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Toxicological Effects of Fine Particulate Matter ($PM_{2.5}$): Health Risks and Associated Systemic Injuries—Systematic Review

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Abstract Previous studies focused on investigating particulate matter with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$) have shown the risk of disease development, and association with increased morbidity and mortality rates. The current review investigate epidemiological and experimental findings from 2016 to 2021, which enabled the systemic overview of $PM_{2.5}$'s toxic impacts on human health. The Web of Science database search used descriptive terms to investigate the interaction among $PM_{2.5}$ exposure, systemic effects, and COVID-19 disease. Analyzed studies have indicated that cardiovascular and respiratory systems have been extensively investigated and indicated as the main air pollution targets. Nevertheless, $PM_{2.5}$ reaches other organic systems and harms the renal, neurological, gastrointestinal, and reproductive systems. Pathologies onset and/or get worse due to toxicological effects associated with the exposure to this particle type, since it can trigger several reactions, such as inflammatory responses, oxidative stress generation and genotoxicity. These cellular dysfunctions lead to organ malfunctions, as shown in the current review. In addition, the correlation between COVID-19/Sars-CoV-2 and $PM_{2.5}$ exposure was also assessed to help better understand the role of atmospheric pollution in the pathophysiology of this disease. Despite the significant number of studies about $PM_{2.5}$'s effects on organic functions, available in the literature, there are still gaps in knowledge about how this particulate matter can hinder human health. The current review aimed to approach the main findings about the effect of $PM_{2.5}$ exposure on different systems, and demonstrate the likely interaction of COVID-19/Sars-CoV-2 and $PM_{2.5}$.

Keywords Diseases · Inflammation · Oxidative stress · Particulate matter · Systems · Toxicity

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1 Introduction

Over the last few years, epidemiological and experimental studies have been reporting association between adverse effects of individuals' exposure to particulate

matter (PM) and the development of several diseases (Jang et al., 2018; Kioumourtzoglou et al., 2016; Nephew et al., 2020; Tanwar et al., 2017; Zhang et al., 2018). PM is classified based on its particles' size; thus, coarse particles (PM_{10}) range from 10 to 2.5 μm; fine particles ($PM_{2.5}$), from 2.5 to 0.1 μm; and ultrafine particles ($PM_{0.1}$) are smaller than 0.1 μm (Al-Thani et al., 2018). $PM_{2.5}$ toxicity has been assessed in many studies focused on investigating its health-related risks (Gallo et al., 2020; Yang et al., 2020; Younan et al., 2020). $PM_{2.5}$ can derive from natural sources, such as volcanoes, fire events, dust storms, as well as from anthropogenic activities, mainly from biomass and fuel combustion, and from industrial processes (Al-Thani et al., 2018). The human body is constantly exposed to $PM_{2.5}$, which can get to individuals' respiratory tract and reach other systems through the bloodstream; particles' translocation triggers tissue responses to these airborne pollutants in one's body (Milani et al., 2020). Mechanisms involved in organic system injuries resulting from individuals' exposure to $PM_{2.5}$ are based on biomolecular damage, as well as on signaling pathway alterations and involvement in cell function and survival processes (Fu et al., 2017; Li et al., 2017; Ribeiro et al., 2016; Wei et al., 2016). $PM_{2.5}$-organic systems' interaction induces immune system responsiveness, whereas activated pathways include multiple inflammatory cells' recruitment, cytokine production and increased reactive oxygen species (ROS) production in tissues (Jan et al., 2020; Li et al., 2019a, 2019b; Libalova et al., 2018). Stressful conditions triggered by excessive ROS production lead to an unbalanced normal redox cycle, which, in its turn, triggers prooxidant reactions capable of destabilizing the cellular environment and, consequently, of compromising tissues (Jan et al., 2020; Ribeiro et al., 2016). $PM_{2.5}$ exposure has been associated with systemic disorders in several epidemiological and experimental studies. A broad spectrum of respiratory system-related diseases, such as asthma (Jung et al., 2019; Zhao et al., 2018), lung cancer (Tomczak et al., 2016; Zhang et al., 2020), chronic obstructive pulmonary disease, (COPD) (Liu et al., 2017b) and pneumonia (Lv et al., 2017), can onset and/or worsen due to exposure to $PM_{2.5}$. Changes in the cardiovascular system, such as arrhythmias, increased blood pressure and variations in heart rate (Folino et al., 2017; Fuks et al., 2016; Gallo et al., 2020; Honda et al., 2018; Kim et al., 2019; Xie et al., 2018; Yang et al., 2020) are also observed in the aforementioned context. Studies focused on investigating the human nervous system evidenced that exposure to $PM_{2.5}$ increased individuals' risk of developing Parkinson's disease, Alzheimer's disease, memory deficit and dementia (Kioumourtzoglou et al., 2016; Liu et al., 2016a, 2016b; Younan et al., 2020). Harmful effects of exposure to $PM_{2.5}$ and their association with damage in the human renal system were reported in different studies, which evidenced the risk of chronic kidney disease (CKD) (Blum et al., 2020; Bo et al., 2021; Bragg-Gresham et al., 2018; Chan et al., 2018), of progression to end-stage kidney disease—ESKD (Bowe et al., 2018) and of lower glomerular filtration rate (GFR) (Mehta et al., 2016). The aforementioned data indicate the scientific community's growing interest in investigating the association between exposure to $PM_{2.5}$ and renal dysfunction (Mehta et al., 2016; de Paula et al., 2019; Xu et al., 2016). Concerning the gastrointestinal system, studies have also reported increased mortality rates associated with liver, colorectal, and gastrointestinal cancer, as well as with dysbiosis resulting from exposure to $PM_{2.5}$ (Liu et al., 2021; Pan et al., 2016; Weinmayr et al., 2018; Wong et al., 2016). As for the reproductive system, studies have indicated that exposure to $PM_{2.5}$ has a negative effect on individuals' fertility (Guo et al., 2020), hinders fetal development (Liu et al., 2016b; Percy et al., 2019; Soto et al., 2017) and leads to plancentary and circulatory impairment (Kingsley et al., 2017; Liu et al., 2016b; Soto et al., 2017; Wylie et al., 2017). In addition, the world was exposed to the COVID-19 pandemic, whose causative virus mainly enters individuals' bodies through their respiratory system. Therefore, studies were conducted to help better understand the association between exposure to $PM_{2.5}$, viral cycle and clinical state worsening (Loaiza-Ceballos et al., 2021; Yang et al., 2020). Investigating particulate matter interactions is essential to help develop strategies to reduce global pollution and to help better understand the association between air pollution and health issues. The current review aimed to gather information about organic system alterations and the pathways that contribute to this process, and present epidemiological and experimental findings about exposure to $PM_{2.5}$ and systemic damages resulting from it (Fig. 1).

