Effects of air pollution on human health – mechanistic evidence suggested by *in vitro* and *in vivo* modelling

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Abstract

Airborne particulate matter (PM) comprises both solid and liquid particles, including carbon, sulphates, nitrate, and toxic heavy metals, which can induce oxidative stress and inflammation after inhalation. These changes occur both in the lung and systemically, due to the ability of the small-sized PM (i.e. diameters ≤2.5μm, $PM_{2.5}$) to enter and circulate in the bloodstream. As such, in 2016, airborne PM caused ~4.2 million premature deaths worldwide. Acute exposure to high levels of airborne PM (eg. during wildfires) can exacerbate pre-existing illnesses leading to hospitalisation, such as in those with asthma and coronary heart disease. Prolonged exposure to PM can increase the risk of non-communicable chronic diseases affecting the brain, lung, heart, liver, and kidney, although the latter is less well studied. Given the breadth of potential disease, it is critical to understand the mechanisms underlying airborne PM exposure-induced disorders. Establishing aetiology in humans is difficult, therefore, in-vitro and in-vivo studies can provide mechanistic insights. We describe acute health effects (e.g. exacerbations of asthma) and long term health effects such as the induction of chronic inflammatory lung disease, and effects outside the lung (e.g. liver and renal change). We will focus on oxidative stress and inflammation as this is the common mechanism of PM-induced disease, which may be used to develop effective treatments to mitigate the adverse health effect of PM exposure.

Keywords: PM, neurological, respiratory, renal, endocrine, preventative treatment

1. Introduction

Air pollution poses a major threat to global health (Cattani-Cavalieri et al., 2020). The World Health Organisation (WHO) air quality data shows 99% of the world's population inhale high levels of pollutants, and as a result of poor air quality an estimated 4.2 million people die each year, with the majority death (91%) from low- and middle-income countries (World Health Organisation, 2021). Particularly, people in South-East Asia and Western Pacific regions have the greatest exposure and,

43 therefore risk (World Health Organisation, 2021). An individual's vulnerability to being affected by
44 airborne particulate matter (PM) depends on their age and underlying health status. Vulnerable groups
45 include people with lung or cardiovascular disease, pregnant women and their unborn infants,
46 children, and older adults (NSW Government, 2013).

47 Studies have shown that PM with a diameter of 10μm (PM10) can enter the lungs (Chan et al., 2019b;
48 Xu et al., 2019a). PM particles with a diameter of 2.5μm or less (PM2.5) can further reach the distal
49 lung segments, including the alveoli, pass into the bloodstream, and are capable of penetrating blood-
50 organ barriers affecting multiple organ systems, such as the brain, heart, liver and kidney (Chan et
51 al., 2019b; Xu et al., 2019a). According to the most recent report on the mortality burden due to
52 PM2.5 in European cities, where air pollution is generally below EU quality guidelines (0.7 – 30.8
53 g/m3, with a median value of 12.3 g/m3), PM2.5 exposure accounts for up to 15% of preventable
54 annual mortality in cities such as Bresica and Saronno (Khomenko et al., 2021). Airborne PM
55 pollution consists of both organic and inorganic particles, derived from dust, pollen, fossil fuel,
56 biomass burning, or road traffic (Chan et al., 2019b). Common constituents include nitrates,
57 sulphates, carbon, polycyclic aromatic hydrocarbons, biological compounds, and metals (Kim et al.,
58 2015; World Health Organisation, 2021).

59 Many studies have shown the detrimental health effects of direct exposure to PM. This review will
60 first cover the sources of air pollution and then describe the epidemiological evidence of the
61 association between pollution and morbidity and mortality. Potential underlying mechanisms will be
62 discussed along with disorders observed in humans using evidence from basic research, including
63 details of experimental approaches in both *in vitro* and in *vivo animal* models (Tables 1 and 2). An
64 extensive search was undertaken on PubMed, Ovid Medline, Google Scholar, and Web of Science
65 for peer-reviewed research papers published in English only, using search terms "PM", "particulate
66 matter", "mice", "mouse", "rat". The abstract was first examined to determine the relevance of the
67 topic, and the full text was read by two authors (Chen and Pant) to determine the research quality
68 before inclusion in Tables 1 and 2 for information extraction. Studies with incomplete groups (eg.

without negative control) or design flaws (eg. insufficient power) were not included. No limitations were imposed on the paper publication dates. The review will focus on oxidative stress and the inflammatory responses induced by PMs, given that PMs are strong oxidants (Daellenbach et al., 2020) and appear to be the common pathological mechanism in different organs.

2. Air pollution

2.1 Sources of air pollution

Air pollution can be categorised into natural phenomena, for example, volcanic eruptions, bushfires, dust storms) or due to human or anthropogenic activities (eg. urbanisation, industry, aquaculture) (Kampa and Castanas, 2008; Lee et al., 2014). Man-made sources of airborne PMs can release hazardous chemicals into the environment from industrial facilities (e.g. SO_2) or vehicle exhausts (e.g. carbon monoxide (CO)) (Kampa and Castanas, 2008; Lee et al., 2014). These air pollutants are diverse and differ based on chemical and reactivity properties, emission, and potential harm to human health (Bernstein et al., 2004; Kampa and Castanas, 2008; Lee et al., 2014). They can be further grouped into primary and secondary emissions. Primary pollutants are directly emitted into the atmosphere, while secondary pollutants are products of chemical reactions of the primary emissions (Bernstein et al., 2004; Lee et al., 2014). Secondary air pollution is a mixture of gaseous substances (e.g. CO, carbon dioxide (CO_2), NO_2), ozone (O_3), and also PM (Lee et al., 2014).

Air pollution is increasing due to spiralling energy usage, traffic emissions and animal agriculture (Kelly and Fussell, 2015b). The key culprits for air pollution in our urban areas are ozone (O_3), nitrogen dioxide (NO_2), and PM (Kelly and Fussell, 2015b). However, historical findings of carbon deposits in the lungs of ancient Egyptian mummies suggest that even the earliest populations were exposed to environmental pollution in the form of biomass smoke (Kelly and Fussell, 2015b; Zweifel et al., 2009).

Climate change and its effects on air quality is not an obscure topic in scientific research. The impact of human activities (i.e. extreme land and water usage, agricultural development, and deforestation)

94 is associated with a positive trend in greenhouse gas emissions and temperature (Mahmoud and Gan,
95 2018). Multiple studies have associated the shifts in climate and weather with an amplified
96 distribution of air pollution concentrations (Hong et al., 2019; Kinney, 2018; Orru et al., 2017).
97 Anthropogenic climate change is known to have direct effects on the severity of heat waves, food
98 production, and ecosystems (Haase et al., 2014; Hong et al., 2019; Mahmoud and Gan, 2018; Orru et
99 al., 2017; Springmann et al., 2016; Theurl et al., 2020). Air pollution is another important secondary
100 effect of climate change, as the weather systems have the potential to influence the movement and
101 dispersion of air pollutants (Kinney, 2018). Climate change worsens air quality through
102 meteorological variables, e.g. temperature, humidity, precipitation, vertical mixing, and wind
103 activities (Hong et al., 2019; Kinney, 2018; Orru et al., 2017). In some countries, this is more related
104 to the frequency of bushfires and sand storms. Air pollutants, such as PMs, tend to increase at higher
105 atmospheric temperatures, and as a result, secondary reactions may develop faster (Kinney, 2018).

106 **2.2 PMs**

107 Airborne PMs are responsible for around 4.2 million deaths in 2016 worldwide due to PM related
108 conditions, such as stroke, myocardial infarction, and lung cancer (Chang et al., 2005; Kim et al.,
109 2015; Shah et al., 2013; World Health Organisation, 2021). PM has the potential to exacerbate a range
110 of pre-existing pulmonary diseases associated with 800,000 premature deaths each year (EEA, 2017;
111 GBD 2015 Mortality and Causes of Death Collaborators, 2016; Losacco and Perillo, 2018). The
112 impact of PM on human health is greater than ground-level O_3 or other common air pollutants (e.g.
113 CO) due to its heterogeneity in the range of chemical constituents that they carry (Kim et al., 2015).

114 PM refers to anything solid or liquid particles suspended in air and can serve as a carrier of other
115 chemicals (Dockery, 2009; NSW Government, 2013; Wang et al., 2017b). The composition of PM
116 reflects the source; for example, levels in underground railway systems contain high concentrations
117 of metals, such as iron, chromium, nickel, copper, manganese, and cadmium (Loxham and
118 Nieuwenhuijsen, 2019), from tracks and wheels and brakes. The components of PM can originate
119 from either direct emission into the air or gaseous precursors, e.g. SO, ammonia, and nitrogen oxides

120 (NO_x) (Kim et al., 2015).

121 These particles can differ in size, distribution, shape, chemical composition, surface area, solubility,
122 and derivation (Pope and Dockery, 2006). The toxicity and absorption potentially relate to the particle
123 size and surface area to mass ratio (Chan et al., 2016). Smaller particles have a higher surface area to
124 mass ratios and therefore, an increased ability to exert biological effects (Chan et al., 2016). The
125 toxicity of air pollution is dependent on the composition of PM, which is influenced by the source
126 and environmental conditions (season, weather, etc.) (Wu et al., 2018). The particle size can vary
127 from few nanometres to tens of micrometres (μm), and this can influence the way PM affects cells
128 and organs (Brunekreef and Holgate, 2002; Lee et al., 2014). PM can be classified according to
129 various parameters, including total mass concentration/distribution, the modality of size distribution,
130 and count median aerodynamic diameter (Morawska et al., 1999). Air quality standards are currently
131 categorised as mass concentrations of particles in certain size bins (i.e. PM_{10} or $PM_{2.5}$) (Karakatsani
132 et al., 2012; Morawska et al., 1999). Coarse particles, or PM10, are the largest inhalable particles with
133 an aerodynamic diameter of less than 10 μm but greater than 2.5 μm (Lee et al., 2014; Pope and
134 Dockery, 2006). Fine particles, or $PM_{2.5}$, have an aerodynamic diameter of less than or equal to 2.5
135 μm. The ultrafine particles are defined by an aerodynamic diameter less than 0.1 μm (Lee et al., 2014;
136 Pope and Dockery, 2006).

137 $PM_{2.5}$ is mainly formed during combustion (e.g. coal burning, wood burning, car gasoline, and diesel)
138 and from the use of industrial processes like cement plants and smelters (Bernstein et al., 2004; Pope
139 and Dockery, 2006). Inorganic compounds like ammonium sulphates and nitrates make up a large
140 fraction of $PM_{2.5}$ (Losacco and Perillo, 2018). Average mass fractions of ammonium sulphate, for
141 example, are 51% and 31% of total emission in Houston and Los Angeles, respectively (Ghio et al.,
142 2018).

