

# Literature Review on Particulate Matter–Mediated Aging and Age-Related Diseases

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Although the respiratory and cardiovascular effects of particulate matter (PM) are well known, their role as a promoter of biological aging remains undetermined. This review examines the literature to assess how chronic PM exposure is incorporated into the molecular trajectory of aging and if it relates to a range of age-related pathologies. A systematic search of peer-reviewed studies published from 2000 to 2025 was conducted in PubMed, Embase, and the Web of Science. In accordance with PRISMA guidelines, studies were selected based on their mechanistic examination on the association between PM<sub>10</sub>, PM<sub>2.5</sub>, and PM classified by aerodynamic diameter as ultrafine particles and on biological indicators of aging. Data were extracted and synthesized on the themes of long-term specific effects and molecular mechanisms. This synthesis shows that PM exposure is a significant environmental factor across several physiological systems. Chronic inhalation of particulate matter is associated with the progression of immune aging, abnormal fat metabolism, and metabolic disorders and associated fatty liver disease. Moreover, it is associated with early musculoskeletal decline and accelerated renal aging. These systemic effects are driven by a synergistic molecular cascade that includes NLRP3 inflammasome activation, sustained NF- $\kappa$ B signaling, mitochondrial-derived oxidative stress, and disruption of autophagic-lysosomal fluxes. PM exposure overwhelms cellular antioxidant defenses and protein-fixation mechanisms, acting as a multisystemic accelerator of biological aging. These findings highlight the need for targeted public health interventions to mitigate pollutant-induced aging and promote longevity in the increasingly polluted global environment.

**Keywords:** Particulate matter, biological aging, oxidative stress, age-related diseases

## Introduction

The World Health Organization (WHO) reports that more than 90% of urban residents live in areas where air quality does not meet safety standards, resulting in approximately 4.2 million premature deaths each year<sup>1,2</sup>. Particulate matter (PM), a major component of air pollution, has become the center of extensive toxicological research<sup>3,4</sup>. Particulate matter is a heterogeneous mixture of micro-solid and liquid droplets. The toxicity of PM is largely determined by its aerodynamic diameter<sup>3,5</sup>. According to the standard classification, PM<sub>10</sub> is defined as a coarse particle, PM<sub>2.5</sub> is defined as a fine particle (diameter 2.5  $\mu$ m), and both can reach alveoli via the respiratory system<sup>3,6</sup>. Notably, ultrafine particles (ones with a diameter less than 0.1  $\mu$ m) can bypass the lung epithelium to enter the systemic circuit and accumulate in distal organs<sup>2,6</sup>. These particles have complex toxic components including elemental carbon, polycyclic aromatic hydrocarbons (PAHs), heavy metals, and inorganic ions<sup>1,3</sup>. Although the physiological effects of PM on the respiratory and cardiovascular systems are

well documented<sup>7,8</sup>, its specific role as a cause of systemic biological aging remains a new area of inquiry requiring comprehensive synthesis<sup>1</sup>.

Biological aging is characterized by a gradual decline in physiological integrity, which leads to decreased function and increased vulnerability to chronic diseases such as type 2 diabetes, neurodegenerative disease, and osteoporosis<sup>9,10</sup>. New evidence suggests that chronic PM exposure may act as a potent environmental promoter of these aging-related pathologies<sup>11,12</sup>. Recent longitudinal observations have identified a significant association between PM exposure and the increased prevalence of conditions such as Parkinson's disease, senile dementia, and macular degeneration<sup>13–15</sup>. Understanding the intersection of environmental pollutants and aging is critical to developing public health strategies in the increasingly aging and polluted global environment.

This review aims to synthesize the current literature on the effects of PM on the progression of biological aging and aging-related diseases. The scope of this paper includes assessing organ-level outcomes in the immune, adipose, liver, musculoskeletal, and renal systems and analyzing basic molecular mechanisms such as NLRP3 inflammasome

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activation, oxidative stress, and autophagy-lysosome dysfunction. It also includes discussions on the limitations of the literature, including the translation gap between animal models and human aging. By reviewing these pathways, the paper seeks to provide theoretical insights for the development of interventions that promote healthy aging.

## Theoretical Framework

Particulate matter is a heterogeneous atmospheric suspension consisting of both solid and liquid phases. It is classified into PM<sub>10</sub> ( $\leq 10 \mu\text{m}$ ), PM<sub>2.5</sub> ( $\leq 2.5 \mu\text{m}$ ), and ultrafine particles (UFP,  $< 0.1 \mu\text{m}$ )<sup>3,5</sup> depending on the aerodynamic diameter of the particles. The physiological effects of these particles are dictated by their chemical complexity and their ability to bypass biological barriers<sup>1,3</sup>. For example, particles can contain elemental carbon, polycyclic aromatic hydrocarbons (PAHs), heavy metals, and inorganic ions.

