JACC: CARDIOONCOLOGY VOL. 6, NO. 3, 2024

STATE-OF-THE-ART REVIEW

Air Pollution in Cardio-Oncology and Unraveling the Environmental Nexus

JACC: CardioOncology State-of-the-Art Review

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ABSTRACT

Although recent advancements in cancer therapies have extended the lifespan of patients with cancer, they have also introduced new challenges, including chronic health issues such as cardiovascular disease arising from pre-existing risk factors or cancer therapies. Consequently, cardiovascular disease has become a leading cause of non-cancer-related death among cancer patients, driving the rapid evolution of the cardio-oncology field. Environmental factors, particularly air pollution, significantly contribute to deaths associated with cardiovascular disease and specific cancers, such as lung cancer. Despite these statistics, the health impact of air pollution in the context of cardio-oncology has been largely overlooked in patient care and research. Notably, the impact of air pollution varies widely across geographic areas and among individuals, leading to diverse exposure consequences. This review aims to consolidate epidemiologic and preclinical evidence linking air pollution to cardio-oncology while also exploring associated health disparities and environmental justice issues. (J Am Coll Cardiol CardioOnc 2024;6:347–362) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The development of cancer therapies has substantially improved the overall 5-year survival rate for patients with cancer, rising from 49% in the 1970s to 68% in the 2010s.[1] As the lifespan of cancer patients increases, chronic health problems like cardiovascular disease have emerged as a significant threat. The leading noncancer causes of death among patients with cancer have shifted from infections to cardiovascular disease, representing over 40% of deaths in 2017.[2]

The term "cardio-oncology" refers to the research and clinical practice of predicting, preventing, and treating cardiotoxicity caused by cancer therapy, such as anthracyclines, targeted anticancer treatments, immune therapy, and radiation therapy. Over time, the concept of cardio-oncology has expanded to include the bidirectional and multifaceted links between cardiovascular disease and cancer.[3] For example, studies have reported that patients with heart failure have an increased risk of developing

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 20, 2023; revised manuscript received March 26, 2024, accepted April 4, 2024.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2024.04.003

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CHD = coronary heart disease

LMIC = low- and middle-income country

NO_2 = nitrogen dioxide

NO_x = nitrogen oxides

PAH = polycyclic aromatic hydrocarbons

PM = particulate matter

$PM_{0.1}$ = particulate matter ≤0.1 μm

$PM_{2.5}$ = particulate matter ≤2.5 μm

PM_{10} = particulate matter ≤10 μm

ROS = reactive oxygen species

WHO = World Health Organization

cancer.[4] This interaction between cardiovascular disease and cancer has largely been attributed to shared genetic predispositions and common risk factors,[5,6] although the contribution of environmental factors remained unclear.

A comprehensive analysis of global burden of disease revealed that environmental factors contributed significantly to poor health, accounting for 23% of global deaths and 22% of global disability-adjusted life years.[7] Among these factors, air pollution stands out as the world's fourth-ranked risk factor for all-cause mortality and has emerged as an important environmental risk factor for cancer and cardiovascular disease.[8] In separate studies, air pollution has been implicated in activating shared pathways such as oxidative stress, metabolic remodeling, and immune response, which can amplify the impact of risk factors on cardiovascular disease and cancer.[9,10]

Exposure to air pollution is ubiquitous. In 2019, about 86% of global urban inhabitants were living in areas with air quality higher than standards recommended by the World Health Organization (WHO).[11] However, the concentration and composition of pollution vary significantly worldwide. Uneven heavy exposure to air pollution has translated into disproportionately high mortality for both cardiovascular disease and cancer, especially for the poor and the vulnerable.[12] The air pollution-associated mortality rate is estimated to be 100-fold higher in low- and middle-income countries (LMICs) than in high-income countries.[13] Not surprisingly, more than 65% of all cancer deaths[14] and 70% of cardiovascular disease deaths[15] occur in LMICs.

Although air pollution is recognized as a significant risk factor for both cancer and cardiovascular disease, its role and the related health disparities within the field of cardio-oncology have received limited attention. Additionally, there is a notable lack of recommendations and guidelines for risk assessment, patient care, and personalized interventions for patients in the field of cardio-oncology. This review provides a comprehensive and in-depth examination of the coexistence and interplay between cardiovascular disease and cancer in relation to air pollution exposure. By doing so, we aim to broaden the understanding of environmental determinants in cardio-oncology and to advance the multidisciplinary care of vulnerable individuals.

In this review, we present both epidemiologic and preclinical evidence linking cardiovascular disease and cancer, with a specific focus on the impact of air pollution on cardio-oncology and the shared risk factors between these 2 conditions. Additionally, we discuss the health disparities associated with cardiovascular disease and cancer, highlighting inequalities in air pollution exposure as contributing factors.

HIGHLIGHTS

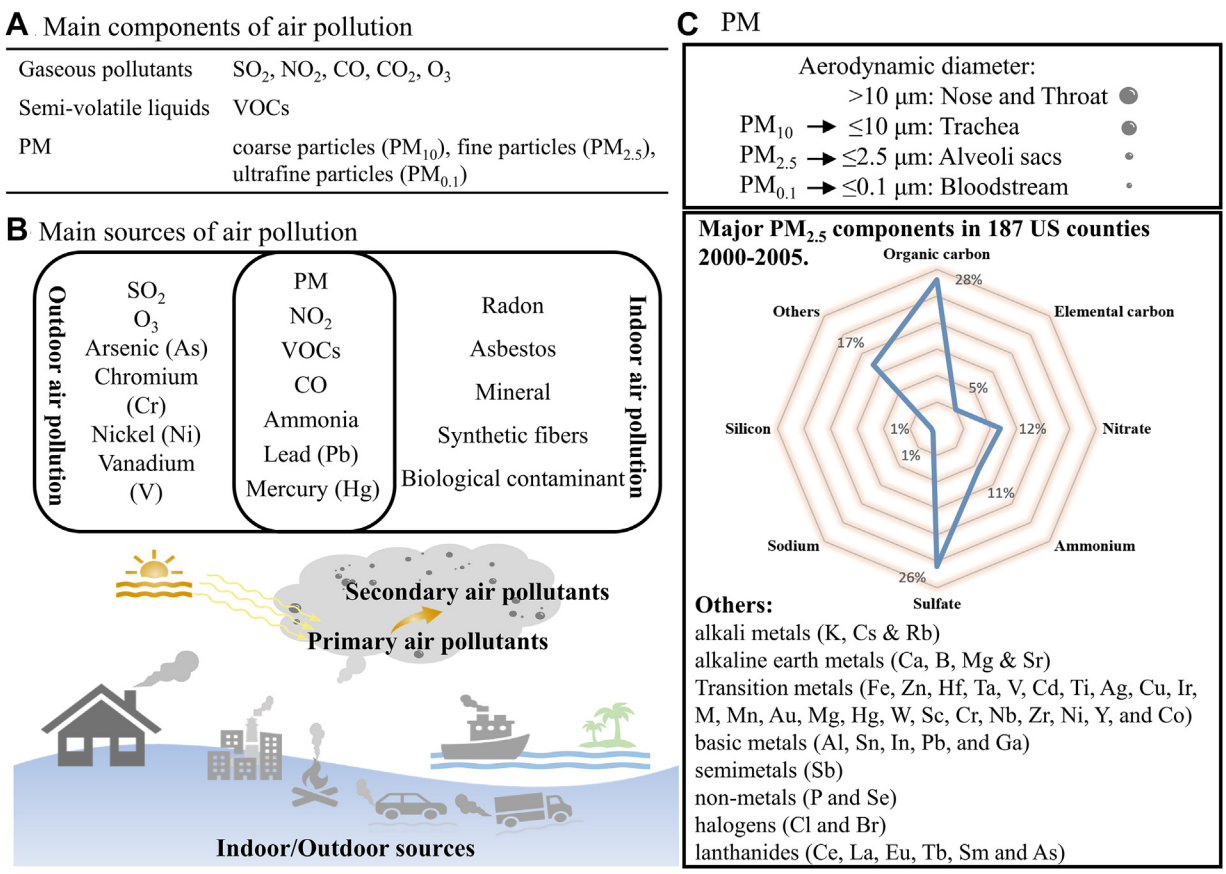
- Air pollution exposure has been linked to both cancer and cardiovascular disease.
- Air pollution is an overlooked environmental risk factor for cardio-oncology.
- Air pollution may interact with various common risk factors for cancer and cardiovascular disease.
- Air pollution assessment and interventions are recommended to improve cardio-oncology care.

