Risk Management and Healthcare Policy

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REVIEW

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 $PM_{2.5}$ and PM_{10}. 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 $PM_{2.5}$

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and <1 μm as PM_1.[10] Ultrafine particles with aerodynamic diameter <0.2 μm[15–17] or ≤0.1 μm[18,19] 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] WHO[45] and the International Osteoporosis Foundation[46] 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.[2,53–62] 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 function[71] by reducing the surface solar[72] 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.

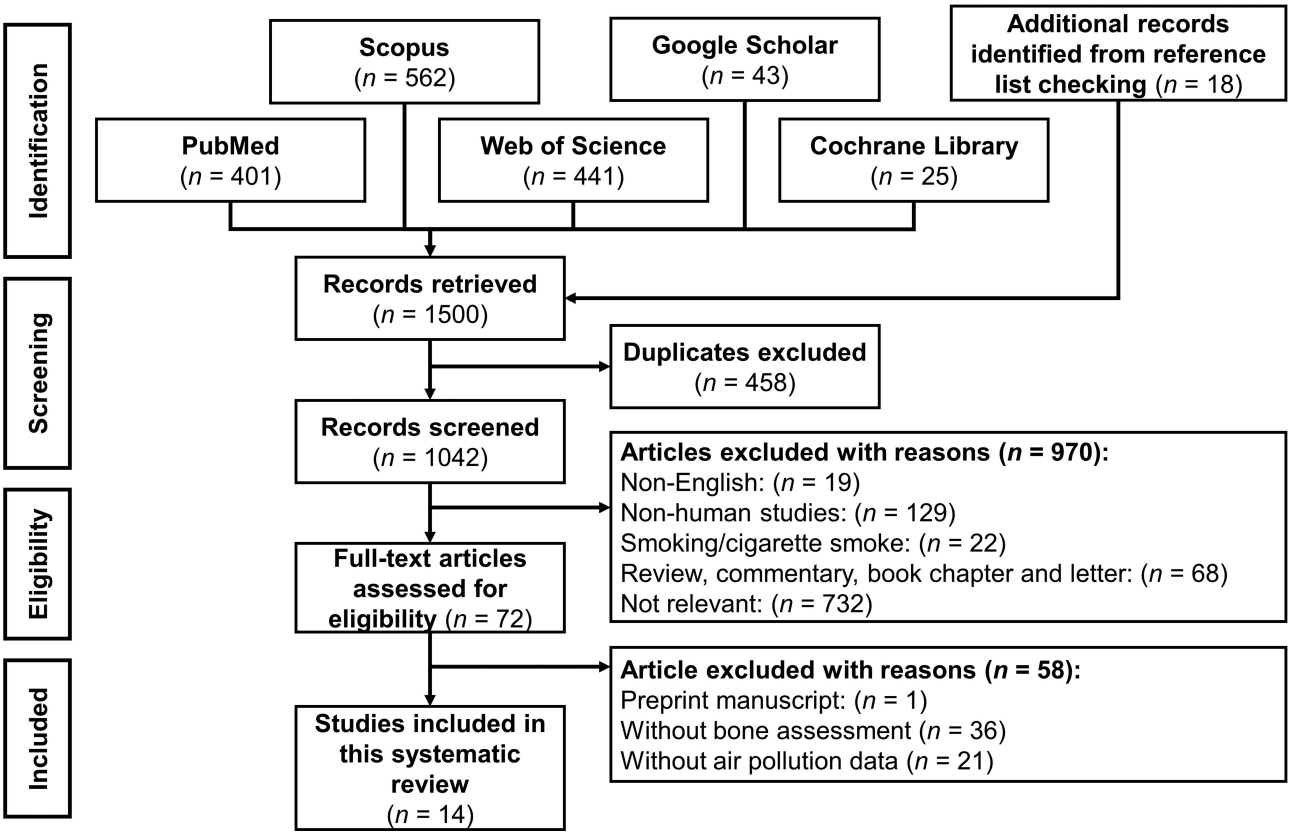

Figure 1 PRISMA flow chart of the systematic literature search.
Notes: PRISMA figure adapted from Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.[78] Creative Commons.