The main conceptual pillar of the article is the theory of oxidative stress on aging, which assumes that the cumulative imbalance between reactive oxygen species (ROS) and antioxidant defenses causes cellular aging<sup>9,16</sup>. PM exposure is thought to enhance this process by introducing exogenous ROS or stimulating endogenous production through mitochondrial interference<sup>17,18</sup>. Such oxidative damage can lead to dielectric instability, lipid peroxidation, and protein carbonylation, and thus mimic or accelerate the natural trajectory of molecular aging<sup>16,19</sup>.

The “inflammatory” model further clarifies how PM-induced chronic low-grade inflammation promotes age-related pathology<sup>20</sup>. PM can act as a potent activator for innate immune sensors, such as the NLRP3 inflammasome<sup>21,22</sup>. The continued involvement of these inflammatory pathways is a hallmark of biological aging, suggesting that environmental pollutants may worsen the systemic inflammatory environment in older organisms<sup>20,23</sup>.

Recent frameworks have highlighted autophagy-lysosome flux and disruption of nutrient-sensing pathways as major causes of PM-mediated aging. Efficient autophagy is essential for the removal of damaged organelles and proteins. However, chronic PM exposure is associated with impaired autophagy-lysosome fusion and the inhibition of autophagy flux<sup>24,25</sup>. This damage results in the accumulation of damaged cellular components, which supports the role of PM as a significant environmental factor in the aging process when combined with changes in Nrf2-mediated antioxidant responses and metabolic imbalances<sup>19,26–28</sup>.

In sum, the interaction between PM and aging is not defined by a single pathway but by a synergistic chain of oxidative, inflammatory, and protein failures. While certain studies suggest a strong correlation, interpreting it as a causal relationship requires additional research, especially when bridging the gap

between controlled experimental models and complex human aging phenotypes<sup>4</sup>.

## Methodology

This review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure a systematic, transparent, and reproducible synthesis of existing literature regarding the impact of particulate matter (PM) on biological aging.

### Search strategies and data sources

A comprehensive electronic search was conducted across three major academic databases: PubMed, Embase, and Web of Science. The search period was set as January 2000 to March 2025 to capture the latest developments in toxicology and epidemiological studies<sup>1,13</sup>. The search strategy utilized a complex combination of Boolean operators and Medical Subject Headings (MeSH). The search terms included outcome-related terms such as “biological aging,” “cell aging,” and “inflammatory,” as well as pollutant-related keywords such as “particle matter,” “PM<sub>2.5</sub>,” and “ultrafine particles”. Additional terms for specific physiological systems such as “myelopenia,” “metabolic dysfunction-associated fatty liver disease (MASLD),” and “chronic kidney disease,” were incorporated into the search protocol to ensure systematic coverage<sup>27,29,30</sup>. All of the search terms were cross-referenced.

To ensure methodological transparency and address the systemic diversity of the reviewed literature, the key parameters of the studies cited herein—including their respective model systems, specific PM fractions, exposure windows, clinical or molecular endpoints, and primary limitations—are systematically compiled and evaluated in Table 1.

### Inclusion and Exclusion Criteria

In order to maintain strict academic standards, studies were selected according to pre-defined eligibility criteria. We limited our inclusion to peer-reviewed primary research papers, including *in vitro*, *in vivo*, and human epidemiological studies, which investigated the mechanical association between PM exposure and biological aging markers. We also considered only papers published in English. Furthermore, we applied exclusion criteria to filter out nonacademic sources such as blogs, websites, and news reports, as well as gray literature including academic abstracts, editorials, and white papers<sup>1,4</sup>. In addition, studies that did not address chronic aging or age-related degenerative processes and focused solely on acute respiratory toxicity were excluded.