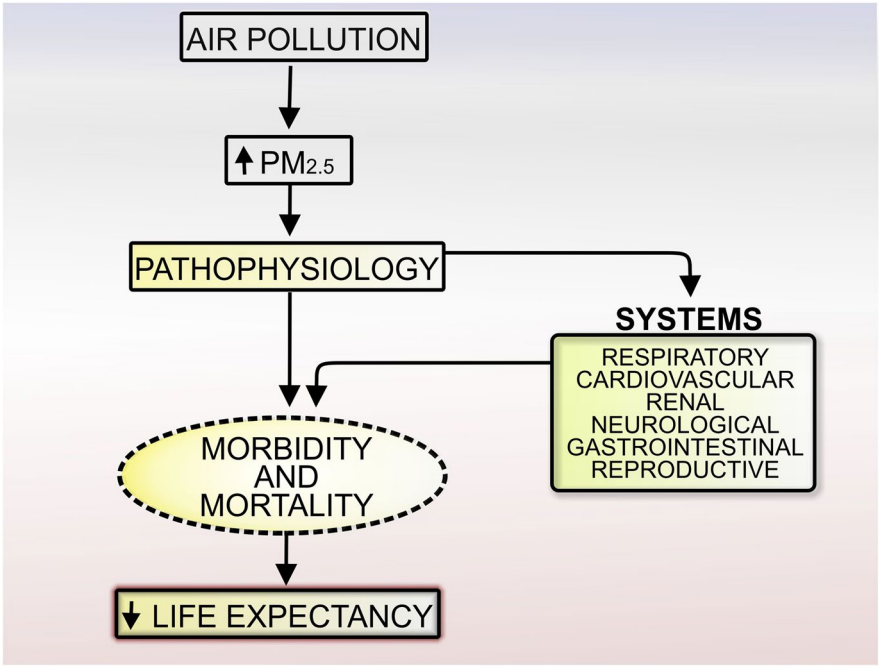

Fig. 1 Schematic drawing of the general effects caused by $PM_{2.5}$

2 Cellular Environment and $PM_{2.5}$ Interactions

2.1 *Inflammation and Exposure to $PM_{2.5}$*

The inflammatory state is the most common response to individuals' exposure to $PM_{2.5,}$ whose chemical compounds are linked to several changes in body systems, a fact that can onset and/or worsen different pathological conditions (Guan et al., 2019). The interaction of $PM_{2.5}$ and its compounds with airways induces the formation of local pro-inflammatory and pro-oxidant molecules that use individuals' bloodstream to reach other organs and change tissue functions (Li et al., 2019a, 2019b). $PM_{2.5}$ changes cellular biomolecules and activates the immune response; this process starts with immune cells' recruitment and cytokine production to promote pro-inflammatory signaling (Li et al., 2019a, 2019b; Xu et al., 2020). Cytokines are chemical messengers used as inflammatory markers capable of changing cellular activity (Zheng et al., 2019). Their secretion is susceptible to exposure to $PM_{2.5}$. Assays conducted in vitro have evidenced increased IL-6, IL-8, and IL-1β cytokine levels in human bronchial epithelial cells, after 24-h exposure to $PM_{2.5}$ (Zou et al., 2020). Increased cytokine mRNA expression was observed in experimental studies, after individuals' exposure to $PM_{2.5}$; this event was associated with neural changes (Liu et al., 2018). Modified mRNA expression of IL4, IL13 and IL17 inflammatory cytokines and decreased number of autophagy markers (ULK1 and LC3A/B) were observed in bronchoalveolar fluid and lungs in asthmatic mice, and it indicated loss of an important inflammation control mechanism, namely: autophagy (Wang et al., 2016). Studies have shown that exposure to $PM_{2.5}$ for 3, 6, and 12 weeks increased plasma neutrophil and monocyte concentrations, as well as the level of pro-inflammatory cytokines, such as Interferon-gamma (IFN-γ) and Interleukin-10 (IL-10), in mice (Li et al., 2019a, 2019b). These findings corroborate experimental results described by Yang et al. (2019), according to whom, increased levels of immune cells (lymphocytes, neutrophils, eosinophils), Interleukin 4 (IL-4), tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF beta) were observed in the serum and lungs of mice, after three-month exposure to $PM_{2.5}$. Mast cells are an important target used in studies focused on investigating exposure to $PM_{2.5}$ since they a play key part in allergic and inflammatory processes, besides being involved in innate and adaptive immune responses (Jin et al., 2019). Wang et al. (2021) have shown that pretreatment for instillation with $PM_{2.5}$ in mice at different concentrations (0.187, 0.375, 0.75 mg kg^{-1}), induced mast cells' activation through immunoglobulin E (IgE) highlighting by β-hexosaminidase (mast degranulation

marker) levels. This finding has evidenced that $PM_{2.5}$ compounds contribute to worsening allergic processes. As previously described, exposure to $PM_{2.5}$ -at early stages—triggers local immune system activation, and respiratory system inflammatory state, leading to tissue dysfunction (Guan et al., 2019; He et al., 2017; Yang et al., 2018).

2.2 *Oxidative Stress and Exposure to $PM_{2.5}$*

Exposure to $PM_{2.5}$'s organic and inorganic compounds is linked to increased reactive oxygen species (ROS) formation, and to unbalanced antioxidant defense. The resultant oxidative stress leads to biomolecular injuries (Fang et al., 2019; Lakey et al., 2016). Antioxidant defenses (enzymatic and non-enzymatic) account for protecting the body from damage to macromolecules resulting from ROS production. It does so, by neutralizing ROS action and by maintaining the appropriate cellular environment (Zeng et al., 2018). $PM_{2.5}$ presents heterogeneous composition, and its compounds can interact in different ways. Among the aforementioned compounds, metals emerge as an important pro-oxidative factor capable of increasing ROS formation (Fang et al., 2019; Ribeiro et al., 2016; de Paula et al., 2019). Although metallic ions are closely related to ROS formation, researchers attribute the oxidative condition to quinones, such as polycyclic aromatic hydrocarbons (PAHs). Both aggravating $PM_{2.5}$ compounds can interact with biomolecules and lead to oxidative stress condition (Fang et al., 2019; Lakey et al., 2016; Li et al., 2019b; Libalova et al., 2018). Based on findings observed both in vitro and in vivo, $PM_{2.5}$ inhalation has induced ROS formation, a fact that indicates redox imbalance (Cao et al., 2016; Jin et al., 2019; Park et al., 2018; Ren et al., 2020) and contributes to local and systemic inflammatory state (Crobeddu et al., 2020; Guan et al., 2019). An assay performed in vitro by Xu et al., (2020) has evidenced that macrophage cells exposed to $PM_{2.5}$ solution (200 μg mL^{-1}) for 6 h showed increased ROS levels and secretion of pro-inflammatory cytokines, such as IL-1β and TNF-α, which are associated with systemic inflammation. Reports have indicated that exposure to $PM_{2.5}$ decreased antioxidant defense in different organs, such as heart, kidney, liver and lung, by reducing antioxidants' mechanism, and by affecting glutathione levels and total antioxidant capacity (Ribeiro et al., 2016; de Paula et al., 2019), as well as the activity of enzymes such as superoxide dismutase and glutathione peroxidase (Wu et al., 2016). Exposure to $PM_{2.5}$ plays a critical part in oxidative stress conditions, since it increases lipoperoxidation (Qiu et al., 2019; de Paula et al., 2019; Wang et al., 2019; Yu et al., 2017) and leads to mitochondrial damage (Guo et al., 2017; Jin et al., 2018; Wang et al., 2019). Accordingly, mitochondrial injury opens the transition pore and hinders the potential of the mitochondrial membrane (Qiu et al., 2019; Wang et al., 2019). Studies have suggested that ROS exacerbation deriving from exposure to $PM_{2.5}$ accounts for cellular apoptosis and necrosis processes (Santa-Helena et al., 2021; Shan et al., 2021), as well as for increased DNA damage rate and cellular senescence (Gao et al., 2016).

2.3 *DNA Changes and Cell Death Pathways Associated with Exposure to $PM_{2.5}$*

Exposure to $PM_{2.5}$ has been associated with genotoxicity (DNA strand breaks) and DNA damage signaling (Kim et al., 2018; Lemos et al., 2016), as well as with chromosomal abnormalities (Miousse et al., 2016) and with changes in DNA methylation (Jiang et al., 2019; Liu et al., 2017a, 2017b; Panni et al., 2016; Shi et al., 2019; Wei et al., 2016, 2017). DNA methylation is a DNA repair mechanism that tends to adjust gene transcription (Harris et al., 2018); however, methylation changes associated with oxidative-stress increase can lead to epigenetic changes (Wei et al., 2017) and induce the development of different diseases (Miousse et al., 2016; Sun et al., 2018;). The study conducted invitro by Wei et al. (2017) exposed SH-SY5Y nervous cell lineage to $PM_{2.5}$ for 72 h at concentrations of 0, 2.5, 5, 10, 20, 40, 80, 160, and 320 μg mL^{-1} for the cell viability tests. For the assays, a proportion of 15% of these values was used from organic fraction of $PM_{2.5}$ (0, 0.375, 0.75, 1.5, 3, 6, 12, 24, and 48 μg mL^{-1}); results have shown changes in DNA methylation associated with redox imbalance, a fact that was attenuated by the use of antioxidants, indicated close correlation between DNA damage and oxidative stress generation. Xu et al. (2018) have shown that $PM_{2.5}$ compounds found in human bronchial epithelial cells and mouse lungs have activated the early growth-response gene expression (Egr-1) involved in different signaling pathways associated with pathological processes. However, further studies should be performed to help better understand the association between methylation and oxidative stress, as well as the

