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Air Pollution and Cardiovascular Disease: A Focus on Vulnerable Populations Worldwide

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Abstract

Purpose of review: Certain subgroups defined by sociodemographics (race/ethnicity, age, sex and socioeconomic status [SES]), geographic location (rural vs. urban), comorbid conditions and country economic conditions (developed vs. developing) may disproportionately suffer the adverse cardiovascular effects of exposure to ambient air pollution. Yet, previous reviews have had a broad focus on the general population without consideration of these potentially vulnerable populations.

Recent findings: Over the past decade, a wealth of epidemiologic studies have linked air pollutants including particulate matter, oxides of nitrogen, and carbon monoxide to cardiovascular disease (CVD) risk factors, subclinical CVD, clinical cardiovascular outcomes and cardiovascular mortality in certain susceptible populations. Highest risk for poor CVD outcomes from air pollution exist in racial/ethnic minorities, especially in blacks compared to whites in the U.S, those at low SES, elderly populations, women, those with certain comorbid conditions and developing countries compared to developed countries. However, findings are less consistent for urban compared to rural populations.

Summary: Vulnerable subgroups including racial/ethnic minorities, women, the elderly, smokers, diabetics and those with prior heart disease had higher risk for adverse cardiovascular outcomes from exposure to air pollution. There is limited data from developing countries where concentrations of air pollutants are more extreme and cardiovascular event rates are higher than that of developed countries. Further epidemiologic studies are needed to understand and address the marked disparities in CVD risk conferred by air pollution globally, particularly among these vulnerable subgroups.

Keywords

Air pollution; Risk factors; Atherosclerosis; CVD; Mortality; Vulnerable populations; Global Health

Introduction

Air pollution is a major public health concern globally [1, 2]. According to the World Health Organization (WHO), approximately 7 million people die each year from exposure to fine particles in polluted air [3]. In the United States (US), the Clean Air Act requires the Environmental Protection Agency (EPA) to set National Ambient Air Quality Standards (NAAQS) for 6 common air pollutants also known as the “criteria air pollutants” [4]. These pollutants include ground-level ozone (O₃), lead, carbon monoxide (CO), sulfur dioxide, nitrogen dioxide (NO₂) and particulate matter (PM). The latter mostly results from a chemical reaction between other pollutants in the atmosphere. PM varies in size and is usually divided into those with diameters of 2.5 micrometers and smaller (PM_{2.5}, “fine PM”) and those with diameters between 2.5 and 10 micrometers (PM₁₀, “coarse PM”). Black Carbon (BC) is a major component of PM emitted from gas and diesel engines, coal-fired power plants, and other sources that burn fossil fuel. BC, NO₂ and oxides of nitrogen (NO_x) are all measures of traffic-related air pollution. It is estimated that about 90% of the world’s population is exposed to levels of air pollution above the WHO Air Quality Guidelines (AQG) for a range of air pollutants [3].

While the role of air pollution on acute and chronic respiratory diseases has been long recognized [5], the understanding of the major impact of air pollution on cardiovascular disease (CVD) has increased in recent years. Indeed, it is estimated that more than 50% of the health burden of air pollution is through CVD [6]. Epidemiologic studies have linked short- and long-term air pollution exposure to increased risk for subclinical CVD [7–14], major cardiovascular events [15–27], and cardiovascular mortality [28–45, 27, 46, 47]. The proposed mechanisms include through the promotion of CVD risk factors [48–67], as well as through increased systemic inflammation and coagulation [9•]. For example, Bell et al. recently reported a 1.68 mg/dL lower high-density lipoprotein (HDL)-cholesterol level for each 0.7×10⁻⁶ m⁻¹ higher 3-month cumulative exposures to BC and a 0.64 μmol/L lower HDL particle number for each 5μg/m³ higher 3-month cumulative exposures to PM_{2.5} among a multi-ethnic cohort from six major US cities [59•].

