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Air Pollution and its Association with Cardiovascular Diseases

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Abstract

Cardiovascular Diseases (CVD) is considered as one of the leading causes of mortality and morbidity worldwide including India. The aim of this review is to explore and summarize the relationship between air pollution and CVD. Studies have demonstrated that exposures to air pollution have both short and long term effects on mortality. Air pollution comprises of particulate matter (PM), carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), dust, fumes and gases. Therefore, in the recent past there is growing affirmation that long time exposure to air pollution is linked to the development of various CVD like coronary artery disease, heart failure, cardiac arrhythmias and arrest and cerebrovascular diseases. The biological mechanisms such as inflammation and oxidative stress seem to contribute to the occurrence of these diseases due to the exposure to ambient air pollutants. Air pollution can be considered as a modifiable risk factor for the prevention and the treatment of various cardiovascular diseases. Therefore, future research should focus on ways to reduce or eradicate air pollution methods so that these could be implemented in the public domain.

Keywords: Cardiovascular Diseases; Air Pollution; Mortality; Ambient Air Pollutants.

Introduction

Cardiovascular Diseases (CVD) is considered as one of the leading causes of mortality and morbidity worldwide including India [1, 2]. Concerns regarding the global impact of environmental air pollution on human health have been increasing over the last two decades. The long term exposure to elevated levels of air pollution has been associated with the increased risk of various cardiac events like myocardial infarction (MI) and stroke [3]. Air pollution comprises of particulate matter (PM), carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), dust, fumes and gases [4-6]. The pollutants present in the atmosphere has been linked to various mechanisms such as oxidative stress, endothelial dysfunction, prothrombotic and coagulant changes, pulmonary and systemic inflammation, atherothrombosis, and arrhythmogenesis [7]. Therefore, in the recent past there is growing affirmation that long term exposure to air pollution is linked to the development of various CVD. The aim of this review is to explore and summarize the relationship between air pollution and CVD.

Common air pollutants

The air quality index (AQI) which is also formerly known as the Pollutant Standards Index (PSI), is a numerical scale that is utilized for reporting daily air quality in terms of human health and environment. The AQI is calculated based on five major air pollutants such as ground level ozone, PM, CO, SO_2 and NO_2 [8]. The outdoor air pollution comprises of a heterogeneous and complex mixture of airborne PM and the gaseous pollutants ozone, NO_2, volatile organic compounds (including benzene), CO, and SO_2 [9, 10]. There are three types of atmospheric PM namely: coarse particles (diameter<10μm, ≥ 2.5μm), fine particles (diameter < 2.5μm, ≥ 0.1μm) and ultrafine

particles (nano-particles, diameter < 0.1 μm). This PM is a complex and heterogeneous mixture which is released into the atmosphere during the combustion of coal, wood, gasoline, diesel, or fossil fuels, as well as from natural sources (road dust, fires, volcanic emissions, etc.) [11]. Some of the gaseous pollutants include nitrogen oxides including NO_2 and nitric oxide (NOx), ozone, SO_2, volatile organic compounds and CO. SO_2 and nitrogen oxides (NO) also contribute to the formation of particle formation via the complex mechanisms like the atmospheric photochemical reactions and the ammonia released in the atmosphere through agriculture. These particles are termed as secondary particles. The photochemical reactions that involve sunlight and gaseous precursors such as NO or volatile organic compounds are involved in the formation of ozone, which is a secondary gaseous pollutant [12].

Air pollution and cardiovascular diseases

There has been a substantial increase in the evidence that the levels of air pollution have an impact on the development of CVD. There is strong evidence that PM has greater adverse effects compared to the other gaseous pollutants. The exposure to the components of the air pollutants leads to several CVD such as the coronary artery diseases (CAD), heart failure (HF), cardiac arrhythmias and arrest, CVD and venous thromboembolism. Studies have demonstrated that exposures to air pollution have both short and long term effects on mortality (Table 1). In the recent past, several studies have been done which has evaluated the relationship between air pollution and cardiovascular diseases [7, 13].

