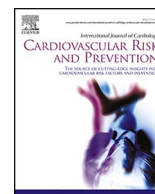




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PM_{2.5} and cardiovascular diseases: State-of-the-Art review

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ABSTRACT

Air pollution, especially exposure to particulate matter 2.5 (PM_{2.5}), has been associated with an increase in morbidity and mortality around the world. Specifically, it seems that PM_{2.5} promotes the development of cardiovascular risk factors such as hypertension and atherosclerosis, while being associated with an increased risk of cardiovascular diseases, including myocardial infarction (MI), stroke, heart failure, and arrhythmias. In this review, we seek to elucidate the pathophysiological mechanisms by which exposure to PM_{2.5} can result in adverse cardiovascular outcomes, in addition to understanding the link between exposure to PM_{2.5} and cardiovascular events. It is hypothesized that PM_{2.5} functions via 3 mechanisms: increased oxidative stress, activation of the inflammatory pathway of the immune system, and stimulation of the autonomic nervous system which ultimately promote endothelial dysfunction, atherosclerosis, and systemic inflammation that can thus lead to cardiovascular events. It is important to note that the various cardiovascular associations of PM_{2.5} differ regarding the duration of exposure (short vs long) to PM_{2.5}, the source of PM_{2.5}, and regulations regarding air pollution in the area where PM_{2.5} is prominent. Current strategies to reduce PM_{2.5} exposure include personal strategies such as avoiding high PM_{2.5} areas such as highways or wearing masks outdoors, to governmental policies restricting the amount of PM_{2.5} produced by organizations. This review, by highlighting the significant impact between PM_{2.5} exposure and cardiovascular health will hopefully bring awareness and produce significant change regarding dealing with PM_{2.5} levels worldwide.

1. Introduction

Air pollution has been associated with an increase in morbidity and mortality, not only in the United States, but around the world. Specifically, there have been many studies evaluating the effects of pollution on cardiovascular diseases (CVD), including myocardial infarction (MI), stroke, heart failure, and arrhythmias. PM_{2.5} refers to particulate matter in air that is less than 2.5 μm or less in diameter. This is significant because particulate matter that is less than 10 μm in diameter can be inhaled into the lungs and lead to adverse health effects [1]. In this review, we seek to elucidate the pathophysiological mechanisms by which exposure to particulate matter (PM_{2.5}) can result in adverse

cardiovascular outcomes, in addition to understanding the link between exposure to PM_{2.5} and cardiovascular events.

2. Pathophysiology

There is growing evidence to support that particulate matter such as PM_{2.5} is associated with cardiovascular disease. One of the mechanisms by which this may occur is through the small size, and large surface area per unit mass, of PM_{2.5} particles, allowing them to enter the systemic and pulmonary circulation [2,3]. A study conducted by Seaton and colleagues demonstrated that, once particulate air matter enters the pulmonary circulation, it causes inflammation which can then extend to

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the systemic circulation. Inflammation was measured by the release of inflammatory mediators and blood coagulation factors. The increased systemic inflammation can lead to hemostatic abnormalities, such as thrombosis or endothelial damage [4], potentially resulting in cardiovascular diseases such as stroke and myocardial infarction. A study by Kilinc and colleagues proposed a mechanism for the pro-coagulant properties of PM_{2.5}. They found how long-term exposure to particulate matter was mediated by factor XII driven thrombin formation [5]. Another proposed mechanism for PM_{2.5} causing endothelial dysfunction and inflammation is through NLRP3 inflammasome activation as shown by Hu and colleagues [6].

At the cellular level, it is hypothesized that PM_{2.5} may exert its detrimental effects by altering the function of the mitochondria. The mitochondria is often referred to as the “powerhouse” of the cell, owing to the fact that it performs many biologically significant functions, such as ATP production, lipid metabolism, and ion regulation [7]. It has been suggested that environmental toxins can alter mitochondrial DNA and alter gene expression, as they seem to accumulate more easily in mitochondria given the high membrane lipid profile of the mitochondria [8, 9]. In rat models, exposure to PM_{2.5} resulted in mitochondrial membrane dysfunction [10]. This dysfunction of the mitochondria can lead to cell death, which is a nidus for inflammation in different tissues. It is hypothesized that the mechanism for the inflammation is the release of mitochondrial DNA into the circulation, or via the generation of reactive oxygen species [11,12].