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.[78] 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) (osteoporosis 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.

Table 1 The Design and Major Findings of the Included Studies

Cross-Sectional Studies								
Author	**Study Period**	**Study Location**	**Study Design**	**Sample Size**	**PM Assessment**	**Bone Health, Osteoporosis or Fracture Assessment**	**Outcomes**	**JBI Score**
Alvær et al, 2007[81]	2000–2001	Oslo, Norway	Cross-sectional study	590 men aged 75–76 years old	Annual mean $PM_{2.5}$ and PM_{10} 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 $PM_{2.5}$ [β= −47, 95% CI= (−77, −17)] and PM_{10} [β= −28, 95% CI= (−48, −8)] after BMI, smoking, physical activity and education adjustment Risk of low total body BMD was positively associated with $PM_{2.5}$ [OR= 1.33, 95% CI= (1.05, 1.70)] and PM_{10} levels [OR= 1.28, 95% CI= (1.00, 1.63)] after multivariate adjustment	8
Alver et al 2010[82]	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 $PM_{2.5}$ and PM_{10} 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 $PM_{2.5}$ and PM_{10} regardless of age and sex (all $p>0.05$) Distal forearm BMD was not associated with $PM_{2.5}$ and PM_{10} 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[83]	Jan – Dec 2009	Oradea, Romania	Cross-sectional study	105 subjects aged 62.2 ± 3.98 years old	Annual mean PM_{10} 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_{10} without covariate adjustment	6
Lee et al 2014[84]	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_{10} 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_{10} 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

Chen et al 2015[85]	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 $PM_{2.5}$ level from the US Environmental Protection Agency's Air Quality System	Total body and pelvic BMD by DXA	$PM_{2.5}$ 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.	8
Lin et al 2020[86]	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 $PM_{2.5}$ and PM_{10} 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	$PM_{2.5}$ and PM_{10} exposures were significantly higher among subjects with normal BMD (all p<0.05). NS association between BMD T-score and $PM_{2.5}$ [β= −0.002; 95% CI (−0.006, 0.002); p= 0.311] and PM_{10} [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.	7

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

Table 1 (Continued).

Cross-Sectional Studies								
Author	**Study Period**	**Study Location**	**Study Design**	**Sample Size**	**PM Assessment**	**Bone Health, Osteoporosis or Fracture Assessment**	**Outcomes**	**JBI Score**
Qiao et al 2020[87]	July 2015-Sept 2017 (based on Henan Rural Cohort study)	Five rural regions (Suiping county, Yuzhou county, Xinxiang county, Tongxu county and Yima county) of Henan province, China	Cross-sectional study	8033 subjects with men (n=3001) and women (n= 5032) aged 55.8 ± 10.8 years old	3-year average PM_1, $PM_{2.5}$ and PM_{10} 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 PM_1 [56.5–57.7 μg/m^3: OR= 1.068, 95% CI= (1.357, 1.907); >57.7 μg/m^3: OR= 2.075, 95% CI= (1.724, 2.497)], $PM_{2.5}$ [>73.2 μg/m^3: OR= 2.280, 95% CI= (1.899, 2.738)] and PM_{10} [128.3–133.0 μg/m^3: OR= 1.770, 95% CI= (1.492, 2.100); >133.0 μg/m^3: OR= 1.929, 95% CI= (1.602, 2.322)] after adjusting for age, sex, education level, marital status, smoking, drinking, physical activity, dietary habits, and region. PM_1, $PM_{2.5}$ and PM_{10} (for each 1 μg/m^3 increase) were associated with a 14.9%, 14.6% and 7.3% higher risk of osteoporosis. An estimated 20.29% (PM_1), 23.20% ($PM_{2.5}$) and 24.36% (PM_{10}) osteoporosis cases could be prevented by reducing the exposed PMs below their respective first quartile limit.	7
Ranzani et al 2020[88]	2009–2012	Hyderabad, South India	Cross-sectional study	3717 subjects with men (n= 2006) and women (n= 1711) aged 35.7 ± 14 years old	Annual mean exposures of $PM_{2.5}$ 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	$PM_{2.5}$ (for every 3 μg/m^3 increase) was negatively associated with lumbar spine BMC [mean difference= −0.57 g, 95% CI= (−1.06, −0.07)] after adjusting for the bone area, DXA type, age, sex, sex-by-age interaction, percentage lean, percentage fat body mass, fruit intake, vegetable intake, calcium intake, physical activity, smoking, household cooking fuel, occupation, education and standard of living index. NS association between $PM_{2.5}$ and lumbar spine BMD, hip BMC and hip BMD. Subgroup analysis revealed that $PM_{2.5}$ was negatively associated with hip and spine BMC and hip (but not spine) BMD for those aged ≥ 40 years old.	8