Coronary Artery Disease (CAD)

Several epidemiological studies have sought to understand the association between air pollution and the development and exacerbation of CAD. Cohort studies have revealed that long-term exposures to air pollution leads to an increased risk of the incidence of fatal and non-fatal CAD [14-16]. A prospective 10-year cohort study was done among 6795 participants within the age group 45-84 across

Table 1: Studies evaluating short and long term effects of air pollution on cardiovascular mortality:

Long-term effects				
Sl. No.	**Name of the study**	**Authors Name**	**Ethnicity**	**Main outcomes**
1.	Short term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the APHEA project [35]	Katsouyanni et al.	Caucasian	In the western European cities the study showed that an increase of 50 $\mu g/m^3$ in sulphur dioxide or black smoke was associated with a 3% (95% CI 2% to 4%) increase in daily mortality and for PM_{10} the increase in daily mortality was 2% (1% to 3%). In the central eastern European cities the study showed that a 50 $\mu g/m^3$ change insulphur dioxide was associated with increase in mortality of0.8% (-0.1% to 2.4%) and in black smoke was 0.6% (0.1% to 1.1%).
2.	Short-term effects of air pollution on a range of cardiovascular events in England and Wales: case-crossover analysis of the MINAP database, hospital admissions and mortality [36]	Milojevic et al.	Caucasian	For mortality, none of the cardiovascular (CVD) outcomes analysed was clearly associated with any pollutant, except for $PM_{2.5}$ with arrhythmias, atrial fibrillation and pulmonary embolism. For hospital admissions, only NO_2 was associated with a raised risk: CVD 1.7% (95% CI 0.9 to 2.6), non-MI CVD 2.0% (1.1 to 2.9), arrhythmias 2.9% (0.6 to 5.2), atrial fibrillation 2.8% (0.3 to 5.4) and heart failure 4.4% (2.0 to 6.8) for a 10th–90th centile increase.
3.	Short-term effects of nitrogen dioxide on mortality: an analysis within the APHEA project [37]	Samoli et al.	Caucasian	A significant association of NO_2 with total, cardiovascular and respiratory mortality was found, with stronger effects on cause-specific

Sl. No.	Name of the study	Authors Name	Ethnicity	Main outcomes
				mortality. There was evidence of confounding in Respiratory mortality with black smoke.
4.	Short-term effects of air pollution on cardiovascular mortality in elderly in Niš, Serbia [38]	Stanković et al.	Caucasian	All age cardiovascular mortality and among person ≥65 years are not related to ambient air pollutants concentrations. There is a risk of cardiovascular death with increase of 10 μg/m^3 in SO_2 and black smoke, but it was not statistically significant.
Long-term effects				
1.	Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project [39]	Beelen et al.	Caucasian	A significantly increased hazard ratio (HR) for $PM_{2.5}$ of 1·07 (95% CI 1·02–1·13) per 5 μg/m^3 was recorded HRs for $PM_{2.5}$ remained significantly raised even when only participants exposed to pollutant concentrations lower than the Europe an annual mean limit value of 25 μg/m^3 (HR 1·06, 95% CI 1·00–1·12) or below 20 μg/m^3 (1·07, 1·01–1·13).
2.	Cardiovascular Effects of Long-Term Exposure to Air Pollution: A Population-Based Study With 900 845 Person-Years of Follow-up [40]	Kim et al.	Asian	The risk of major cardiovascular events increased with higher mean concentrations of $PM_{2.5}$ in a linear relationship, with a hazard ratio of 1.36 (95% confidence interval, 1.29–1.43) per 1 μ/m^3 $PM_{2.5}$. Other pollutants including $PM_{2.5\text{-}10}$ of CO, SO_2, and NO_2, but not O_3, were significantly associated with increased risk of cardiovascular events.

six metropolitan areas in the USA. In this study the association between the long-term exposure to ambient air pollution and the progression of coronary artery calcium and common carotid artery intima-media thickness was evaluated. The exposures to the air pollutants was measured using the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA) air exposure assessment approach, where the measurement of air pollution was done at the homes and the communities of a subset of participants in each of the study areas [17]. The study demonstrated that for each 5 μg $PM_{2.5}$/m^3 increase, the amount of coronary calcium progressed by 4.1 Agatston units per year (95% CI 1.4–6.8). The coronary calcium progressed by 4.8 Agatston units per year (0.9–8.7) for every 40 ppb NO_x. However, there was no association between pollutant exposures and change in the intima-media thickness. Therefore, the long-term exposure to outdoor PM and traffic related air pollutions, $PM_{2.5}$ and NO_X are associated with the development of atherosclerosis in CAD [18]. In another study, the acute effects of PM exposure and coronary heart disease (CHD) were studied among people aged above 40 in Shanghai. The daily $PM_{2.5}$ and O_3 was obtained from Pudong meteorological service and Shanghai Center Of Urban Environmental Meteorology respectively. The average concentrations of PM_{10}, SO_2 and NO_2 from the year 2005–2012 was obtained from Shanghai environmental monitoring center. The study showed that an elevation in the exposure to PM_{10} and $PM_{2.5}$ were related to an increased risk of the occurrence of CHD. The increase in the 10 μg/m^3 exposure to the two day PM_{10} [0.23% (95% CI: 0.12%, 0.34%)] and $PM_{2.5}$ [0.74% (95% CI: 0.44%, 1.04%)] was found to be associated with the increase risk of CHD morbidity. The associations were more common among males and elderly populations [19]. A prospective cohort study and meta-analysis was performed among 11 European Cohorts comprising of 5157 participants from the ESCAPE project. The long-term exposure to airborne pollutants and its association with the incidence of acute coronary events were evaluated. The ogawa diffusion badge was used for the measurement of NO_2 and NO_X. The meta-analysis revealed that there was a 13% increased risk of coronary events (hazard ratio 1.13, 95% CI 0.98 to

