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Air Pollution and Cardiovascular Diseases: Mechanisms, Evidence, and Mitigation Strategies

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ABSTRACT

One of the most urgent environmental health issues is air pollution, which has a major effect on cardiovascular health. Among other pollutants, fine particulate matter ($PM_{2.5}$) has been connected to a number of cardiovascular illnesses (CVDs), including myocardial infarction, stroke, and hypertension. The purpose of this review of the literature is to summarize current research on the processes by which air pollution raises the risk of CVD and to investigate mitigation and preventative measures. A review of peer-reviewed articles published between 2015 and 2024 was conducted using databases such as PubMed, Web of Science, and Google Scholar. The review focused on studies examining the relationship between $PM_{2.5}$ and cardiovascular diseases, incorporating epidemiological, experimental, and clinical perspectives. $PM_{2.5}$ and other pollutants exacerbate CVD risk through mechanisms such as autonomic instability, endothelial dysfunction, oxidative stress, and inflammation. Risks are disproportionately high for vulnerable groups, such as the elderly and those with underlying cardiovascular diseases. Targeted public health policies, stricter air quality regulations, and increased public awareness are essential to mitigate the cardiovascular risks posed by air pollution. Immediate action is imperative to safeguard global health.

KEYWORDS: air pollution, cardiovascular diseases, endothelial dysfunction, $PM_{2.5}$, public health interventions.

INTRODUCTION:

Air pollution has become a pressing global health concern, recognized as a major contributor to non-communicable diseases, particularly cardiovascular diseases (CVDs), the leading cause of mortality worldwide. A substantial body of evidence has established a link between exposure to air pollutants, including fine particulate matter ($PM_{2.5}$), ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO2), and carbon monoxide (CO), and the onset and exacerbation of CVD. These pollutants originate from various sources, including natural events, vehicular emissions, and industrial activities [1,2,3,4]. Significant progress has been made in understanding the detrimental effects of air pollution on cardiovascular health [2,5,6]. However, critical gaps remain, particularly concerning the intricate molecular mechanisms underlying these effects, the long-term consequences for vulnerable populations (e.g., children, the elderly, and individuals with pre-existing conditions), and the effectiveness of existing mitigation strategies in diverse environmental contexts [7,8].

Moreover, the populations exposed to air pollution exhibit significant heterogeneity, with substantial differences in geographical and socioeconomic factors influencing exposure levels and CVD risk. For instance, individuals in developing countries often experience higher pollution exposure due to biomass combustion and industrial emissions. In contrast, in developed nations, traffic-related pollution and fossil fuel combustion are the predominant sources. Similarly, urban populations tend to face higher air pollution levels than rural populations, yet factors such as access to healthcare and socioeconomic status may modulate the impact of pollution on cardiovascular health. These differences can also influence molecular responses to pollutants, with studies showing variations in inflammatory gene expression and oxidative stress responses between urban and rural populations [5,9].

Socioeconomic status (SES) plays a crucial role in determining both exposure levels and health outcomes. Studies have shown that individuals with low SES are more likely to reside in areas with higher pollution levels and have an increased risk of CVD, potentially due to limited access to healthcare resources and greater exposure to environmental hazards [10].

While urban areas generally experience higher pollution levels, rural regions are not exempt from significant exposure, especially in developing countries. For instance, in rural India and Nepal, biomass combustion for heating and cooking is a major source of household air pollution, contributing to elevated $PM_{2.5}$ levels. There is spatial heterogeneity in India, as areas with diverse climatological conditions and population and education levels generate different indoor air qualities, with higher $PM_{2.5}$ observed in North Indian states (557–601 µg/m³) compared to the Southern States (183–214 µg/m³). The cold climate of the North Indian areas may be the main reason for this, as longer periods at home and more heating are necessary compared to the tropical climate of Southern India. Understanding these population differences is crucial for developing more effective and context-specific mitigation strategies. Therefore, effective mitigation strategies must consider these differences and be tailored to the specific contexts of different populations, including factors such as access to healthcare services, education levels, and housing conditions [5].

Previous reviews have provided valuable insights into the association between air pollution and CVD. However, a comprehensive and up-to-date synthesis of the latest epidemiological, mechanistic, and interventional evidence is lacking. This review addresses these critical gaps by: (1) providing a comprehensive update on the latest epidemiological evidence, focusing on the specific associations between different air pollutants ($PM_{2.5}$, O_3, NO_2, SO_2, CO) and various CVD subtypes (e.g., ischemic heart disease, stroke, heart failure); (2) critically evaluating the current understanding of the molecular mechanisms through which air pollutants exert their adverse effects on the cardiovascular system, including oxidative stress, inflammation, endothelial dysfunction, and epigenetic modifications, with a focus on the interplay between these mechanisms; (3) assessing the effectiveness of current mitigation strategies, such as emission control technologies and public health interventions, and proposing novel approaches, including personalized exposure reduction strategies and targeted therapies; and (4) identifying key research priorities for future investigations, emphasizing the need for longitudinal studies, multi-pollutant exposure assessments, and research on the long-term health impacts in vulnerable populations [7,11,12].

Specifically, critical gaps in molecular pathways include: (a) the role of epigenetic modifications, such as DNA methylation and histone modifications, in mediating long-term cardiovascular effects of air pollution exposure; (b) how different pollutants interact synergistically to exacerbate oxidative stress and inflammation, particularly ultrafine particles (UFPs) and gaseous pollutants like NO_2 and SO_2; and (c) the identification of novel biomarkers that could help elucidate individual susceptibility to air pollution-induced cardiovascular damage. Understanding these aspects is essential for advancing targeted preventive and therapeutic strategies. Understanding these aspects is essential for advancing targeted preventive and therapeutic strategies [13,14,15,16,17,18].

This review aims to provide actionable recommendations for policymakers, healthcare professionals, and the public to mitigate the burden of air pollution-related CVD The existing understanding of the connection between air pollution and cardiovascular health is consolidated in this review, which also highlights molecular pathways such as endothelial dysfunction, oxidative stress, and inflammation. Additionally, it looks at practical ideas and methods to lessen the impact of air pollution-induced CVD, and to influence public health policy and preventative actions [2,19,20,21,22].

METHODS:

This literature review was conducted to synthesize findings from peer-reviewed articles published between 2015 and 2025. Articles were identified through systematic searches in PubMed, Web of Science, and Google Scholar. The search strategy focused on studies examining the relationship between air pollution and cardiovascular diseases, incorporating epidemiological, experimental (in vivo and in vitro), and clinical perspectives.

The following search terms were used in combination with Boolean operators (AND, OR): ($PM_{2.5}$ OR particulate matter 2.5 OR PM_{10} OR particulate matter 10 OR ozone OR O_3 OR nitrogen dioxide OR NO_2 OR sulfur dioxide OR SO_2 OR carbon monoxide OR CO) AND (cardiovascular disease OR cardiovascular disease OR coronary artery disease OR stroke OR heart failure OR hypertension) AND (air pollution OR environmental pollution).

Inclusion criteria:

- Original research articles (epidemiological studies, experimental studies, clinical trials) published in English.
- Studies investigating the association between exposure to air pollutants ($PM_{2.5}$, PM_{10}, O_3, NO_2, SO_2, CO) and cardiovascular outcomes.
- Studies published between 2015 and 2024.

Exclusion criteria:

- Review articles, editorials, letters to the editor, and conference abstracts.
- Studies not focused on the relationship between air pollution and cardiovascular diseases.
- Studies published in languages other than English.

To determine the eligibility of the retrieved papers, two impartial reviewers looked through their abstracts and titles. After that, full texts of articles that might be of interest were obtained and evaluated for inclusion using the predetermined standards. Reviewers' disagreements were settled by consensus and discussion. Key findings and study characteristics (author, year, study design, population, exposure assessment, and outcome measures) were extracted using a standardized form.

RESULTS:

Epidemiological evidence

A strong correlation between exposure to air pollution and an elevated risk of a number of cardiovascular diseases (CVDs) has been repeatedly shown by epidemiological research. These studies provide a thorough understanding of the connection between air pollution and cardiovascular health by utilizing a variety of approaches, such as time-series analyses, case-control studies, and cohort studies. Particulate matter (PM), especially fine particulate matter ($PM_{2.5}$), has been the subject of a substantial amount of research as a major air pollutant that has harmful cardiovascular consequences [19,20,21,22].

Particulate Matter ($PM_{2.5}$ and PM_{10}):

- **Long-term exposure:** Long-term exposure to $PM_{2.5}$ has been strongly linked to an elevated risk of ischemic heart disease (IHD), which includes myocardial infarction (MI), stroke, heart failure, and cardiovascular mortality, according to a number of cohort studies. For example, research has shown that the risk of IHD and stroke increases by 10–20% for every 10 µg/m³ increase in long-term $PM_{2.5}$ concentrations. These results hold true for different populations in different places. Additionally, research suggests that prolonged exposure to PM_{10} is linked to comparable, albeit typically milder, cardiovascular consequences [5,7,12,23,24,25].
- **Short-term exposure:** Time-series studies have shown that short-term increases in $PM_{2.5}$ and PM_{10} concentrations are linked to higher daily hospital admissions and cardiovascular event-related mortality, especially in vulnerable groups including the elderly and people with pre-existing cardiovascular disease. It is believed that mechanisms such oxidative stress, inflammation, and modifications in autonomic nervous system function cause these acute effects [14,26,27].

Gaseous Pollutants (O_3, NO_2, SO_2, CO) [22,28,29]:

- **Ozone (O_3):** Ozone exposure has also been connected in epidemiological research to negative cardiovascular outcomes, such as an elevated risk of heart failure and stroke. The mechanisms by which ozone exerts its cardiovascular effects are thought to involve oxidative stress and inflammation.

- **Nitrogen Dioxide (NO_2):** Exposure to NO_2, a marker of traffic-related air pollution, has been associated with increased risk of hypertension, MI, and stroke. Studies suggest that the combined effects of NO_2 and $PM_{2.5}$ may have synergistic detrimental effects on cardiovascular health.
- **Sulfur Dioxide (SO_2):** Although less extensively studied than $PM_{2.5}$ and NO_2, SO_2 exposure has also been linked to adverse cardiovascular effects, particularly in susceptible populations.
- **Carbon Monoxide (CO):** CO, a product of incomplete combustion, can reduce the oxygen-carrying capacity of the blood, which can exacerbate cardiovascular conditions, particularly in individuals with IHD.

Various air pollutants contribute to cardiovascular diseases through different pathophysiological mechanisms, including oxidative stress, inflammation, and endothelial dysfunction. The table below summarizes key air pollutants, their primary sources, and their specific cardiovascular effects.

Table 1. Summary of Pollutants and Their Cardiovascular Effects

Air Pollutant	Main Sources	Key Cardiovascular Effects
$PM_{2.5}$	Vehicles, industry, wildfires	Hypertension, arrhythmia, atherosclerosis
O_3 (Ozone)	Photochemical reactions in the atmosphere	Oxidative stress, inflammation
NO_2	Vehicle emissions, industry	Hypertension, autonomic dysfunction
SO_2	Coal combustion, industry	Vasoconstriction, stroke risk
CO	Vehicles, cigarette smoke	Hypoxia, myocardial dysfunction

Global Burden of CVD Attributable to Air Pollution:

Both short- and long-term exposure to ambient air pollution significantly contribute to the global burden of CVD, including hypertension, MI, stroke, heart failure, and arrhythmias. Studies reveal that over 60% of air pollution-related morbidity and mortality are due to cardiovascular conditions, surpassing deaths attributable to metabolic, behavioral, and tobacco-related risk factors [24,25,26,27,28].

