and detailed scoring was shown in Supplementary Table S3 and S4.

Result
Search Results and Study Selection
We identified 1500 articles, of which 401 were obtained from PubMed, 562 from Scopus, 441 from the Web of Science, 42 from Google Scholar, 25 from Cochrane Library and 18 additional articles from the reference list of included articles and reviews. A total of 1042 unique records were identified after excluding 458 duplicates. A total of 970 articles were excluded based on the inclusion and exclusion criteria where 19 articles were not written in English, 68 articles were not primary articles, 129 articles were non-human studies, 22 articles studied cigarette smoking and 732 articles were irrelevant to the topic. A total of 72 articles fulfilling the criteria were assessed for eligibility. After examining the full-text, we excluded 58 articles, of which 1 article was a preprint manuscript, 36 articles did not perform bone health assessment and 21 articles did not measure the PM level. Finally, 14 articles were included in this systematic review.

Study Characteristics
The included studies were published between 2007 and 2020, wherein 9 articles were cross-sectional studies, 4 were retrospective studies and 2 were prospective studies. All the articles are considered high quality according to JBI critical appraisal checklist as shown in Table S3 and S4. However, some studies have validity confounding factors and subjects follow-up issues. Four studies were conducted in North and South America (the United States, Chile and Mexico); 4 studies were conducted in Europe (Norway, Romania and Spain), and the remaining 6 studies were conducted in Asia (Taiwan, Henan province of China, India and South Korea). The total number of participants was 1,024,864, wherein 68,861 were from cross-sectional studies and 956,003 were from cohort studies. Two cohort studies had a sample size >100,000 participants, whereas 8 studies had a sample size of 1000–100,000 participants. Finally, 5 studies enrolled <1000 patients. The participants were mainly elderly, followed by middle-aged adults, young adults and pregnant women.

One study investigated PM1, 11 studies investigated PM2.5, 5, 56, 59, 65, 67, 68 and 1 study investigated PM10 and 1 study investigated PM with aerodynamic diameter between 2.5 and 10 μm (PM2.5–10). Most of the studies reported the annual mean concentration of PM, except studies by Mazzucchelli et al and Wu et al that used the daily mean PM levels (averaged across the study period). WHO air quality guidelines stated that the annual mean PM2.5 and PM10 levels should not exceed 10 and 20 μg/m3 respectively. The permissible limit for PM1 has not been established by WHO or other organisations. Most of the study locations had PM level exceeding the permissible limit with an annual mean PM2.5 levels ≤10 μg/m3, 10–20 μg/m3, 20–30 μg/m3, 30–40 μg/m3, 40–50 μg/m3, 50–60 μg/m3, 60–70 μg/m3, 70–80 μg/m3, 80–90 μg/m3, 90–100 μg/m3, 100–110 μg/m3, 110–120 μg/m3, 120–130 μg/m3, 130–140 μg/m3, 140–150 μg/m3, 150–160 μg/m3, 160–170 μg/m3, 170–180 μg/m3, 180–190 μg/m3, 190–200 μg/m3, 200–210 μg/m3, 210–220 μg/m3, 220–230 μg/m3, 230–240 μg/m3, 240–250 μg/m3, 250–260 μg/m3, 260–270 μg/m3, 270–280 μg/m3, 280–290 μg/m3, 290–300 μg/m3, 300–310 μg/m3, 310–320 μg/m3, 320–330 μg/m3, 330–340 μg/m3, 340–350 μg/m3, 350–360 μg/m3, 360–370 μg/m3, 370–380 μg/m3, 380–390 μg/m3, 390–400 μg/m3, 400–410 μg/m3, 410–420 μg/m3, 420–430 μg/m3, 430–440 μg/m3, 440–450 μg/m3, 450–460 μg/m3, 460–470 μg/m3, 470–480 μg/m3, 480–490 μg/m3, 490–500 μg/m3, 500–510 μg/m3, 510–520 μg/m3, 520–530 μg/m3, 530–540 μg/m3, 540–550 μg/m3, 550–560 μg/m3, 560–570 μg/m3, 570–580 μg/m3, 580–590 μg/m3, 590–600 μg/m3, 600–610 μg/m3, 610–620 μg/m3, 620–630 μg/m3, 630–640 μg/m3, 640–650 μg/m3, 650–660 μg/m3, 660–670 μg/m3, 670–680 μg/m3, 680–690 μg/m3, 690–700 μg/m3, 700–710 μg/m3, 710–720 μg/m3, 720–730 μg/m3, 730–740 μg/m3, 740–750 μg/m3, 750–760 μg/m3, 760–770 μg/m3, 770–780 μg/m3, 780–790 μg/m3, 790–800 μg/m3, 800–810 μg/m3, 810–820 μg/m3, 820–830 μg/m3, 830–840 μg/m3, 840–850 μg/m3, 850–860 μg/m3, 860–870 μg/m3, 870–880 μg/m3, 880–890 μg/m3, 890–900 μg/m3, 900–910 μg/m3, 910–920 μg/m3, 920–930 μg/m3, 930–940 μg/m3, 940–950 μg/m3, 950–960 μg/m3, 960–970 μg/m3, 970–980 μg/m3, 980–990 μg/m3, 990–1000 μg/m3.

The bone health status was reported either as fracture incidence, BMC and BMD assessed via DXA or QUS method. BMDs of total body, pelvic, hip, femoral neck, lumbar spine, distal forearm, distal radius and ultradistal radius were measured. Besides, Lin et al, Qiao et al and Wu et al measured bone health via QUS method without DXA validation. Four studies adopted the WHO definition of osteopenia and/or osteoporosis to classify the subjects, defined subjects with Z-score ≤ −1 as having low BMD, which does not comply with the existing recommendation. Adjusted regression coefficient (β), odd ratio (OR), mean differences or Pearson correlation coefficient were used in these studies to
demonstrate the association between PM and bone mass. For the association between PM and bone fracture, β, adjusted hazard ratio, incidence rate ratio (IRR), OR and risk ratio were used.

**Relationship Between PM Exposure and Bone Health or Osteoporosis Risk**

The relationship between PM and bone health was scarce. Only a study by Qiao et al demonstrated that osteoporosis risk was positively associated with PM exposure after multivariate adjustment. Logistic regression analysis also showed that every 1 μg/m³ increase in PM was associated with a 14.9% increased risk of osteoporosis. Besides, an estimated 20.29% of PM-related osteoporosis cases could be prevented if PM exposure was <55.2 μg/m³. Subgroup analysis revealed that the association between PM and osteoporosis was significantly higher among non-alcoholic drinkers, but it was not affected by age, sex, smoking, vegetable or fruit consumption and physical activity. However, this study classified osteoporosis based on QUS assessment of non-dominant foot without DXA validation, which could introduce misclassification bias in the study.

