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Editorial

Air pollution and its impact on cardiovascular health – It's time to act fast!

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1. Introduction

Pollution has always existed and may be as old as the human civilization. The concern for environmental health and maintenance of proper public hygiene was deeply embedded in the ancient Indian customs and traditions. It has been mentioned in Charaka Samhita (BC1500) and Sushruta Samhita (BC2500) of Ayurveda the "Science of life". Charaka and Sushruta the two ancient masters of Indian medicine (Ayurveda) observed not only that bodily health as a personal problem, but also its relation to heredity, geographical environment, climate, water supply, quality of air, time and seasonal variation. Charaka Samhita described air pollution as, 'The air which is against the virtues of season, full of moisture, speedy, hard, icy cool, hot dry, terribly roaring, colliding from two or three sides, bad smelling, oily, full of dirt, smoke, sand and steam, creates diseases in body and is polluted'.[1,2] The title "Janpadodwamsa" in Charaka Samhita has mentioned the cause of unhealthy environment as the "adharma of rulers and residents". Sushrut Samhita, too has mentioned that the pollution was used as weapon by weak king in the way of strong king.[3,4] Air pollution in the form of increase in environmental methane has also been traced in the period between 100 BC and 1600 AD. The Roman, Chinese and Indian civilizations activity, notably metallurgy and large-scale agriculture, starting around 100 BC increase the amount of methane in the environment and thus causing air pollution.[5]

But the alarming bell of environmental pollution ranged during industrial revolution in the mid 20th century. On the 3rd December 1930, citizens of Meuse valley, Belgium had sudden onset dyspnea, cough and chest pain which led to more than 60 deaths. This was marked as one of the first significant air pollution events to demonstrate the potential of atmospheric pollution to cause death.[6] The main cause of the Meuse event was speculated to be the air pollution due to toxic emissions from the densely populated nearby factories, along with the temperature inversion in the valley which led the smoke from industries to remain at ground level known as "smog". The intentional ignorance and the continuing expansion of the industries has led to another event in October 1948, the Donora smog, this time in the United States. A fog full of particulates and other industrial contaminants saturated the air of Donora, a small industrial town (Hub of the American Steel and wire plant and Zinc Works) on banks of the river Monongahela near Pittsburgh. This lead to the smog formation which resulted in half of the population to become sick and 20 deaths.[7] Higher number of deaths than expected from cardiovascular disease has been found in the decade following this tragedy.[8,9] The great London smog of December 1952, primarily due to extensive burning of high sulfur coal has killed as many as 12,000 people. The health effects of this pollution were both immediate and long lasting.[10]

2. Air pollution

Air pollution is a mixture of particulate matter (PM), gases (ranging in size from a few nanometers to several micrometres) and gaseous co-pollutants that can exist in a particulate phase.[11] Particulate matter may be coarse PM_{10} (mean aerodynamic diameter 10–2.5 μm) or fine $PM_{2.5}$ (0.1–2.5 μm) or ultrafine (<0.1 μm). Gaseous pollutants consist mainly of nitrogen, sulfur oxide and other semivolatile and volatile organic chemicals (VOCs). Ozone is the most prevalent secondary pollutant, in addition to a number of inorganic and organic acids, found in both the gas and particle phases.[12] Air pollution due to PM_{10} is mainly because of dust from industries, mining and construction, whereas pollution from $PM_{2.5}$ is from combustion and burning of fossil fuel and biomass or stubble burning after harvesting paddy crops. Ultrafine along with VOCs such as acrolein, benzene and butadiene are from fresh emission from vehicles. Air pollution during winter seasons in northern part of India is mainly because of smog, which is a mixture of atmospheric pollutants mainly $PM_{2.5}$ and fog.

According to World Health Organization (WHO) the daily acceptable level of $PM_{2.5}$ is 10 $\mu g/m^3$ annual mean and 25 $\mu g/m^3$ 24-h mean and of PM_{10} is 20 $\mu g/m^3$ annual mean and 50 $\mu g/m^3$ 24-h mean. However Indian standards are less stringent for $PM_{2.5}$ it is 40 $\mu g/m^3$ annual mean and 60 $\mu g/m^3$ 24-h mean and of PM_{10} is 60 $\mu g/m^3$ annual mean and 100 $\mu g/m^3$ 24-h mean.[13]

3. Air pollution: a global health burden

In current decade air pollution is getting worse in many part of world. The ecological–economic shifts during the past few decade have resulted in $PM_{2.5}$ disproportionately affecting countries such as China and India.[14–16] According to WHO report 2018, 9 out of 10 people worldwide breathe air containing high levels of pollutants and termed air pollution as "the new tobacco". Over 90% of the global population live in areas with $PM_{2.5}$ exposure exceeding

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WHO recommended thresholds. The global $PM_{2.5}$ exposure has increased from 39.6 μg/m^3 in 1990 to 49.6 μg/m^3 in 2016, with the majority of the increase occurred between 2010 and 2016.[17] Thought the household air pollution (HAP) and water pollution are declining ambient air, chemical, and soil pollution are rising mainly in developing and industrializing low and middle-income countries.