AIR POLLUTION, CARDIOVASCULAR DISEASE, AND CANCER

OVERVIEW OF AIR POLLUTION AS A CRITICAL ENVIRONMENTAL DETERMINANT. Air pollution is the presence of contaminants in the air, including chemical, physical, and biological components, that exert harmful effects on the environment and human health. These pollutants can be broadly categorized into gaseous pollutants (eg, ozone, sulfur dioxide, nitrogen oxides, and carbon monoxide), semivolatile liquids, and particulate matter (PM), which result from complex interactions involving multiple emissions and chemical reactions (**Figures 1A and 1B**). Sources of air pollution can be natural, such as wildfires and volcanic eruptions, and anthropogenic, including emissions from vehicles, industrial processes, and the burning of fossil fuels. Long-term exposure to air pollution is associated with a range of health problems, including respiratory and cardiovascular diseases, as well as environmental concerns such as smog formation and acid rain.

Significant evidence linking air pollution exposure to adverse health events emerged from historical incidents such as the Meuse Valley fog (1930), Donora smog (1948), and London smog (1952). However, the full magnitude of this problem has not been widely recognized until recent years. According to the 2019 Global Burden of Disease Study, air pollution accounted for 6.7 million deaths worldwide, with 4.1 million deaths attributed to ambient air pollution and 2.3 million to indoor air pollution, ranking it as the fourth leading global risk factor for death.[8] The global exposure mortality model has predicted that there

FIGURE 1 Classification, Sources, and Constituents of Air Pollution



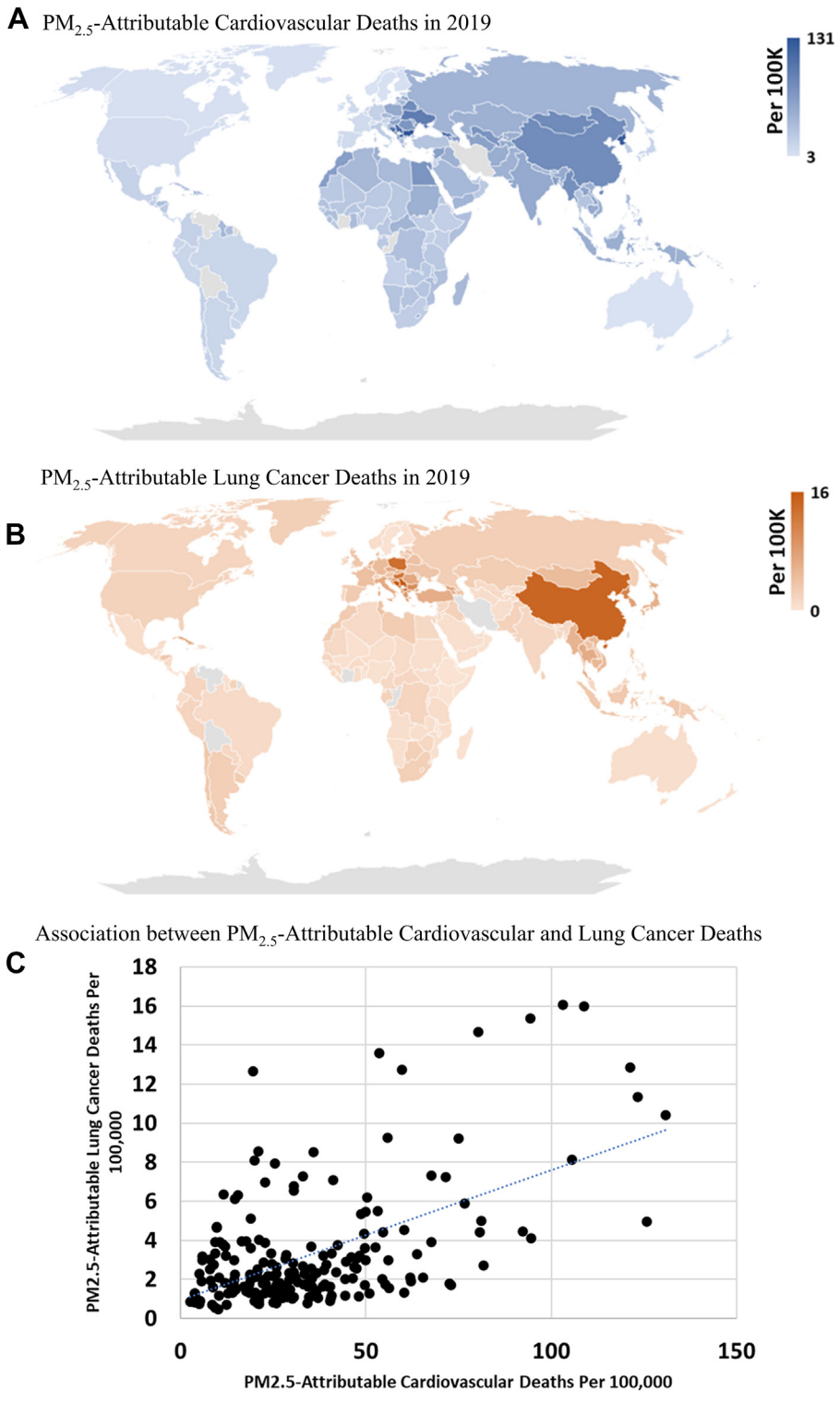
(A) Air pollution comprises gaseous pollutants, semivolatile liquids, and particulate matter (PM) and (B) has diverse sources. (C) PM is categorized based on aerodynamic diameters, and its constituents exhibit high heterogeneity. Figure 1C was reproduced with permission from Bell et al.[18] CO = monoxide; CO_2 = carbon dioxide; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{0.1}$ = particulate matter ≤0.1 μm; $PM_{2.5}$ = particulate matter ≤2.5 μm; PM_{10} = particulate matter ≤10 μm; SO_2 = sulfur dioxide; VOC = volatile organic compound.

could be up to 8.9 million excess deaths annually caused by air pollution.[16] Deaths from ambient air pollution have increased by 51% since 1990 and are expected to double by 2050, driven by global demographic aging and rapid industrialization in countries across South and East Asia.[17]

In a recent study, the concentration and composition of airborne pollutants varied across geographic areas because of diverse sources and physicochemical features.[18] Among these components, PM, particularly particulate matter ≤2.5 μm ($PM_{2.5}$), was extensively studied and was found to be strongly associated with many adverse health outcomes, especially cardiovascular disease and cancer.[19,20] PM is a complex mixture of chemically and physically diverse aerosols comprising hazardous solid and liquid particles suspended in the air. PM has been classified based on aerodynamic diameter as follows: particulate matter ≤0.1 μm (PM_{10}), $PM_{2.5}$, and particulate matter 0.1 μm ($PM_{0.1}$). Smaller size fractions have a larger reactive surface area, enabling greater penetration into the deepest recesses of the alveoli and bloodstream (Figure 1C). Epidemiologic studies have consistently demonstrated that $PM_{2.5}$, with its highly heterogeneous constituents, exhibits the strongest associations with adverse health effects.[21] In a prior study, it was estimated that lifelong exposure to $PM_{2.5}$ reduced lifespan by 3 to 6 months in moderately polluted countries and by 1 to 2 years in heavily polluted countries.[22]