143 Airborne PM concentrations are generally described as micrograms per cubic metre ($\mu g/m^3$)
144 measured and reported with respect to annual mean concentrations (World Health Organisation,

2021). The safe or the average annual and daily mean concentrations of $PM_{2.5}$ were 10 μg/m^3 and 25 μg/m^3, respectively. These were reduced to 5 and 15 μg/m^3, respectively, in 2021 (World Health Organisation, 2021), due to the increased recognition of the adverse health impact of PM2.5 even at levels below the formal WHO standard (Khomenko et al., 2021; Yazdi et al., 2021). Nevertheless, An analysis of 117 countries, spanning 250 urban cities worldwide, shows that the median $PM_{2.5}$ concentrations were 29 μg/m^3 (Anenberg et al., 2019). The population-weighted mean concentrations were nearly three times greater than the WHO annual average for $PM_{2.5}$ of 5 μg/m^3,(Anenberg et al., 2019). Further, only 8% of those cities (all in Sweden, USA, Canada, Australia, and Brazil) were in the lowest quartile of both mean concentrations and $PM_{2.5}$-related mortality (Anenberg et al., 2019). The top 10 cities for high $PM_{2.5}$ levels are mostly in Africa, while cities in Asia and Europe constituted the top 10 for PM2.5-related mortality (Anenberg et al., 2019).

Smaller particles have been linked with significant adverse health effects and a greater potential to cause problems than larger PMs (He et al., 2017; United States Environmental Protection Agency, 2020). The first organ that comes in contact with the chemical agents and biological compounds in the PM is the respiratory system (Losacco and Perillo, 2018). PMs can easily lodge at the level of the bronchial bifurcations and lymph nodes, resulting in immune responses (Losacco and Perillo, 2018). Previous studies have shown airborne carbon dust in lymph node macrophages of farm animals from industrial areas (Fornero et al., 2009; Perillo et al., 2009). While PM_{10} mainly deposits in the extrathoracic and upper tracheobronchial regions (Cattani-Cavalieri et al., 2020; NSW Government, 2013; Wu et al., 2018), fine particles within $PM_{2.5}$ can reach the terminal bronchioles and alveoli (Wang et al., 2017b), followed by evading into the circulation, causing systemic oxidative stress and inflammatory responses (Anderson et al., 2012; Karakatsani et al., 2012; Losacco and Perillo, 2018). Micro-pollutants reside longer in the lung parenchyma, affecting the whole lung compartment (Falcon-Rodriguez et al., 2016; Kelly and Fussell, 2015a), which are also easier to diffuse through the blood-air barrier in the alveoli and enter the circulation. Ultrafine particles have an increased ability to avoid macrophage clearance due to their minute size (Upadhyay and Palmberg, 2018).

Depending on the pollution levels, it can take days, months, or even years for organ dysfunction to be apparent, affecting how people perceive the danger of PM exposure.

2.3 Traffic-related air pollution (TRAP)

TRAP is a combination of gasses and particles from vehicle exhaust and non-exhaust emissions (Hime et al., 2018; Kelly and Fussell, 2015b; Matz et al., 2019). The dominant vehicle emissions include both black and elemental carbon, CO, CO_2, NO_x, hydrocarbons, PMs, in addition to toxic compounds (e.g. benzene, 1,3-butadiene, formaldehyde, acetaldehyde) (Hime et al., 2018; Khreis, 2020; Pollution, 2010; Zhang and Batterman, 2013). Diesel exhaust is the main contributor to TRAP, and in certain occupations, such as construction and docking, exposures can go above 200-300 $\mu g/m^3$ (Costa et al., 2017; Ghio et al., 2012; Pronk et al., 2009a). Miners, for instance, can be exposed to the highest levels of diesel exhaust PM, up to 1000 $\mu g/m^3$ (Pronk et al., 2009b). TRAP PMs in urban areas also vary in particle size (Khreis, 2020).

Although PM exposure has a greater impact on those living in developing countries where air quality is poor, those living in countries with relatively good air quality, such as Australia, still suffer from the impacts of TRAP, especially for drivers, commuters, and residents nearby. For example, in Australia 13% of the total PM is TRAP (Chan et al., 2019b), while in Europe, approximately 30% of PM emissions are from road transport (Khreis, 2020; World Health Organisation, 2021), due to congestion and increased traffic activity on major roadways (Khreis, 2020; Zhang and Batterman, 2013). Those living within 50 to 500m of main roads are at a higher risk of chronic low-level TRAP exposure and the associated adverse health effects, such as increased hospitalisation for asthma exacerbation, type 2 diabetes mellitus, cardiopulmonary disease, and adverse birth outcomes (Beelen et al., 2008; Brauer et al., 2008; Jerrett et al., 2009; Krämer et al., 2010; Wu et al., 2011).

2.4 Bushfire PMs

Bushfires/wildfire have become a great health threat which is linked to increased emergency admission for not only respiratory disorders but also cardiovascular events (Chen et al., 2021b; Morgan et al., 2010; Wettstein et al., 2018). An increase of 10 $\mu g/m^3$ in PM2.5 within two days is

197 sufficient to raise the daily all-cause mortality by 0.68% (Liu et al., 2019). The prolonged Australian
198 summer bushfire of 2019-2020 highlighted that effects can be local and global. For example, as a
199 result of this event, there was an increase in the burden of smoke-related symptoms in nearby regions
200 not restricted to people with pre-existing respiratory conditions, such as eye and throat irritations,
201 cough, breathlessness, and chest pain (Di Virgilio et al., 2021; Howard et al., 2020; MacIntyre et al.,
202 2021). About 65.1% of the participants living in the epicentre of bushfire (Hunter New England Local
203 Health District, NSW, Australia) reported at least one symptom, compared with 16.1% of those living
204 in Hobart (Tasmania, Australia) ~1,732km away (odds ratio [OR] 10.4; 95% confidence interval [CI]
205 8.3, 13.0; $p < 0.001$) (Howard et al., 2020). The fine particles arising from the wildfire smoke
206 travelled in the atmosphere, reaching out to the South Pacific Ocean and South America, significantly
207 affecting aerosol optical depth (Li et al., 2021). This has become a concern in multiple communities,
208 especially in Australia and North American, as well as European countries affected in the summer of
209 2021 (Dennekamp and Abramson, 2011; Jones et al., 2020; Milton and White, 2020; Nguyen et al.,
210 2021; Osborne et al., 2020; Walter et al., 2020; Wettstein et al., 2018). There have been a number of
211 large wildfires in North America, such as the latest ones in California, which may last until Christmas
212 2021. In fact, rising temperatures due to global warming have increased the frequency of bushfires
213 in recent decades (Johnston et al., 2011; Youssouf et al., 2014). Hence, the deterioration of air quality
214 is inevitable (Johnston et al., 2011). Bushfire smoke contains thousands of individual chemical
215 compounds, including mostly CO_2, water vapour and in low levels, e.g. CO, formaldehyde,
216 polyaromatic hydrocarbons, and PM (Nakayama Wong et al., 2011; Stone et al., 2017; Youssouf et
217 al., 2014). Black and elemental carbon constitute 80-90% of PM in bushfire smoke (Hardy, 2001;
218 Youssouf et al., 2014).

219 PM levels can be extreme and exposure vast in communities when environmental conditions foster
220 uncontrolled bushfires. During these transitory episodes, bushfire PM concentrations are much higher
221 compared to TRAP PM (Dennekamp and Abramson, 2011; Johnston et al., 2011). A previous
222 epidemiological study examined cardiopulmonary hospitalisations among adults aged ≥ 65 years

(DeFlorio-Barker et al., 2019). It was shown that bushfire smoke-related $PM_{2.5}$ was strongly associated with increased respiratory and cardiovascular related hospitalisation (DeFlorio-Barker et al., 2019). Bronchitis and asthma were observed at much higher rates in these people attending emergency departments. Other vulnerable groups include smokers, firefighters, and individuals with smaller airways or pre-existing cardiopulmonary conditions (Greven et al., 2011; Malilay, 1999; Mott et al., 2005; Youssouf et al., 2014). Australian cities reported a 6% increase in respiratory-related hospital admissions associated with bushfire events between 1994 to 2007 (Hamon et al., 2018; Martin et al., 2013).

2.5 Airborne PM as a potent oxidant in the body system

Oxidative stress has been considered an important mechanism for PM-induced cellular toxicity (Cho et al., 2018; Daellenbach et al., 2020; Deng et al., 2013a; Hadei and Naddafi, 2020). Oxidative stress can be induced by high levels of free radicals and oxidants in airborne PM (Daellenbach et al., 2020; Hadei and Naddafi, 2020; Wang et al., 2020b) and reactive oxygen species (ROS) produced by PM components when they enter the cells (Risom et al., 2005; Valavanidis et al., 2013). Chemicals in the PM (e.g. metals) and free radicals can also trigger inflammatory responses when engulfed by immune cells and thereafter amplify ROS production (Cho et al., 2018; Hime et al., 2018). Such responses are not restricted to the lung but also occur in other organs. Therefore, PM may activate the endogenous redox system at a systemic scale leading to multiple organ dysfunction, including the brain, cardiovascular system and liver (Gangwar et al., 2020; Li et al., 2008; Lodovici and Bigagli, 2011; Reyes-Caballero et al., 2019) (Figure 1). The effects of airborne PM-related oxidative stress in different organ systems has been reviewed in different organ systems by respective review papers (Gangwar et al., 2020; Li et al., 2008; Lodovici and Bigagli, 2011). Data summarising the impact on PM in *in vitro* studies and in *in vivo* studies are presented in Tables 1 and 2, respectively.

Overproduction of ROS can overwhelm endogenous antioxidants by directly consuming antioxidant enzymes, including superoxide dismutase (SOD), manganese superoxide dismutase (MnSOD), glutathione peroxidase, and catalase (Chirino et al., 2010; Pamplona and Costantini, 2011). The

249 imbalance between oxidant and antioxidant activities results in oxidative stress (Wang et al., 2020b).
250 Airborne $PM_{2.5}$ has been shown to inhibit endogenous antioxidant enzymes and decrease their gene
251 expression (Wang et al., 2017a). Oxidative stress predisposes the mitochondria, proteins, lipids,
252 membranes, and DNA to injury (Chan et al., 2019b; Gutteridge and Halliwell, 2018; Hadei and
253 Naddafi, 2020; Nel, 2005; Tan et al., 2009; Xin et al., 2019; Xu et al., 2019a; Yang et al., 2014).

