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# Air Pollution and Cardiovascular Diseases

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## 1. Introduction

Two parallel observations have historically linked poor air quality to human disease. The first of these is the recognition that substances in inspired air can pose health risks, and the second is the view that growing industrialization at the global level has contributed to deteriorating air quality. In the case of the latter, environmental scientists, economists and urban planning experts have spoken and written about the impact of industrial growth, income and urban development in the context of an "EKC" relationship (Environmental Kuznets Curve; "inverted U shaped" curve). This concept is predicated on the fact that as human activities related to industry and urban growth increase, an initial and sharp deterioration in air quality ensues. Subsequently, as income levels in a society inevitably rise, regulation, awareness and increasing attitudes of social and environmental responsibility intervene and the air quality standards improve [1]. However, since many emerging economies and industrial powers (such as China and Brazil) find themselves on the left-hand limb of the curve, the consequent impact of their industrial growth and urban expansion contribute to the aggregate decline in global air quality and pollution.

## 2. Historical perspective

It is believed that in 1872 Smith published the first scientific report of air pollution [2]. This and subsequent studies have laid the foundation for the scientific examination of pollutants as hazardous components of breathable air and its impact on human populations. In subsequent decades, particularly in the 20th century, several major incidents came to prominence which underscored the importance of air pollution in human health. For example, in 1930 a combination of high atmospheric pressure and mild winds created a heavy fog in Belgium. It is estimated that about 60 deaths were attributable, directly or indirectly to this significant fog event. Later investigations revealed that trapped potent pollutants from chimney exhausts created a toxic cloud that resulted in these fatalities [2]. Seven years later in 1948, an industrial accident caused 20 deaths with thousands of acute illnesses reported because of the smelting plant in Pennsylvania[3]. Another severe event occurred in London in 1952 when pollutants from the use of stoves as well as from

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industrial plants nearly paralyzed the city. It is estimated that there was a 48% increase in hospital admissions and 163% increase in respiratory illnesses resulting in direct hospital admissions. This event was soon followed by significant increase in numbers of deaths from respiratory illnesses. Such incidents and other related events prompted the establishment of clean air and air quality acts in the United States in 1963 and 1967.

## 3. Ambient air particulate pollutants and their classification

Particulate pollution in inspired air comprises coarse and fine particles of various sizes. Particles that are considered significant, usually have an aerodynamic diameter (AD) of between 2.5 and 10 μ (PM10). Finer particles are those that are less than 2.5 μ (PM2.5), while ultrafine particles have aerodynamic diameters of less than 0.1 μ (UFPs). The chemical nature and composition of these particles exhibits tremendous diversity and depends on numerous geographical, meteorological and source specific variables. In a general sense, ambient particles include inorganic components such as sulfates, nitrates, ammonium, chloride, and trace metals. In addition, organic materials, crystalline compounds, and biological components are also observed.

The sources of particulate air pollutants can be human, biological but nonhuman, and natural. PM10 particles generally relate to human activities and come from dust, burning of wood, construction and demolition sites, and from sites involved in mining operations. For the size of particle, natural sources include windblown dust and wildfires. Finer particles are generally generated by gaseous materials when they convert to particulate phases during combustion of fuel and industrial activities. PM2.5 sources include power plants, oil refineries, metal processing facilities, automobile exhaust, residential fuel combustion, as well as wildfires. The primary sources of UFP is automobile tailpipe emissions from a variety of vehicles, including aircraft and marine vessels [2].

With regard to human health, of particular importance are particles that are equal to or less than 10 μ in diameter, because these ultimately enter the lung parenchyma[4]. As mentioned above, particles of 10 μ aerodynamic diameters and smaller can be further divided based on size and biological effect. *Coarse* particles range in size from 2.5 to 10 μ, *fine* particles are less than 2.5 μ in diameter, and *ultrafine* particles are less than 0.1 μ. Because of their very small size, particles that are between 0.1 and 2.5 μ are deeply inhaled into the lung parenchyma. If these inhaled particles get deposited in the alveoli they enter the pulmonary circulation and are presumed to also continue to the systemic circulation. This indirect observation has been the presumed mechanism through which particulate pollution impacts the cardiovascular system, which has been reported in a series of major EP immunological and observational studies[5-7]. Recently, considerable research and attention has been given to ultrafine particles as well. These UFPs are less than .1 μ in aerodynamic diameter and are usually attributable to combustion processes from the burning of fossil fuels, for example. These ultrafine particles tend to be short-lived, because they agglomerate and coalesce into larger particles rather quickly[8]. However, these pollutants exhibit a very high rate of deposition in human alveoli and account for a major proportion of the actual numbers of particles in the lung. They also have a high surface area-mass ratio, and this potentially leads to enhanced biological toxicity[9].

