Abstract: Background: Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in the elderly and the ambient concentration of PM$_{2.5}$ has been associated with several cardiovascular diseases. Methods: We describe the present state of planetary air pollution, analyze epidemiological studies linking PM$_{2.5}$ and CVD, and discuss multiple pathophysiological mechanisms linking PM$_{2.5}$ and CVD. Results: A few epidemiological studies show that the elderly appear specifically susceptible to adverse cardiovascular effects triggered by PM$_{2.5}$ exposure. Plausible pathophysiological mechanisms include inflammatory dysfunction, oxidative stress, abnormal activation of the hemostatic system and disturbance of the autonomic nervous system. Conclusions: An in-depth knowledge of the chemical compounds, pathophysiological mechanisms, and epidemiological studies of PM$_{2.5}$ are recommended to understand this important and modifiable factor contributing to geriatric CVD burden. We offer public health recommendations to reduce this preventable cause of disease and death.
1. Introduction

Cardiovascular diseases (CVD) include disorders of the heart (arrhythmias, coronary vessel and vascular disease, heart failure) and blood vessels (peripheral arterial diseases and venous thrombosis), particular those supplying the brain (ischemic and hemorrhagic stroke). Together, these disorders constitute the leading cause of death across the globe, with low- and middle-income countries most heavily affected. According to the World Health Organization (WHO), each year about 17.3 million people die of cardiovascular disease, accounting for 30% of all deaths [1]. In addition to genetic and behavioral risk factors (unhealthy diet, physical inactivity, tobacco, and alcohol use), the inhalation of air containing fine particulate matter (particle size less than or equal to 2.5 \( \text{μm} \)) is associated with CVD. Some researchers including Brook [2] have proven that PM\(_{2.5}\) is a modifiable exposure factor that contributes to cardiovascular morbidity and mortality. Elderly people have the highest rates of CVD and thus are the most susceptible population [3]. We discuss plausible PM\(_{2.5}\)-related pathophysiological mechanisms of CVD and epidemiological studies linking PM\(_{2.5}\) and CVD, especially in susceptible people, to make recommendations for future public health and reduce this avoidable cause of disease and death.

2. Review of PM\(_{2.5}\)

Atmospheric particulate matter (PM) is classified into four categories according to aerodynamic diameter: Total suspended particulate (TSP \( \leq 100 \ \text{μm} \)); particulate matter \( \leq 10 \ \text{μm} \); fine particulate matter \( \leq 2.5 \ \text{μm} \), and ultrafine particles \( \leq 0.1 \ \text{μm} \). PM\(_{2.5}\) refers to atmospheric particles with diameters less than or equal to 2.5 micrometers. The influence of PM on humans depends on particle size, which is linked with its aerodynamic diameter (AD) (Table 1). The range of most PM\(_{10}\) particles is from 2.5 \( \text{μm} \) to 10 \( \text{μm} \) while PM\(_{2.5}\) and PM\(_{0.1}\) have ADs \( \leq 2.5 \ \text{μm} \) and \( \leq 0.1 \ \text{μm} \). PM\(_{2.5}\) and PM\(_{0.1}\) particles may permeate the lung alveoli and enter into the bloodstream, and then cause adverse health effects [4–6]. Compared with PM\(_{10}\), PM\(_{2.5}\) has a small particle size, light quality and a relatively large specific surface area [7]. The smaller particle size may pose a higher risk for systemic cardiovascular effects [8].

| Particulate | Particle Size (\( \leq \text{μm} \)) | Influences on Human Health |
|-------------|----------------------------------|---------------------------|
| PM\(_{100}\) | 100                              | Persist in the air and no evidence of adverse effects on human health |
| PM\(_{10}\)  | 10                               | Enter the respiratory system, deposit in the respiratory tract and cause respiratory diseases |
| PM\(_{2.5}\) | 2.5                              | Get into the alveoli through the respiratory tract and then enter into the blood circulation, causing various diseases |
| PM\(_{0.1}\) | 0.1                              |                                                                         |
The major sources of particulate matter are broadly divided into two parts, human activities and natural phenomena, including wildfires, volcanoes, and land dust [9]. In addition, chemical reactions of primary emissions in the atmosphere cause the formation of secondary pollutants and the composition varies according to the pollution source [9–11].

We may recall the Great Smog event in London in December 1952, when severe air pollution from domestic and industrial coal burning caused thousands of excess deaths, especially among the very young and elderly, and led to the passage in the UK of the 1956 Clean Air Act [12,13]. Nowadays, PM$_{2.5}$ is considered the main culprit for the adverse effects of air pollution on human health [2]. PM$_{2.5}$ pollution affects the whole planet, particularly densely populated metropolitan areas of eastern and southern China, northern India, and the emerging countries of South-East Asia. Parts of Europe and America are not spared as well (Figure 1). The concentration of PM$_{2.5}$ in the area mentioned above may even exceed 100 $\mu$g/m$^3$ [14]. By contrast, in 2012, the revised annual arithmetic mean in the USA was 12 $\mu$g/m$^3$ for primary PM$_{2.5}$ and 15 $\mu$g/m$^3$ for secondary PM$_{2.5}$, with a 24-hour 98th percentile value of 35 $\mu$g/m$^3$ for both [15].