254 ROS increases the production of inflammatory cytokines (Bugianesi et al., 2007; Cusi, 2016; Laing
255 et al., 2010; Rui, 2014). It needs to be noted that components in the PM can also induce strong pro-
256 inflammatory responses, even at a very low dose considered to be "below the safe threshold" (Chan
257 et al., 2019a). Inflammation and oxidative stress are additive in their effect on cells and subcellular
258 organelles. The increase in pro-inflammatory cytokines, such as tumour necrosis factor-α (TNFα) and
259 monocyte chemoattractant protein-1 (MCP1), has been found to occur in parallel with the increase in
260 resident macrophages after $PM_{2.5}$ exposure (Chan et al., 2019b; Sun et al., 2020; Tan et al., 2009; Xu
261 et al., 2019a; Zheng et al., 2013). The aforementioned pro-inflammatory cytokines are predominantly
262 induced through the nuclear factor-κB (NF-κB) pathway (Liu et al., 2017; Zheng et al., 2013), which
263 has also been linked with the primary pathogenesis of a number of inflammatory diseases such as
264 chronic obstructive pulmonary disease and asthma (Li et al., 2012; Liu et al., 2017).

265 $PM_{2.5}$ induced oxidative stress and inflammation may further induce systemic injury to the organs via
266 promoting autophagy and apoptosis. $PM_{2.5}$ not only causes direct damage via extracellular ROS, but
267 can induce mitochondrial ROS and ultimately, disrupt mitochondrial function affecting cellular
268 energy metabolism. The released pro-inflammatory cytokines can increase collagen production,
269 leading to fibrosis and concomitant loss of normal tissue integrity, structure and function in different
270 organs, such as the lung, kidney and liver (Sun et al., 2020; Tan et al., 2009; Tavera Busso et al.,
271 2018).

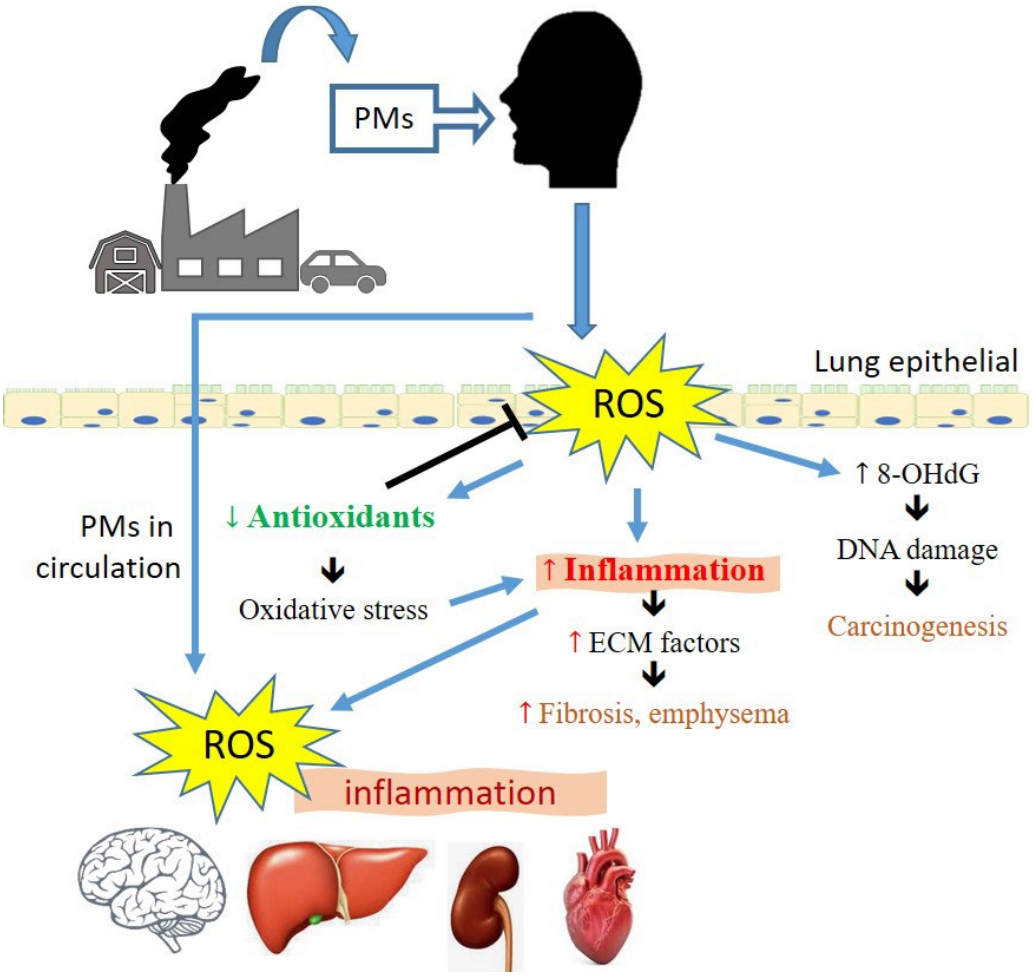

Figure 1: Schematic overview of oxidative stress and inflammatory response induced by PMs exposure in the respiratory system where they are inhaled and other vital organs where PMs gain access via the circulation.

3. Adverse health effects due to PM exposure

It was perceived that PM mostly affects people living in developing countries, since 9 out of 10 people whose health suffers from air pollution live in those regions (World Health Organisation, 2021; Xu et al., 2019a). Indeed, epidemiological studies from countries with high PM levels have raised the need to lower PM levels in order to significantly reduce morbidity and mortality. In China, one of the countries with the highest PM pollution levels, airborne PM accounts for approximately 1 million deaths annually, and was ranked as the 4th leading risk for premature death (Ji et al., 2019; Yue et al.,

2020). Studies in both China and Mexico (a country also with high PM pollution levels) suggest that reducing PM concentration would reduce preventable deaths by 30% and 8.1%, respectively (Ji et al., 2019; Trejo-Gonzalez et al., 2019). This PM reduction is achievable through local and national governments establishing multisectoral policies in areas such as transport, energy, agriculture, waste management, and urban planning (Ji et al., 2019; Trejo-Gonzalez et al., 2019; World Health Organisation, 2021). A study in India, another county with high pollution levels, showed that life expectancy would increase by 1.7 years if PM levels were below the threshold associated with adverse health outcomes (Balakrishnan et al., 2019). These studies indicate that PM air pollution is of importance to public health. According to the WHO, developing countries could see a 15% reduction in premature deaths from air pollution by reducing the annual mean concentrations of PM2.5 from 35 $\mu g/m^3$ to 10 $\mu g/m^3$ (World Health Organisation, 2021). The latest guideline released by WHO in 2021 further lowered the annual concentration to 5 $\mu g/m^3$ to reduce adverse health effects induced by PM exposure (World Health Organisation, 2021). However, it needs to be noted that there is no evidence of a safe threshold in the health effects of ambient airborne PM exposure, as illustrated by two recent studies in *Lancet Planetary Health* and *Circulation* (Khomenko et al., 2021; Yazdi et al., 2021).

Short-term health effects of PM exposure include irritations of the eyes, nose, and throat, or exacerbating of pre-existing diseases, e.g. asthma exacerbation and myocardial infarction in people with coronary heart disease (NSW Government, 2013; Wang et al., 2020a). Long-term exposure can cause the induction of chronic diseases such as atherosclerosis, dementia, diabetes, chronic kidney disease, and are more likely to affect the individual for many years reducing life expectancy by up to 8.6 months (Aztatzi-Aguilar et al., 2016a; Kim et al., 2015; Li et al., 2019a; Nemmar et al., 2014; NSW Government, 2013; Pan et al., 2016a; Pope and Dockery, 2006). While short term effects due to a sudden deterioration of air quality (eg. bush fire, volcano eruptions) can be recognised by the general public and the government, long-term effects due to continuous exposure to low levels of PM can be easily ignored. The spectrum of morbidity and mortality due to this under-appreciated chronic

exposure can be much larger than that caused by a sudden increase in PM concentration, especially in countries where air quality is relatively good.

3.1 Pulmonary effects

The lung is the main entry point and the first site of insult for PM. PM exposure accounts for 43% of cases of chronic obstructive pulmonary disease (COPD) and 29% of lung cancer deaths (Chan et al., 2019b; World Health Organisation, 2021). COPD, in particular, has been associated with inflammatory responses to harmful particle exposure, such as PM2.5 and cigarette smoke (Li et al., 2020; Vogelmeier et al., 2017). Due to the lack of human studies, we can only use our own mouse study to suggest that chronic (12 weeks) exposure to a low level of PM2.5, commonly considered safe, is a significant risk factor for developing emphysema (Wang et al., 2021a).

Adverse health effects of PM on the lung are suggested to be mediated by oxidative stress and inflammation, leading to fibrosis and genotoxicity (Figure 1) (Chen et al., 2021a; Wang et al., 2021a). Bronchial epithelial cells produce proinflammatory cytokines in response to cellular stress, leading to acute inflammation (Cho et al., 2018). Inhaled particles can enter alveolar macrophages and activate inflammatory signalling within the pulmonary parenchyma (Davel et al., 2012; Losacco and Perillo, 2018). In mice, after 3 months of exposure to PM2.5 (5μg/mouse or 83.64 μg/mouse), the lung tissues developed marked inflammatory cell infiltration, and emphysema (Li et al., 2020; Wang et al., 2021a). Moreover, PM2.5 exposure correlated with increased markers of macrophages, neutrophils, and proinflammatory cytokines (eg. interferon gamma (IFN-γ), tumour necrosis factor-alpha (TNF-α), interleukin (IL) - 17A, IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1)), contributing to the development of COPD (Cho et al., 2018; Goldklang et al., 2013; Li et al., 2020; Southworth et al., 2012; Traves et al., 2002; Wang et al., 2021a).

PM-induced injury of the bronchial epithelial cells induces the production of transforming growth factor β1 (TGF-β) for wound repair (Geng et al., 2018; Weiskirchen et al., 2019). TGF-β activates the intracellular SMAD family member 3 (SMAD3), suggesting that PM2.5 could trigger airway

fibrosis via epithelial-mesenchymal transition (EMT) (Xu et al., 2019b). Indeed, the TGF-β/SMAD3 pathway activation leads to altered levels of EMT biomarkers, such as increasing N-cadherin and decreasing E-cadherin (Xu et al., 2019b). As a consequence, lung epithelial cells lose their polarity and undergo structural changes to become extracellular matrix-producing fibroblasts (Xu et al., 2019b). Alteration of the TGF-β/SMAD3 pathway in lung cells also induces collagen type I (COL1) and α-smooth muscle actin (α-SMA), which contributes to excessive build-up of extracellular matrix (Xu et al., 2019b). PM2.5 exposure-induced extracellular matrix accumulation is ultimately responsible for the progression of fibrosis (Rout-Pitt et al., 2018; Xu et al., 2019b). In addition, the development of pulmonary fibrosis is associated with other pathological changes in the lung, such as congested alveolar capillaries, thickening of the alveolar wall, and peribronchial neutrophilic infiltration (Li et al., 2019a).