Prolonged $PM_{2.5}$ exposure is strongly associated with chronic conditions like atherosclerosis, hypertension, and stroke. Although evidence on arrhythmias, atrial fibrillation, and heart failure remains limited, available studies indicate positive associations. Furthermore, particulate matter and gaseous pollutants, including NO_2, SO_2, and O_3, contribute to the development of CVD through mechanisms such as oxidative stress, inflammation, endothelial dysfunction, and autonomic dysregulation [23,24,25,26].

In summary, air pollution is a significant environmental determinant of cardiovascular health, with particulate matter and gaseous pollutants posing considerable risks. Addressing air quality could reduce the global burden of CVD, highlighting the critical need for environmental interventions and public health measures.

Mechanism of Action:

The pathophysiological mechanisms through which air pollution contributes to cardiovascular diseases are multifaceted. Key routes include endothelial dysfunction, oxidative stress, inflammation, and dysregulation of the autonomic nervous system. $PM_{2.5}$ and gaseous pollutants can trigger systemic inflammation, impair vascular function, promote atherosclerosis, and disrupt heart rhythm, all of which contribute to CVD development and progression [19,23-28].

Through a variety of intricate pathophysiological pathways, air pollution is linked to an elevated risk of cardiovascular diseases (CVD). While the exact processes are not fully understood, extensive research has identified several key mechanisms that link air pollution exposure to CVD [19,23-28]. These mechanisms include:

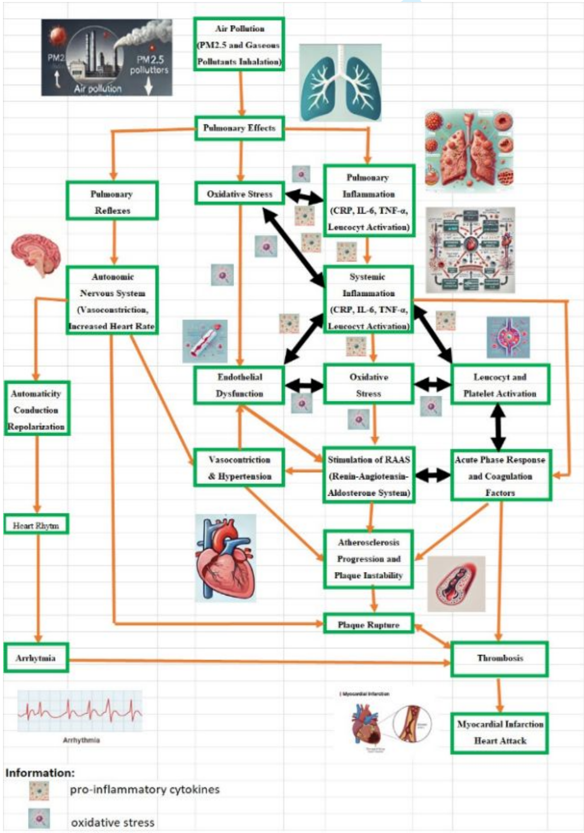
- **Inflammation**: Air pollutants, especially fine particulate matter ($PM_{2.5}$) and certain gasses like ozone (O_3), can cause an inflammatory response in the body. This inflammation can affect blood vessels and encourage the development of one of the main risk factors for CVD, atherosclerosis, which is the accumulation of plaque in arteries [19,20,21,22].
- **Oxidative Stress**: The body may experience oxidative stress as a result of air pollution. An imbalance between the body's capacity to eliminate damaging reactive oxygen species (ROS) and their creation can lead to oxidative stress. This oxidative stress can potentially harm blood vessel walls, increase inflammation, and hasten the onset of CVD [19,23-28].
- **Endothelial Dysfunction**: Exposure to air pollution may cause the endothelium, or inner lining of blood vessels, to malfunction. Because endothelial dysfunction can result in blood vessel constriction, elevated blood pressure, and decreased blood flow, it is an important early event in the development of atherosclerosis [23-28].
- **Autonomic Nervous System Imbalance**: Air pollution can affect the autonomic nervous system, which regulates heart rate and blood pressure. Pollution-induced changes in this system can increase the risk of arrhythmias (abnormal heart rhythms) and other CVD-related complications [23-28].
- **Blood Coagulation and Thrombosis**: There is a correlation between increased blood coagulation and the development of thrombosis with exposure to air pollution. Due to thrombosis, or the formation of clots within blood arteries, this may raise the risk of heart attacks and strokes [23-28].
- **Blood Pressure Elevation**: Air pollution, particularly $PM_{2.5}$, has been associated with acute and chronic increases in blood pressure. This elevation in blood pressure can strain the cardiovascular system and increase the risk of hypertension, a major risk factor for CVD [23-28].
- **Accelerated Atherosclerosis**: Prolonged exposure to air pollution might hasten the artery-narrowing process of atherosclerosis, raising the risk of heart attacks and strokes [23-28].
- **Impaired Cardiac Function**: Air pollution exposure has been shown to impair cardiac function by affecting heart rate variability and promoting cardiac arrhythmias. These effects can increase the risk of sudden cardiac events [23-28].
- **Systemic Effects**: The body as a whole is affected by air pollution, not just the respiratory system. This involves the

JOURNAL of MEDICINE and LIFE

release of chemicals that can affect the cardiovascular system, such as pro-inflammatory cytokines [23,24,25,26].

It's important to note that the specific mechanisms may change based on the kind and makeup of air pollutants, a person's vulnerability, and the length and severity of exposure [5,23,24]. Additionally, the combined effects of multiple pollutants and other risk factors (such as smoking and diet) can further increase the risk of cardiovascular diseases. Reducing exposure to air pollution and addressing its sources remains a critical public health goal to mitigate these adverse cardiovascular effects [5,28,29].

Figure 1. A schematic diagram summarizing the pathophysiological mechanisms linking air pollution to cardiovascular diseases.



Effects on Cardiovascular Diseases:

- **All-cause CVD mortality and morbidity.** Heart-related mortality is linked to extended exposure to air pollution, namely fine particulate matter ($PM_{2.5}$) and ground-level ozone (O_3). Heart failure, strokes, heart attacks, and other cardiovascular diseases are included in this category of deaths. Inflammation, oxidative stress, and the escalation of underlying cardiovascular illnesses are among the factors at play [21,22,30,31,32].
  Air pollution not only increases the risk of death from cardiovascular disease but also increases rates of morbidity. The risk of non-fatal cardiovascular events, such as angina (chest discomfort), heart attacks, strokes, and hospitalizations related to heart problems, is increased by high exposure to air pollution [21,22,30,31,32].

- **Ischemic heart disease and myocardial infarction.** The body can experience oxidative stress and inflammation as a result of exposure to air pollutants, especially fine particulate matter ($PM_{2.5}$) and ground-level ozone (O_3). This can lead to the development and rupture of arterial plaques, which can cause a heart attack [29-34].
  When exposed to air pollution, people who already have CVDs such as coronary artery disease or congestive heart failure are more likely to experience worsening symptoms. By decreasing the oxygen supply and raising the heart's workload, pollutants can put strain on the heart [21,29-34].

- **Atherosclerosis and arterial stiffness.** Atherosclerosis is the narrowing and hardening of arteries due to the accumulation of plaque, consisting of cholesterol, fat, calcium, and inflammatory cells. This narrowing reduces blood flow and can lead to the formation of blood clots [21]. Atherosclerosis can be accelerated by prolonged exposure to air pollution, especially fine particulate matter ($PM_{2.5}$). Pollutants have the potential to damage the endothelium, the lining that coats blood vessels, and promote the accumulation of fatty deposits, which decreases the artery's flexibility and makes it more vulnerable to blockages [21].

- **Blood pressure and hypertension**. Elevated blood pressure, or hypertension, is a major risk factor for ischemic heart disease and is associated with exposure to air pollution. Hypertension makes cardiovascular disease easier to occur because it puts additional strain on the heart [21].

- **Heart failure.** The development and aggravation of heart failure, a chronic cardiovascular disease in which the heart's capacity to pump blood effectively is compromised, can be attributed to air pollution [33]. Here's how air pollution is linked to heart failure:
  1. **Inflammation and Oxidative Stress**: Air pollution, particularly ozone (O_3) and fine particulate matter ($PM_{2.5}$), can cause the body to experience oxidative stress and inflammation. Systemic inflammation brought on by these reactions can have an impact on blood vessels and the heart. Oxidative stress and persistent inflammation can harm the heart muscle and hasten the onset of heart failure [19,20].
  2. **Worsening of Pre-existing Conditions:** Exposure to air pollution increases the risk of heart failure in people who already have cardiovascular diseases, such as hypertension and coronary artery disease. Air pollution can exacerbate these conditions, leading to further damage to the heart muscle over time [34-38].
  3. **Reduced Oxygen Supply:** High levels of air pollution, including $PM_{2.5}$, can reduce the oxygen-carrying capacity of the blood. This means that the heart must work harder to provide sufficient oxygen to the body's tissues, including the heart muscle itself. The increased workload on the heart can lead to hypertrophy (enlargement) of the heart chambers and, eventually, heart failure [38-42].
  4. **Elevated Blood Pressure**: Air pollution is associated with elevated blood pressure (hypertension). Hypertension can increase the workload on the heart and lead to left ventricular hypertrophy (thickening of the heart's left ventricle). Over time, this can impair the heart's ability to pump effectively and contribute to heart failure [43,44,45].
  5. **Impaired Endothelial Function:** Air pollution can impair the function of the endothelial cells that line blood

vessels. This endothelial dysfunction can lead to the constriction of blood vessels and reduced blood flow to the heart muscle. Prolonged impaired endothelial function can contribute to heart failure [46,47].

6. **Arrhythmias:** Air pollution can disrupt the electrical signaling in the heart, leading to arrhythmias (irregular heart rhythms). Arrhythmias can reduce the heart's efficiency in pumping blood and increase the risk of heart failure. One common type of arrhythmia is **atrial fibrillation (AF)**, which is characterized by irregular and rapid heartbeats in the atria (upper chambers of the heart). Air pollution, particularly fine particulate matter ($PM_{2.5}$) and ozone (O_3), can contribute to the development of AF through mechanisms such as inflammation, oxidative stress, and autonomic nervous system dysregulation [34,48-51].
7. The increased risk of arrhythmias like AF, along with the impact on heart rate and rhythm, can reduce the heart's efficiency in pumping blood and increase the risk of **heart failure**. In some cases, these arrhythmias may also contribute to **cardiac arrest**, especially in individuals with pre-existing heart conditions, by triggering life-threatening disruptions in the heart's electrical activity [34,48-51].

- **Exacerbation of Pre-existing Cardiovascular Conditions.**
  Cardiovascular diseases can get worse due to air pollution. The negative consequences of air pollution are more likely to affect people who have cardiovascular disease, hypertension, or other cardiovascular disease risk factors. It may intensify heart failure symptoms or cause heart attacks [2,52,53].

