IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Medical Sciences

2026; 23(12): 3822-3845. doi: 10.7150/ijms.137232

Review

Air Pollution and Lung Cancer–Cardiovascular Disease Comorbidity: Epidemiological Evidence, Shared Mechanisms, and Research Gaps

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Received: 2026.05.04; Accepted: 2026.10.29; Published: 2026.11.13

Abstract

Air pollution is a major global health risk factor. The air pollution-associated comorbidity of lung cancer, the leading cause of cancer-related death, and cardiovascular disease (CVD), a major cause of morbidity and mortality worldwide, warrants greater attention. Although epidemiological studies using comorbidity as an endpoint under air pollution exposure remain limited, three lines of evidence support the potential role of air pollution in promoting this comorbidity: air pollution is a shared risk factor for both lung cancer and CVD; the two diseases frequently coexist and may mutually promote each other, resulting in a substantial comorbidity burden; and patients with cancer, including but not limited to lung cancer, have an increased risk of CVD under air pollution exposure, and vice versa. This review provides an in-depth discussion of the shared mechanistic pathways underlying lung cancer–CVD comorbidity, including chronic inflammation, oxidative stress, epigenetic alterations, communication between the lung and the cardiovascular system (the lung–heart axis), and the lung–gut–heart axis mediated by alterations in the gut microbiota. Among these mechanisms, chronic inflammation, oxidative stress, and tumor-promoting angiogenesis represent the best-supported shared pathways, whereas the other mechanisms mainly play auxiliary roles in amplifying or accelerating the development of comorbidity, with most ultimately converging on chronic inflammation. Significant gaps remain in the translation of mechanistic findings into clinical evidence. Future priorities in comorbidity research should include epidemiological studies of air pollution exposure using comorbidity as an endpoint, validation of relevant biomarkers, and interventional studies targeting inflammation, selective modulation of specific oxidative stress pathways, and microbiota modulation. In regions with severe air pollution and a high disease burden, greater attention should be paid to the prevention, treatment, and long-term management of such comorbidities.

Keywords: air pollution, cardiovascular disease, comorbidity, incidence, lung cancer, mechanism

1. Introduction

Air pollution has emerged as a significant global environmental and public health issue. The World Health Organization's (WHO) revised air quality guidelines in 2021 indicate that approximately 99% of the global population is exposed to pollution levels that exceed established air quality standards, making it the second leading risk factor for death [1]. Major air pollutants, including particulate matter (PM), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3), pose substantial challenges for atmospheric pollution control due to their considerable contributions to the disease burden [2]. The Global Burden of Disease Study 2021 identified PM pollution as the leading global contributor to disease burden, accounting for 8.0% of total Disability-Adjusted Life Years (DALYs) [3]. Ambient $PM_{2.5}$ and household solid fuel pollution cause approximately 4.7 million and 3.1 million deaths each year,

respectively [4].

Lung cancer ranks among the malignancies with the highest incidence and mortality rates globally. In 2022, approximately 1.8 million deaths and 2.5 million new cases of lung cancer were reported worldwide, making it the leading cause of cancer-related mortality [5]. Cardiovascular diseases (CVDs) encompass a range of disorders affecting the circulatory system, mainly including ischemic heart disease (IHD) or coronary heart disease (CHD), arrhythmia, hypertension, heart failure (HF) and cardiomyopathy. As the primary cause of death globally, CVD accounted for an estimated 19.2 million deaths in 2023 [6].

Exposure to air pollution is closely linked to the incidence and mortality of both lung cancer and CVD. Approximately 15% of global lung cancer deaths are attributable to air pollution annually, with even higher proportions in severely polluted areas [7, 8]. The WHO International Agency for Research on Cancer (IARC) has classified outdoor air pollution and $PM_{2.5}$ as a Group 1 carcinogen [9]. Moreover, both short-term and long-term exposure to polluted environments significantly increases the risk of CVD incidence and associated adverse health outcomes. Data from 2021 indicated that approximately 2.46 million CVD deaths and 58.3 million CVD-related DALYs could be attributed to air pollution [10].

Therefore, air pollution represents a prevalent environmental risk factor for both lung cancer and CVD. Notably, these two conditions frequently coexist within the same patient population. A bidirectional association may exist between these diseases: lung cancer can elevate the risk of CVD, while CVD may similarly heighten the risk of developing lung cancer, potentially exacerbated by air pollution [11, 12]. The presence of comorbidities accelerates disease progression, significantly reduces patients' quality of life, and makes disease management more complex. Investigating whether air pollution influences the occurrence, progression, and prognosis of comorbidity between lung cancer and CVD through shared mechanisms is of considerable scientific and public health significance.

Nevertheless, current research predominantly examines the relationship between air pollution and individual diseases. Although studies have reviewed air pollution in cardio-oncology, little attention has been paid to lung cancer and the mechanistic crosstalk between lung carcinogenesis and cardiovascular pathogenesis under air pollution remains unintegrated [12]. This review focuses on the de novo comorbidity of lung cancer and CVDs induced by environmental exposure, and addresses whether air pollution establishes a shared epidemiological and pathophysiological basis that promotes the co-occurrence, mutual exacerbation and adverse prognosis of these two disorders. It aims to strengthen the understanding of air pollution as a shared risk factor for the co-occurrence of these two diseases, thereby facilitating the prevention and management of complications associated with air pollution-related chronic diseases. The literature search strategy for this review is shown in **Supplementary Table S1**.

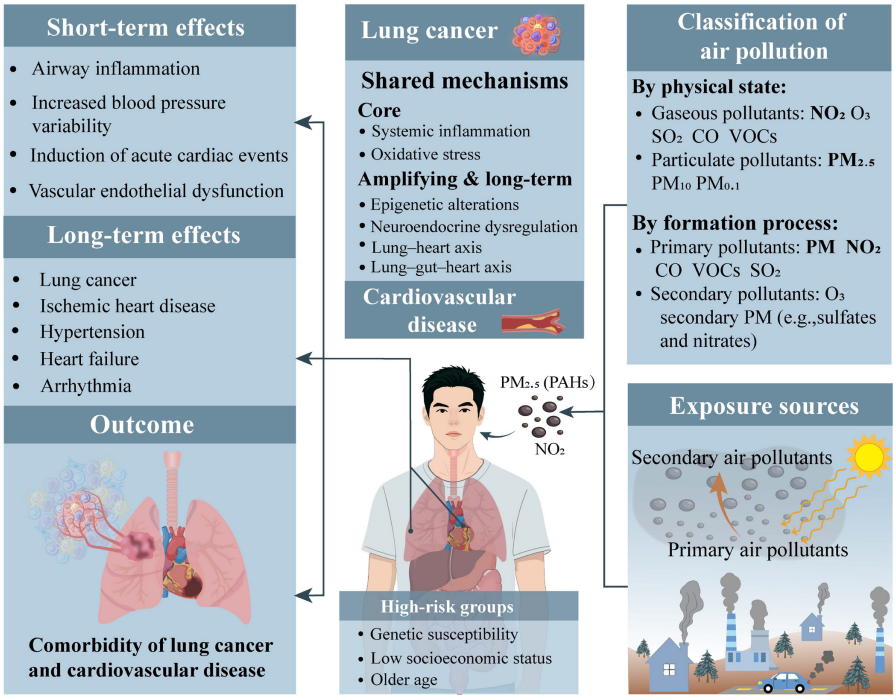


Figure 1. Graphical abstract: conceptual framework of air pollution-related lung cancer–CVD comorbidity.

2. Comorbidity of lung cancer and CVD: an issue worth attention

2.1 High comorbidity burden and bidirectional association

Multiple studies have shown that lung cancer and CVD do not occur independently. Compared with other types of cancer, lung cancer patients have a higher prevalence of comorbid CVD, a finding that has been confirmed across different regions. Two studies from the US and the UK both demonstrated that, compared with individuals without CVD, patients with CVD had an increased risk of developing lung cancer (**Table 1**).

Notably, the definitions of CVD vary across studies, so direct comparisons should be made with caution. Nevertheless, the findings consistently indicate a bidirectional association between lung cancer and CVD. The coexistence of CVD and lung cancer is linked to a poorer prognosis, characterized by elevated risks of short-term readmission and in-hospital mortality [13]. For long-term cancer survivors, the risk of CVD death may ultimately exceed that from cancer itself [14].

Table 1. The high comorbidity burden of lung cancer and CVD

First Author/Year	Area	Participants	Key Findings
Battisti et al, 2022 [15]	England	634,240 cancer patients	The prevalence of CVD among non-small cell lung cancer (NSCLC) patients was 36.1% (95% CI: 35.7%–36.4%), with IHD being the most prevalent (22%)
Mitchell et al, 2023 [16]	US	839,934 cancer patients	The cumulative incidence rate of major adverse cardiovascular events (including CHD, HF and stroke) in lung cancer patients was 26%.
He et al, 2024 [17]	China	85,787 cancer patients	The risk of CVD was 69% (95% CI: 54%–84%) higher in lung cancer patients.
Zhu et al, 2021 [13] [a]	China	10,175 lung cancer patients	The proportion of lung cancer patients with hypertension was 5.4%
Gon et al, 2023 [18]	Japan	682,886 cancer patients	The mortality risk from heart disease in lung cancer patients was 2.3 times greater (95% CI: 2.2–2.5) than that of the general population
S. Zhang et al, 2024 [11]	UK	44,871 CVD patients	Compared with non-CVD individuals, patients with CVD had an increased lung cancer risk (HR, 1.50; 95% CI: 1.31–1.71)
Bell et al, 2023 [19]	US	27,195,088 individuals	Compared with non-CVD individuals, patients with CVD had an increased lung cancer risk (HR, 1.73; 95% CI: 1.69–1.77)

Note: [a] In Zhu et al., hypertension was identified based on ICD codes under the Elixhauser Comorbidity Index using a 5% random sample of medical insurance claims data. Hypertension that was not identified or coded in the claims records may have been missed, and this estimate likely underestimates the true burden of hypertension.