Most of the urban population in India is living in cities with air quality index (AQI) below WHO standards. At present India is severely suffering from this medical emergency. Out of the most polluted 20 cities in terms of $PM_{2.5}$ levels in the world, 14 are located in India.[17,18] The AQI in major cities in India ranges from 150 to 300 μg/m^3 during winter seasons which is very high than the recommended limits. The pollution is increased significantly in last 10–12 years in the northern part of the country.[19] This lead to increased morbidity and mortality which has huge economic impact upto 1.36% of India's Gross Domestic Product (GDP) in 2019.[20] Population-weighted mean annual ambient $PM_{2.5}$ exposure in India in the year 2015, is estimated to have been 55 μg m^3, this vary widely across India, with the largest (>100 μg/m^3) exposure observed over the Delhi National Capital Region.[21] India State-Level Disease Burden Initiative Air Pollution Collaborators[22] estimated the exposure to air pollution and its impact on deaths, disease burden, and life expectancy in every state of India in 2017 and found that the annual population-weighted mean exposure to ambient particulate matter $PM_{2.5}$ in India was 89·9 μg/m^3 in 2017. Around 76·8% of the population of India, were exposed to annual population-weighted mean $PM_{2.5}$ greater than 40 μg/m^3, which is the limit recommended by the national ambient air quality standards in India.

The impact of air pollution on health is equivalent to its rivals like smoking, hypertension and physical inactivity.[23] It causes premature deaths, the main cause for which is cardiovascular diseases in 70–80% of the cases and rest are due to respiratory diseases and malignancies.[24] Diseases caused by pollution were responsible for an estimated 9 million premature deaths in 2015 which is 16% of all deaths worldwide. In the most severely affected countries, pollution-related disease is responsible for more than one death in four. Nearly 92% of pollution-related deaths occur in low-income and middle-income countries. Children are at high risk and even extremely low-dose exposures to pollutants is hazardous in utero and in early infancy.[14]

In India around 1·24 million deaths (12·5% of the total deaths) were attributable to air pollution in 2017. Around 60% is from ambient PM pollution and 40% from HAP.[22] In 2019 it increase to 1.67 million deaths which accounts for 17.8% of the total deaths in the country. Ambient air pollution is a major contributor (0.98 million) as compared to household air pollution (0.61 million). The death rate from 1990 to 2019 has increased due to ambient PM and ozone pollution, whereas death rate of household air pollution decreased significantly.[20]

Even short-term elevations in $PM_{2.5}$ levels in the regions with low daily levels of exposure to $PM_{2.5}$ (<35 μg/m3) translates to a 0.3–1.0% increase in the relative risk of cardiovascular mortality per 10 μg/m^3 increase in $PM_{2.5}$. At higher levels of daily exposure each 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 0.35% excess risk of cardiovascular death.[25] Short-term increases in $PM_{2.5}$ and ozone in the medicare population (61 million U.S. citizens) were associated with increase risk of death.[26] Analysis of 445,860 adults enrolled in the American Cancer Society Cancer Prevention Study-II showed that long-term $PM_{2.5}$ exposures from fossil fuel combustion, especially coal burning and diesel traffic, were associated with increases in ischemic heart disease (IHD) mortality. The risk of IHD mortality associated with $PM_{2.5}$ derived from coal combustion was five times higher than the risk associated with overall $PM_{2.5}$ mass.[27] A study examining short-term variations in NO_2 reported an increase in cardiovascular mortality of 0.4–0.88% for a 10 μg/m^3 daily increase in NO_2.[28]