## 4. Air pollution and disease: Evidence from laboratory studies

While a large number of epidemiological studies have clearly implicated particulate air pollutants in the etiology of human cardiovascular disease, controversy remains regarding the underlying biological mechanisms that might explain this phenomenon. Several distinct mechanisms have been hypothesized:

1.  *Inflammation, oxidative stress, and endothelial function.* It has been established that inhaled particles can induce inflammation in the lung parenchyma, either directly or by generating free oxygen radicals and increasing oxidative stress, particularly by activating NAD(P)H oxidase[10]. Activation of this oxidase in turn triggers intracellular signaling pathways such as those of MAP kinases and oxidation sensitive transcription factors, such as NFκB and API which control the expression of several genes coding for proinflammatory factors. These include but are not limited to, cytokines, particularly, interleukin 1β, interleukin 6, and interleukin 8. In addition, TNFα and granulocyte-macrophage colony-stimulating factor (GM-CSF), chemokines, and adhesion molecules are also robustly expressed by the signaling systems[11, 12]. These signaling events are critically linked to macrophage and epithelial cell function at the level of pulmonary alveoli and bronchi. Once particulate material inspired air reaches these locations, in systemic as well as local inflammation ensues. These inflammatory changes are evidenced by acute rises in C-reactive protein and fibrinogen as well as increased viscosity of plasma. Stimulation of bone marrow with leukocytosis and circulating immature polymorphonuclear neutrophils, and activated platelets and other procoagulant factors are also involved in this process[10]. It has been demonstrated, for example, that exposure to exhaust from diesel engines contains ingredients that attenuate the acute release of tissue plasminogen activator (t-PA) by the endothelium, resulting in diminished endogenous fibrinolytic capacity[10]. In blood vessels, particulate matter, causes, endothelial dysfunction by inhibiting the formation of nitric oxide, and stimulating the production of endothelin 1, angiotensin II, and thromboxane A2[13, 14]. Angiotensin II, in turn, contributes further to oxidative stress, by increasing the generation of superoxide and through the enhancement of NAD(P)H oxidase activity. These are some of the possible explanations for alterations in endothelium-dependent vasomotor activity induced by particulate pollution. Several studies have demonstrated endothelium-independent alterations as well, which are also related to mechanisms of vasoactivity, such as through the stimulation of sympathetic ennervation as well as by the direct stimulation of angiotensin II AT1 receptors. Cumulatively, these alterations contribute to the development and progression of atherosclerosis, the destabilization of atherosclerotic plaques, and promotion of ischemia antithrombotic states[15]. Experimental models have confirmed that atherosclerosis progresses quite rapidly and plaques have a greater vulnerability to rupture in laboratory animals exposed to PM2.5 and PM10 air pollution over a period of several weeks or several months. In fact, C-reactive protein, which is an acute phase reactant, has been shown to express in greater quantities in the presence of particulate pollution. CRP is a known cardiovascular risk factor because it facilitates its uptake of lipids by macrophages and the expression has been associated with increased fragility atherosclerotic plaques leading to destabilization[16]. Investigators have found a direct correlation between the severity of coronary and aortic atherosclerosis and the number of alveolar macrophages that phagocytose PM10 over several weeks exposure in rabbits who have heritable hyperlipidemia[10].

Several other studies have found that ultrafine particles alongside soluble components can also reach the systemic circulation directly and quickly lead to oxidative stress and inflammation in the heart and arterial vessels, resulting in endothelial dysfunction, without necessarily inducing pulmonary inflammation[17]. Acute exposure to particles of 2.5 μ diameter has also been shown to associate with high levels of circulating markers of lipid and protein oxidation.

Investigators have also determined that the inflammatory reaction to inhaled particulate material is less due to their mass or volume, but rather is a result of the chemical composition and surface area. Fine and ultrafine or even nanoscale particles have greater surface areas in proportion to their mass compared with other particles. The larger surface area of particles results in greater oxidative stress, which itself is consequent upon the larger number of reactive groups present on the surface leading to greater synthesis of reactive oxygen species[18].