2.2 Comorbidity is not coincidental but shares a common risk architecture

Several underlying factors contribute to the comorbidity of lung cancer and CVD. On one hand, they share key risk factors: smoking, air pollution, unhealthy lifestyles, low socioeconomic status, aging and genetic susceptibility [20-23]. Additionally, metabolic disorders such as diabetes and obesity, along with systemic inflammation, contribute to the development and progression of these diseases [24, 25]. The association between metabolic syndromes, including hypertension, dyslipidemia, and hyperglycemia, and CVD is well established. Recent research suggests a strong association between lung cancer and systemic metabolic dysregulation. Cancer cells adapt their metabolism to support rapid growth by favoring glycolysis over oxidative phosphorylation, known as the Warburg effect. This metabolic shift not only fuels tumor cell proliferation but also reshapes the tumor microenvironment, facilitating metastasis and immune escape [26]. Some studies indicate that patients with diabetes or insulin resistance have a higher risk of lung cancer, which may be linked to hyperinsulinemia, hyperglycemia, and chronic inflammation [27, 28]. Metformin is a classic treatment for diabetes and has shown potential antitumor effects in some preclinical studies. However, randomized clinical trials have not demonstrated clear improvements in progression-free survival or overall survival, and its potential benefits in specific populations, such as those with high levels of air pollution exposure, remain to be further investigated and validated [29]. Furthermore, genes exhibit polymorphism, and the lungs and cardiovascular system share genes that regulate inflammation and metabolism. Dysregulation of these genes may contribute to the pathogenesis of both diseases. For example, variation in inflammatory cytokine genes such as interleukin-6 (IL-6) can disrupt immune homeostasis, promoting pulmonary fibrosis and lung cancer in the lungs [30], while accelerating atherosclerosis and thrombosis in blood vessels [23]. Similarly, abnormalities in metabolic genes like CYP1A1 can impair detoxification, leading to toxin accumulation, oxidative stress, and genotoxic damage in both the pulmonary and vascular systems, thereby elevating the risk of lung cancer and CVD [31, 32].

In this review, comorbidity refers primarily to co-occurring or mutually reinforcing lung cancer and CVD in the context of shared exposure and host susceptibility. Currently, the cardiotoxicity induced by antitumor treatments (including surgery, chemotherapy, targeted therapy, radiotherapy, and immunotherapy) has received increasing attention, these treatments all increase the risk of CVD, thereby

giving rise to the field of cardio-oncology [33-36]. However, cardio-oncology primarily focuses on treatment-related cardiovascular events, making it difficult to explain why the prevalence of CVD remains high in lung cancer patients who have not received any anti-tumor therapy, or why CVD patients subsequently face an increased risk of developing lung cancer. This suggests the existence of common pathogenic factors independent of treatment effects, such as the air pollution we have discussed.

3. Air pollution as a shared exposure context

3.1 The pollutants that matter most

Particulate matter (PM) is the most extensively studied pollutant in research linking lung cancer and CVD. It originates primarily from household combustion and transportation. PM with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) can penetrate deep into the alveoli and enter the systemic bloodstream. Its surface can adsorb heavy metals, polycyclic aromatic hydrocarbons (PAHs), and reactive organic compounds, forming a complex toxic mixture that induces lung injury and systemic damage [37]. PAHs are produced by incomplete combustion of organic matter. Higher molecular weight PAHs (4–6 rings), such as benzo[a]pyrene (BaP), are less volatile and mainly adsorb onto particulate matter. BaP is classified as a Group 1 carcinogen by the IARC (2012) and is associated with high exposure in areas where coal combustion is common [38, 39].

NO_2 serves as a characteristic marker of traffic-related pollution. Even independent of PM, NO_2 itself poses established health risks [40]. The World Health Organization (WHO) substantially tightened the annual NO_2 guideline limit from 40 μg/m^3 to 10 μg/m^3 in its 2021 global air quality guidelines [41].

The health hazards of ground-level O_3 are becoming increasingly prominent. O_3 is a secondary pollutant formed by photochemical reactions of nitrogen oxides (NO_x) and volatile organic compounds (VOCs). Unlike PM, there are currently no effective personal protective measures to avoid O_3 exposure, and its harms are often greater than those of primary pollutants [42].

SO_2 and CO are important components of the air pollution mixture and remain major air pollutants in developing countries, with their exposure also being associated with adverse health effects in the population [43]. A brief introduction to the sources and classification of air pollution is shown in **Fig. 1**.

3.2 Exposure characteristics of pollutants

In recent years, the global upward trend in $PM_{2.5}$ pollution has been reversed. The global population-weighted $PM_{2.5}$ concentration rose from 28.3 μg/m^3 in 1998 to 38.9 μg/m^3 in 2011, after which it gradually declined [44]. However, studies have found that although exposure concentrations of NO_2 and $PM_{2.5}$ continue to decrease, their health risks have not declined correspondingly; adverse health effects can still be observed even at very low exposure levels [45]. For lung cancer and CVDs, genetic and other factors may increase population susceptibility to these conditions, and long-term exposure to air pollution may further promote the early onset of their comorbidities [46].

Although $PM_{2.5}$ pollution has gradually eased, O_3 pollution continues to intensify, and the issue of secondary pollution has become increasingly prominent [47]. The reduction in $PM_{2.5}$ is mainly attributable to the control of precursors such as sulfur dioxide and primary particulate matter, whereas nitrogen oxides and VOCs have not yet achieved coordinated and deep emission reductions. These changes suggest a gradual transition from pollution dominated by coal-combustion-related particulate matter toward a more complex pollution pattern characterized by the coexistence of $PM_{2.5}$ and O_3, potentially posing additional challenges for the prevention of lung cancer and CVD [48].

3.3 Limitations of single-pollutant assessment

In real-world environments, exposures are mostly mixed and vary by region. Atmospheric NO_2 can generate nitrate and secondary PM, accompanied by ozone formation; traffic sources simultaneously emit NO_2 and PM; indoor biomass combustion typically releases PM and CO together in relatively stable proportions [49, 50]. These atmospheric chemical processes and real-world exposure characteristics determine that NO_2, $PM_{2.5}$ and O_3 inevitably coexist. Furthermore, urban exposures are dominated by traffic-related components, while rural areas are significantly affected by agricultural activities and residential solid fuel combustion. Attributing comorbidities solely to a single pollutant may seriously underestimate the overall disease burden posed by air pollution [51].

4. Epidemiological evidence

4.1 Air pollution and lung cancer risk

$PM_{2.5}$ has the strongest association with lung cancer. In studies from different regions published after 2020, $PM_{2.5}$ is consistently linked to an increased risk of lung cancer even at very low concentrations. Specific risks are shown in the **Supplementary Table S2**. PAHs are one of the components of $PM_{2.5}$. Studies

have found that at the same $PM_{2.5}$ concentration, lung cancer risk increases significantly with elevated PAHs content [52]. This suggests that regional differences in $PM_{2.5}$-associated lung cancer risk may be largely attributed to variations in $PM_{2.5}$ chemical composition. Multiple studies have confirmed the association between NO_2 exposure and lung cancer, with its carcinogenic effect second only to $PM_{2.5}$. However, this association is sometimes undetectable at low exposure concentrations [53].

The association between O_3 exposure and lung cancer risk remains inconsistent, with some studies showing a positive correlation [54] or no association [55], while others, interestingly, even showing a negative correlation [56]. O_3 and NO_2 exhibit an inverse relationship in the natural environment. In areas with high ozone levels, the relatively low nitrogen dioxide concentrations may give rise to spurious associations, and thus the observed negative correlation should not be interpreted as a protective effect of O_3. As mentioned above, O_3 is a secondary pollutant, and its pollution has become increasingly prominent in recent years. Therefore, it is necessary to adjust for other pollutants (especially NO_X and VOCs) before reassessing the true association of O_3. Studies on SO_2 and CO are relatively scarce. SO_2 may be associated with lung cancer, but current evidence is still insufficient to establish a definitive link [54]. The IARC currently classifies SO_2 as a Group 3 carcinogen, meaning its carcinogenicity to humans cannot be classified. In two recent studies, CO tended to show no association with lung cancer [54, 57]. In recent years, with the substantial reduction in the use of sulfur-containing fuels and household coal burning, the statistical associations of SO_2 and CO with lung cancer incidence are likely to gradually weaken.

Regarding population susceptibility, individuals living in cities with low economic or educational levels, males, older adults, and those with a family history of lung cancer demonstrate higher sensitivity to air pollution exposure.

4.2 Air pollution and CVD risk

The effects of air pollution on the incidence of CVD are presented in **Supplementary Table S3**, which distinguishes between short-term and long-term exposure. Recent evidence shows that short-term exposure to NO_2, $PM_{2.5}$, SO_2, O_3, and CO has clear cardiovascular effects, with NO_2 and $PM_{2.5}$ having the greatest impact. The most significant adverse event is the triggering of acute coronary syndrome (ACS). In addition, short-term exposure increases blood pressure variability. Several meta-analyses have also found that short-term exposure to air pollution can induce atrial fibrillation (AF) (significantly associated with PM2.5, NO_2, and O_3) [58], and worsen HF (significantly associated with PM2.5, NO_2, SO_2, and CO) [59].

