


CONTEMPORARY REVIEW

Cumulative Lifetime Burden of Cardiovascular Disease From Early Exposure to Air Pollution

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ABSTRACT: The disease burden associated with air pollution continues to grow. The World Health Organization (WHO) estimates ≈7 million people worldwide die yearly from exposure to polluted air, half of which—3.3 million—are attributable to cardiovascular disease (CVD), greater than from major modifiable CVD risks including smoking, hypertension, hyperlipidemia, and diabetes mellitus. This serious and growing health threat is attributed to increasing urbanization of the world's populations with consequent exposure to polluted air. Especially vulnerable are the elderly, patients with pre-existing CVD, and children. The cumulative lifetime burden in children is particularly of concern because their rapidly developing cardiopulmonary systems are more susceptible to damage and they spend more time outdoors and therefore inhale more pollutants. World Health Organization estimates that 93% of the world's children aged <15 years—1.8 billion children—breathe air that puts their health and development at risk. Here, we present growing scientific evidence, including from our own group, that chronic exposure to air pollution early in life is directly linked to development of major CVD risks, including obesity, hypertension, and metabolic disorders. In this review, we surveyed the literature for current knowledge of how pollution exposure early in life adversely impacts cardiovascular phenotypes, and lay the foundation for early intervention and other strategies that can help prevent this damage. We also discuss the need for better guidelines and additional research to validate exposure metrics and interventions that will ultimately help healthcare providers reduce the growing burden of CVD from pollution.

Key Words: air pollutants, environmental ■ cardiovascular abnormalities ■ cardiovascular disease ■ epithelial barrier

Cardiovascular disease (CVD) is a leading cause of death worldwide, and evidence suggests that the disease process can begin early in life.¹ Several factors contribute to the development of CVD; greater than half of the risk is modifiable, including hypertension, hyperlipidemia, diabetes mellitus, and smoking, while the remaining risks are thought to be heritable.² A substantial body of epidemiological evidence has demonstrated significant associations between air pollution exposure and increased CVD risk.³ Here, we focus on the cumulative lifetime burden of air pollution, especially the evidence of pollution exposure that begins in childhood, by surveying the association between CVD risk from exposure to ambient and indoor pollution and discuss interventional strategies to prevent and mitigate risk.

Every year, >3 million people worldwide die of ischemic heart disease or stroke attributed to air pollution,

more than from other modifiable cardiac disease risks such as obesity, diabetes mellitus, or cigarette smoking.⁴ Both acute and chronic exposures to components of air pollution, including fine particulate matter (PM) and polycyclic hydrocarbons (PAH), have been associated with increased cardiovascular events such as ischemic heart disease, heart failure, cardiac arrhythmias, hypertension, and others.⁵

The cardiopulmonary systems of children are rapidly developing, and are therefore more vulnerable to injury and inflammation caused by pollutants.⁶ Emerging observations from the World Health Organization (WHO) suggest that early exposure to pollution during childhood and adolescent years can alter a child's health trajectory and result in increased prevalence of risks for CVD later in life, including obesity, metabolic syndrome, and hypertension.⁷ The most recent WHO

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report concluded that the millions of children exposed to unsafe levels of air pollution suffer a “life sentence” of illness, pushing them to a “path of chronicity, suffering...and challenge.”⁸ Furthermore, economically disadvantaged groups are disproportionately vulnerable to air pollution and its adverse health effects.⁹ As such, there is an urgent need to formulate more effective policy responses and health guidelines, aimed at protecting the most vulnerable, particularly children and the elderly.

Air pollution is a complex mixture containing both particles and gases. The air pollutants for which the Environmental Protection Agency has set National Ambient Air Quality Standards include carbon monoxide, nitrogen dioxide, sulfur dioxide and ozone, PM, and lead.⁵ The most well-researched air pollutant related to cardiovascular events is fine PM (particles ≤ 2.5 μm in diameter [$\text{PM}_{2.5}$]), of which a large fraction is comprised of particles generated by a combustion of fossil fuels, including black elemental carbon, metals, and a variety of complex organic molecules.¹⁰ These fine particles penetrate deeply into the small airways and alveoli of the lungs where they stimulate macrophages and epithelial cells to release proinflammatory cytokines.^{4,11,12} The US Environmental Protection Agency regulates air pollutants such as lead, sulfur dioxide, nitrogen dioxides, carbon monoxide, PM, and ozone, all of which have been associated with cardiovascular events.⁵

Although the association between exposures to a pollutant like $\text{PM}_{2.5}$ and CVD risk is now well established, the specific mechanisms by which these exposures promote CVD are not completely understood.³ From epidemiological studies, one hypothesis argues that upon entering the lungs, pollutants produce local inflammation and oxidative stress that leads to subsequent systemic inflammation, which contributes to endothelial dysfunction, thrombosis, and enhanced atherosclerosis.¹³ A second hypothesis suggests that pollutants activate the pulmonary autonomic nervous system which can lead to life-threatening arrhythmias.⁵ A third hypothesis suggests that PM, particularly, ultrafine particles (<0.1 μm in diameter), enter the blood stream, directly damaging tissues and cells within the cardiovascular system.⁵

This paper is meant to be a contemporary review, rather than a comprehensive review. It focuses on relevant and recent published articles. Using available evidence, including from our own research, it intends to inform readers about the complex issue of the cumulative lifetime burden of CVD from exposure to air pollution. Search terms and keywords included hypertension, obesity, glucose metabolism, and diabetes mellitus, hyperlipidemia, dyslipidemia, cardiac arrhythmias, stroke, atherosclerosis, cardiac disease, as well as pollution, PAH, $\text{PM}_{2.5}$, concurrently with keywords including early exposure, fetal exposure, infants, children, or adolescent. We searched for exact phrases

such as “pollution and CVD and children” and included wildcard searches to find other possible results such as “cardiovascular disease * pollution”. Finally, to make our online searches more comprehensive, we conducted citation searches to determine whether articles have been cited by other authors, and to find more recent papers on the same or similar subject(s). All citations were confirmed and entered using EndNote.

GLOBAL AIR POLLUTION: A GROWING LIFETIME BURDEN

Much of the world’s population lives in places where air quality exceeds the limits of the health-protective guidelines set by the WHO (Figure 1), making air pollution the largest environmental risk to health worldwide.¹⁴ Here, we discuss the risks from ambient and indoor air pollution, as well as pollution from tobacco smoke, which shares common pathways to air pollution-induced CVD.

Ambient and Indoor Pollution

Although there are many sources of air pollution, both natural (eg, volcanic eruptions) and man-made (eg, cookstoves, power plants, motor vehicles), the latter is the primary source, because even most catastrophic wildfires are started by human activities.^{14,15} Outdoor air pollution is typically produced by combustion of fossil fuels and industrial processes while indoor or household air pollution is produced by smoke from poorly ventilated domestic cookstoves that burn solid fuels such as wood, crop waste, dried dung, and coal/lignite or kerosene mostly in low and middle-income countries.¹⁴ Nearly 3 billion people worldwide are exposed to household air pollution from inefficient cooking and heating stoves,¹⁴ and almost the entire global population is exposed to detectable levels of outdoor air pollution from traffic, industry, and other sources.

Recent data released by WHO show that outdoor and household air pollution has a vast negative impact on both adult and child health and survival.¹⁴ United Nations Children’s Fund (UNICEF) recently reported that deaths in Africa from outdoor air pollution increased from 164 000 in 1990 to 258 000 in 2017—a growth of nearly 60%—affecting especially the poorest children.¹⁶ In Asia, deaths attributable to $\text{PM}_{2.5}$ increased from 3.5 million in 1990 to 4.2 million in 2015,¹⁷ many of them in children exposed to household air pollution from unventilated stoves and wood fires.¹⁴ In 2010 in China alone, outdoor air pollution was associated with >300 000 deaths, 20 million cases of respiratory illness, and annual healthcare costs $>\$500$ billion, with children particularly susceptible.¹⁸ Especially in children whose organs are still developing, exposure to PM can result in adverse cardiopulmonary effects early in life¹⁹

