

Air particulate matter and cardiovascular disease: the epidemiological, biomedical and clinical evidence

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Abstract: Air pollution is now becoming an independent risk factor for cardiovascular morbidity and mortality. Numerous epidemiological, biomedical and clinical studies indicate that ambient particulate matter (PM) in air pollution is strongly associated with increased cardiovascular disease such as myocardial infarction (MI), cardiac arrhythmias, ischemic stroke, vascular dysfunction, hypertension and atherosclerosis. The molecular mechanisms for PM-caused cardiovascular disease include directly toxicity to cardiovascular system or indirectly injury by inducing systemic inflammation and oxidative stress in peripheral circulation. Here, we review the linking between PM exposure and the occurrence of cardiovascular disease and discussed the possible underlying mechanisms for the observed PM induced increases in cardiovascular morbidity and mortality.

Keywords: Particulate matter (PM); cardiovascular disease; morbidity; mortality

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Introduction

Air pollution has now emerged as a leading problem for environmental health in the world. Especially in developing countries, it has become more serious than ever before. The potentially detrimental to health of air pollution has long been recognized, and many large epidemiological studies have clearly demonstrated the strong association between air pollution exposure and increased morbidity and mortality (1-3). Air pollutants include gaseous pollutants (e.g., carbon mono oxide, oxides of nitrogen, ozone and sulfur dioxide) and particulate matters (PMs). The relationship between respiratory vulnerability and air pollution has been well documented, and much attention has now been focused on the air pollution-induced cardiovascular risk in the past 15 years (4-6). Of those air pollutants, the ambient PM has become a major concern for cardiologists and

specialists in environmental medicine. There is a mounting epidemiological, biomedical and clinical evidence that indicates the effects of ambient PM on cardiovascular health (5,7,8). In this review we summarize the main findings on the impact of PM particles on cardiovascular system and discuss the underlying molecular mechanisms of the effects of PM particles on cardiac muscle and vasculature.

The definition and composition of ambient particulate matter (PM)

Ambient PM is defined as the material suspended in the air in the form of minute solid particles or liquid droplets, which are derived from both human and natural activities. It is a heterogeneous mixture with varying size and chemical composition. In terms of their potential

influence on health, they are classified as PM₁₀, PM_{2.5} and ultrafine particles (UFPs) subgroup according to their diameter. PM₁₀ includes coarse particles with the aerodynamic diameter (AD) from 2.5 to 10 μm . The PM₁₀ particles come from road and agricultural dust, tire wear emission, construction and demolition works or the mining operations (8). In addition, the natural activity such as wildfires and windblown dust are also the sources for PM₁₀. Compared to PM₁₀, the primary contributors of PM_{2.5} mainly come from the traffic and industry includes fuel combustion from power plant and oil refinery or the brake emissions of mobile. PM_{2.5} indicates those fine particles with AD less than 2.5 μm . Based on numerous epidemiological studies and large clinical observation, the PM_{2.5} has been considered as the main culprit of the adverse cardiovascular effects of air pollution on human health (5,6). UFPs include those particles diameters less than 0.1 μm , and the primary sources of UFPs are tailpipe emissions from mobile sources. Theoretically, PM₁₀ particles preferentially deposit in the upper airways, meanwhile the PM_{2.5} and UFPs particles are much more easier to reach the smallest airways and alveoli and UFPs may further penetrate the alveolar-capillary membrane, which eventually spread into the systemic circulation. It has been reported that the UFPs particles can be found in remote organs (9). This finding may indicate that UFPs could induce specific organ toxic effects. In addition, the secondary particular matters, ambient aerosols appear when ambient particles interact with atmospheric gases (ozone, sulfur and nitric oxides and carbon monoxide) (8). Each of those aerosols can have independent and potentially synergistic or antagonistic effects with each other and with PM; however, at present, the cardiovascular health impact of exposure to combinations of those air pollutants is not well understood (5).