Long-term exposure to air pollution is associated with CHD, HF, arrhythmia, and hypertension. $PM_{2.5}$ is the primary pollutant, while NO_2 and O_3 also pose high cardiovascular health risks.

Regarding population susceptibility, individuals with genetic risk, the elderly, obese individuals, and low-income populations in urban areas are more susceptible.

4.3 Evidence supporting the association between air pollution and lung cancer–CVD comorbidity

Current epidemiological evidence remains incomplete because no prospective cohort study has directly evaluated incident lung cancer–CVD comorbidity as a composite outcome in relation to air pollution exposure. Nevertheless, three lines of evidence consistently suggest an association between air pollution and lung cancer–CVD comorbidity.

The first line of evidence comes from studies examining the associations between air pollution and each disease separately. A large body of high-quality epidemiological evidence has consistently shown that exposure to air pollutants is associated with increased risks of both lung cancer and CVD (**Supplementary Tables S2 and S3**). Among the pollutants investigated, the evidence is strongest for $PM_{2.5}$ and NO_2. These findings indicate that air pollution represents a shared environmental risk factor for both diseases and that exposure to the same pollutants is associated with an increased risk of each. However, an important limitation of this evidence is that it cannot determine whether lung cancer and CVD develop concurrently within the same individuals as a result of the shared exposure.

The second line of evidence comes from bidirectional associations observed in single-disease cohorts (summarized in **Table 2**). Among cancer survivors, including those with lung cancer, air pollution has been associated with an increased risk of incident CVD [60-62]. Among patients with CVD, traffic-related air pollution has been associated with an increased risk of incident malignancies; however, in both studies, lung cancer was evaluated as a component subgroup rather than as a primary endpoint [63, 64]. These findings suggest that air pollution may exert cross-system effects in individuals with pre-existing disease and further imply a pathophysiological interplay between lung cancer and CVD. However, these findings should be interpreted with caution. Because these studies enrolled individuals with an established disease at baseline,

they could not capture the entire disease trajectory from a healthy state to the development of comorbidity and therefore cannot independently demonstrate that air pollution initiates primary lung cancer–CVD comorbidity. In addition, most available studies evaluated all cancer types rather than lung cancer specifically, limiting the direct evidence for lung cancer.

The third line of evidence comes from disease coexistence and pathophysiological interactions. As discussed in Section 2, lung cancer and CVD frequently coexist and mutually exacerbate each other even in the absence of treatment. Subsequent sections further describe their shared molecular mechanisms, including chronic inflammation and oxidative stress. These observations provide biological plausibility for the interaction between the two diseases. However, because these studies generally investigate broad risk factors rather than air pollution specifically, they cannot establish air pollution as the direct cause of lung cancer–CVD comorbidity.

These three lines of evidence arise from different study designs but provide complementary support. Evidence from independent disease associations establishes the epidemiological basis for the relationship between air pollution exposure and each disease. Bidirectional findings from single-disease cohorts provide epidemiological evidence of cross-system health effects associated with air pollution, while studies of disease coexistence and shared biological pathways offer biological plausibility. Collectively, these findings support the cautious conclusion that air pollution is a plausible risk factor for lung cancer–CVD comorbidity. Nevertheless, current evidence remains insufficient to determine whether air pollution simultaneously initiates both diseases, triggers one disease that subsequently accelerates the development of the other, or simply exacerbates pre-existing disease, resulting in the manifestation of comorbidity. Therefore, prospective cohort studies using incident lung cancer–CVD comorbidity as a composite outcome remain an essential next step.

In addition, current evidence consistently suggests that individuals with lower socioeconomic status, older adults, and those with genetic susceptibility may be more vulnerable to the adverse health effects of air pollution. These populations should therefore be prioritized in future strategies for the prevention of lung cancer–CVD comorbidity.

4.4 High-risk populations and high-priority settings

The Wumeng Mountains area in Yunnan, particularly Xuanwei, exemplifies a region with one of the highest lung cancer incidence and mortality rates in China. Data from 2014–2016 showed that the age-standardized lung cancer mortality rate in Xuanwei was 65.75 per 100,000, which was approximately 1.5 times the average level of rural China [65]. Lung cancer here displays strong familial aggregation [66], with comparable rates between males and females, contrasting with the typical male predominance elsewhere. This pattern is closely linked to local coal distribution and usage [67, 68]. Coal combustion releases large amounts of PM and adsorbed PAHs. The annual average outdoor $PM_{2.5}$ concentration in Xuanwei reached 45.3 μg/m^3, far exceeding the WHO standard of 5 μg/m^3 [67]. Although authoritative epidemiological data on lung cancer–CVD comorbidity in Xuanwei remain limited, existing research indicates that CVD mortality there is significantly higher than among Shanghai residents, suggesting a similarly high burden [69]. The extreme air pollution exposure in Xuanwei represents a unique regional exposure paradigm. Although it provides invaluable mechanistic proof-of-principle, its exposure characteristics may not be fully generalizable to ambient urban outdoor smog.

Table 2. Bidirectional effects of air pollution on patients with cancer and CVD

First Author/Year	Area	Participants	Pollutants	Key Findings
Choi *et al.*, 2020 [60]	Korea	40,899 cancer survivors	$PM_{2.5}$ PM_{10}	Patients in the highest quintile of $PM_{2.5}$ had an increased risk of CVD (HR, 1.31; 95% CI, 1.07–1.59)
Coleman *et al.*, 2021 [61]	US	5,591,168 cancer patients	$PM_{2.5}$	A 10 μg/m^3 increase in $PM_{2.5}$ was associated with CVD mortality risk (HR, 1.32, 95% CI: 1.26–1.39).
Xiao *et al.*, 2025 [62]	UK	50,923 cancer patients	$PM_{2.5}$, PM_{10}, NO_2	Long-term exposure increases the risk of HF with HRs of 1.22 (1.07, 1.38) for $PM_{2.5}$, 1.16 (1.03, 1.32) for PM_{10}, and 1.20 (1.06, 1.36) for NO_2
Cohen *et al.*, 2018 [63]	Israel	9,816 CHD patients undergoing PCI	traffic-related air pollution (TRAP, NO_X)	A 10 ppb increase in NO_X was associated with an increased risk of TRAP-related cancers (including lung cancer) (HR, 1.16; 95% CI: 1.05–1.28).
Cohen *et al.*, 2021 [64]	Israel	2,040 CHD patients	NO_X	A 10 ppb increase in NO_X was associated with an elevated cancer risk: HR, 1.19 (1.03–1.37)