target genes and the mechanisms involved in this process. Besides being associated with DNA damage, exposure to $PM_{2.5}$ also affects cell survival rates. Studies have indicated that cellular interaction with $PM_{2.5}$ compounds decreased cell viability by activating different cell death pathways (apoptosis, necrosis, and autophagy) depending on PM composition, concentration, exposure time and on cell type (Cao et al., 2016; Fu et al., 2017; Shan et al., 2021). Studies conducted with human corneal epithelial cells (Fu et al., 2017) have shown decreased cell viability associated with the activation of apoptosis and autophagy pathways, after treatment application with $PM_{2.5}$ solution (50 μg mL^{-1}). This finding has evidenced time-dependent exposure effects on the investigated cells. According to Santa-Helena et al. (2021), acute exposure of another cell type—H9c2 cardiomyocyte—to $PM_{2.5}$ for 24 h increases cell apoptosis and necrosis rates associated with ROS formation. The aforementioned authors also reported the activation of different cell death signaling pathways; lower $PM_{2.5}$ concentrations activated apoptosis, whereas higher concentrations of it led to necrosis and resulted in decreased cell viability (Santa-Helena et al., 2021). In addition, studies in vitro conducted with cortical neurons exposed to different $PM_{2.5}$ concentrations (12.5, 25, 50, 100, and 200 μg mL^{-1}) have shown that this pollutant triggered cell apoptosis and neurotoxicity (Chen et al., 2017b). $PM_{2.5}$ also induced pro-apoptotic events due to Bax proteins' expression; these proteins are associated with apoptotic mechanisms, as well as with anti-apoptotic BCL-2 proteins' inhibition. As for the seasonal factor, Chen et al. (2017b) reported that winter was the most critical season associated with both exposure to $PM_{2.5}$ and neurotoxicity events (Chen et al., 2017b). Apoptotic events were also described in mast cells (Jin et al., 2018), as well as in human bronchial epithelial cells (Dornhof et al., 2017) exposed to different $PM_{2.5}$ concentrations (Table 1). These studies aimed to explain how cellular toxicity occurs after cellular exposure to $PM_{2.5}$ to help better understand the mechanisms underlying cellular damage (Fig. 2).

Table 1 Scientific findings (2016–2021) related to inflammatory processes, ROS production, DNA changes, and cell death pathways associated with exposure to $PM_{2.5}$

Authors	Damage caused by $PM_{2.5}$ exposure
Inflammation	
(Li et al., 2019a, 2019b; Wang et al., 2021; Yang et al., 2019)	Imune cells activation
(Li et al., 2019a, 2019b; Liu et al., 2018; Wang et al., 2016; Xu et al., 2020; Yang et al., 2019; Zou et al., 2020)	Increased pro-inflammatory cytokines
(Jin et al., 2019; Wang et al., 2021)	Allergic reactions
Reactive Oxygen Species (ROS)	
(Cao et al., 2016; Crobeddu et al., 2020; Fang et al., 2019; Guan et al., 2019; Jin et al., 2018; Jin et al., 2019; Lakey et al., 2016; Li et al., 2019b; Libalova et al., 2018; Park et al., 2018; Qiu et al., 2019; Ren et al., 2020; Santa-Helena 2021; Shan et al., 2021; Xu et al., 2020)	ROS generation
(Crobeddu et al., 2020; Ribeiro et al., 2016; de Paula et al., 2019; Wang et al., 2019; Wu et al., 2016)	Antioxidants changes
(Qiu et al., 2019; Ribeiro et al., 2016; de Paula et al., 2019; Yu et al., 2117; Wang et al., 2019; Wu et al., 2016)	Lipoperoxidation
(Guo et al., 2017; Jin et al., 2018; Wang et al., 2019; Zhang et al., 2018)	Mithocondrial damage
DNA	
(Kim et al., 2018; Lemos et al., 2016)	DNA damage
(Jiang et al., 2019; Harris et al., 2018; Shi et al., 2019; Wei et al., 2016, 2017)	DNA methylation changes
(Miousse et al., 2016)	Chromossomal anomalies
(Wei et al., 2017)	Interruption of the cell cycle and inhibition of cell proliferation
Apoptosis, necrosis, and autophagy	
(Cao et al., 2016; Chen et al., 2017b; Dornhof et al., 2017; Fu et al., 2017; Jin et al., 2019 Santa- Helena et al., 2021)	Apoptosis
(Dornhof et al., 2017; Santa-Helena et al., 2021)	Necrosis
(Chen et al., 2017b; Fu et al., 2017; Wang et al., 2016)	Autophagy

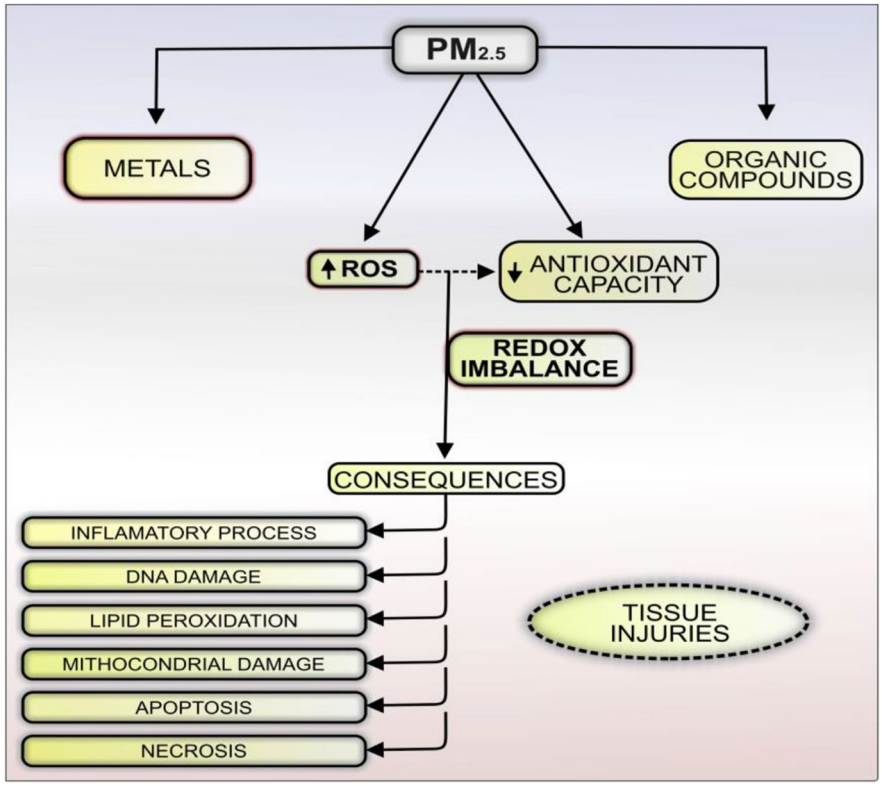

Fig. 2 Events involved in the cellular dysfunctions caused by $PM_{2.5}$ compounds to different tissues

3 Methodology

The research question guiding the current Systematic Literature Review was: "What are the $PM_{2.5}$ effects on different systems?" The present study aimed to assess $PM_{2.5}$ exposure-related risks to human health, based on experimental and epidemiological findings. Inclusion and exclusion criteria were adjusted to generate sensitive research, as described: 1) articles published in internationa1 journals; 2) studies on exposure to $PM_{2.5}$ that have excluded PM_{10} and $PM_{0.1}$; and 3) articles published in peer-reviewed journals. A search for eligible experimental and epidemiological studies published from January 2016 to December 2021 was carried out in the Web of Science database (Fig. 3).

The following descriptors were used: "fine particulate matter and systems' diseases" (respiratory, cardiovascular, kidney, gastrointestinal, neurological and reproductive); "fine particulate matter and toxicity"; "fine particulate matter and COVID-19 or Sars-CoV-2". The herein used descriptors resulted in 4,413 articles, as shown (Fig. 3 and Table 2).

Applied the search in the databases mentioned above, the works found were downloaded and uploaded to the Rayyan semi-automatic platform. Duplicates and triplicates were detected automatically, but the exclusions were made manually. Next, 26 of the eligibility criteria for selecting articles by titles and abstracts were applied. After the inclusion and exclusion criteria application, 109 articles were eligible for the current review. Using the Rayyan software, the most referred keyword found was "particulate." Two authors in the current study have independently analyzed articles' titles, abstracts and full texts, based on the herein adopted inclusion and exclusion criteria.