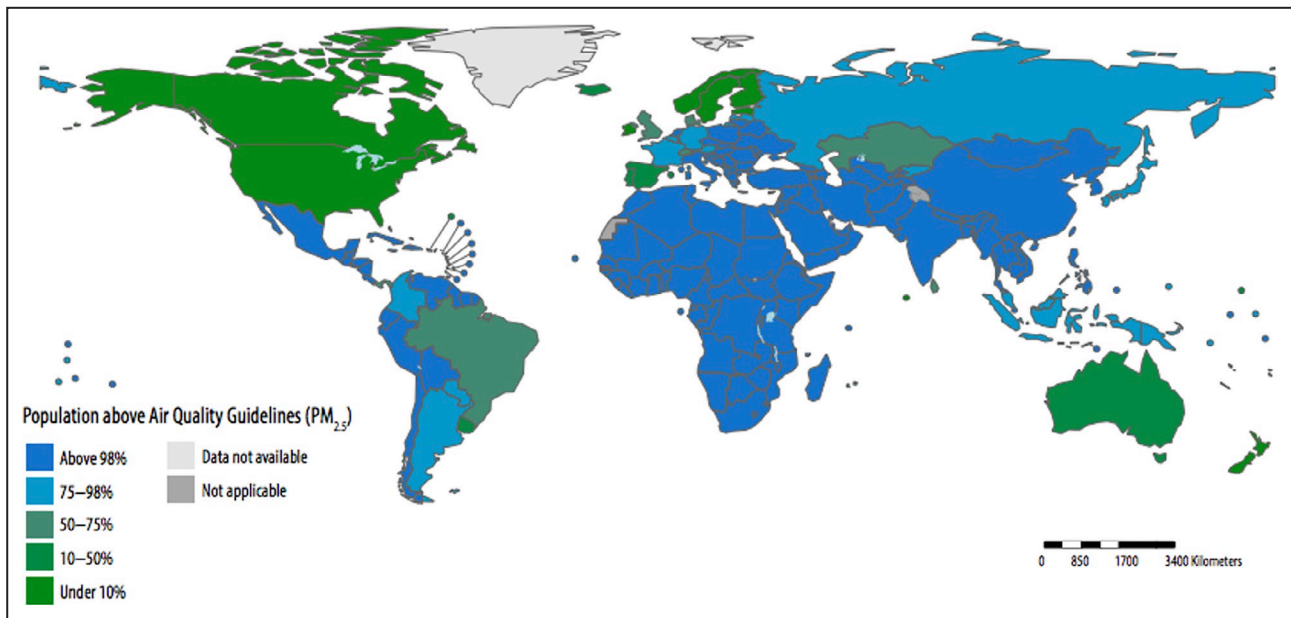


Figure 1. Proportion of children aged <5 years of age living in areas in which World Health Organization air quality guidelines (particulate matter <2.5 μm) are exceeded (by country, 2016).

From World Health Organization report on air pollution.¹⁴ PM_{2.5} indicates particulate matter <2.5 μm .

and WHO estimates about 93% of the world's children aged <15 years (1.8 billion children) breathe air that is so polluted it puts their health and development at serious risk.⁷ In fact, the damage from air pollution often has already been inflicted even before birth, as maternal exposure to air pollutants during pregnancy has been shown to be associated with increased adverse birth outcomes such as stillbirth, low birth weight, and preterm birth.^{20–22} In particular, families living in environments with high levels of household air pollutants have low child survival rates²³ and increased neonatal morbidity and mortality.^{24–29} A new, yet-unpublished study from the Cardiff School of Medicine that followed 8 million live births in the U.K. and Wales between 2001 and 2012, found that babies who grow up breathing polluted air—compared with those living in non-polluted regions—have a higher risk of death as a neonate (38%), between 1 and 12 months of age (54%), or during infancy (43%).³⁰

Tobacco Smoke Pollution

Tobacco use significantly increases the risk for many serious human diseases, but its greatest effect on morbidity and mortality is through promoting CVD^{31,32} and the tobacco-related risk for symptomatic atherosclerotic CVD is \approx 40%.³³ Air pollution-induced CVD shares common pathways with tobacco-induced CVD, and air pollution from combustion sources is a complex mixture of carbon-based particles and gases similar to tobacco smoke.³⁴ Although a greater body of literature exists on studies of tobacco smoke exposure, the precise toxic components and the mechanisms involved

in smoking-related cardiovascular dysfunction are not completely known, but we know that cigarette smoking increases inflammation, thrombosis, and oxidation of low-density lipoprotein cholesterol,³² similar effects produced by pollution exposure. Also, increased hypertension, obesity, and insulin resistance—components of metabolic syndrome—have been reported to be associated with tobacco exposure,³⁵ similar to what has been reported for ambient pollution exposure (Table). As with indoor and outdoor pollution, we have seen similar patterns of epigenetic changes including increased methylation in newborns and adults exposed to tobacco smoke.^{36–38}

Particulate Matter Pollution

Both chronic and acute exposure to pollutants like PM_{2.5}, as well as to tobacco, activate the release of proinflammatory and vasoactive factors that contribute to cardiopulmonary pathology⁴. The pulmonary effects of PM_{2.5} and PM₁₀ are well known and include decreased lung function and increased risks of lung infection, asthma, bronchitis, disorders for which children are particularly vulnerable, as well as chronic obstructive pulmonary disease and lung cancer in adults.^{73–77} Epidemiological and clinical studies have increasingly shown that air pollution is associated with not only respiratory diseases but also CVD.⁶ In fact, PM_{2.5} is the pollutant with the most compelling observational and experimental evidence of association with increased risk of cardiovascular mortality.⁷⁸ As we detail in this review, ambient PM_{2.5} is strongly associated

with increased CVD such as myocardial infarction (MI), cardiac arrhythmias, ischemic stroke, vascular dysfunction, hypertension and atherosclerosis⁷⁸ (Table). Ambient PM_{2.5} exposure is among the leading causes of world-wide mortality, particularly from CVD⁷⁹ and exposure to PM_{2.5} increases the risk of hospitalizations from CVD.⁸⁰ Accordingly, reducing exposure to PM_{2.5} would benefit public health by decreasing both immediate and long-term CVD risk.^{4,12,79,81–83}

Pollution in the Disadvantaged

In addition, economically disadvantaged groups are disproportionately vulnerable to air pollution and its negative health effects.⁸⁴ An underprivileged environment is clearly linked to increased risks for CVD and other diseases.² This is because low-income residents in urban settings often live closer to major roadways, power plants, and industrial facilities, and in neighborhoods with other environmental risk factors (noise, crime, little green space, food deserts) and poor-quality housing compared with those living under better conditions.⁸⁵ Indoor pollution caused by cooking with fires burning solid fuels or dirty stoves fueled by kerosene is of particular concern for children living in such households.⁸⁵ In poorly ventilated houses with families living in low- and middle-income countries, the burning of solid fuels, kerosene, incense, and mosquito coils increases indoor PM, irritating respiratory tract, eyes, and skin^{86,87} and, according to WHO, is responsible for around nearly 4 million deaths from serious cardiopulmonary diseases.¹⁵

CVD RISK FROM POLLUTION: FROM BIRTH TO ADULTHOOD

The large and growing body of scientific evidence points to a causal relationship between elevated air pollution and cardiovascular morbidity and mortality.³ Such evidence places nearly 2 billion children at serious lifetime CVD risk.^{7,14} These children are disproportionately in low-socioeconomic-status households, with little control over their home and social environment. Further, maternal exposures to pollution during pregnancy has also been linked to increased propensity towards developing future CVD risk.⁸⁸ The published evidence about the adverse effects of pollution exposure on major CVD risks and cardiovascular phenotypes in pregnant women, neonates, children, and adults is summarized in Table and discussed in detail below.