Pathophysiological mechanisms linking particulate matter (PM) particles and cardiovascular disease

In the past 15 years, numerous studies and in-depth reviews have demonstrated that PM particles play a significant role in the process of cardiovascular disease. *Table 1* summarizes the most recent studies [2014-2015] on PM-induced short-term and long-term cardiovascular effects. There is a strong link between the PM particles and the deaths caused due to cardiovascular diseases (4,21,28,31-33), and several pathways have recognized that can explain the link between PM particles

and cardiovascular diseases, the first is the direct pathway. In this way, PM_{2.5}, in particular UFPs directly translocate into the blood stream and remote target organ, and the other two pathways are indirect. For the indirect pathways, the one is mediated by pulmonary oxidative stress and inflammatory response, which is less acute and occur after several hours or days of inhalation (6,34). Interaction on the autonomic nervous system via specific lung receptors is another indirect pathway well documented by many authors (6,8).

Direct actions of ultrafine particles (UFPs) on cardiovascular system

Due to the size, charge, chemical composition of UFPs, it is much easier to cross the pulmonary epithelium and the lung-blood barrier than PM₁₀ and other coarse particulate. Thus, the translocation of UFPs into the blood stream and specific organ has been documented in animal studies (35-39). This exposure, even at low concentration, can translocate into blood stream and remote organ to cause potential cumulative toxicity (39). The translocation of UFPs to the blood stream has detrimental effects on cardiovascular system. After deposit on vascular endothelium, the UFPs can aggravate the local oxidative stress and inflammation, resulting the atherosclerotic plaque instability, and finally may lead to thrombus formation (40). Furthermore, increased ejection fraction and premature ventricular beats was observed in rats intravenously injected with UFPs isolated from ambient air (41). This inotropic effect of UFPs may be harmful to coronary heart disease patients, which increase the oxygen demand of the diseased hearts and aggravate the ischemic symptom. However, the *in vitro* results of UFPs on cardiac performance demonstrated that the UFPs have the cardiac depression effects, which can cause myocardial stunning and cardiac function deterioration (42). The seemed contradictable *in vivo* and *in vitro* results might be explained as the difference in circulation-mediated or direct cardiotoxicity of UFPs in these two models (8). Although not observed in human beings so far, these studies still indicated that UFPs has the cardiotoxicity effects and can directly affect the cardiac performance.

Indirect pathways of particulate matter (PM) particulates on cardiovascular system

Increased oxidative stress and activated inflammatory pathway in pulmonary due to exposure to PM particulate play a substantial role in this indirect pathway. Considerable

Table 1 The representative recent studies [2014–2015] on the short-term and long-term effects of exposure to PMs on cardiovascular system