The relationship of PM and/or PM exposure with bone mass or osteoporosis risk was heterogeneous in other reports, whereby they revealed an insignificant or negative association. A cross-sectional study (Oslo Health study) on 1039 subjects aged 59–60 and 75–76 years old by Alver et al demonstrated that the distal forearm BMD was not significantly associated with PM and PM exposure regardless of age and sex after multivariate adjustment. Similarly, a cross-sectional study by Chen et al reported that ambient PM exposure was not significantly associated with total body and pelvic BMDs among 1173 Mexican American women with an average age of 34.4 years after covariate adjustment. Lee et al reported that osteoporosis risk was not significantly associated with PM exposure among 70 COPD patients aged 75.2 ± 5.5 years after multivariate adjustment. Similarly, Prada et al also reported that PM exposure was not significantly associated with femoral neck and ultradistal radius BMDs in a population-based prospective cohort study with 692 men aged 30–79 years old after 8-year of follow-up. Another recent cross-sectional study by Lin et al on 4595 Taiwanese (49.7 ± 10.7 years old) also revealed that PM exposure was not significantly associated with QUS readings of the non-dominant foot. In their study, the bone health of subjects remained normal even they were exposed to higher levels of PM.

Other studies demonstrated that PM exposure is a significant risk factor for osteoporosis. The cross-sectional Oslo study (590 men aged 75–76 years) demonstrated that total body BMD was negatively associated with PM and PM exposure. Besides, the risk of low total body BMD (Z-score <1) was positively associated with PM and PM exposures. Similarly, a cross-sectional study involving 105 Romanians by Cevei and Stoicanescu reported that the total body BMD (but not hip) was negatively associated with PM exposure without covariate adjustment. Additionally, a similar negative association of PM and PM exposure with bone health was reported in two recent cross-sectional studies by Qiao et al and Ranzani et al. The osteoporosis risk was positively associated with PM and PM exposure among 8033 Chinese (55.8 ± 10.8 years old) from the rural area after multivariate adjustment. Subsequent logistic regression analysis also demonstrated that every 1 μg/m³ increase in PM and PM exposure were associated with a respective 14.6% and 7.3% increase in osteoporosis risk. Besides, an estimated 23.20% and 24.36% of PM and PM-related osteoporosis cases could be prevented if PM and PM exposure were less than 70.5 and 125.8 μg/m³ respectively. Subgroup analysis also demonstrated similar associations between osteoporosis risk and PM and PM exposure among non-alcoholic drinkers or subjects with low physical activity. Ranzani et al reported that PM was associated with lumbar spine BMC but not with left hip BMC, left hip BMD and lumbar spine BMD among 3717 Indian (35.7 ± 14 years old) after multivariate adjustment. Subgroup analysis revealed PM exposure was also negatively associated with left hip BMC and BMD, as well as lumbar spine BMC among subjects aged ≥40 years old.

Another recent prospective cohort study on 941 Mexican pregnant women with 3-year of follow-up by Wu et al also reported that maternal trabecular bone health was negatively associated with PM exposure during first- and third-trimester exposure. Besides, maternal cortical bone health was also negatively associated with PM exposure during the first trimester. A time-specific subgroup analysis revealed that these associations were biphasic across the time of exposure. PM exposure during 60-day preconception was positively associated with maternal bone health during mid-to-late gestation.
but turned into a negative association during 1 to 6 months post-partum period.\textsuperscript{94} PM\textsubscript{2.5} exposures during the first- and second-trimester were initially negatively associated with trabecular and cortical bone health during mid-to-late gestation but then positively associated with bone health during 1 to 6 months post-partum.\textsuperscript{94} Higher PM\textsubscript{2.5} exposure during the third trimester and first month post-partum predicted a slower post-partum bone health recovery.\textsuperscript{94} Wu et al considered the radius and proximal phalanx of the middle finger to represent trabecular and cortical bones respectively. We believed that it is a misnomer as QUS cannot differentiate between trabecular and cortical bone, particularly at the radius, which consists of both trabecular and cortical bones.

**Relationship of PM Exposure and Bone Fractures**

Similar to bone health, the relationship between PM exposure with bone fracture was also heterogeneous, wherein insignificant\textsuperscript{82,89–91} or positive associations\textsuperscript{89–91} have been reported. A cross-sectional study from Alver et al\textsuperscript{82} reported that self-reported forearm fracture was not significantly associated with PM\textsubscript{2.5} and PM\textsubscript{10} exposure among 5976 elderly regardless of age and sex. Besides, a retrospective cohort study by Mazzucchelli et al\textsuperscript{90} reported PM\textsubscript{2.5} and PM\textsubscript{10} were not significantly associated with hip fracture among 4271 elderly aged 83.8 ± 8.9 years after univariate or multivariate adjustment. Parallelly, another retrospective study by Ormeño Illanesalso and Quevedo Langenegger\textsuperscript{91} on 8322 Chilean people aged ≥65 years also reported that the association between PM\textsubscript{2.5} and osteoporotic hip fracture was not significant regardless of sex. Subjects from Magallanes (the lowest PM\textsubscript{2.5} region in Chile) and Aysén region (the highest PM\textsubscript{2.5} region) showed similar IRR for bone fractures.\textsuperscript{91} Nevertheless, the results of this study were not adjusted for confounding factors.\textsuperscript{91}

On the other hand, a recent cross-sectional study from Sung et al\textsuperscript{89} on 44,602 South Korean women aged ≥50 years old revealed that PM\textsubscript{2.5} exposure but not PM\textsubscript{2.5–10} and PM\textsubscript{10} was positively associated with osteoporotic fractures, including both spine and non-spine fractures. A similar positive association was also reported after excluding the subjects with an osteoporotic fracture in the recent 1 to 2 years.\textsuperscript{88} Additionally, retrospective cohort studies by Prada et al\textsuperscript{93} demonstrated a positive association between osteoporotic-related bone fracture and PM\textsubscript{2.5} exposure among 763,630 residents aged ≥65 years old from Northeast-mid-Atlantic US states, which also present in men and women subgroups.\textsuperscript{93} A nearly linear relationship between PM\textsubscript{2.5} exposure and bone fracture rate was reported across the range between 3 and 22 μg/m\textsuperscript{3} PM\textsubscript{2.5} level.\textsuperscript{93} Besides, a recent retrospective cohort study on 178,147 South Korean aged 49.5 ± 12 years old by Oh et al\textsuperscript{92} also demonstrated that PM\textsubscript{10} was positively associated with hip fracture incidence after multivariate adjustment. Nevertheless, this study was limited by the relatively low hip fracture incidence (n = 919) compared to healthy control (n = 177,228).\textsuperscript{92}