**Table 1** Methodological Matrix and Key Findings of Foundational Studies on PM-Mediated Systemic Senescence

| Cited Study                        | Model System                                                       | PM Fraction                                            | Exposure Window                    | Main Endpoint (Target System/Mechanism)                                                                             | Principal Limitation                                                                                     |
|------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------|------------------------------------|---------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Bowe et al. <sup>31</sup>          | Human Longitudinal Cohort (U.S. Veterans, $N \approx 2.4$ million) | PM <sub>2.5</sub>                                      | 8.5 years median follow-up         | <b>[Renal]</b> Significant, independent risk of CKD incidence, eGFR linear decline, and ESRD progression.           | Cohort predominantly consisted of male, older veterans; limits generalizability to broader demographics. |
| Ward-Caviness et al. <sup>32</sup> | Human Cohort (Myocardial infarction survivors)                     | PM 2.5, PM 10                                          | Long-term chronic exposure         | <b>[Mechanism]</b> Acceleration of blood-based Epigenetic Aging markers (DNA methylation age / DNAmAge).            | Cohort restricted to individuals with pre-existing cardiovascular vulnerabilities.                       |
| Jafari et al. <sup>33</sup>        | Human Systemic Review & Meta-analysis                              | PM 2.5, PM 10, NO <sub>2</sub>                         | Lifespan/Late-life exposures       | <b>[Systemic]</b> Robust risk association with the development of Frailty Syndrome and functional physical decline. | High heterogeneity in frailty assessment tools across pooled primary studies.                            |
| Adami et al. <sup>34</sup>         | Human Cohort (Postmenopausal females)                              | PM <sub>2.5</sub> , PM <sub>10</sub>                   | Long-term chronic ambient exposure | <b>[Musculoskeletal]</b> 16% increase in osteoporosis risk; accelerated bone mineral density (BMD) decline.         | Residual confounding from dietary calcium intake and physical activity levels.                           |
| Wang et al. <sup>35</sup>          | <i>In vitro</i> (Primary osteoblasts & RAW264.7)                   | PM <sub>2.5</sub>                                      | 24–48 hours acute incubation       | <b>[Mechanism]</b> Suppression of Wnt/beta-catenin pathway; promotion of RANKL-mediated osteoclastogenesis.         | High-dose acute <i>in vitro</i> delivery lacks systemic regulatory feedback loops.                       |
| O'Sullivan et al. <sup>36</sup>    | Human Cohort                                                       | PM <sub>2.5</sub>                                      | Multi-year longitudinal follow-up  | <b>[Musculoskeletal]</b> Significant correlation with sarcopenia, muscle mass attrition, and gait speed reduction.  | Relies on proximity-based exposure models rather than personal monitor tracking.                         |
| Chen et al. <sup>26</sup>          | <i>In vivo</i>                                                     | PM <sub>2.5</sub>                                      | 12 weeks concentrated inhalation   | <b>[Adipose]</b> Compromised thermogenic capacity in BAT; induced insulin resistance and inflammation in WAT.       | Murine metabolic rate and BAT distribution differ fundamentally from aging humans.                       |
| Guo et al. <sup>37</sup>           | Human Cohort (Chinese Adult Survey)                                | PM <sub>1</sub> , PM <sub>2.5</sub> , PM <sub>10</sub> | Chronic baseline exposure          | <b>[Hepatic]</b> Positive correlation between multi-fraction PM exposure and MASLD prevalence.                      | Cross-sectional design limits ability to determine absolute longitudinal causality.                      |
| Xu et al. <sup>38</sup>            | <i>In vitro</i> (Human vascular endothelial cells)                 | PM <sub>2.5</sub>                                      | 72 hours incubation                | <b>[Mechanism]</b> Disruption of autophagic flux; accumulation of damaged mitochondria and pro-apoptotic signaling. | Cell culture models omit the complex inter-organ cross-talk found <i>in vivo</i> .                       |
| Gao et al. <sup>39</sup>           | <i>In vitro</i> (Microglial cell culture)                          | PM <sub>2.5</sub>                                      | 24 hours acute stress              | <b>[Mechanism]</b> NLRP3 inflammasome activation via mitochondrial ROS; elevated IL-1 $\beta$ secretion.            | Exogenous PM doses exceed typical real-world physiological tissue concentrations.                        |
| VoPham et al. <sup>27</sup>        | Human Cohort (U.S. Nationwide Sample)                              | PM <sub>2.5</sub> , NO <sub>2</sub>                    | Spatial-temporal model estimation  | <b>[Hepatic]</b> Heightened risk of advanced steatotic liver disease and hepatic fibrosis in high-exposure zones.   | Potential exposure misclassification due to reliance on outdoor air quality stations.                    |
| Huang et al. <sup>40</sup>         | <i>In vivo</i> (Aged murine model)                                 | PM <sub>2.5</sub>                                      | 8 weeks inhalation                 | <b>[Renal]</b> Tubular epithelial edema, capillary congestion, and accelerated glomerular atrophy.                  | Shorter lifespan of mice restricts modeling of true multi-decade human renal aging.                      |
| Lai et al. <sup>29</sup>           | Human Cohort                                                       | PM <sub>2.5</sub> , PM <sub>10</sub> , NO <sub>x</sub> | Long-term prospective follow-up    | <b>[Musculoskeletal]</b> Independent correlation between ambient PM and lower appendicular lean mass (Sarcopenia).  | Muscle mass evaluated via bioelectrical impedance rather than gold-standard DXA.                         |
| Li et al. <sup>30</sup>            | Human Cohort                                                       | PM <sub>2.5</sub>                                      | Chronic multi-year exposure        | <b>[Renal]</b> Diminished estimated glomerular filtration rate (eGFR); accelerated chronic kidney disease (CKD).    | Lack of historical indoor air pollution data (e.g., secondary smoking, cooking).                         |
| Lingappan <sup>41</sup>            | <i>In vitro</i> / <i>In vivo</i> Review                            | PM <sub>2.5</sub> , UFP                                | Mixed acute/chronic regimes        | <b>[Mechanism]</b> Redox-sensitive NF- $\kappa$ B activation; upregulation of pro-inflammatory cytokine cascades.   | High programmatic heterogeneity among synthesized molecular protocols.                                   |
| Ma <sup>19</sup>                   | <i>In vitro</i> (Hepatocytes & Adipocytes)                         | PM <sub>2.5</sub>                                      | 48 hours exposure                  | <b>[Mechanism]</b> Depletion of cellular antioxidant reservoirs; age-dependent decline in Nrf2 protective activity. | Static cell models do not capture the dynamic systemic adaptive responses of aging organisms.            |
| Mou et al. <sup>42</sup>           | Human PBMCs (RNA-seq Transcriptomics)                              | PM <sub>10</sub>                                       | Ambient winter exposure variations | <b>[Immune]</b> Downregulation of pathogen-recognition genes; transcriptomic shift toward immunosenescence.         | Small transcriptomic sample size limits generalizability across diverse ethnicities.                     |
| Zhang et al. <sup>43</sup>         | <i>In vivo</i> (Diet-induced obese mice)                           | PM <sub>2.5</sub>                                      | 10 weeks inhalation                | <b>[Adipose]</b> Exacerbated visceral adiposity, adipocyte hypertrophy, and severe WAT macrophage infiltration.     | Synergistic effect with high-fat diet masks isolated toxicological impacts of PM.                        |
| O'Sullivan et al. <sup>44</sup>    | Structural/Clinical Review                                         | PM <sub>2.5</sub> , PM <sub>10</sub>                   | Synthesis of human/animal data     | <b>[Renal]</b> Multi-systemic mapping of pollutant-induced vascular intimal thickening and interstitial fibrosis.   | Qualitative synthesis limits quantitative meta-analytical pooling of effect sizes.                       |
| Tan & Finkel <sup>10</sup>         | Mechanistic Cohort Review                                          | PM <sub>2.5</sub> , UFP                                | Lifespan-wide exposures            | <b>[Immune]</b> Acceleration of "inflammaging" and premature systemic immune exhaustion.                            | Mechanistic pathways are largely inferred from disparate animal toxicology datasets.                     |