4 Results

4.1 *Systems' Imbalance Versus Exposure to $PM_{2.5}$*

4.1.1 Respiratory System and Exposure to $PM_{2.5}$

With respect to exposure to $PM_{2.5}$ types, individuals' respiratory system is the major pathway enabling PM

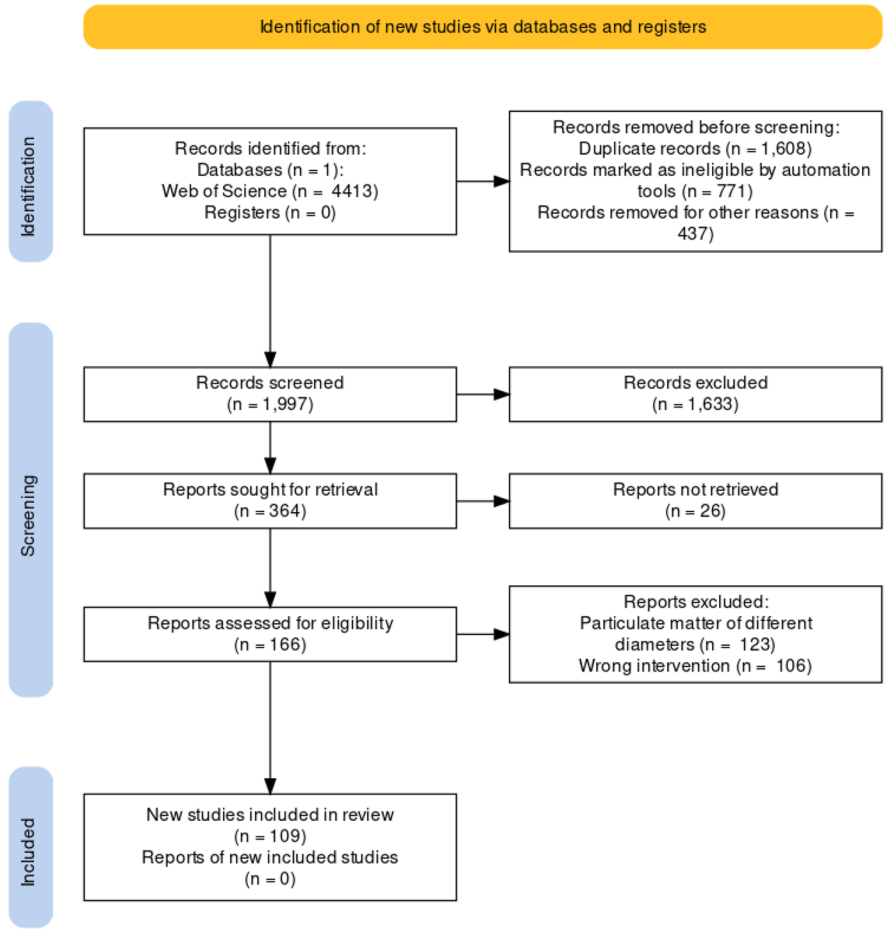

Fig. 3 Flow diagram representing the selection criteria for the articles found and included in the systematic review

penetration in, and damage to lung tissues (Kilian and Kitazawa, 2018; Yang et al., 2019). Scientific evidence has suggested an association between respiratory system exposure to $PM_{2.5}$ and exacerbation of pre-existing cardiopulmonary diseases, which, in their turn, leads to increased morbidity and mortality rates (Lin et al., 2016a; Morantes-Caballero et al., 2019). Studies observed respiratory disorders, such as chronic obstructive pulmonary

Table 2 Scientific articles focused on investigating $PM_{2.5}$ effects on different physiological systems, based on articles published from 2016 to 2021

Keywords	Total number (2016–2021)	2016	2017	2018	2019	2020	2021
Fine particulate matter and toxicity	1.390	186	199	208	322	234	241
Fine particulate matter and respiratory diseases	1.395	181	248	257	344	295	261
Fine particulate matter and cardiovascular diseases	1.318	179	199	218	276	248	198
Fine particulate matter and kidney disease	67	4	7	12	12	19	13
Fine particulate matter and neurological diseases	49	5	6	7	9	10	12
Fine particulate matter and gastrointestinal diseases	21	2	3	3	5	6	2
Fine particulate matter and reproductive system	20	1	1	2	5	6	5
Fine particulate matter and COVID-19 or Sars-CoV-2	153	-	-	-	-	56	97
Total	4.413	558	663	707	974	853	829

disease (COPD), pneumonia, lung cancer, asthma and morphological changes in the epithelium of individuals exposed to this pollutant (Gharibvand et al., 2017; Jung et al., 2019; Liu et al., 2017a, 2017b; Lv et al., 2017; Sun et al., 2017; Yoshizaki et al., 2017; Zhang et al., 2020; Zhao et al., 2018). Data derived from population cohort studies have indicated that $PM_{2.5}$ induced systemic inflammatory response and increased hospitalization rates due to lung diseases, such as asthma (Tian et al., 2017), pneumonia, and influenza (Croft et al., 2019; Zhang et al., 2017). Asthma is the most common respiratory disease associated with exposure to $PM_{2.5}$. Jung and collaborators (2019) conducted a cohort study comprising children born in Taichung City from 2004 to 2011. Results have evidenced the incidence of this pathology after individuals were exposed to $PM_{2.5}$ during pregnancy and childhood, as well as a positive correlation between such exposure and subsequent asthma emergence. Tian et al. (2017) investigated $PM_{2.5}$ effects on asthma-related morbidity rates in Beijing City, China (2010–2012) and found an association between high $PM_{2.5}$ levels and the risk of asthma worsening. The ssociation between pediatric pneumonia and environmental $PM_{2.5}$ levels (10 μg m^{-3}) were reported for Lv and collaborators (2017) , since the interaction between $PM_{2.5}$ compounds and individuals' respiratory epithelium that induced an inflammatory response and, in its turn, increased children's hospitalization rate due to pneumonia. Another study adopted case-crossover methods to analyze adult individuals in New York City, from 2005 to 2016. The authors of the aforementioned study found increased pneumonia and influenza rates associated with increased $PM_{2.5}$ concentrations the week before disease diagnosis (Croft et al., 2019). A cross-sectional study conducted in four cities of Guangdong province, in Southern China, associated $PM_{2.5}$ levels with an increased risk of chronic COPD development. COPD prevalence was significantly associated with high $PM_{2.5}$ concentrations (10 μg m^{-3}), and with the spirometric decrease in individuals forced expiratory volume and vital capacity, indicating decreased lung capacity (Liu et al., 2017b). In meta-analysis study performed by Li et al., (2016a, 2016b) associated the same increase (10 μg m^{-3}) in daily exposure to $PM_{2.5}$ with increase by 3.1% in the rate of hospitalizations due to COPD, and by 2.5%, in COPD-related mortality rates. In addition, Chinese study conducted with school-age children exposed to acute $PM_{2.5}$ levels has shown airway inflammation, pulmonary function loss and changes in oral mucosal microbiota (Wu et al., 2021). The authors of the aforementioned study have also suggested that long-term exposure to this pollutant can lead to different respiratory disease-development patterns. In addition to increased respiratory disease development caused by impaired lung function, PM can also increase the risk of lung cancer incidence rates (Raaschou-Nielsen et al., 2016; Zhang et al., 2020). According to recent studies, the genotoxicity caused by $PM_{2.5}$ is key mechanism in cancer development processes (Gharibvand et al., 2017; Zhang et al., 2020). Accordingly, a study focused on monitoring a Canadian cohort exposed to $PM_{2.5,}$ based on remote sensing data, has shown that lung cancer incidence was also associated with prolonged periods of $PM_{2.5}$ presence in airborne (Tomczak et al., 2016). Factors such as air pollution enhance the chance of lung cancer development with the elevation of 10 μg m^{-3} of $PM_{2.5}$ in airborne (Gharibvand et al., 2017). Likewise, a study conducted in the US has shown that lung cancer rates increased by 31% as $PM_{2.5}$ concentrations increased by 10 μg m^{-3} (Gharibvand et al., 2017). An experimental study conducted with rats indicated worsened asthma after exposure to $PM_{2.5}$ for 4 h per day, for 8 weeks (Zhao et al., 2018). Yoshizaki et al. (2017) compared the $PM_{2.5}$ effects in male and female mice and, based on the analyzed parameters reported differences in $PM_{2.5}$ response between sexes; the male sex was more susceptible to exposure to PM. Interactions among estrogen-like molecules, such as polycyclic aromatic hydrocarbons in $PM_{2.5}$ can explain this differences. Airway epithelial cells are the first line of defense against $PM_{2.5}$; besides working as barrier, they account for mucociliary clearance, as well as for secreting antimicrobial proteins and peptides. According to He et al. (2017), exposure to $PM_{2.5}$ can affect mucociliary movement in rats by increasing mucus production. Furthermore, morphological injuries and changes in lung tissue during short-term exposure to $PM_{2.5}$, such as alveolar collapse, neutrophilic inflammation and increased TNF-α production, were also reported (Wang et al., 2017a). A study conducted in vivo with mice has proved that $PM_{2.5}$ triggers lung fibrosis, since lung inflammation and fibrosis symptoms were observed after models' exposure to this pollutant (Xu et al., 2019). Other studies have indicated that individuals' exposure to $PM_{2.5}$ is an important epidemiological factor for respiratory disease development and/or worsening, as well as that such exposure could be associated with the population's increased susceptibility to different lung disorders (Hehua et al., 2017). Yang et al. (2018) have shown that rats exposed to $PM_{2.5}$ for two weeks presented increased total protein expression