Studies	Study population	Main findings
Short-term exposure studies		
Li <i>et al.</i> (10)	Case-crossover study in eight Chinese large cities	An increase of 10 $\mu\text{g}/\text{m}^3$ in 2-day moving average concentrations of PM ₁₀ , SO ₂ and NO ₂ , was significantly associated with increases of daily CHD mortality
MONICA/KORA study (11)	Case-crossover study of 15,417 MI cases in Germany	An association between short-term PMs concentration and numbers of MI, especially for nonfatal and recurrent events
MCAPS (12)	12-year of time series study in USA	Daily variation in PM _{10-2.5} is associated with emergency hospitalizations for cardiovascular diseases among elderly population (≥ 65 years)
MED-PARTICLES project (13)	Case-crossover study in ten southern European cities	Wildfires and PM ₁₀ were associated with increased cardiovascular mortality in urban residents
Chang <i>et al.</i> (14)	Case-crossover study in Taiwan from 2006–2010	Higher levels of PM _{2.5} enhance the risk of hospital admissions for CVD on cool days ($< 25^\circ\text{C}$)
EPHT program (15)	Case-crossover study in seven US states within the CDC EPHT network	Multiple cardiovascular outcomes in addition to AMI may be impacted by particulate air pollution in state-wide
MINAP (16)	Case-crossover study of over 400,000 MI events in England and Wales	The strong associations with air pollution were observed with selected non-MI CVD outcomes, while no clear evidence was found for pollution effects on STEMIs
Zhao <i>et al.</i> (17)	Time-series study of 56,940 outpatient in China	A 10 $\mu\text{g}/\text{m}^3$ increase in the present-day concentrations of PM ₁₀ , SO ₂ , and NO ₂ corresponded to increases of 0.56%, 2.07%, and 2.90% in outpatient arrhythmia visits
Raza <i>et al.</i> (18)	Case-crossover study of 5,973 cases in Stockholm county from 2000–2010	Short-term exposure (in 2 h) to moderate levels of O ₃ is associated with an increased risk of out-of-hospital cardiac arrest (OHCA)
Bell <i>et al.</i> (19)	Time-series study of aged persons from four countries in USA	PM _{2.5} total mass and PM _{2.5} road dust were associated with increased cardiovascular hospitalizations, as were the PM _{2.5} constituent calcium, black carbon, vanadium, and zinc
Long-term exposure studies		
MESA project (20)	Time-series study in USA from 2000 to 2012	Long-term exposure to air pollution is related to the markers of inflammation and fibrinolysis
Qin <i>et al.</i> (21)	Cross-sectional study of 24,845 adults in Northeastern metropolitan China	Being overweight and obese may enhance the effects of air pollution on the prevalence of CVDs
Wolf <i>et al.</i> (22)	Cohort study of 100,166 persons in European followed on average for 11.5 years	A 100 ng/m^3 increase in PM ₁₀ and a 50 ng/m^3 increase in PM _{2.5} were associated with a 6% and 18% increase in coronary events
Wong <i>et al.</i> (23)	Cohort study of 66,820 aged persons in Hong Kong followed for 4 years	Mortality HRs per 10 $\mu\text{g}/\text{m}^3$ increase in PM _{2.5} were 1.22 for cardiovascular causes and 1.42 for ischemic heart disease
Chan <i>et al.</i> (24)	Cross-sectional study of 43,629 women in USA	Long-term PM _{2.5} and NO ₂ exposures were associated with higher blood pressure (BP)
Pope <i>et al.</i> (25)	Cross-sectional study of 669,046 participants in USA	Long-term exposure may contribute to the development or exacerbation of cardiometabolic disorders, increasing risk of CVD, and cardiometabolic disease mortality
Kim <i>et al.</i> (26)	Cross-sectional study of 5,488 MESA participants in USA	Long-term concentrations of sulfur and OC, and possibly silicon, were associated with CIMT
Wilker <i>et al.</i> (27)	Cohort study of 5,112 participants in the Framingham Offsprings.	Higher levels of spatially PM _{2.5} at participant residences are associated with impaired conduit artery and microvascular function in middle-aged and elderly adults
Weichenthal <i>et al.</i> (28)	Cohort study of 83,378 participants in the USA	Rural PM _{2.5} may be associated with cardiovascular mortality in men, but not in women
Beelen <i>et al.</i> (29)	A joint analysis of data from 22 European cohorts consisted of 367,383 participants	Most hazard ratios for the association of air pollutants with mortality from overall CVD and with specific CVDs were approximately 1.0
Zhou <i>et al.</i> (30)	Prospective cohort study of 71,431 middle-aged Chinese men	Each 10 $\mu\text{g}/\text{m}^3$ PM ₁₀ was associated with a 1.8% increased risk of cardiovascular mortality

PM, particulate matter; MI, myocardial infarction.

evidence has proved that particulate air pollutants can trigger an inflammation related cascade when they deposit in the lung (43-46). Increased circulating level of pro-inflammatory cytokines such as CRP, IL-6, IL-8 and IL-1 β were observed in healthy subjects when exposure to ambient PMs (46-50). Similar results have been reported in *in vivo* animal models and *in vitro* cellular models (51,52). Systemic inflammation is a well-known risk factor for atherosclerosis progression, and those pro-inflammatory mediators are close related to increased blood coagulability and endothelial dysfunction and which finally can exacerbate myocardial ischemia. In addition, ROS-dependent mechanism was shown to involved in the PM particulates triggered pro-inflammatory pathway (47). Increased amounts of ROS were reported in rat lung and heart by means of *in situ* chemiluminescence after exposure to PMs (47). ROS was shown to be linked to atherosclerosis, vascular dysfunction, cardiac arrhythmias and myocardial injury (53,54).