Hypertension

Children with high systolic blood pressures are at increased risk of hypertension and the metabolic syndrome later in life.⁸⁹ Recent evidence suggests that air pollution exposure in pregnancy may also portend

increased risk for the next generation. In the prospective Boston Birth Cohort of 1200 mothers, Zhang et al³⁹ found that PM_{2.5} exposure during pregnancy was associated with elevated blood pressure in children ages 3 to 9 years; further, in another study, these authors found long-term exposure to ambient PM was also associated with higher prevalence of hypertension in children and adolescents.⁴⁰ In addition, exposure to PM_{2.5} during late pregnancy was positively associated with systolic hypertension in newborns⁴¹ and in a cohort of 1131 mother-infant pairs exposed to PM_{2.5}, newborn infants showed systolic hypertension,⁴¹ an association also seen in smoking mothers.⁹⁰ Children attending school on days with higher concentrations of PM (diameter <100 nm) had higher systolic blood pressures.⁴² In addition, children aged 6 to 12 years exposed to ultrafine PM or PM_{2.5} in combination with NO₂ demonstrated increased systolic and diastolic blood pressures.^{42,43} Curto et al⁴⁴ found that adult women aged 18 to 84 years living in India exposed to PM_{2.5} had increased systolic blood pressure. Finally, even short-term exposure to air pollution from cookstoves elicited increases in systolic blood pressure in adults.⁴⁵

Obesity

Airborne polycyclic aromatic hydrocarbons (PAHs) is a family of pollutants that have been most strongly associated with obesity, although PM_{2.5} and NO₂ have been linked with obesity as well. PAH are created during incomplete combustion processes and are known to have endocrine disrupting effects, and alter the behavior of adipocytes, promoting obesity.^{91–95} Alderete et al⁴⁶ found pregnant women exposed to traffic-related air pollution had higher cord blood levels of leptin and high-molecular-weight adiponectin, which were associated with increased infant weight gain, which may have implications for future obesity risk. Adolescents exposed to air pollution and PAH during the pre-term/neonatal period had increased prevalence of obesity and diabetes mellitus.⁴⁷ In 1 study, Jerrett et al⁴⁸ examined traffic pollution around family homes in the United States and found that higher levels of vehicular traffic and pollution were associated with higher attained body mass index in children aged 10 to 18 years, particularly females aged 18 years. In 1 community of Southern California, pollution from automobiles was positively associated with higher body mass index in children aged 5 to 11 years.⁴⁹ Infants exposed to black carbon and PM_{2.5} emissions from traffic pollution in early life exhibited rapid postnatal weight gain.⁵⁰ Wang et al⁵¹ found a positive association between several pollutants and obesity in a meta-analysis of 35 studies.

Insulin Resistance and Diabetes Mellitus

Animals exposed to air pollutants during pregnancy show an increased risk of metabolic syndrome, birth

Table. CVD Risks From Pollution Exposure in Pregnant Women, Neonates, Children, and Adults

Cardiovascular Risk	Timing of Exposure	Exposure	Effect	Reference
Hypertension	Neonatal	PM _{2.5}	Increased blood pressure in ages 3 to 9 y	Zhang M (2018) ³⁹
	Children 1 to 10 y; Adolescents 10 to 19 y	PM _{2.5}	Increased blood pressure	Zhang M (2019) ⁴⁰
	Newborns	PM _{2.5}	Increased systolic blood pressure	Van Rossem L (2015) ⁴¹
	School children, 6 to 12 y	Ultrafine particles (<100 nm)	Increased systolic blood pressure	Pieters N (2015) ⁴²
	12 y	Long-term exposure to NO ₂ and PM _{2.5}	Increased diastolic blood pressure	Bilenko N (2015) ⁴³
	Women 18 to 84 y	PM _{2.5}	Increased blood pressure	Curto A (2019) ⁴⁴
	adults	Pollution from cookstoves	Increased systolic pressure	Fedak KM (2019) ⁴⁵
Obesity	Pregnant women	Traffic-related air pollution	Higher cord blood levels of leptin and high molecular weight adiponectin, adipokines associated with increased infant weight change in female infants.	Alderete TL (2018) ⁴⁶
	5 to 14 y	Polycyclic aromatic hydrocarbons and fine PM	The prevalence of obesity was 20.6% at age 5 y and increased across follow-ups until age 11 y when it was 33.0%	Rundle A (2019) ⁴⁷
	10 to 18 y	Traffic-related pollution	Increased BMI, mostly in females at age 18 y	Jerrett M (2010) ⁴⁸
	5 to 7 y	Traffic-related air pollution	A 13.6% increase in the rate of average annual BMI growth between the children exposed to the lowest to the highest tenth percentile of air pollution	Jerrett M (2014) ⁴⁹
	Birth to 6 mo	Black carbon, PM _{2.5}	Infants exposed to higher traffic-related pollution in early life may exhibit more rapid postnatal weight gain and reduced fetal growth in mothers exposed to PM _{2.5}	Fleisch AF (2015) ⁵⁰
	Adults, meta-analysis	Chemical pollutants (polychlorinated biphenyls, others)	Positive associations between pollutants and obesity	Wang Y (2016) ⁵¹
Glucose metabolism abnormalities, Diabetes mellitus	Pregnant women	NO ₂ , PM _{2.5}	Gestation diabetes mellitus in first and second trimester	Choe S (2019) ⁵²
	8 to 18 y	Ambient and traffic-related ambient pollution	Higher insulin resistance and secretion, which was observed in conjunction with higher glycemia	Toledo-Corral C (2018) ⁵³
	6 to 13 y	Medium-term exposure to ambient PM _{2.5} and PM ₁₀	Higher fasting blood glucose levels	Cai L (2019) ⁵⁴
	5 y	Traffic-related exposure to ozone and PM ₁₀ .	Increased ozone exposure may be a contributory factor to the increased incidence of type 1 diabetes mellitus. PM ₁₀ may be associated with development of type 1 diabetes mellitus before 5 y of age	Hathout E (2002) ⁵⁵
	10 y	Traffic-related air pollution	Insulin resistance increased by 17% for every 2 SD of increase in ambient PM and NO ₂	Thiering E (2013) ⁵⁶
	12 to 19 y	Tobacco smoke	Environmental second-hand tobacco smoke exposure was independently associated with the metabolic syndrome and type 2 diabetes mellitus	Weitzman M (2005) ⁵⁷
Dyslipidemia	45 to 84 y	PM _{2.5} and black carbon exposure 2 wk, 3 mo, 1 mo	Air pollution is adversely associated with HDL	Bell G (2017) ⁵⁸
	18 to 29 y (23±5 y)	PM _{2.5} , black carbon, NO ₂ , CO	High ambient air pollution concentrations associated with impairments in HDL functionality from systemic inflammation and oxidative stress	Li J (2019) ⁵⁹
	Children and adults	PM ₁₀	PM ₁₀ associated with elevated triglycerides, apolipoprotein B, and reduced HDL	Chuang K (2010) ⁶⁰
	Adults	PM _{2.5}	Long-term PM _{2.5} exposure associated with lipoprotein increases	McGuinn L (2019) ⁶¹

(Continued)

Table. Continued

Cardiovascular Risk	Timing of Exposure	Exposure	Effect	Reference
Cardiac arrhythmias	Adults	Second-hand smoke	Exposure during gestational development and during childhood was associated with having atrial fibrillation later in life	Dixit S (2016) ⁶²
	Adults	PM _{2.5} and PM ₁₀	Increased risk of atrial fibrillation	Liu X (2018) ⁶³
	Older adults (median 71 y)	PM _{2.5} and PM ₁₀	In patients exposed to PM ₁₀ and PM _{2.5} followed for 1 y, ventricular tachycardia and ventricular fibrillation correlated significantly with PM _{2.5} but not PM ₁₀	Folino F (2017) ⁶⁴
	Young adults	Ultrafine particles (5–560 nm), black carbon, NO ₂ and CO, SO ₂ , and O ₃	Significant increases in QTc, indicating cardiac repolarization abnormalities particularly in males overweight/obese and with higher C-reactive protein levels	Xu H (2019) ⁶⁵
Stroke	Post-menopausal women	NO ₂ and NO _x	In a large cohort of postmenopausal women, strong association between daily NO ₂ and NO _x exposure and hemorrhagic stroke more pronounced among non-obese participants	Sun S (2019) ⁶⁶
	Adults	PM _{2.5} and PM ₁₀ , NO ₂ , NO _x , SO ₂ , and O ₃	Air pollutants are significantly associated with ischemic stroke mortality	Hong YC (2002) ⁶⁷
	Adults	PM ₁₀ , NO ₂ , NO _x , SO ₂ , and O ₃	All pollutants associated with primary intracerebral hemorrhage and ischemic stroke patients	Tsai SS (2003) ⁶⁸
Atherosclerosis	Adults	PM _{2.5}	In older men and women (>60 y), significant associations between PM _{2.5} and carotid thickness	Kunzli N (2005) ⁶⁹
	Adults 45 to 84 y	PM _{2.5}	Concentrations of PM _{2.5} and traffic-related air pollution within metropolitan cities associated with coronary calcification, consistent with acceleration of atherosclerosis	Kaufman JD (2016) ⁷⁰
	Adults	PM _{2.5}	PM _{2.5} exposure associated with increased likelihood of having mild and especially severe coronary atherosclerosis	Hartiala J (2016) ⁷¹
	Adults	PM _{2.5}	Exposure to higher concentrations of PM _{2.5} in ambient air was significantly associated with development of high-risk coronary plaques	Yang S (2019) ⁷²