levels in bronchoalveolar lavage fluid, as well as increased levels of cytokines, such as IL-6, IL-10, and MCP-1, in blood tissue. Such an exposure has also activated macrophages, induced oxidative stress and generated acute inflammatory response, which led to damage in lung tissues. According to Jeong et al. (2019), tracheal exposure to $PM_{2.5}$ led to macrophage activation in the lung tissue of mice, as well as significant changes in the IL-17 signaling pathway.

4.1.2 *Cardiovascular Damages and Exposure to $PM_{2.5}$*

Exposure to $PM_{2.5}$ can reach distant organs causing numerous dysfunctions in individuals exposed to it. Among them, one finds the cardiovascular system, which is significantly affected by air pollution and presents several changes already reported in experimental studies (Dai et al., 2017; Li et al., 2017; Ribeiro et al., 2016; Wan et al., 2019). Epidemiological studies conducted with humans have indicated an association between increased $PM_{2.5}$ concentrations in inhaled air and disorders, such as cardiac arrhythmias (Folino et al., 2017; Yang et al., 2020), cardiac fibrillation (Gallo et al., 2020; Kim et al., 2019), hypertension (Fuks et al., 2016; Honda et al., 2018) and variations in heart rate (Xie et al., 2018). Chen et al. (2017c) have analyzed individuals with pre-existing cardiovascular comorbidities and their association with environmental exposure to $PM_{2.5}$. Their findings have evidenced a decline in indices, such as heart rate, autonomic imbalance, increased thrombosis development risk and inflammation state. Epidemiological cohort study was performed in China with participants aged 18–80, who lived in different geographic regions and were exposed to different pollution rates, by considering mean $PM_{2.5}$ concentrations in the air, from 2014 to 2016 (Cao et al., 2021). Collected data have indicated that long-term exposure to $PM_{2.5}$ was significantly associated with first-stage hypertension parameters—i.e., systolic blood pressure (SBP): 130–139 Torr and diastolic blood pressure (DBP): 80–89 Torr (Cao et al., 2021). Lozano-Sabido et al. (2021) conducted an epidemiological study associated with air pollution in individuals hospitalized in Mexico City who presented with pre-existing coronary disease. This work was accomplished from January 2012 to April 2019 and results have shown ST segment elevation in the electrocardiogram, which was associated with myocardial infarction owing raise $PM_{2.5}$ concentrations. Another epidemiological study investigated the effects of exposure to $PM_{2.5}$ on variations in the heart rate of 35 individuals living in an urban community in Taiwan. The adopted correlated variables comprised different weather conditions, seasons, and normal-weight and overweight individuals; $PM_{2.5}$ mass concentrations were monitored in real-time. The major finding in the aforementioned study concerned changes in the heart rate of overweight individuals right after their exposure to $PM_{2.5}$, compared to that of normal-weight individuals. This report corroborates the understanding that being overweight is a risk factor for the development of cardiovascular disease and that exposure to pollutants can worsen this condition (Tsou et al., 2021). Experimental studies have also provided evidence that exposure to $PM_{2.5}$ leads to tissue damage. Li et al. (2017) investigated the association between exposure to $PM_{2.5}$ and myocardial infarction (MI) in mice models exposed to this pollutant through intranasal instillation. Collected data have indicated cardiac remodeling due to increased apoptosis (increased Caspase 3 and Bax expression), reduced left ventricular function and increased size of infarction area. Ribeiro et al. (2016) exposed rat models to $PM_{2.5}$ samples collected from two different areas (urban and industrial). Their findings comprised metal bioaccumulation, increased oxidative stress, as well as histological changes, such as decreased number of cardiomyocytes and an increased number of fibroblast cells in the heart of rats from both regions. Wan et al. (2019) observed an association between exposure to $PM_{2.5}$ and atherosclerosis development in the vascular system of ApoE $^{-/-}$ mice. The aforementioned models presented increased IL-6 and TNF-α cytokine levels, which account for accelerating atherosclerosis progress, as well as decreased IL-10 and TGF-β levels that, in turn, inhibit atherosclerotic plaques' formation. Heart failure induction in mice, which were subsequently exposed to $PM_{2.5}$, resulted in inflammation and vascular remodeling in their lungs, as well as in cardiac hypertrophy (Yue et al., 2019). Furthermore, exposure to $PM_{2.5}$ was associated with endothelial vascular dysfunction. The study conducted with Sprague Dawley rats exposed to $PM_{2.5}$ for 4 weeks reported abnormalities in miRNA (miR-21) which account for regulating the endothelial barrier; these abnormalities resulted in vascular endothelial-cadherin gene regulation suppression and led to endothelial integrity impairment (Dai et al., 2017). A recent study conducted invitro by Santa-Helena et al. (2021) investigated $PM_{2.5}$'s toxicological effects on cardioblast cells (H9c2). The cells were treated with $PM_{2.5}$ extracts, at different concentrations,

for 24 h. Post-treatment findings comprised cell damage, evidenced by increased lactate dehydrogenase activity, lipid membrane damage, increased ROS formation and decreased antioxidant catalase activity.

4.1.3 Nervous System and Exposure to $PM_{2.5}$

Several studies associated neurotoxicity with inhaled $PM_{2.5}$, which reaches the central nervous system through individuals' bloodstream and olfactory pathways (Wang et al., 2017c). Reports in the literature have indicated strong association between exposure to PM and a wide variety of neurological disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD) and dementia. Younan et al. (2020) conducted a study in California (USA) and observed episodic memory decline in women in the age group over 65 years, who did not have dementia symptoms. Results suggested a correlation between such a decline and AD caused by grey matter atrophy due to long exposure to $PM_{2.5}$. Kioumourtzoglou et al. (2016) had previously observed correlations between long-term exposure to $PM_{2.5}$ and hospitalizations due to neurological causes in epidemiological studies carried out in different cities in the United States. Collected data have indicated an association between exposure to $PM_{2.5}$ and the incidence of AD, PD and dementia. Mortamais et al. (2019) also linked behavioral disorders to air pollution, in a study carried out in Barcelona (Spain). Maternal exposure to $PM_{2.5}$ during the third pregnancy trimester has indicated that an increase of 7 μg m^{-3} in the concentration of this pollutant in the household was associated with decreased volume in children's *corpus callosum*. This finding can be linked to behavioral changes. Female pregnant and lactating rats were exposed to traffic tunnel $PM_{2.5}$ (200 μg m^{-3}) over 6 weeks in order to assess nervous tissue formation in their offspring. Newborn rats exposed to $PM_{2.5}$ recorded lower scores for social activities, as well as presented anxiety and decreased cognition levels; changes observed in their social behavior suggested an association with autism (Nephew et al., 2020). Kang et al. (2021) developed a cell-based human brain model to investigate neuroinflammation induced by chronic pulmonary exposure to $PM_{2.5}$. They reported that such an interaction can disrupt the tight junctions between adjacent endothelial cells, increase neuroinflammation levels and compromise astrocytes, as well as that these impairments can lead to neurodegeneration. The association between AD development and exposure to $PM_{2.5}$ was investigated in a study conducted in vitro by Wang et al. (2018), who treated mouse microglial cells (C57BL/6) with $PM_{2.5}$ (50 μg mL^{-1}) for 4 h. Findings comprised neuronal lesions, inflammatory state, apoptotic pathway induction and increased ROS formation (Wang et al., 2018). In addition, experimental studies conducted with an AD model exposed to $PM_{2.5}$ observed glial activation and increased β—amyloid (Aβ) deposits, which are indicators of AD in the hippocampus of individuals exposed to this pollutant (Jang et al., 2018). Furthermore, astrocyte models investigated in study conducted in vitro produced a significant number of pro-inflammatory chemokines and cytokines capable of recruiting and activating microglia. This outcome has indicated that brains exposed to $PM_{2.5}$ are more susceptible to present synaptic dysfunction and to develop dementia (Kang et al., 2021). In addition, an assay conducted in vitro with SH-SY5Y cells exposed to $PM_{2.5}$ has indicated changes in DNA methylation and mRNA expression of genes likely linked to autism (Wei et al., 2016). Thus, if one consider $PM_{2.5}$'s effect on neurodevelopment and nervous functions, it is essential to investigate the mechanism underlying neurodegeneration associated with air pollution to help minimize neurological injuries associated with this process.