3.2 Cardiovascular effects

A plethora of epidemiological studies have investigated the association between PM exposure and cardiovascular disease (Yazdi et al., 2021; Zhang et al., 2020). These studies have suggested that exposure to PM exaggerates pre-existing cardiovascular conditions (Brunekreef and Forsberg, 2005; Chen et al., 2014; Dai et al., 2016; Friis, 2018; Hadei and Naddafi, 2020; He et al., 2017; Hoek et al., 2013; Huang et al., 2019; Li et al., 2017a; Manzano-León et al., 2013a; NSW Government, 2013; Pan et al., 2018; Peters et al., 1997; Qin et al., 2018b). For example, during the 2006-2007 bushfire events in Victoria, Australia, the incidence of out-of-hospital cardiac arrests were increased by 7%, which was associated with an increase of 9.04 μ/m^3 in mean PM2.5 concentration (Haikerwal et al., 2015).

Endothelial integrity and cell viability are paramount in supporting a healthy cardiovascular system. Any disturbances to the endothelium) caused by PM are likely to disrupt vascular tone (Dong et al., 2017). Data taken from participants in metropolitan Los Angeles indicated a strong relationship between carotid intima-media thickness (CIMT) and PM2.5 exposure (concentrations ranged from 5.2 to 26.9 $\mu g/m^3$), especially in older people who endured longer term PM exposure (Künzli et al., 2005; Manzano-León et al., 2013a). PM2.5 exposure has been shown to impair endothelium-

dependent relaxation and also decrease NO-induced vasodilation in isolated arterial vessels which can promote hypertension (Courtois et al., 2008; Davel et al., 2012; Ikeda et al., 1995).

In animal studies, mice exposed to PM2.5 had enlarged heart size, the thickness of the right ventricular free wall, increased heart rate, reduced stroke volume, cardiac diastolic dysfunction, and worsened myocardial infarct size (Li et al., 2017a; Li et al., 2017b; Qin et al., 2018a), suggesting impaired myocardial function. PM exposure also exacerbates the progression of atherosclerosis, including advanced atherosclerotic plaques in the coronary arteries and aorta, and larger atherosclerotic lesions (Araujo et al., 2008b; Suwa et al., 2002a). In human umbilical vascular endothelial cells, PM exposure provoked a heightened procoagulant state (Pan et al., 2018). These PM-treated cells expressed higher levels of prothrombotic factors and reduced antithrombotic genes (thrombomodulin) in association with augmented ROS (Pan et al., 2018), associated with prothrombotic formation (Chu, 2005; Davel et al., 2012; Tatsumi and Mackman, 2015). High PM levels have been shown to trigger the establishment of fibrin clots and alter their structure and function (Pan et al., 2016b).

ROS generation by PM exposure can activate coagulation cascades that have been identified as an important trigger for endothelial dysfunction, associated with vascular damage and cardiovascular events (eg. embolism, myocardial infarction, stroke) (Budinger et al., 2011b; Davel et al., 2012; Peters et al., 2001). Chronic PM2.5 exposure promotes the release of monocytes into the circulation (Kampfrath et al., 2011). Increased monocytes in the blood are associated with higher levels of superoxides, including Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX)-derived ROS in the aorta and perivascular fat (Kampfrath et al., 2011). Thus, monocyte infiltration is a likely source of ROS generation in the vasculature, affecting endothelial integrity and foam cell formation (Batalha et al., 2002; Chan et al., 2016; Chen et al., 2014; Dai et al., 2016; Kampfrath et al., 2011). Chronic PM exposure also results in vascular endothelial hypoxia and apoptosis, thus increasing endothelial permeability (Dai et al., 2016; Li et al., 2017a). Manzano-Leon et al. (Manzano-León et al., 2013a) demonstrated that PM2.5 promotes the oxidation of low-density

lipoprotein (LDL) and subsequently its uptake by macrophages, contributing to atherosclerotic plaque formation, reduction in blood supply and impaired myocardial function.

3.3 Neurological effects

Several studies have associated exposure to air pollution with neurotoxicity and cognitive dysfunction throughout the lifespan (Clifford et al., 2016). PM exposure has been associated with significantly impaired motor and cognitive function. In childhood, exposure to high levels of airborne PM impairs neurodevelopment, and academic performance (Clifford et al., 2016), which may be due to changes in brain morphology, as exposure to urban PM in the brain leads to micro-abscesses in the cortex and hippocampal neuronal shrinkage (Bai et al., 2019; Gerlofs-Nijland et al., 2010; Li et al., 2019a; Shih et al., 2018). Major depression and schizophrenia are other high risk mental disorders in children exposed to high levels of PM2.5 (Antonsen et al., 2020; Latham et al., 2021; Pignon et al., 2020). Anxiety and depression have been linked to air pollution after adjusting for confounders (Altug et al., 2020; Power et al., 2015). The situation of depression is more significant in people living within 100 metres of major roads (Altug et al., 2020). Animal models of perinatal PM exposure also suggest increased risk of autism spectrum disorder and depression (Nephew et al., 2020; Woodward et al., 2018).

In older adults, heavy air pollution correlates with accelerated cognitive decline, higher hospital admissions for dementia, and an increased risk of Parkinson's disease (Bai et al., 2019; Clifford et al., 2016; Kioumourtzoglou et al., 2016; Power et al., 2011; Ritz et al., 2016; Weuve et al., 2012). It is important to note that around half of later life cognitive decline is not due to Alzheimer's disease, and thus other important environmental determinants of dementia may exist, such as chronic exposure to ambient PMs (Clifford et al., 2016).

In addition, both long-term and short-term exposures have been shown to be associated with adverse cerebrovascular risks, the long-term effects being greater. A meta-analysis has also confirmed that a 10 $\mu g/m^3$ increase in short-term exposure to PM was associated with a 1% increased risk of stroke

and stroke mortality (Zhou et al., 2010). While most of the previous studies were in the setting of heavily polluted air quality, a recent study in the US also raised the alarm about the danger of chronic exposure to low levels of air pollution (Yazdi et al., 2021). In this study, there was a 0.0091% (95% CI, 0.0086–0.0097) increase in the risk of stroke with each 1 $\mu g/m^3$ increase in annual PM2.5 levels (Yazdi et al., 2021). Long-term exposure to relatively low levels of air pollution is associated with a 2536 (95% CI, 2383–2691) case / year increase in the hospitalisation of ischemic stroke (Yazdi et al., 2021).

Current literature has consistently shown that the cytotoxic effects of air pollution extend to the central nervous system (Costa et al., 2019; Lochhead et al., 2010; Oberdörster and Utell, 2002; Wang et al., 2019). A very small fraction of PM (<0.1μm) has been shown to translocate into the brain parenchyma via the blood-brain barrier (Heusinkveld et al., 2016; Kreyling, 2016). The nasal mucosa is another route where PM can reach the brain and result in adverse effects on the central nervous system (Heusinkveld et al., 2016). When the nasal olfactory bulbs are exposed to PMs, ultrafine particles can translocate along the olfactory nerve into the cerebral cortex and the cerebellum (Calderón-Garcidueñas et al., 2008; Costa et al., 2019; Wang et al., 2019).

Ultrafine PMs may disrupt the blood-brain barrier to allow their direct access to brian tissue and activate the brain's innate immune responses, by stimulating adjacent glial cells to inflict inflammatory damage in brain regions (Calderón-Garcidueñas et al., 2008; Heusinkveld et al., 2016). Microglia are resident innate immune cells within the brain that respond to stimuli (cell stress, tissue damage, pathogens, etc.) (Bai et al., 2019; Hickman et al., 2013). The ultrafine PM has been shown to exacerbate TNFα and ROS production by activating microglia, associated with increased cytotoxicity, oxidative damage, and inflammation (Bai et al., 2019; Linse et al., 2007; Woodward et al., 2018; Woodward et al., 2017). Studies on recent suddenly deceased healthy children and young adults from Mexico City who were chronically exposed to polluted air found positive correlations between PM exposure levels and neuroinflammatory markers cyclooxygenase-2, IL-1δ and CD14 in the frontal cortex, substantia nigra, vagus nerve, and the olfactory bulb (Calderón-Garcidueñas et al.,

2004; Calderón-Garcidueñas et al., 2008).

Male animals are also at a higher risk of having increased inflammatory cytokine, reduced anti-inflammatory cytokines, as well as damaged blood brain barrier functions, which allow more PMs access to the brain tissue due to perinatal and early postnatal PM exposures, akin to humans (Bolton et al., 2013; Clifford et al., 2016; Woodward et al., 2018). The neurological disorders due to PM exposure may also be induced by the inflammatory responses of microglia commonly seen in conditions like Alzheimer's disease, increasing the risk of early onset dementia if individuals live in polluted air from a young age (Bai et al., 2019; Block et al., 2007; Hickman et al., 2013; Woodward et al., 2018; Woodward et al., 2017).

3.4 Metabolic effects

Populational study in children has shown an increase in the risk of obesity by 10.0% (95% confidence interval: 3.0–16.0%) per 10 μg/m^3 increase in $PM_{2.5}$ exposure (Guo et al., 2020). Such correlation was also found in adults with increased risk of obesity (OR 1.12 (95% CI 1.09-1.14)) and abdominal obesity (OR 1.10 (95% CI 1.07-1.13)) for every 10 μg/m^3 increase in $PM_{2.5}$ exposure, more so in those who are elderly, women, individuals with low level of education and income, and those who had high fat diet (Chen et al., 2022; Liu et al., 2020). This risk is even higher in a study in Mexico with an overall pooled OR of 1.96 (95% CI: 1.21, 3.18) (Tamayo-Ortiz et al., 2021). There was also a trend of increasing odds in adolescents with a 10 μg/m^3 increase in $PM_{2.5}$ from 3.53 (95% CI: 1.45, 8.58) in 2006 to 3.79 (95% CI: 1.40, 10.24) in 2012 (Tamayo-Ortiz et al., 2021). A meta-analysis suggested living in polluted air can increase the susceptibility to nutrition metabolic impairment in women with gestational diabetes and their offspring (Elshahidi, 2019). PM exposure may interact with diabetes and potentially enhance the risk of chronic complications emerging from diabetes, including macrovascular diseases, e.g. cardiovascular diseases, and microvascular diseases, e.g. diabetic nephropathy, retinopathy, and neuropathy (Fowler, 2008; Yan et al., 2014). As one of the most important vasodilator mediators, NO bioavailability is increased in response to cellular stress (eg. hyperglycaemia induced endothelial oxidative stress (Georgescu, 2011)) to prevent leukocyte

adhesion and maintain an anti-inflammatory state in the endothelium (Tabit et al., 2010). It is suggested that exposure to PM2.5 may accelerate the disruption of NO formation regulated by eNOS (Tabit et al., 2010), leading to increased mortality due to endothelial dysfunction (Yan et al., 2014).