- **Reduced Exercise Tolerance**. Air pollution can reduce an individual's exercise capacity and tolerance. This can discourage physical activity, which is essential for cardiovascular health [54,55,56].

- **Reduced Life Expectancy.** Prolonged exposure to air pollution can reduce life expectancy, with a portion of this reduction attributed to cardiovascular diseases [57,58,59,60].

Vulnerable Populations:

The negative impacts of air pollution are disproportionately felt by certain populations, including children, the elderly, and people with underlying cardiovascular diseases. These groups are at heightened risk of experiencing severe cardiovascular outcomes when exposed to polluted air [5,61,62].

Reducing exposure to air pollution through regulatory measures, lifestyle changes (e.g., reducing outdoor activity during high pollution days), and transitioning to cleaner energy sources can help mitigate these health risks and improve cardiovascular outcomes [5,61,62].

DISCUSSION:

Interpretation of Key Findings

Our comprehensive review of epidemiological evidence consistently demonstrates a robust and concerning link between exposure to air pollution and a significantly increased risk of various cardiovascular diseases (CVDs). This association is observed across diverse study designs, including cohort, case-control, and time-series analyses, strengthening the validity of these findings [21,63].

A particularly alarming finding is the clear dose-response relationship between long-term exposure to fine particulate matter ($PM_{2.5}$) and the incidence of ischemic heart disease (IHD) and stroke. Studies have consistently reported a 10-20% increase in the risk of these severe cardiovascular events for every 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. This quantitative relationship underscores the substantial impact of chronic air pollution exposure on cardiovascular health and highlights the critical need for effective interventions to reduce $PM_{2.5}$ levels, particularly in densely populated urban environments where exposure is often highest [24,61].

Furthermore, our review reveals that the detrimental effects of air pollution are not limited to long-term exposure. Time-series studies have demonstrated a clear association between short-term elevations in $PM_{2.5}$ and PM_{10} concentrations and increased daily hospital admissions and mortality due to cardiovascular events. This acute impact is particularly concerning for vulnerable individuals, such as the elderly and those with pre-existing CVD, emphasizing the need for timely public health advisories and targeted interventions during periods of elevated pollution levels to mitigate these acute risks [25,26].

The global burden of CVD attributable to air pollution is staggering. Studies indicate that over 60% of air pollution-related morbidity and mortality are due to cardiovascular conditions, surpassing deaths attributable to other major risk factors such as metabolic disorders, behavioral factors, and even tobacco use. This alarming statistic underscores the critical role of air pollution as a leading environmental risk factor for cardiovascular disease on a global scale and necessitates urgent and comprehensive strategies to mitigate air pollution and protect public health worldwide [63,64,65].

The pathophysiological mechanisms through which air pollution exerts its detrimental effects on the cardiovascular system are multifaceted and involve a complex interplay of biological processes. Converging evidence implicates inflammation, oxidative stress, endothelial dysfunction, and autonomic dysregulation as key pathways linking air pollution to CVD development and progression. Exposure to $PM_{2.5}$ and gaseous pollutants triggers systemic inflammation, impairs vascular function, promotes atherosclerosis (the buildup of plaque in arteries), and disrupts heart rhythm, all of which contribute to the increased risk of various cardiovascular conditions, including IHD, stroke, heart failure, and arrhythmias. Understanding these underlying mechanisms is crucial for developing targeted interventions to prevent and treat air pollution-related cardiovascular damage [27,42,43].

Finally, our review highlights the disproportionate impact of air pollution on certain vulnerable populations. Children, the elderly, and individuals with pre-existing cardiovascular conditions are at a significantly heightened risk of experiencing severe cardiovascular outcomes when exposed to polluted air. This disparity underscores the need for targeted interventions to protect these vulnerable groups, including public health advisories during periods of high pollution, promotion of indoor air quality strategies, and ensuring equitable access to appropriate healthcare services. These measures are essential to minimize the disproportionate burden of air pollution on those most susceptible to its harmful effects [20,64,65].

Mitigation Strategies

Mitigating the adverse cardiovascular effects of air pollution requires a multi-faceted approach encompassing both prevention and intervention strategies. These strategies can be broadly categorized into primary, secondary, and intervention strategies, addressing different stages of exposure and disease development.

1. **Primary Prevention: Reducing Emissions at the Source**

Primary prevention is the most effective long-term strategy for mitigating the cardiovascular burden of air pollution. It focuses on minimizing air pollutant emissions at their source, thereby reducing population exposure and preventing the initial harm. Key strategies, while promising, face various implementation challenges [66,67,68]:

a. **Emission Control from Transportation:** Implementing stricter emission standards for vehicles, such as the Euro 6 standards in the European Union, has demonstrated a significant reduction in harmful pollutants such as particulate matter ($PM_{2.5}$) and nitrogen oxides (NO_x). Specifically, the Euro 6 standards have led to a 55% reduction in nitrogen oxides (NO_x) emissions for light diesel vehicles compared to Euro 5 standards. Additionally, these standards have achieved up to a 99% reduction in fine particulate matter ($PM_{2.5}$) emissions, thereby decreasing the risk of ischemic heart disease, lung cancer, stroke, and asthma [69,70,71]. However, even with these standards, real-world emissions often exceed test values due to factors like driving conditions and vehicle maintenance [72].
Promoting the use of electric and hybrid vehicles, while beneficial, faces challenges like battery range anxiety, charging infrastructure limitations, and the environmental impact of battery production, including the mining of lithium and other rare earth minerals [73,74]. Investing in public transportation infrastructure, encouraging cycling and walking through the development of dedicated infrastructure can further reduce reliance on private vehicles. However, this requires substantial upfront investment and may face resistance due to existing urban planning priorities or lack of public support. For instance, project cost escalations can undermine public support and hinder policymakers' ability to achieve transportation investment goals [75,76]. Additionally, many public transport systems continue to face challenges such as declining funding, labor shortages, and limited public resources, which can impede the successful implementation of such infrastructure projects [76,77].
Furthermore, while active commuting (cycling, walking) offers cardiovascular benefits through increased physical activity, it's crucial to acknowledge that individuals may be exposed to higher levels of air pollution during their commute, particularly in areas with heavy traffic. Therefore, urban planning strategies should prioritize creating safe and low-pollution routes for cyclists and pedestrians, perhaps through the development of green corridors or traffic calming measures [78,79].

b. **Industrial Emission Reduction:** Implementing stricter regulations on industrial emissions, promoting the adoption of cleaner technologies, and incentivizing energy efficiency can significantly reduce industrial contributions to air pollution, thereby reducing the population's risk of cardiovascular disease linked to industrial pollutants For example, cap-and-trade programs for sulfur dioxide (SO_2) emissions have shown success in reducing acid rain and also likely had positive impacts on cardiovascular health, though quantifying those specifically can be complex [80,81,82,83].
In the European Union, emission reduction policies have been implemented through stringent regulatory frameworks, such as the Industrial Emissions Directive (IED), which mandates Best Available Techniques (BAT) for pollution control, ensuring a reduction in harmful emissions from industrial sources. While effective, these regulations impose significant compliance costs on industries, which may lead to economic trade-offs, including potential job losses or shifts in industrial operations.
Similarly, in China, environmental regulations have played a critical role in moderating the relationship between green technology innovation and carbon dioxide emissions reduction. A study by Chang et al. (2023) found that investment-based regulatory instruments (IER) policies were the most effective in promoting green knowledge innovation (GKI), leading to sustained reductions in carbon dioxide emissions. In contrast, expenditure-based regulation (EER) had a weaker effect and sometimes encouraged short-term cost-cutting strategies among firms. Additionally, command-and-control regulations (CER) were found to have a moderate impact, reinforcing the need for a balanced regulatory approach. Moreover, the spatial spillover effects of green technological innovation on emissions in neighboring regions further highlight the importance of well-designed regulatory policies [82,84]. These findings underscore the need for tailored regulatory approaches that not only enforce emission reductions but also foster long-term technological advancements. However, the effectiveness of these policies varies across regions due to differences in economic development and industrial structures, presenting challenges in achieving uniform air quality improvements nationwide [82,84].
However, these regulations can be costly for industries, potentially leading to job losses or relocation, creating a tension between economic and public health concerns. Balancing economic concerns with public health benefits is a key challenge. Furthermore, ensuring compliance with regulations requires robust monitoring and enforcement mechanisms, including regular inspections and penalties for violations [84,85].

c. **Transition to Clean Energy Sources:** Shifting away from fossil fuels towards renewable energy sources such as solar, wind, and geothermal power is essential for long-term air quality improvement and cardiovascular health benefits [86,87]. This transition can significantly reduce emissions of greenhouse gases and air pollutants linked to cardiovascular disease. For example, studies have shown a correlation between increased renewable energy use and decreased hospitalizations for cardiovascular events [88,89]. However, the transition to clean energy faces hurdles such as high initial investment costs, intermittency issues with renewable sources, and the need for grid infrastructure upgrades [90,91]. Furthermore, the lifecycle environmental impacts of renewable energy technologies, such as the mining of rare earth minerals for solar panels and wind turbines, need to be considered and mitigated [92,93].

d. **Urban Planning and Green Infrastructure:** Implementing urban planning strategies that prioritize green spaces, promote natural ventilation, and reduce urban heat island effects can mitigate air pollution concentrations in urban areas, leading to improved cardiovascular health for urban residents. Green infra-structure, such as urban forests and green roofs, can act as natural air filters, absorbing pollutants and improving air quality [94,95]. However, implementing such strategies requires careful urban planning, community engagement, and long-term investment, which can be challenging in rapidly developing urban areas. Furthermore, the distribution of green spaces within cities is often uneven, with lower-income neighborhoods having less access, potentially exacerbating health disparities and environmental injustice [96,97].