Sung et al 2020[89]	2002–2013	Seoul, Incheon and Busan, South Korea	Cross-sectional study	44,602 women aged > 50 years old	Annual mean $PM_{2.5}$, $PM_{2.5–10}$ and PM_{10} levels from the Air Korea database based on residential address estimation	Osteoporotic fracture data from the National Health Insurance Service database, South Korea	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. NS association between osteoporotic fracture and $PM_{2.5–10}$ and PM_{10} 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] 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).	8
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[90]	1 Jan 2000–31 Dis 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 Fundacion Alcorcon 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[91]	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[92]	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

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

Table 1 (Continued).

Cross-Sectional Studies								
Author	**Study Period**	**Study Location**	**Study Design**	**Sample Size**	**PM Assessment**	**Bone Health, Osteoporosis or Fracture Assessment**	**Outcomes**	**JBI Score**
Prada et al 2017[93]	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 $PM_{2.5}$ concentrations estimated using a validated spatio-temporal prediction model	Annual osteoporotic-related bone fractures data (hip, wrist, spine and pelvis) from hospital data	$PM_{2.5}$ 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 $PM_{2.5}$ 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
	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 $PM_{2\cdot5}$ 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 [$25(OH)D_{2/3}$]	$PM_{2.5}$ was not significantly associated with BMDs of the femoral neck, total hip, lumbar spines, 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 $PM_{2\cdot5}$ [β= −7.39; 95% CI (−14.17, −0.61); p<0.05] after multivariate adjustment.	8

Wu et al 2020[94]	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 [β= −0.18; 95% CI (−0.35, −0.01); p< 0.05] and third trimester exposure [β= −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 [β= −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).	8

Abbreviations: aHR, adjusted hazard ratio; β, 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_1, PM with aerodynamic diameter < 1 μm; $PM_{2.5}$, PM with aerodynamic diameter < 2.5 μm; $PM_{2.5–10}$, PM with aerodynamic diameter between 2.5 and 10 μm; PM_{10}, PM with aerodynamic diameter < 10 μm; QUS, quantitative ultrasound; r, Pearson correlation coefficient; RR, risk ratio; SOS, speed-of-sound; WHO, World Health Organization.

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

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.[79,80] 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,[81–89] 4 were retrospective studies[90–93] and 2 were prospective studies.[93,94] 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,[81,82,86,87,94] confounding factor[83,91] and subjects follow-up issues.[93,94] Four studies were conducted in North and South America (the United States,[85,93] Chile[91] and Mexico[94]); 4 studies were conducted in Europe (Norway,[81,82] Romania[83] and Spain[90]), and the remaining 6 studies were conducted in Asia (Taiwan,[84,86] Henan province of China,[87] India[88] and South Korea[89,92]). 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,[92,93] whereas 8 studies had a sample size of 1000–100,000 participants,[82,85–91] and the remaining 5 studies enrolled <1000 patients.[81,83,84,93,94] The participants were mainly elderly,[81–84,89–91,93] followed by middle-aged adults,[86,87,89,92,93] young adults[85,88,93] and pregnant women.[94]