Several studies have also provided critical evidence for the association between PM2.5 exposure and high fat diet-induced obesity in animal models (Liu et al., 2014; Vesterdal et al., 2014). In a rat model, 16 weeks of PM2.5 exposure correlates with high levels of glycated haemoglobin, a surveillance marker of glycaemic control (Yan et al., 2014). It is recognised from an animal model that early-life exposure to PM2.5 alone induces obesity and insulin resistance (Xu et al., 2010), by increasing lymphocyte infiltration and necrotic cells in the pancreas with insulin resistance leading to hyperglycaemia (Yi et al., 2017). PM2.5 exposure can worsen high fat diet induced impairment of systemic insulin/glucose homeostasis via the PI3K/Akt pathway (Engelman et al., 2006; Sun et al., 2009). In obesity, increased adiposity and elevated levels of free fatty acids correlate with low-grade inflammation (Borgeson E and Sharma K, 2013), which inhibits the PI3K/Akt pathway (Sun et al., 2009). PM2.5-induced inflammation can also inhibit this insulin signalling in both adipose tissue and the liver by targeting the insulin receptor substrate 1 (Ye, 2013).

The first epidemiological study to confirm the association between $PM_{2.5}$ exposure and the development of metabolic dysfunction caused non-alcoholic fatty liver disease was published in 2021, with the odds ratios (ORs) of 1.13 (95% CI 1.10–1.17) and 1.29 (1.25–1.34) for each 10 μg/m3 increase in PM1 and PM2.5(Guo et al., 2021). Before this study, several animal studies had already suggested such a risk (Tan et al., 2009; Xin et al., 2019; Xu et al., 2019a; Zheng et al., 2013). $PM_{2.5}$ can act as a “hit” that triggers hepatic steatosis-like phenotype (Zheng et al., 2013). This “hit” is due to an upregulation of systemic inflammatory responses, leading to increased local ROS generation and inflammation in the liver (Zheng et al., 2013), which eventually results in the accumulation of lipids (Vesterdal et al., 2014). In addition, sub-chronic exposure to PM2.5 has also been demonstrated to exacerbate hepatic fibrosis in mice fed on a high fat diet (Ding et al., 2018), which is yet to be confirmed by human studies. Nevertheless, this is due to the activation of the hepatic stellate cells

and fibrogenic TGF-β/SMAD pathway by ROS (Ding et al., 2018; Gangwar et al., 2020; Qin et al., 2018a; Wynn, 2008). This further supports oxidative stress, inflammation, and fibrosis as key mechanisms underlying the metabolic effects of PM on the liver.

3.5 Kidney effects

PMs can affect kidney health directly or through the impact of comorbidities due to the abovementioned effects. Chronic exposure to PM has been associated with reduced kidney function among adults in several population studies (Bowe et al., 2019; Chan et al., 2018; Ran et al., 2020; Yang et al., 2017; Zhao et al., 2020). For example, decreased renal function and increased risk of chronic kidney disease (CKD) were found in US veterans from states with higher levels of PM and other air pollutants, e.g. NO and CO_2 (Bowe et al., 2017; Bowe et al., 2018). In particular, exposure to PM2.5 at the highest quartile significantly correlates with increased renal failure and a gradual progression to end-stage kidney disease (Bowe et al., 2019; Ran et al., 2020). It is worth mentioning that patients with diabetes, hypertension, and obesity are already at a high risk for underlying renal damage (Zhou and Yang, 2020). The concurrence of these factors and the additional effects of PM exposure could aggravate the potential impact on the kidney and the likelihood of developing CKD. Thus, the kidney has become another extrapulmonary target of PMs that has gained interest (Bowe et al., 2018; Chan et al., 2019b; Nemmar et al., 2009; Nemmar et al., 2016).

The mechanisms of PM-induced renal damage have not been fully understood, yet the urinary system is well-known to be highly susceptible to environmental toxins, such as drugs, heavy metals and ionising radiation (Finn, 1977; Kim, 2017; Möhner et al., 2017; Pesch et al., 2000; Schlondorff, 2008; Soderland et al., 2010). In mice exposed to ultrafine particles from motorcycle exhaust emissions twice a day for 10 days, an increased concentration of ultrafine PM was found in the kidney (Wardoyo et al., 2018). More recently, PM2.5 has been found to cause direct renal toxicity (Kim, 2017; Möhner et al., 2017). PMs containing heavy metals (e.g. lead, cadmium, arsenic, and mercury) from both workplace and industrial contamination have been associated with renal tubular and interstitial damage (Kim, 2017; Möhner et al., 2017). Transition metals especially have the ability to exacerbate

516 oxidative stress by attaching to glycated proteins, which in turn enhance free radical reactions (Shah
517 et al., 2007). Acute PM exposure causes direct injury in proximal tubules, while chronic PM exposure
518 may induce interstitial nephritis and renal fibrosis resulting in the elevation of biomarkers of kidney
519 damage (i.e. haematuria, albuminuria), changes in haemodynamics, and hypertension (Al Suleimani
520 et al., 2017; Kim, 2017; Navarro-Moreno et al., 2009; Soderland et al., 2010; Tavera Busso et al.,
521 2018). High PM dosage induces more pathological features to both glomerular and tubular
522 compartments in the kidney, including loss of glomerular integrity due to glomerular atrophy, loss of
523 epithelial cells, increased Bowman's space, significant oedema, and tubular dilation and vacuolation
524 (Al Suleimani et al., 2017; Wardoyo et al., 2018). PM2.5 in occupational solvents (e.g. paints, mineral
525 oils and asbestos) may even increase the risk of malignant renal diseases (Möhner et al., 2017; Pesch
526 et al., 2000), and augment underlying kidney damage and thus, instigate progression to end-stage
527 kidney disease (Soderland et al., 2010).

528 However, how PM exposure impacts renal health still needs more investigation, as both *in vitro* and
529 *in vivo* studies are limited in the literature, representing an understudied risk factor for kidney
530 disorders. The proposed mechanisms based on currently available evidence are inflammation and
531 oxidative stress leading to increased apoptosis. Toxic compounds in PM are also an inflammatory
532 stimulus that may promote macrophage infiltration and the upregulation of renal proinflammatory
533 cytokines (MCP-1, IL-1, IL-6, and TNF-α), which are known to induce TGF-β and collagen III,
534 resulting in fibrogenesis (Aztatzi-Aguilar et al., 2016b; Hsu and Couser, 2003; Li G et al., 2018; Li
535 et al., 2019b). Under stress, glomerulus-resident mesangial cells release inflammatory markers that
536 induce infiltration of monocytes and amplify oxidative stress (Duni A et al., 2019; Mihai et al., 2018).
537 TGF-β signalling can also provoke the interaction between endothelin-1 and receptor to allow
538 crosstalk between podocytes and glomerular endothelium (Schlondorff DO, 2008). This leads to
539 mitochondrial damage and dysfunction within the endothelial cells, inducing podocyte apoptosis and
540 subsequently endothelial dysfunction (Schlondorff DO, 2008). Endothelial dysfunction results in the
541 disruption of the glomerular filtration barrier and hyperfiltration (Kanwar et al., 2011; Mihai et al.,

2018). PMs are strong oxidants, which can directly induce oxidative stress leading to apoptosis in a dose-dependent manner (Daellenbach et al., 2020; Huang et al., 2020). As a result of exposure to PM2.5, the combination of a heightened inflammatory response, oxidative stress, and DNA damage may contribute to the progression of fibrotic scarring and irreversible CKD (Che et al., 2014; Daenen et al., 2019; Gewin et al., 2017; Wu et al., 2016).

4. Antioxidants and perspective

Reducing air pollution, including PM, is the ultimate solution to reducing air pollution related morbidity and mortality (Khomenko et al., 2021; United States Environmental Protection Agency, 2020). However, there is still a long way to go, despite international calls for environmental protection, because not every country is willing to commit to reducing industrial activities and petrol/diesel-powered cars to reduce pollution.

PMs are difficult to eradicate once entering the body system. Therefore, preventative measurements are more important to protect individuals from PM-induced disorders. Masks have been used to prevent the inhalation of PMs; however, it is not always effective when the wrong type is used, or it is not properly fitted, or during hot days. In places with relatively good air quality, people are not consciously using masks to protect themselves from TRAP PMs.

PMs, especially the organic aerosols from vehicle emissions and biomass burning, are strong oxidants (Daellenbach et al., 2020). Animal studies have demonstrated that antioxidants improve lung, vascular and renal function in models of environmental toxin exposure induced oxidant injury (Sukjamnong et al., 2018; Sukjamnong et al., 2017). The commonly used antioxidants are those available over-the-counter at the pharmacy, including vitamin C, vitamin E, β-carotene (a precursor of vitamin A), and omega-3 polyunsaturated fatty acids mainly supplied in the fish oil. As dietary supplements, human trials can directly enter Phase 2 without the need for safety data from pre-clinical studies and Phase 1 clinical trials. However, there have been no randomised controlled trials to examine antioxidant treatment on chronic PM exposure induced disorders, possibly due to limited

567 understanding of PM-related health risks in the past. As such, early studies mainly focused on the
568 effect of gaseous components of polluted air on lung function (reviewed by (Tashakkor et al., 2011)).
569 An observational study using a self-reporting mechanism has suggested the benefit of antioxidant-
570 rich diets on blood pressure control in individuals exposed to $PM_{2.5}$ (Schulz et al., 2015). However,
571 even with such dietary modification, the adverse effect of PM exposure is not completely prevented.
572 The major limitation of a study design like this is the accuracy of the antioxidant dose from the diet,
573 which is largely affected by how fresh the food is, how the meal is prepared, and the effectiveness of
574 absorption. Therefore, it is difficult to determine the moderate effect is due to insufficient doses, or
575 limited efficacy of antioxidants themselves. Another study also observed a positive correlation
576 between blood levels of antioxidant of vitamin E and metabolite of vitamin C and lung functions
577 among individuals with the same levels of ambient PM exposure (Menni et al., 2015). It also indicated
578 that people don't increase the intake of such supplements due to increased air PM pollution. One of
579 the major drawbacks of antioxidant supplement therapies is that it is difficult to administer
580 antioxidants at effective therapeutic doses. This means that newer antioxidants of higher efficacy are
581 needed, representing a significant gap in research.