![Figure 1. The global distribution of PM$_{2.5}$ averaged over 2001–2006 (Credit: Dalhousie University, Aaron van Donkelaar, http://www.nasa.gov/topics/earth/features/healthappoing.html).](image)

3. Plausible Pathophysiological Mechanisms Linking PM$_{2.5}$ Exposure and CVD

Several studies suggest that the elderly are especially susceptible to the harmful effects of PM exposure [2]. Older adults also represent a potentially susceptible population compared with children or younger adults because of the higher prevalence of preexisting cardiovascular and respiratory diseases. Epidemiological studies assessing the relationship between air pollution and CVD have appeared in the past 20 years [16]. High concentrations of PM$_{2.5}$ have been associated with morbidity and mortality in both short- and long-term epidemiological studies [17].

Air particulate matter enters the human body mainly in two ways: (1) PM$_{2.5}$ enters the respiratory system causing pulmonary and systemic inflammation, oxidative stress, affecting the coagulation system, changing autonomic nerve function, injuring the vascular endothelium and affecting vasomotor function; (2) Part of the particulate matter causes the above reaction through other routes, such as entering into the circulatory system via the digestive tract. Animal studies have shown that
PM$_{2.5}$ can be devoured by macrophages and endothelial cells, indicating that air pollution may have direct effects on the vascular system [4–6,18].

The relationship between air pollution and respiratory diseases, such as asthma and chronic obstructive pulmonary disease, is well established. Nevertheless, the relationship between air pollution and CVD remains unclear. The plausible pathophysiological mechanisms can be divided into the following several aspects [19].

3.1. Oxidative Stress and Inflammation

Both animal and human studies [20–24] have shown that inhaled particles may cause inflammation of the respiratory tract; in particular, PM$_{2.5}$ inhalation can lead to the occurrence of systemic inflammation, increasing the risk of cardiovascular stress. PM$_{2.5}$ can enter the alveolar epithelium, cause local inflammation and oxidative stress, resulting in the release from lung cells into bronchial fluid and the blood stream of several inflammatory mediators, such as IL-6, IL-8, TNF-$\alpha$ and interferon-$\gamma$ [25]. These spread to the general circulation where they can plausibly modulate systemic effects. When mice are exposed to PM$_{2.5}$ for six hours, there is increased expression of inflammation-related genes such as mRNA of TNF-$\alpha$, TNF-$\beta$ and IL-6, IL-8. A recent study finds that IL-6 can make a rapid response to air pollution and increase the production of C-reactive protein (CRP) [26]. CRP is the most important protein in acute phase reactants (APR), and it is also a sensitive indicator of inflammation associated with the risk of cardiovascular disease. Blood CRP increases in proportion to the concentration of PM$_{2.5}$; for every increase of 100 $\mu$g/m$^3$, blood CRP increases 8.1 mg/L [27]. Interestingly, coarse PM has been suggested to directly trigger inflammation by binding to toll-like receptor (TLR) 2 and 4 [28]. Higher TLR2 methylation may confer susceptibility to adverse cardiac autonomic effects of PM$_{2.5}$ exposure in older individuals [29].

3.2. Abnormal Activation of the Haemostatic System

Another probably detrimental effect of PM$_{2.5}$ exposure is an abnormal activation of the hemostatic system. Epidemiological studies have associated PM$_{2.5}$ inhalation with venous thrombosis and a shorter prothrombin plasma-clotting time. The diffuse pulmonary inflammation caused by PM$_{2.5}$ may spread to the circulatory system, causing abnormal activation of the hemostatic system [30]. Animal models and in vitro cell studies show that PM$_{2.5}$ increases fibrinogen and tissue factors [31], and fine particulate matter in blood vessels can directly activate platelets. Platelets play an important role in thrombus formation and can make the blood hypercoagulable states. PM$_{2.5}$ exposure may increase the risk of acute thrombosis, as in myocardial infarction and ischemic stroke. At the same time, fibrinogen is also an important risk factor for stroke [32].