One study investigated PM_1,[87] 11 studies[81,82,85–91,93,94] investigated $PM_{2.5}$,[55,56,59–65,67,68] 9 studies investigated PM_{10}[81–84,86,87,89,90,92] and 1 study investigated PM with aerodynamic diameter between 2.5 and 10 μm ($PM_{2.5–10}$).[89] Most of the studies reported the annual mean concentration of PM, except studies by Mazzucchelli et al[90] and Wu et al[94] that used the daily mean PM levels (averaged across the study period). WHO air quality guidelines stated that the annual mean $PM_{2.5}$ and PM_{10} levels should not exceed 10 and 20 μg/m^3 respectively.[95] The permissible limit for PM_1 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 $PM_{2.5}$ levels ≤10 μg/m^3,[81,82,91] 10–20 μg/m^3,[85,86,91,93] or >20 μg/m^3,[87–89,91] and the annual mean PM_{10} levels ≤20 μg/m^3,[81,82] or >20 μg/m^3.[83,84,86,87,89,92] Mazzucchelli et al[90] reported a daily mean $PM_{2.5}$ and PM_{10} of 9.52–12.34 μg/m^3 and 23.47–31.02 μg/m^3 respectively, while Wu et al[94] reported a daily mean $PM_{2.5}$ of 22.3–23.5 μg/m^3.

The bone health status was reported either as fracture incidence,[82,89–93] BMC and BMD assessed via DXA[81–85,88,93] or QUS method.[86,87,94] BMDs of total body,[81,83,85] pelvic,[85] hip,[84,88,93] femoral neck,[83,84,93] lumbar spine,[83,84,88,93] distal forearm,[82] distal radius[93] and ultradistal radius[93] were measured. Besides, Lin et al.[86] Qiao et al[87] and Wu et al[94] measured bone health via QUS method without DXA validation. Four studies[83,84,86,87] adopted the WHO definition of osteopenia and/or osteoporosis to classify the subjects.-[57,58,60,61] Besides, Alvær et al[81] defined subjects with Z-score ≤ −1 as having low BMD, which does not comply with the existing recommendation. Adjusted regression coefficient (β),[81,82,85,86,93,94] odd ratio (OR),[81,82,84,87] mean differences,[86,88] or Pearson correlation coefficient (r)[83] were used in these studies to

demonstrate the association between PM and bone mass. For the association between PM and bone fracture, β,[82] adjusted hazard ratio,[89] incidence rate ratio (IRR),[90] r,[91] OR[92] and risk ratio[93] were used.

Relationship Between PM Exposure and Bone Health or Osteoporosis Risk

The relationship between PM_1 and bone health was scarce. Only a study by Qiao et al[87] demonstrated that osteoporosis risk was positively associated with PM_1 exposure after multivariate adjustment. Logistic regression analysis also showed that every 1 μg/m^3 increase in PM_1 was associated with a 14.9% increased risk of osteoporosis.[87] Besides, an estimated 20.29% of PM_1-related osteoporosis cases could be prevented if PM_1 exposure was <55.2 μg/m^3.[87] Subgroup analysis revealed that the association between PM_1 and risk of osteoporosis were significantly higher among non-alcoholic drinkers, but it was not affected by age, sex, smoking, vegetable or fruit consumption and physical activity.[87] 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 $PM_{2.5}$ and/or PM_{10} with bone mass or osteoporosis risk was heterogeneous in other reports, whereby they revealed an insignificant[82,84–86,93] or negative association.[81,83,87,88,94] A cross-sectional study (Oslo Health study) on 1039 subjects aged 59–60 and 75–76 years old by Alver et al[82] demonstrated that the distal forearm BMD was not significantly associated with $PM_{2.5}$ and PM_{10} exposures regardless of age and sex after multivariate adjustment. Similarly, a cross-sectional study by Chen et al[85] also reported that ambient $PM_{2.5}$ 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[84] reported that osteoporosis risk was not significantly associated with PM_{10} exposure among 70 COPD patients aged 75.2 ± 5.5 years after multivariate adjustment. Similarly, Prada et al[93] also reported that $PM_{2.5}$ 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[86] on 4595 Taiwanese (49.7 ± 10.7 years old) also revealed that $PM_{2.5}$ and PM_{10} exposures were 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 $PM_{2.5}$.[86]