Researchers have found that the pro-atherogenic effects of particulate pollution inhalation, in ApoE deficient mice, results in higher susceptibility to atherosclerotic lesions with more significant and more extensive lesions following particulate exposure compared with controls. It has been determined that the greater oxidative effect of ultrafine particles is related to the higher organic carbon content. In addition, it has also been suspected that particles of this small size modulate intracellular calcium concentrations by interfering with the opening of calcium channels on cell membranes, a phenomenon which itself indirectly leads to the synthesis of reactive oxygen species in the cell[13].

The effect of increased oxidative stress, consequent upon exposure to ultrafine particles, leads to mitochondrial dysfunction as well. This increases the production of superoxide radical and activation of p53, a transcription factor which modulates programmed cell death, through the release of pro-apoptotic factors like cytochrome C and AIF.

2. *Autonomic dysfunction*: The autonomic nervous system is also particularly susceptible to the effect of particulate material in the systemic circulation. For example, autonomic dysfunction has been demonstrated after stimulation of pulmonary nerve receptors, following exposure to 10 and 2.5 μ particulate materials. These changes were shown to be either as a direct effect of the particles, or by the instigation of local oxidative stress and inflammation in the lung parenchyma leading to reflex increases in heart rate, reduced variability of the heart rate, as well as heart rate rhythm anomalies[13].

It has been postulated that the fine and ultrafine particles may also lead to the rhythm anomalies in the heart by virtue of their effects on ion channels in cardiac myocytes [13]. Alternatively, disruption of cardiac autonomic function may also be related to the effect of these particles on oxidative homeostasis in the cardiovascular regulatory nuclei in the central nervous system[19]. Intriguingly, the reverse has also been demonstrated in that autonomic dysregulation can itself trigger cardiac oxidative stress[20].

3. *Dysregulation of intravascular thrombotic system*: inhalation of particulate matter has been shown to enhance arterial thrombosis and coagulation[21]. In this regard, empirical work has resulted in conflicting data. Some studies have shown a positive correlation between particulate matter inhalation and thrombotic dysregulation, while others have not[17]. However, it has been hypothesized that, against the background of vulnerable atherosclerotic plaques in individuals who already have these lesions, disturbances of the thrombotic milieu, are likely to trigger arterial thrombosis, ischemic events, and

catastrophic rupture, leading to embolism. Studies have shown, that increases in fibrinogen and blood viscosity, elevated CRP, increased platelet reactivity, altered levels of coagulation factors, disturbed histamine levels, enhanced interleukin 6 dependent signaling, expression of adhesion molecules, and attenuated release of fibrinolytic factors all appear to be mechanistic underpinnings of the impact of particulate matter on the cardiovascular system[22, 23]. One aspect of these mechanistic theories remains unresolved. It is not known, what relative roles are played by systemic inflammation, disturbed autonomic balance, and the effect of blood-borne mediators of thrombosis, on overall cardiovascular health and disease[8].

4. *PM and heart failure:* exposure to particulate air pollution has also been linked to an increased risk of heart failure as well as hospital admissions resulting from heart failure[24]. It is believed that both pro-ischemic, and dysrhythmic effects of particulate exposure could be responsible for these phenomena. However, a more recent study in mice has also shown that the deposition of particulate material in lung parenchyma can impair the ability of the alveoli to clear fluid because of reduced membrane Na-K-ATPase activity[25]. In these experiments, this effect was abrogated by the use of antioxidants, suggesting that oxidative stress, might play a primary role in such phenomena.

5. *Evidence implicated PM in blood pressure regulation:* in animal studies, evidence has been accumulating that relates particulate air pollution exposure to induced changes in blood pressure. For example, in a Sprague-Dawley rat model, where, angiotensin II was employed to induce hypertension, exposure to concentrated 2.5 μ the particulate pollution for 10 weeks, caused prolonged blood pressure compared with control groups[26]. In this study, aortic vasoconstriction in response to particulate exposure was potentiated with exaggerated relaxation to the Rho-kinase inhibitor Y-27632. Investigators in this paper also demonstrated an increase in ROCK-1 messenger RNA levels and superoxide production in animals exposed to PM, suggesting that even short-term exposure to PM can induce hypertension via superoxide-mediated upregulation of the Rho/ROCK signaling pathway. In other studies, in Murine models of PM exposure, angiotensin II, infusion in conjunction with a rho kinase antagonist, potentiation of the hypertensive phenotype was also reported[27]. Other studies have also shown that exposure to 2.5 μ particulate material increases angiotensin II-induced cardiac hypertrophy, collagen deposition, cardiac RhoA activation, and vascular RhoA activation, suggesting that cardiovascular health effects are consequences of air pollution[4].