According to GBD study 2015, ambient $PM_{2.5}$ was the fifth-ranking mortality risk factor in 2015 and there is significant increase in death (from 3.5 million to 4.2 million) attributed to $PM_{2.5}$ from 1990 to 2015. Exposure to $PM_{2.5}$ caused around 4·2 million deaths and around 103·1 million disability-adjusted life-years (DALYs) in 2015. This amounts to about 7·6% of total global deaths and 4·2% of global DALYs. More than 50% of these are in east and south Asia.[29] On the basis of the dose response relationship between $PM_{2.5}$ and mortality, no lower concentration threshold exists at which exposures can be considered safe at the population level.[12] Longer term increases in exposure by 10 μg/m^3 of $PM_{2.5}$ during the previous year (annual average $PM_{2.5}$ of 6–15.6 μg/m^3), and of 10 parts per billion ozone were associated with a 7.3% and 1.1% relative increase in all-cause mortality. Although. cause-specific mortality data were not provided, a wealth of evidence supports that more than one-half of deaths attributable to air pollutants are due to cardiovascular causes.[30] Even in developed countries like 28 countries of the European Union, annual excess mortality rate from ambient air pollution is 659000 and between 40% and 80% are due to cardiovascular events.[31] Studies from Europe and Canada reported an almost linear relationship between $PM_{2.5}$ and mortality to levels as low as 2 μg/m^3 $PM_{2.5}$.[32,33]

HAP is an important contributors to global air pollution related health effects. Instead of declining trend in HAP it still account for approximately 75% of all PM air pollution mainly in low and middle income countries. In low and middle income country and especially in villages where low-efficiency combustion of biomass fuels is used, the household air pollution levels are several times higher than ambient out-door levels ranging between 200 and 2000 μg/m^3. During periods of cooking with low-efficiency combustion of biomass fuels may lead to peak exposures of >30,000 μg/m^3.[34] These levels exceed ambient outdoor levels even in the most polluted outdoor urban environments.

The composition of household air pollution vary widely, depending on socioeconomic, cultural and geographical factors. It is very difficult to differentiate from outdoor air pollution to HAP as more that 50% outdoor particles are inhaled when people are indoor. Though there is decline by 13% in attributed death and 20.3% in disease burden due to HAP from 2005 to 2015, the attributable deaths is still very high due to household air pollution estimated to be 2·9 million deaths (2·2 million to 3·6 million) in 2015.[35] The association of household air pollution and respiratory outcomes and lung cancer is well established and its association with cardiovascular outcomes is emerging. In contrast to the level of evidence of outdoor air pollution with cardiovascular disease, there is a paucity of data of association between cardiovascular disease and HAP.[34] A prospective study involving 271,217 adults in China followed up for a mean of 7.2 years showed that, the use of solid fuel, compared with clean energy, was significantly associated with increased cardiovascular mortality.[36]

4. Mechanisms of air pollution mediated cardiovascular disease

The effect of air pollution on cardiovascular health may be acute or chronic and multiple mechanisms are involved in mediating the cardiovascular effects of $PM_{2.5}$ inhalation. These mechanisms, are closely linked and can be broadly divided into primary initiating responses to pollutant inhalation, transmission pathways and end organ effector mechanisms. After exposure to PM, pollution mediated oxidative stress, local inflammation and ion channel or receptor

activation occurs. Then transmission mediated pathway is initiated which include: increase inflammatory response leading to the systemic release of many biological intermediates (such as oxidized lipids, cytokines, activated immune cells, microparticles, C-reactive protein, endothelin's etc.). There is autonomic imbalance and activation of the hypothalamic pituitary adrenal (HPA) axis leading to brown adipose dysfunction, white adipose inflammation, elevation in glucocorticoids and insulin resistance. At last these pathways lead to end organ effector mechanisms responsible for cardiovascular events, including endothelial dysfunction, vascular inflammation, increase thrombosis, increased potential for cardiac arrhythmia and autonomic imbalance or HPA activation. Finally, chronic end organ changes occurs due to long-term exposures. These changes include systemic hypertension, diabetes mellitus, left ventricular hypertrophy, vascular hypertrophy, renal disease.[11,12]

Chronic and persistent exposure (months to years) leads to progression of atherosclerosis.[11,12,15,37–40] A positive correlation was demonstrated between long-term exposure to $PM_{2.5}$ and atherosclerosis, measured in terms of carotid intima media thickness and coronary and abdominal aortic calcium levels.[12] The Multi-Ethnic Study of Atherosclerosis and Air Pollution showed that a 5 μg/m3 increase in long-term exposure to $PM_{2.5}$ was significantly associated with progression of coronary artery calcification.[41] A meta-analysis of eight cross-sectional (n = 18,349) and three prospective (n = 7268) studies found a significant association between $PM_{2.5}$ and increased carotid intima media thickness.[42]