Subclinical markers of CVD can provide early insight into disease processes and the identification of individuals at heightened risk for later clinical CVD events. Coronary artery calcium (CAC) is a well-established surrogate marker of total atherosclerotic burden, and CAC (and its progression) is a potent prognostic indicator of future CVD risk [68]. Other established markers of subclinical CVD include carotid intima-media thickness (IMT) and calcification of the left sided heart valves [aortic valve calcium (AVC) and mitral annular calcification (MAC)] [12•]. Perhaps the most impactful recent evidence linking air pollution to subclinical CVD, as well as systemic inflammation, among individuals without known clinical CVD emanated from the Multi-Ethnic Study of Atherosclerosis and Air Pollution

(MESA Air) cohort, a large, multiethnic, prospective, cohort study from six metropolitan cities in the US [12•, 10••, 9••, 69–75, 8, 76–79]. In MESA Air, Kaufman et al. reported a 4.1 Agatston units per year increase in CAC score for each 5 $\mu\text{g}/\text{m}^3$ increase in long-term (10-year) exposure to $\text{PM}_{2.5}$, independent of established CVD risk factors [10••]. In a related MESA Air analysis from our group, this association with CAC remains significant even after considering a shorter follow-up period of 2.5 years [12•]. In this analysis, which also included AVC and MAC, we found evidence of increased 2.5-year progression of MAC with exposure to ambient $\text{PM}_{2.5}$ [12•]. Given that the same biological mechanisms may underlie MAC and CAC [80], the association of air pollution with CAC is most likely specific rather than with vascular calcification in general. Similarly, higher exposure to $\text{PM}_{2.5}$ has been shown to increase the progression of carotid IMT as well in the MESA Air study [69, 77••].

Many subgroups defined by sociodemographics (race/ethnicity, age, sex and SES) [81, 82, 51, 49, 83], geographic location (rural vs. urban populations) [81, 28, 84] and country economic conditions (developed vs. developing countries) [85] show striking disparities in adverse cardiovascular outcomes resulting from exposure to air pollution. Yet, all the reviews thus far have discussed this topic very broadly in the general population. The objective of this review is to provide healthcare professionals and researchers with a comprehensive summary of research within the past 5–10 years on air pollution and CVD, with a specific focus on these vulnerable populations.

Sociodemographics (age, sex, racial/ethnic minorities and low SES populations)

Race/ethnicity

In the US, exposure to air pollution is strikingly different by race/ethnicity due to racial segregation in housing [86, 87]. Racial/ethnic minorities are more likely to be of low SES and live in dense urban centers [86, 87]. Consequently, racial/ethnic minority groups, especially African Americans, have consistently shown an increased risk for CVD due to air pollution [81, 82, 51, 49, 83]. For example, Coogan et al. found that higher O_3 level was associated with a 9% increased incidence of hypertension [HR=1.09 (95% CI = 1.00, 1.18)] in a large cohort of black women after a median follow-up of 11 years (total of 348,154 person-years) [49]. In another analysis in this cohort, NO_x but not $\text{PM}_{2.5}$ was associated with increased risk of incident diabetes mellitus in black women living in Los Angeles. In a study using data from MESA Air, differences in annual $\text{PM}_{2.5}$ concentrations did not contribute to differences in carotid IMT among blacks or Hispanic participants compared to white participants in the only study that specifically examined differential impact of air pollution exposure according to racial/ethnicity in atherosclerosis [77••]. On the contrary, smaller carotid IMT measurements were noted in Chinese-Americans compared to whites after controlling for $\text{PM}_{2.5}$ concentrations which were higher among Chinese-Americans [77••].

Furthermore, evidence exists for the association of air pollution with cardiac structure and function, including among racial/ethnic minority groups in the US [70, 88, 79]. Van Hee et al. revealed that living within 50 meters of a major roadway is significantly associated with higher left ventricular (LV) mass index but not with ejection fraction (EF) in the MESA Air

cohort [70]. Susceptibility for subclinical systolic dysfunction among African Americans was confirmed in the Jackson Heart Study where living near roads was associated with LV end-systolic diameter [89]. Racial/ethnic minority groups, especially blacks, had a higher risk for adverse clinical cardiovascular outcomes due to air pollution compared to non-Hispanic whites in California [90]. Hackbarth et al. reported an excess attributable risk in cardiovascular admission rates due to exposure to O_3 and $PM_{2.5}$ among black residents compared to white residents in California [90]. Recently, Erqou et al. also reported a 45% increase in the risk of cardiovascular events among blacks compared to whites in Western Pennsylvania (greater Pittsburgh) partly because of higher chronic exposure to $PM_{2.5}$ among blacks [91••]. Interestingly, this association was no longer statistically significant after further adjustments for measures of SES, including income and education. The findings from Erqou et al. are consistent with some suggestions that air pollution may not be causal but may only be closely correlated with different markers of low SES which cause CVD [92, 93, 86]. Specifically, for subgroups defined by low SES and minority race/ethnicity, adverse dietary and lifestyle factors may be contributing to CVD risk, in addition to higher air pollution levels. Epidemiologic studies with designs targeted at accounting for all of these confounders are needed in this domain to explore whether differences in air pollution could explain disparities in CVD endpoints among subgroups defined by race/ethnicity or SES.