Other studies demonstrated that PM exposure is a significant risk factor for osteoporosis. The cross-sectional Oslo Health study (590 men aged 75–76 years) demonstrated that total body BMD was negatively associated with $PM_{2.5}$ and PM_{10} after multivariate adjustment.[81] Besides, the risk of low total body BMD (Z-score <-1) was positively associated with $PM_{2.5}$ and PM_{10} exposures.[81] Similarly, a cross-sectional study involving 105 Romanians by Cevei and Stoicanescu[83] reported that the total body BMD (but not hip) was negatively associated with PM_{10} exposure without covariate adjustment. Additionally, a similar negative association of $PM_{2.5}$ and PM_{10} exposures with bone health was reported in two recent cross-sectional studies by Qiao et al[87] and Ranzani et al.[88] The osteoporosis risk was positively associated with $PM_{2.5}$ and PM_{10} exposures among 8033 Chinese (55.8 ± 10.8 years old) from the rural area after multivariate adjustment.[87] Subsequent logistic regression analysis also demonstrated that every 1 μg/m^3 increase in $PM_{2.5}$ and PM_{10} were associated with a respective 14.6% and 7.3% increase in osteoporosis risk.[87] Besides, an estimated 23.20% and 24.36% of $PM_{2.5}$ and PM_{10}-related osteoporosis cases could be prevented if $PM_{2.5}$ and PM_{10} exposure were less than 70.5 and 125.8 μg/m^3 respectively.[87] Subgroup analysis also demonstrated similar associations between osteoporosis risk and $PM_{2.5}$ and PM_{10} among non-alcoholic drinkers or subjects with low physical activity.[87] Ranzani et al[88] reported that $PM_{2.5}$ 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 $PM_{2.5}$ exposure was also negatively associated with left hip BMC and BMD, as well as lumbar spine BMC among subjects aged ≥40 years old.[88]

Another recent prospective cohort study on 941 Mexican pregnant women with 3-year of follow-up by Wu et al[94] also reported that maternal trabecular bone health was negatively associated with $PM_{2.5}$ exposure during first- and third-trimester exposure. Besides, maternal cortical bone health was also negatively associated with $PM_{2.5}$ exposure during the first trimester.[94] A time-specific subgroup analysis revealed that these associations were biphasic across the time of exposure. $PM_{2.5}$ 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.[94] $PM_{2.5}$ 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.[94] Higher $PM_{2.5}$ exposure during the third trimester and first month post-partum predicted a slower post-partum bone health recovery.[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[82,89–91] or positive associations[89,92,93] have been reported. A cross-sectional study from Alver et al[82] reported that self-reported forearm fracture was not significantly associated with $PM_{2.5}$ and PM_{10} exposure among 5976 elderly regardless of age and sex. Besides, a retrospective cohort study by Mazzucchelli et al[90] reported $PM_{2.5}$ and PM_{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[91] on 8322 Chilean people aged ≥65 years also reported that the association between $PM_{2.5}$ and osteoporotic hip fracture was not significant regardless of sex. Subjects from Magallanes (the lowest $PM_{2.5}$ region in Chile) and Aysén region (the highest $PM_{2.5}$ region) showed similar IRR for bone fractures.[91] Nevertheless, the results of this study were not adjusted for confounding factors.[91]