AIR POLLUTION IN CARDIOVASCULAR DISEASE AND CANCER. The links between air pollution and cardiovascular disease and cancer have been firmly established through extensive research. A previous study showed that exposure to $PM_{2.5}$ was associated

FIGURE 2 **Global $PM_{2.5}$-Attributable Cardiovascular and Lung Cancer Deaths in 2019**



(A) The geographic distributions of particulate matter ≤2.5 μm ($PM_{2.5}$)-attributable cardiovascular and (B) lung cancer deaths in 2019 are shown on the world map, revealing similar patterns. (C) A positive correlation between these 2 types of death is shown. Figure was drawn using data from the 2019 Global Burden of Disease project.[30]

TABLE 1 Studies About Air Pollution in Cardio-Oncology From 2000 to Present

First Author, Year	Location (y)	Participants	Main Findings
The effects of air pollution on cardiovascular disease in patients with cancer			
Choi et al, 2020[34]	South Korea (2008-2011)	40,899 cancer survivors	Cancer survivors in the highest quintile of $PM_{2.5}$ had a higher risk of cardiovascular disease (HR: 1.31; 95% CI: 1.07-1.59) compared to those with the lowest quintile.
Coleman et al, 2021[33]	USA (2000-2016)	5,529,005 patients with cancer and survivors	A 10-μg/m^3 increase in $PM_{2.5}$ was associated with increased cardiopulmonary mortality (HR: 1.24; 95% CI: 1.19-1.29) and cardiovascular disease mortality (HR: 1.31; 95% CI: 1.25-1.38).
Coleman et al, 2021[32]	USA (2000-2016)	5,591,168 patients with cancer in the primary cohort and 2,318,068 patients in the 5-year survivor cohort	A 10-μg/m^3 increase in $PM_{2.5}$ was associated with increased cardiovascular disease mortality in the primary cohort (HR: 1.32; 95% CI: 1.26-1.39) and in the 5-year survivor cohort (HR: 1.17; 95% CI: 1.09-1.26).
Choi et al, 2021[35]	South Korea (2015-2018)	22,864 5-year cancer survivors	The fourth quartiles of lag0-3 PM_{10} (OR: 1.13; 95% CI: 1.06-1.21) and $PM_{2.5}$ (OR: 1.11; 95% CI: 1.05-1.18) were associated with a higher risk of cardiovascular disease compared to their respective first quartiles.
Cheng et al, 2022[31]	California (1993-2013)	3,089 patients with breast cancer	The HRs of cardiovascular disease mortality were 1.60 (95% CI: 1.08-2.37) per 50 ppb NO_x, 1.49 (95% CI: 0.92-2.40) per 20 ppb NO_2, 1.44 (95% CI: 0.95-2.17) per 10 μg/m^3 kriged $PM_{2.5}$, and 1.25 (95% CI: 0.97-1.62) per 10 μg/m^3 kriged PM_{10}.
The effects of air pollution on cancer in cardiovascular disease patients			
Cohen et al, 2017[36]	Israel (1992 to 1993-2013)	1,393 patients with myocardial infarction	The HRs of cancer incidence and mortality were 1.06 (95% CI: 0.96-1.18) and 1.08 (95% CI: 0.93-1.26) per 10-ppb increase in nitrogen oxide exposure.
Cohen et al, 2018[37]	Israel (2004-2014)	9,816 patients with percutaneous coronary interventions	The HRs of all-site cancer, breast cancer, and TRAP-related cancer incidence were 1.07 (95% CI: 1.00-1.15), 1.43 (95% CI: 1.12-1.83), and 1.16 (95% CI: 1.05-1.28), per 10-ppb increase in nitrogen oxide exposure.
Cohen et al, 2020[38]	Israel (patient cohorts: 1992-1993 and 2006-2014); matched control cohorts: 1999-2001 and 2005-2006)	2,040 patients with CHD and 2,040 individuals without CHD	With a 10-ppb increase in nitrogen oxide exposure, patients with CHD had a higher risk of cancer incidence (HR: 1.19; 95% CI: 1.03-1.37) compared to the matched controls (HR: 0.93; 95% CI: 0.84-1.04) ($P_{interaction}$ = 0.01).

CHD = coronary heart disease; NO_2 = nitrogen dioxide; NO_x = nitrogen oxides; $PM_{2.5}$ = particulate matter ≤2.5 μm; PM_{10} = particulate matter ≤10 μm; ppb = parts per billion; TRAP = traffic-related air pollution.

with hypertension, atherosclerosis, heart attacks, and strokes (Supplemental Table 1).[10] **Figure 2A** illustrates the global $PM_{2.5}$-attributable cardiovascular disease deaths in 2019. Air pollution has also been linked with various types of cancer, with lung cancer showing the strongest and most consistent association with the carcinogenic risk of $PM_{2.5}$ (Supplemental Table 2).[23] According to the Global Burden of Disease Study, PM pollutants contributed to 15.1% of global lung cancer deaths (**Figure 2B**).[24] The rising number of cancer survivors has led to a higher prevalence of coexisting cardiovascular disease and cancer. Studies indicate that patients with cancer had a higher risk of cardiovascular disease,[25-28] whereas individuals with pre-existing heart failure had higher incidence and mortality rates of cancer compared to those without heart failure.[29] Importantly, global analysis of $PM_{2.5}$-attributable cardiovascular and lung cancer deaths in 2019 showed a positive correlation[30] (**Figure 2C**). Given the important role of air pollution in both cardiovascular disease and cancer, it is plausible that air pollution plays a role in the coexistence and interaction of these 2 diseases.

AIR POLLUTION IN CARDIO-ONCOLOGY

Literature search strategy. A literature search conducted from 2000 to 2023 yielded 8 relevant studies that directly explored the effect of air pollution on cardiovascular disease within cancer cohorts or on cancer within cardiovascular disease cohorts (**Table 1**). Detailed information regarding the search strategy and process is presented in Supplemental Figure 1. A total of 8 studies were included. These studies, despite being conducted by a limited number of research teams and being geographically restricted, provide current evidence that strongly emphasizes the pivotal role of air pollution in cardio-oncology.