## 5. Air pollution and disease: Evidence from epidemiological studies

A large number of studies have focused on the acute effects of air pollution. In one study, which was carried out in as many as 29 European cities with 43 million inhabitants demonstrated that for each 10 μg per cubic meter increase in 10 μ particulate matter, cardiovascular mortality rose by 69%[28]. In the United States, a survey of 90 cities with 15 million participants revealed a short-term increase in cardiopulmonary mortality of .31% for each 10 μg per cubic meter increase in PM10 when measured over a 24-hour period[29]. Many other studies have also demonstrated significant rises of between .8% and .7% respectively in hospital admissions from heart failure and ischemic heart disease for every 10 μg per cubic meter rise in PM10[30]. The studies have also shown an increase of 1.28% and 4.5%, respectively, and risk of heart failure and acute coronary syndromes for every 10 μg per

cubic meter rise in PM2.5[30]. Furthermore, links have also been discovered between short-term rises in PM 2.5 and the incidence of myocardial infarction, occurring within a few hours. Following exposure, ST-segment depression occurs during exercise testing in patients with stable coronary disease, increased heart rates, enhanced incidence of arrhythmias in several different studies[31]. Overall, it has been estimated that between 60,000 and 350,000 sudden cardiac deaths in the United States occur which can be attributed to particulate air pollution.

Investigators have found that exercise-induced myocardial ischemia is exacerbated when humans are exposed to diesel exhaust products which are mainly composed of ultrafine particles, in concentrations similar to those found in heavy traffic in large urban centers (300 μg per cubic meter)[22]. Links have also been demonstrated between pollution from fine particles found in motor vehicle emissions and ST-segment depression recorded via Holter ECG monitoring[32]. In addition, a higher incidence of ischemic and hemorrhagic stroke has also been reported with higher mortality and more hospital admissions, directly connected to short-term increase in airborne PM 10[33]. In a study undertaken in nine US cities of individuals older than 65 years demonstrated that there was a strong association with ischemic stroke, with a rise of 1.03% in hospital admissions for every 23 μg per cubic meter increase in PM 10[34]. In this study an association was also found between specific gaseous co-pollutants and increase in ischemic stroke (carbon monoxide [CO] nitrous oxide [NO2] and sulfur dioxide [SO2]). Indeed, several others have reported links between levels of these gaseous pollutants and mortality or hospitalization rates due to stroke, as well as re-hospitalization in survivors of myocardial infarction[10]. In Germany during the 1985 air pollution episode, epidemiological observations revealed that plasma viscosity, heartrate, and concentrations of C-reactive protein, were increased during this episode[35]. In the United States, in the city of Boston, nitrogen dioxide in the atmosphere and PM2.5 were associated with life-threatening cardiac arrhythmias, leading to the need for drug interventions, including the implantation of cardioverter defibrillators. In addition PM2.5 concentrations were noted to be higher in the hours and days before onset of myocardial infarction in a large group of patients[36, 37]. In a study of individuals older than 65 years, a positive association between stroke mortality and the concentration of fine particles was also demonstrated. In this study, a rise of 6.9% for each interquartile increase in PM2.5 on the day of death, and a 7.4% increase in the 24 hours prior to death, was demonstrated[10]. Such observations have been made on other continents and in other countries as well outside the strict confines of the Western hemisphere. For example, in studies in Shanghai, levels of PM2.5 have been reported to influence daily overall cardiopulmonary mortality, this effect was not observed for particles smaller than 2.5 μ[10]. In other Asian countries as well, rise in urban air pollution and the rise of cardiovascular morbidity has been well documented. In order to understand the effect of air pollution on human health on the vast Asian continent and in particular in countries where a sixth to a fifth of humanity reside (namely China and India), the Health Effects Institute (a Boston based, U.S. non-profit health research corporation) funded the large PAPA (Public Health and Air Pollution in Asia) study. The first phase of this project was undertaken in Thailand from 1999 to 2003, in Hong Kong in China from 1996 to 2004, and in Shanghai and Wuhan in China between 2001 and 2004 [38]. This study documented several common pollutants such as NO2, SO2 and PM<10μ and their effect on cardiovascular and respiratory mortality. One interesting conclusion of the investigators (speculative) was that Asian populations might be exposed to outdoor air