Other mechanisms for particulate matter (PM)-induced cardiovascular disorders

In addition to the sizes of PMs, the quality of PMs (components) also played an important role in PM-related harmful effects. The components of PMs varies spatially and temporally, which includes health hazardous metals, such as copper, lead, iron, nickel and chromium originate from industrial combustion processes or traffic combustion. Other gaseous pollutants (e.g., CO, NO₂, NO_x, O₃ and SO₂ etc.) have also been demonstrated to be close related to the adverse outcomes of cardiovascular disease (10,17,18,24,26).

Furthermore, PM particulates are thought to stimulate autonomic nervous system (55), impairing autonomic balance and favoring sympathetic tone (56). The over activated sympathetic tone is closely related to increased cardiovascular risk through induction of pro-hypertensive vasoconstriction and the predisposition to arrhythmias (56). Recently, microRNAs (miRNAs) have emerged as attractive candidates to explore the impact of PM exposures on cardiovascular system (57,58). Experimental and clinical studies indicated that PMs can modulate those miRNAs involved in processes of systemic inflammation, endothelial dysfunction and atherosclerosis. Meanwhile, SNPs in miRNA-processing genes may also modify the associations between ambient pollution and cardiovascular disease (58,59). However, further work remains need to be addressed include linking specific PM exposures to subsequent health outcomes based on established miRNA

expression profiles and experimentally validating putative downstream targets of the deregulated miRNAs.

The linking between ambient particulate matters (PMs) and cardiovascular disease

Cardiovascular (CV) mortality and particulate matter (PM) particulates exposure

The positive relationship between CV mortality and PM particulates exposure has been proved in many large time-series and case-crossover studies. Even a 10 $\mu\text{g}/\text{m}^3$ increase in short-term (<24 h) PM_{2.5} level increases the relative risk (RR) of daily cardiovascular mortality by ~0.4% to 1.0% (60). In addition, several landmark time-series studies have been conducted worldwide in recent years to address the daily PM-related CV and all-cause mortality. One of the largest was the National Morbidity, Mortality and Air Pollution Study (NMMAPS) (61,62). The APHEA (Air pollution and Health: A European Approach) and APHEA-2 projects investigated the relationship between short-term PM exposure and CV mortality in multiple European cities (63,64). Those large studies revealed that PM particulates including the coarse particulates, PM₁₀, were significantly associated with daily all-cause and CV mortality. Similar time-series studies conducted in Asia countries (China, Thailand and Indian) further confirmed the relationship between the daily PM-exposure and CV mortality (65-67).

In addition to the short-term exposure of PM particulates, the longer-term exposure may have more deleterious effects on healthy and cardiovascular mortality giving the more accumulated PM exposure during the extended periods of time. Miller *et al.* revealed that long-term exposure to fine particulate air pollution was associated with the incidence of cardiovascular disease and death among postmenopausal women based on the data from 36 USA metropolitan areas (33). Many large prospective cohort studies and fine meta-analysis have further provided us with clear answers on the correlation between longer-term PM-exposure and CV mortality (29,68,69). However, a most recent large cohort study performed by Beelen *et al.* (29) did not found any association between PM and cardiovascular mortality. The explanation for the difference between this study and those of previous studies may be because of the changes in cardiovascular risk profile (e.g., reduced smoking and increased medication and medical treatment). And the changed risk profile finally altered the relationship between

air pollution and cardiovascular mortality. The extended reanalysis of the two large cohort studies—the Harvard Six Cities and ACS Studies further emphasized the notorious effects of PM_{2.5} on CV mortality (2,32,70). Furthermore, studies demonstrated that significantly reduction of PM_{2.5} level was associated with reduced mortality risk (70,71). However, unlike the results observed in short-term exposure studies, the reanalysis of ACS study demonstrated that the coarse particles (PM₁₀) were generally not significantly related to CV mortality (32).