Air pollution and cardiovascular mortality in patients with cancer. Among these 8 studies, 3 investigated the association between air pollution and cardiovascular mortality in patients with cancer. These studies consistently reported elevated cardiovascular disease mortality and cardiopulmonary mortality attributed to $PM_{2.5}$ exposure in patients with cancer, with HRs ranging from 1.17 to 1.44 per 10-μg/m^3 increase in $PM_{2.5}$.[31-33] In a study by Cheng et al,[31] increased cardiovascular disease mortality was

associated with individual exposure to nitrogen oxides (NO_x), nitrogen dioxide (NO_2), and PM_{10} among patients with breast cancer, with higher mortality HRs observed in patients with pre-existing cardiovascular disease (HR: 1.45-2.05) compared to those without (HR: 0.88-1.22). Additionally, 2 studies[32,33] encompassing a broader spectrum of cancer types revealed that chemotherapy and/or radiation therapy enhanced the risk of air pollution–associated cardiopulmonary death in patients with cancer. These studies[32,33] found a higher risk of cardiopulmonary death in chemotherapy or radiation therapy groups compared to the control groups without these therapies, with HRs of 1.33 vs 1.21 and 1.34 vs 1.18, respectively. Individuals diagnosed with cancer types with poor survival rates and distant metastatic neoplasms exhibited greater susceptibility to $PM_{2.5}$ exposure compared to those with cancers with higher survival rates and carcinoma in situ. The HRs for individuals with low-survivability cancers were 1.37 (95% CI: 1.27-1.49) and 1.34 (95% CI: 1.23-1.46) in the studies by Coleman et al[32] and Coleman et al,[33] respectively. Conversely, those with high-survivability cancers showed HRs of 1.20 (95% CI: 1.14-1.28) and 1.19 (95% CI: 1.12-1.26) in the same studies. Similarly, individuals with distant metastatic neoplasms exhibited higher HRs of 1.45 (95% CI: 1.30-1.63) and 1.45 (95% CI: 1.29-1.63) compared to those with carcinoma in situ (HR: 1.35; 95% CI: 1.16-1.58 and HR: 1.35; 95% CI: 1.15-1.59 in studies by Coleman et al[32] and Coleman et al[33], respectively).

Air pollution and cardiovascular disease incidence in patients with cancer. In addition to studies examining mortality, 2 studies conducted by the same research group in Korea during different time periods (2008-2011 and 2015-2018) discovered a higher risk of cardiovascular disease incidence associated with $PM_{2.5}$ and PM_{10} among all types of cancers.[34,35] Further analysis showed that cardiovascular disease incidence was particularly significant in breast cancer.[34] Additionally, exposure to $PM_{2.5}$ revealed stronger correlations with coronary heart disease (CHD) compared with stroke across various concentrations of $PM_{2.5}$.[34]

Air pollution and cancer risks in patients with cardiovascular disease. Three studies conducted by Cohen et al[36-38] in Israel have significantly contributed to our understanding of the relationship between air pollution and cancer risk in cardiovascular disease patients.[36-38] These studies specifically examined the association between NO_x, a proxy measure for traffic-related air pollution (TRAP), and cancer incidence or mortality in patients with different forms of cardiovascular disease, including myocardial infarction,[36] percutaneous coronary interventions,[37] and CHD.[38] They observed significantly positive associations between NO_x and the incidence of TRAP-related cancers (lung, prostate, kidney, and bladder cancer) among cardiovascular disease patients (HR: 1.16; 95% CI: 1.00-1.33;[36] HR: 1.16; 95% CI: 1.05-1.28).[37] Of note, TRAP-related cancer incidence remained significant when persistent heavy smokers were excluded (HR: 1.17; 95% CI: 1.01-1.36).[36] This association was particularly notable in breast cancer, with an HR of 1.43 (95% CI: 1.12-1.83).[37]

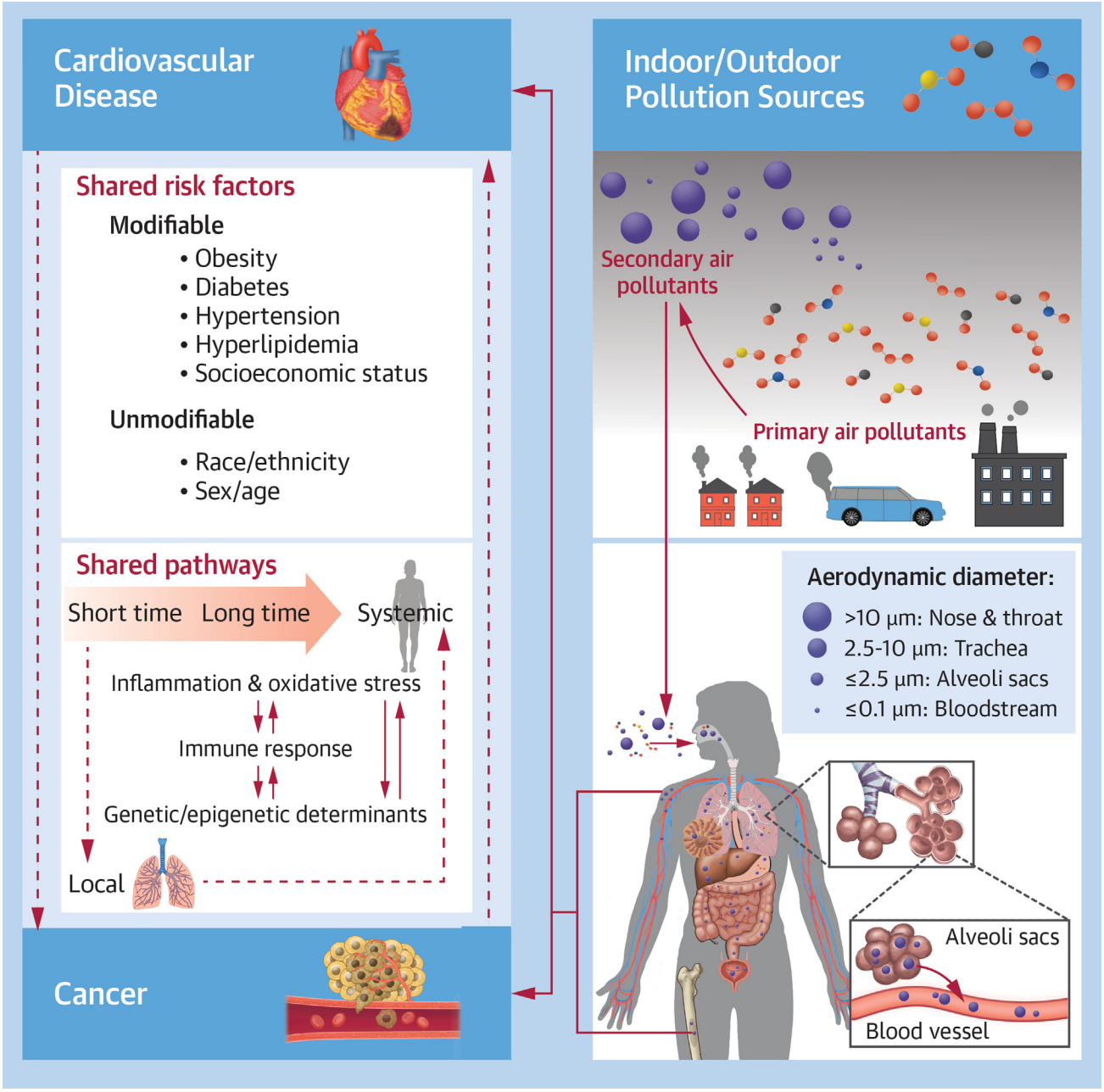
Building on these findings, a study with 2,040 matched pairs (individuals with pre-existing CHD and without CHD) was conducted to further explore this relationship. This study showed that patients with pre-existing CHD had a higher incidence of all cancers associated with air pollution (HR: 1.19; 95% CI: 1.03-1.37) and increased all-cause mortality (HR: 1.13; 95% CI: 1.05-1.22) compared to individuals without CHD. Moreover, the association was particularly pronounced for specific cancers such as lung, breast, or prostate (HR: 1.29; 95% CI: 1.02-1.62) compared to other cancer types combined (HR: 1.14; 95% CI: 0.95-1.36).[38]

Knowledge gaps in air pollution–related cardio-oncology. Despite the valuable contributions of these studies, it is crucial to highlight the substantial gaps that still need to be addressed. First, there is a need to consider the impact of different assessment models in data collection and analysis.[31] Second, only a few studies have included subgroup analysis by incorporating individual-level covariates, highlighting the need for further control of potential confounding factors such as blood pressure, lipids, diabetes, smoking, physical activity, and medication use. Lastly, it is evident that the field of air pollution in cardio-oncology has been overlooked. Given the challenge posed by the lack of direct epidemiologic evidence, exploring shared risk factors and potential mechanistic links would be instrumental in unraveling the role of air pollution in cardio-oncology.