In terms of inflammation, it is hypothesized that particulate matter can propagate the human body’s natural inflammatory response through different mediators, such as reactive oxygen species, tumor necrosis factor, c-reactive protein and IL-6 [13]. Some research has also suggested that PM_{2.5} may have an effect on the autonomic nervous system. Increased arrhythmias have been reported with acute exposure to PM_{2.5}, which can lead to CVD such as heart failure [14]. Also, it has been shown that Transforming Growth Factor-Beta-containing small extracellular vesicles may promote cardiotoxicity through PM_{2.5} activation of macrophages [15].

A recent review conducted by Chen and colleagues sought to elucidate the various mechanisms in which PM_{2.5} could lead to ischemic stroke [16]. They cited a cohort study of 25,355 participants in China which found that platelet counts increased by 0.29 % for every 1 µg/m³ increase of PM_{2.5} exposure, with a stronger effect in male and non-DM participants [17]. In addition, a positive association between long-term PM_{2.5} exposure and mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P-LCR) has been documented [18]. There is some evidence that PM_{2.5} exposure causes abnormal miRNA expression in endothelial cells, resulting in fragile endothelial cells [19]. Finally, PM_{2.5} exposure induces neuroinflammation in astrocytes and microglia, which further aggravates neuronal damage [20].

Munzel and colleagues also looked at the various mechanisms in which PM_{2.5} could cause CVD [21]. They believed oxidative stress to be the common denominator in the various vascular effects of PM_{2.5}. Essentially the lung has a protective surfactant layer that includes proteins, lipids, and alveolar macrophages. PM_{2.5} may induce changes in the chemical structure of this surfactant layer, while promoting oxidative stress and the ability of particles to directly penetrate the lung [22].

3. CV risk

PM_{2.5} is associated with many clinical risk factors for cardiovascular disease, such as hypertension. Studies have shown that both acute and chronic exposure to PM_{2.5} levels can result in elevated blood pressure and hypertension [23,24]. Liang and colleagues examined 22 studies and found that there was an increase in systolic and diastolic blood pressure per 10 µg/m³ of PM_{2.5} by 1.393 mmHg and 0.895 mmHg respectively [25]. There are many proposed mechanisms by which PM_{2.5}

can lead to hypertension. One suggested mechanism is via the generation of reactive oxygen species which leads to impairment in nitric oxide (NO) mediated vasodilation. This lack of NO mediated vasodilation leads to vasoconstriction of blood vessels and thus hypertension [26,27]. In addition, it has been suggested that PM_{2.5} exposure can result in increased levels of endothelin-1, which is a known vasoconstrictor and can lead to endothelial dysfunction [28,29].

PM_{2.5} also may have an association with diabetes mellitus, which is an established risk factor for cardiovascular disease. He and colleagues found that for every 10 µg/m³ increase in PM_{2.5} levels, there was a 25 % increased risk of developing diabetes mellitus with long term exposure to PM_{2.5} levels [30]. Similarly, Chilian-Herrera and colleagues found that there was an association with increased PM_{2.5} levels and development of diabetes mellitus in individuals living in Mexico City [31]. What was interesting about this study was that it seemed to suggest that in areas with PM_{2.5} levels that exceed the guidelines set by the WHO (WHO guidelines recommend an annual PM_{2.5} Air Quality Guidance level of 5ug/m³), individuals living in those areas were more likely to develop diabetes mellitus. In terms of the mechanism behind PM_{2.5} exposure and development of diabetes mellitus, it is hypothesized that the cause may be insulin resistance secondary to oxidative damage, inflammation, and endothelial dysfunction [32–34].