**Discussion**

The relationships between PM exposure, including PM\textsubscript{1}, PM\textsubscript{2.5}, PM\textsubscript{2.5–10} and PM\textsubscript{10}, with bone health and fracture incidence are not conclusive based on current evidence. PM\textsubscript{2.5} and/or PM\textsubscript{10} exposures were demonstrated to be associated with bone fracture positively\textsuperscript{89,92,93} or not significantly\textsuperscript{82,89–91} Similarly, the association between PM\textsubscript{2.5} and/or PM\textsubscript{10} with bone mass was negative\textsuperscript{81,83,87,88,94} or not significant.\textsuperscript{82,84–86,93} Interestingly, Wu et al demonstrated a time-specific biphasic association between PM\textsubscript{2.5} exposure and bone health measured by QUS among pregnant women. On the other hand, relevant findings on PM\textsubscript{1} are scarce as only one study demonstrates a positive association with osteoporosis.\textsuperscript{87} The relationship between PM\textsubscript{1} and bone fracture is yet to be determined. Besides, only one study reported a non-significant association between PM\textsubscript{2.5–10} and osteoporotic fractures,\textsuperscript{89} and its relationship with bone mass is yet to be determined.

The inconsistent findings in the relationship between PM and bone mass/fracture may be partly due to the heterogeneous sample size. Five included studies with sample sizes of less than 1000 patients may not accurately represent the studied population and introduce bias in interpretation.\textsuperscript{81,83,84,93,94} Besides, an appropriate adjustment for confounding factors is essential to avoid confounding effects and false interpretation of causality. For instance, Alver et al\textsuperscript{82} reported that distal forearm BMD was negatively associated with PM\textsubscript{2.5} and PM\textsubscript{10} levels among men aged 75–76 years old. However, these associations were not significant after adjustment for education, smoking, years of smoking, physical activity and years after menopause. Similarly, Ranzani et al\textsuperscript{88} also reported that the negative association between PM\textsubscript{2.5} exposure and lumbar spine BMD became insignificant after
adjusting for additional covariates. Additionally, several included studies did not perform covariate adjustment,\textsuperscript{83,91} casting some doubts on the validity of the results. Furthermore, critical covariates such as sunlight exposure, vitamin D level, dietary pattern and inflammatory status were not considered in most of the included studies, contributing to the inconsistency of findings.

Additionally, the detection methods of PM may partly contribute to the inconsistent findings in the relationship between PM and bone mass/fracture. PM metric like particle mass is commonly measured using gravimetric and optical methods.\textsuperscript{96} However, these detection technologies vary in terms of practicability (cost, size, noisiness and mobility), precision, accuracy and sensitivity/detection limits.\textsuperscript{96} Studies included in the current review assessed the PM data, but the underlying detection technologies were not disclosed. Additionally, PM statistical modelling is commonly used to estimate and predict indoor air quality and individual exposure to PM because direct individual PM exposure measurement is technically impractical or difficult to be performed.\textsuperscript{97} There are several factors needed to be considered in developing and calibrating the PM levels, including geographical location, meteorological/climate conditions and aerosol optical depth.\textsuperscript{97,98} Most studies employed a spatiotemporal prediction model by adjusting the subjects’ geographical or residential location. However, some studies did not describe how individual PM exposure estimation was performed or PM modelling was developed.\textsuperscript{83,84,89,91,92} Some studies employed the previously reported prediction model\textsuperscript{81,82} or self-developed spatiotemporal prediction model without disclosing the cross-validation values.\textsuperscript{85,86,90} In several studies, the PM model was adjusted/calibrated for climate, weather and/or traffic conditions.\textsuperscript{85,87,93,94} However, some studies like Lee et al and Mazzucchelli et al measured the climate and weather conditions but did not include them in PM model calibration.\textsuperscript{84,90} The remaining studies did not disclose the PM modeling calibration. It is noteworthy that variations in PM modelling may contribute to inaccurate individual PM exposure estimation, leading to inconsistency in the findings between PM exposure and bone health.

Osteoporosis is diagnosed based on the BMD T-score of any major common bone fracture sites, such as at the spine, hip or mid-radius.\textsuperscript{44} However, T-score discordance at different bone sites is not an unusual observation,\textsuperscript{100–103} probably due to the non-homogeneous process of bone loss.\textsuperscript{103,104} Increasing the number of bone sites scanned will increase the chance of discordance and detecting osteoporosis.\textsuperscript{105} Thus, the number of bone sites examined could influence the relationship between PM exposure and osteoporosis risk. As evidence, Cevei and Stoicanescu\textsuperscript{83} and Ranzani et al\textsuperscript{88} demonstrated inconsistent associations between PM and bone mass at different sites. Moreover, several studies\textsuperscript{81,83,85} employed the total body BMD as the skeletal outcome of interest, which is less sensitive than regional BMDs.\textsuperscript{106} Although total body BMD correlates with regional BMDs,\textsuperscript{103} this value is not used to diagnose osteoporosis per WHO recommendation. Besides, some studies used QUS to define the bone health of the subjects.\textsuperscript{86,87,94} DXA and QUS adopt different technology in identifying bone health, so their results are not interchangeable.\textsuperscript{48} The WHO classification system to diagnose osteoporosis based on BMD T-score cannot be used for QUS.\textsuperscript{106} Although QUS indices correlate with bone mass and several bone microarchitectural indices,\textsuperscript{48} they cannot be used directly to infer bone strength as in the studies of Wu et al.\textsuperscript{94} A biomechanical assessment, like the three-point bending flexural test,\textsuperscript{107} can indicate bone strength directly.\textsuperscript{105} However, the destructive nature of this test prohibits its use among live subjects. Reference point indentation or micro-indentation test is an alternative method to estimate bone strength in vivo directly.\textsuperscript{109} Additionally, PM species are generally present together\textsuperscript{82,87} and coexist with other air pollutants like nitrogen monoxide, NO\textsubscript{2} and SO\textsubscript{2}.\textsuperscript{87,90} These air pollutants were reported positively correlated with osteoporosis risk.\textsuperscript{86,99} Besides, there are synergistic effects between CO-nitrogen oxide and SO\textsubscript{2}-NO\textsubscript{2}, which could further reduce BMD.\textsuperscript{86} Therefore, it is impossible to attribute the skeletal effects to a single PM species or single air pollutants. Additionally, residential proximity to the nearest freeway (≤500 m) but not PM\textsubscript{2.5}, NO\textsubscript{2} and O\textsubscript{3} exposure was negatively associated with total body and pelvic BMD after multivariate adjustment, including the pollutants levels.\textsuperscript{85} This observation suggests that other air pollutants like PAHs or black carbon from vehicle exhaust emissions might also contribute to BMD reduction.\textsuperscript{85,88}