EFFECTS OF AIR POLLUTION ON COMMON RISK FACTORS OF CARDIOVASCULAR DISEASE AND CANCER

MODIFIABLE RISK FACTORS. In this section, we explore the effects of air pollution on shared modifiable risk factors in both cardiovascular disease and cancer, focusing particularly on individual-level metabolic factors such as obesity, diabetes, and dyslipidemia (**Central Illustration**). Collectively, these cardiometabolic factors play a pivotal role in both cardiovascular disease and cancer. For example,

CENTRAL ILLUSTRATION Air Pollution in Cardio-Oncology



Zhu W, et al. J Am Coll Cardiol CardioOnc. 2024;6(3):347-362.

Air particulate matter (PM), originating from diverse sources, exhibits varying aerodynamic diameters and compositions. PM affects both cardiovascular disease and cancer through shared risk factors and common molecular pathways. Multidisciplinary management is essential to mitigate the health impact of air pollution in cardio-oncology.

according to studies, adipose tissue in obese patients produced proinflammatory cytokines and adipokines that accelerated both atherosclerosis[39] and cancer apoptosis.[40] Similarly, increased levels of insulin, blood glucose, and insulin-like growth factor 1 were found to be associated with both cardiovascular disease and cancer.[41-43] Dyslipidemia, obesity, and insulin resistance were interconnected and contributed

synergistically to the development of cardiovascular events and cancer.[44] Although we discuss these factors individually later, it is essential to recognize their interactive and synergistic effects within the body.

Air pollution and obesity. Previous studies have explored the relationship between air pollution and obesity risk across various life stages, from prenatal and early life to childhood and adulthood. Here, we present selected evidence, with a more comprehensive overview available in a review by Shi et al.[45] In the Ulaanbaatar Gestation and Air Pollution Research randomized controlled trial, children at 23.8 months whose mothers received portable high-efficiency particulate air filters during pregnancy showed a slight reduction in body mass index (BMI) compared to controls.[46] Similarly, a large-scale longitudinal study in Spain found that prenatal and early postpartum exposures to NO_2, $PM_{2.5}$, and PM_{10} were associated with modest changes in BMI during the first 5 years of life. Specifically, the study reported an average increase in BMI of 0.018 kg/m^2 per 21.3-$\mu g/m^3$ increase in NO_2, 0.007 kg/m^2 per 1.5-$\mu g/m^3$ increase in $PM_{2.5}$, and 0.023 kg/m^2 per 6.3-$\mu g/m^3$ increase in PM_{10}.[47] In a cross-sectional study of Chinese school children 6 to 17 years of age, a per 10-$\mu g/m^3$ increment in $PM_{2.5}$ was associated with a 10.0% increase (95% CI: 3.0-16.0) in obesity incidence. This association was particularly prominent among teenagers 15 to 18 years of age (OR: 4.89) and in urban areas (OR: 6.10).[48] Importantly, similar results were observed in adult cohorts, paralleling those observed in infants and children.[49]

Air pollution and diabetes. Studies have demonstrated an association between air pollution and an increased risk of diabetes.[50] According to a systematic review by Eze et al[51] in 2015, 13 epidemiologic studies found that a per 10-$\mu g/m^3$ increase in $PM_{2.5}$ and NO_2 was associated with an 8% to 10% elevation in the risk of diabetes, corresponding to relative risks of 1.10 and 1.08, respectively. Since then, an expanding body of evidence has emerged, suggesting a positive association between air pollution and diabetes incidence/mortality among children, adolescents, and adults.[52] Furthermore, gestational air pollution exposure not only elevated the risk of gestational diabetes but also increased the likelihood of diabetes in their offspring.[52] Mechanistically, air pollution appeared to induce adipose tissue redistribution (eg, enhancing visceral fat accumulation[53] and promoting the transition of brown adipose tissue to white adipose tissue[54]), worsen insulin resistance, and trigger systemic inflammation.

Air pollution and dyslipidemia. Exposure to air pollution is believed to accelerate the progression of atherosclerosis by increasing atherogenic lipoproteins and decreasing protective lipoproteins. In a longitudinal study involving midlife women, a 3-$\mu g/m^3$ increase of 1-year exposure to $PM_{2.5}$ led to a decrease of 0.7% in high-density lipoprotein cholesterol and a 0.6% decrease in apolipoprotein A1 along with increases of 3.8% in lipoprotein(a) and 1.4% in apolipoprotein B/A1.[55] Several studies from China have also shown a positive association between $PM_{2.5}$ exposure and low-density lipoprotein cholesterol levels.[56,57] Furthermore, other pollutants such as PM_{10} and NO_2 have been implicated in various forms of dyslipidemia.[58,59] It is important to note that although these findings suggest a link between air pollution and dyslipidemia, there may be significant residual confounding influencing these associations.

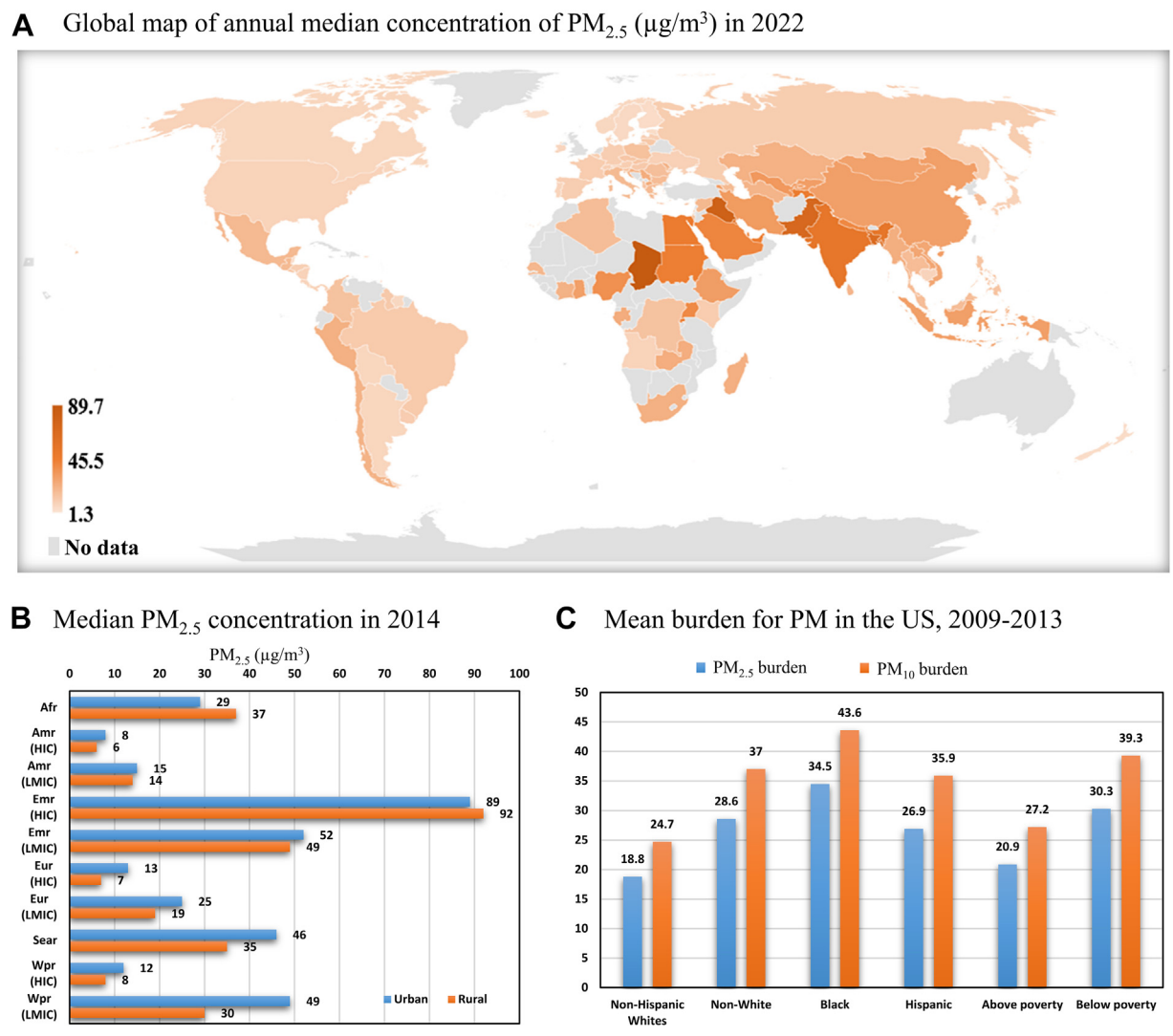
Air pollution and hypertension. According to a recent umbrella review,[60] strong evidence was found linking both short-term and long-term exposure to $PM_{2.5}$ with the incidence of hypertension. $PM_{2.5}$ was associated with both systolic and diastolic blood pressure.[21] Additionally, a cohort study that focused on dynamic cardiovascular disease trajectories associated with air pollution revealed that higher $PM_{2.5}$ exposure increased the transition from prehypertension to hypertension, cardiovascular disease, and death.[61] Furthermore, sham-controlled randomized trials of portable air cleaners to reduce air pollution exposure have confirmed a causal relationship between $PM_{2.5}$ exposure and elevations in blood pressure.[62]