582 **5. Advantages and limitations of pre-clinical models and future perspectives**

583 The *in vitro* cell system provides the advantage of investigating the isolated cellular response to PM
584 (Table 1), although it can omit any systemic influences, such as unknown hormone effects from the
585 endocrine system and systemic inflammation sourced from other cell types. Animal models can
586 include the systemic response that can also affect individual organs (Table 2). However, most studies
587 adopt very high doses of PM, especially in some in vitro studies, which may only represent areas with
588 heavily polluted air, or an acute increase in air pollution due to natural disasters, such as bush fires
589 and volcano eruptions. Therefore, despite the current number of studies on the effect of exposure to
590 high levels of PM2.5 on health outcomes, there is a significant gap in the literature on chronic
591 exposure to low levels of $PM_{2.5}$. In humans, only recently, a study in the US suggested that chronic
592 exposure to low dose PM (below national standard level) significantly increased the risk and

hospitalisation due to stroke, atrial fibrillation, and pneumonia in the elderly population (Yazdi et al., 2021). There is also a European study demonstrating that low level PM exposure causes COPD (Strak et al., 2021). As such, there seems to be no evidence of a safe limit for PM exposure in terms of cerebrovascular, cardiovascular, and pulmonary health. However, the impact of chronic exposure to low dose PM2.5 on other systems, such as metabolic and renal functions, as well as reproductive health, is still unclear. Thus, future studies should also focus on the scenario of chronic low-level PM exposure, which may have even longer term implications for human health than intermittent high levels of airborne pollution.

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Table 1: Summary of the effect of PM exposure on individual cell types *in vitro*

Cell type	Treatment protocol	Effects	Ref
Human bronchial epithelial cell line BEAS-2B cells	TRAP $PM_{2.5}$ (25 µg/mL) Treatment for 30 passages	Activation of TGF-β1/SMAD3 pathway, increased TGF-β1 excretion and epithelial-mesenchymal transition (EMT, reflected by increased N-Cadherin and collegen1, decreased E-Cadherin), reduced *smurf (a SMAD3 inhibitor).*	(Xu et al., 2019b)
	TRAP PM, wood smoke PM, and mixture of both 1, 3, 10 mg/cm^2	Wood smoke and TRAP/wood smoke mixture are more toxic than TRAP alone. Increased IL-6 and IL-8 at 10 mg/cm^2	(Wang et al., 2021b)
Human bronchial epithelial cells (HBE) from a 29 year old female	urban ambient PM (APM) wildfire (WF) PM 10 µg/mL for 3 h	APM: activated genes related to xenobiotic metabolism (CYP 1B1), endogenous ROS generation and response genes (DUOX1, SOD2, PTGS2), and pro-inflammatory responses associated with asthma or COPD (such as IL-1α, IL-1β, IL-8, and CCL20, TNFα, Tumor necrosis factor, alpha-induced protein 3 (TNFAIP3)); activates transcription factor genes (activating transcription factor 4 (ATF4), v-maf musculoaponeurotic fibrosarcoma	(Nakayama Wong et al., 2011)

		oncogene homolog F (MAFF) and B-cell CLL/lymphoma 3 (BCL3)); WFPM: more robust xenobiotic metabolism and oxidative stress response; increased CYP1B1, CYP1A1, GM-CSF, and IL-1α; APM induced a greater inflammatory response partially due to endotoxin; while WF PM had more marked metabolism and ROS related responses.	
Human lung epithelial A549 cells	$PM_{2.5}$ at 8km away from an iron and steel factory 25, 50, 100, 200 μg/ml for 4, 12, 24, 48 h	Toxicity in all concentrations at 24-48h; dose-dependent increase in ROS generation; suppressed the activities of SOD and CAT; increased autophagy.	(Deng et al., 2013b)
Human lung epithelial A549 cells	5, 20, 50 μg / cm^2	dose-dependent increase in TF mRNA and protein expression	(Budinger et al., 2011a)
Human pulmonary fibroblast cell line HFL-1 cells	TRAP $PM_{2.5}$ (25, 50, 100, 200 μg/mL), 15min-24h culture medium of 30-	activation of TGF-β1/SMAD3 pathway, increased TGF-β1 excretion and cell differentiation. activation of TGF-β1/SMAD3 pathway, increased α-SMA and collegen1	(Xu et al., 2019b)

	passage $PM_{2.5}$-exposed BEAS-2B		
Mouse macrophage cell line RAW264.7 cells	TRAP $PM_{2.5}$ (0, 25, 50, 100, and 200 μg/mL) for 24h	activation of TGF-β/SMAD3 pathway, increased TGF-β1 production, increased α-SMA and collegen1	(Xu et al., 2019b)
	Wildfire smoke PM, 100 μg/ml for 1h	ultrafine (0.042–0.24 μm) and the fine (0.42–2.4 μm) sizes produced the highest ROS levels, lipid peroxidation, and DNA damage	(Leonard et al., 2007)
Human monomyelocytic leukemia (THP-1) cell line	Airborne $PM_{2.5}$ 0.4-200 μg/mL for 24h	Activation of NLRP3 inflammasome through cathepsin B release, ROS production, and potassium efflux, with potent IL-1β secretion. Phagocytosis, clathrin-mediated endocytosis, and caveolin-mediated endocytosis are all involved in cellular uptake of $PM_{2.5}$	(Zheng et al., 2018)
Human pulmonary artery endothelial cells (HPAECs)	Wood fire smoke PM extracts 10 mg/ml for 24 h	increase in intracellular levels of ROS ($O2^{-\cdot}$ and H2O2) and Cu/Zn SOD and HO-1. decrease in intracellular GSH level in a time-dependent manner. increase caspase-independent apoptosis, by increasing mitochondrial-to-nuclear translocation of apoptosis-inducing factor (AIF) or endonuclease G (EndoG).	(Liu et al., 2005)
Human lung type II alveolar-like	50 μg/ml PM10 for 24 h	Increase IL-8 release by macrophages and 16HBE cells. reduce the macrophage mediated clotting time.	(Gilmour et al.,

epithelial cells (A549) and human bronchial epithelial cells (16HBE), Human peripheral blood monocyte derived macrophages		increase Macrophage tissue factor.	2005)
Human umbilical vein endothelial cells (HUVECs)	0.1, 1, 10, and 50 ug/ml of PM10, PM0.2, total DPM and filtered DPM respectively for 4 hours	denser fibrin clotting in a dose-dependent manner, associated with increased levels of tissue factor, decreased antithrombotic genes (thrombomodulin) while promoting prothrombotic genes (von Willebrand factor and plasminogen activation inhibitor-1).	(Pan et al., 2016b)
Rat myocardial cell line H9c2	Ambient $PM_{2.5}$, 1, 2.5, 5, 7.5, 10, 20 and 30 μg/cm^2 for 24h; Mechanistic study 10 μg/cm^2	Supress myocardial ATP production. Reduced β-oxidation of fatty acid and cinreased glycolysis. Reduced PPARα is the underlying mechanism.	(Zhang et al., 2020)
AC16 cell	Series of concentrations (25,	Increase ROS and malondialdehyde.	(Yang et

	50, and 100 μg/mL) for 24h	decrease superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px). damage mitochondria and DNA increase apoptotic markers Caspase-3, Caspase-9 and Bax while reduce the anti-apoptotic protein, Bcl-2	al., 2018)
Human LDL Chinese hamster ovary (CHO), SR-transfected CHO (CHO-SR), and RAW264.7 cells	$PM_{2.5}$ or PM_{10} (20, 40, and 80 μg/mg LDL) for 24 h	PM_{10} increases H_2O_2 induced LDL oxidation by altering scavenger and LDL receptor function	(Manzano-León et al., 2013b)
Mouse microglial BV-2 cell line	carbon black and diesel exhaust particles 0, 50, and 100 μg/mL for 24 h	increase IL6 and TNF-α levels. increase autophagy.	(Bai et al., 2019)
Primary olfactory epithelium from postnatal day 3	Nano-sized particulate matter (nPM; <0.2 μm in diameter, 12 μg/ml) in	nPM rapidly induced TNFα in olfactory neuroepithelium. nPM induced more TNFα production in microglia than astrocytes. Media from nPM-treated glia caused TNFα dependent inhibition on neurite	(Cheng et al., 2016)

C57BL/6J mice (both sexes); Mixed glia from the cerebral cortex of postnatal day 3 Sprague Dawley rats (both sexes)	artificial cerebral spinal fluid for 2 h/37 °C Whole nasal cavity ex vivo incubation. Mixed glia (3:1 astrocytes:microglia) treated with nPM (12 µg/ml) in neuronal media for 24 h.	outgrowth.	
HepG2 cells	0, 0.1, 10, 50 or 100 µg/ml CB (corresponding to 0, 0.06, 6.3, 31.3 or 62.5 µg/cm2).	Increase accumulation of lipids in HepG2 cells (50 or 100 µg/ml (corresponding to 31.3 or 62.5 µg/cm2)). concentration-dependent relationship DNA damage in HepG2 cells. bell-shaped concentration–response relationship in terms of concomitant DCFH-DA fluorescence, where 10 µg/ml generated high levels of ROS. Reduce *Srebp-1* expression.	(Vesterdal et al., 2014)

Human proximal tubule epithelial cells (HK-2 cells)	Ambient PM2.5 25, 50, 100, 200, 400 μg/ml	Increase kidney injury molecule-1 (KIM-1) in a dose-dependent manner. Increase cellular apoptosis pathway, by increasing pro-apoptotic protein Bax, caspase-3 and caspase-8 and decreasing anti-apoptotic protein Bcl-2. Increase ROS production and; activate the antioxidant pathway, upregulating Nrf2, HO-1 and NQO1, and downregulating Keap1.	(Huang et al., 2020)

Table 2: Summary of the long-term effect of PM exposure on organ system *in vivo*

Species	**Treatment protocol**	**Organs**	**Effects**	**Ref**
C57BL/6 mice, male	Continuous whole-body exposure to real-time ambient air for 3, 6, and 12 weeks (mean daily chamber PM2.5 concentration = 151.40, 132.58, and 130.22	Lung	3 weeks - alveolar capillary congestion and increased peribronchiolar neutrophils infiltration; 6 weeks - alveolar hemorrhage, diffuse parenchymal congestion, pleural-based congestion, interstitial haemorrhage, chronic pulmonary inflammation, alveoli structural damage. Lung function: reduced FVC, FEV_1, and FEV_1/FVC;	(Li et al., 2019a)

	μg/m^3 for weeks 1-3, 1-6 and 1-12 respectively)		BALF: increased total cell counts (neutrophils and macrophages dominate), total protein and albumin, and lactate dehydrogenase; increased TNF-α and IL-10; mRNA: increased IFN-γ, IL-12p70, IL-5, and TGF-β1; reduced TNF-α, IL-1β, IL-4, IL-6, IL-10, KC/GRO, and TGF-β2.	
C57BL/6 mice, mixed sexes	Intranasal instillation 100 μg TRAP $PM_{2.5}$/day for 4 weeks (equal to daily exposure to 1543.2 μg/m^3 of PM)	Lung	widened alveolar spaces and alveolar structure damage, increased inflammatory cell infiltration; Increased fibrotic response reflected by increased TGF-β1, α-Smooth muscle actin (α-SMA), and Collagen type I (COL1)	(Xu et al., 2019b)
Balb/c mice, male	Oropharyngeal instillation 2.5, 10, 20 μg/mouse/day $PM_{2.5}$ 21 days	Lung	BALF: increased IL-1β and TGF-β1; Lung: increased collagen deposition around small airways;	(Zheng et al., 2018)
	Intranasal instillation	Lung	BALF: increased total cell, lymphocytes, macrophage	(Chan et al.,