Finally, it is hypothesized that PM_{2.5} levels is associated with hyperlipidemia. Li and colleagues in China found that reductions in PM_{2.5} levels were correlated with a decrease in LDL-C and total cholesterol levels [35]. Likewise, McGuinn and colleagues found that among cardiac catheterization patients residing in North Carolina, increases in PM_{2.5} levels were associated with an increase in lipoprotein concentrations [36]. Similarly, Zhang and colleagues found how PM_{2.5} leads to altered lipid metabolism which can then result in the development of atherosclerosis [37]. The specific mechanism for PM_{2.5} alteration of lipid metabolism seems to be caused by disturbances to the lipolysis and fatty acid oxidation pathways [38].

4. PM_{2.5} and MI

PM_{2.5} exposure has also been shown to cause myocardial infarctions (MI). A large meta-analysis conducted by Farhadi and colleagues analyzed 26 studies that evaluated the association between short term exposure to PM_{2.5} and the risk of developing myocardial infarction [39]. They found a 2 % increased risk of myocardial infarction with each 10 µg/m³ exposure to PM_{2.5} (RR = 1.02; 95 % CI 1.01–1.03; P < 0.0001). Similarly, Madrigano and colleagues sought to show that not only short term, but long term exposure to PM_{2.5} can be associated with MI. The study they conducted was a case-control study looking at residents living in Massachusetts who had developed MI between 1995 and 2003. This study found that long term exposure to PM_{2.5} was associated with an increased odds of MI [40]. An interesting study was conducted by Liao and colleagues, that sought to understand the cardiovascular effect of PM_{2.5} exposure on individuals with prior CVD history compared to individuals with no CVD history. They found that among individuals with prior stroke or MI, that these individuals were at increased risk of developing MI even when PM_{2.5} levels were less 12 µg/m³ [41]. This study highlights the importance of developing strict regulations in regards to PM_{2.5} levels worldwide in order to prevent the development of CVD. Confounding due to social determinants of health which frequently co-exist with higher levels of PM_{2.5} cannot be totally excluded to be at least partly responsible for the observed associations in these studies.

5. PM_{2.5} and stroke

PM_{2.5} exposure has also been associated with stroke. Rhinehart and colleagues sought to evaluate the risk of stroke in patients with Atrial Fibrillation who were exposed to PM_{2.5} levels. They found that for every 1 standard deviation increase in PM_{2.5} levels, there was an 8 % increased

risk of developing ischemic stroke [42]. Interestingly, O'Donnell and colleagues in Ontario, Canada looked at patient's hospitalized with ischemic stroke and who lived within 50 km of a PM_{2.5} monitor. They found no significant association with short-term PM_{2.5} exposure and risk of developing ischemic stroke. However, when they stratified patient's based on risk factors, they found that in individuals with diabetes mellitus that there was an 11 % increase risk of ischemic stroke [43]. This again highlights the significance of adverse CVD outcomes for individuals with CVD risk factors who are exposed to PM_{2.5}. A large systematic review and meta-analysis of 16 cohort studies that included over 2.2 million individuals found that long-term exposure to PM_{2.5} levels was associated with stroke. Yuan and colleagues found that the pooled hazard ratio (HR) for each 5 µg/m³ increment in PM_{2.5} was 1.11 (95 % CI: 1.05, 1.17) (CI for confidence interval) for incidence of stroke and 1.11 (95 % CI: 1.05, 1.17) for mortality from stroke [44]. Likewise, in China, Yang and colleagues found that for every 10 µg/m³ increase in PM_{2.5} levels, there was a 31 % increased risk of stroke mortality [45].