Age

Elderly populations are among the most vulnerable to the risk of adverse cardiovascular outcomes from air pollution [94, 95]. For subclinical CVD, Kaufman et al. found that the association of long-term exposure to $PM_{2.5}$ with increased annual CAC progression was somewhat stronger among individuals older than 65 years of age compared to younger individuals [10••]. In the ESCAPE Project, which was a meta-analysis of 11 European cohorts with a total of 100,166 participants, each $5\mu g/m^3$ increase in long-term exposure to $PM_{2.5}$ was associated with a 13% increase in nonfatal acute coronary events [20••]. Participants 60 years of age or older were found to have the highest risk associated with $PM_{2.5}$ exposure compared to their younger counterparts [20••].

Some evidence has also linked acute exposure to CO , SO_2 , NO_2 , and $PM_{2.5}$ to increased heart failure exacerbations among the elderly [17]. In all, it was estimated that a $3.9\mu g/m^3$ reduction in $PM_{2.5}$ would prevent almost 7,978 heart failure hospitalizations each year in the US alone [17]. Even at the relatively lower concentrations of air pollution in Europe, each $5\mu g/m^3$ increase in long-term exposure to $PM_{2.5}$ was associated with a 40% (HR = 1.40, 95% CI: 1.05, 1.87) increase in the risk of stroke among adults 60 years of age and older in the ESCAPE project [21]. Results were no longer significant when the entire ESCAPE cohort, including younger adults, were analyzed. Finally, in a large cohort of 18.9 million Medicare beneficiaries from across the US, Pun et al. observed an increased risk for cardiovascular mortality with exposures to long-term $PM_{2.5}$ [95].

Sex

Evidence suggests that women may be more vulnerable than men to develop cardiovascular events upon air pollution exposure [10••, 96–99]. In MESA Air, Kaufman et al. found that women may have an increased CAC progression due to long-term exposure to $PM_{2.5}$

compared to men [10••]. Additionally, stronger associations between long-term exposure to PM with incident ischemic heart disease, stroke, heart failure and atrial fibrillation were noted among women compared to men even at relatively low levels of exposures in Gothenburg, Sweden [98]. Similarly, women were reported to have increased CVD mortality compared to men due to short-term exposure to PM₁₀ and SO₂ in Hefei, China [97].

Urban vs. rural

Globally, air pollutant levels are disproportionately higher in urban centers compared to rural settings [100, 41, 40, 101–103, 86, 32, 104]. Acute exposure to both PM_{2.5} and PM₁₀ led to acute rises in arterial blood pressure (BP) in urban centers in the US mostly inhabited by minority groups, namely African Americans [57, 52]. In a first-ever randomized double-blind crossover study in Michigan involving 2-hour exposures to concentrated ambient PM₁₀ vs. filtered air, Dvornchik et al. found that both systolic (1.9 mm Hg; 95% CI: 0.96, 2.8) and diastolic (1.9 mm Hg; 95% CI: 1.1, 2.7) BP remained elevated during exposure to PM₁₀ compared to filtered air [52]. In a similar trial conducted among young adults in Shanghai, higher short-term exposure to PM_{2.5} caused a surge in blood levels of stress hormones including cortisol, cortisone, epinephrine, and norepinephrine [105••]. Both acute and chronic stressors are well known risk factors for CVD including myocardial infarction and sudden cardiac death.