	1, 5 µg/mouse/day of PM_{10} 21 days		numbers by 5 µg PM only; Lung: increased inflammasome protein (NLRP3, IL-1 β), and Akt activity, reduced AMPK activity, increased mitochondrial fission and reduced fusion, autophagy and mitochondrial MnSOD levels by 5 µg PM only.	2019a)
Balb/c mice, mixed sexes	Intranasal instillation 5 µg TRAP $PM_{2.5}$ daily for 12 weeks in the dams, no additional treatment in offspring	Lung	Dams - BALF: increased number of macrophages, eosinophils, neutrophils, and lymphocytes. Lung: airways hyper-responsiveness (AHR) with mucus hypersecretion and emphasyma like pathology, increased mitochondrial reactive oxygen species (ROS) and mitochondrial dysfunction. Femail offspring - BALF: increased number of macrophages, eosinophils, neutrophils. Lung: AHR with increased lung inflammation; after ovalbumin challenge, AHR was increased in female	(Wang et al., 2021a)

			offspring from $PM_{2.5}$ dams. Male offspring – BALF: increased number of macrophages, and neutrophils. Lung: increased lung inflammation.	
$TLR4^{wt}$ mice; male	Whole-body exposure Facility ambient 10.7 ± 2.1 μg/m^3; Chamber 92.4 ± 2.1 μg/m^3. 6h/day, 5 days/week for 20 weeks	lung	Lung: Increased TNFα, MCP-1 and IL12p70 and a decrease of IL-10 levels; increased $p47^{phox}$ phosphorylation suggesting increased NADPH oxidase activation. BALF: increased oxidized phospholipid (1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine)	(Kampfrath et al., 2011)
Sprague Dawley rats, male	Oropharyngeal instillation Ambient PM2.5, 5 mg/week (25 mg/kg/week), once a week, 3 consecutive	Lung	Reduced endogenous antioxidants and eNOS, increased lipid peroxidation; disrupt global pulmonary metabolome involved in the metabolism of lipid, amino acids and nucleotide.	(Wang et al., 2017a)

	months			
C57BL/6 and IL-6 knock out (IL-$6^{-/-}$) mice	Whole body Ambient $PM_{2.5}$ 88.5±13.4 μg/m^3 in the chamber, 8 hours daily for three days urban PM 10, 20, 200 μg, intratracheally	Lung	Ambient PM Lung: increased IL-6, surfactant protein B (SFPB) and tissue factor (TF) mRNA BALF: increased pro-inflammatory cytokines IL-6, MCP-1 and TNF-α Urban PM Lung: increased TF and PAI-1 mRNA and protein, higher fibrin level, acute lung injury at 200 μg, BALF: dose-dependent increase in IL-6 and protein level; an increase in macrophages and neutrophils; an increase in PAI-1;	(Budinger et al., 2011a)
Adult male Wistar rat	Whole-body exposure of concentration of dusty PM 150 μg/m^3, or factual dust storm with PM at 200–500 μg/m^3, 500–	Brain	Impairment of spatial memory and hippocampal long-term potentiation. Disruption of blood brain barrier integrity, increased brain edema, inflammatory cytokines excretion and oxidative stress.	(Hajipour et al., 2020)

	2000 μg/m^3 and 2000–8000 μg/m^3. 4 consecutive weeks (exposure was during 1-4, 8-11, 15-16 and 20-23 days, 30 min, twice daily)			
Sprague-Dawley rats male	16.3 ± 8.2 μg/m^3 PM_1 daily for 3 and 6 months	Brain	microglial activation	(Bai et al., 2019)
Sprague-Dawley male rats (2 months old) No sex information	Intratracheal injection of 20 mg/kg PM2.5 (10 ml/kg·body weight) once every 7 days, 3-months, 6-months, 12-months.	Brain	time-dependent impairment in spatial learning memory, inquiring ability, and sensory function; changes of mitochondrial and myelin sheath structure, time-dependent increase in apoptosis-related proteins (Caspase-3, Caspase-9).	(Zhang et al., 2018)
Sprague-Dawley rats and male offspring	Whole-body exposure to re-aerosolized PM of 200 μg/m^3 (measured as	Brain	No difference in milk intake and weight of the pups. Behavioral testing between the ages of 32 and 40 days autism spectrum disorder, lower levels of whole cage	(Nephew et al., 2020)

	PM2.5), 5 hours a day, 5 days a week for the duration of gestation (~22 days) and lactation (21 days)		social play and allogrooming; increase latencies to climb down in the elevated platform; more rearing and fecal boli; lower L-18 and VEGF. lower fractional anisotropy in both the anterior cingulate and hippocampus.	
Sprague-Dawley rats Male offspring	Whole-body $PM_{0.2}$ exposure, 5 h/day, 3 days/week beginning gestational day 2, through gestation, until 25 weeks of age. 340 μg/m^3	Brain	10% reduction in fat mass. Reduce serum IL-4, IL-10, IL-13. impaired neurogenesis; microglial activation; increase iron deposits in s. oriens and s. radiatum; decrease tight junction protein ZO-1, indicating blood brain barriar leakage; microbleeds. depressive behaviour, contextual memory impediments and impaired food-seeking behaviours.	(Woodward et al., 2018)
C57BL/6 mice, male	Continuous whole-body exposure to real-time ambient air for 3, 6, and	Brain	abnormal neuronal morphology in the prefrontal cortex, necrosis, eosinophilic cell infiltration; loosening pyramidal cells in the hippocampal CA1	(Li et al., 2019a)

	12 weeks (mean daily chamber PM2.5 concentration = 151.40, 132.58, and 130.22 μg/m^3 for weeks 1-3, 1-6 and 1-12 respectively)		region; impaired activity and response in open field test and tail suspension test. mRNA: increased IFN-γ, IL-10, IL-12p70, IL-5, KC/GRO, TNF-α, IL-6, and IL-1β.	
C57BL/6J mice, female 3 and 18 months	Traffic-related air pollution Nano-PM <0.2 mm diameter Total mass and number concentrationswere 342 ± 49 mg/m3, and 1.4 x 10^5 ± 9.7 x 10^3 particles/cm^3, respectively 5 h/d, 3 d/wk, for 10 weeks	Brain	Young mice: changes in the hippocampal CA1 region, including neurite atrophy, decreased white matter myelin basic protein, increased microglia (Iba1), decreased Glutamatergic receptor AMPA receptor GluA1 protein and increased TNFa mRNA expression; NMDA subunits not affected; hippocampal dentate gyrus not affected. No change in memory function, but reduced exploratory activity. Mid-aged mice: no brain changes in response to nano-PM exposure, but reduced short term memory and	(Woodward et al., 2017)

			exploratory activity	
C57BL/6, male and female embryo day 18, postnatal day 30, and postnatal day 60-90	diesel exhaust particles intermittent exposure to 50 μg via oropharyngeal aspiration, every 3 days during embryo day 2-17 for six doses.	Brain	At embryo day 18, brain IL-10 was decreased in male's brain, but increased in female's brain. At postnatal day 30, no significant change in neuroimmune gene TLR4 and Casp1 expression in either sex. At postnatal day 60-90, no impact on fear and anxiety; increased brain IL-1β and reduced IL-10 in male's brain, but no change in female's brain.	(Bolton et al., 2013)
C57BL/6 mice, male	Continuous whole-body exposure to real-time ambient air for 3, 6, and 12 weeks (mean daily chamber PM2.5 concentration = 151.40, 132.58, and 130.22 μg/m^3 for weeks 1-3, 1-6 and 1-	Heart	increasing thickness of the right ventricular free wall; increased heart rate; reduced stroke volume.	(Li et al., 2019a)

	12 respectively)			
C57/BL6 mice, male	Intranasal instillation 10μg PM2.5 twice a week, a week before surgery and for four weeks after surgery	Heart	exacerbates cardiac dysfunction in mice with myocardial infarction increase cardiomyocyte apoptosis	(Li et al., 2017b)
C57BL/6 mice, Male,	3 ages (4 weeks, 4 months, and 10 months) Oropharyngeal aspiration 3mg/kg every other day for 4 weeks; 4 months, and 10 months for 4 weeks and withdrawal $PM_{2.5}$ 1 or 2 weeks.	Lung Heart Blood pressure	cardiac diastolic dysfunction, elevated the heart rate and systolic blood pressure in 10 months old mice. impaird cardiac functionin 10 months old mice. fibrosis in both 4 weeks and 10 months old mice. increased Col1a1, Col3a1, NOX-4, activated Smad3, and generated more reactive oxygen species in the myocardium of 4 weeks and 10 months old mice. increased TGFβ1 IL-6 and malondialdehyde in hearts and lungs of 4 weeks and 10 months old mice. PM withdraw restored blood pressure, heart rate,	(Qin et al., 2018a)

			cardiac function, and collagens in 4 weeks and 10 months old mice.	
C57BL/6, $TLR4^{wt}$ mice; male	Whole-body exposure Facility ambient 10.7 ± 2.1 μg/m^3; Chamber 92.4 ± 2.1 μg/m^3. 6h/day, 5 days/week for 20 weeks	Aortic tissue	Increase oxidative stress in aortic tissue and perivascular fat mediated by TLR4 and NADPH oxidase; Increased macrovascular constriction mediated by TLR4;	(Kampfrath et al., 2011)
APOE-/-(C57BL/6J) mice, male	Whole-body exposure concentrated ambient particles Filtered air <5000 particles/cm^3 (26.78 μg/m^3) Fine particles 4.56 (±1.06)×10^5 particles/cm^3 (438.29 μg/m^3)	Atherosclerosis	exacerbate early atherosclerotic lesions increase systemic oxidative stress and Nrf2-regulated antioxidant genes increase lipid peroxidation. inhibit HDL anti-inflammatory properties.	(Araujo et al., 2008a)