Previous studies observed a higher bone mass and fewer bone fractures among subjects from rural areas than urban areas.\textsuperscript{110–121} Several factors such as occupation, lifestyle, physical activity, dietary pattern and traffic accident are attributed to this observation. It would be interesting to ask whether air quality could contribute to the difference in bone health between rural and urban populations. However, studies included in this review showed that it might be erroneous to presume rural areas are less polluted. For instance, Qiao et al\textsuperscript{87}
demonstrated 6 to 7 times high annual mean PM$_{2.5}$ and PM$_{10}$ levels in the rural area than the WHO air quality standard. High PM levels in the rural area could be contributed by increasing numbers of factory and biomass usage or burning fuel activities.\textsuperscript{53,59,87,122} Besides, biomass cooking in the rural area had been demonstrated to produce significantly higher PM$_{2.5}$ and/or PM$_{10}$ levels compared with liquid petroleum gas.\textsuperscript{53,59}

This systematic review, like others, has its limitations. This review did not include unpublished, grey literature and proceeding articles without complete data. Besides, we limited those studies in the recent 30 years as PM-related research began receiving attention from 1990 onwards.\textsuperscript{123} However, it is still possible that we might miss out on some important studies. We tried to minimise this limitation by referring to the reference lists of included articles. Moreover, we did not perform a meta-analysis due to the heterogeneity of the study design, outcomes and analysis. The included studies consisted of cross-sectional, retrospective and prospective cohort studies adopting various statistical strategies, the definition of bone health and PM types, hindering meta-analysis from being conducted.

**Conclusion**

The current literature suggests an inconclusive association between PM exposures and osteoporosis risk and/or fracture, potentially due to the heterogeneity in subject characteristics, study design, sample size, outcome measurement and covariate adjustment during analysis among various studies. Further validation in human studies is required to validate the positive association between PM$_{2.5}$ and/or PM$_{10}$ and osteoporosis risk or fracture. Furthermore, most of the studies emphasised on PM$_{2.5}$ and PM$_{10}$ with a limited number of studies on PM$_{1}$. It is crucial to investigate the potential relationship between PM$_{1}$ and other ultrafine particles with bone health/fracture.

**Acknowledgments**

The authors thank the Universiti Kebangsaan Malaysia for the Research University Grant under grant number GUP-2020-021. K.-L.P. and S.O.E are post-doctoral researchers funded by Universiti Kebangsaan Malaysia through RGA-1 and FPR-1 grants.

**Disclosure**

The authors report no conflicts of interest in this work.

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**References**

1. World Health Organization. Air pollution; 2021. Available from: https://www.who.int/health-topics/air-pollution#tab-tab_1. Accessed March 23, 2021.

2. Chau TT, Wang KY. An association between air pollution and daily most frequently visits of eighteen outpatient diseases in an industrial city. Sci Rep. 2020;10. doi:10.1038/s41598-020-58721-0

3. Liu C, Ying Z, Harkema J, et al. Epidemiological and experimental links between air pollution and type 2 diabetes. Toxicol Pathol. 2013;41:361–373. doi:10.1177/01926331244531

4. Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci. 2009;32 (9):506–516. doi:10.1016/j.tins.2009.05.009

5. Brook Robert D, Rajagopalan S, Pope CA, et al. Particulate matter air pollution and cardiovascular disease. Circulation. 2010;121(21):2331–2378. doi:10.1161/CIR.0b013e3181dbee1

6. Jiang X-Q, Mei X-D, Deng D. Air pollution and chronic airway diseases: what should people know and do? J Thorac Dis. 2016;8 (1):E31–E40. doi:10.3978/j.issn.2072-1439.2015.11.50

7. Michalska M, Zorena K, Wąz P; et al. Gaseous pollutants and particulate matter (pm) in ambient air and the number of new cases of type 1 diabetes in children and adolescents in the pomeranian voivodeship, poland. Biomed Res Int. 2020;2020:1648264. doi:10.1155/2020/1648264.

8. Ou JY, Hanson HA, Ramsay JM, et al. Fine particulate matter and respiratory healthcare encounters among survivors of childhood cancers. Int J Environ Res Public Health. 2019;16(6):1081. doi:10.3390/ijerph16061081

9. Garcia-Perez J, Gomez-Barroso D, Tamayo-Uria I, et al. Methodological approaches to the study of cancer risk in the vicinity of pollution sources: the experience of a population-based case-control study of childhood cancer. Int J Health Geogr. 2019;18. doi:10.1186/s12942-019-0176-x

10. World Health Organization. Air quality and health; Types of pollutants; 2021. Available from: https://www.who.int/teams/environment-climate-change-and-health/air-quality-and-health/pollutants;environment-climate-change-and-health/air-quality-and-health/health-impacts/types-of-pollutants. Accessed March 23, 2021.

11. Najar YSH. Gaseous pollutants formation and their harmful effects on health and environment. Innov Energy Policies. 2011;1:1–9. doi:10.4303/iep/E101203

12. Chow JC, Watson JG. Guideline on Speciated Particulate Monitoring. New York city, USA: US Environmental Protection Agency; 1998.