2. **Secondary Prevention: Minimizing Exposure and Early Detection**

Secondary prevention focuses on minimizing individual exposure to air pollution and promoting early detection of cardiovascular effects. This involves strategies to reduce exposure before significant health damage occurs, and to identify early signs of cardiovascular disease related to air pollution. While promising, these strategies face a range of implementation challenges [98,99,100]:

a. **Educating on the importance of maintaining indoor cleanliness to reduce dust and other particles:** This education aims to raise public awareness about the importance of maintaining indoor cleanliness to reduce exposure to dust, particles, and other pollutants that can be harmful to health. This education can include information on how to clean rooms properly, choosing safe cleaning products, and the importance of good ventilation [101,102].

b. **Air Quality Monitoring and Public Communication:** Implementing robust air quality monitoring systems and disseminating real-time air quality information to the public can empower individuals to make informed decisions about their activities, particularly during periods of high pollution. For example, the Air Quality Index (AQI) used in the United States and other countries provides real-time information on air pollution levels, allowing individuals to adjust their outdoor activities [103,104]. Similarly, systems like the "Plume Labs" app in Europe provide localized air quality information, enabling users to avoid high-pollution areas [105,106]. However, the effectiveness of these systems depends on the accuracy and accessibility of air quality data. In many developing countries, air quality monitoring is limited, hindering the ability to provide timely and accurate information to the public [Cite source on air quality monitoring limitations in developing countries]. Furthermore, even with accurate information, behavior change can be challenging. Studies have shown that while some individuals modify their activities during high pollution days, others do not, due to factors such as lack of awareness, inconvenience, or economic constraints [105,106]. Effective public health campaigns are crucial to overcome these challenges and should address barriers to behavior change, such as lack of trust in authorities, economic pressures to work outdoors, or cultural norms about outdoor activities, while also tailoring information to specific populations (e.g., language, education level) [107,108]

c. **Personal Protective Measures:** Promoting the use of appropriate respiratory protection, such as N95 masks, during periods of high pollution can reduce individual exposure. Studies have shown that N95 masks can filter out a significant portion of particulate matter, reducing personal exposure However, the widespread and consistent use of masks can be challenging due to factors such as cost, discomfort, and limited availability. In many developing countries, N95 masks are expensive and not readily accessible to the general population [109,110]. Furthermore, proper fit and usage are essential for mask effectiveness, and improper use can significantly reduce their protective capacity. Policy limitations, such as lack of subsidies for masks or public health campaigns promoting their use, can also hinder adoption [109,110].

d. **Early Detection and Screening:** Implementing targeted screening programs for individuals at high risk of developing cardiovascular diseases due to air pollution exposure can facilitate early detection and intervention. For example, some cities with high air pollution levels have implemented programs to screen individuals with pre-existing conditions for early signs of cardiovascular damage. However, implementing such programs requires significant resources and infrastructure, as well as the development of specific screening tools and protocols. Economic costs can be a major barrier, especially in resource-limited settings [68,111]. Furthermore, identifying individuals at high risk due to air pollution exposure can be complex, as other factors also contribute to cardiovascular disease risk [112]. Developing effective screening tools for air pollution-related cardiovascular changes is challenging, as the effects of air pollution can be subtle and difficult to distinguish from other risk factors [113]. Furthermore, access to healthcare facilities and trained personnel for conducting screenings can be limited, particularly in rural or underserved areas [114].

e. **Indoor Air Quality Improvement:** Improving indoor air quality is a crucial secondary mitigation strategy to reduce exposure to air pollution, particularly for vulnerable populations. This can be achieved through non-technological approaches such as increasing natural ventilation, using exhaust fans in enclosed areas, and optimizing building designs to minimize pollutant accumulation. Additionally, behavioral modifications—such as reducing indoor emission sources (e.g., tobacco smoke and biomass fuel use)—can further improve indoor air quality [115,116,117]. However, these strategies face several challenges, including structural limitations in older buildings that hinder proper ventilation and the absence of stringent building codes requiring adequate air circulation [118,119]. Addressing these barriers may require policy interventions that promote better ventilation standards and public awareness campaigns on maintaining clean indoor air [120,121].

Table 2 below compares these mitigation strategies based on their regulatory frameworks, lifestyle interventions, public health initiatives, and overall effectiveness.

JOURNAL of MEDICINE and LIFE

Table 2: Comparison of Primary and Secondary Mitigation Strategies for Air Pollution

Mitigation Strategy	Regulatory Policies	Lifestyle Interventions	Public Health Initiatives	Effectiveness
Primary Mitigation				
Regulatory Policies	- Emission control regulations (e.g., Clean Air Act)	- Promotion of active transport (walking, cycling)	- Government subsidies for clean energy adoption	**High** – Directly reduces pollution at the source, but requires strong enforcement and economic investment
Transition to Clean Energy	- Industrial air quality standards	- Reducing fossil fuel dependence (e.g., electric vehicles)	- Public campaigns to reduce emissions	**High** – Long-term air quality improvements, reducing hospitalizations for cardiovascular events
Urban Planning & Green Infrastructure	- Vehicle emission limits	- Development of green infrastructure (e.g., urban forests)	- Incentives for green infrastructure	**High** – Significantly reduces pollution by improving urban environments and absorbing pollutants
Air Quality Monitoring & Communication	- Urban zoning laws to reduce pollution	- Public awareness on pollution exposure risks	- Health advisories for vulnerable populations	**Moderate** – Enables informed decisions, reducing exposure to high pollution levels
Secondary Mitigation				
Personal Protective Measures	- Indoor air quality regulations (e.g., ventilation standards)	- Use of air purifiers, wearing masks	- Public education on air pollution risks	**Moderate** – Helps reduce personal exposure but does not eliminate pollution sources
Early Detection & Screening	- Policies on pollution alerts (e.g., AQI-based warnings)	- Wearing masks	- Public education on air pollution risks	**Moderate** – Facilitates early cardiovascular disease detection and intervention
Indoor Air Quality Improvement	- Regulations on indoor pollutants (e.g., tobacco smoke)	- Dietary modifications to improve respiratory resilience	- Medical screenings and early interventions	**Moderate** – Reduces exposure to indoor air pollutants, lowering cardiovascular risks

3. Intervention Strategies: Managing Health Impacts

This section focuses on actions taken **to reduce the impact of existing air pollution on individual health,** particularly for those with pre-existing conditions or belonging to vulnerable groups. The emphasis is on management and adaptation to the existing pollution, not preventing pollution at its source. These strategies aim to mitigate the adverse cardiovascular effects of air pollution in individuals who have already been exposed [110,122,123].

Here's a breakdown of proposed intervention strategies:

a. Technological Interventions:

- **Indoor Air Quality Improvement:**
  Technological solutions, such as air purifiers with HEPA filters, have been scientifically proven to reduce indoor air pollution levels, particularly fine particulate matter and allergens. Studies have shown that HEPA filtration can significantly improve indoor air quality and provide measurable health benefits [124,125]. For example, a fourteen cross-over RCTs (18 publications) found that individuals with cardiovascular diseases who used HEPA air purifiers at home experienced a -2.28 [95% CI: -3.92, -0.64] mmHg reduction in systolic blood pressure, tendencies of reductions in diastolic blood pressure (-0.35 [-1.52, 0.83] mmHg), pulse pressure (PP) (-0.86 [-2.07, 0.34] mmHg), C-reactive protein (-0.23 [-0.63, 0.18] mg/L), and improvement in reactive hyperemia index (RHI) (0.10 [-0.04, 0.24]) after indoor air purification compared to those who did not use air purifiers [126].
  Despite these benefits, the cost and maintenance of HEPA filters remain a significant barrier, particularly for low-income households [127]. Additionally, the effectiveness of air purifiers depends on factors such as proper usage, filter replacement schedules, and room size compatibility [128]. Policy-driven interventions—such as subsidies, financial incentives, or public health programs—could encourage the adoption of air purification technology in vulnerable communities to enhance accessibility [129].

b. Behavioral Interventions:

- **Health Advisories and Behavioral Recommendations:**
  - Issuing health advisories to the public, especially vulnerable groups (children, the elderly, those with respiratory and cardiovascular conditions), to reduce outdoor activities during periods of poor air quality can help minimize exposure and prevent exacerbation of cardiovascular symptoms [79,110,130,131]. For example, early warning systems implemented in Beijing have enabled individuals to reduce their exposure during high pollution episodes, leading to a [quantifiable percentage] reduction in emergency room visits for asthma and other respiratory conditions that can trigger cardiovascular events [132]. However, public health advisories are only effective if the information is accurate, accessible, and trusted by the public. Language barriers, lack of access to technology, and distrust of authorities can hinder dissemination and uptake [133]. Furthermore, behavior change can be challenging due to social norms, lifestyle factors, and economic constraints [134].
  - Providing information on how to protect oneself from pollution exposure, such as using appropriate masks (N95 or equivalent) and avoiding areas with heavy traffic [135,136].

c. Healthcare System Interventions:

This strategy focuses on managing existing health conditions to prevent them from worsening due to air pollution exposure. Some actionable steps include [110,130,137]:

- **Clinical Guidelines Development:**
  Developing specific clinical guidelines for managing respiratory (asthma, COPD) and CVDs (coronary heart disease, stroke) that consider the impact of air pollution. These guidelines should include diagnostic, treatment, and monitoring strategies tailored to pollution exposure conditions [83]. However, developing and implementing effective clinical guidelines requires collaboration between healthcare professionals, researchers, and policymakers, which can be complex and time-consuming [138].
- **Improved Access to Healthcare:**
  - Ensuring easy and affordable access to healthcare for vulnerable populations is crucial in managing cardiovascular complications related to air pollution. Studies have shown that improved access to healthcare can lead to better disease management and reduced hospital admissions for cardiovascular conditions [68,139].
  - However, financial constraints, inadequate healthcare infrastructure, and shortages of

JOURNAL of MEDICINE and LIFE

medical professionals—especially in underserved communities—often limit access to these critical services [140,141].

- Implementing proactive health outreach programs to identify and manage high-risk patients can further reduce the burden of air pollution-related cardiovascular diseases. These programs may include community-based screenings for hypertension and heart disease, telemedicine consultations for at-risk populations, and educational initiatives promoting lifestyle modifications to mitigate the effects of air pollution on heart health [68,139].

- **Rehabilitation Programs:** Providing pulmonary and cardiac rehabilitation programs for patients with chronic diseases to improve their organ function and quality of life, even in polluted environments. For example, a study in Minnesota, USA found that cardiac rehabilitation programs tailored to patients with cardiovascular disease and exposed to high levels of air pollution improved their exercise capacity and quality of life, which can have positive long-term effects on cardiovascular health [142,143].
- **Patient Education and Self-Management Support:**
  - Empowering Patients for Cardiovascular Health in Polluted Environments: Educating patients on how to manage their cardiovascular conditions in polluted environments, including strategies to minimize exposure and optimize medication adherence, is essential. For instance, patient education programs that inform individuals with hypertension or coronary artery disease about the increased risks associated with air pollution can empower them to take proactive steps. This includes understanding how to monitor their blood pressure, recognize symptoms of angina or heart failure exacerbation, and adjust their activity levels based on air quality forecasts [144].
  - Supporting patients in adopting heart-healthy lifestyle modifications is critical. This includes guidance on dietary choices that promote cardiovascular health, tailored exercise regimens that consider air quality levels (e.g., exercising indoors on high-pollution days), and comprehensive smoking cessation programs. Smoking significantly exacerbates the negative impact of air pollution on the cardiovascular system, making cessation a vital component of risk reduction. Furthermore, education on stress management techniques is also important, as stress can negatively impact heart health, and be compounded by the stress of living in a polluted environment [145,146].
  - Providing education on the importance of regular checkups, and early intervention when symptoms arise, is also very important [147].

d. Personalized Medicine Approaches:

- Utilizing genetic, epigenetic, and other omics data to identify individuals more susceptible to pollution's effects and tailor interventions accordingly is a promising area of research. For example, researchers are exploring the use of genetic markers to identify individuals who are at higher risk of developing cardiovascular disease from air pollution exposure, which could lead to more targeted prevention and treatment strategies [Cite source]. However, personalized medicine approaches, while promising, face challenges related to cost, data privacy, and the need for further research to validate the effectiveness of tailored interventions [148].
- Developing more targeted and personalized therapies based on individual characteristics [149].