|                                     |                                              |                          |                        |                                                                                                                  |                                                                                        |
|-------------------------------------|----------------------------------------------|--------------------------|------------------------|------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| <b>Ranzani et al.</b> <sup>45</sup> | Human Cohort (Peri-urban India)              | PM2.5, BC (Black Carbon) | Annual average metrics | <b>[Musculoskeletal]</b> Inverse association between ambient PM2.5 and bone mineral density at the lumbar spine. | Confounded by high prevalence of baseline nutritional vitamin D deficiency.            |
| <b>Wei et al.</b> <sup>24</sup>     | <i>In vivo</i> (Zebrafish and Murine models) | PM2.5                    | Sub-chronic exposure   | <b>[Mechanism]</b> Lysosomal alkalization; leakage of cathepsin B; complete blockade of autophagosome fusion.    | Translational distance between aquatic/rodent models and complex human biology.        |
| <b>Deng et al.</b> <sup>46</sup>    | Human Cohort (Longitudinal elderly pool)     | PM2.5                    | 5-year moving averages | <b>[Hepatic]</b> Elevated serum alanine aminotransferase (ALT) and rigorous association with MASLD progression.  | Unable to fully account for individual genetic predispositions to metabolic disorders. |
| <b>Xu et al.</b> <sup>25</sup>      | <i>In vitro</i> (Human keratinocytes)        | PM2.5                    | 24–72 hours dosage     | <b>[Mechanism]</b> Proteostatic failure; accumulation of carbonylated proteins and cellular debris.              | Monolayer cell culture lacks the complex multi-layered tissue defense barriers.        |

## How to extract and synthesize data

Structured approaches have been used for data extraction to ensure consistency in various literatures. For each study selected, specific parameters were recorded, including experimental model system, PM concentration, duration of exposure, primary molecular or physiological outcome. After extraction, the findings were synthesized into a thematic framework that classifies the evidence into two main domains: long-term specific effects and overall molecular mechanisms. This synthesis focused on key pathways, such as NLRP3 inflammatory activation, oxidative stress, and disruption of autophagy flux<sup>16,21,24</sup>. By adhering to this methodological approach, the subsequent discussion and conclusion are based on evidence drawn from high-quality primary studies.

## Findings

### Particulate matter and immunomodulatory disorders

Although the immune system serves as an important biological barrier, it is highly vulnerable to systemic destruction by inhaled environmental pollutants. Larger particles are typically isolated by mucosal clearance mechanisms in the upper respiratory tract, but PM2.5 can bypass these defenses to penetrate the alveolar space<sup>3,6</sup>. Upon reaching the alveoli, these particles interact directly with the resident macrophages and other immune cells, often causing abnormal allergic and autoimmune chain reactions<sup>2,47</sup>.