1.30) when exposed to an increase of 5 μg/m^3 in the estimated annual mean $PM_{2.5}$. Furthermore, the increase in the 10 μg/m^3 in estimated annual mean PM_{10} was associated with a 12% increased risk of coronary events (1.12, 1.01 to 1.25). Therefore, the long-term exposure to PM is associated with the increased incidences of coronary disease events and these associations also persist at levels of exposure below the current European limit values [20]. Therefore, studies reveal that both long and short-term exposure to air pollutants lead to the development of CAD.

Heart Failure (HF)

HF is one of the leading CVD and there are about 26 million HF patients world-wide, which resulted in more than 1 million hospi-talizations per annum in both United States and Europe [21].The disease is considered to be an epidemic disease affecting 1-2% of the overall adult population. The prevalence rate of HF in India was estimated to be 1% of the overall population and the re-hospitalization rates have increased over the years posing a major burden on public health [22]. Systematic review and meta-analysis was conducted to study the associations between air pollution and acute decompensated HF including hospitalization and HF mortality. In the study, it was observed that increases in CO (3.52% per 1 part per million; 95% CI 2.52-4 ·54), SO_2 (2.36% per 10 parts per billion; 1.35-3.38), and nitrogen dioxide (1.70% per 10 parts per billion; 1.25-2.16) was associated with the rise in incidences of HF hospitalizations and mortality. Furthermore, increases in the PM concentration ($PM_{2.5}$ 2.12% per 10 μg/m^3, 95% CI 1.42-2.82; PM_{10} 1.63% per 10 μg/m^3, 95% CI 1.20-2.07) were also associated with increased incidences of HF mortality and hospitalizations. The robust association was observed in the day time exposure of $PM_{2.5}$ [23]. Thus, it is pertinent to avoid exposure to a polluted environment among patients diagnosed with HF.

Cardiac arrhythmias and arrest

The last five years has seen an increase in the association between air pollution and cardiac arrhythmias, where the data has shown strong associations between exposure to air pollution and development of ventricular arrhythmias. However, there is also increasing evidence which shows that the exposure to air pollution has effects on supraventricular arrhythmias [24]. A case-crossover study was conducted among 211 patients with Implantable Cardioverter Defibrillator where investigations were done to measure the effect of PM_{10} and NO_2. The measurements of air pollutants and other meteorological data were obtained from the centrally located roof-top monitor in each city that reflected the urban background levels. The study demonstrated that there was associations between 2 h moving averages of PM_{10} and ventricular arrhythmia [odds ratio (OR) 1.31, 95% confidence interval (CI) 1.00-1.72], but the odds ratio for 24 h moving averages was 1.24 (95% CI 0.87-1.76). Furthermore, the corresponding odds ratio for the events that occurred closest to air pollution monitoring were 1.76 (95% CI 1.18-2.61) and 1.74 (95% CI 1.07-2.84), respectively [25]. In contrast the Environmental Protection Agency had reviewed studies where patients were on implantable defibrillators and found that the evidence was inconsistent for the associations between arrhythmia and air pollution [26]. Therefore, the current evidence for the association between air pollution and cardiac arrhythmia is weak and more studies may be required to establish the effect of air pollution on cardiac arrhythmias.