BMI indicates body mass index; HDL, high-density lipoprotein; and PM, particulate matter.

defects, and diabetes mellitus.⁹⁶ Animal studies have also demonstrated that PM_{2.5} exposure enhances insulin resistance and visceral inflammation/adiposity, providing a strong link between air pollution and type 2 diabetes mellitus.⁹⁷ This has been borne out in human studies. In a large cohort of singleton births in New York City, mothers' exposure to NO₂ in the first trimester and PM_{2.5} in the second trimester were associated with higher odds of gestational diabetes mellitus.⁵² In a cohort of 429 overweight and obese minority children in Los Angeles, increased prior-year exposure to traffic-related air pollution adversely affected type 2 diabetes mellitus-related pathophysiology.⁵³ Further, in 4234 children aged 6 to 13 years, Cai et al⁵⁴ found exposure to ambient PM_{2.5} and PM₁₀ was associated with higher fasting blood glucose levels. Hathout et al⁵⁵ reported that exposure to fine particulates such as PM₁₀ was a specific contributing factor for type 1 diabetes mellitus in children aged <5 years. In another study, insulin resistance and type 2 diabetes mellitus were greater in 10-year-old children exposed to high levels

of traffic-related air pollution compared with those children exposed to lower levels.⁵⁶ Finally, indoor exposure from second-hand tobacco smoke was associated with an increase in metabolic syndrome and type 2 diabetes mellitus in adolescents aged 12 to 19 years.⁵⁷

Dyslipidemia

In Chinese men and women, Bell et al⁵⁸ found that exposures to PM_{2.5} and black carbon (2 weeks, 3 months, and 1 year) was associated with lower concentrations of high-density lipoprotein. In a 2-year study, 73 young adults (23±5 years) exposed to traffic-related pollution (PM_{2.5}, black carbon, NO₂, CO) had significant reductions in high-density lipoprotein and apolipoprotein A-I (ApoA1) indicating impairments in lipoprotein functionality as a result of systemic inflammation and oxidative stress.⁵⁹ In a cohort of Taiwanese children and adults, Chuang et al⁶⁰ found that individuals exposed to PM₁₀ over time had elevated triglycerides, apolipoprotein B, and reduced high-density lipoprotein levels,

indicating a link between air pollution and progression of atherosclerotic disease. In a recent 9-year study of 6587 adults in the United States, long-term exposure to PM_{2.5} was associated with increased lipoprotein concentrations.⁶¹

Cardiac Arrhythmias

Arrhythmia is another potential manifestation of air pollution exposure that could lead to cardiovascular morbidity and mortality.⁹⁸ Adults having had a smoking parent during gestational development and those living with a smoker during childhood were each significantly associated with atrial fibrillation, which was more pronounced among adults without risk factors for atrial fibrillation.⁶² In a study of 100 adults exposed over to PM_{2.5} and PM₁₀ over several months, an increased risk of atrial fibrillation was seen.⁶³ In another study of 281 patients (mean 71 years) exposed to PM₁₀ and PM_{2.5} followed for 1 year,⁶⁴ ventricular tachycardia and ventricular fibrillation correlated significantly with PM_{2.5} ($P < 0.001$) but not PM₁₀. In these older adults, an analysis of the ventricular fibrillation episodes alone correlated significantly with higher PM_{2.5} and PM₁₀ exposure. Finally, Xu et al⁶⁵ followed 73 healthy young adults living in China under continuous pollution (particulates 5–560 nm diameter, black carbon, NO₂, CO, SO₂, and O₃) using 24-hour electrocardiographic recordings, and found that the young participants showed cardiac repolarization abnormalities (increased QTc interval), which were most strongly associated with nano-sized PM, with traffic-related pollutants (black carbon, NO₂, and CO), and with SO₂, and O₃. The associations were stronger in males who were overweight and had higher levels of C-reactive protein levels.

Stroke

Evidence from epidemiological studies has demonstrated a strong association between air pollution and stroke.⁹⁹ Among 5417 confirmed strokes in 5224 women between 1993 and 2012 in Asia exposed daily to particulate matter (PM_{2.5} and PM₁₀), NO₂, NO_x, SO₂, and O₃, Sun et al⁶⁶ found a positive association between risk of hemorrhagic stroke and NO₂ and NO_x but not with the other pollutants in the 3 days before a stroke. A 7-year study in Korea showed significant associations between PM_{2.5} and PM₁₀, NO₂, NO_x, SO₂, and O₃ and the incidence of ischemic but not hemorrhagic stroke mortality, suggesting clinically significant alterations in the cerebrovascular system induced by air pollution.⁶⁷ Finally, in a study of 23 179 stroke admissions in Taiwan between 1997 and 2000, Tsai et al⁶⁸ reported significant positive associations between levels of PM₁₀, NO₂, SO₂, O₃, and CO and primary intracerebral hemorrhage as well as ischemic stroke.

Atherosclerosis

In mice prone to developing atherosclerotic lesions, chronic exposure to concentrated ambient PM produced aortic plaques that were significantly more advanced compared with non-exposed mice, indicating long-term exposure to PM can produce adverse cardiovascular effects by enhancing atherosclerosis.¹⁰⁰ The atherosclerotic disease process begins early as suggested by human autopsy studies that have found fatty streaks, indicating the early stages of atherosclerosis, in coronary arteries of teenagers.¹ In fact, fatty streaks have been observed in children as young as 3 years of age with coronary involvement identified at adolescence.¹⁰¹ Several studies confirm that the risk factors observed in adults (eg, elevated low-density lipoprotein, obesity, hypertension, tobacco exposure, and diabetes mellitus) also contribute to atherosclerosis in children.^{102,103} In particular, pollution has been shown to induce the progression of atherosclerosis and CAD. In a study of 798 adults in 2 clinical trials, among older participants (≥60 years), women, never smokers, and those reporting lipid-lowering treatment at baseline, showed significant associations between PM_{2.5} and carotid intimal-media thickness, with the strongest associations found in women aged ≥60 years.⁶⁹ In a prospective, 10-year cohort study of 6795 adults aged 45 to 84 years living in metropolitan cities, it was found that increased concentrations of PM_{2.5} and traffic-related air pollution commonly encountered worldwide, were associated with the progression of coronary calcification, consistent with acceleration of atherosclerosis.⁷⁰ In a longitudinal study of 6575 adults undergoing coronary angiography, exposure to PM_{2.5} was associated with increased likelihood of having coronary atherosclerosis that was mild to severe.⁷¹

MECHANISMS OF CVD FROM POLLUTION EXPOSURE

Currently available evidence has demonstrated that systemic inflammation and immunological responses—derived from pollutants coming into contact with the epithelial lung lining and entering the systemic circulation—initiate a cascade of events leading to the acute and chronic effects of pollution on CVD.¹⁰⁴ Based on our current knowledge, plausible pathophysiological mechanisms linking exposure to pollutants (primarily PM_{2.5}) and CVD include: (1) increased systemic inflammation, which produce cardiovascular stress^{105,106}; (2) activated platelets in the bloodstream, increasing the risk of acute thrombosis, as in MI and ischemic stroke^{107,108}; (3) alterations of the autonomic nervous system and the autorhythmic cells in the sinoatrial node, which leads to decreased heart rate variability, a prognostic risk factor for heart disease^{109,110}; and

(4) direct changes in the vascular cell types, including macrophages, endothelial and smooth muscle cells, thereby increasing CVD risk.¹⁰⁶ However, because of the lack of a standard modeling platform, the mechanisms underlying PM-induced cardiopulmonary toxicity in humans are still not well understood, making clinical management of air pollution-related cardiovascular risks difficult and impeding the development of effective preventive approaches.¹¹¹

Improving our understanding of the specific molecular or immunological pathways underpinning pollution-driven CVD will allow us to develop targeted therapies for individuals living in areas of high pollution or those genetically predisposed to pollution-driven CVD.