3.3. Disturbance of Autonomic Nervous System

PM particles disturb the autonomic nervous system (ANS) [33]. Under normal circumstances, the rhythmic activity of the heart is controlled by the activity of autorhythmic cells in the sinoatrial node, which is regulated by the vagus nerve. Acute exposure to PM$_{2.5}$ can stimulate the ANS and increase the risk of arrhythmia and acute cardiovascular events, with serious impact on the elderly [34]. A number of studies in a recent meta-analysis support an inverse association between PM exposure and
heart rate variability [35]. Heart rate variability (HRV) refers to the cyclical changes of sinus rhythm, and it is an important index of tonicity and sympathetic-parasympathetic balance. Some research finds that exposure of PM$_{2.5}$ is linked with HRV change in the elderly. Compared with exposure to clean air for two hours, HRV drops 35.7% after inhalation of 21.2–80.3 $\mu$g/m$^3$ PM$_{2.5}$ [36]. Moreover, in a 48-hour moving average, PM$_{2.5}$ was found to have a strong effect on the decrement in HRV [37]. Additionally, the effects of PM$_{2.5}$ on subjects with hypertension were larger than on the subjects without hypertension [38]. The decrease of HRV reflects direct perturbation of the cardiac autonomic nervous system, and may serve as a prelude to heart disease.

3.4. Injury of Endothelial Cells

Because vascular endothelial injury is an important pathological basis of cardiovascular disease, the damage of vascular endothelial cells by PM$_{2.5}$ is one possible CVD mechanism. Cardiovascular endothelial cells treated in vitro with PM$_{2.5}$ for 24 hours display adhesion molecules and apoptosis [39]. Cell mortality rates increase with PM$_{2.5}$, suggesting that PM$_{2.5}$ may damage the vascular endothelium, thereby causing CVDs. Recently, some studies suggest that specific metals may be important components responsible for PM$_{2.5}$-induced cardiovascular effects and that the reduced capacity of endothelial repair may play a critical role [40].

4. Epidemiological Studies Linking PM$_{2.5}$ and CVD in the Elderly

Though several studies have shown exposure to PM$_{2.5}$ can increase risk of CVD [2,19,41–57], few studies focused on the elderly, one of susceptible subpopulations, Kan et al. found that risk of CVD exposed to PM$_{10}$ increased 0.26%, compared with people 5–44 years of age or 45–64 years of age[58,59]. Another Chinese studies in Beijing showed that ambient PM$_{2.5}$ adversely affected cardiac autonomic function of the elderly people with heart diseases [38]. Dominici and colleagues analyzed acute effect of fine particulate air pollution on elderly people (age > 65 years) and found that the largest association between PM$_{10}$ and congestive heart failure, a 0.72% increase in risk per 10 $\mu$g/m$^3$ elevation in same-day PM$_{10}$ concentration [49]. This is more than the results reported by Brook with an increasing of 0.18% in the general population [2]. However, annual average exposure to higher levels of black carbon (per 0.26 $\mu$g/m$^3$ elevation), a marker of traffic-related PM, was associated with a 1.1% increase in carotid intima media thickness (CIMT) in a cohort of elderly men living in the Boston area [60]. Short-term PM exposure has been more strongly associated with cardiac mortality among older individuals [61]. In an elderly population (aged 65 and older) across Eastern USA, researchers found that both short-term and long-term exposure were significantly associated with risk of deep vein thrombosis (DVT) [62]. While the majority of studies and expert-consensus opinions consistently agree that PM$_{2.5}$ can increase the risk of CVD, it is noteworthy that some studies had not find relationships between PM$_{2.5}$ and risk of CVD [63–66].

5. Conclusions

From a point of pathophysiology, the elderly is a susceptible population to cardiovascular injury by PM$_{2.5}$ and a few epidemiological studies showed more risk of CVD increased in the elderly exposed to the same levels of PM$_{2.5}$. Due to increasing of PM$_{2.5}$ level and aged populations, more attention should
be paid to CVD risk and PM$_{2.5}$ exposure in the elderly. In addition, the relationship between PM$_{2.5}$ concentration and CVD risk appears not to have a “safe” threshold. The “alarm” threshold periodically claimed by regulatory agencies during certain seasons should therefore be considered advisory, and efforts should be made to keep level of pollutants as low as possible [2]. Thus, besides of reducing air pollution, avoidance of exposure to PM$_{2.5}$ pollution and societal and personal measures to reduce other risk factors should be recommended for the elderly [67,68]:

- Walking or cycling in parks or country roads instead of busy streets during rush hours.
- Using more public transport rather than private cars and motorbikes.
- Avoiding outdoor exercise at times of high PM$_{2.5}$ (especially those with cardiorespiratory disorders).
- Using an air purifier to optimize indoor air quality.
- Choosing appropriate respirators that fit snugly on the face if air pollution is severe.
- Reducing other known cardiovascular risk factors, such as smoking and alcohol.
- Warranting more aggressive use of primary and secondary preventive therapies, including antiplatelet agents, lipid-lowering agents, and treatments for hypertension or diabetes.

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Author Contributions

Chenchen Wang and Yifan Tu drafted the manuscript. Chenchen Wang and Yifan Tu provided key input in the literature search and contributed equally to the article. As the mentor, Rongzhu Lu oversaw idea formation, editing and coordination. Zongliang Yu reviewed and edited the manuscript focusing on assessment of clinical data. All authors read and approved the manuscript.

Conflicts of Interest

The authors declare that they have no competing interests.

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