6. PM_{2.5} and heart failure

PM_{2.5} exposure has also been shown to be associated with heart failure. Shah and colleagues sought to evaluate the association between PM_{2.5} levels and development of heart failure and heart failure mortality. They evaluated 35 studies and found that increases in particulate matter exposure was associated with heart failure hospitalization or death. They hypothesized that an average reduction of PM_{2.5} levels by 3.9 µg/m³ in the US would result in 7978 fewer heart failure hospitalizations a year and would save the U.S. healthcare system a third of a billion dollars in expenses [46]. Similarly, a study in China sought to evaluate the role of PM_{2.5} exposure and heart failure in 26 large Chinese cities. They found that an interquartile range increase in PM_{2.5} levels was associated with a 1.3 % risk of heart failure hospitalizations [47]. Likewise, Wang and colleagues sought to understand the relationship between long term exposure to particulate matter and incidence of heart failure. They analyzed 432,530 patients from 2006 to 2010 and followed them until 2018. The hazard ratio [95 % confidence interval (CI)] of HF for a 10 µg/m³ increase in PM_{2.5} was 1.85 (1.34–2.55). These results indicated that long term exposure to PM_{2.5} was associated with an increased risk of heart failure [48]. Furthermore, Zhang and colleagues also provided more evidence for PM_{2.5} and increased risk of heart failure. In an analysis of 35 studies, for long-term exposure, the growing risk of HF was significantly associated with each 10 µg/m³ increase in PM_{2.5} (OR = 1.196, 95% CI: 1.079–1.326; I² = 76.8%) [49].

7. PM_{2.5} and cardiac arrhythmias

PM_{2.5} exposure is associated with many different types of cardiac arrhythmias, but the most notable one seems to be atrial fibrillation. Lee and colleagues found in a study conducted in Taiwan that there was a 22 % increased risk of atrial fibrillation in patients exposed to an interquartile increase of 26.2 µg/m³ in same day PM_{2.5} levels [50]. Wang and colleagues conducted a robust systematic review and meta-analysis of 16 observational studies including over 10 million individuals and found that PM_{2.5} levels had an adverse effect of causing atrial fibrillation among elderly individuals. Specifically, they found an increased odds of 11 % of atrial fibrillation per 10 µg/m³ of PM_{2.5} levels, and that the risk of atrial fibrillation was increased in areas that were exposed to a PM_{2.5} level of greater than 25 µg/m³ [51]. Likewise, it is hypothesized that individuals with high risk of cardiovascular deterioration are at an increased risk of developing atrial fibrillation when exposed to increased PM_{2.5} levels. Gallo and colleagues found this to be true as they evaluated patients with devices (CRT, pacemakers) and found that exposure to PM_{2.5} was associated with developing atrial fibrillation in these patients [52]. There is also some evidence that PM_{2.5} exposure can lead to ventricular arrhythmias as well. Data taken from the Penn State Child Cohort study and analyzed by He and colleagues found that a 10 µg/m³

increment in PM_{2.5} was associated with a 5 % (95 % CI, 1%–10 %) increase in premature ventricular contraction counts within 2 h after exposure [53]. In addition, there was some evidence provided by the European Society of Cardiology that PM_{2.5} exposure is related to the development of ventricular arrhythmias [54].

8. PM_{2.5} and CVD mortality

There have been many studies that have sought to analyze the relationship between PM_{2.5} levels and cardiovascular mortality. In general, it is hypothesized that the increasing level and duration of exposure to PM_{2.5}, the greater the risk of cardiovascular mortality there is. One study suggested that five percent of myocardial infarctions are caused by exposure to PM_{2.5} levels since millions of people around the globe are continuously affected. In the United States, the National Institutes of Health-AARP found that long term exposure to PM_{2.5} levels (in the range of 8–12 µg/m³) increased cardiovascular disease related mortality by a relative 10 % [55]. Likewise, in China a meta-analysis of 59 studies found that for every 10 µg/m³ increase in PM_{2.5} levels there was an 0.63 % increase in cardiovascular mortality. However, it should be noted that the PM_{2.5} levels ranged from 39 to 177 µg/m³ [56]. In addition, there have been studies in Canada that have shown that even relatively minimal levels of PM_{2.5} levels are associated with cardiovascular disease [57,58]. Given that exposure to PM_{2.5} and other particulate matter occurs throughout an individual's lifetime, it is plausible to support that the mechanism behind the cardiovascular mortality also occurs slowly throughout an individual's lifetime. One of the mechanisms proposed is that PM_{2.5} level exposure throughout a person's lifetime facilitates the development of atherosclerosis and thus predisposes individuals to cardiovascular disease [59]. Finally, Liu and colleagues analyzed daily mortality (total, cardiovascular, and respiratory) and air pollution data from 205 cities in 20 countries/regions. They found that a 10 µg/m³ increase in PM_{2.5-10} concentration on lag 0–1 day was associated with increments of 0.51 % (95 % confidence interval [CI], 0.18%–0.84 %), 0.43 % (95 % CI, 0.15%–0.71 %), and 0.41 % (95 % CI, 0.06%–0.77 %) in total, cardiovascular, and respiratory mortality, respectively. This suggested that short term exposure to particulate matter resulted in increased mortality [60].