4.1.4 Renal System and Exposure to $PM_{2.5}$

Environmental exposure to $PM_{2.5}$ has been associated with kidney issues, such as chronic kidney disease (CKD) (Blum et al., 2020; Bo et al., 2021; Bragg-Gresham et al., 2018; Chan et al., 2018; Li et al., 2021), progression to end-stage kidney disease (ESKD) (Bowe et al., 2018) and lower glomerular filtration (GFR) (Mehta et al., 2016). The combination of pre-existing CKD and exposure to $PM_{2.5}$ can lead to cardiovascular dysfunction development (Ran et al., 2020). $PM_{2.5}$-CKD associations in Taiwanese individuals were investigated for an extended period, based on GFR analysis. Results have evidenced that an increase of 10 μg m^{-3} in $PM_{2.5}$ concentrations was associated with significant risk (6%) of developing CKD (Chan et al., 2018). Data have indicated likely ESKD progression associated with an increase of 10 μg m^{-3} in $PM_{2.5}$ concentrations, as well as with GFR decrease by more than 30% (Bowe et al., 2018). Bo et al. (2021) reported association between $PM_{2.5}$ concentration and CKD incidence; they also observed that a reduction in airborne $PM_{2.5}$ (5 μg m^{-3}) concentrations was associated with significant CKD decline (Bo et al.,

2021). A study reported kidney injuries in Spontaneously Hypertensive Rats (SHR) subjected to subchronic exposure to environmental $PM_{2.5}$ (29.4 μg m^{-3}, over three months). The aforementioned study has evidenced a slight increase in the number of leukocytes in the renal interstice, fibrosis, decreased number of glomerular lumens and increased urea level in the investigated models (Tavera Busso et al., 2018). Inhalation-based exposure to $PM_{2.5}$ for 5 h per day, four days per week, for eight weeks in rats also resulted in kidney dysfunction, featured by altered kidney injury markers, such as creatinine β-2-microglobulin and cystatin- C. Exposure to $PM_{2.5}$ has also contributed to investigated individuals' fibrotic state (Aztatzi-Aguilar et al., 2016). Renal redox imbalance was observed in rats exposed to $PM_{2.5}$, as well as a significant decrease in glutamate-cysteine ligase activity and increased glutathione S-transferase activity. Changes observed in total antioxidant capacity (ACAP) in the cortex and renal medulla have shown that the models' kidneys were sensitive to oxidative stress caused by exposure to $PM_{2.5}$ (de Paula et al., 2019). Morphological changes (glomerular atrophy, tubular damage), creatinine rise and caspase-3 expression were observed in animals exposed to $PM_{2.5}$ for six months (Hsu et al., 2019). Although studies focused on assessing the renal system of individuals exposed to $PM_{2.5}$ have gained room in this research field, it is necessary to conduct further investigations about this topic to help fill the gaps in current knowledge about the effects of this pollutant on individuals' renal system.

4.1.5 Gastrointestinal System and Exposure to $PM_{2.5}$

Studies have shown that the gastrointestinal tract and its annex glands are also susceptible to the components present in $PM_{2.5}$. The exposure of this system owing to air pollution occurs through pulmonary ventilation (way circulation) but also through mucociliary movement of the respiratory system and contaminated water and food (Feng et al., 2020). A study has investigated deaths from liver, colorectal and gastrointestinal cancer and confirmed the positive correlation between them and long-term exposure to $PM_{2.5}$ (Guo et al., 2020). Similar findings were observed in an epidemiological cohort study conducted in six European countries; results have indicated the development of gastric cancer and risk of death associated with cancer in the upper digestive tract (Weinmayr et al., 2018), as well as in other digestive tract organs, breast and lung (Wong et al., 2016). The epidemiological study in Beijing (China) reported increased peptic ulcer blood loss in elderly individuals who sought emergency hospital services after short-term exposure to increasing $PM_{2.5}$ concentrations (Duan et al., 2019). In experimental assays, mice exposed to $PM_{2.5}$ inhalation for 3 weeks have shown changes in intestinal absorptive epithelium, as well as in microbiota composition and quantity, in different parts of the gastrointestinal tract. These changes were associated with the risk of inflammatory processes taking place in the intestine (Mutlu et al., 2018). Inflammation, immune reaction, and metabolic changes were pointed out as likely consequences of changes observed in murine microbiota and gut environment deterioration attributed to exposure to $PM_{2.5}$ in the study conducted by Liu et al. (2021). Intestinal microbiota coordinates lipid metabolism and triggers inflammatory and intestinal diseases (Feng et al., 2020). Accordingly, metabolic pathways in the liver tissue of mice subjected to $PM_{2.5}$ instillation were analyzed in the study conducted by Shi et al. (2019); pollutant concentrations of 7.5, 20 and 37.5 mg mL^{-1} were classified by them as low, moderate and high pollution levels, respectively. Based on results in the aforementioned study, the authors inferred that $PM_{2.5}$ instillation had changed amino acids' metabolism, which led to decreased threonine, alanine and serine levels, affected tricarboxylic acid cycle (TCA), changed the urea cycle and increased purine levels, as well as that such an increase has contributed to ROS formation. However, similar to what was reported for the renal system, only few studies focused on investigating bowel diseases resulting from exposure to $PM_{2.5}$ are available in the literature. Further studies should be conducted to help better understand the origin of the herein mentioned damages and pathologies, as well as to fill the gap in knowledge about the consequences of $PM_{2.5}$-gastrointestinal system interaction.

4.1.6 Reproductive System and Exposure to $PM_{2.5}$

Like the others, the reproductive system also seems susceptible to increased levels of atmospheric pollution. A study conducted by Percy et al. (2019), focused on investigating the likely association between increased $PM_{2.5}$ indices and pregnancy issues observed in the third gestational trimester, from 2007 to 2010. Analyzed data have indicated inadequate fetal size in pregnant women exposed to high $PM_{2.5}$ indices during the investigated period. Kingsley et al. (2017) observed links between air pollution and changes in the