Experimental evidence obtained from a mouse model of misalbumin-induced asthma shows that PM2.5 inhalation exacerbates allergic inflammation. It is characterized by the upregulation of Th2-associated cytokines such as interleukin (IL)-4 and IL-13<sup>48</sup>. In addition, transcriptomic insights obtained from RNA sequencing (RNA-seq) of peripheral blood mononuclear cells of individuals exposed to PM10 show a decreased immune profile<sup>42</sup>. Specifically, these studies show a decreased expression of genes essential for pathogen recognition and a marked increase in the secretion of pro-inflammatory cytokines and chemokines. These molecular changes suggest that PM exposure may not only trigger a tran-

sient response but also progressively impair the functional integrity of immune cells<sup>42,47</sup>.

The consequences of chronic, contaminant-induced inflammation reflect the gradual decline in immune effects, which is a biological feature of aging<sup>10,20</sup>. In particular, they reflect decline in immune aging. This process is characterized by the decreased ability to respond to novel antigens, an increased baseline of systemic inflammation (inflammation), and weakened defenses against pathogens. By promoting this early immune deterioration, PM exposure appears to act as an environmental catalyst that accelerates the development of age-related systemic vulnerability<sup>10,20,42</sup>.

### Particulate Matter and Dysregulation of Adipose Tissue Metabolism

Adipose tissue is a multifaceted metabolic organ essential for lipid homeostasis, energy consumption, and maintaining systemic glucose balance. The biological aging of adipose tissue is characterized by a decrease in lipid-degrading ability and lipid storage disorders. These age-related changes often lead to increased fat, adverse lipid deposition, redistribution, and chronic low-grade inflammation, which are considered risk factors for obesity, dyslipidemia, and type 2 diabetes<sup>49,50</sup>.

Emerging toxicological and epidemiological evidence suggests that adipose tissue may be an important target for metabolic disorders caused by PM. Recent studies have shown that there is an association between chronic PM2.5 inhalation and abnormal fat accumulation<sup>26,43</sup>. For example, PM2.5 exposure has been shown to decrease the thermogenic and oxidative capacity of brown adipose tissue (BAT), while inducing an inflammatory response and insulin resistance within white adipose tissue (WAT)<sup>26</sup>. Changes in cellular function due to these contaminants resemble the metabolic decline commonly observed during physiological aging.

Population-based data from the Chinese Longitudinal Health Longevity Survey (2000–2018) further support these findings, confirming that PM2.5 exposure is a significant environmental factor contributing to the increased risk of obesity<sup>50</sup>. These human observations are supported by long-term mouse models. In this model, chronic PM2.5 inhalation re-

sulted in a marked increase in visceral fat, adipocyte hypertrophy, and the enlargement of white adipose stores<sup>43,51</sup>. In vitro studies using 3T3-L1 adipocytes at the molecular level, it was demonstrated that PM<sub>2.5</sub> stimulates lipid uptake and intracellular accumulation in a dose-dependent manner<sup>35,51</sup>. This effect seems to be mediated through activation of the peroxisome proliferator-activating receptor gamma pathway, which is a major regulator of adipogenesis. Collectively, these findings suggest that PM exposure may act as an environmental promoter of age-related metabolic dysfunction.

### **Particulate Matter and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)**

Biological aging is an important determinant of the severity and progression of various liver pathologies, especially metabolic dysfunction-associated fatty liver disease (MASLD). Previously, MASLD was known as non-alcoholic fatty liver disease (NAFLD)<sup>52,53</sup>. MASLD is characterized by the excessive accumulation of triglycerides within hepatocytes in the absence of high alcohol consumption. The prevalence of liver dysfunction is expected to increase as the global population ages<sup>53,54</sup>. Major clinical risk factors, such as hypertension, type 2 diabetes, and obesity, which are common in aging cohorts, further exacerbate physiological decline and hepatic homeostasis<sup>49,53</sup>.

Age-related liver deterioration is highlighted by specific cellular abnormalities such as chronic inflammation, mitochondrial dysfunction, increased reactive oxygen species (ROS) production, and protein dysfunction<sup>54</sup>. Recent epidemiological evidence suggests that PM exposure is closely related to the pathogenesis of fatty liver disease<sup>27,46</sup>. A cross-sectional analysis including U.S. national inpatient sample data and a Chinese adult cohort found that there was a positive correlation between elevated PM<sub>2.5</sub> levels and the increased risk of MASLD<sup>37,46</sup>. In particular, exposure to a variety of pollutants including PM<sub>1</sub>, PM<sub>2.5</sub>, PM<sub>10</sub>, and nitrogen dioxide is associated with increased metabolic risk<sup>23,27,55</sup>. These human observations have been supported by experimental models. For example, a rat study shows that chronic PM<sub>2.5</sub> inhalation interferes with lipid and amino acid metabolism, resulting in a significant increase in triglyceride and free fatty acid levels in the liver<sup>51,56</sup>.