On the other hand, a recent cross-sectional study from Sung et al[89] on 44,602 South Korean women aged >50 years old revealed that $PM_{2.5}$ exposure but not $PM_{2.5–10}$ and PM_{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.[89] Additionally, retrospective cohort studies by Prada et al[93] demonstrated a positive association between osteoporotic-related bone fracture and $PM_{2.5}$ exposure among 763,630 residents aged ≥65 years old from Northeast-mid-Atlantic US states, which also present in men and women subgroups.[93] A nearly linear relationship between $PM_{2.5}$ exposure and bone fracture rate was reported across the range between 3 and 22 $\mu g/m^3$ $PM_{2.5}$ level.[93] Besides, a recent retrospective cohort study on 178,147 South Korean aged 49.5 ± 12 years old by Oh et al[92] also demonstrated that PM_{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).[92]

Discussion

The relationships between PM exposure, including PM_1, $PM_{2.5}$, $PM_{2.5–10}$ and PM_{10}, with bone health and fracture incidence are not conclusive based on current evidence. $PM_{2.5}$ and/or PM_{10} exposures were demonstrated to be associated with bone fracture positively[89,92,93] or not significantly.[82,89–91] Similarly, the association between $PM_{2.5}$ and/or PM_{10} with bone mass was negative[81,83,87,88,94] or not significant.[82,84–86,93] Interestingly, Wu et al demonstrated a time-specific biphasic association between $PM_{2.5}$ exposure and bone health measured by QUS among pregnant women. On the other hand, relevant findings on PM_1 are scarce as only one study demonstrates a positive association with osteoporosis.[87] The relationship between PM_1 and bone fracture is yet to be determined. Besides, only one study reported a non-significant association between $PM_{2.5–10}$ and osteoporotic fractures,[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.[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[82] reported that distal forearm BMD was negatively associated with $PM_{2.5}$ and PM_{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[88] also reported that the negative association between $PM_{2.5}$ exposure and lumbar spine BMD became insignificant after

adjusting for additional covariates. Additionally, several included studies did not perform covariate adjustment,[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.[96] However, these detection technologies vary in terms of practicability (cost, size, noisiness and mobility), precision, accuracy and sensitivity/detection limits.[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.[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.[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.[83,84,89,91,92] Some studies employed the previously reported prediction model[81,82] or self-developed spatiotemporal prediction model without disclosing the cross-validation values.[85,86,90] In several studies, the PM model was adjusted/calibrated for climate, weather and/or traffic conditions.[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.[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.[44] However, T-score discordance at different bone sites is not an unusual observation,[100–102] probably due to the non-homogeneous process of bone loss.[103,104] Increasing the number of bone sites scanned will increase the chance of discordance and detecting osteoporosis.[100] Thus, the number of bone sites examined could influence the relationship between PM exposure and osteoporosis risk. As evidence, Cevei and Stoicanescu[83] and Ranzani et al[88] demonstrated inconsistent associations between PM and bone mass at different sites. Moreover, several studies[81,83,85] employed the total body BMD as the skeletal outcome of interest, which is less sensitive than regional BMDs.[105] Although total body BMD correlates with regional BMDs,[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.[86,87,94] DXA and QUS adopt different technology in identifying bone health, so their results are not interchangeable.[48] The WHO classification system to diagnose osteoporosis based on BMD T-score cannot be used for QUS.[106] Although QUS indices correlate with bone mass and several bone microarchitectural indices,[48] they cannot be used directly to infer bone strength as in the studies of Wu et al.[94] A biomechanical assessment, like the three-point bending flexural test,[107] can indicate bone strength directly.[108] 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.[109] Additionally, PM species are generally present together[82,87] and coexist with other air pollutants like nitrogen monoxide, NO_2 and SO_2.[87,90] These air pollutants were reported positively correlated with osteoporosis risk.[86,99] Besides, there are synergistic effects between CO-nitrogen oxide and SO_2-NO_2, which could further reduce BMD.[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 $PM_{2.5}$, NO_2 and O_3 exposure was negatively associated with total body and pelvic BMD after multivariate adjustment, including the pollutants levels.[85] This observation suggests that other air pollutants like PAHs or black carbon from vehicle exhaust emissions might also contribute to BMD reduction.[85,88]

Previous studies observed a higher bone mass and fewer bone fractures among subjects from rural areas than urban areas.[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[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.[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.[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.[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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