Increased Systemic Inflammatory Burden of Pollution: Interleukin-1 β and the Inflammasome

Exposure to pollutants generates airway oxidative stress and inflammation.¹¹² Furthermore, these local lung responses spill over, and ultrafine PM can cross the alveolar capillary membrane to the blood stream and produce systemic inflammatory and immunological responses by activating circulating immune cells.¹¹³ Multiple studies indicate an increase in the systemic inflammatory burden in response to air pollution exposure as measured by biomarkers, including interleukin (IL)-6, IL-8, C-reactive protein, IL-1 β , and monocyte chemoattractant protein-1 (MCP-1).^{113–115} Gruzieva et al measured a panel of blood inflammatory markers from 8-year-old children (n=670) who had been exposed to traffic NO₂ and PM₁₀ in early life and also examined gene data from 16-year-olds that had been exposed to traffic NO₂ and PM₁₀. In this cohort, a 10 $\mu\text{g}/\text{m}^3$ increase of NO₂ exposure during their infancy was associated with a 13.6% increase in IL-6 levels, as well as with a 27.8% increase in IL-10 levels, which was limited to children with asthma. Results were similar using PM₁₀, which showed a high correlation with NO₂ exposure. The functional analysis of 16-year-olds in this study identified several differentially expressed genes in response to air pollution exposure during infancy, including *IL10*, *IL13*, and tumor necrosis factor (TNF). In a group of healthy young adults, episodic PM_{2.5} exposure was associated with increased levels of circulating monocytes and T cells along with increased levels of TNF- α , MCP-1, IL-6, IL-1 β , and chemoattractants including soluble intercellular adhesion molecule-1 (sICAM-1) and circulating vascular cell adhesion molecule-1 (sVCAM-1).¹¹⁴ This response appears to be dose-dependent, and several components of air pollution including PAHs—NO₂, PM_{2.5}, and PM₁₀—have been associated with increases in inflammatory biomarker signatures. The inflammatory cytokines are likely derived mainly from

the cells in the lung epithelium and the circulating immune cells. Additionally, PM₁₀ was found to stimulate alveolar macrophages to release the prothrombotic cytokine IL-6, which activates pathways that can accelerate arterial thrombosis and increase the risk of cardiovascular events.¹¹⁶ Both chronic and acute exposures to PM_{2.5} activate the release of proinflammatory and vasoactive factors that contribute to cardiopulmonary pathology and accordingly, reducing exposure to PM_{2.5} would benefit cardiopulmonary health by decreasing both immediate and long-term cardiopulmonary disease risk.^{4,12,79,81–83}

A sensor of cell injury called the “inflammasome,” which includes an IL-1 β -processing platform, plays a crucial role in IL-1 β maturation and secretion from cells. Nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasomes monitor membrane integrity and pore-forming toxins, crystals, and many other noxious stimuli and are involved in IL-1 β processing and maturation.^{117–119} Produced by epithelial and inflammatory cells, IL-1 β plays a central role in the inflammatory processes in blood, lung, cardiac, and vascular tissues. IL-1 β is initially synthesized as pro-IL-1 β , an inactive precursor. Pro-IL-1 β is then cleaved inside the cell by the inflammasome complex.¹²⁰ Once pro-IL-1 β is processed, the mature IL-1 β product is secreted and binds to the IL-1 receptor (Figure 2¹²¹). In non-lymphoid organs, IL-1 β is expressed in tissue macrophages in the lung.^{122,123} There are 2 cell-surface IL-1 receptors, IL-1 type receptor (IL-1R1) and IL-1R2, a decoy receptor. IL-1R1 initiates inflammatory responses when binding to IL-1 β and has been reported to be expressed by T-lymphocytes, cardiac-derived and lung-derived fibroblasts, alveolar epithelial type II cells and vascular endothelial cells. IL-1R2, which does not initiate signal transduction, is expressed in a variety of hematopoietic cells, especially in B lymphocytes, mononuclear phagocytes, polymorphonuclear leukocytes, and bone marrow cells. Notably, expression levels of IL-1R1 and IL-1R2 are different among the cell types; for example, alveolar epithelial type II cells express IL-1R1, but not IL-1R2. The IL-1 β pathway has been targeted effectively by different products available as inhibitors for human use as recombinant human or soluble inhibitors (Figure 2).¹²⁰

IL-1 β is linked to exposure to air pollution. PM_{2.5} exposure has been shown to increase rates of reactive airway disease and MI associated with the release of IL-1 β from monocytes and macrophages.^{7,8} Components of PM from air pollution, including PAHs, activate human monocytes by stimulating cells such as pulmonary endothelial cells, showing that inhaled PM from pollution induces pulmonary and systemic inflammation.¹²⁴ Different mechanisms have been proposed for the activation of the inflammasome by

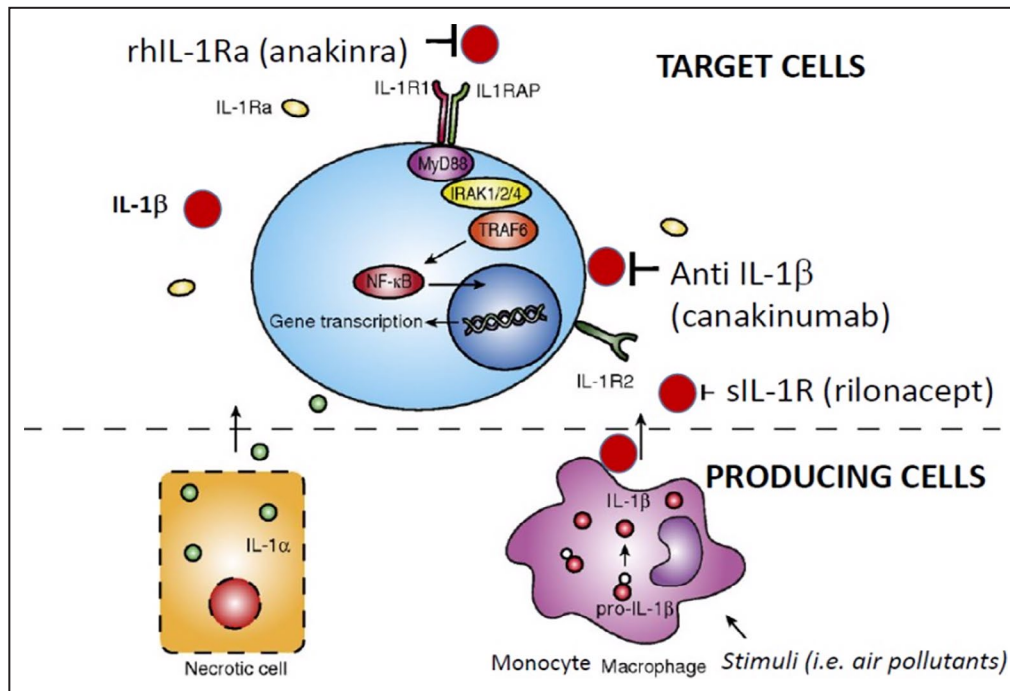


Figure 2. Potential therapeutic targets on the interleukin-1 pathway.

IL indicates interleukin; IL1RAP, Interleukin-1 receptor accessory protein; IL-1R1, Interleukin 1 receptor, type I; IL-1R2, Interleukin 1 receptor, type II; IRAK 1/2/4, interleukin-1 receptor-associated kinase 1, 2, 4; MyD88, Myeloid differentiation primary response 88; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; rh, recombinant human; rhIL-1RA, recombinant human interleukin-1 receptor antagonist; sIL-1R, soluble type 1 interleukin-1 receptor; and TRAF6, TNF receptor associated factor 6.

air pollution.^{125,126} Among them, the NLRP3 inflammasome is a prototype inflammasome, which has been reported to be activated by diesel exhaust, tobacco smoke, e-cigarette liquid, ozone, and reactive oxygen species in pollution.¹²⁷ Provoost et al¹²⁸ recently published a study in a murine model demonstrating that air pollution particle-induced pulmonary inflammation was mediated by IL-1β, but was NLRP3/caspase-1-independent. Our research using blood samples from 100 adolescents exposed to known quantities of ambient air pollution show that, even after 1 week of ambient air pollution exposure, there was a significant ($P=0.017$) association between IL-1β increases in plasma and increases in ambient air pollution exposure, specifically PM_{2.5}.¹²⁹

Epithelial Activation Barrier and Inflammation From Pollution

In considering the pathways that pollutants gain entry to the bloodstream, epithelial cells should be considered the first line of defense, as they are essential components of the innate immune response and are barriers to pollutants. Upper and lower respiratory epithelial cells are exposed to air pollution, whereas gastrointestinal epithelial cells are exposed to food and water pollution. Mucosal epithelium produces

antimicrobial peptides, cytokines, and chemokines, activates intraepithelial and subepithelial cells, which supports the physical, chemical, and immunological barrier.^{130–136} Epithelial cells respond to pollution by releasing cytokines such as IL-25, IL-33, and TSLP, which initiate inflammation by activating dendritic cells, T helper cells, innate lymphoid cells, and mast cells.¹³⁷ Once exposed to pollution, the epithelial tight-junctions barrier in the nasal and oral mucosa open, allowing pollutants to enter directly into the bloodstream and deeper tissues,^{132,138–148} which initiate distant tissue inflammation like in the cardiovascular systems. For example, exposure to PM_{2.5} has shown to break down the nasal epithelial barrier by breaking down cellular tight junctions and release proinflammatory cytokines,¹⁴⁹ which play key roles in the progression of cardiovascular and cardiopulmonary diseases.^{150–153}