### **Particulate Matter and Sarcopenia**

The progression of aging is associated with a gradual decrease in skeletal muscle mass and a decrease in the number and cross-sectional area of muscle fibers. Progressive loss of muscle integrity, commonly referred to as sarcopenia in the medical community, not only impairs physical function but also accelerates systemic aging and increases the risk of death in

the elderly population<sup>36,57</sup>.

Although the impact of environmental pollutants on musculoskeletal health is a relatively early-stage field, a recent study has shown that PM exposure affects skeletal muscle homeostasis negatively<sup>1,29</sup>. A large epidemiological survey analysis of a high-resolution air pollutant dataset with approximately 350,000 participants and biobank cohorts such as the UK Biobank reveals a significant correlation between PM<sub>2.5</sub>, PM<sub>10</sub>, and chronic exposure to nitrogen oxides, which causes a high prevalence of muscle loss<sup>29,57</sup>. In addition, a targeted study of individuals aged 65 and older found that long-term PM<sub>2.5</sub> exposure is associated with a quantifiable reduction in skeletal muscle mass<sup>57,58</sup>. Multiple linear regression analyses of these cohorts indicate that high ambient PM levels correlate independently with low accessory fat mass, suggesting that PM exposure may contribute to the early onset of sarcopenia phenotypes<sup>29,57</sup>.

### **Particulate Matter and Osteoporosis**

Osteoporosis is a prevalent and progressive musculoskeletal disease in the elderly population. The disease is characterized by a decrease in bone mass and deterioration of the skeletal microstructure, which increases bone fragility and fracture susceptibility<sup>34,59</sup>. Even when bone density seems relatively stable, overall bone mass decline remains an important cause of fractures<sup>45,60</sup>.

Recent toxicological and epidemiological studies have suggested that ambient air pollutants, specifically PM, are detrimental to skeletal integrity. In a large longitudinal study of a female cohort, chronic exposure to high PM<sub>2.5</sub> concentrations increased the risk of osteoporosis by 16%, while PM<sub>10</sub> levels exceeding 30  $\mu\text{g}/\text{m}^3$  by 15%<sup>45,59</sup>. These findings suggest that airborne particles may interfere with the bone remodeling process. In particular, new evidence suggests that PM exposure may decrease bone density<sup>34,35</sup>. However, accurate molecular trajectories require further elucidation<sup>4,59</sup>.

### **Particulate Matter and Renal Aging**

The kidneys undergo severe anatomical and physiological changes during aging and are characterized by decreased renal mass, loss of functional nephron, and progressive glomerulosclerosis<sup>44</sup>. Histological changes, such as endovascular thickening and interstitial fibrosis, further reduce the filtering efficiency and regenerative capacity of renal tissue. These changes make the elderly vulnerable to acute and chronic kidney injury<sup>30,44</sup>.

Beyond traditional risk factors, PM has emerged as a significant environmental stressor targeting kidney health. In an extensive cross-sectional analysis of approximately 200,000 older adults, higher ambient PM exposure was associated with

lower estimated glomerular filtration rate (eGFR), which is a clinical feature of renal impairment<sup>30</sup>. This epidemiological association is strongly supported by experimental data from mouse models. Mice receiving chronic PM2.5 inhalation exhibited physiological disorders, including changes in fluid homeostasis and elevated arterial pressure, along with histopathological features that are characteristic of accelerated renal aging, such as coronary epithelial edema, capillary congestion, and glomerular atrophy<sup>1,40</sup>.

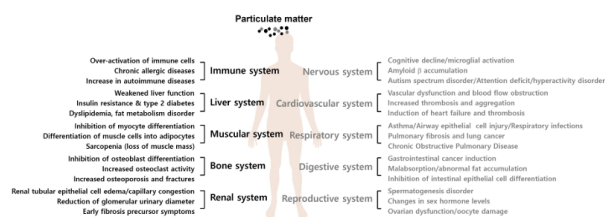


**Figure. 1** Diagram of adverse event pathways associated with PM-related human toxicity.

These observations imply that PM exposure serves as an environmental catalyst for chronic kidney disease and other senescence-related renal pathologies. As illustrated in the adverse event pathways associated with PM-related toxicity (see Fig. 1), a comprehensive understanding of the molecular trajectories—spanning oxidative stress, DNA damage, and dysfunctional autophagy—is essential for mitigating the multi-systemic impact of PM on biological aging and fostering resilience in increasingly polluted environments<sup>1,22,44</sup>.

## The Role of NLRP3 Inflammasome in PM-Induced Senescence

NOD-like receptors, the pyrin domain-containing 3 (NLRP3) inflammasome, is a cytoplasmic multiprotein complex that functions as an important sensor within the innate immune system. The primary role of this substance is to detect various cellular stressors and pathogens<sup>21,61</sup>. Once activated, it initiates an inflammatory response by promoting caspase-1-mediated maturation of interleukin (IL)-IL-1 $\beta$  and IL-18. While this mechanism is essential for protective immunity, chronic or abnormal activation of the NLRP3 inflammasome is increasingly closely associated with biological aging and progression of age-related pathologies such as obesity and insulin resistance<sup>21,62</sup>.