13. Davidson CI, Phalen RF, Solomon PA. Airborne particulate matter and human health: a review. Aerosol Sci Technol. 2005;39 (8):737–749. doi:10.1080/02786820500191348

14. Harrison RM, Yin J. Particulate matter in the atmosphere: which particle properties are important for its effects on health? Sci Tot Environ. 2000;249(1):85–101. doi:10.1016/S0048-9697(99)00513-6

15. Li D, Li Y, Li G, et al. Fluorescent reconstitution on deposition of pm2.5 in lung and extrapulmonary organs. Proc Natl Acad Sci. 2019;116(7):2488. doi:10.1073/pnas.181834116

16. Cao L, Zeng J, Liu K, et al. Characterisation and cytotoxicity of pm<0.2, pm<0.2-2.5 and pm<2.5-10 around mswi in shanghai, china. Int J Environ Res Public Health. 2015;12(5):5076–5089. doi:10.3390/ijerph12055076

17. Haghani A, Johnson R, Safi N, et al. Toxicity of urban air pollution particulate matter in developing and adult mouse brain: comparison of total and filter-elfuted nanoparticles. Environ Int. 2020;136:105510. doi:10.1016/j.envint.2020.105510

18. Brezina J, Kůbůlová K, Adamec V. Nanoparticle number concentration in the air in relation to the time of the year and time of the day. Atmosphere. 2020;11(5):523. doi:10.3390/atmos11050523
19. Corbin JC. Pm0.1 particles from aircraft may increase risk of vascular disease. BMJ. 2013;347:f6783. doi:10.1136/bmj.f6783
20. Cao G, Zhang X, Gong S, et al. Emission inventories of primary particles and pollutant gases for china. Chin Sci Bull. 2011;56(8):781–788. doi:10.1007/s11434-011-4373-7
21. Dominici F, Greenstone M, Sunstein CR. Particulate matter matters. Science. 2014;344(6181):257. doi:10.1126/science.1247348
22. Pope CA 3rd, Dockery DW. Acute health effects of pm10 pollution on symptomatic and asymptomatic children. Am Rev Respir Dis. 1992;145(5):1123–1128. doi:10.1164/ajrccm/145.5.1123
23. Dong L, Sun W, Li F, et al. The harmful effects of acute pm2.5 exposure to the heart and a novel preventive and therapeutic function of ceos. Sci Rep. 2019;9(1):3405. doi:10.1038/s41598-019-40204-6
24. Zhang L, Yang Y, Li Y, et al. Short-term and long-term effects of pm2.5 on acute nasopharyngitis in 10 communities of Guangdong, China. Sci Tot Environ. 2019;688:136–142. doi:10.1016/j.scitotenv.2019.05.470
25. Hvidtfeldt UA, Sørensen M, Geels C, et al. Long-term residential exposure to pm2.5, pm10, black carbon, no2, and ozone and mortality in a Danish cohort. Environ Int. 2019;123:265–272. doi:10.1016/j.envint.2018.12.010
26. Klooj I, Ridgway B, Koutrakis P, et al. Long- and short-term exposure to pm2.5 and mortality: using novel exposure models. Epidemiology (Cambridge, Mass). 2013;24(4):555–561. doi:10.1097/ede.0b013e318294beaa
27. Pope CA, Burnett RT, Thurston GD, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation. 2004;109:71–77. doi:10.1161/01.CIR.0000108927.80044.7F
28. Consonni D, Carugno M, De Matteis S, et al. Outdoor particulate matter (pm10) exposure and lung cancer risk in the eagle study. PLOS One. 2018;13(9):e0203539. doi:10.1371/journal.pone.0203539
29. Madureira J, Slezakova K, Silva AI, et al. Assessment of indoor air exposure at residential homes: inhalation dose and lung deposition of pm10, pm2.5 and ultrafine particles among newborn children and their mothers. Sci Tot Environ. 2020;717:137293. doi:10.1016/j.scitotenv.2020.137293
30. Chen C-H, Wu C-D, Chiang H-C, et al. The effects of fine and coarse particulate matter on lung function among the elderly. Sci Rep. 2019;9(1):14790. doi:10.1038/s41598-019-51307-5
31. Manoj Kumar N, Sm BS, SN. Quantification of size segregated particulate matter deposition in human airways. J Adv Res Altern Energy Environ Ecol. 2018;5:15–22. doi:10.24321/2455.3093.201803
32. Guo Z, Hong Z, Dong W, et al. Pm2.5-induced oxidative stress and mitochondrial damage in the nasal mucosa of rats. Int J Environ Res Public Health. 2017;14(2):134. doi:10.3390/ijerph14020134
33. He M, Ichinose T, Yoshida Y, et al. Urban pm2.5 exacerbates allergic inflammation in the murine lung via a tlr2/tlr4/myd88-signaling pathway. Sci Rep. 2017;7(1):1–9. doi:10.1038/s41598-016-0028-x
34. Li T, Hu R, Chen Z, et al. Fine particulate matter (pm2.5): the culprit for chronic lung diseases in china. Chronic Dis Transl Med. 2018;4(3):176–186. doi:10.1016/j.cdtm.2018.07.002
35. O’Callaghan-Gordo C, Fthenou E, Pedersen M, et al. Outdoor air pollution exposures and micronuclei frequencies in lymphocytes from pregnant women and newborns in Crete, Greece (rhea cohort). Environ Res. 2015;143:170–176. doi:10.1016/j.envres.2015.10.011
36. Dumax-Vorzet AF, Tate M, Walmsley R, et al. Cytotoxicity and genotoxicity of urban particulate matter in mammalian cells. Mutagenesis. 2015;30(5):621–633. doi:10.1093/mutage/gev025
37. Wang T, Xia Z, Wu M, et al. Pollution characteristics, sources and lung cancer risk of atmospheric polycyclic aromatic hydrocarbons in a new urban district of Nanjing, China. J Environ Sci (China). 2017;55:118–128. doi:10.1016/j.jes.2016.06.025
38. Ginaldi L, Di Benedetto MC, De Martinis M. Osteoporosis, inflammation and ageing. Immun Ageing. 2005;2:14. doi:10.1186/1742-4933-2-14
39. Chin K, Pang K, Soelaiman IN. Tocotrienol and its role in chronic disease. In: Gupta SC, Prasad S, Aggarwal BB, editors. Anti- Inflammatory Nutraceuticals and Chronic Diseases. Vol. 928. Switzerland: Springer International Publishing; 2016:97–130.
40. Wong SK, Chin K-Y, Suhaimi FH, et al. The relationship between metabolic syndrome and osteoporosis: a review. Nutrients. 2016;8(6). doi:10.3390/nu8060347
41. Looker AC, Sarafrazi Isfahani N, Fan B, et al. Trends in osteoporosis and low bone mass in older us adults, 2005–2006 through 2013–2014. Osteoporos Int. 2017;28(6):1979–1988. doi:10.1007/s00198-017-3996-1
42. Alsawat KA. Gender disparities in osteoporosis. J Clin Med Res. 2017;9(5):382–387. doi:10.14740/jocm2970w
43. Frost SA, Nguyen ND, Center JR, et al. Excess mortality attributable to hip fracture: a relative survival analysis. Bone. 2013;56(1):23–29. doi:10.1016/j.bone.2013.05.006
44. World Health Organization. Assessment of Fracture Risk and Its Application to Screening for Postmenopausal Osteoporosis: Report of a Who Study Group. World Health Organization; 1994:9241208430.
45. World Health Organization. Who Scientific Group on the Assessment of Osteoporosis at Primary Health Care Level. Brussels, Belgium; May 5–7, 2004.
46. International Osteoporosis Foundation. Diagnosis. 2021; Available from: https://www.osteoporosis.foundation/patients/diagnosis. Accessed March 20, 2021.
47. Subramaniam S, Chan CY, Soelaiman IN, et al. The performance of a calcaneal quantitative ultrasound device, cm-200, in stratifying osteoporosis risk among Malaysian population aged 40 years and above. Diagnostics (Basel). 2020;10(4). doi:10.3390/diagnostics10040178
48. Chin KY, Ima-Nirwana S. Calcaneal quantitative ultrasound as a determinant of bone health status: what properties of bone does it reflect? Int J Med Sci. 2013;10(12):1778–1783. doi:10.7150/ijms.6765
49. Compton J, Cooper A, Cooper C, et al. UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos. 2017;12(1):43. doi:10.1007/s11575-017-0324-5
50. Nguyen TV. Air pollution: a largely neglected risk factor for osteoporosis. Lancet Planet Health. 2018;2:e311–e312. doi:10.1016/S2542-5196(17)30143-2
51. Nguyen VH. Environmental air pollution and the risk of osteoporosis and bone fractures. J Prev Med Public Health. 2018;51:215–216. doi:10.3961/jpmph.18.114
52. Prada D, López G, Solleiro-Villavicencio H, et al. Molecular and cellular mechanisms linking air pollution and bone damage. Environ Res. 2020;185:109465. doi:10.1016/j.envres.2020.10.09465
53. Saha H, Mukherjee B, Bindhani B, et al. Changes in rankl and osteoprotegerin expression after chronic exposure to indoor air pollution as a result of cooking with biomass fuel. J Appl Toxicol. 2015;36:969–976. doi:10.1002/jat.3275
54. Peters A, Frohlich M, Doring A, et al. Particulate air pollution is associated with an acute phase response in men - results from the Monica-Augsburg study. Eur Heart J. 2001;22:1198–1204. doi:10.1053/euhj.2000.2483
55. Vossoughi M, Schikowski T, Vierkotter A, et al. Air pollution and subclinical airway inflammation in the salia cohort study. Immun Ageing. 2014;11. doi:10.1186/1742-4933-11-5
56. Su TC, Hwang JJ, Yang YR, et al. Association between long-term exposure to traffic-related air pollution and inflammatory and thrombotic markers in middle-aged adults. *Epidemiology*. 2017;28:574–581. doi:10.1097/EDE.0000000000000715