Currently there are substantial data showing that pollutants such as cigarette smoke, particulate matter, diesel exhaust, ozone, nanoparticles, detergents, as well as cleaning agents and chemicals in household substances all can damage and open the epithelial barrier.^{149,154–163} Opening this barrier initiates the inflammatory cascade in tissues, especially cardiac and pulmonary tissues, which become vulnerable to systemic inflammation and the damaging

effects of air pollution, particularly in children and young adults.¹⁶⁴

Vascular Remodeling

Research has shown that fine and ultrafine particles can cross the alveoli, and enter the bloodstream, directly affecting tissues involved in CVD.¹⁶⁵ Specifically, one study found in patients undergoing carotid endarterectomy that inhaled gold nanoparticles entered the blood stream and became deposited in the carotid artery.¹⁶⁶ In fetuses of pregnant mice, pollutants alter vascular development manifested at birth as atrial septal defects and coronary malformation.¹⁶⁷ Brook et al¹⁶⁸ found that after only 2 hours of inhalation of fine PM and ozone at concentrations found in urban environments, healthy young adults showed significant brachial artery vasoconstriction. Also, healthy college students with a history of prenatal exposure to air pollution, compared with those not exposed, had significant carotid artery stiffness.¹⁶⁹ These studies suggest that the increased inflammatory signal is derived not only from the pulmonary exposure, but also a direct exposure of the vascular wall to systemic oxidative stress and inflammation, leading to activation of the pathways causing vascular injury and vascular remodeling via atherosclerosis and plaque buildup. In children whose vasculature is still developing, exposure to pollution can alter the structure and function of the vascular wall and potentially predispose them for future cardiovascular complications as shown by a recent study of 733 Dutch children aged 5 years demonstrating that exposure to PM_{2.5} and nitrogen oxides caused decreased arterial distensibility.¹⁷⁰

Endothelial Injury

Individuals exposed to fine PM from pollution have signs of endothelial injury and dysfunction along with increased markers of systemic inflammation.¹⁷¹ Specifically, episodic PM_{2.5} exposure in young adults was associated with increased antiangiogenic plasma profiles and elevated levels of circulating monocytes and T (but not B) lymphocytes, indicating increased endothelial cell apoptosis.¹¹⁴ Similarly, healthy young non-smoking males exposed to ultrafine PM and gases demonstrated 50% reduction in endothelial function, as measured by flow-mediated dilation of the brachial artery.¹⁷² These authors concluded that gaseous pollutants affect large artery endothelial function, whereas PM inhibit the post-ischemic dilating response of small arteries. Further, patients with diabetes mellitus exposed to PM_{2.5}, black carbon, and sulfates showed decreased endothelium-dependent and endothelium-independent vascular reactivity, particularly to PM_{2.5} and black carbon, and the effect was more pronounced in those with type-2 diabetes mellitus.¹⁷³

Plaque Instability

In mice exposed to diesel emissions, formed plaques were advanced to a fragile, vulnerable state.¹⁷⁴ Chronic pollution exposure of children, adolescents, and adults can potentially lead to a shift in the plaque morphology and content towards a more vulnerable state. In adults, even short-term pollution exposure was associated with higher levels of biomarkers consistent with reduced plaque stability.¹⁷⁵ Furthermore, Yang et al¹⁷² found that PM_{2.5} exposure was correlated with the development of plaque with higher-risk characteristics based on CT analysis suggesting that pollution exposure can modify plaque stability, which increases the risk of MI.

Platelet Aggregation and Thrombosis

Another potential CVD outcome is increased MI and stroke from acute exposure to pollution. Specifically, PM exposure has been linked to CVD and stroke, possibly mediated through proinflammatory or pro-thrombotic mechanisms.^{176,177} As noted above, exposure to PM_{2.5} has been linked to an increase in systemic oxidative stress and inflammation as well as a modulatory effect on tissue factors that have all been implicated as potential mechanisms of increased platelet activation.¹⁷⁸ The aryl hydrocarbon receptor pathway has also been implicated in increasing tissue factor production from vascular smooth muscle cells in response to ligand activation, leading to increased thrombosis.¹⁷⁹ This has been confirmed by research in adults exposed to air pollution.¹⁸⁰ In healthy adults exposed to traffic-related pollution, Xu et al¹⁷⁵ reported increased thrombogenicity as measured by prothrombin time and fibrin degradation products. Additionally, in a 10-year study of 870 patients with deep vein thrombosis and 1210 controls, Baccarelli et al¹⁸¹ found that higher mean PM₁₀ exposure during the year before examination was associated with shortened prothrombin time and increased deep vein thrombosis risk.

Epigenetics and Gene-Environment Interactions

Exposure to pollution has also been linked to an altered epigenetic state. Specifically, exposure to PAH and tobacco smoke contribute to gene expression modifications through epigenetic remodeling by 3 primary targets: CpG methylation, amino acid tail modification on histones, and aberrant microRNAs expression.¹⁸² Histone modification via methylation occurs post-translationally while miRNAs can control expression of other genes post-transcriptionally.¹⁸³ Changes to these targets can influence DNA folding, DNA-transcription factor interaction, transcript stability, and other methods of gene silencing (heterochromatin) or activation (euchromatin). Several studies indicate a role of pollution-produced epigenetic remodeling on the immune system. DNA

methylation has been associated with changes in IL-4 and IFN- γ transcription.¹⁸³ Studies with mouse models demonstrate that increases in immunoglobulin E levels are associated with hypomethylation at IL-4 promoter CpG sites and hypermethylation of IL-4 and IFN- γ promoter CpG sites.¹⁸⁴ Histone acetylation is associated with IL-4, IL-13, IL-5, IFN- γ , CXCL10, and FOXP3+ transcription patterns.¹⁸³ Finally, miRNA-mediated silencing has been found to repress transcripts associated with human leukocyte antigen G, or HLA-G, IL-13, IL-12p35, transforming growth factor beta, or TGF β , and the pituitary-specific, Octamer, Neural, or POU domain, a bipartite DNA binding domain.¹⁸³ Importantly, we believe these epigenetic modifications from exposure to air pollution may have the greatest consequences to prenatal and infant populations.¹⁸²

We and others have found an increase in the global methylation signal in the peripheral blood of children and adults exposed to pollution.^{129,185–188} Furthermore, pollution exposure-related effects may be inherited to the fetus through epigenetic mechanisms.¹⁸⁹ The inheritance of epigenetic modification in the mother could potentially result in babies and children more prone to increased obesity and hypertension. Gruziova et al³⁶ examined associations between NO₂ exposure and cord blood DNA methylation in pregnant women and also NO₂ exposure in children aged 4 and 8 years. Exposure to NO₂ during pregnancy was associated with differential offspring DNA methylation in mitochondria-related genes and was also linked to differential methylation as well as expression of genes involved in antioxidant defense pathways. In this study, Gruziova et al³⁶ also found NO₂ exposure of young children was linked to differential methylation as well as increased expression of genes involved in antioxidant defense pathways.

Genetic alterations also likely contribute to susceptibility of a child to the development of cardiovascular alterations in response to air pollution exposure. Eze et al⁹⁰ found that a common functional variant in the *IL6* gene interacted with PM₁₀ exposure-dependent IL-6 levels in the circulation. We have shown that an environment sensing transcription factor for the aryl hydrocarbon receptor, which has been shown to be activated by several components of pollution and tobacco smoke, is regulated both transcriptionally and epigenetically by *TCF21*, a gene associated with increased risk for atherosclerosis and MI.¹⁹¹

LIFETIME DISEASE RISK— STRATEGIES FOR PREVENTION AND INTERVENTION

As we have discussed, the evidence of air pollution exposure affecting cardiovascular health begins in

the neonatal period and continues throughout childhood and adolescence. The lifetime risk of CVD is the accumulated risks from the developmental period into childhood, adolescence, and adulthood (Figure 3). Because children are most vulnerable to environmental influences, improving their environment and reducing pollutant exposure during this critical phase can have significant long-term health benefits by altering the overall disease trajectory. Accordingly, this window of time offers an important opportunity for intervention.