The activation of the NLRP3 inflammasome takes place through a sophisticated two-step process. The initial priming phase is typically mediated by nuclear factor- $\kappa$ B type  $\kappa$  (NF- $\kappa$ B type  $\kappa$ ) transcription factors. It upregulates the expression of inflammasome components and inflammatory promoter mediators, which are sustained by mitochondrial-derived reactive oxygen species (ROS)<sup>21,41</sup>. This phase may be amplified

due to the failure of the autophagy-lysosome pathway. Under homeostatic conditions, autophagy maintains the protein identity of the cell by removing damaged proteins and organelles, but it leads to the accumulation of cell fragments, which exacerbates the NF- $\kappa$ B type  $\kappa$  signal and is primed to activate the inflammasome<sup>22,24</sup>.

Recent experimental models have shown that PM exposure acts as a potent trigger for these inflammatory chain reactions. For example, in microglia models of ischemic injury, PM2.5 exposure significantly increased the expression of NLRP3 components, including NLRP3, apoptosis-associated spot-like proteins (ASCs), and (pro)caspase-1, resulting in increased secretion of IL-1 $\beta$  and IL-18<sup>22,39</sup>. Conversely, inhibition of NLRP3 has been shown to reduce ROS production, whether genetic knockdown or pharmacological inhibition, thus mitigating damage caused by PM2.5<sup>39,62</sup>. These findings suggest that regulating NLRP3 activation may be a valid strategy for mitigating aging-like cellular responses associated with contaminant-induced chronic inflammation<sup>22,61,62</sup>.

## Oxidative Stress and Mitochondrial Dysfunction

Mitochondria act as major sites of oxidative metabolism and play essential roles in cell energy production and survival<sup>18</sup>. However, these metabolic processes generate reactive oxygen species (ROS), which can cause excessive oxidative damage to DNA, proteins, and lipids<sup>16,17</sup>. This molecular degradation is recognized as a fundamental cause of aging and neurodegenerative diseases, including Alzheimer's disease and dementia<sup>9,63</sup>.

To mitigate oxidative damage, cells rely on a complex network of antioxidants. One of the hallmarks of biological aging is a gradual decrease in these antioxidant defenses, which shifts the redox balance of cells to chronic oxidative stress<sup>9,16</sup>. An important regulator in this homeostasis process is transcription factor nuclear factor erythroid 2 related factor 2 (Nrf2). As Nrf2 activity declines with age, the cell's ability to neutralize ROS diminishes, thereby accelerating the aging pathway<sup>19</sup>. PM exposure exacerbates this vulnerability by stimulating exogenous ROS production and depleting antioxidant reservoirs in already strained senescent cells<sup>1,16,17</sup>.

## NF- $\kappa$ B Signaling: A Mediator of Systemic Inflammation

Nuclear factor- $\kappa$ B (NF- $\kappa$ B) is a redox sensitive transcription factor that plays a central coordinator in aging and age-related pathologies<sup>41</sup>. NF- $\kappa$ B, which is activated by a variety of genotoxic and inflammatory stressors, regulates genes involved in cytokine production, cell death, and cellular aging<sup>20,41</sup>. The sustained activation of NF- $\kappa$ B in several tissues is a molecular feature of aging, which contributes to degenerative diseases such as dementia, type 2 diabetes, and os-

teoporosis<sup>14,49,64</sup>. Conversely, studies have shown that pharmacological or genetic suppression of NF- $\kappa$ B signaling may delay the onset of aging-related phenotypic and pathological metastases<sup>41</sup>.

Current studies have shown that PM exposure triggers systemic inflammatory responses as potent activators of the NF- $\kappa$ B pathway<sup>41,64</sup>. For example, in macrophages, PM2.5 exposure significantly enhances NF- $\kappa$ B transcriptional activity, leading to robust inflammatory chain reactions<sup>42,43</sup>. PM inhaled from the respiratory system stimulates mitogen-activated protein kinase (MAPK) pathway through ROS production, triggering NF- $\kappa$ B signaling and exacerbating airway inflammation<sup>2,64</sup>. Similar PM induced NF- $\kappa$ B activation was observed in vascular smooth muscle cells and retinal pigment epithelial cells, highlighting their role in pollutant-mediated multicenter dysfunction<sup>64</sup>.

### Autophagy–Lysosomal Dysfunction and Proteostatic Failure

The autophagy-lysosome system is essential for maintaining cell homeostasis by degrading dysfunctional organelles, misfolded proteins, and other macromolecules<sup>24</sup>. Lysosomes facilitate this process by breaking down cellular waste in acidic environments using specialized digestive enzymes. The disruption of this system leads to the accumulation of cell debris and damaged mitochondria, impairing metabolic health and accelerating the trajectory of biological aging<sup>24,25</sup>.