Ischemic heart disease (IHD) and particulate matter (PM) particulates exposure

An earlier hospital-based study (72) demonstrated that the incidence of myocardial infarction (MI) and angina was found to associate with atmospheric gases and/or black smoke. Another studies conducted in USA (4-year in 204 counties) and European (10-year in five major cities) indicated that hospital admission for IHD were positively associated with increased level of fine PM particulates (73,74). Furthermore, a very recent large prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE project confirmed that long term exposure to PM is associated with incidence of coronary events, and this association persists at levels of exposure even below the current European limit values (25 µg/m³ for PM_{2.5}, 40 µg/m³ for PM₁₀) (75). They concluded that with a 5 µg/m³ increase in estimated annual mean PM_{2.5} was associated with a 13% increased risk of coronary events (HR 1.13, 95% confidence interval 0.98 to 1.30), and a 10 µg/m³ increase in estimated annual mean PM₁₀ was associated with a 12% increased risk of coronary events (1.12, 1.01 to 1.25). In California teachers cohort study (76), Lipsett *et al.* provided evidence linking long-term exposure to PM_{2.5} with increased risks of incident IHD mortality, particularly among postmenopausal women. Meanwhile, exposure to nitrogen oxides was also associated with elevated risks for IHD and all cardiovascular mortality. In addition to the long-term effects of PM on IHD, short-term elevated ambient fine PM concentrations has also been reported to increase the IHD hospital admission, which was further proved by numerous time-series, case-crossover and meta-analysis studies (69,77,78). Recently a large cohort study investigated the relationship between occupational particle exposure and the incidence of IHD in Swedish workers. They found that either exposure to a small job-

exposure matrix (<1 µm) or large (>1 µm) was associated with an increased HR for acute MI, and the association was somewhat stronger for those exposed to small particles for more than 5 years (79).

Although few direct evidence for the induction of cardiac ischemia by exposure to ambient level of PM has been documented in real patient world, the experimental MI model provided more evidence linking PM exposure and increased infarct size and/or potential myocardial ischemia (80-82). The mechanisms for PM exposure induced myocardial ischemic injury can be attributed to increased systemic inflammation, altered endothelial function and enhanced thrombotic tendency (80,83). In addition, the PM exposure was found to be associated with a small but significant decrease in myocardial flow, especially in ischemic area in a conscious canine myocardial ischemic model (82). Moreover, traffic-related PM in patients with coronary artery disease was found to be strongly related to the incidence of ST-segment depression during 24-hour Holter monitoring.

Cardiac arrhythmias, out-of-hospital cardiac arrest (OHCA) and particulate matter (PM) particulates exposure

Several studies have observed a positive association between exposure to ambient PM and the incidence of ventricular arrhythmias in patients implanted with automatic defibrillators (84,85). A 5-year prospective study (86) in Taipei demonstrated that increased numbers of emergency room cardiac arrhythmia visits were significantly associated with PM_{2.5} on both warm days (>23 °C) and cool days (<23 °C), with an interquartile range rise associated with a 10% and 4% elevation in number of ER visits for cardiac arrhythmias, respectively. Very recently, another prospective follow-up study evaluated the association of air pollution with the onset of atrial fibrillation (AF) in 176 patients with dual chamber implantable cardioverter-defibrillators (ICDs). The authors revealed that PM_{2.5} is an acute trigger of AF, which was associated with increased odds of AF onset [26% (95% CI: 8-47%) increase for each 6.0 mg/m³ increase in PM_{2.5} concentration] within hours following exposure in patients with known cardiac disease (87). Similarly, PM_{2.5} or fine PM-exposure has been reported to be associated with OHCA in Melbourne (88), Houston (89), New York (90), and many other cities or countries but not in Demark (91) and Seattle (92). These seemed inconsistent results may reflect different PM compositions due to different sources among the cities and countries. Furthermore, the lower

exposure levels in Demark and Seattle than in New York and Houston should also be considered.