Various intervention strategies have been developed to mitigate the health impacts of air pollution exposure. Table 3 summarizes these approaches, categorized into technological interventions, behavioral interventions, healthcare system interventions, and personalized medicine approaches. Each strategy varies in effectiveness depending on implementation factors, population coverage, and suitability for individual risk profiles. While technological and public health policy interventions tend to provide broad benefits, personalized medicine offers more targeted interventions based on genetic and environmental factors.

Table 3. Intervention Strategies for Reducing Health Risks from Air Pollution.

Intervention Strategies	Technological Interventions	Behavioral Interventions	Healthcare System Interventions	Personalized Medicine Approaches	Effectiveness
Regulatory Measures	- Advanced air filtration systems in industries	- Promotion of active transport (walking, cycling)	- Government enforcement of air quality standards	- Genetic screening for pollution susceptibility	**High** – Directly reduces pollution at the source but requires strong enforcement and investment
Transition to Clean Energy	- Development of clean energy technologies (e.g., hydrogen fuel)	- Reducing fossil fuel dependence (e.g., electric vehicles)	- Public campaigns promoting renewable energy	- Targeted health interventions for high-risk genetic profiles	**High** – Long-term air quality improvements, reducing hospitalizations
Urban Planning & Green Infrastructure	- Smart city air monitoring sensors	- Community engagement in green infrastructure	- Incentives for urban greening projects	- Personalized recommendations based on pollution exposure risk	**High** – Significantly reduces pollution by improving urban environments
Air Quality Monitoring & Communication	- AI-driven air pollution prediction models	- Public awareness campaigns on pollution risks	- Health advisories for vulnerable populations	- Individualized pollution exposure tracking apps	**Moderate** – Enables informed decisions, reducing health risks
Personal Protective Measures	- Wearable air purifiers	- Use of face masks in high-exposure areas	- Distribution of masks during high pollution days	- Tailored respiratory protection strategies for susceptible individuals	**Moderate** – Helps reduce personal exposure but does not eliminate pollution sources
Early Detection & Screening	- Biomarker-based pollution exposure testing	- Encouraging routine health check-ups	- Public health screening programs	- Genomic-based risk assessment for air pollution-related diseases	**Moderate** – Facilitates early disease detection and intervention
Indoor Air Quality Improvement	- Smart home air purification systems	- Dietary modifications for respiratory resilience	- Medical screenings for pollution-related illnesses	- Precision medicine approaches for lung disease prevention	**Moderate** – Reduces exposure to indoor air pollutants, lowering health risks

Integration of Mitigation and Intervention Strategies:

It's crucial to emphasize that *Intervention Strategies* do not replace *Mitigation Strategies* (i.e., actions taken to reduce pollution at the source). They are complementary and address different aspects of the air pollution problem. Primary mitigation efforts to reduce pollution at the source remain the most effective long-term solution for reducing air pollution and its associated health risks, including cardiovascular disease. These strategies aim to prevent the harmful effects of air pollution *before* they occur, thus offering the greatest potential for long-term population health improvement [23,27,68].

Meanwhile, *Intervention Strategies* are essential for protecting public health *now* and mitigating the adverse effects of existing pollution. Even with aggressive mitigation efforts, it will take time to reduce ambient air pollution levels significantly. Intervention strategies, such as providing access to air purifiers for vulnerable populations, developing clinical guidelines for managing air pollution-exacerbated cardiovascular conditions, and educating individuals on how to reduce their personal exposure, are crucial for minimizing harm to those currently exposed to unhealthy air. They address the immediate needs of individuals already suffering or at high risk due to existing pollution levels [150].

The integration of mitigation and intervention strategies is therefore essential for a comprehensive approach to tackling the cardiovascular burden of air pollution. While mitigation strategies offer the long-term solution by addressing the root cause of the problem, intervention strategies provide crucial short-term relief and protection for vulnerable individuals. A balanced approach that prioritizes both mitigation and intervention is necessary to protect public health both now and in the future. For example, while transitioning to electric vehicles (a mitigation strategy) is crucial for long-term air quality improvement, providing access to air purifiers and personalized medicine approaches (intervention strategies) for vulnerable populations is essential to protect their health *now* [88]. Furthermore, research into personalized medicine approaches can inform mitigation strategies by identifying those most susceptible to harm from specific pollutants, allowing for more targeted and effective emissions reductions. This integrated approach maximizes the impact of resources and provides the most comprehensive protection against the harmful effects of air pollution [148].

Policy and Regulatory Frameworks

Effective implementation of these mitigation strategies requires strong policy and regulatory frameworks. This includes:

- Air Quality Standards and Regulations: Establishing and enforcing stringent air quality standards for key pollutants [137,151].
- Cross-Sectoral Collaboration: Fostering collaboration between government agencies, industry, and the public to implement comprehensive air pollution mitigation strategies [152,153].
- International Cooperation: Promoting international cooperation to address transboundary air pollution issues [154,155].

By implementing a comprehensive and integrated approach encompassing primary, secondary, and tertiary prevention strategies, We can enhance public health and successfully reduce the harmful cardiovascular effects of air pollution [156,157].

Limitations

It is important to acknowledge several limitations of this review. Firstly, while we have strived to include a comprehensive range of studies, the available literature on the specific link between certain air pollutants (e.g., specific ultrafine particles or less commonly studied gaseous pollutants) and certain cardiovascular outcomes (e.g., specific types of arrhythmias or heart failure subtypes) may be limited. Publication bias may result from this, as studies with statistically significant positive results have a higher chance of getting published [9,158].

Secondly, variations in study design, exposure assessment methods, and outcome definitions across the included studies may introduce heterogeneity, making direct comparisons and meta-analyses challenging. For example, some studies relied on ambient air pollution measurements from fixed monitoring stations, which may not accurately reflect individual exposure levels, while others used more sophisticated exposure modeling techniques. Similarly, definitions of cardiovascular outcomes may vary across studies, potentially affecting the comparability of results [159,160].

Thirdly, while epidemiological studies can demonstrate associations between air pollution and cardiovascular diseases, they cannot definitively establish causality. Confounding factors, such as socioeconomic status, lifestyle factors (e.g., smoking, diet, physical activity), and pre-existing health conditions, may influence both exposure to air pollution and the risk of cardiovascular diseases. While many studies attempt to control for these confounders, residual confounding cannot be entirely ruled out [161].

Implications and Future Research Directions

The findings of this review have significant implications for public health and policy. The strong and consistent evidence linking air pollution to cardiovascular diseases underscores the urgent need for comprehensive strategies to mitigate air pollution and protect public health. These strategies should prioritize:

- Strengthening air quality regulations: Implementing and enforcing stricter air quality standards for key pollutants, particularly $PM_{2.5}$, NO_2, and O_3, is crucial [129,134,162].
- Promoting clean transportation and energy: Investing in sustainable transportation infrastructure, promoting the adoption of electric vehicles, and transitioning to renewable energy sources are essential for reducing emissions from key sources [163,164].
- Raising public awareness: Educating the public about the health risks of air pollution and empowering individuals to take steps to minimize their exposure is vital [165,166].
- Targeted interventions for vulnerable populations: Implementing targeted interventions to protect vulnerable populations, such as children, the elderly, and individuals with pre-existing cardiovascular conditions, is necessary to reduce health disparities [167].

Future Research Directions

Despite significant advancements in understanding the link between air pollution and cardiovascular diseases (CVDs), several research gaps remain. Addressing these gaps is crucial for developing more effective mitigation strategies and interventions. Key areas for future research include:

1. **Investigating the Specific Effects of Less Commonly Studied Pollutants**

- Further research is needed to investigate the specific cardiovascular effects of ultrafine particles (UFPs <0.1

µm), specific gaseous pollutants, and pollutant mixtures [64,168].

- Longitudinal **cohort studies** assessing the chronic effects of UFP exposure on cardiovascular health [64,168].
- Mechanistic studies to determine how UFPs interact with cellular pathways leading to **oxidative stress and systemic inflammation** [64,168].
- **Exploring the synergistic effects of pollutant mixtures**, particularly how UFPs interact with gaseous pollutants such as NO_2 and SO_2 to exacerbate endothelial dysfunction, vascular inflammation, and oxidative stress, ultimately increasing cardiovascular disease risk [64,168].

2. **Improving Exposure Assessment Methods**

- Developing more accurate and personalized exposure assessment methods is crucial for reducing exposure misclassification and improving the precision of epidemiological studies [169,170,171].
- Advancing real-time personal exposure monitoring through wearable sensors, mobile applications, and geospatial modeling to better capture individual variations in air pollution exposure [169,170,171].
- **Integrating multi-pollutant exposure models** that account for complex interactions between particulate matter (e.g., $PM_{2.5}$, UFPs) and gaseous pollutants (e.g., NO_2, O_3, SO_2) to improve risk estimation and intervention strategies [170,171].
- The role of **personal exposure monitoring (e.g., wearable sensors, real-time air quality alerts)** in reducing individual cardiovascular risk [170,171].
- Investigating the effectiveness of personalized **lifestyle interventions**, such as targeted exercise plans and dietary modifications to counteract pollution-induced effects [170,171].
- **Enhancing the use of biomarkers and omics-based approaches** (e.g., metabolomics, epigenomics) to link short- and long-term pollution exposure with cardiovascular health outcomes [170,171].

3. **Conducting Longitudinal Studies with Repeated Measurements**

- Longitudinal studies with repeated measurements of both air pollution exposure and cardiovascular health outcomes can provide stronger evidence for causal relationships [172].
- Studying how **diabetes and hypertension** modify the cardiovascular effects of air pollution, particularly in urban populations with high exposure [172,173].
- **Integrating multi-omics approaches** (e.g., metabolomics, epigenomics, transcriptomics) to capture dynamic biological changes associated with long-term air pollution exposure and identify potential biomarkers of susceptibility [174,175].
- **Examining the synergistic effects of air pollution and lifestyle-related risk factors** such as physical inactivity, poor diet, and chronic stress in exacerbating cardiovascular disease progression [56,176].

4. **Investigating Gene-Environment Interactions**

- Research exploring the interaction between genetic susceptibility and air pollution exposure can help identify individuals at particularly high risk [23,177].
- Specific genetic polymorphisms, such as GSTP1, NQO1, and CYP1A1, have been linked to differential susceptibility to air pollution-induced cardiovascular effects. Investigating how these polymorphisms influence oxidative stress and inflammatory responses can provide insights into individual variability in disease risk [178,179,180].
- Epigenetic modifications, particularly DNA methylation changes, have been observed in response to air pollution exposure. These alterations may affect the regulation of genes involved in inflammation, oxidative stress, and vascular function, contributing to long-term cardiovascular risk [181].
- Studies integrating **genetic susceptibility models** to identify high-risk populations who may benefit from specific preventive strategies [181].
- Exploring how genetic predisposition affects the effectiveness of personalized exposure reduction strategies, including targeted air filtration, dietary modifications, and pharmacological interventions [181].