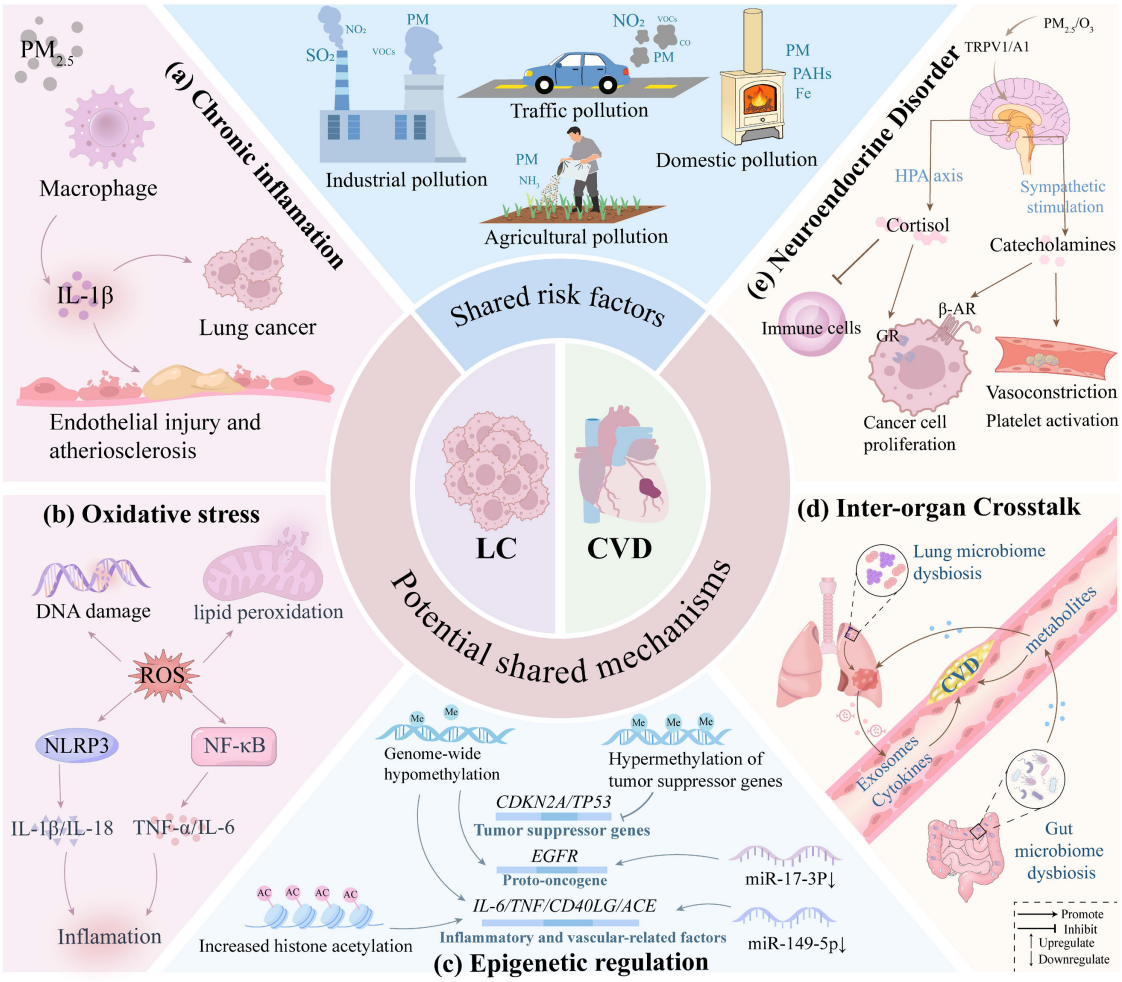


Figure 2. Shared mechanisms of air pollution-induced comorbidity of lung cancer (LC) and cardiovascular disease (CVD). (**a**) Air pollution promotes the release of IL-1β, leading to chronic inflammation, which contributes to the development of both lung cancer and CVD. (**b**) ROS can directly cause cellular damage and also promote inflammatory pathways. (**c**) Epigenetic regulation includes genome-wide hypomethylation, hypermethylation of tumor suppressor genes, increased acetylation of certain genes, and regulation by non-coding RNAs. (**d**) Organs interact through cytokines, exosomes, and metabolites following microbiota disruption, forming a vicious cycle. (**e**) Air pollution can activate the HPA axis and sympathetic nervous system, leading to metabolic and immune dysregulation. LC = Lung cancer, ROS = Reactive Oxygen Species, *CD40LG* = soluble CD40 Ligand, *ACE* = Angiotensin Converting Enzyme, TRPV1/A1 = Transient Receptor Potential Vanilloid 1 / Ankyrin 1, GR = Glucocorticoid receptor, β-AR = β-Adrenergic receptor, HPA axis = Hypothalamic-Pituitary-Adrenal axis (Italicized text represents gene symbols).

Northeastern China is another region with a high burden of both lung cancer and CVD. In 2021, the standardized annual rates of lung cancer incidence across provinces ranged from 59.61 to 73.48 per 100,000, exceeding the national average (44.01 per 100,000). Among various risk factors, air pollution accounted for approximately 25% of lung cancer deaths [70]. Furthermore, northeast China also bears the nation's highest burden of CVD, with a standardized high-risk rate of 12.6% (95% CI: 12.4%–12.8%), exceeding the national average of 10.3%. While unhealthy diet is a primary risk factor, long-term exposure to pollutants from coal combustion, heavy metals, and chemicals in this industrial region likely contributes to the elevated CVD incidence [71]. In a comorbidity study of 1,510 lung cancer patients in Northeast China, 18%, 7.4%, 6.8%, and 4.6% of the patients had comorbid hypertension, HF, CHD and arrhythmia, respectively [72].

These regions represent high-priority natural settings for future research on pollution-related comorbidity because they combine heavy exposure, high disease burden, and potentially distinctive susceptibility patterns.

5. A shared mechanistic framework for air pollution-related lung cancer–CVD comorbidity

5.1 Core shared pathway: systemic inflammation and immune dysregulation

Inflammation is one of the most consistently supported and mechanistically coherent shared pathways through which air pollution may contribute to both lung cancer and CVD. Following pollutant deposition in the respiratory tract, local inflammatory responses can extend beyond the lung and contribute

to systemic inflammation and vascular injury. This inflammatory cascade also interacts closely with oxidative stress, epigenetic alterations, and immune dysregulation, thereby providing an important mechanistic link between pulmonary and cardiovascular injury.

5.1.1 Pulmonary deposition and local inflammatory microenvironment

Traditional models of pollutant-induced carcinogenesis have largely emphasized genotoxic mechanisms, whereby carcinogenic exposures induce DNA damage and mutations that initiate malignant transformation [73]. In recent years, this classic genotoxic model of carcinogenesis has been re-examined: the tumor-promoting effects of $PM_{2.5}$ may not necessarily depend on directly inducing new DNA mutations, but rather on promoting the clonal expansion of pre-existing carcinogenically mutated cells in the lung by inducing inflammatory responses and altering the tissue microenvironment. $PM_{2.5}$ deposited in the distal lung can induce the recruitment and activation of alveolar macrophages, thereby promoting the release of interleukin-1β (IL-1β) and other inflammatory mediators. IL-1β can drive alveolar type II epithelial cells harboring *EGFR* mutations into a progenitor-like proliferative state, thereby promoting tumorigenesis [74]. Similar tumor-promoting effects have also been observed in experimental models involving *KRAS*-mutant cells.

Persistent inflammatory activation further induces the production of IL-6, IL-8, tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF), and matrix metalloproteinases (MMPs), establishing a chronic inflammatory microenvironment that promotes epithelial proliferation, angiogenesis, extracellular matrix remodeling, and immune dysregulation [75]. In mouse intervention studies, blockade of the IL-1β signaling pathway reduced lung tumor burden, further supporting the important role of this inflammatory pathway in lung cancer initiation and progression [76].

5.1.2 Spillover into the systemic circulation

Pollutant-induced inflammation is not restricted to the lung. Inflammatory mediators generated within the pulmonary microenvironment, including cytokines, chemokines, and ROS, can enter the systemic circulation and induce extrapulmonary effects. Animal studies have shown that intratracheal instillation of $PM_{2.5}$ induces inflammatory responses beyond the lung, characterized by increased levels of pro-inflammatory cytokines and endothelial adhesion molecules in the circulation and vascular tissues, accompanied by marked macrophage infiltration into the vascular wall [77]. In the Multi-Ethnic Study of Atherosclerosis (MESA), long-term $PM_{2.5}$ exposure was associated with increased circulating IL-6 levels, whereas NO_X exposure was associated with elevated coagulation-related biomarkers, including D-dimer. Short-term $PM_{2.5}$ exposure was also associated with increased levels of CRP, fibrinogen, and soluble E-selectin [78]. Another population-based cohort similarly reported associations between long-term exposure to $PM_{2.5}$ and NO_2 and elevated circulating inflammatory biomarkers [79].

This systemic inflammatory state is strongly implicated in the development and progression of CVD. In a study involving 84,399 patients with CHD, approximately 59% had CRP levels ≥2 mg/L [80], suggesting that persistent inflammatory activation is common among patients with established CVD and may contribute to residual cardiovascular risk.

5.1.3 Pathological consequences

In the lungs, sustained IL-1β signaling appears to awaken mutated epithelial cells and promote malignant proliferation. The inflammatory microenvironment promotes tumor cell survival, angiogenesis, and immune evasion, converting latent oncogenic potential into lung cancer, particularly lung adenocarcinoma.

In the cardiovascular system, circulating inflammatory mediators induce endothelial activation and dysfunction, increase the expression of vascular adhesion molecules, and promote the recruitment and activation of circulating monocytes and pro-inflammatory macrophage phenotypes within the arterial wall. These inflammatory cells further amplify local inflammatory signaling, promote lipid uptake and foam cell formation, and contribute to the initiation, progression, and destabilization of atherosclerotic plaques [81]. Meanwhile, inflammatory activation can increase the expression of tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1), activate coagulation pathways, and promote platelet activation, thereby shifting the vascular environment toward a prothrombotic state (**Fig. 2a**) [37].

5.2 Oxidative stress: a mechanism of comorbidity amplification

Oxidative stress is closely associated with inflammation. It can amplify both upstream and downstream inflammatory signals, while simultaneously contributing to carcinogenesis and cardiovascular damage (**Fig. 2b**). In a population-based case-control study, levels of oxidative stress biomarkers such as 8-isoprostane and 8-OHdG were elevated in urine following air pollution exposure [82].

This provides direct evidence of oxidative stress. In another randomized controlled trial, exposure to traffic-related air pollution (PM, BC, NO_2, CO) for four hours led to alterations in dozens of molecules related to systemic inflammation, oxidative stress, endothelial dysfunction, coagulation, and lipid metabolism, as measured by multi-omics approaches. Multiple pathways, including oxidative stress, were simultaneously activated systemically, and oxidative stress is more likely to contribute to pathological effects together with chronic inflammation [83].

Pollutants including PM (and adsorbed heavy metals/PAHs), NO_2, O_3, SO_2, and high concentrations of CO can generate reactive oxygen species (ROS) through multiple convergent mechanisms: activation of NADPH oxidase in lung epithelial cells, vascular endothelial cells, and alveolar macrophages; induction of mitochondrial dysfunction leading to electron transport chain leakage; and iron-catalyzed Fenton reactions generating hydroxyl radicals [84-86]. Furthermore, ROS engage in a positive feedback loop with inflammation: ROS activate NF-κB signaling and the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, driving further release of IL-1β and IL-6 and amplifying inflammatory signals [87].

In the lungs, ROS can directly induce oxidative DNA base damage and strand breaks. Additionally, PAHs can directly form covalent DNA adducts via the AhR-Arnt-CYP1A1/1B1-BDPE axis, causing DNA damage [88]. The combination of chronic inflammation and DNA damage may be a key factor in the malignant progression of mutated epithelial cells. ROS can also disrupt cell membrane integrity through lipid peroxidation and deplete antioxidant defenses such as glutathione, creating conditions conducive to tumor development [89].