expression of seven genes found in the human placenta that, in turn, can negatively affect fetal growth. Women's daily exposure to $PM_{2.5}$, associated with different levels of traumatic events during pregnancy, have indicated mitochondrial changes in cord blood samples. In contrast, placental samples have shown reduced mitochondrial indicators and multiple mitochondrial DNA copies (mtDNAcn), which are used to check the fetal health status (Brunst et al., 2018). Studies have pointed toward a possible association between increased exposure to $PM_{2.5}$ and worsened placental pathologies, such as fetal thrombotic vasculopathy, as reported in a cohort study conducted with Tanzanian pregnant women (Wylie et al., 2017). An experimental study was recently conducted with mice exposed to concentrated $PM_{2.5}$ (115.60 ± 7.77 μg m^{-3}) or filtered air (14.07 ± 0.38 μg m^{-3}) for 12 weeks before pregnancy, in order to investigate $PM_{2.5}$-exposure effects on mice reproductive system (Guo et al., 2021). The investigated experimental model presented decreased anti-Müllerian hormone and oocyte levels. This outcome has evidenced that $PM_{2.5}$ triggered ROS production increase and degeneration, altered mitochondrial expression genes, increased degeneration rate observed for these cells and interfered in embryos' development (Guo et al., 2021). According to Liu et al. (2016b), pregnant rats exposed to $PM_{2.5}$ through intratracheal instillation (15 mg kg^{-1}, in two days) have shown reduced maternal and fetal weight, as well as placental thrombus, whereas blood analysis has evidenced an increased number of platelets, IL-6 and mononuclear cells. Based on an experimental study conducted by Soto et al. (2017), Wistar rats exposed to $PM_{2.5}$ (15 days, 600 μg m^{-3} per day) during pregnancy presented changes in placental mass, size and surface area. According to the aforementioned study, renin-angiotensin system destabilization in the placenta was observed, as well as decreased levels of both angiotensin II and its receptors (AT1R and AT2R) (Soto et al., 2017). Besides, pregnant rats exposed to $PM_{2.5}$ (1.0 mg kg^{-1}) through the oropharyngeal route have shown increased blood pressure in adult offspring, as well as reduced sodium and water excretion rates (Ye et al., 2018). Ye et al. (2018) have shown decreased expression of the dopamine receptor, which accounts for blood pressure regulation, sodium excretion, and its regulatory kinase (kinase 4). Table 3 shows a broad overview of damage caused to different tissues, as well as epidemiological and experimental findings associated with $PM_{2.5}$'s toxic effects.

5 COVID-19 and Exposure to $PM_{2.5}$

Severe restrictions on people's movement and economic activities were imposed on global society in 2020, due to the COVID-19 pandemic, and it decreased $PM_{2.5}$ concentrations in the air from 9 to 60%, if one compares air-quality data from early 2020 to data recorded in the same period in previous years (IQAir 2020). Scholars from different countries have assessed $PM_{2.5}$ levels in different cities, on all five continents, between December 2019 and March 2020; they compared collected data with those recorded in the same period, in previous years. Studies pointed towards significant reductions, of up to 60%, in $PM_{2.5}$ concentrations, and it has clearly shown improved air quality (Berman & Ebisu, 2020; Chauhan & Singh, 2020; Collivignarelli et al., 2020; Nakada & Urban, 2020; Sharma et al., 2020; Shrestha et al., 2020). A valid explanation for this phenomenon lies in the fact that anthropogenic $PM_{2.5}$ levels observed in big cities during regular working days are higher than those observed in smaller and less urbanized cities (Zhao et al., 2009). $PM_{2.5}$ reduction can also be attributed to a simultaneous reduction in the concentration of other pollutants, such as volatile organic compounds, which act as precursors for $PM_{2.5}$ formation (Chen et al., 2017a, 2017b, 2017c; Han et al., 2018). An epidemiological study published in 2003 suggested positive correlation between PM concentration and SARS lethality: mortality rate increased by 100 and 84% in patients living in regions recording high and moderate air pollution rates, respectively, in comparison to rates recorded in areas presenting low air pollution index (Cui et al., 2003). This finding was corroborated by another epidemiological study, according to which, each increment by 10 μg m^{-3} of PM in 5 days resulted in a mean increase of 1.06 in the risk of daily mortality rate linked to SARS (Kan et al., 2005). PM can act as a virus carrier or intensifier, and it has a sublayer capable of keeping the virus alive in air flows, for hours or even days (Setti et al., 2020a). Chen et al. (2017a, 2017b, 2017c) observed an association between short-term exposure to PM and the incidence of measles in several Chinese cities; this finding has confirmed the association between PM and viral diseases. Based on these data, air pollution is expected to play an essential part in the pandemic caused by the new coronavirus, given the positive correlation between the number of COVID-19 cases and $PM_{2.5}$ concentrations in the air. A recent epidemiological study in Wuhan City investigated the association between PM levels and

Table 3 Dysfunctions associated to the risk posed by exposure to $PM_{2.5}$ to different physiological systems, in experimental and epidemiological studies

$PM_{2.5}$ and damage to the respiratory system	
(Jung et al., 2019; Tian et al., 2017; Zhao et al., 2018)	Asthma exacerbation
(Gharibvand et al., 2017; Nielsen et al., 2016; Tomczak et al., 2016; Zhang et al., 2020)	Risk of developing lung cancer
(Liu et al., 2017a, 2017b)	Risk of developing the chronic obstructive pulmonary disease
(Croft et al., 2019; Lv et al., 2017; Zhang et al., 2017)	Risk of developing pneumonia
(Wang et al., 2017a, 2017b, 2017c)	Reduction in epithelial integrity biomarker activity
(Wu et al., 2021)	Changes in the oral mucosal microbiota
(Zhao et al., 2018)	Bronchial epithelial losses, smooth muscle hyperplasia, increased inflammatory infiltrate, and altered Bax-Bcl levels
(Sun et al., 2017)	Increased neutrophil count and neutrophil penetration in peribronchiolar regions
(Yoshizaki et al., 2017)	Elevation of IL-8Rα and IL-1β, COX-2, TGF-α aand high levels of isoprostane and matrix metalloproteinase (MMP-9)
(Xu et al., 2019)	Risk of developing lung fibrosis
$PM_{2.5}$ and damage to the cardiovascular system	
(Folino et al., 2017; Yang et al., 2020)	Arrhythmias
(Gallo et al., 2020; Kim et al., 2019)	Fibrillation
(Cao et al., 2021; Honda et al., 2018; Zhang et al., 2018)	Hypertension
(Chen et al., 2017b; Tsou et al., 2021; Xie et al., 2018)	Heart rate Variation
(Li et al., 2021; Lozano-Sabido et al., 2021)	Miocardyal infarct
(Wan et al., 2019)	Atherosclerosis
(Dai et al., 2017)	Endothelial dysfunction
(Ribeiro et al., 2016; Yue et al., 2019)	Histological changes
$PM_{2.5}$ and nervous system damage	
(Younan et al., 2020)	Declines in episodic memory
(Jang et al., 2018; Kioumourtzoglou et al., 2016; Wang et al., 2018)	Risk of developing Alzheimer's disease
(Kioumourtzoglou et al., 2016)	Parkinson's disease association
(Nephew et al., 2020)	Anxiety and low cognition
(Kang et al., 2021)	Neurodegeneration
(Mortamais et al., 2019; Nephew et al., 2020)	Behavioral changes
(Wei et al., 2016)	Autism risk
(Kang et al., 2021)	Dementia association
$PM_{2.5}$ and damage to the renal system	
(Blum et al., 202; Bo et al., 2021; Bragg-Gresham et al., 2018; Chan et al., 2018; Li et al., 2021;)	Risk of Chronic Kidney Disease (CKD)
(Bowe et al., 2018)	Risk of end-stage renal disease
(Hsu et al., 2019; Mehta et al., 2016; Tavera Busso et al., 2018)	glomerular filtration rate changes
(Aztatzi-Aguilar et al., 2016; Hsu et al., 2019; Tavera Busso et al., 2018)	Histological changes
$PM_{2.5}$ and damage to the gastrointestinal system	
(Feng et al., 2020; Kim et al., 2019; Liu et al., 2021)	Changes in the intestinal microbiota
(Guo et al., 2020; Weinmayr et al., 2018; Wong et al., 2016)	Risk of gastrintestinal cancer
(Pan et al., 2016; Wang et al., 2016; Weinmayr et al., 2018)	Liver cancer risk
(Shi et al., 2019)	Metabolism changes (tricarboxylic acid, urea cycle and purine levels)

Table 3 (continued)