9. Variability in effects as a function of particle size, source, and composition

Some PM_{2.5} health effects research has evaluated the variability in CVD health impacts as a function of fine particle size, source, and composition. For example, Thurston and colleagues, considering the large and well characterized ACS cohort, found that fossil fuel combustion PM_{2.5} (e.g., from coal burning and traffic) had a larger ischemic mortality effect per µg/m³ than PM_{2.5} from other sources, such as windblown soil and biomass (wood) burning [61]. Kazemparkouhi et al. found confirmatory variations in CVD mortality effects from PM_{2.5} exposure as a function of emission source in the nationwide Medicare population [62]. With regard to composition, Weichenthal and colleagues recently found that PM_{2.5} enriched in both sulfur and transition metals lead to greater particulate oxidative potential, consistent with PM_{2.5} of fossil fuel combustion origins [63]. With regard to size, sub-micrometer, and especially ultrafine particulate matter (<0.1 µm in diameter) have been found to have among the most toxic particulate matter [64,65].

10. Strategies to reduce PM_{2.5} exposure

Given the significant cardiovascular adverse outcomes associated with both short and long term exposure to PM_{2.5}, measures need to be undertaken to limit exposure. Carlsten and colleagues provided some suggestions on how best to do so [66]. One such measure that could be undertaken is to wear facemasks in high pollution cities [67]. However,

the effectiveness of facemasks is limited by factors such as facial hair, facial structure and type of mask used [68]. Another recommendation that could be implemented is for pedestrians to avoid taking travel routes that would expose themselves to heavy road-air pollution. It seems that the highest particle concentrations are often found in congested areas such as traffic interesections, partly due to the significant automobile exhaust present there [69]. This would expose individuals to lower amount of particulate matter, as was found in a study that looked at particulate exposure for cyclists biking in crowded interesections as compared to off road interesections [70]. Another recommendation would be to design cars that decrease the amount of toxic emissions. As the shift to more electric based vehicles is ongoing, one strategy to minimize exposure to the toxic fumes of cars would be to keep windows rolled up in traffic. A study found that while in traffic, opening car windows increased in-car cabin black carbon and UFP concentrations by 2–4-fold versus driving with windows closed [71].

11. Conclusion

In this review, we sought to illustrate the mechanism behind how PM_{2.5} results in adverse cardiovascular outcomes. Primarily, it is hypothesized that PM_{2.5} functions via 3 mechanisms: increased oxidative stress, activation of the inflammatory pathway of the immune system, and stimulation of the autonomic nervous system. These pathways promote endothelial dysfunction, atherosclerosis, and systemic inflammation that can thus lead to CVD such as heart failure, MI, stroke, and arrhythmias. This review found evidence that both short-term and long-term exposure to PM_{2.5} levels is associated with CVD outcomes such as mortality, stroke, heart failure, MI, and cardiac arrhythmias. Future studies are needed, and consensus opinion is warranted to try and elucidate an approach to minimize PM_{2.5} levels in areas that are densely inhabited by humans. In general, it is hypothesized that the lower the level of PM_{2.5} and the less time exposed, the lower the risk of developing cardiovascular complication. Nevertheless, given the lack of strict guidelines, it is imperative to have an expert consensus regarding what type and level of PM_{2.5} components constitute safe vs. unsafe exposures to PM_{2.5} levels, given the overwhelming evidence that particulate matter contributes to CVD morbidity and mortality.

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