pollution to a larger extent than Western cohorts because they tend to spend more time outside than indoors while Westerners have more access to air conditioning which tends to mitigate pollution with the use of filters and recirculated ventilation. In the initial data published in the PAPA study, Wuhan in mainland China exhibited highest concentrations of PM10 and $O_3$, while Shanghai has the highest concentrations of $NO_2$ and $SO_2$. In comparison with cities of comparable size in the U.S. (analyzing data from the National Morbidity and Mortality and Air Pollution Study {NMMAPS}), the concentrations of PM10 and $SO_2$ were found to be much higher for cities included in the PAPA study. For example, the concentrations of PM10 in PAPA had means of 52-142 µg/m3 versus 33 µg/m3 in NMMAPS. In the case of $NO_2$ and $O_3$, the results were similar in that U.S. had lower concentrations than those in China [38]. When these results were correlated with mortality figures for cardiovascular and respiratory diseases, predictable patterns emerged. Cause of death ratios were the highest in Wuhan (4:1), followed by Shanghai (3:1) with lower figures documented for Bangkok and Hong Kong [38].

Banerjee et al have recently reported from India that exposure to poor air quality can alter hematological and immunological parameters negatively. In their study, these investigators reported results from 2218 individuals residing in the large urban metropolis of New Delhi ranging in age from 21-65 years who were exposed to vehicular exhaust (the main polluter of air quality in Asia in general and in India in particular). The authors found the prevalence of hypertension 4 fold higher than matched controls (Bannerjee M et al, Int J Hyg Environ Health 2011 Sep 16 Epub). Platelet P-selctins were significantly upregulated in this cohort while CD4+ T-helper cells and CD19+ B cells were found to be depleted and CD56+ NK cells were upregulated. These changes in the immune profile is positively correlated with hypercoagulable states and higher cardiovascular risk[39]. These findings have been effectively reproduced in other Indian studies as well. For example, Barman and colleagues have recently published data from Lucknow (a city in Northern India) in which PM and pollutant heavy metals were also linked to elevated risk of cardiovascular risk [40]. Even earlier studies have shown strong correlation between air pollution levels and cardiovascular risk. Nautiyal et al reported in a study completed in the Indian state of Punjab (a pilot study) demonstrated positive correlations between angina pectoris and PM10 pollution [41].

Aside from cardiovascular mortality, other parameters of cardiovascular function have also been correlated with greater air pollution. For example, in studies from central Europe, a rise in blood pressure at times of greater air pollution has been reported. In the MONICA study from Germany, a significant rise in blood pressure was noted in relation with particulate air pollution even after adjustment for other cardiovascular risk factors[42]. Significant elevations of diastolic blood pressure in 23 normotensive individuals following two hours of exposure to PM2.5 were reported by Urch and colleagues[43]. In Brazil,, monocyte levels also appear to significantly influence systolic, diastolic blood pressure levels per quartile of monocyte concentration. In this setting, sulfur dioxide levels were also noted to affect blood pressure, validating the importance of gaseous co-pollutants[44]. Intriguingly, a large volume of data also suggests that the deleterious effects of particulate air pollution can be aggravated by the presence of cofactors such as diabetes, obesity, hypertension, chronic pulmonary disease, and previous cardiovascular disease, as well as an additive effect of advancing age[45, 46].

A consensus seems to be gathering between clinicians and scientists that the adverse cardiovascular effects of air pollution depend not only on the concentrations of these materials but also on the length of exposure. Prolonged exposure appears to have a cumulative effect as well as a stronger impact and more persistent consequences then shorter exposure. For example, a decrease in PM2.5 over a period of eight years, was shown to significantly attenuate the overall cardiovascular and pulmonary mortality by Laden et al[47].