$PM_{2.5}$ and damage to the respiratory system	
$PM_{2.5}$ and damage to the reproductive system	
(Kingsley et al., 2017; Liu et al., 2016b; Soto et al., 2017; Ye et a., 2018)	Placental changes
(Guo et al., 2021)	Decrease in anti-Müllerian hormone level and increased oocytes degeneration rate;
(Kingsley et al., 2017; Liu et al., 2016b; Percy et al., 2019)	Size gestational variation

the COVID-19 lethality rate. A positive correlation was observed between PM_{10} and $PM_{2.5}$ concentrations and COVID-19 lethality rate (Yao et al., 2020b). Another national study conducted in China included more than 60 cities in and outside the province most affected by the virus; results have shown that short-term exposure to PM_{10} and $PM_{2.5}$ was strongly associated with COVID-19 mortality rates (Yao et al., 2020a). The European Public Health Alliance recently reported that individuals living in polluted cities are the ones mostly threatened by COVID-19 disease (European Public Health Alliance 2020), a fact that was confirmed in further research conducted in Italy. Recent studies have suggested that the expansion of COVID-19 cases in Northern Italy, mainly in Lombardy, was promoted by high PM concentrations in the air, based on the idea that atmospheric particles act as virus carriers (Sterpetti, 2020). Furthermore, only 0.003% of dwellers in the least polluted provinces were infected with this virus, whereas highly polluted regions recorded approximately nine times more COVID-19 cases than the least polluted ones (Setti et al., 2020b, 2020c). Two independent studies have evidenced that continuous exposure to particulate matter in Northern Italy was the leading cause of COVID-19 cases (Fattorini & Regoli, 2020; Coker et al., 2020). A United States national comprehensive cross-sectional study has shown that each increase of 1 μg cm^{-3} in long-term exposure to $PM_{2.5}$ significantly increased COVID-19-related mortality rates (Wu et al., 2020). A similar observation was made in the Netherlands, where exposure to $PM_{2.5}$ was closely associated with confirmed COVID-19 cases since an increase of approximately 1/5 in pollution concentrations has doubled the number of COVID-19 cases (Andree, 2020). Studies conducted so far aimed at investigating individuals' sensitivity to the SARS-CoV-2 virus after exposure to $PM_{2.5}$. However, only epidemiological studies have suggested biomolecular mechanisms acting behind this sensitivity; however, it is yet to be experimentally confirmed through studies conducted both in vitro and in vivo. In addition to reduced PM levels during the COVID-19 pandemic, studies have suggested that long-term exposure to $PM_{2.5}$ was associated with higher likelihood of hospitalization among patients with COVID-19. $PM_{2.5}$ can impair both the mucociliary clearance of different pathogens and natural killer cell response, which can increase individuals' susceptibility to and severity of COVID-19 (Mendy et al., 2021). Changes in host defense mechanisms caused by exposure to $PM_{2.5}$ may be the key to individuals' susceptibility to respiratory system infections. The study review conducted by Yang et al. (2020) has shown that exposure to $PM_{2.5}$ enables the adhesion, colonization and growth of different microorganisms, such as viruses, and makes removing them from individuals' respiratory system hard. Likely mechanisms pointed out by the aforementioned authors may be associated with mitigation of the host defense function played by the airway epithelium, changes in the natural microbiota of the respiratory tract and insufficient number of, or dysfunction in, immune cells. According to Loaiza-Ceballos et al. (2021), exposure to air pollutants, such as PM, induces ROS production, which, in its turn, leads to an oxidative state, to the activation of transcription factors such as NF-kB and AP-1 and, subsequently, to cytokine production. These mechanisms worsen inflammatory processes in the respiratory tract by changing the respiratory tract homeostasis and making it more susceptible to viral infections (Loaiza-Ceballos et al., 2021). Likewise, pre-existing baseline inflammatory conditions worsened by pollution can easily contribute to better explain why individuals exposed to pollution appear to be at greater risk of developing severe COVID-19 cases (Gao et al., 2020, 2021).

6 Conclusion

The present study addressed the effects of $PM_{2.5}$ in several potential health-damage contexts, by comparing epidemiological studies to experimental findings. Based on the analyzed results, $PM_{2.5}$ is strongly associated with the pathological genesis of the most diverse systems. Its toxicological potential is linked to inflammation generation pathways, which comprise genes involved in inflammation processes and signaling molecules. Based on the analysis of the herein selected studies, $PM_{2.5}$ is remarkably capable of generating ROS, which is well-known for its involvement in inflammatory processes, cell death, genotoxicity, and epigenetic changes. It was also proved that the antioxidant defenses of individuals exposed to $PM_{2.5}$ are affected and contribute to the emergence of cellular oxidative stress. $PM_{2.5}$ an damage several organs, likely due to its ability to travel through individuals' bloodstream and cause systemic damage. Organs are affected at the cellular level, and injury accumulation associated with exposure time can generate different pathologies, as seen in the epidemiological studies mentioned above. Cardiopulmonary, nervous, renal, gastrointestinal, and even the reproductive system, suffer from exposure to $PM_{2.5}$, which harms individuals' health and hinders their quality of life. Studies linking $PM_{2.5}$ emissions to the current COVID-19 pandemic were performed in 2020. They reported a significant decrease in $PM_{2.5}$ emissions when different cities and countries adopted partial or total lockdown measures. Interestingly, several researchers associated high environmental $PM_{2.5}$ concentrations with a higher likelihood of being contaminated with and, consequently, of dying of COVID-19. This phenomenon can be related to virus permanence in $PM_{2.5}$ particles; therefore, places presenting a larger number of particles would also enable longer virus permanence. Thus, although many studies focus on explaining mechanisms linked to the toxicity caused by $PM_{2.5}$, several points need to be further investigated to help better understand $PM_{2.5}$ interactions in the body. Nevertheless, these data, altogether, make us reason about how important it is to establish measures to help mitigate $PM_{2.5}$ emissions and avoid its associated damages (Fig. 4).

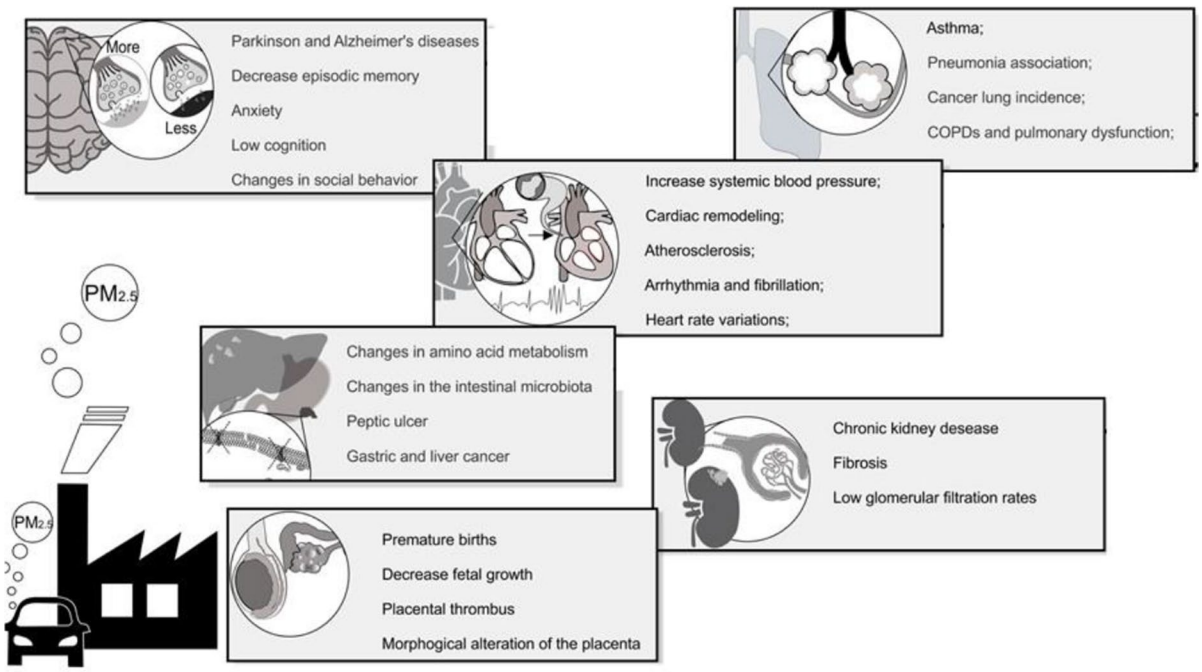

Fig. 4 Summary of disorders associated to $PM_{2.5}$ exposure

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Data Availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest The authors declare no competing interests.

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