	Ultra fine partiles 5.59 (±1.23)×10^5 particles/cm^3 (112.61 μg/m^3), 75h over 40 day period.			
Watanabe heritable hyperlipidemic rabbits	intrapharyngeal instillation PM_{10} 5 mg, twice a week for 4 weeks	Atherosclerosis	enhanced atherosclerotic plaque, increase vol/vol of atherosclerotic lesions, greater vol/vol of smooth muscle cells, extracellular matrix and extracellular lipid pools, cell nuclei, and higher percentage of BrdU-positive nuclei. Incease counts for polymorphonuclear leukocyte; no change in total circulating leukocyte, red blood cell, platelet or mononuclear cell counts. No change in Total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL)	(Suwa et al., 2002b)
Wistar rats; male	Whole body exposure PM2.5 at an accumulated daily dose of	endothelial function in isolated	Endothelial dysfunction in pulmonary arteries from PM2.5-exposed rats, with oxidative stress despite high SOD expression;	(Davel et al., 2012)

	approximately 600 μg/m3 1-5 hours, daily for 2 weeks	pulmonary arteries	Endothelial nitric oxide synthase (eNOS) was reduced, while TNF-α was increased by PM2.5 inhalation. Positive correlation between eNOS expression and maximal relaxation response (Emax) to acetylcholine. Negative correlation between vascular TNF-α expression and Emax to acetylcholine.	
Sprague–Dawley rats; male	Whole body flow rate of 79 ± 1 m3/h PM2.5 13.30 μg/m^3, 24 h/day, 7 days/week, for 16 weeks	Glycaemic control, Heart, Kidney	In healthy rats, increase fasting insulin level and HOMA-IR, and blood IL-6. in type 1 diabetic rats, increase HbA1c and blood IL-6, cause focal myocarditis, and increased glomerulosclerosis.	(Yan et al., 2014)
Sprague–Dawley rats; Female dams	Maternal intratracheal instillation PM2.5, 15 mg/kg for at gestational days 10 and 18.	Gestational diabetes;	Supress maternal body weight gain and reduce foetal weight at embryo day 19; increase blastocyst absorption. increase pancreatic inflammation and oxidative stress (reduced homogenate glutathione peroxidase (GSH-Px), and increased methane dicarboxylic aldehyde	(Yi et al., 2017)

			(MDA)), reduce GLUT2 expression. increase postprandial blood glucose, blood mono-nuclear cells, platelets, and IL-6 levels; no change in blood insulin and HOMA-IR.	
C57BL/6J mice 11-12-week old F1 and F2 offspring (sex not specified)	Whole-body exposure during gestation or lactation. 600 μg/m^3/day, 3h/day daily, during pregnancy or lactation	Glycaemic control	exposure during gestation or lactation cause higher fasting blood glucose and lower serum insulin levels in F1 and F2 offspring; induce insulin resistance in F1. exposure during gestation increase Pdx1 DNA methylation and NEUROG3 within the pancreatic islets in F1 and F2.	(LIMA et al., 2019)
C57BL/6J mice mice deficient in the cytosolic subunit of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase $p47^{phox}$ ($p47^{phox-/-}$)	Whole-body exposure from 3 weeks of age for 10 weeks 111.0 μg/m^3/day, 6h/day, 5 day/week for 10 weeks. normal diet (13% calories from fat) or a high-fat	Glycaemic control, adiposity.	Wild type Increase glucose intolerance and insulin resistance, blood TNFα, visceral and subcutaneous fat contents in both dietary groups; increase adipocyte size in normal diet group. increased $O2^{\cdot-}$ production in the epididymal fat, but not in the subcutaneous fat; increased M1	(Xu et al., 2010)

	diet (42% calories from fat) for the same period of time.		macrophages in epididymal adipose tissue; increase mRNA levels of TNF-α, NO synthase 2, and IL-6. The underly mechanism is functional NADPH oxidase. chemotactic responses in response to PM2.5 exposure in the visceral fat of wild-type C57BL/6 mice were abolished in the p47phox−/− mice. enhanced constriction response to phenylephrine and a decreased relaxation response to endothelium-dependent vasodilator acetylcholine. Induces $p47^{phox}$ Phosphorylation	
C57BL/6J mice, male c-*fms*^{YFP} mice	Intratracheal instillation $PM_{2.5}$ 1.6 mg/kg, 6h/day, 5 days/week for 24 weeks ($7.7\ \mu g/m^3$, human equivalent to 13.0 $\mu g/m^3$)	Glycaemic control, vescular function, adiposity.	elevated fasting glucose, insulin, homeostasis model assessment indexes, and abnormalities in lipid profile. a decrease in peak relaxation and ED_{50} to acetylcholine and decreased peak relaxation to insulin; reducing vascular nitric oxide bioavailability by the increment	(Sun et al., 2009)

			in tension in preconstricted aortic rings to N^G-monomethyl-l-arginine. Reduce phosphorylation of Akt in endothelial and intact aorta; reduce PKC-βII in aorta. Increase tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), E-selectin, intracellular adhesion molecule-1 (ICAM-1), plasminogen activator inhibitor-1, and resistin; reduce IL-10 and the alternative (M2) macrophage activation marker galactose-*N*-acetylgalactosamine–specific lectin (Mgl1). increase visceral and mesenteric fat. increase leukocyte cell infiltration in the mesenteric fat and cell adhesion to endothelium.	
C57BL/6J and CCR2$^{-/-}$ (CCR2) mice, male	Whole-body exposure $PM_{2.5}$ 116.9 ± 34.2 vs control 9.56 ± 2.9 μg/m^3/day,	Glycaemic control, adipose inflammation,	elevated fasting glucose level and HOMA-IR index, decreased HOMA-β function, abnormal glucose tolerance, and attenuation of whole-body insulin sensitivity.	(Liu et al., 2014)

	6h/day, 5 days/week for 117 days =~ 17 weeks HFD (60% of calories from lipids)	hepatic steatosis	increase in circulating $CD11b^{+}Gr\text{-}1^{low}7/4^{hi}$ cells, which was reduced in reduced in $CCR2^{-/-}$ mice, which was not affected by $CCR2^{-/-}$. increase in adipose F4/80, which was not changed in $CCR2^{-/-}$ mice. reduce PPARγ expression in fat. decrease in relaxation in response to both acetylcholine and insulin. Increase in hepatic triglycerides and plasma triglycerides; increase in liver synthesis enzymes [acetyl-CoA carboxylase 2 (ACC2), fatty acid synthase (FAS), and diacylglycerol acyl transferase (DGAT2)] , SREBP1, and *FABP1* (fatty acid binding protein 1). inhibition of G6pase, FBPase, pyruvate carboxylase (PC), *GLUT-2*, and ChREBP (carbohydrate response element binding protein) in the liver; no difference in expression of the C/EBP-α, PGC1α, GSK3β.	

			Decrease liver M2 macrophage activation marker galactose-*N*-acetylgalactosamine-specific lectin (*MgI1*); increae liver activated p38. Reduce fat Phosphorylated AKT (Ser473) and AMPK (Thr172), and insulin receptor substrate-1 (IRS1) at the Tyr612 site.	
db/db mice db/+m mice	Intratracheal instillation diesel exhaust particles 100 μg once every two weeks, for 12 or 18 weeks (7 or 9 times)	Adiposity Liver	Icrease AST and ALT greater in the db/db mice than in the db/+m mice under exposure to either DEP or vehicle; Increase ratio of liver weight to body weight. Increase liver fatty change. Increae liver exanoyl-lysine (marker of oxidative stress at an earlier stage).	(Tomaru et al., 2007)
C57BL/6J mice, male	Whole-body exposure $PM_{2.5}$ and PM_{10} in the exposure chamber were 135.90 μg m^{-3} and	liver	increased hepatic fibrotic grade, with an interaction between PM exposure and HFD treatment; increase in α-SMA protein. increased the activated TGFβ in serum.	(Ding et al., 2018)

	200.75 μg m^{-3}, 6 h/day, 7 day/week for 18 weeks HFD (fat, 41.26%; carbohydrates, 39.61%; protein, 19.13%)		Increase hepatic mRNA expression of TGFβ and collagen 1. expansion of the ER compartment and an increased number of mitochondria. Increase liver ROS, ER stress markers (*CHOP*,*GRP78,* *p*-SMAD2 and *p*-SMAD3). ROS-endoplasmic reticulum stress-TGFβ/SMADs	
Zucker rats	Oral carbon black 0.064, 0.64 or 6.4 mg/kg body weight, one does. 0.064 and 0.64 mg/kg of, one dose/week (10 doses). 10 doses of CB (one dose/week of 0.64 mg/kg bodyweight) and allowed to recover for 13 weeks.	Liver	Increase in lipids in liver. did not affect the gene expression level of *Srebp-1*, *Srebp-2*, *Scd-1*, *Fasn*, *Abcg5* and *Abcg8* in the liver.	(Vesterdal et al., 2014)

C57BL/6 mice, male	Continuous whole-body exposure to real-time ambient air for 3, 6, and 12 weeks (mean daily chamber PM2.5 concentration = 151.40, 132.58, and 130.22 $\mu g/m^3$ for weeks 1-3, 1-6 and 1-12 respectively)	Testis	reduced seminiferous tubules and spermatogenesis; disorganised spermatogenic cells; increased interstitial area; interrupted basement membrane; normal sperm count with abnormal sperm morphology mRNA: increased IFN-γ, IL-12p70, IL-1β, IL-4, IL-5, and TGF-β2.	(Li et al., 2019a)
C57BL/6 mice, male	Continuous whole-body exposure to real-time ambient air for 3, 6, and 12 weeks (mean daily chamber PM2.5 concentration = 151.40, 132.58, and 130.22	White blood cells, serum and urine	Increased neutrophils and monocytes in peripheral blood. Increased plasma cytokines IFN-γ, IL-1β, and IL-10. Increased urinary 8-OHdG suggesting systemic oxidative stress	(Li et al., 2019a)

	μg/m^3 for weeks 1-3, 1-6 and 1-12 respectively)			
C57BL/6, c-*fms*^{YFP} mice; male	Whole-body exposure Facility ambient 10.7 ± 2.1 μg/m^3; Chamber 92.4 ± 2.1 μg/m^3. 6h/day, 5 days/week for 20 weeks	White blood cells	Promotes Ly6C^{high} inflammatory monocyte egress from bone-marrow into tissue mediated by TLR4 and Nox2; Increase oxidative stress in macrophages mediated by TLR4 and NADPH oxidase; Increased leukocyte adherence in microvasculature;	(Kampfrath et al., 2011)
C57BL/6 and IL-6 knock out (IL-$6^{-/-}$) mice	Ambient $PM_{2.5}$ 88.5±13.4 μg/m^3 in the chamber, 8 hours daily for three days urban PM 200 μg, intratracheally	Clotting function	Ambient PM: increases transcription of PAI-1 in the white adipose tissue mediated by TNF-α; alveolar macrophage IL-6-dependent activation of coagulation after 24h of PM administration; increased plasma levels of thrombin antithrombin complexes (TAT); Urban PM: dose-dependent increase in plasma TAT.	(Budinger et al., 2011a)

			An increased in white adipose tissue PAI-1 mRNA	
C57BL/6 mice, male	Continuous whole-body exposure to real-time ambient air for 3, 6, and 12 weeks (mean daily chamber PM2.5 concentration = 151.40, 132.58, and 130.22 $\mu g/m^3$ for weeks 1-3, 1-6 and 1-12 respectively)	Intestine	oedema and lesions in epithelial and submucosa layers; inflammatory cell infiltration; mRNA: increased TNF-α, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p70, TGF-β1, and TGF-β2	(Li et al., 2019a)