In Europe, long-term exposure to PM₁₀ was associated with atherosclerosis as measured by carotid IMT in urban centers as evidenced by an analysis of 2,348 adults who lived in Greater London [106]. For cardiovascular mortality, Crouse et al. found that long-term exposure to outdoor NO₂ was positively associated with a 4% increased mortality from all CVD (HR per 5 p.p.b.: 1.04; 95% CI: 1.01–1.06) and 5% increased mortality from ischemic heart disease (HR per 5 p.p.b.: 1.05; 95% CI: 1.02–1.08) in a cohort from 10 of the largest cities in Canada (~735,590 participants, 16 years of follow-up) [32]. Notably, it was found that these associations were determined largely by within-city contrasts in exposure, as opposed to between-city contrasts [32].

Nevertheless, rural exposure to air pollution has also been linked to increased risk for CVD in certain high-risk groups [107, 108]. In the agricultural health study cohort (which included 83,378 farmers, their spouses, and commercial pesticide applicators residing primarily in Iowa and North Carolina), long-term exposure to PM_{2.5} was associated with increased cardiovascular mortality among men but not women [107]. At the other end of the spectrum, a significant association was observed between BC and higher systolic BP among women from rural China where biomass fuels are commonly used; the association was even stronger among women who lived near a highway [108]. Overall, few studies have assessed the contributions of air pollution to CVD in rural populations. More research is needed in this area, in particular because of the distinct features of air pollution in rural settings as characterized by the presence of coal fire, power plants, incineration of residual waste and other environmental challenges.

Comorbidities

Certain comorbid conditions have been noted to predispose individuals to the adverse cardiovascular effects of air pollution [30, 109–116]. For example, children with mood disorders or poor mental health were found to be more vulnerable to rises in BP resulting from exposures to air pollution [109]. Kalsch et al. reported an association of long-term exposure to PM_{2.5} with subclinical atherosclerosis as measured by thoracic aortic calcium in a German cohort [110]. In this study, participants with prevalent CHD and those taking statins seemed most vulnerable to the effects of PM [110]. Additionally, exposure to PM_{2.5} was associated with elevated lipoprotein associated phospholipase A₂ among participants who had a previous acute myocardial infarction in Augsburg, Germany [111]. Importantly, Kaufman et al. also reported that the association of long-term exposure to PM_{2.5} with CAC progression might be greater in hypertensive individuals in MESA Air [10••].

Populations with underlying coronary heart disease had a much higher burden of acute coronary syndromes due to short-term exposure to PM_{2.5} as demonstrated in an analysis of 5,679 residents of North Carolina who underwent a clinically indicated cardiac catheterization at Duke University between 2002 and 2009 [23]. In this cohort with high prevalence of coronary heart disease, each 1 µg/m³ increase in PM_{2.5} within the year prior to cardiac catheterization was associated with a 14.2% (95% CI: 3.7–25.8%) increase in the odds of having a myocardial infarction. Conceivably, acute exposure to PM_{2.5} may precipitate the rupture of vulnerable atherosclerotic plaques.

Also, individuals with diabetes were reported to have the highest risk of adverse cardiovascular events from air pollution [114, 116]. In a recent analysis of patients who had undergone primary percutaneous intervention for myocardial infarction in Tehran, Iran, patients with diabetes were found to have a higher risk of myocardial infarction due to acute exposure to both PM_{2.5} and PM₁₀ compared to non-diabetics [116]. Similarly, Villeneuve et al. found that people with prior history of stroke (OR = 2.31; 95% CI: 1.39, 3.83), heart disease (OR = 1.99; 95% CI: 1.20, 3.28) and those on medications for diabetes (OR = 2.03; 95% CI: 1.14, 3.59) were the most susceptible to ischemic stroke from exposure to air pollution [112].

Smoking is one of the leading causes of CVD. Smokers consistently had the greatest risk for metabolic syndrome and cardiovascular mortality due to air pollution [63, 113]. It is important to note that each 10µg/m³ increment in PM_{2.5} is equivalent to passively smoking 5.5 cigarettes per day [117]. Other vulnerable groups at higher risk of cardiovascular mortality risk attributed to air pollution are survivors of myocardial infarction [30]. The relation of air pollution with other strong CVD risk factors such as chronic kidney disease [118] and chronic inflammatory conditions such as lupus and rheumatoid arthritis have yet to be explored in detail.