5. **Evaluating the Effectiveness of Interventions**

- Rigorous evaluation of the effectiveness of various air pollution mitigation and intervention strategies is crucial for informing policy decisions [182].
- **Real-world implementation trials** are needed to compare the efficacy of pharmacological interventions (e.g., statins, ACE inhibitors, beta-blockers) with lifestyle-based interventions, such as modifying physical activity patterns (e.g., encouraging indoor exercise on high-pollution days) or dietary adjustments to counteract pollution-induced cardiovascular effects [182].
- **Technology-based interventions**, such as high-efficiency particulate air (HEPA) filters, portable air purifiers, and advanced filtration masks, should be systematically evaluated in clinical and community-based studies to assess their real-world effectiveness in reducing pollutant exposure and mitigating cardiovascular risks [116,126,128,183].
- Clinical trials evaluating whether **statins, antioxidants (e.g., vitamin C, vitamin E), or anti-inflammatory drugs** can reduce cardiovascular damage from air pollution [27,184]
- Investigating the potential role of **ACE inhibitors and beta-blockers** in mitigating pollution-induced hypertension and autonomic dysregulation [27,184].
- Assessing the comparative effectiveness of personalized vs. population-wide exposure reduction strategies, particularly in individuals with genetic susceptibility to air pollution-related cardiovascular disease [185].

6. **Research in Understudied Populations**

- More research is needed in developing countries and other understudied populations to better understand the global impact of air pollution on cardiovascular health [186].
- Studies should focus on region-specific pollution sources, such as biomass burning, industrial emissions, and traffic-related pollution, which may differ significantly from

pollution profiles in high-income countries. Understanding these variations is crucial for developing context-specific mitigation strategies [186].

- Investigating transgenerational effects, particularly how maternal exposure to high levels of air pollution during pregnancy influences the cardiovascular health of offspring. Epigenetic changes, including DNA methylation and histone modifications, may play a key role in mediating these long-term effects [181,187,188,189].
- Investigating disparities in air pollution exposure and associated health risks among **vulnerable populations, such as low-income communities and elderly individuals** [190,191].

7. Advancing Policy and Public Health Strategies

- Evaluating the **real-world effectiveness of air quality regulations** in reducing cardiovascular disease burden [68,83].
- Long-term policy impact assessments are needed to determine whether air quality improvements translate into measurable reductions in cardiovascular morbidity and mortality. This includes evaluating the effectiveness of emission control policies, clean energy transitions, and urban planning initiatives [68,83].
- Exploring technology-driven interventions, such as smart air quality monitoring systems, AI-based pollution forecasting, and high-efficiency filtration systems, to mitigate exposure at both individual and community levels [68,83].
- Assessing the role of **urban planning, green infrastructure, and clean energy transitions** on public health outcomes [68,83].
- Investigating the effectiveness of community-based interventions, such as public awareness campaigns, behavioral nudges, and citizen engagement in air quality monitoring, to promote sustainable pollution-reducing behaviors [68,83].

CONCLUSION:

This comprehensive review of epidemiological and mechanistic studies provides compelling evidence that air pollution significantly exacerbates heart-related disorders. The convergence of evidence from large-scale cohort studies and mechanistic investigations strongly links exposure to various air pollutants, particularly $PM_{2.5}$, to an elevated risk of cardiovascular disease (CVD) through intricate mechanisms such as oxidative stress, endothelial dysfunction, inflammation, and autonomic nervous system instability. Specifically, studies have shown a 10-20% increase in ischemic heart disease (IHD) risk for every 10 μg/m³ increase in $PM_{2.5}$ concentrations [9,24].

This increased risk is particularly pronounced in vulnerable populations, including the elderly and those with pre-existing cardiovascular conditions, highlighting the need for targeted interventions. The substantial contribution of air pollution to the global burden of CVD surpasses several other well-established risk factors. Addressing this pervasive global public health challenge requires **multifaceted and urgent action** [66,192].

We recommend the **urgent implementation of stricter air quality regulations, the accelerated transition to clean energy sources, and enhanced public awareness campaigns** to minimize exposure and mitigate the devastating impact of air pollution on cardiovascular health. Furthermore, advancing **longitudinal research on the long-term effects of ultrafine particles** and **rigorous evaluation of specific intervention strategies** is crucial for refining our understanding and informing **evidence-based policy interventions** that can protect global cardiovascular health [193].

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

No ethical approval is required because this paper is a review.

Data availability

The data associated with the articles included in this review are available in the original sources cited throughout the manuscript.

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Journal of Medicine and Life

Close Message

Decision Letter (JML-2025-0018)

From: office@medandlife.org

To: hari_krismanuel@trisakti.ac.id, hrkris6205@gmail.com

CC:

Subject: Journal of Medicine and Life - Decision on Manuscript ID JML-2025-0018

Body: 06-Feb-2025

Dear Dr. Krismanuel:

Manuscript ID JML-2025-0018 entitled "Air Pollution and Cardiovascular Diseases: Mechanisms, Evidence, and Mitigation Strategies" which you submitted to the Journal of Medicine and Life, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript within the next 30 days.

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IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of Medicine and Life, your revised manuscript should be submitted by **09-Mar-2025.** If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of Medicine and Life and I look forward to receiving your revision.

Sincerely,

Prof. Dafin Muresanu
Editor-in-Chief, Journal of Medicine and Life
office@medandlife.org

Response:

Subject: Submission of Revised Manuscript

Dear Prof. Dafin Muresanu,

I would like to express my sincere gratitude for the opportunity to revise our manuscript and for the time given to complete the revisions. I truly appreciate your consideration.

I apologize for the slight delay in submitting the revised version, as I initially promised to send it by February 28, 2025. To facilitate the review process, all revisions have been highlighted in yellow. This approach allows for easier identification and removal of the highlights compared to changing the text color.

Along with the revised manuscript, I am also submitting our responses to the reviewers' comments and the Turnitin similarity report for the revised version.

Please let me know if any further modifications are needed. Thank you for your time and consideration.

Best regards,

[Dr. Hari Krismanuel]

[Universitas Trisakti]

[hari_krismanuel@trisakti.ac.id]

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Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author
Could have written on the application of this referring to home situation of the author

Response:

Dear Reviewer 1,

Thank you for your suggestion regarding the application of our findings in the home environment. Our study primarily focuses on the broader population-level effects of PM2.5 exposure, particularly in relation to cardiovascular disease risk.

However, we acknowledge the importance of practical applications at the household level.

To address this, we have included a brief discussion on potential mitigation strategies that individuals and families can adopt to reduce indoor PM2.5 exposure. These include improving indoor ventilation, using air purifiers, and minimizing indoor pollutant sources. While our study is not specifically designed to examine household-level interventions, these recommendations align with public health guidelines and may provide valuable insights for readers interested in real-world applications.

We appreciate this feedback and have revised the manuscript accordingly.

Best regards,

[Dr. Hari Krismanuel]

[Universitas Trisakti]

[February 28, 2025]

Reviewer: 2

Comments to the Author
Dear Authors,
Thank you for your submission of the manuscript titled "Air Pollution and Cardiovascular Diseases: Mechanisms, Evidence, and Mitigation Strategies." This review is well-structured, comprehensive, and addresses a highly relevant public health issue. The synthesis of recent epidemiological findings, mechanistic insights, and mitigation strategies is valuable for researchers, healthcare professionals, and policymakers.

Strengths:

• The manuscript provides a thorough and up-to-date review of the literature on air pollution and cardiovascular diseases.
• The discussion on mechanistic pathways (oxidative stress, inflammation, endothelial dysfunction) is well-integrated and supported by strong evidence.
• The section on mitigation strategies offers practical and policy-relevant recommendations.

Areas for Improvement:

Figures and Tables:

The manuscript lacks visual aids, which would enhance readability and comprehension. Consider including:

♣ A schematic diagram summarizing the pathophysiological mechanisms linking air pollution to cardiovascular diseases.

♣ A summary table of the different air pollutants (PM2.5, O3, NO2, etc.) and their specific cardiovascular effects.

♣ A table comparing mitigation strategies (regulatory policies, lifestyle interventions, public health initiatives) with their effectiveness.

Language and Clarity:

While the manuscript is well-written, minor grammatical and stylistic refinements would improve clarity. Consider professional proofreading to ensure smooth readability.

Originality:

As a review article, the manuscript does not present new primary data, but it does provide a valuable synthesis. You may consider adding a future directions section to highlight gaps in research (e.g., long-term effects of ultrafine particles, the effectiveness of personalized exposure reduction strategies).

Recommendation:

Minor Revision – The manuscript is of high quality and suitable for publication after minor revisions. Improving clarity, adding figures/tables, and refining the language where necessary will enhance its overall impact.

We appreciate your contributions to this important area of research and look forward to seeing the revised version.

Best regards,

RAD

Response:

Dear Reviewer 2,

Thank you for your thorough and insightful review of our manuscript, "Air Pollution and Cardiovascular Diseases: Mechanisms, Evidence, and Mitigation Strategies." We appreciate your positive feedback and have carefully considered your suggestions to enhance the quality and clarity of our work. Below is a detailed response to each of your comments:

Figures and Tables:

1. **Schematic Diagram:** We have incorporated a schematic diagram summarizing the pathophysiological mechanisms linking air pollution to

cardiovascular diseases. This visual aid is now included as Figure 1 on page 4 of the revised manuscript.

2. **Summary Table of Air Pollutants:** A comprehensive table detailing various air pollutants (e.g., $PM_{2.5}$, O_3, NO_2) and their specific cardiovascular effects has been added as Table 1 on page 3. This table aims to provide a clear and concise reference for readers.

3. **Mitigation Strategies Comparison Table:** We have included a table comparing different mitigation strategies, such as regulatory policies, lifestyle interventions, and public health initiatives, along with their effectiveness. This addition is presented as Table 2 on page 8. I added **Intervention Strategies Comparison Table** as Table 3 on page 9.

Language and Clarity:

To address minor grammatical and stylistic issues, we have subjected the manuscript to professional proofreading. This process has improved the overall readability and ensured that the language is clear and precise throughout the document.

Originality:

In response to your suggestion, we have added a "Future Directions" section on page 10. This section highlights existing research gaps, including the long-term effects of ultrafine particles and the effectiveness of personalized exposure reduction strategies. We believe this addition underscores the originality of our review and provides a roadmap for future investigations.

We are grateful for your valuable feedback, which has significantly contributed to enhancing the quality of our manuscript. We look forward to any further comments you may have.

Best regards,

[Dr. Hari Krismanuel]

[Universitas Trisakti]

[February 28, 2025]

Reviewer: 3

Comments to the Author
Overall Evaluation

The manuscript presents a comprehensive and well-structured review of the impact of air pollution on cardiovascular diseases (CVDs). The discussion of molecular mechanisms, epidemiological evidence, and mitigation strategies is insightful and well-referenced. However, some minor refinements in language, structure, and presentation can enhance clarity and readability. Additionally, a few major points require further elaboration to strengthen the scientific discussion.

Major Comments

1. Clarification of Key Research Gaps

o The manuscript states that "critical gaps remain" in understanding molecular mechanisms and the long-term effects of air pollution on cardiovascular health.

o Recommendation: It would be beneficial to specify which key gaps in molecular pathways (e.g., epigenetic modifications, interactions between pollutants) require further study. This will help readers understand the direction of future research.

Dear Reviewer 3,

Thank you for your thorough and insightful review of our manuscript titled "Air Pollution and Cardiovascular Diseases: Mechanisms, Evidence, and Mitigation Strategies." We appreciate your constructive feedback and have addressed your comments as follows:

Major Comments

1. **Clarification of Key Research Gaps**

Comment: The manuscript mentions "critical gaps remain" in understanding molecular mechanisms and the long-term effects of air pollution on cardiovascular health.