In general, the incidence of sudden cardiac death and cardiac arrhythmias is closely related to the activity of the autonomic nervous system, and its activity in susceptible patients can be evaluated by measuring the changes in heart rate variability (HRV). HRV is mediated by a balance between sympathetic and parasympathetic branches of autonomous nervous system (34), which is recognized as a marker for prognosis the incidence of ventricular arrhythmia. Reduced HRV often predict the likelihood of developing ventricular arrhythmias in post-MI and heart failure patients (93,94). The reductions in HRV were observed on exposure to ambient, household or occupational PMs in healthy volunteer, susceptible patients, housewives and workers (95-97). In the studies in Beijing, the authors demonstrated an increase in HRV in healthy volunteers and CHD patients when exposure to ambient PM particles. On the contrary, the protective effects were observed when the participants used the highly efficient facemask (98,99). Although the mechanisms for PMs induced HRV and other changes in ECG remain largely unknown, some studies demonstrated that PM-induced cardiac electrophysiological changes can be prevented by inhibiting the transient receptor potential vanilloid receptor 1 (TRPV1) in the lungs (100). In addition, there have been relatively few researchers studied on the gene-PM exposure interactions, and most have done on a small number of loci for genetic polymorphisms. Some authors indicated that the associations between PM_{2.5} and HRV can be modified by gene polymorphisms of apolipoprotein E (APOE), lipoprotein lipase (LPL), vascular endothelial growth factor (VEGF) and glutathione S-transferase (GST) in general population, and the biological metabolism for PM related HRV changes might be related to the action on autonomic function via the lipid/endothelial metabolism and oxidative stress pathways (101,102).

Vascular function, blood pressure (BP), atherosclerosis and particulate matter (PM) particulates exposure

Experiments demonstrated that PM particulates can cause excess ROS formation thus leading to impairment of nitric oxide-dependent vascular dilation and enhancing vasoconstrictor in ex vivo and *in vivo* studies (5,103). Furthermore, exposure to PM has found to be associated with an increase in plasma concentration of endothelin-1 (ET-1),

which is a putative potent endogenous vasoconstrictor to cause vascular endothelial dysfunction (104,105). Although the PM-related vascular dysfunction is documented in many articles, the results for BP response to acute PM exposure is inconsistent. Some controlled studies reported that PM exposure cause no changes among healthy adults, while other recent findings suggested that actual period of exposure to concentrated ambient particulate (CAP) significantly increase the diastolic BP (106), whereas no changes was observed with longer time of exposure (24 h) to PM (107). In that, those results suggested that this CAP induced BP changes might be more related to the PM-induced ANS imbalance which favored sympathetic over parasympathetic cardiovascular tone.

Although a recent meta-analysis from four European cohort studies in the ESCAPE study only find a positive but not significant associations between CIMT and long-term exposure to the PM_{2.5} (108), many epidemiological and animal evidences still documented that exposure to PMs plays a role in the development of atherosclerosis. Sun and his colleague demonstrated that exposure to environmentally relevant PM_{2.5} (regional northeastern of US) in conjunction with a high-fat chow diet in ApoE^{-/-} mice for 6 months can cause endothelial dysfunction, increase the vascular plaque burden and accelerate the progression of atherosclerosis (109). The same results were reported in Beijing, Los Angeles and many other places when the ApoE^{-/-} mice were exposure to the local ambient particle (110,111). To investigate the relation between individual-level estimates of long-term air pollution exposure and the progression of subclinical atherosclerosis, a large prospective, multicenter study named Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air) was initiated in 2004. That study demonstrated that long-term PM_{2.5} exposure was significantly associated with decreased endothelial function with increased IMT progression even over a relatively short follow-up period, which add to the literature on air pollution and the progression of atherosclerotic processes in humans (112,113). Even more, the authors observed that the slower IMT progression was related to greater reductions in PM_{2.5}. A very recent study recalled the data [2000-2003] from the German Heinz Nixdorf Recall Study, which included a population-based cohort of 4,814 randomly selected participants. The study used a reliable indice, the thoracic aortic calcification (TAC), to evaluate the subclinical atherosclerosis. Their results demonstrated that long-term exposure to fine PM is independently associated with subclinical atherosclerosis (114). Taken together,

these findings may elucidate important pathways linking air pollution to the development of atherosclerosis.