In the cardiovascular system, ROS mediate endothelial nitric oxide synthase uncoupling, reducing nitric oxide (NO) bioavailability and leading to vasomotor dysfunction, an early mechanism of hypertension and atherosclerosis [84]. ROS modify low-density lipoprotein (LDL) to form oxidized LDL (ox-LDL), promoting atherosclerotic plaque development and instability [90]. Moreover, ROS can drive myocardial fibrosis through iron-dependent mechanisms: excess iron initiates Fenton reactions, upregulates transforming growth factor-β1 (TGF-β1) secretion, drives endothelial-to-mesenchymal transition, and activates cardiac fibroblasts, ultimately potentially leading to chronic heart failure and malignant arrhythmias [91]. Cardiac MRI studies have confirmed a significant association between long-term $PM_{2.5}$ exposure and diffuse myocardial fibrosis in humans [92]. In animal models, inhibition of NADPH oxidase 4 significantly reduced ROS production and effectively suppressed myocardial fibrosis, demonstrating a causal role of oxidative stress in cardiac dysfunction [93].

5.3 Epigenetic reprogramming and persistent disease memory

Air pollution induces long-lasting health effects through epigenetic modifications. PM, NO_2, PAHs, heavy metals, and others have been associated with epigenetic alterations in the body [94, 95]. These alterations may sustain a state of inflammation, proliferation, and vascular damage even after exposure ceases, perpetuating disease risk.

Multiple population-based cohort studies and epigenome-wide association studies (EWAS) have demonstrated that exposure to air pollution can induce extensive epigenetic remodeling. The Multi-Ethnic Study of Atherosclerosis (MESA) reported that long-term $PM_{2.5}$ exposure was associated with differential methylation at multiple CpG sites, and some of these methylation alterations were accompanied by changes in the expression of nearby genes, suggesting that DNA methylation may contribute to the development of air pollution-mediated atherosclerosis and CVD [96]. Further population-based EWAS have revealed that $PM_{2.5}$-associated differentially methylated regions are primarily enriched in pathways related to inflammatory responses, oxidative stress, immune regulation, cardiovascular function-related genes, and carcinogenesis-related processes [97, 98]. Beyond DNA methylation, air pollution may regulate gene transcription through alterations in histone modifications and chromatin architecture. For example, oxidative stress induced by air pollution exposure can alter the activity of histone acetyltransferases (HATs) and histone deacetylases (HDACs), resulting in persistent dysregulation of inflammation- and metabolism-related gene expression [99, 100]. In addition, circulating microRNAs (miRNAs), which function as important post-transcriptional regulators, are also influenced by air pollution exposure. Experimental studies have shown that $PM_{2.5}$ exposure can alter circulating miRNA expression profiles, thereby regulating inflammatory responses, oxidative stress, endothelial function, and tumor-related signaling pathways [101]. These findings suggest that epigenetic remodeling represents one of the key intermediate molecular mechanisms linking environmental pollutant exposure to the risk of chronic diseases.

Animal studies suggest that prenatal exposure to $PM_{2.5}$ may exert persistent effects on offspring through epigenetic mechanisms and may potentially induce

transgenerational epigenetic effects [102]. If this phenomenon can be confirmed in human populations, it would suggest that environmental air pollution exposure may exert long-term effects on cardiovascular and respiratory health in subsequent generations through epigenetic mechanisms and may alter susceptibility to related diseases. However, direct epidemiological evidence demonstrating that such epigenetic alterations can increase the transgenerational risk of lung cancer or CVD remains lacking.

5.3.1 DNA methylation: gene silencing and activation

The overall pattern of methylation alterations induced by air pollution exposure is characterized by global hypomethylation across the genome, accompanied by hypermethylation of specific genes [103]. $PM_{2.5}$ and other air pollutants can inhibit DNA methyltransferase 1 (DNMT1) through the generation of ROS, resulting in global DNA hypomethylation and increased genomic instability, which may contribute to aberrant activation of oncogenes. Conversely, oxidative stress and inflammation-related signaling pathways can induce abnormal expression of DNMT3A/DNMT3B, leading to promoter hypermethylation and transcriptional silencing of tumor suppressor genes (e.g., *TP53* and *CDKN2A*), thereby promoting tumor initiation and progression [104, 105]. Experimental studies have demonstrated that long-term exposure to PM components can alter DNA methylation patterns in pulmonary epithelial cells and activate pro-tumorigenic signaling pathways, including the MAPK and PI3K-AKT pathways. These alterations may have particular clinical relevance in individuals harboring oncogenic driver mutations such as *EGFR* and *KRAS*: epigenetic remodeling can establish a microenvironment conducive to tumor growth and facilitate the clonal expansion of genetically altered cells [106].

In cardiovascular tissues, air pollution–associated DNA methylation alterations can reduce the methylation levels of inflammation-related genes (*CD40LG*), coagulation-related genes (tissue factor *F3* and *SERPINE1*), vasoconstriction-related genes (*ACE*), and endothelial repair-related genes (*NOS3*), thereby promoting the expression of these genes and ultimately contributing to hypercoagulability and endothelial dysfunction [107, 108]. Furthermore, long-term exposure to moderate concentrations of PM_{10} has been associated with hypermethylation of antioxidant pathway genes (*SRXN1* and *AKR7A2*), which may weaken the antioxidant defense response of the organism [109]. These epigenetic alterations are closely involved in the development of CVDs. Among these, the pro-inflammatory pathways induced by DNA methylation alterations have been repeatedly validated [107, 110]. Exposure to air pollutants can modify the methylation status of regulatory regions of inflammation-related genes, including *TNF*, *CD40LG*, and *ICAM1*, resulting in increased inflammatory mediator release (**Fig. 2c**). These inflammatory pathways not only represent critical mechanisms linking air pollution exposure to CVD but also play an important role in lung cancer progression.

5.3.2 Histone modification: sustained transcriptional dysregulation

Pollutants can exert their biological effects by disrupting histone methylation, acetylation, and lactylation. PAHs can inhibit the histone methyltransferase DOT1L, thereby reducing H3K79me2 levels involved in DNA damage responses and repair, suggesting that the DOT1L–H3K79me2 axis may contribute to PAH exposure-associated genomic instability [111]. Persistent PM exposure can disrupt NAD^+ metabolism in macrophages and reduce the activity of the NAD^+-dependent deacetylase SIRT1, resulting in increased histone acetylation and subsequent upregulation of pro-inflammatory gene transcription [112]. In addition, animal studies have shown that gestational $PM_{2.5}$ exposure increases myocardial p300/CBP expression and H3K9 acetylation in adult offspring and enhances H3K9ac enrichment at the promoter regions of cardiac hypertrophy-related genes, including *GATA4* and *MEF2C*, ultimately contributing to cardiac hypertrophy in adulthood [113]. Recent experimental studies further demonstrated that $PM_{2.5}$ promotes glycolysis and lactate accumulation in pulmonary macrophages and increases histone lactylation, whereas inhibition of glycolysis effectively attenuates pulmonary inflammation and lung tissue remodeling. These findings suggest that histone lactylation may represent one of the mechanisms underlying air pollution–induced lung tissue injury [114].

5.3.3 Non-coding RNA dysregulation: post-transcriptional regulation

A recent experimental study by Lin *et al*. found that PM2.5 exposure upregulated miR-21-5p in NSCLC, which subsequently targeted and suppressed Phosphodiesterase 4D interacting protein (PDE4DIP), thereby promoting NSCLC cell proliferation, migration, and invasion, suggesting a tumor-suppressive role for PDE4DIP [115]. However, another study conducted during the same period reported that PDE4DIP knockdown activated the PKA/CREB signaling pathway, induced apoptosis, and inhibited cell-cycle progression in NSCLC cells, suggesting a pro-tumorigenic role for PDE4DIP [116]. These

apparently contradictory findings may be context-dependent. Under baseline tumor conditions, PDE4DIP may promote tumor growth through regulation of PKA signaling, whereas under $PM_{2.5}$ exposure, PDE4DIP is downregulated by miR-21-5p, and restoration of PDE4DIP expression may attenuate the malignant phenotypes induced by $PM_{2.5}$. This context-dependent mechanism warrants further investigation.

At the population level, a case–control study found that increased BaP exposure was associated with the downregulation of multiple circulating miRNAs. Among these, reduced expression of the tumor-suppressive miR-17-3p may relieve its inhibitory effect on oncogenes such as *EGFR*, thereby contributing to an increased risk of lung cancer [117].

In addition, experimental studies have shown that $PM_{2.5}$ exposure can downregulate miR-149-5p in human bronchial epithelial cells and mouse lung tissues, thereby activating the downstream TAB2/TAK1-mediated MAPK/AP-1 and IKK/NF-κB signaling pathways and promoting the expression of pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, and TNF-α [118]. Population-based studies further suggest that $PM_{2.5}$-associated miRNA dysregulation may exert broader inflammatory and cardiovascular effects. Higher $PM_{2.5}$ exposure has been associated with reduced circulating levels of miR-187-3p, miR-146a-5p, miR-1-3p, and miR-199a-5p, accompanied by increased expression of inflammation, coagulation, and vasoconstriction-related factors, including IL-1, IL-6, TNF, TLR2, F3, and ET-1 (**Fig. 2c**) [119]. These dysregulated miRNAs may act as persistent post-transcriptional regulators, thereby contributing to sustained activation of pathological signaling pathways.