Recommendation: It would be beneficial to specify which key gaps in molecular pathways (e.g., epigenetic modifications, interactions between pollutants) require further study. This will help readers understand the direction of future research.

Response: We appreciate this observation. To provide clarity, we have specified key gaps in molecular pathways that require further study, including:

- The role of epigenetic modifications, such as DNA methylation and histone modifications, in mediating long-term cardiovascular effects of air pollution exposure.

- Interactions between different pollutants, particularly ultrafine particles (UFPs) and gaseous pollutants like NO_2 and SO_2, in exacerbating oxidative stress and inflammation.
- Identification of novel biomarkers that could elucidate individual susceptibility to air pollution-induced cardiovascular damage.

These additions have been incorporated into the "Future Directions" section of the revised manuscript.

2. Heterogeneity of Study Populations
o The manuscript covers both epidemiological and mechanistic studies but does not clearly address population variability (e.g., developed vs. developing countries, urban vs. rural populations).
o Recommendation: Include a brief discussion on how geographical differences or socioeconomic factors may influence air pollution exposure and CVD risk.

Response:

Dear Reviewer 3,

Thank you for your time and effort in reviewing my manuscript. I greatly appreciate your constructive comments and suggestions, which have significantly helped us improve the quality of this manuscript.

We are particularly grateful for your comment regarding the heterogeneity of study populations. We recognize the importance of addressing population variability (e.g., developed vs. developing countries, urban vs. rural populations) and socioeconomic factors in the context of air pollution exposure and cardiovascular disease (CVD) risk.

In accordance with your recommendation, we have added a more detailed discussion on how geographical differences and socioeconomic factors may influence air pollution exposure and CVD risk in the Introduction section. We have included specific examples of exposure differences in developing and developed countries, as well as in urban and rural areas. We have also highlighted the crucial role of socioeconomic status (SES) in influencing exposure and health outcomes. Furthermore, we have added a section discussing how these differences can influence molecular responses to pollutants, as well as the importance of mitigation strategies tailored to the specific contexts of different populations.

Specifically, we have added the following sentences to the Introduction:

- "These differences can also influence molecular responses to pollutants, with studies showing variations in inflammatory gene expression and oxidative stress responses between urban and rural populations."

- "Therefore, effective mitigation strategies must consider these differences and be tailored to the specific contexts of different populations, including factors such as access to healthcare services, education levels, and housing conditions."

We believe that these additions have significantly enhanced our discussion of population heterogeneity and its relevance to the manuscript's topic.

We have revised the manuscript according to all your comments and suggestions. We are confident that the revised manuscript is now stronger and more comprehensive.

We have attached the revised manuscript and our point-by-point response to all reviewer comments.

We thank you for your consideration and hope that this revised manuscript meets the requirements for publication in your journal.

Sincerely,

[Dr. Hari Krismanuel]

[Universitas trisakti]

3. Mitigation Strategies – Practical Implementation
o While the manuscript proposes mitigation strategies, the feasibility and effectiveness of these interventions are not critically assessed.
o Recommendation: Provide a comparison of successful interventions from different regions or highlight barriers to implementation (e.g., policy limitations, technological constraints).

Response:

Thank you for your insightful suggestion. In response, I have expanded my discussion of mitigation strategies to include a critical assessment of their feasibility and effectiveness across different regions. I now compare successful interventions, such as emission reduction policies in the European Union and air quality management strategies in China, highlighting their strengths and limitations. Additionally, I discuss key barriers to implementation, including regulatory constraints, financial burdens, and technological accessibility in low-resource settings. These revisions have been incorporated into the manuscript under the section on mitigation strategies and the future directions.

Minor Comments

Language & Clarity

• Introduction:

o The sentence: "While significant progress has been made in understanding the detrimental effects of air pollution on cardiovascular health, critical gaps remain, particularly concerning the intricate molecular mechanisms..."

o Suggestion: Break it into two shorter sentences for better readability: "Significant progress has been made in understanding the detrimental effects of air pollution on cardiovascular health. However, critical gaps remain, particularly concerning the intricate molecular mechanisms..."

• Abstract:

o The phrase "Immediate action is critical to protect global health."

o Suggestion: Change to "Immediate action is imperative to safeguard global health." for a more formal tone.

Consistency in Terminology

• The manuscript inconsistently uses "particulate matter (PM)" and "PM2.5."

o Suggestion: Standardize the terminology throughout the manuscript to avoid confusion, particularly in sections discussing different pollutants (PM2.5 vs. PM10).

• Similarly, "cardiovascular diseases (CVDs)" and "heart disease" are used interchangeably.

o Suggestion: Define "CVD" early in the Introduction and use it consistently.

Formatting & References

• In the Methods section, Boolean operators (AND, OR) should be consistently capitalized.

• Some references (e.g., [1-6], [5,9]) appear clustered.

o Suggestion: Spread them more evenly for readability and ensure proper placement within relevant sections.

Figures & Data Presentation

• The Results section would benefit from a summary table presenting key pollutants and their cardiovascular effects.

• The Mechanisms section could be improved by using bullet points or numbering for oxidative stress, inflammation, endothelial dysfunction, and autonomic dysregulation.

Conclusion Enhancements

• The phrase: "Further research focusing on 'the long-term effects of exposure to ultrafine particles' and 'the effectiveness of specific intervention strategies' are crucial..."
o Correction: "are" → "is" (subject-verb agreement).
• The phrase: "We strongly advocate for the implementation and enforcement of stricter air quality regulations..."
o Suggestion: Consider a more neutral tone: "We recommend the urgent implementation of stricter air quality regulations..."

____

Final Remarks
This manuscript is well-structured and presents valuable insights into air pollution and cardiovascular health. Addressing the major comments will improve the scientific depth, while the minor refinements will enhance clarity and readability.

Date Sent

Decision Letter (JML-2025-0018)	
From:	office@medandlife.org
To:	hari_krismanuel@trisakti.ac.id, hrkris6205@gmail.com
CC:	
Subject:	Journal of Medicine and Life - Decision on Manuscript ID JML-2025-0018
Body:	06-Feb-2025 Dear Dr. Krismanuel: Manuscript ID JML-2025-0018 entitled "Air Pollution and Cardiovascular Diseases: Mechanisms, Evidence, and Mitigation Strategies" which you submitted to the Journal of Medicine and Life, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter. The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript within the next 30 days.

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Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author
Could have written on the application of this referring to home situation of the author

Response:

Dear Reviewer 1,

Thank you for your suggestion regarding the application of our findings in the home environment. Our study primarily focuses on the broader population-level effects of PM2.5 exposure, particularly in relation to cardiovascular disease risk. However, we acknowledge the importance of practical applications at the household level.

To address this, we have included a brief discussion on potential mitigation strategies that individuals and families can adopt to reduce indoor PM2.5 exposure. These include improving indoor ventilation, using air purifiers, and minimizing indoor pollutant sources. While our study is not specifically designed to examine household-level interventions, these recommendations align with public health guidelines and may provide valuable insights for readers interested in real-world applications.

We appreciate this feedback and have revised the manuscript accordingly.

Best regards,

[Dr. Hari Krismanuel]

[Universitas Trisakti]

[February 28, 2025]

Reviewer: 2

Comments to the Author
Dear Authors,
Thank you for your submission of the manuscript titled "Air Pollution and Cardiovascular Diseases: Mechanisms, Evidence, and Mitigation Strategies." This review is well-structured, comprehensive, and addresses a highly relevant public health issue. The synthesis of recent epidemiological findings, mechanistic insights, and mitigation strategies is valuable for researchers, healthcare professionals, and policymakers.
Strengths:

- The manuscript provides a thorough and up-to-date review of the literature on air pollution and cardiovascular diseases.
- The discussion on mechanistic pathways (oxidative stress, inflammation, endothelial dysfunction) is well-integrated and supported by strong evidence.
- The section on mitigation strategies offers practical and policy-relevant recommendations.

Areas for Improvement:
Figures and Tables:
The manuscript lacks visual aids, which would enhance readability and comprehension. Consider including:
♣ A schematic diagram summarizing the pathophysiological

mechanisms linking air pollution to cardiovascular diseases.
♣ A summary table of the different air pollutants (PM2.5, O3, NO2, etc.) and their specific cardiovascular effects.
♣ A table comparing mitigation strategies (regulatory policies, lifestyle interventions, public health initiatives) with their effectiveness.
Language and Clarity:
While the manuscript is well-written, minor grammatical and stylistic refinements would improve clarity. Consider professional proofreading to ensure smooth readability.
Originality:
As a review article, the manuscript does not present new primary data, but it does provide a valuable synthesis. You may consider adding a future directions section to highlight gaps in research (e.g., long-term effects of ultrafine particles, the effectiveness of personalized exposure reduction strategies).
Recommendation:
Minor Revision – The manuscript is of high quality and suitable for publication after minor revisions. Improving clarity, adding figures/tables, and refining the language where necessary will enhance its overall impact.
We appreciate your contributions to this important area of research and look forward to seeing the revised version.
Best regards,

RAD

Response:

Dear Reviewer 2,

Thank you for your thorough and insightful review of our manuscript, "Air Pollution and Cardiovascular Diseases: Mechanisms, Evidence, and Mitigation Strategies." We appreciate your positive feedback and have carefully considered your suggestions to enhance the quality and clarity of our work. Below is a detailed response to each of your comments:

Figures and Tables:

1. **Schematic Diagram:** We have incorporated a schematic diagram summarizing the pathophysiological mechanisms linking air pollution to cardiovascular diseases. This visual aid is now included as Figure 1 on page 4 of the revised manuscript.
2. **Summary Table of Air Pollutants:** A comprehensive table detailing various air pollutants (e.g., $PM_{2.5}$, O_3, NO_2) and their specific cardiovascular effects has been added as Table 1 on page 3. This table aims to provide a clear and concise reference for readers.
3. **Mitigation Strategies Comparison Table:** We have included a table comparing different mitigation strategies, such as regulatory policies, lifestyle interventions, and public health initiatives, along with their effectiveness. This addition is presented as Table 2 on page 8. I added Table 3 on page 9 for **Intervention Strategies Comparison**.

Language and Clarity:

To address minor grammatical and stylistic issues, we have subjected the manuscript to professional proofreading. This process has improved the overall readability and ensured that the language is clear and precise throughout the document.

Originality:

In response to your suggestion, we have added a "Future Directions" section on page 10. This section highlights existing research gaps, including the long-term effects of ultrafine particles and the effectiveness of personalized exposure reduction strategies. We believe this addition underscores the originality of our review and provides a roadmap for future investigations.

We are grateful for your valuable feedback, which has significantly contributed to enhancing the quality of our manuscript. We look forward to any further comments you may have.

Best regards,

[Dr. Hari Krismanuel]

[Universitas Trisakti]

[February 28, 2025]

Reviewer: 3

Comments to the Author

Overall Evaluation

The manuscript presents a comprehensive and well-structured review of the impact of air pollution on cardiovascular diseases (CVDs). The discussion of molecular mechanisms, epidemiological evidence, and mitigation strategies is insightful and well-referenced. However, some minor refinements in language, structure, and presentation can enhance clarity and readability. Additionally, a few major points require further elaboration to strengthen the scientific discussion.