New evidence has identified the autophagy-lysosome axis as the primary target of PM toxicity<sup>28,38</sup>. Although some models suggest that initial induction of autophagy is an adaptive response to PM-mediated stress, chronic exposure generally leads to the disruption of autophagic fluxes<sup>25,28</sup>. PM2.5 has been shown to induce lysosomal alkalization and increase membrane permeability. This results in cathepsin B leaking into the cytoplasm and autophagy-lysosome fusion failing<sup>28</sup>. Injuries to autophagy fluxes observed in various cell types, including endothelial cells and keratinocytes, result in the accumulation of damaged cell components and cause apoptotic signals<sup>25,38</sup>. Collectively, these findings suggest that PM-induced protein congestion failure due to lysosomal dysfunction is a fundamental mechanism of accelerated cell aging<sup>24,28</sup>.

### Discussion

Recent scientific investigations suggest that exposure to particulate matter (PM) is a potent environmental promoter of biological aging and an important modifier of aging-related pathologies<sup>1,3</sup>. Micro-particles (PM2.5) and hyper-fine particles are characterized by their ability to penetrate deep into the lungs and move through the bloodstream. They closely

reflect the natural trajectory of aging by inducing molecular and cellular responses<sup>2,6</sup>. The intersection between PM exposure and aging is defined as a multifaceted interaction of oxidative stress, “inflammation,” mitochondrial dysfunction, immunomodulatory disorders, and damage to the autophagy-lysosomal pathway<sup>16,20,24</sup>.

The main pathway by which PM accelerates the aging process is the progressive weakening of the immune system. PM2.5 disrupts the functional integrity of macrophages and lymphocytes by bypassing the upper respiratory defense and infiltrating the alveoli, causing abnormal allergic inflammation and impairing host defense mechanisms<sup>42,47</sup>. Transcriptome profiles of human immune cells exposed to PM show the downregulation of pathogen-recognizing genes and increased levels of inflammatory cytokines, indicating “immune depletion” that is commonly observed in elderly cohorts<sup>10,42</sup>. Furthermore, PM exposure is increasingly associated with abnormal lipid accumulation and metabolic deterioration including insulin resistance<sup>26,43</sup>. Longitudinal data suggest that chronic PM2.5 inhalation is associated with increased visceral fat and adipocyte hypertrophy, which mimics the metabolic changes characteristic of physiological aging<sup>50,51</sup>.

The liver and musculoskeletal systems are also targets for PM-mediated toxicity. Epidemiologic and animal studies have shown that PM2.5 exposure exacerbates the risk of metabolic dysfunction-associated fatty liver disease (MASLD) by increasing liver triglycerides and interfering with lipid homeostasis<sup>27,46</sup>. Similarly, PM exposure contributes to the loss of skeletal muscle mass and the development of sarcopenia<sup>29,57</sup>. In the context of skeletal health, PM2.5 decreases bone density, thereby reducing osteoblast differentiation and promoting RANKL-mediated osteoblast activity<sup>34,35</sup>. The disruption of these bone remodeling pathways and altered calcium homeostasis increase fracture susceptibility significantly<sup>45,59</sup>. At the molecular level, PM appears to incorporate several aging-related pathways. It activates the NLRP3 inflammasome, inducing the continued secretion of IL-18, and stimulate the production of mitochondrial-derived ROSs that overwhelm antioxidant defenses such as the Nrf2 pathway<sup>19,21,39</sup>.

### Conclusion

Evidence from epidemiological, clinical, and experimental fields suggests that PM exposure is a significant factor in biological aging<sup>1,4</sup>. This review demonstrates how PM initiates synergies among oxidative, inflammatory, and protein-identity stressors by integrating multisystem data. By identifying these specific pathways, this study highlights how environmental pollution affects a variety of chronic diseases, including neurodegeneration, cardiovascular disease, type 2 diabetes, and osteoporosis<sup>11–13,49</sup>.

Despite compelling evidence, some limitations remain. The

main constraint is the translation gap between controlled animal models of high-dose PM exposure and the chronic, low-dose exposure patterns characteristic of human aging<sup>4</sup>. Furthermore, heterogeneity of PM chemical composition among geographic regions complicates the generalization of toxicological results<sup>3,5</sup>. Future studies should prioritize longitudinal human studies utilizing individual exposure monitoring and multiple approaches to better define causal relationships between specific PM components and aging biomarkers.

As global urbanization continues, a comprehensive understanding of PM-mediated aging is crucial. Developing targeted public health strategies and therapeutic interventions to mitigate these environmental risks is an important step toward promoting human resilience and longevity in the increasingly polluted global environment<sup>1,2</sup>.

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