5.4 Neuroendocrine and autonomic nervous system imbalance

Air pollutants activate transient receptor potential (TRP) channels in lung tissue, primarily TRPV1 and TRPA1, which trigger autonomic reflex arcs and lead to excessive sympathetic nervous system activation [120, 121]. Short-term exposure to pollutants such as $PM_{2.5}$ can rapidly elevate catecholamine levels within minutes, inducing vasospasm, acute coronary syndrome, or arrhythmias [122]. A randomized controlled trial observed that short-term exposure to PM was associated with increased levels of hormones such as corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), supporting activation of the hypothalamic–pituitary–adrenal (HPA) axis. In addition, blood pressure, insulin resistance, oxidative stress, and inflammatory markers were significantly higher following PM exposure [123]. Further research by Chen *et al*. found that long-term exposure to PM was closely associated with the development of metabolic syndrome, including hyperglycemia, hyperlipidemia, and hypertension [124]. Metabolic syndrome is an important risk factor for CVDs such as atherosclerosis. It is reasonable to hypothesize that if the HPA axis activation and its accompanying inflammation, oxidative stress, and insulin resistance observed in short-term exposure studies persist and gradually accumulate with long-term or repeated exposure, they may increase the risk of CVD. Furthermore, preclinical studies suggest that abnormally elevated glucocorticoids may suppress anti-tumor immunity and activate glucocorticoid receptor (GR) in cancer cells, potentially promoting proliferation and metastasis; similarly, catecholamines have been shown experimentally to enhance EGFR signaling via β-adrenergic receptors (β-AR) [125, 126]. These interconnected pathways help explain why long-term pollution exposure simultaneously amplifies both pro-tumor and cardiovascular stress pathways (**Fig. 2e**).

5.5 Inter-organ crosstalk: the lung–heart axis

Existing studies suggest that multiple potential forms of inter-organ signaling may mediate communication between the lungs and the cardiovascular system. As the lungs are the first organs in which inhaled air pollutants are deposited and interact with tissues, pollution-induced pulmonary inflammation, oxidative stress, and alterations in barrier function may exert distal effects through the systemic circulation. Therefore, we propose a plausible hypothesis that pulmonary inflammatory signals and extracellular vesicles induced by air pollution exposure may participate in lung–heart inter-organ crosstalk, thereby affecting vascular and myocardial function. Conversely, cardiovascular injury induced by air pollution exposure may also influence pulmonary disease progression through inflammatory mediators, tissue hypoxia, pulmonary congestion, and other circulating signals (**Fig. 2d**). However, current evidence regarding inter-organ interactions between lung cancer and CVD is derived predominantly from disease models, animal experiments, and single-disease cohort studies. Direct human evidence demonstrating that air pollution exposure mediates the comorbidity of lung cancer and CVD through such mechanisms remains lacking.

5.5.1 Exosome and inflammatory cytokine-mediated lung-heart crosstalk

Exosomes are a subtype of extracellular vesicles derived from the endosomal system that can carry bioactive molecules, including non-coding RNAs,

proteins, and lipids, and participate in long-distance intercellular communication. They are widely considered potential diagnostic biomarkers, with non-coding RNAs being among the most extensively studied molecular cargos. Cytokines such as IL-6 and TNF-α can be present within exosomes or secreted directly by cells [127].

Previous reviews have separately summarized the effects of exosomes released by lung cancer cells and cardiovascular cells on their respective disease processes. Lung cancer cells can actively release exosomes that promote epithelial-mesenchymal transition (EMT), induce angiogenesis, and shape the tumor microenvironment [128]. Similarly, in CVDs, cardiac fibroblasts, cardiomyocytes, and macrophages release exosomes that promote inflammation, fibrosis, vascular dysfunction, and myocardial remodeling [129].

Importantly, exosomes derived from lung cancer and from the cardiovascular system may engage in a bidirectional pro-pathogenic crosstalk: in a mouse model of lung cancer, cancer-cell-secreted miR-485-3p delivered to cardiomyocytes causes mitochondrial dysfunction by suppressing PGC-1α [130]. Under hypoxic conditions, lung-cancer-derived miR-23a disrupts the endothelial barrier by inhibiting prolyl hydroxylase (PHD) and the tight junction protein (ZO-1) [131]. Lung cancer and its inflammatory microenvironment can produce inflammatory and profibrotic mediators, including IL-6 and TGF-β. Previous studies have demonstrated that IL-6 and TGF-β can act synergistically within the lung cancer microenvironment to promote fibroblast activation. These mediators are also important regulators of cardiac fibroblast activation and myocardial fibrosis and may influence distal cardiac fibroblasts through the IL-6/TGF-β pathway, thereby contributing to ventricular remodeling [132]. In lung cancer, CXCL13-mediated reprogramming of stromal macrophages within the pulmonary microenvironment may induce platelet aggregation through the secretion of prothrombotic small extracellular vesicles carrying integrin β2, a process associated with an increased risk of thrombosis [133]. Conversely, in mouse models of myocardial infarction or HF, cardiac mesenchymal stromal cells (cMSCs) have been observed to secrete exosomes carrying high levels of pro-inflammatory cytokines (IL-6, TNF-α), pro-angiogenic factors (VEGF), as well as pro-cancer proteins (osteopontin) and RNAs (miR-21). In the setting of HF complicated by pulmonary congestion, these exosomes may accumulate in the lungs and thereby accelerate tumor growth [134]. Furthermore, following myocardial infarction, cardiomyocytes can release exosomes enriched in miR-22-3p, which have been observed to suppress erastin-induced ferroptosis and thereby promote tumor cell survival (**Fig. 3**) [135].

In this bidirectional pro-pathogenic process, air pollution may act as an accelerator of the vicious cycle. Experimental studies have shown that $PM_{2.5}$ exposure promotes the sustained release of exosomes containing TGF-β from the lungs and increase collagen production in mouse cardiomyocytes, which is closely associated with myocardial fibrosis [136]. In addition, in cellular and animal models, $PM_{2.5}$ has been shown to activate the STAT3/miR-21 signaling axis, which suppresses TIMP3 and activates MMP9, thereby disrupting the vascular barrier. This process may increase the risk of CVDs such as atherosclerosis and hypertension, although its clinical significance remains to be further validated in human populations [137].

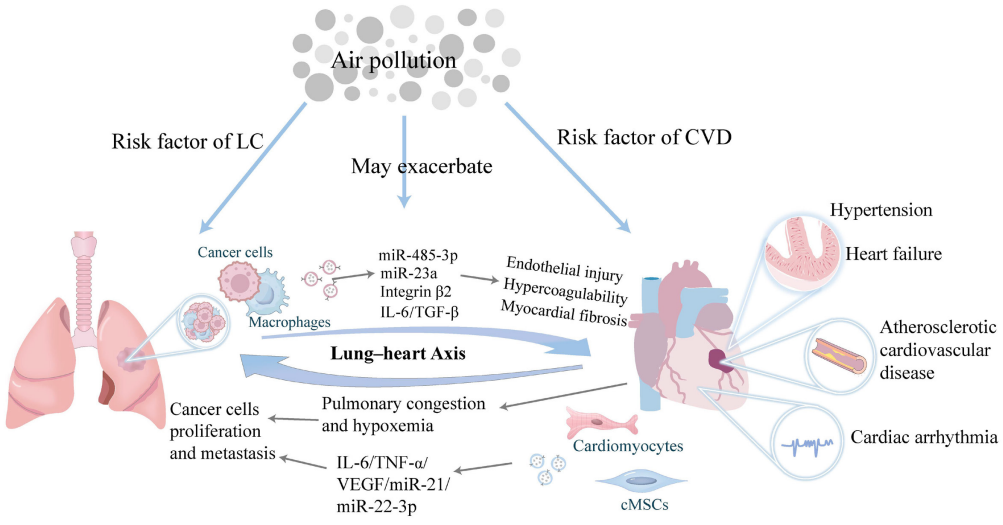


Figure 3. Lung cancer (LC) and cardiovascular disease (CVD) mutually promote each other via exosomes and cytokines. Exosomes carrying molecules can induce endothelial injury, hypercoagulable state, myocardial fibrosis, etc. Meanwhile, CVD can promote the proliferation and metastasis of lung cancer cells through pulmonary congestion, hypoxemia, and molecules released by cardiac mesenchymal stromal cells (cMSCs) and cardiomyocytes. This process may be exacerbated by exposure to air pollution.

5.5.2 Alterations of the lung microbiome: a potential mechanism of lung–heart crosstalk

The healthy lung harbors a low-biomass microbial community, whose composition is influenced primarily by factors such as microaspiration from the upper respiratory tract and may contribute to local immune regulation and inflammatory homeostasis [138]. Previous studies have shown that exposure to air pollutants, including $PM_{2.5}$ and diesel exhaust, can alter the composition and functional characteristics of the pulmonary microbiome, potentially through mechanisms involving disruption of the airway barrier, impairment of mucociliary clearance, and changes in the local metabolic environment [139, 140]. However, the direction of changes in microbial diversity and specific bacterial genera varies across studies. Overall, a general pattern appears to include reduced microbial richness and diversity, enrichment of opportunistic pathogens (e.g., *Staphylococcus*) and pollutant-degrading bacteria (e.g., *Sphingomonas*), as well as enrichment of host signaling pathways related to carcinogenesis and inflammation [141, 142].