57. Shepherd A, Mullins JT. Arthritis diagnosis and early-life exposure to air pollution. *Environ Pollut*. 2019;253:1030–1037. doi:10.1016/j.envpol.2019.07.054

58. Abolahsem S, Osborne MT, Dar T, et al. A leucopoietic-arterial axis underlying the link between ambient air pollution and cardiovascular disease in humans. *Ear Heart J*. 2021;42:761–772. doi:10.1093/eurheartj/ehaa982

59. Dutta A, Bhattacharya P, Lahiri T, et al. Immune cells and cardiovascular health in premenopausal women of rural India chronically exposed to biomass smoke during daily household cooking. *Sci Tot Environ*. 2012;438:293–298. doi:10.1016/j.scitotenv.2012.08.065

60. Hart JE, Laden F, Pueff RC, et al. Exposure to traffic pollution and increased risk of rheumatoid arthritis. *Environ Health Perspect*. 2009;117:1065–1069. doi:10.1289/ehp.0900503

61. Sigaux J, Biton J, Andre E, et al. Air pollution as a determinant of rheumatoid arthritis. *Joint Bone Spine*. 2018;86:37–42. doi:10.1016/j.jbspin.2018.03.001

62. Calderon-Garciduenas L, Mora-Tiscareno A, Francisco L, et al. Exposure to urban air pollution and bone health in clinically healthy six-year-old children. *Arch Hig Rada Toksikol*. 2013;64:23–34. doi:10.2478/10004-1254-6-2013-2219

63. Schett G. Effects of inflammatory and anti-inflammatory cytokines on the bone. *Earl Clin Invest*. 2011;41(12):1361–1366. doi:10.1111/j.1365-2362.2011.02545.x

64. Chin K-Y, Wong SK, Ekeuku SO, et al. Relationship between metabolic syndrome and bone health - an evaluation of epidemiological studies and mechanisms involved. *Diabetes Metab Syndr Obes*. 2020;13:3667–3690. doi:10.2147/DMSO.S275560

65. Ekeuku SO, Pang K-L, Chin K-Y. Effects of caffeic acid and its derivatives on bone: a systematic review. *Drug Des Devel Ther*. 2020;14:241–256. doi:10.2147/DMSO.S291828

66. Mohd Ramli ES, Sukalingam K, Kamaruzzaman MA, et al. Direct and indirect effect of honey as a functional food against metabolic syndrome and its skeletal complications. *Diabetes Metab Syndr Obes*. 2021;14:241–256. doi:10.2147/DMSO.S291828

67. Afzar B, Elsurer afsar R, Kanbay A, et al. Air pollution and kidney disease: review of current evidence. *Clin Kidney J*. 2019;12(1):19–32. doi:10.1093/ckj/ssf111

68. Bowe B, Xie Y, Li T, et al. Associations of ambient coarse particulate matter, nitrogen dioxide, and carbon monoxide with the risk of kidney disease: a cohort study. *Lancet Planet Health*. 2017;1(7):e267. doi:10.1016/S2542-5196(17)30117-1

69. Bowe B, Xie Y, Li T, et al. Particulate matter air pollution and the risk of incident CKD and progression to esrd. *J Am Soc Nephrol*. 2018;29(1):218–230. doi:10.1681/ASN.2017030253

70. Xu X, Wang G, Chen N, et al. Long-term exposure to air pollution and increased risk of membranous nephropathy in china. *J Am Soc Nephrol*. 2016;27(12):3739–3746. doi:10.1681/ASN.2016010093

71. Wang N, Li M, Huang L, et al. The relationship between pm2.5 and the action spectrum of ultraviolet radiation for vitamin d production based on a manikin model. *IEEE Access*. 2020;1.