The preponderance of evidence supports rapid and persistent effects of particulate air pollutants on vascular function in both animals and humans. The air pollution can altered vasomotor tone, induced vascular inflammation, increased the accumulation of oxidized lipids and potentiated atherosclerosis. It causes progression of atherosclerotic lesion formation and make them more vulnerable, endothelial dysfunction and impaired blood pressure regulation has been demonstrated.[11,12,15,37–40] Ultrafine particles thought to be less harmful, has also shown to cause endothelial dysfunction. Inhalation of elemental carbon as well as diluted diesel exhaust, have shown to cause rapid endothelial dysfunction.[43] Small magnitude of epigenetic changes are also associated with exposure to air pollution.[44] Exposure to air pollution may lead to rapid alterations in sympathetic and parasympathetic imbalance as evidenced by changes in blood pressure and heart rate variability in response to both coarse and fine particle. In animal model it has been shown that exposer to concentrated air particles lead to development of hypertension, with evidence of central sympathetic nervous system activation in response to $PM_{2.5}$ exposure which is likely mediated by neuroinflammation.[45,46] Ultrafine particulates, nanomaterials, and ozone are shown to directly disrupt the blood–brain barrier or result in circulating factors that may influence neuronal function in humans and mice.[47,48]

5. Cardiovascular health effect of air pollution

Cardiovascular system is the main target of air pollution, mainly due to $PM_{2.5}$.[12,35,49] The adverse effect of air pollution depends on individual susceptibility and on the environmental factors. It also depend upon length and dose of exposure, age, pre-existing medical conditions and sources or composition of the air pollutants. Exposure to environmental pollutants occurs via three general routes: inhalation, ingestion, and absorption (dermal).[23]

The individuals who are having cardiovascular disease or their risk factors like diabetes, smoking, and dyslipidemia are more prone for the adverse effects of air pollution as compared to healthy population. But even healthy population living in polluted environment have vascular endothelial dysfunction which may not be clinically manifesting. The environmental factors affecting the impact of air pollution on health consists of proximity to major roadways or industries, the available green area in the locality, ambient air temperature and exposure to dust specially in desert areas. Population residing in areas near to roadways with heavy traffic have increased carotid-intima thickness, hypertension and increased abdominal adiposity and also increased chronic inflammation which leads to increased risk of cardiovascular event like increased risk of sudden cardiac death, mortality after stroke and heart failure.[50,51] This link between air pollutants and increased risk for cardiovascular events is supported by animal models but the exact underlying mechanism is still not known and many theories has been proposed.

Although many gases have been shown to have adverse effects on health, the largest evidence supports fine PM (≤2.5 μm in diameter ($PM_{2.5}$)) as the most severe environmental threat. Although $PM_{2.5}$ has been implicated as a cause in numerous non-communicable diseases, more than half of all the deaths associated with these diseases are from cardiovascular causes.[11,37,52] A significant increase in cardiovascular disease, from 0.5% to 1.5%, for every 5–6 $\mu g/m^3$ increase in $PM_{2.5}$ was found. Acute exposure to $PM_{2.5}$ resulted in a higher rate of death due to cardiovascular than respiratory disease (69% versus 28%).[53] The relation of time frames of exposure that are required to mediate acute/chronic cardiovascular events is still not clear.

$PM_{2.5}$ component is one-third the size of red blood cell and enters blood circulation through the lung alveoli either by directly crossing the barrier or translocating through macrophages.[54] The cardiovascular effects of $PM_{2.5}$ are known to vary according to source and pollutant composition. It is unlikely that all components of particulate matter have the same potency in causing health effects. There are many components contributing to the health effects of $PM_{2.5}$, but not sufficient evidence to differentiate those constituents (or sources) that are more closely related to specific health outcomes.[55] From a compositional perspective, particulate sulfates, nitrate and organic carbon are most consistently associated with cardiovascular mortality than other $PM_{2.5}$ constituents, such as iron, potassium, silicon and zinc.[55–58]