In patients with advanced lung cancer, studies have observed enrichment of oral commensal bacteria, such as *Veillonella*, in the lower respiratory tract microbiota, and suggested that these bacteria may influence tumor-associated inflammation and cell proliferation through signaling pathways including IL-17/MAPK/PI3K/ERK [143]. The carriage rate of *Staphylococcus aureus* in the respiratory tract is higher in patients with lung cancer than in healthy individuals. Its metabolite lactate may upregulate monocarboxylate transporter 1 (MCT1) in tumor cells, thereby promoting lactate uptake and activating pseudohypoxic signaling pathways, which may enhance the metastatic capacity of lung cancer cells [144]. In addition, pulmonary microbial signals such as lipopolysaccharide (LPS) and peptidoglycan may activate lung-resident γδ T cells through the TLR2/4–MYD88–IL-1β/IL-23 pathway, thereby promoting inflammatory responses [145]. These findings provide clues that the pulmonary microbiome may be involved in the development and progression of lung cancer; however, it remains unclear whether pollution-induced alterations in the pulmonary microbiome directly contribute to lung carcinogenesis.

Currently, direct causal evidence linking pulmonary microbiome dysbiosis to CVD remains limited. Recent observational studies have reported an association between reduced airway microbial diversity and subclinical atherosclerosis; however, such associations cannot establish a causal relationship [146]. Theoretically, air pollution-induced pulmonary microbiome dysbiosis may affect the cardiovascular system through two potential pathways: first, by enhancing local pulmonary inflammation and promoting its dissemination through the systemic circulation; and second, by allowing microbial-derived molecules to enter the systemic circulation. These pathways may promote endothelial activation, vascular inflammation, and thrombosis, thereby potentially contributing to the progression of CVD [147]. However, these proposed mechanisms require further validation.

5.6 Microbiota-mediated amplification: the lung–gut–heart axis

The gut microbiota has been increasingly recognized as an important regulator of systemic metabolism, immunity, and inflammatory responses, giving rise to concepts such as the gut–lung axis and the gut–heart axis. However, there is currently no direct evidence from human populations demonstrating that air pollution-induced gut microbiome dysbiosis mediates the development or progression of lung cancer–CVD comorbidity, and this remains an important direction for future research. Therefore, we propose a potential mechanism by which gut microbiota disruption contributes to comorbidities involving the lung–gut–heart axis under air pollution exposure: the lung serves as the initial site of exposure, leading to gut microbiota disruption, which in turn accelerates both lung cancer and CVD. The detailed mechanisms and potential convergence points are illustrated in **Fig. 4**.

Air pollution may affect the gut microbiota through multiple pathways. PM deposited in the respiratory tract can be transported to the pharynx by the mucociliary clearance system and subsequently swallowed, thereby directly entering the gastrointestinal tract. Meanwhile, pulmonary oxidative stress and inflammatory responses may promote the release of reactive ROS, cytokines, and other inflammatory mediators into the systemic circulation, which can subsequently impair intestinal epithelial integrity and disrupt intestinal immune homeostasis [148, 149]. A systematic review has shown that exposure to PM, particularly diesel exhaust particles, can alter both the composition and metabolic functions of the gut microbiota. However, the direction and magnitude of changes in specific microbial taxa are not entirely consistent across studies, likely owing to differences in pollutant composition, exposure dose, route of exposure, and host susceptibility. Therefore, entire phyla such as *Bacteroidetes, Proteobacteria,* and *Verrucomicrobia* should not be simplistically classified as beneficial or harmful. More consistently reported alterations include

disruption of gut microbial community structure, reduced microbial diversity, depletion of certain short-chain fatty acid (SCFA)-producing bacteria, and impairment of intestinal barrier function [150]. In parallel, increased circulating levels of lipopolysaccharide (LPS), TNF-α, and CVD-related biomarkers, including sICAM-1 and sP-selectin, have also been observed [148].

5.6.1 Regulatory effects of gut microbiota metabolites on lung cancer

The gut microbiota produces a wide range of metabolites, including short-chain fatty acids (SCFAs), secondary bile acids (SBAs), bacteriocins, phenylpropanoid derivatives, tryptophan metabolites, polyamines, and trimethylamine (TMA) [151]. Among these metabolites, SBAs and SCFAs may represent the most biologically plausible mediators linking gut microbiota dysbiosis to the initiation and progression of lung cancer [152].

SBAs are derivatives of primary bile acids modified by the gut microbiota. Under normal conditions, they play important roles in maintaining digestive function, gut homeostasis, regulating systemic metabolism, and immunity. Gut dysbiosis may disrupt SBA metabolism, potentially increasing their production [153]. Tang *et al*. found that per standard deviation increase in the concentration of taurodeoxycholic acid 3-sulfate was associated with a 33% elevated risk of lung cancer [154]. In lung cancer, SBAs can activate the TGR5 receptor, which has been associated with advanced tumor stage and poor prognosis, thereby triggering the JAK2/STAT3 signaling pathway and promoting tumor proliferation and metastasis through upregulation of downstream proteins, including Cyclin D1, MMP2/9 [155]. High concentrations of hydrophobic bile acids may induce ROS production, activate NF-κB-dependent inflammatory signaling, and cause oxidative DNA damage, with reported pro-inflammatory and pro-tumor effects. However, mechanistic studies of these effects have primarily focused on intestinal tumors and macrophages, and their relevance to lung cancer remains to be further validated [156, 157].

SCFAs, primarily including acetate, propionate, and butyrate, are key metabolites produced by gut microbiota through fermentation of dietary fiber. They provide energy for colonic epithelial cells and maintain the intestinal barrier. Deficiency of SCFAs disrupts the intestinal barrier, allowing microorganisms and their metabolites (e.g., LPS) to enter the circulatory system [158]. LPS can activate the TLR4/NF-κB pathway, leading to persistently elevated levels of inflammatory cytokines [159, 160].

SCFAs play an important role in immune regulation, primarily by inhibiting histone deacetylase (HDAC). In $CD8^+$ T cells, HDAC inhibition epigenetically upregulates the expression of Interferon-γ (IFN-γ) and granzyme B (GzmB), thereby enhancing cytotoxic activity [161]. HDAC inhibition also upregulates the expression of the transcriptional regulator *ID2*, relieves the inhibition of IL-12 receptor (IL-12R), thereby enhancing IL-12 signaling, and promoting the production of IFN-γ and GzmB through downstream signaling pathways [162]. In regulatory T cells (Tregs), HDAC inhibition enhances FOXP3 expression, promotes Treg differentiation, and facilitates the secretion of inhibitory cytokines such as IL-10 and TGF-β, thereby preventing inflammatory damage caused by uncontrolled immune responses [163]. Furthermore, HDAC inhibition blocks NF-κB signaling, reduces the release of pro-inflammatory cytokines such as TNF-α and IL-6 [164]. Additionally, SCFAs can activate the G protein-coupled receptor GPR43 (also known as FFAR2), which triggers the mTOR/STAT3 pathway to promote Treg differentiation [165]. However, studies indicate that GPR43 expression is minimal in T cells and likely not the primary mechanism involved [166].

A decrease in SCFAs levels may weaken the aforementioned immunoregulatory and anti-inflammatory protective effects, thereby creating a more favorable environment for the development and progression of lung cancer. In vitro experiments have shown that sodium butyrate significantly reduces lung cancer cell viability by inducing apoptosis and modulating immune cell function, suggesting that restoration of SCFA levels may have therapeutic potential [167].

5.6.2 Mechanisms of cardiovascular injury mediated by gut microbiota metabolites

The relationship between the gut microbiota and its metabolites and cardiovascular health has attracted increasing research attention. Current evidence suggests that microbiota-related metabolites, including LPS, SCFAs, SBAs, and trimethylamine N-oxide (TMAO), may contribute to processes such as endothelial dysfunction and vascular remodeling through oxidative stress and inflammatory responses, thereby affecting cardiovascular health [168]. In animal studies, reduced levels of SCFAs have been shown to impair anti-inflammatory and immunoregulatory capacity. Among them, propionate has been reported to alleviate cardiac remodeling, vascular dysfunction, and hypertension in mice through regulatory T cell-mediated anti-inflammatory immunomodulation [169].

Here, the focus is on trimethylamine N-oxide (TMAO). Choline-metabolizing gut bacteria convert

dietary choline into TMA, which is subsequently oxidized in the liver to form TMAO. Gut microbiota dysbiosis may be accompanied by elevated TMAO levels, which have been associated with CVDs, including atherosclerosis, HF, and hypertension [170-172]. Cellular and animal studies have shown that TMAO can upregulate the expression of scavenger receptors such as CD36 in macrophages, promoting oxLDL uptake and foam cell formation [173]. In vascular endothelial cells, TMAO can suppress the SIRT3–SOD2 antioxidant pathway, thereby increasing mitochondrial ROS (mtROS) production and activating the NLRP3 inflammasome, ultimately promoting vascular inflammation [174]. In addition, both TMAO and mtROS can activate the NF-κB and MAPK pathways, promoting vascular inflammation and endothelial injury [175]. In a mouse model, TMAO interferes with the TGF-β/Smad2 signaling by upregulating TGF-βR1, inducing fibroblast transformation and the expression of fibrotic markers α-smooth muscle actin (α-SMA) and type I collagen (COL1A1), thereby promoting myocardial fibrosis [176]. TMAO can also inhibit endothelial nitric oxide synthase activity to impair vasodilation [177], and potentiate angiotensin II–dependent pressor responses [178].

Intervention studies targeting the gut microbiota have provided further mechanistic support. Animal studies demonstrate that probiotics significantly reduce plasma TMAO and cecal TMA levels in mice [179]. Berberine inhibits TMA and TMAO synthesis; atherosclerotic patients taking Berberine experienced a 37% and 35% reduction in plasma TMA and TMAO, respectively [180]. Puerarin also ameliorates atherosclerosis by reducing TMAO production [181]. These findings offer new therapeutic avenues for microbiome-related CVD.