SOCIAL DETERMINANTS OF HEALTH, ENVIRONMENTAL JUSTICE, AND HEALTH DISPARITIES.

Health disparities disproportionately affect vulnerable individuals based on structural factors including race, ethnicity, and socioeconomic status. Recognizing and addressing health inequalities related to air pollution are crucial for identifying vulnerable populations and devising personalized health management strategies.

Inequalities of air pollution exposure. Disparities in exposure to ambient air pollution have been observed across various regions and among populations of varying ethnicity and socioeconomic status (**Figure 3**).[63-66] Air pollution levels exceed the WHO guideline for $PM_{2.5}$ in the majority of global regions, particularly impacting the Eastern Mediterranean, Southeast Asian, and Western Pacific regions (**Figure 3A**). $PM_{2.5}$ exposure disproportionately affects LMICs (**Figure 3B**). Inequalities were also observed within countries; urban populations, except in Africa and the Eastern Mediterranean regions near deserts, generally experienced more severe $PM_{2.5}$ exposure compared to their rural counterparts, as shown in

FIGURE 3 **Inequalities in $PM_{2.5}$ and PM_{10} Exposure**



(A) Global map showing the annual median concentration of $PM_{2.5}$ (μg/m³). (B) Median $PM_{2.5}$ concentration in different regions. (C) Mean burden for PM in the United States from 2009 to 2013. Figure 3A was created using data from IQAir. Figure 3B was reproduced with permission from WHO.[67] Figure 3C was drawn using data from the literature.[64] Unit for PM burden is tons/y. Afr = Africa; Amr = Americas; Emr = Eastern Mediterranean; Eur = Europe; Sear = South-East Asia region; Wpr = western pacific region; LMIC = low- and middle-income country; HIC = high-income country; other abbreviations as in Figure 1.

Figure 3B.[67] In the United States, disadvantaged populations including individuals living in poverty, Black individuals, and non-White groups experienced 1.35, 1.54, and 1.28 times higher exposure to $PM_{2.5}$ compared to the general population (Figure 3C).[64] In the Multi-Ethnic Study of Atherosclerosis, Black and Hispanic/Latino communities, especially those with low socioeconomic status, often resided closer to high-traffic areas and had limited access to green space, resulting in exposure to higher concentrations of $PM_{2.5}$ and NO_x.[68,69] These factors related to air pollution ultimately contributed to disparities in cancer and cardiovascular disease. Another emerging study identified 71 sociodemographic and environmental risk factors in the United States, highlighting that differences of air pollution exposure, race/ethnicity, and income levels contributed to injustices in cardio-oncology mortality.[70]

Inequalities of air pollution in cardio-oncology. Table 1 summarizes studies focusing on the impact of air pollution on cardiovascular disease within cancer cohorts and vice versa. Coleman et al[33] assessed the

effects of $PM_{2.5}$ on cardiopulmonary mortality in patients with cancer. Their results suggested that Black individuals may be more susceptible to the adverse effects of $PM_{2.5}$ than White individuals (HR: 1.43 vs 1.22), although these differences were not statistically significant.[33] Coleman et al[32] found that $PM_{2.5}$-associated cardiopulmonary mortality was higher for Black individuals (HR: 1.42; 95% CI: 1.21-1.66) compared to White individuals (HR: 1.24; 95% CI: 1.19-1.29). Sensitivity analyses for $PM_{2.5}$-associated cardiopulmonary mortality conducted by age, sex, and race yielded an HR of 1.39 (95% CI: 1.37-1.41), although a more in-depth comparison was not performed.[32]

Another study investigating cardiovascular disease incidence in cancer survivors, contrary to expectations, yielded higher adjusted ORs for individuals in the upper half of household income when exposed to PM_{10} compared to the lower half.[35] A slightly higher OR for individuals in the upper half of household income was noticeable only at the highest level of $PM_{2.5}$ exposure. The Multiethnic Cohort Study provided insights into disparities across racial/ethnic groups,[31] revealing a positive association between air pollution and cardiovascular disease mortality within the breast cancer cohort. Importantly, these adverse effects associated with NO_x, NO_2, $PM_{2.5}$, and PM_{10} were most significant among African Americans, with HRs of 2.16 (95% CI: 1.21-3.84), 3.39 (95% CI: 1.59-7.23), 2.10 (95% CI: 1.13-3.91), and 1.55 (95% CI: 1.04-2.29), respectively.

The risk of cardiovascular disease mortality among African Americans with breast cancer increased significantly, ranging from 1.6-fold to 3.6-fold for all pollutants. Furthermore, patients with cancer of lower socioeconomic status faced a higher risk of cardiovascular disease-related death because of air pollutants compared to those of higher socioeconomic status.

SHARED MOLECULAR AND GENETIC PATHWAYS: ROLE OF AIR POLLUTION IN PREDISPOSING TO BOTH CARDIOVASCULAR DISEASE AND CANCER

INFLAMMATION AND OXIDATIVE STRESS IN CARDIO-ONCOLOGY. The co-occurrence of cancer and cardiovascular disease, along with their shared risk factors, suggests overlapping pathophysiological mechanisms (**Central Illustration**). These mechanisms encompass a range of pathways, including inflammation, immune activation, metabolic pathways, neurohormonal mechanisms, and gut microbiome. Within this intricate network, inflammation and oxidative stress play central and dominant roles, demonstrating not only a cause-and-effect relationship but also interacting with other pathological factors to collectively exert both cardiovascular and carcinogenic effects. It is important to note that the involvement of these common pathways in both cardiovascular disease and cancer has been extensively documented and reviewed elsewhere.[5,6] Furthermore, exposure to air pollution has been shown to intricately interact with these shared pathways between cardiovascular disease and cancer.