Currently, clinical guidelines do not provide physicians with any guidance on how to manage potential air pollution exposure among patients with previous CVD. For instance, physicians do not routinely ask about living close to a road or highway. Furthermore, there exist no recommendations on what patients should do to protect themselves from air

pollution exposure, especially if they need to go back to a home environment characterized by high air pollution exposure. Developing clinical guidelines to help physicians with the management of patients who might be exposed to moderate-to-high air pollution may reduce the global burden of pollution-attributable CVD [2, 119].

Developed vs. developing countries

In a recent meta-analysis of 23 studies, short-term exposure to all major air pollutants, except for O₃, were associated with cardiac arrhythmia [19]. Short-term exposure to PM_{2.5} led to a 1.5% increase in cardiac arrhythmia (per 10µg/m³) [19]. The highest risk was noted in Asia where air pollution concentrations are exceedingly high in countries like China and India compared to other countries [19]. Additionally, urban cities in Asia like New Delhi, Hong Kong and Beijing have cardiovascular mortality rates nearly twice as high as urban cities in Europe and North America [17, 120]. These Asian megacities have air pollution levels up 10 times the US NAAQS [38, 37]. In a nationwide time-series analysis in 272 major Chinese cities, both short-term exposure to SO₂ (per 10µg/m³ increments) and CO (per 1 µg/m³ increments) were associated with a 0.70% increase and a 1.12% increase in overall CVD mortality, respectively [41, 42]. In a meta-analysis of 59 studies from China where mean PM_{2.5} exposures were between 39 to 177 µg/m³, each 10µg/m³ increment was associated with a 0.63% increase in overall CVD mortality [37]. Additionally, Zhang et al. reported a 23% increase in CVD mortality [HR = 1.23 (95% CI, 1.19, 1.26)] per 10µg/m³ increase in PM₁₀ exposure in an analysis of 39,054 participants from four cities in northern China where the mean PM₁₀ levels for the entire 12-year period was 144 µg_{2.5}/m³ [38].

Conversely, in two Canadian populations with average PM_{2.5} exposure levels as low as 8.7µg/m³ and 6.3µg/m³, each 10µg/m³ increment was associated with a 31% increase in CHD mortality [44] and a 19% increase in cardiovascular mortality [31]. Similarly, in a multi-state analysis of 517,041 US adults with an average PM_{2.5} concentration of 12 µg/m³, each 10µg/m³ increment was associated with a 10% increase in CVD mortality (HR = 1.10; 95% CI: 1.05, 1.15) [47]. Taken together, the results from North America suggest that there may be no “safe levels” for the effect of PM_{2.5} on CVD mortality since exposures in the Canadian studies were on average below the WHO AQG of <10µg/m³ [3]. Comparably, data are lacking on vulnerable subgroups from developing countries where concentrations of air pollutants are extreme and cardiovascular event rates are high. Research is needed to address this important gap.

Conclusion

In summary, recent epidemiologic studies have consistently shown a higher adverse CVD outcomes resulting from exposures to short- and long-term ambient air pollution among certain vulnerable subgroups including racial/ethnic minorities, the elderly, low SES individuals, smokers, diabetics and those with a history of heart disease. Some data also suggest poor air pollution-related CVD outcomes among women compared to men. Urban cities in Asia like New Delhi, Hong Kong and Beijing, with higher air pollution levels, had cardiovascular mortality rates nearly twice as high as urban cities in Europe and North America. Despite all that we have learned so far from the extensive evidence linking air

pollution to CVD, gaps in our understanding remain. To date research has mainly considered air pollutants individually, however we know that exposures to multiple pollutants occur simultaneously. Thus, integrating different types of air pollutants into a single weighted exposure may better characterize the cumulative effect of air pollution on cardiovascular outcomes. Of major concern is the paucity of data from developing countries where concentrations of air pollutants are even more extreme and cardiovascular event rates are higher than developed countries. Also, far fewer studies have assessed the contributions of air pollution to CVD in rural populations compared to urban centers. Features of air pollution in rural settings are very distinct and warrant more epidemiologic studies. Finally, given the strength of evidence implicating air pollution in CVD, especially among these vulnerable subgroups, clinical guidelines regarding the management of patients with CVD who might be exposed to moderate-to-high air pollution may help reduce the global burden of pollution-attributable CVD morbidity and mortality.

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