72. Luo H, Han Y, Lu C, et al. Characteristics of surface solar radiation under different air pollution conditions over Nanjing, China: observation and simulation. *Adv Atmos Sci*. 2019;36(10):1047–1059. doi:10.1007/s00376-019-9010-4

73. Liu J, Zhang W. The influence of the environment and clothing on human exposure to ultraviolet light. *PLoS One*. 2015;10:e0124758. doi:10.1371/journal.pone.0124758

74. Agarwal KS, Mughal MZ, Upadhyay P, et al. The impact of atmospheric pollution on vitamin d status of infants and toddlers in Delhi, India. *Arch Dis Child*. 2002;87(2):111–113. doi:10.1136/adc.87.2.111

75. Hosseimpanah F, Pour SH, Heibatollahi M, et al. The effects of air pollution on vitamin d status in healthy women: a cross sectional study. *BMC Public Health*. 2010;10. doi:10.1186/1471-2458-10-519

76. Feizabad E, Hossein-nezhad A, Maghbbooli Z, et al. Impact of air pollution on vitamin d deficiency and bone health in adolescents. *Arch Osteoporos*. 2017;12(1). doi:10.1007/s11571-017-0323-6

77. Matsuawaa M, Amano Y, Endo K, et al. The aryl hydrocarbon receptor activator benzo[a]pyrene enhances vitamin d3 catabolism in macrophages. *Toxical Sci*. 2009;109(1):50–58. doi:10.1093/toxsci/kfp104

78. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the prisma statement. *BMJ*. 2009;339:b2535. doi:10.1136/bmj.b2535

79. Ma LL, Wang YY, Zhang ZH, et al. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? *Mil Med Res*. 2020;7(1).7

80. JBI. Critical appraisal tools; 2020. Available from: https://jbi.global/critical-appraisal-tools. Accessed February 18, 2021.

81. Alver K, Meyer HE, Falch JA, et al. Outdoor air pollution and bone mineral density in elderly men - the Oslo health study. *Osteoporos Int*. 2007;18(12):1669–1674. doi:10.1007/s00198-007-0424-y

82. Alver K, Meyer HE, Falch JA, et al. Outdoor air pollution, bone density and self-reported forearm fracture: the Oslo health study. *Osteoporos Int*. 2010;21:1751–1760. doi:10.1007/s00198-009-1130-8

83. Cevei M, Stoicanescu D. Air pollution and genetic influences on bone mineral density and osteoporosis. *Analele Univ din Oradea Fasc Biol*. 2010;Tomi XVI.1/84–89.

84. Lee K-Y, Liu W-T, Kuo HP, et al. Air pollution exposure and osteoporosis among retired workers with chronic obstructive pulmonary disease. *Occup Med Health Aff*. 2014;2:167.

85. Chen Z, Salam MT, Karim R, et al. Living near a freeway is associated with lower bone mineral density among Mexican americans. *Osteoporos Int*. 2015;26(6):1713–1721. doi:10.1007/s00198-015-3051-z

86. Lin YH, Wang CF, Chiu H, et al. Air pollutants interaction and gender difference on bone mineral density t-score in Taiwanese adults. *Int J Environ Res Public Health*. 2020;17(24):1–15. doi:10.3390/ijerph17249165

87. Qiao D, Pan J, Chen G, et al. Long-term exposure to air pollution might increase prevalence of osteoporosis in Chinese rural population. *Environ Res*. 2020;183:109264. doi:10.1016/j.envres.2020.109264

88. Ranzani OT, Milá C, Kulkarni B, et al. Association of ambient and household air pollution with bone mineral content among adults in peri-urban south India. *JAMA Network Open*. 2020;3(1):e1918504. doi:10.1001/jamanetworkopen.2019.18504

89. Sung JH, Kim K, Cho Y, et al. Association of air pollution with osteoporotic fracture risk among women over 50 years of age. *J Bone Miner Metab*. 2020;38(6):839–847. doi:10.1007/s00774-020-01117-x

90. Mazzucchelli R, Crespi Villarias N, Perez Fernandez E, et al. Short-term association between outdoor air pollution and osteoporotic hip fracture. *Osteoporos Int*. 2018;29(10):2231–2241. doi:10.1007/s00198-018-4605-7