INFLAMMATION AND OXIDATIVE STRESS IN AIR POLLUTION: INITIATION AND PROGRESSION. Inflammation and oxidative stress are pivotal mechanisms underpinning the carcinogenic and vascular effects of air pollution. A number of air pollutants, particularly $PM_{2.5}$ and $PM_{0.1}$, can breach the upper respiratory tract barrier and deposit into the alveoli, initiating the following steps: 1) certain pollutants, particularly gaseous ones and $PM_{0.1}$, directly enter the bloodstream, causing systemic effects; 2) local inflammation and oxidative stress in the local pulmonary system can rapidly overwhelm the body's natural defenses, leading to systemic inflammation that spreads throughout the entire body within 2 to 3 days;[71] and 3) both inflammatory and oxidative pathways, whether local or systemic, contribute to inflammatory dysregulation and oxidative injury, ultimately leading to cardiovascular damage and a predisposition to cancer. Additionally, inflammation and oxidative reactions can affect systemic penetration of these pollutants.

Airborne pollutants pronouncedly increased reactive oxygen species (ROS) levels both directly from the pollutants themselves and indirectly from cells interacting with the pollutants, such as alveolar epithelial cells and macrophages. In addition, different pollutants interacted synergistically to generate ROS.[72] Maintaining a balance between antioxidants and ROS is crucial. An imbalance in the pulmonary antioxidant barrier promoted the transition from local to systemic inflammation,[73,74] whereas an imbalance in target organs resulted in cardiovascular injury, creating a favorable microenvironment for carcinogenesis.[75]

Robust supporting evidence has shown the important role of oxidative stress and its interplay with inflammation in the progression of air pollution–associated cardiovascular disease. Studies have shown that overexpression of extracellular superoxide dismutase, a key antioxidant that scavenges ROS, in the lungs counteracted $PM_{2.5}$-induced reduction of plasma NO and aided in the recovery of hind limb

perfusion by increasing circulating endothelial progenitor cells.[76] This underscores the importance of the pulmonary antioxidant barrier. We found that a prolonged 6-month exposure to $PM_{2.5}$ accelerated the accumulation of 7-ketocholesterol, an oxidatively modified form of cholesterol, in both the low-density lipoprotein fraction and aortic plaque.[77] This elevation of 7-ketocholesterol resulted in macrophage activation, as manifested by upregulated CD36 expression, which further enhanced the deposition of oxidized lipid in macrophages and the aortic wall.[77] Furthermore, increased levels of oxidized phospholipids in bronchioalveolar lavage fluid were revealed, accompanied by elevated macrophage infiltration in both vasculature and visceral adipose tissue. Subsequently, these changes were found to be associated with nicotinamide adenine dinucleotide phosphate oxidase p47, Toll-like receptor 4, and Nox2, all of which are linked to the generation of ROS.[78,79]

Inflammation and ROS also have important roles in promoting tumor growth and facilitating metastasis through various mechanisms.[80] An in-depth analysis using global transcriptome profiling unveiled that exposure to $PM_{2.5}$ induced heightened proliferation, migration, and invasion of A549 cells, a human non-small-cell lung cancer cell line. This effect was closely associated with interleukin-1β.[81] Furthermore, polycyclic aromatic hydrocarbons (PAHs), the primary organic component in $PM_{2.5}$, have been implicated in causing lung cancer through chemokine CXCL13. This is supported by evidence showing that deficiency of CXCL13 or its receptor significantly alleviated PAH-induced lung cancer in mice.[82] In a recent study, air pollution has been shown to promote carcinogenesis by fostering an inflammatory microenvironment that facilitates the growth and proliferation of cells with existing cancer-driving sequence variations.[83]

GENETIC/EPIGENETIC INTERACTION WITH INFLAMMATION AND OXIDATIVE STRESS IN AIR POLLUTION. Genetic/epigenetic sequence variations are also important consequences of air pollution-induced chronic inflammation and oxidative stress. $PM_{2.5}$ was shown to carry certain types of mutagens and carcinogens (PAHs, SO_3, H_2SO_4, dioxins, metals, and so on)[20], forming DNA adducts.[84] This process, in turn, induced gene instability,[85] epigenetic modifications (especially DNA methylation),[86] and transcriptional changes in microRNA[87] and long noncoding RNA.[88] Studies have shown that these changes played a significant role in cardio-oncology, directly facilitating the malignancy of somatic cells and cardiovascular dysfunction and indirectly exacerbating the detrimental effects of common risk factors such as obesity[89] and diabetes.[90]

Genetic variation and instability are important mechanisms that induce the adverse effects of air pollution. For instance, human bronchial epithelial cells exposed to $PM_{2.5}$ exhibited dose-dependent changes in the expression of DNA damage–related genes accompanied by elevated inflammatory and immune responses.[91]

In addition to genetic instability and variation, epigenetic modifications represent another major mechanism mediating the health effects of air pollution in cardio-oncology. Among various epigenetic modifications, DNA methylation and histone acetylation, specifically the methylation of PM-sensitive CpG sites within the genes associated with cardiopulmonary diseases, stood out as the most prominent epigenetic change induced by air pollution.[92] A recent study found that exposure to $PM_{2.5}$ led to downregulation of histone deacetylases 2, 3, and 4, along with increased promoter occupancy by the histone acetyltransferase p300, as confirmed by chromatin immunoprecipitation.[93] Using data from SAPALDIA (Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults), Eze et al[94] found a notable enrichment of DNA methylation in genes associated with inflammation and cardiovascular development after exposure to $PM_{2.5}$ and NO_2.