Cerebrovascular diseases

Data obtained from the Global Burden of Diseases 2013, that comprised data from around 188 countries between the years 1990 and 2013 revealed that the exposure to air pollution contributed to the increased incidences of stroke and mortality [27]. The European Study of Cohorts for Air Pollution Effects (ESCAPE) project evaluated the association between long-term exposure to multiple air pollutants and the incidences of stroke among the European cohorts. The data showed that an increase of 5 μg/m^3 increase of annual $PM_{2.5}$ exposure was associated with 19% increased risk of stroke incident [Hazard ratio (HR) = 1.19, 95% CI: 0.88, 1.62]. Consistent and similar findings were observed with PM_{10}. Furthermore, the association between $PM_{2.5}$ and cerebrovascular events among participants aged ≥ 60 years was (HR = 1.40, 95% CI: 1.05, 1.87), with $PM_{2.5}$ among never smokers was (HR = 1.74, 95% CI: 1.06, 2.88), and among participants with $PM_{2.5}$ exposure <25 μg/m^3 (HR = 1.33, 95% CI: 1.01, 1.77) [28]. However, in a recent report the researchers found no clear association between air pollution and stroke [29]. The results so far show that further studies are required to obtain clarity on the association between air pollution and the occurrence of cerebrovascular events.

Association between air pollution and biomarkers of oxidative stress and inflammation

Both long and short-term exposures to air pollution have been associated with the increased

risk of oxidative stress and inflammation. The two biological mechanisms may be partly associated with the occurrence of cardiovascular events such as myocardial infarction, HF, stroke, etc [30, 31]. In the Framingham Heart Study, short-term exposure to air pollution and biomarkers of oxidative stress was studied. The circulating oxidative stress biomarkers such as blood myeloperoxidase and urinary creatinine indexed 8 epi prostaglandin F2a (8 epi PGF 2a) were measured among 2035 Framingham offspring cohort partici-pants who were non-smokers and living within 50 km of the Harvard Boston Supersite. During the data analysis, models were adjusted for demographic variables, individual and area level measures of socioeconomic position, clinical and lifestyle factors, weather, and temporal trend. A positive association was observed between $PM_{2.5}$ and black carbon with myeloperoxidase across multiple moving averages. Furthermore, the 2 to 7 day moving averages of $PM_{2.5}$ and sulfate were positively associated with 8 epi PGF 2a. The study also found substantial positive associations of black carbon and sulfate with myeloperoxidase among diabetic and non-diabetic participants. Therefore, in this community based study, strong associations between selected markers of ambient air pollution and circulating markers of oxidative stress was found [32]. However, more studies involving individuals with different ethnicities are required to establish the relationship between air pollution and biomarkers of oxidative stress. Different studies have reported the link between air pollution and inflammatory markers such as interleukin-1, interleukin-6, tumour necrosis factor-α, C-reactive protein) and fibrinogen [33,34]. A total of 28 inflammatory markers were studied among 587 individuals whose samples were bio banked as part of a prospective study [The European Study of Cohorts for Air Pollution Effects (ESCAPE)]. The study revealed that long-time exposure to nitrogen oxide (NO_X) was associated with decreased levels of interleukin (IL)-2, IL-8, IL-10 and tumor necrosis factor-á among the Italian participants, but the same effect was not seen among Swedish participants. Furthermore, the exposures to NO_X were considerably lower among Swedish participants than the Italian participants [Sweden: median (5th, 95th percentiles) 6.65 µg/m3 (4.8, 19.7); Italy: median (5th, 95th percentiles) 94.2 µg/m3 (7.8, 124.5)]. On combining the data obtained from both Swedish and Italian participants a significant association between long-term exposure to NO_X and decreased levels of circulating IL-8 was observed [33]. Therefore, more studies are required to establish a strong association between ambient air pollutants and markers of inflammation.

Conclusion and future directions

In conclusion, there is abundant epidemiological data that both short and long-term exposure to air pollution has an increased risk for a series of various cardiovascular events such as myocardial infarction, stroke and heart failure events. The biological mechanisms such as inflammation and oxidative stress seem to contribute to the occurrence of these diseases due to the exposure to ambient air pollutants. However, larger epidemiological studies need to be conducted among participants of different demographic ethnicity to establish a substantial link between exposure to air pollution and cardiovascular diseases. Air pollution can be considered as a modifiable risk factor for the prevention and the treatment of various cardiovascular diseases. Therefore, future research should focus on ways to reduce or eradicate air pollution methods so that these could be implemented in the public domain. Moreover, there is also an urgent requirement by the government agencies, public and various policy makers to take some serious efforts to reduce air pollution worldwide.

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