91. Ormeño Illanes JC, Quevedo Langenegger EI. Air quality and incidence of osteoporotic hip fracture in chile. *Rev Osteoporos Metab Miner*. 2019;11(4):87–91. doi:10.4321/S1889-836X2019000400002
92. Oh TK, Song IA. Exposure to air pollution and risk of hip fracture: a population-based cohort study with a 6-year follow-up in south korea. *J Occup Environ Med.* 2020;62(12):1034–1039. doi:10.1097/JOM.0000000000002041
93. Prada D, Zhong J, Colicino E, et al. Association of air particulate pollution with bone loss over time and bone fracture risk: analysis of data from two independent studies. *Lancet Planet Health.* 2017;1(8):e237. doi:10.1016/S2542-5196(17)30136-5
94. Wu HT, Kioumourtzoglou MA, Just AC, et al. Association of ambient pm2.5 exposure with maternal bone strength in pregnant women from mexico city: a longitudinal cohort study. *Lancet Planet Health.* 2020;4(5):e537. doi:10.1016/S2542-5196(20)30220-5
95. World Health Organization. Ambient (outdoor) air pollution; 2018. Available from: https://www.who.int/news-room/factsheets/detail/ambient-(outdoor)-air-quality-and-health. Accessed March 20, 2021.
96. Lowther SD, Jones KC, Wang X, et al. Particulate matter measurement indoors: a review of metrics, sensors, needs, and applications. *Environ Sci Technol.* 2019;53(20):11644–11656. doi:10.1021/acs.est.9b03425
97. Whalley J, Zandi S. Particulate Matter Sampling Techniques and Data Modelling Methods. In: Sallis PJ, editors. *Air Quality - Measurement and Modeling*. London: IntechOpen; 2016:29-54.
98. Wang Q, Zeng Q, Tao J, et al. Estimating pm(2.5) concentrations based on modis aod and naqpms data over Beijing-Tianjin-hebei. *Sensors (Basel, Switzerland).* 2019;19(5):1207. doi:10.3390/s19051207
99. Chang KH, Chang MY, Muo CH, et al. Exposure to air pollution increases the risk of osteoporosis: a nationwide longitudinal study. *Medicine (United States).* 2015;94(17):e733.
100. Azami A, Anari H, Iranparvar M, et al. Comparison of bone mineral density at 2 different sites at 3 sites in patients suspicious for osteoporosis. *Clin Med Insights Arthritis Musculoskel Disord.* 2019;12:117954119849017. doi:10.1177/117954119849017
101. Mounach A, Mouinga Abayi DA, Ghazi M, et al. Discordance between hip and spine bone mineral density measurement using DXA: prevalence and risk factors. *Semin Arthritis Rheum.* 2009;38(6):467–471. doi:10.1016/j.semarthrit.2008.04.001
102. Chan CY, Subramaniam S, Mohamed N, et al. Prevalence and factors of t-score discordance between hip and spine among middle-aged and elderly malaysians. *Arch Osteoporos.* 2020;15(1):142. doi:10.1186/s11657-020-00821-5
103. Franck H, Munz M. Total body and regional bone mineral densitometry (BMD) and soft tissue measurements: correlations of BMD parameter to lumbar spine and hip. *Calcif Tissue Int.* 2000;67(2):111–115. doi:10.1007/s00223001124
104. Ott SM. Cortical or trabecular bone: what’s the difference? *Am J Nephrol.* 2018;47(6):373–375. doi:10.1159/000489672
105. Boyanov MA. Whole body and regional bone mineral content and density in women aged 20–75 years. *Acta Endocrinol.* 2016;12(2):191–196. doi:10.4183/aeb.2016.191
106. Krieg MA, Barkmann R, Gonnelli S, et al. Quantitative ultrasound in the management of osteoporosis: the 2007 iscd official positions. *J Clin Densitom.* 2008;11(1):165–187. doi:10.1016/j.jocd.2007.12.011
107. Ekeaku SO, Thong BKS, Quraishia A, et al. The skeletal effects of short-term triple therapy in a rat model of gastric ulcer induced by helicobacter pylori infection. *Drug Des Devel Ther.* 2020;14:5359–5366. doi:10.2147/DDDT.S287239
108. Deckard C, Walker A, Hill BJF. Using three-point bending to evaluate tibia bone strength in ovariectomised young mice. *J Biol Phys.* 2017;43(1):139–148. doi:10.1007/s10867-016-9439-y
109. Arnold M, Zhao S, Ma S, et al. Microindentation – a tool for measuring cortical bone stiffness? *Bone Joint Res.* 2017;6(9):542–549. doi:10.1002/bjr.2016-0317.R2
110. Zeng X, Liu D, Zhao X, et al. Association of bone mineral density with lung function in a Chinese general population: the Xinxiang rural cohort study. *BMC Pulm Med.* 2019;19:239. doi:10.1186/s12890-019-1008-2
111. Mihailov CI, Nelatu MA. Effect of environmental air exposure on rheumatoid arthritis and post-menopausal osteoporosis. *J Environ Prot Ecol.* 2015;16:340–345.
112. Gärdsell P, Johnell O, Nilsson BE, et al. Bone mass in an urban and a rural population: a comparative, population-based study in southern sweden. *J Bone Miner Res.* 1991;6(1):67–75. doi:10.1002/jbmr.5650060112
113. Jönsson B, Gärdsell P, Johnell O, et al. Differences in fracture pattern between an urban and a rural population: a comparative population-based study in southern sweden. *Osteoporos Int.* 1992;2(6):269–273. doi:10.1007/BF01623811
114. Madhok R, Melton LJ 3rd, Atkinson EJ, et al. Urban vs rural increase in hip fracture incidence. Age and sex of 901 cases 1980–89 in Olmsted county, u.S.A.* Acta Orthop Scand.* 1993;64(5):543–548. doi:10.3109/17453679308993689
115. Kaastad TS, Meyer HE, Falch JA. Incidence of hip fracture in Oslo, Norway: differences within the city. *Bone.* 1998;22(2):175–178. doi:10.1016/S8756-3282(97)00247-0
116. Sanders KM, Nicholson GC, Ugoni AM, et al. Fracture rates lower in rural than urban communities: the Geelong osteoporosis study. *J Epidemiol Community Health.* 2002;56(6):466–470. doi:10.1136/jech.56.6.466
117. Meyer HE, Berntsen GK, Sogaard AJ, et al. Higher bone mineral density in rural compared with urban dwellers: the norepos study. *Am J Epidemiol.* 2004;160(11):1039–1046. doi:10.1093/aje/kwh337
118. Specker B, Binkley T, Fahrenwald N. Rural versus nonrural differences in BMC, volumetric BMD, and bone size: a population-based cross-sectional study. *Bone.* 2004;35(6):1389–1398. doi:10.1016/j.bone.2004.09.005
119. Emaas N, Olsen LR, Ahmed LA, et al. Hip fractures in a city in northern Norway over 15 years: time trends, seasonal variation and mortality: the Harstad injury prevention study. *Osteoporos Int.* 2011;22(10):2603–2610. doi:10.1007/s00198-010-1485-x
120. Omsland TK, Ahmed LA, Grønskag A, et al. More forearm fractures among urban than rural women: the norepos study based on the tromso study and the hunt study. *J Bone Miner Res.* 2011;26(4):850–856. doi:10.1002/jbmr.280
121. Gu W, Rennie KL, Lin X, et al. Differences in bone mineral status between urban and rural Chinese men and women. *Bone.* 2007;41(3):393–399. doi:10.1016/j.bone.2007.05.010
122. Sarmah CK, Bhagwati B. Impact of biomass fuels on health of women and children in rural assam: a statistical study. *Indian J Public Health Res Dev.* 2014;5(4):163–166. doi:10.5958/0976-5506.2014.00035.7
123. Fuzzi S, Baltensperger U, Carslaw K, et al. Particulate matter, air quality and climate: lessons learned and future needs. *Atmos Chem Phys.* 2015;15(14):8217–8299.