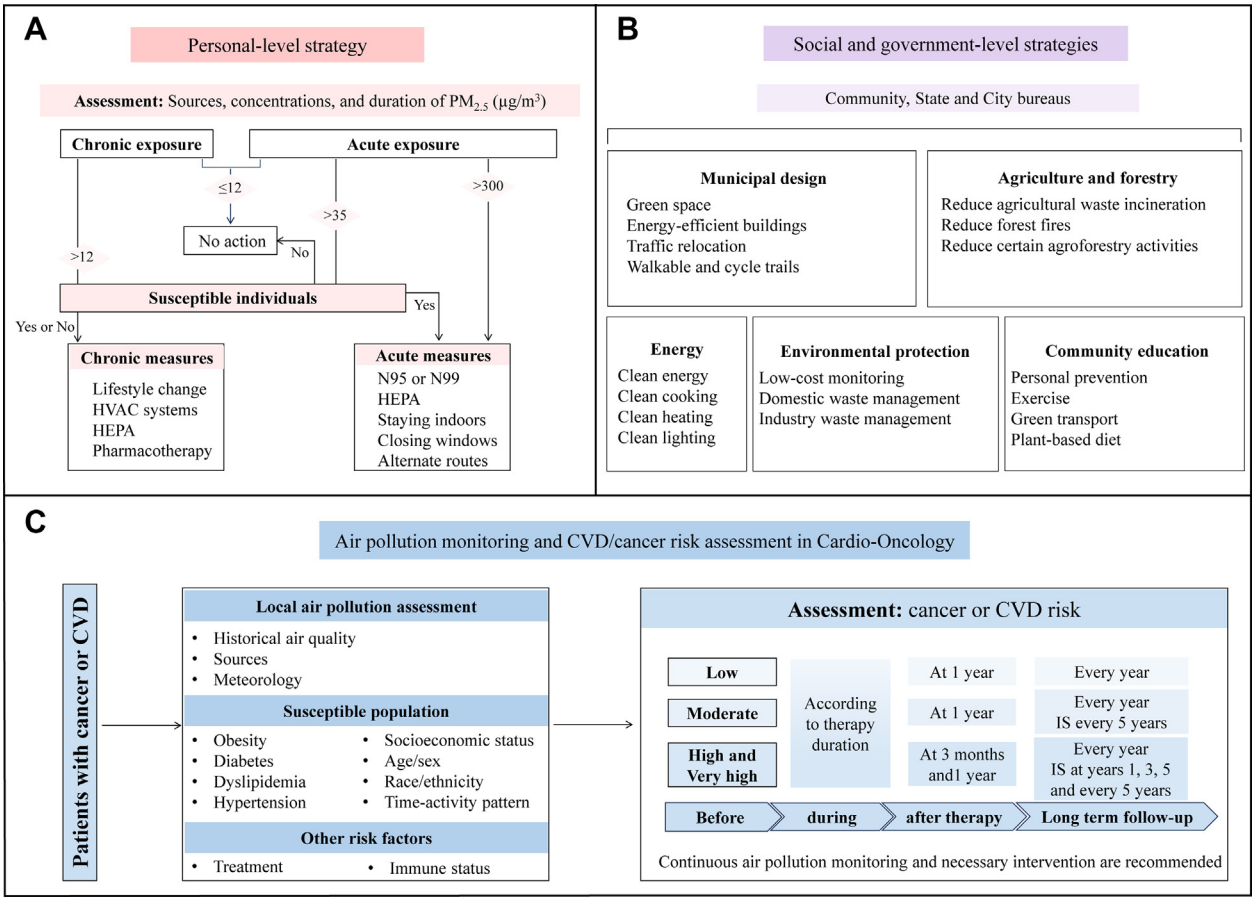
Mechanistically, a randomized, double-blind, controlled human exposure study revealed that exposure to TRAP increased plasma proinflammatory cytokines by upregulating DNA demethylation enzymes in activated T cells.[95] Additionally, other epigenetic changes, including long noncoding RNA[96] and microRNA,[97,98] mediated air pollution–induced inflammation, cardiovascular dysfunction, and cancer development. Importantly, many of these noncoding RNAs, such as miR-21,[97,98] played important roles in both cancer and cardiovascular disease.

In summary, by affecting common pathways and risk factors shared between cancer and cardiovascular disease, air pollution plays an undeniable role in the field of cardio-oncology (**Central Illustration**).

CHALLENGES AND OPPORTUNITIES FOR THE FUTURE

Air pollution has long been overlooked in both cancer and cardiovascular disease, particularly in cardio-oncology care, despite robust evidence linking air pollution to both conditions. Although cardiovascular disease risk is recognized as an important consideration in cancer treatment according to the 2022 guideline on cardio-oncology,[99] environmental

FIGURE 4 Air Pollution Assessment and Intervention Strategy in Cardio-Oncology



(A) Personal-level strategies for air pollution–related cardio-oncology interventions. (B) Social- and government-level strategies to address air pollution in cardio-oncology. (C) Air pollution–related risk assessment considerations in cardio-oncology patient care. Personal preventative measures vary based on individual vulnerability and the duration and concentration of air pollution exposure. Risk assessment and patient care in cardio-oncology should integrate strategies for preventing air pollution exposure and addressing its associated risks. CVD = cardiovascular disease; HEPA = high-efficiency particulate air; HVAC = heating, ventilation, and air conditioning; IS = imaging screening.

factors are currently not adequately addressed because of insufficient awareness of this issue. This emphasizes the critical need to raise awareness about the impact of environmental factors, specifically air pollution, in cardio-oncology care. Increased awareness could lead to reduced risks through improved knowledge of personalized protection strategies against air pollution.

In this review, we build on the 2022 cardio-oncology guidelines as well as statements from the American Heart Association[100] and WHO[101] advocating for the reduction of air pollution exposure. Here, we outline potential intervention approaches aimed at reducing the adverse effects of air pollution exposure (Figure 4). These recommendations include risk assessment, personalized interventions, and key considerations for society and governments (Figures 4A to 4C). Importantly, suggested solutions for monitoring air pollution-related cardio-oncology effects are listed in Figure 4C based on the guidelines from the European Society of Cardiology in 2022.[99]

We propose an expanded perspective on the concept of susceptible populations in both sets of recommendations to integrate environmental factors, including air pollution, into the risk assessments in cardio-oncology. Given the significant variation in air pollutant concentrations and sources across different geographic areas and seasons, it is essential to assess the concentrations and sources of air pollutants, including $PM_{2.5}$, before, during, and after cancer therapy, particularly for vulnerable groups.

Preventative interventions such as using N95/N99 respirators; reducing outdoor activities during heavily polluted days; and improving indoor air quality with portable air cleaners or heating, ventilation, and air conditioning systems are recommended for vulnerable individuals residing in areas with high levels of pollutants.

Research results from cardio-oncology patients or studies involving both cardiovascular disease and cancer have not been effectively translated into clinical practice, particularly in terms of shared biomarkers and consideration of environmental factors in risk assessments. Identifying susceptible and vulnerable populations uniquely at risk remains a challenge. There are substantial gaps in knowledge regarding the impact of air pollution on cardio-oncology patient care and its interaction with the efficacy of anticancer treatments.

The interplay between air pollution and inflammation, ROS-mediated pathways, and genetic/epigenetic modifications in patients at risk of both cancer and cardiovascular disease has not been extensively studied. Metabolic alterations also played a significant role in the pathogenesis of various diseases, including cardiovascular disease (eg, the shift from oxidative phosphorylation to glycolysis) and cancer (eg, dynamically heterogeneous metabolic phenotype during the premalignant, locally invasive, and metastatic processes).[102] The intrinsic and interconnected relationship between these aspects, including their metabolic substrates and products, is an important aspect that has been overlooked in air pollution research.

CONCLUSIONS

Although there is direct evidence linking air pollution to cardio-oncology, it is important to acknowledge the existing limitations and notable gaps in the evidence. Variations in time-activity patterns and residential history among participants may introduce inaccuracies in data related to air pollution exposure, potentially leading to information and measurement biases. Additionally, recall bias has been observed in certain self-reported cases, and there is a potential for selective reporting and publication bias in study results. Therefore, further large-scale prospective cohort studies and preregistration research plans are indispensable to address the carcinogenic effects of air pollution across various cancer types in cardiovascular disease patients and the impact of air pollution on heart damage in cancer patients.

Additionally, cardiovascular risks and conditions may influence the choice of cancer treatment. Cancer therapies with minimal cardiotoxicity may be prioritized for patients at high cardiovascular disease risk, potentially introducing selection bias into investigations of air pollution effects on cardio-oncology. Future studies should also consider further matching or adjusting potential confounding factors, such as cancer treatments and cardiovascular disease risks. There is an urgent need for additional epidemiologic and mechanistic studies to gain a deeper understanding of the role of air pollution in the context of cardio-oncology. This enhanced understanding will pave the way for early prevention strategies and personalized health care delivery, especially in regions with high air pollution levels. Moreover, it will contribute to a more comprehensive appreciation of the health disparities associated with air pollution, necessitating concerted actions at individual, community, governmental, and regional levels.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Drs Al-Kindi and Rajagopalan were supported by the National Institute of Environmental Health Science grant R35ES031702 and National Institute on Minority Health and Health Disparities grant P50MD017351. Dr Rao was supported by the National Natural Science Foundation of China grants 82170470 and 82370465 and Hubei Key R and D Project grant 2023BCB013. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS air pollution, cardio-oncology, environmental risk factor, health disparity, $PM_{2.5}$

APPENDIX For supplemental tables and figures, please see the online version of this paper.