Thrombus formation, blood coagulation and particulate matter (PM) particulate exposure

In vivo as well as *in vitro* studies demonstrated that PM particulates can induce pro-thrombotic effects by producing inflammatory mediators in the lungs and releasing into the blood circulation or directly translocation of small particulates from lung to the circulation. Nemmar *et al.* revealed that exposure of hamster to the diesel exhaust particles after photochemical injury resulted in platelet function abnormalities and thrombus formation both in arteries and veins (115). Mutlu GM and his colleague using IL-6 knockout (KO) mouse model demonstrated that IL-6 and its downstream signaling pathway plays a pivotal role in PM-induced prothrombotic state by increasing the expression of fibrinogen, factor VIII and tissue factor (TF), thus increasing the risk of both venous and arterial thrombosis (34,116). Furthermore, they also found that the prothrombotic effect of PM was further mitigated in macrophage-depleted mice (116). Those results may suggest that IL-6, macrophage and pulmonary inflammation are the necessary initial steps for PM-induced prothrombotic changes. Kiliç *et al.* documented the possible mechanisms for early and chronic exposure of PM (UFPs)-driven procoagulant activity in genetically modified mice [FXII^(-/-)]. They revealed that PM promotes its early procoagulant actions mostly through the TF-driven extrinsic pathway of coagulation, whereas PM-driven long lasting thrombogenic effects are predominantly mediated via formation of activated FXII. Hence, they concluded that FXII-driven thrombin formation may be relevant to an enhanced thrombotic susceptibility upon chronic exposure to PM in humans (40). In addition to increasing the inflammatory mediators and prothrombotic proteins, particulate nanoparticles and other UFPs themselves could reach the circulation and directly enhance thrombus formation as analyzed by scanning electron microscopes (117). In real-world studies, the MONICA survey indicated that plasma viscosity was increased in both men and women when exposure to air pollutions (118). Recently, researchers studied the effects of short-term changes in exposure to UFPs on stroke, separately for ischaemic and hemorrhagic strokes, and ischaemic strokes with (likely embolic) and without (likely thrombotic) AF. Their results demonstrated that exposure to UFPs lead to a

21% increase in hospital admissions (per interquartile range of 5-day averages; 95% CI: 4-41%) for mild ischaemic stroke of without AF (likely thrombotic origin), which may further indicate the thrombotic and procoagulant actions of PM particles (119).

Conclusions

In summary, a wide array of experimental and epidemiological studies have unequivocally provided persuasive evidences on the negative impact of PMs on cardiovascular events and outcomes. In addition, numerous findings indicate that even a few hours to weeks of short-term exposure to PM particulates can trigger CVD-related mortality and events, especially among the susceptible individuals at great risk including the elderly or the patients with preexisting coronary artery disease. The underlying mechanisms for PM-caused cardiovascular disease include directly insults by UFPs translocating to the circulations and remote localization to the heart or indirectly injury by inducing systemic inflammation and oxidative stress in circulation, thus leading to cardiovascular damage. However, even the epidemiology and the biomedical studies will possibly help us better understand the underlying mechanisms and increase the effectiveness of our efforts to reduce the risk of air pollution—related cardiovascular disease, the major strategy in decreasing the harmful effects of air pollution is to reduce the air pollutants themselves. As the air pollution is becoming an ecological and social dilemma in the world, especially in developing countries like China, the social movements backed up by medical doctors, medias and government, therefore, might be great needed to combat with the deteriorating air pollution problem and finally to lower the associated cardiovascular risk.

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Footnote

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