For maximum impact, interventions could be implemented at both the individual and population levels (Figure 4). At the individual level, children and parents can be taught several simple but effective measures to reduce exposures. First, increasing awareness of air quality indices has shown to significantly change pollution-avoiding behaviors.¹⁹² Second, staying indoors and using personal protective devices such as N95 masks during acute periods of intense exposure, as well as use of home air filtration devices can significantly reduce pollution exposure. For example, N95 facemasks reduced acute particle-associated airway inflammation in young healthy adults living in China.¹⁹³

Currently, there is little evidence that dietary intervention or chemoprevention (ie, antioxidant or antithrombotic agents) can have an overall long-term survival benefit from pollution exposure. Carnosine supplementation has been shown to mitigate PM_{2.5}-induced effects on bone marrow stem-cell populations in mice and may be one approach for preventing immune dysfunction in humans exposed to pollution.¹⁹⁴ In addition, cobalamin (vitamin B12) supplementation has been shown to protect against superoxide-induced cell injury in human aortic endothelial cells,¹⁹⁵ one known outcome from oxidative stress after air pollution exposure.¹⁹⁶ Recently, in a large prospective cohort of >500 000 individuals in the United States followed for an average of 17 years, Lim et al⁹⁷ reported that, based on questionnaire of exposure history, there was a correlation between long-term exposure to fine PM and CVD mortality risk, and a Mediterranean diet reduced this risk. Also, in 1 study of young students exposed to high levels of air pollution in China, use of omega-3 fatty acids stabilized the levels of multiple biomarkers of inflammation and oxidative stress.¹⁹⁸

Current Evidence-Based Interventions

Although we know that interventions to reduce air pollution exposure can reduce the incidence of CVD, no randomized clinical trial has yet been proposed to demonstrate that long-term reduction in pollution exposure results in reducing CVD mortality. We need to design

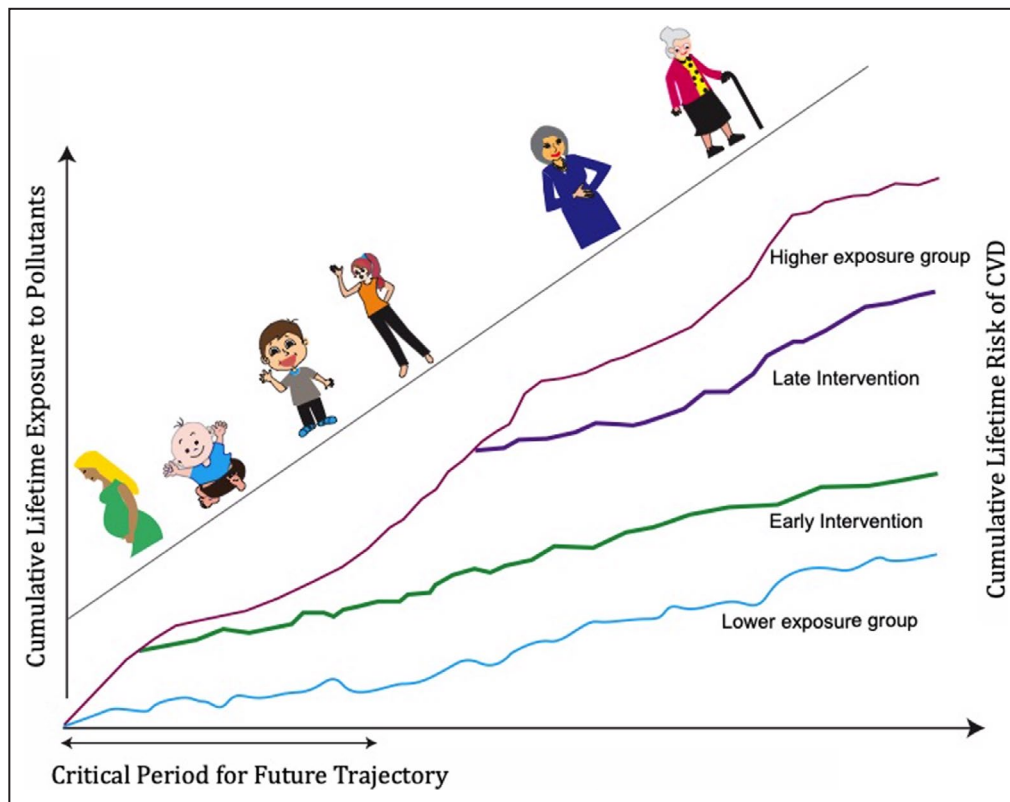


Figure 3. Early intervention can improve cumulative lifetime risk of cardiovascular disease. CVD indicates cardiovascular disease.

randomized clinical trials that will establish the effectiveness of interventions; however, traditional randomized trials would not be practical for this purpose given the large number of participants required and the difficulty of implementing individual monitoring. Several ways to improve participant selection for a more targeted intervention trial would be to develop an individual risk-calculator, and use biomarkers to identify higher-risk patients.^{199,200}

Healthcare providers play a critical role to help reduce the harmful effect of air pollution on children. Not only can they treat children's illnesses, they can also help educate the community about factors that contribute to air pollution and work with community leaders to reduce exposures and mitigate risks. Research should be aimed at developing established consensus guidelines that can help providers effectively counsel patients and families who are dealing with acute or chronic exposures. Recently, Hadley et al¹¹ outlined the role of healthcare providers and clinical approaches that factor in air pollution to preventive cardiac care. This includes a patient-screening tool that indicates known risk factors for air pollution exposure and cardiovascular risks. Developing an individual risk calculator that incorporates pollution exposure with traditional risk metrics—such as the American College of Cardiology/American Heart Association (ACC/AHA) and Atherosclerotic Cardiovascular Disease

(ASCVD) 10-year risk calculator—may help to further stratify patient risks so that interventions can be targeted to the higher-risk groups.¹¹

The 2004 American Academy of Pediatrics recommendations on the health hazards of air pollution in children²⁰¹ underscore the importance of pediatricians who play an important role in educating families and children about the harmful effects of pollution and helping to reduce exposures. Pediatricians who serve as physicians for schools or for team sports should be aware of the health implications of pollution alerts to provide appropriate guidance to school and sports officials, particularly in communities with high levels of pollution.²⁰¹ Physicians can do much to protect children by educating their local policymakers about the need for cleaner air and the need to replace older diesel buses, and limit school bus idling wherever children congregate.²⁰²

Population-Based Approaches

At the population level, we need policy measures to decrease the overall emission of harmful pollutants. The American Heart Association has published several position papers on the role of pollution on cardiovascular health, and concluded that there is an urgent need to advocate for strong regulations and policy to curtail pollution.⁷⁹ Regulations and fiscal