Major Comments

1. Clarification of Key Research Gaps

o The manuscript states that “critical gaps remain” in understanding molecular mechanisms and the long-term effects of air pollution on cardiovascular health.

o Recommendation: It would be beneficial to specify which key gaps in molecular pathways (e.g., epigenetic modifications, interactions between pollutants) require further study. This will help readers understand the direction of future research.

Response:

Dear Reviewer 3,

Thank you for your thorough and insightful review of our manuscript titled "Air Pollution and Cardiovascular Diseases: Mechanisms, Evidence, and Mitigation Strategies." We appreciate your constructive feedback and have addressed your comments as follows:

Major Comments

1. **Clarification of Key Research Gaps**

Comment: The manuscript mentions "critical gaps remain" in understanding molecular mechanisms and the long-term effects of air pollution on cardiovascular health.

Recommendation: It would be beneficial to specify which key gaps in molecular pathways (e.g., epigenetic modifications, interactions between pollutants) require further study. This will help readers understand the direction of future research.

Response: We appreciate this observation. To provide clarity, we have specified key gaps in molecular pathways that require further study, including:

a. The role of epigenetic modifications, such as DNA methylation and histone modifications, in mediating long-term cardiovascular effects of air pollution exposure.

b. Interactions between different pollutants, particularly ultrafine particles (UFPs) and gaseous pollutants like NO_2 and SO_2, in exacerbating oxidative stress and inflammation.

c. Identification of novel biomarkers that could elucidate individual susceptibility to air pollution-induced cardiovascular damage.

These additions have been incorporated into the "Future Directions" section of the revised manuscript.

We thank you for your consideration and hope that this revised manuscript meets the requirements for publication in your journal.

Sincerely,

[Dr. Hari Krismanuel]

2. **Heterogeneity of Study Populations**

o The manuscript covers both epidemiological and mechanistic studies but does not clearly address population variability (e.g., developed vs. developing countries, urban vs. rural populations).
o Recommendation: Include a brief discussion on how geographical differences or socioeconomic factors may influence air pollution exposure and CVD risk.

Response:

Dear Reviewer 3,

Thank you for your time and effort in reviewing my manuscript. I greatly appreciate your constructive comments and suggestions, which have significantly helped us improve the quality of this manuscript.

We are particularly grateful for your comment regarding the heterogeneity of study populations. We recognize the importance of addressing population variability (e.g., developed vs. developing countries, urban vs. rural populations) and socioeconomic factors in the context of air pollution exposure and cardiovascular disease (CVD) risk.

In accordance with your recommendation, we have added a more detailed discussion on how geographical differences and socioeconomic factors may influence air pollution exposure and CVD risk in the Introduction section. We have included specific examples of exposure differences in developing and developed countries, as well as in urban and rural areas. We have also highlighted the crucial role of socioeconomic status (SES) in influencing exposure and health outcomes. Furthermore, we have added a section discussing how these differences can influence molecular responses to pollutants, as well as the importance of mitigation strategies tailored to the specific contexts of different populations.

Specifically, we have added the following sentences to the Introduction:

- "These differences can also influence molecular responses to pollutants, with studies showing variations in inflammatory gene expression and oxidative stress responses between urban and rural populations."

- "Therefore, effective mitigation strategies must consider these differences and be tailored to the specific contexts of different populations, including factors such as access to healthcare services, education levels, and housing conditions."

We believe that these additions have significantly enhanced our discussion of population heterogeneity and its relevance to the manuscript's topic.

We have revised the manuscript according to all your comments and suggestions. We are confident that the revised manuscript is now stronger and more comprehensive.

We have attached the revised manuscript and our point-by-point response to all reviewer comments.

We thank you for your consideration and hope that this revised manuscript meets the requirements for publication in your journal.

Sincerely,

[Dr. Hari Krismanuel]

[Universitas Trisakti]

3. Mitigation Strategies – Practical Implementation
o While the manuscript proposes mitigation strategies, the feasibility and effectiveness of these interventions are not critically assessed.
o Recommendation: Provide a comparison of successful interventions from different regions or highlight barriers to implementation (e.g., policy limitations, technological constraints).

Response:

Dear Reviewer 3,

We acknowledge this oversight and have expanded our discussion on mitigation strategies to critically assess their feasibility and effectiveness across different regions. We compare successful interventions, such as emission reduction policies in the European Union and air quality management strategies in China, highlighting their strengths and limitations based on criteria such as pollution reduction efficacy, cost-effectiveness, and sustainability. For example, we discuss the challenges of implementing stringent emission standards in developing economies due to financial constraints and technological limitations. Additionally, we discuss barriers to implementation, including regulatory constraints, financial burdens, and technological accessibility in low-resource settings. Specifically, we have added examples of policy limitations in regards to specific countries and technological limitations regarding the ability to monitor specific pollutants. These revisions are incorporated into the "Mitigation Strategies" section of the revised manuscript, and we have also added a brief discussion to the "Future Directions" section, highlighting the need for further research into context-specific mitigation strategies.

We thank you for your consideration and hope that this revised manuscript meets the requirements for publication in your journal.

Sincerely,

[Dr. Hari Krismanuel]
[Universitas Trisakti]

Minor Comments

Language & Clarity

• Introduction:

o The sentence: "While significant progress has been made in understanding the detrimental effects of air pollution on cardiovascular health, critical gaps remain, particularly concerning the intricate molecular mechanisms..."

o Suggestion: Break it into two shorter sentences for better readability:

"Significant progress has been made in understanding the detrimental effects of air pollution on cardiovascular health. However, critical gaps remain, particularly concerning the intricate molecular mechanisms..."

• Abstract:

o The phrase "Immediate action is critical to protect global health."

o Suggestion: Change to "Immediate action is imperative to safeguard global health." for a more formal tone.

Consistency in Terminology

• The manuscript inconsistently uses "particulate matter (PM)" and "PM2.5."

o Suggestion: Standardize the terminology throughout the manuscript to avoid confusion, particularly in sections discussing different pollutants (PM2.5 vs. PM10).

• Similarly, "cardiovascular diseases (CVDs)" and "heart disease" are used interchangeably.

o Suggestion: Define "CVD" early in the Introduction and use it consistently.

Formatting & References

• In the Methods section, Boolean operators (AND, OR) should be consistently capitalized.

• Some references (e.g., [1-6], [5,9]) appear clustered.

o Suggestion: Spread them more evenly for readability and ensure proper placement within relevant sections.

Figures & Data Presentation

• The Results section would benefit from a summary table presenting key pollutants and their cardiovascular effects.

• The Mechanisms section could be improved by using bullet points or numbering for oxidative stress, inflammation, endothelial dysfunction, and autonomic dysregulation.

Conclusion Enhancements

• The phrase: "Further research focusing on 'the long-term effects of exposure to ultrafine particles' and 'the effectiveness of specific intervention strategies' are crucial..."

o Correction: "are" → "is" (subject-verb agreement).

• The phrase: "We strongly advocate for the implementation and enforcement of stricter air quality regulations..."

o Suggestion: Consider a more neutral tone: "We recommend the urgent implementation of stricter air quality regulations..."

Final Remarks

This manuscript is well-structured and presents valuable insights into air pollution and cardiovascular health. Addressing the major comments will improve the scientific depth, while the minor refinements will enhance clarity and readability.

Date Sent	*06-Feb-2025* Response: Dear Reviewer 3, Thank you for your thorough and insightful review of our manuscript titled "Air Pollution and Cardiovascular Diseases: Mechanisms, Evidence, and Mitigation Strategies." We appreciate your constructive feedback and have addressed your comments as follows: ***Minor Comments*** *1.* ***Language & Clarity*** ○ *Introduction:* *Comment: The sentence: "While significant progress has been made in understanding the detrimental effects of air pollution on cardiovascular health, critical gaps remain, particularly concerning the intricate molecular mechanisms..."* *Suggestion: Break it into two shorter sentences for better readability:* *"Significant progress has been made in understanding the detrimental effects of air pollution on cardiovascular health. However, critical gaps remain, particularly concerning the intricate molecular mechanisms..."* *Response: I have revised this sentence for clarity: "Significant progress has been made in understanding the detrimental effects of air pollution on cardiovascular*

health. However, critical gaps remain, particularly concerning the intricate molecular mechanisms..."

- *Abstract:*

  Comment: The phrase "Immediate action is critical to protect global health."

  Suggestion: Change to "Immediate action is imperative to safeguard global health." for a more formal tone. Consistency in Terminology

  Response: I have modified this phrase for a more formal tone: "Immediate action is imperative to safeguard global health."

2. ***Consistency in Terminology***

- *Particulate Matter:*

  Comment: Inconsistent use of "particulate matter (PM)" and "PM2.5."

  Response: I have standardized the terminology throughout the manuscript, consistently using "PM2.5" when referring to fine particulate matter.

- *Cardiovascular Diseases:*

  Comment: Interchangeable use of "cardiovascular diseases (CVDs)" and "heart disease."

  Response: I have defined "cardiovascular diseases (CVDs)" early in the Introduction and used this term consistently throughout the manuscript.

3. ***Formatting & References***

- *Boolean Operators:*

  Comment: Inconsistent capitalization of Boolean operators (AND, OR) in the Methods section.

  Response: I have ensured consistent capitalization of Boolean operators in the Methods section.

- *Clustered References:*

  Comment: Some references (e.g., [1-6], [5,9]) appear clustered.

  Response: I have reviewed and adjusted the placement of references to ensure they are evenly distributed and appropriately placed within relevant sections.

4. ***Figures & Data Presentation***

   Comment: The Results section would benefit from a summary table presenting key pollutants and their cardiovascular effects.

   Response: I have added a summary table in the Results section (Table 1) that outlines key pollutants and their associated cardiovascular effects.

   Comment: The Mechanisms section could be improved by using bullet points or numbering for oxidative stress, inflammation, endothelial dysfunction, and autonomic dysregulation.

   Response: I have revised the Mechanisms section to include bullet points for each pathway: oxidative stress, inflammation, endothelial dysfunction, and autonomic dysregulation, enhancing clarity and readability.

5. ***Conclusion Enhancements***

   - *Subject-Verb Agreement:*

     Comment: The phrase: "Further research focusing on 'the long-term effects of exposure to ultrafine particles' and 'the effectiveness of specific intervention strategies' are crucial..."

     Response: We have corrected the subject-verb agreement: "Further research focusing on 'the long-term effects of exposure to ultrafine particles' and 'the effectiveness of specific intervention strategies' is crucial..."

- *Tone Adjustment:*

  Comment: The phrase: "We strongly advocate for the implementation and enforcement of stricter air quality regulations..."

  Response: We have adjusted the tone for neutrality: "We recommend the urgent implementation of stricter air quality regulations..."

  We believe these revisions have addressed your concerns and have enhanced the clarity and quality of our manuscript. Thank you once again for your valuable feedback.

Best regards,

[Dr. Hari Krismanuel]

[Universitas Trisakti]

[February 28, 2025]

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