Short term exposure (hours to days) may increase the risk of various arrhythmias, myocardial infarction (MI), stroke and acute exacerbation of heart failure.[11,12,59,60] Short-term increases in systolic blood pressure (BP) (1–5 mmHg) and diastolic BP (1–3 mmHg) occur in response to PM exposure (fine, coarse and diesel exhaust).[15,61] This may be due to alteration in autonomic tone and endothelial dysfunction. Acute exposure to $PM_{2.5}$ of 10 $\mu g/m^3$ correlated with an increase in systolic BP of 1–3 mmHg. This association is stronger among men, Asian individuals and individuals living in areas with levels of high air pollution.[62] In long term there is a consistent association between $PM_{2.5}$ levels and BP. Chronic exposure to $PM_{2.5}$ is associated with significantly larger increases in BP and has also been associated with increased incidence of hypertension.[62–66] Short term exposure of $PM_{2.5}$ was associated with increase in heart failure hospitalization or death.[67,68] Admissions to hospital for peripheral arterial disease has shown to be increased by 0.26% and 4.40% for every 10 $\mu g/m^3$ increase in acute and chronic exposure to $PM_{2.5}$.[69] The adverse effect on ankle brachial index has also been observed in long term exposure to air pollution.[70]

There is clear association between $PM_{2.5}$ exposure and non fatal MI.[12] In a meta-analysis of 34 studies, each 10 μg/m3 increase in $PM_{2.5}$ (same day levels or lag of 0 days) was associated with a 2.5% relative increase in the risk of MI.[71] In a large prospective study, annual increases of 10 $\mu g/m^3$ in PM_{10} and 5 $\mu g/m^3$ in $PM_{2.5}$ were associated with increased risks of MI of 12% and 13%,

respectively.[72] Inhalation of diesel exhaust PM increased thrombotic response and increased platelet–leukocyte aggregates with exposure.[73] $PM_{2.5}$ levels (per 10 ug/m^3) were associated with increased risk of both deep vein thrombosis and pulmonary embolism.[74] Patients with post MI left ventricular dysfunction and on implantable defibrillator has increased risk of ventricular tachycardia after exposure to $PM_{2.5}$[75,76] Meta-analysis of four studies involving >450,000 individuals showed that each 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 0.89% (95% CI 0.2–1.6%) increase in the relative risk of atrial fibrillation.[77] In patients with no heart diseases study has reported some association between long-term exposure to air pollution and QT prolongation.[78]

A large body of evidence, including both animal and clinical studies, suggests that $PM_{2.5}$ inhalation is associated with induction of insulin resistance and diabetes.[15,79,80] In a meta-analysis of 13 published studies, each 10 μg/m^3 increment in $PM_{2.5}$ was associated with a 10% relative increase in incidence of diabetes with more stronger association in women.[81] Another meta analysis showed that each 10 μg/m^3 increase in long term exposure to $PM_{2.5}$ was associated with a 39% increased risk of developing diabetes, an association that persisted even at very low levels of exposure.[82] Both short-term and long-term risks of stroke and risks of death from stroke is significantly associated with exposure to $PM_{2.5}$ (per 10 μg/m^3 increments).The associations were strongest for ischemic and hemorrhagic stroke. Long-term exposure to $PM_{2.5}$ was also associated with increased risks of dementia, Alzheimer disease and Parkinson disease.[83]

6. Conclusion

Various experimental and epidemiological studies have strengthened our general knowledge on the association of pollution with cardiovascular morbidity and mortality and shown air pollution (especially ambient) as the most common environmental cause for cardiovascular disease. HAP is more important but neglected entity especially from low and middle income countries. It seems reasonable that HAP may be equally or more harmful then ambient air pollution but more studies are required for proving same. Most of the well-studied association of air pollution is with all-cause and cardiovascular mortality,[20,22,24–36,85–87] followed by strong emerging evidence for acute coronary syndrome[12,71,72,84] hypertension,[62–66] diabetes,[15,79–82], stroke,[83] and heart failure,[67] whereas there is insufficient evidence for thromboembolism and atrial fibrillation. Furthermore, there is emerging evidence that even $PM_{2.5}$ concentrations below the upper safe values of the WHO air quality guidelines are associated with increase morbidity and mortality, indicating that, even in the most developed countries, further efforts to reduce air pollution will benefit.

India is on the verge of eruption of volcano of air pollution diseases if not intervene early and effectively. More studies are warranted to know the dose, duration of exposure and mechanism of air pollution effect on human population especially in India. Randomized clinical trials are also warranted to study the effect of various interventions for curbing air pollution and improving over all health especially cardiovascular health in India where it may have huge impact. India needs a multipronged, holistic and proactive approach at both public and government level with cross-ministerial efforts to fight with this unintentionally ignored enemy which in near future will have huge effect not only to the health of the people but economy of the country, if left unattended.

Declaration of competing interest

None declared.

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