## 6. Issues of current and future research focus

An unresolved question is whether the threshold concentrations of particulate air pollution exist below which the risk to the general population dissipates or becomes nonexistent. The importance of this idea is that if such thresholds can be identified, then governmental and private endeavors to reduce air pollution can be pragmatically set to identifiable goals beyond which no further public health benefits would accrue. Some of these issues are now beginning to be analyzed based on epidemiological data. The Health Effects Institute (HEI), conducted a health study beginning in 1996, which is called the National Morbidity, Mortality, and Air Pollution Study (NMMAPS). Subsequent analysis of the study found no evidence of a critical threshold for PM10 in daily all-cause and cardiorespiratory mortality[48]. However, a threshold of about 50 µg/m$^3$ was estimated for non-cardiorespiratory causes of death. These and similar analyses suggest that the threshold for acute effects of ozone on lung function changes are likely to be below 100 µg/m$^3$/hour maximum.

Several time-series studies have shown a link between day-to-day variations in air pollution concentrations and the rate of deaths per day as well as rates of hospital admissions, however, more detailed correlation remains unclear. For example, it is not certain, by how many days, weeks, or months, such events are increased from baseline[49]. For example, Brunekreef and Holgate have suggested that if deaths occurred just a few days earlier than would have occurred without air pollution, the public health significance of these correlations would be much less severe than if mortality was reduced by months or years[49]. In contrast, effect estimates have been shown to increase with increasing duration of exposure to air pollution, which suggests that there is a stronger effect on mortality in comparison with associations between day-to-day variations in air pollution and deaths. Other data has also shown that many deaths associated with air pollution occur outside hospital settings, which further supports the notion that these individuals were often not terminally ill[50].

Another confounding aspect of the relationship between air pollution and cardiovascular disease in general is to tease out the difference between time spent indoors from that spent outdoors. This is because empirical evidence suggests that indoor pollutant concentrations differ both qualitatively and quantitatively from that found out-of-doors. This has become the basis of criticisms in that it has been questioned if measurement of air pollution on the outside without taking into account exposure indoors, is a valid method of assessing exposure to air pollutants. Thus one study found that for particulate matter and gases, there was no appreciable association between the day-to-day variation in personal exposure to nitrogen dioxide, sulfur dioxide, and ozone[51]. In this study, ambient PM2.5, nitrogen dioxide, sulfur dioxide, and ozone were closely associated with personal PM2.5, strongly suggesting that gaseous and PM 2.5 concentrations outdoors act as a surrogate for personal exposure to PM2.5[51].

Because of these unresolved questions and large costs associated with reducing air pollution, questions regarding the relationship between air pollution and health have become an area of considerable debate in recent decades. Early studies have been criticized for the analytical approach and lack of adequate controls for confounding variables such as weather etc., and US cohort studies have been critiqued for inadequate confounder and co-pollutant controls as well[49]. Several re-analyses have been performed on these older studies and the HEI has itself partnered with the US automobile industry as well as the federal government to attempt to resolve this important debate. In one reanalysis called the Philadelphia time-series study, as well as several others revealed new insights into the role of weather-related variables as well as that of spatial association between air pollution, mortality, and other confounding variables[49].

## 7. Conclusions

A wide range of experimental and epidemiological studies have established that air pollution is an important determinant of cardiovascular risk and that it can influence more traditional risk factors. It has been shown that alterations by air pollution, specially by fine and ultrafine particles, significantly contribute to the long-term development and progression of atherosclerosis, promotion of atherosclerotic plaques and their instability, and acute cardiovascular events such as stroke, myocardial infarction, arrhythmias, and sudden cardiac death[10]. However, several key questions remain. With rapid developments in molecular biology, proteomics, and genomics, these questions will likely be clarified within the context of complex biological mechanisms involved in cardiovascular injury and their interaction with particulate air pollution and gaseous air pollution. Thus it is likely, that with increasing understanding of the clinical significance of cardiovascular effects of air pollution, a dual approach of abating air pollution as well as using traditional medical tools and pharmaceutical strategies will, in the future, help in abrogating cardiovascular risk and reducing the incidence of cardiovascular pathology in human communities.
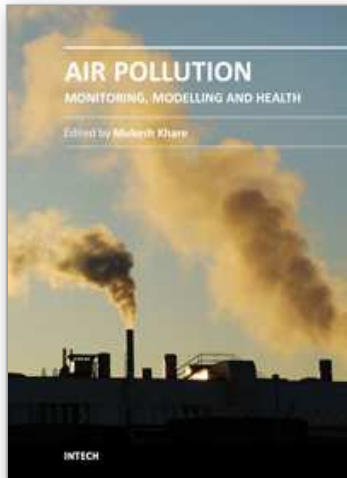
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