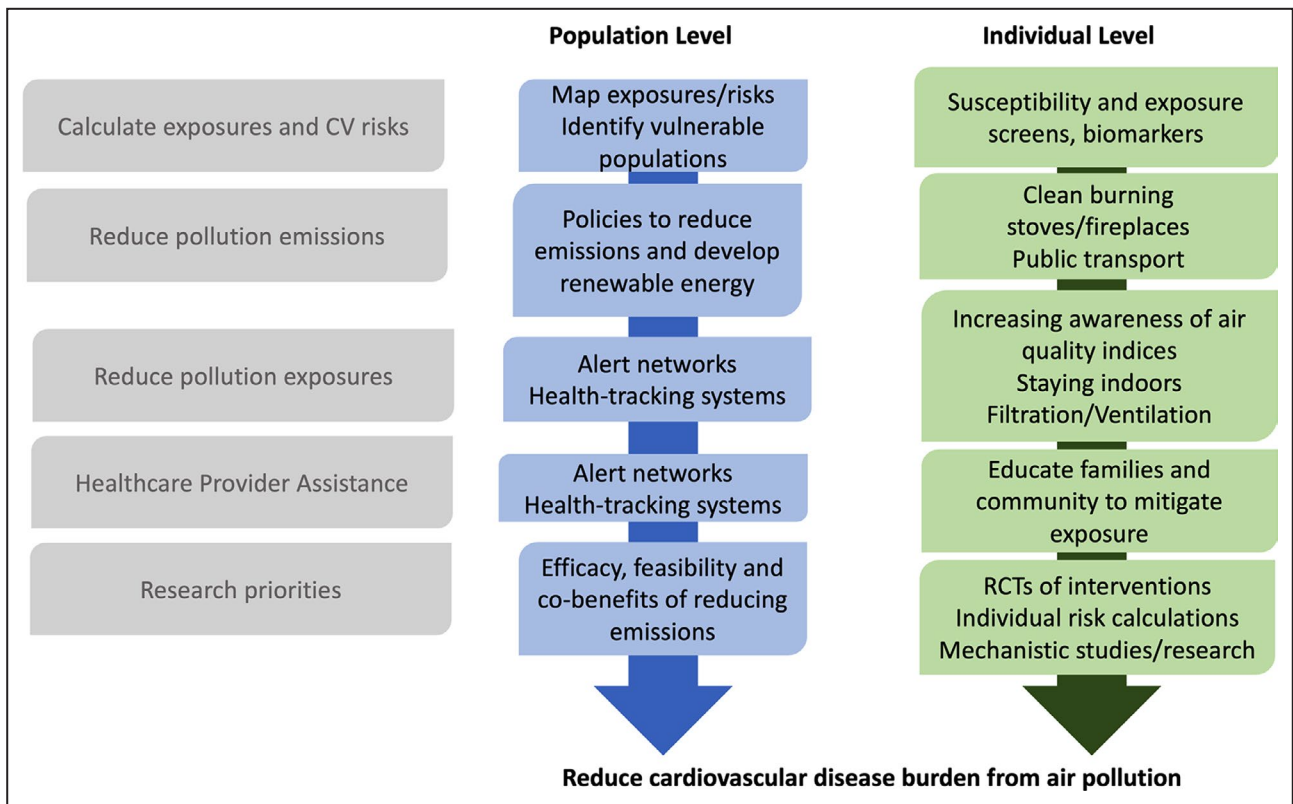


Figure 4. Combined population-level and individual-level approaches for reducing exposures to air pollution and reducing cardiovascular disease burden.

CV indicates cardiovascular; and RCT indicates randomized clinical trial.

strategies such as increased taxation of gasoline and diesel fuels or a carbon tax on emissions would effectively reduce air pollution levels. Other population-level approaches include using monitoring stations to build exposure maps and community alert networks (Figure 4).

We also should consider optimizing air quality standards further. Current research suggests that current United States and European standards are still too high, especially considering the pediatric population that is more susceptible to cardiovascular morbidity and mortality.^{203,204} Furthermore, as discussed by Hadley et al,¹¹ the most effective intervention occurs at lower pollution exposure levels, as most of the increase in conferred risk occurs at PM_{2.5} concentrations of 40 to 100 µg/m³, after which there is a plateau of accrued risk from pollution exposure.^{205,206} Anecdotal and historical observations strongly suggest that interventions to reduce exposures to PM would reduce risk of CVD, just as implementing policies to reduce tobacco exposure can lower hospitalizations for cardiopulmonary diseases. For example, it has been estimated that full implementation of the New York City fuel oil regulations would prevent >300 premature deaths and >500 emergency department visits and

hospitalizations for respiratory or cardiovascular causes each year.^{207,208}

GAPS IN KNOWLEDGE AND RESEARCH NEEDS

While most epidemiologic studies address the effects of short-term pollution exposure on acute CVD outcomes, we believe more research is needed to understand the long-term cumulative effects of air pollution on cardiovascular end points. The differences in the mechanisms leading to cardiovascular events from short-term exposure and long-term exposure are not well understood, and we need to better characterize the mechanisms from short-term exposure (eg, from wildfires) and long-term exposure (eg, from diesel exhaust). Many subclinical physiological changes occur in response to exposure to air pollution, and identifying these subclinical changes is one way to gain insight to the mechanisms leading to cardiovascular events.

Improved measurements of individual exposure are an important prerequisite for personalized care, and currently, pollution exposure to an individual is estimated mostly based on the person’s location of

residence. However, such an estimate does not include the amount of time the person might spend indoors versus outdoors, the amount of time spent at work or school, the extent of exposure to household pollution, as well as the vital capacity and respiratory rate of the person. Even when exposed to similar levels of pollution, children absorb more pollutants because they breathe more often than adults, are often outdoors more than adults, and are lower to the ground where some pollutants may concentrate.¹⁵ Several surrogate markers can be considered as a measure of exposure. A panel of blood biomarkers may allow us to estimate the systemic effect of both short-term and long-term exposures¹¹⁴ and, as we have seen, increased inflammatory markers such as IL-6, IL-1 β , IL-10, DNA methylation, and TNF have been found in young children and adults exposed to pollution.^{36,115,209} Also, measures of exhaled breath condensate, fluid formed by cooling down exhaled air, can be used to measure the amount of oxidative stress biomarkers—reactive aldehydes—and inflammatory markers related to pollution exposure.²¹⁰ These biomarkers should be incorporated and tested for their efficacy in prospective trials of intervention, perhaps including anti-IL-1 β therapies. Future research should also be directed toward better understanding the mechanism of epithelial barrier damage from particulate matter, ozone, nanoparticles, detergents, as well as cleaning agents and chemicals in household substances.

In this contemporary review, we have focused primarily on the effects of ambient air pollution, especially components of PM and PAHs. Although sufficient data are available to support preventive action, it is yet unclear how the different components of pollution—carbon monoxide, nitrogen oxides, sulfur dioxide, ozone, ambient PM, and lead—each affect the cardiovascular system.

Of the different pollution components, fine PM is known to be highly toxic to the cardiopulmonary system. However, we still do not fully understand whether all types of PM (eg, wildfire smoke versus diesel exhaust) are equally toxic or which specific components determine toxicity. The most studied particle matter is PM_{2.5}, which is especially harmful because they can penetrate into the pulmonary alveoli where they can induce a local inflammatory response. Ultrafine particles, a component of PM_{2.5}, can penetrate the alveolar-capillary barrier and enter the bloodstream. Several studies have established that PM induces inflammatory effects^{211–213} and oxidative stress,^{212,214} yet it is not yet clear to what extent such effects are different for PM collected at different locations or from different sources.²¹⁵ The proinflammatory and oxidative potential of PM may be influenced by variations in PM chemical and physical composition.^{216,217}

PM composition is determined by whether the emissions originate from cars, trucks, industry, or agricultural activities, and emissions are further affected by variations in temperature and meteorological conditions through atmospheric changes.²¹⁸ As such, although much research has concentrated on the effects of PM in animals and humans, we still have limited information on PM chemical components from different sources and locations.²¹⁹ PM, especially PM₁₀, includes biological components such as fungal spores and endotoxins, elemental carbon, sulfur, nitrogen, metal compounds, and complex hydrocarbons such as PAH.¹⁰ Some of these PM components have been shown to induce systemic inflammation. For example, endotoxin and PAH initiate monocyte inflammatory responses mediated by reactive oxygen species,^{124,220,221} and transition metals (iron, manganese, chromium, copper) induce cytotoxicity and oxidative stress.²²² While some studies indicate a degree of differential toxicity from such components as endotoxin, specific metals, PAH, and elemental carbon,²¹⁸ current knowledge does not allow us to precisely quantify the health effects of individual PM components or PM from different sources. To better inform regulatory strategies in the future, we must more fully understand the health effects of various PM components from different sources, which will allow us to identify the causal agents. This will help formulate more targeted strategies for harm reduction. It will also help us to appropriately lower the current annual ambient air quality standards, considering the more susceptible populations, especially our children. Collaborating with rapidly developing countries, where extremely unhealthy air quality level is a daily concern, will help us to develop impactful research that will be applicable in both the United States and throughout the world.

CONCLUSIONS

With the rapid rise in industrial development came increased emission of air pollutants harmful to human health. Regardless of the pollution source, polluted air is shared by us all, especially our children, who are most vulnerable. The lifetime cumulative exposure to pollution is increasing in children, and current evidence shows that long-term exposure, even in utero, leads to increased prevalence of hypertension, obesity, and metabolic disorders, resulting in a greater CVD burden in our future generations. The concept of life time and acute exposure should be well integrated to public health and devices to monitor individual and regional exposure should be improved and focused on new dangers of exposure. Development of biomarkers that identify the levels of exposure, tissue and systemic inflammation, and

tissue damage is essential to overcome diseases linked to pollution. We must develop clinical guidelines to effectively mitigate the risk of increased exposure to pollution. Continued research into the mechanisms of pollution-induced CVD and policies to limit emissions and promote preventive efforts to limit exposure, especially during childhood and adolescent years, all will have significant long-term benefits for the future.

ARTICLE INFORMATION

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