Overall, air pollution–associated gut microbiota dysbiosis may amplify the risk of lung cancer–CVD comorbidity through four interconnected processes: impaired SCFA-mediated intestinal barrier protection and immune regulation, LPS translocation, and increased TMAO production. These processes may converge on several shared pathological mechanisms, including ROS generation, activation of NF-κB and NLRP3 signaling, chronic systemic inflammation, endothelial dysfunction, immune remodeling, and tissue fibrosis. It is worth noting that the evidence supporting the above pathways is derived predominantly from in vitro cellular experiments and animal models, while existing human studies are mainly observational, with some interventional studies providing only indirect support. The causal relationships underlying these pathways remain to be further validated.

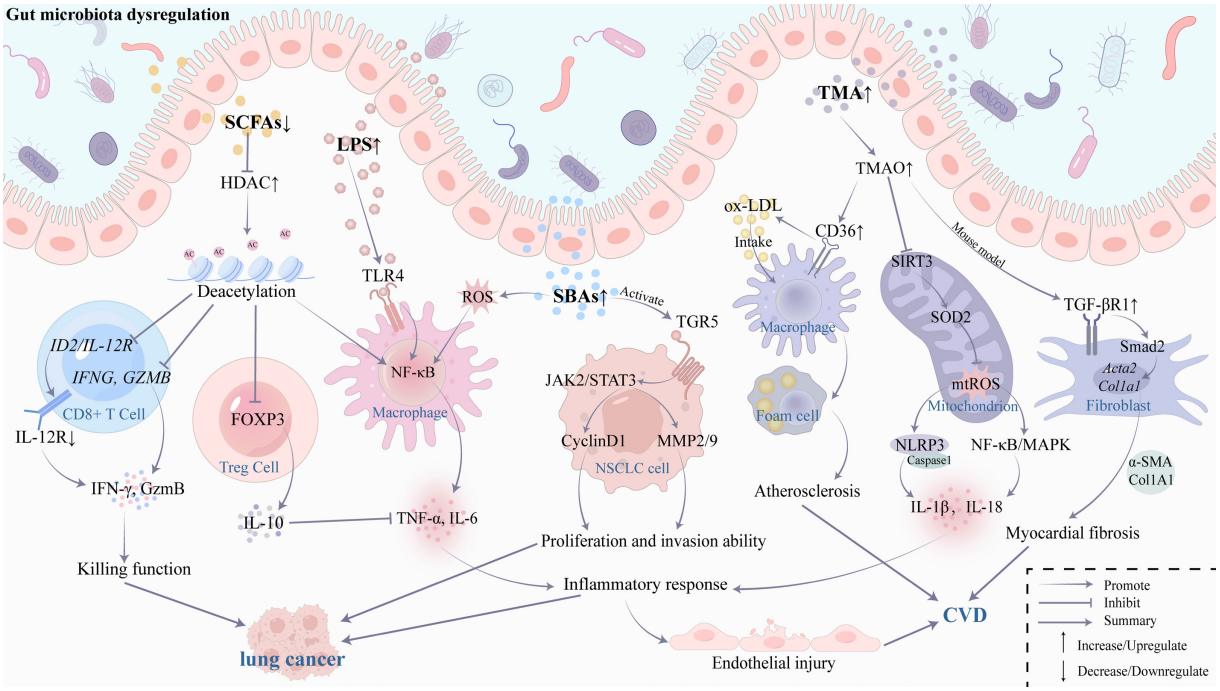


Figure 4. Potential mechanisms by which air pollution-associated gut microbiota dysbiosis may contribute to lung cancer–CVD comorbidity. Air pollution drives gut microbiota dysregulation, characterized by reduced production of short-chain fatty acids (SCFAs), increased generation of trimethylamine N-oxide (TMAO), and elevated systemic levels of secondary bile acids (SBAs) and lipopolysaccharide (LPS). These changes promote lung tumorigenesis by modulating immune function, inducing inflammation, and directly facilitating tumor proliferation and metastasis. Concurrently, they contribute to CVD through mechanisms including chronic inflammation, endothelial injury, atherosclerosis, and myocardial fibrosis. HDAC = Histone Deacetylase, *ID2/IL-12R* = Inhibitor of DNA Binding 2/ Interleukin-12 Receptor, IFN-γ = Interferon-γ, GzmB = Granzyme B, FOXP3 = Forkhead Box Protein P3, TLR4 = Toll-Like Receptor 4, TGR5 = G protein-coupled bile acid receptor 1 (GPBAR1), MMP2/9 = Matrix Metalloproteinase 2/9, ox-LDL = Oxidized Low-Density Lipoprotein; CD36 = Macrophage Scavenger Receptor, SIRT3 = Sirtuin 3, SOD2 = Superoxide Dismutase 2; mtROS = mitochondrial reactive oxygen species, TGF-βR1 = Transforming Growth Factor-β Receptor 1; α-SMA = α-Smooth Muscle Actin; COL1A1 = Type I Collagen (Italicized text represents gene symbols).

5.7 Additional modifiers and vicious cycles

Other pathological states induced by air pollution in the lungs also play significant roles in lung cancer–CVD comorbidity. Alveolar deposition of $PM_{2.5}$ triggers local inflammation and protease–antiprotease imbalance, while long-term exposure is associated with the development of chronic obstructive pulmonary disease (COPD) and progressive decline in lung function [182]. The chronic hypoxia accompanying COPD progression may further activate the HIF-1α signaling pathway, contributing to pulmonary hypertension and subsequently leading to right ventricular remodeling and impaired cardiac function [183]. Hypoxia accelerates tumor growth through multiple mechanisms. Wang *et al*. found that under hypoxic conditions, NSCLC cells release exosomes enriched in circPLEKHM1, which induces M2 macrophage polarization and promotes metastasis [184]. Many CVDs, such as hypertension and CHD, can progress to HF in later stages, which leads to pulmonary congestion, edema, and hypoxia. Similarly, advanced lung cancer causes respiratory dysfunction and hypoxemia, thereby promoting the development of both conditions [134]. This cross-organ influence creates a vicious cycle, typically resulting in poorer prognosis for comorbid patients. Pre-existing metabolic conditions such as hyperglycemia may exacerbate the aforementioned inflammatory responses. Studies indicate that high glucose pre-treatment enhances $PM_{2.5}$-induced IL-1β and ROS generation in these metabolic pathways [185].

The comorbidity state is susceptible to other factors, such as the most common cardiotoxicity associated with cancer therapies. Cytotoxic chemotherapy agents significantly increase the risk of developing CVD [186]. This represents one of the non-negligible factors but must be strictly distinguished from lung cancer–CVD comorbidity under air pollution exposure.

6. Limitations of current evidence: what remains unresolved

The medical costs increase rapidly with each additional chronic disease, highlighting the need for greater attention to the phenomenon of comorbidity [187]. Air pollution is an inevitable consequence of human activity, and its health impacts, as discussed, have been repeatedly confirmed. However, in environmental epidemiology, air pollution exposure cannot be randomly assigned, and lung cancer–CVD comorbidity is characterized by a long latency period. Prospective cohort studies that directly evaluate incident comorbidity as the primary outcome are inherently challenging to conduct. The inference presented here is therefore based on the integration of multiple independent and complementary lines of indirect evidence and should be interpreted with appropriate caution. Current evidence is insufficient to determine whether air pollution simultaneously initiates both diseases, first triggers one disease and subsequently accelerates the development of the other, or merely exacerbates pre-existing disease, ultimately manifesting as comorbidity. Nevertheless, the available evidence provides an important basis for identifying high-risk populations, informing preventive strategies, and guiding future study design. Direct prospective studies using incident lung cancer–CVD comorbidity as the outcome remain necessary to establish causality and to provide a stronger evidence base for prioritizing preventive and intervention strategies.

However, a practical challenge arises in conducting such studies: most patients begin anticancer treatment shortly after being diagnosed with lung cancer, and these treatments themselves may contribute to cardiovascular injury. An important challenge for future cohort studies is how to distinguish cardiovascular risks associated with air pollution exposure from cardiovascular toxicity induced by lung cancer treatment. A feasible approach would be to establish or utilize existing prospective or retrospective population-based cohorts, integrating cancer registry data, medical records, and long-term air pollution exposure data. Following lung cancer diagnosis, patients' cardiovascular status should be assessed, whenever possible, before the initiation of anticancer treatment. If long-term air pollution exposure is associated with pre-treatment CVD status and this association remains after adjustment for smoking, age, and other traditional cardiovascular risk factors, this would provide more direct population-level evidence that air pollution may independently contribute to the development of lung cancer–CVD comorbidity beyond the effects of anticancer treatment. For CVD events occurring after treatment initiation, the timing and type of anticancer treatment should be systematically recorded. After adjustment for long-term air pollution exposure and major cardiovascular risk factors, the risk of CVD should be further compared across different treatment exposure states to determine whether CVD risk increases following the initiation of specific treatments and whether air pollution exposure and treatment-related factors have additive or interactive effects. This approach may help address another important research question: whether environmental exposures can exacerbate treatment-related cardiotoxicity.

Currently, there are technical limitations in air

pollution monitoring. In large-scale epidemiological studies, it is often unavoidable to use fixed-site monitoring values or model-estimated values as proxies for individual actual exposure levels. This error can mislead conclusions when assessing complex outcomes like comorbidity, potentially leading to a severe underestimation of the health effects of air pollution [51]. Additionally, current animal models fail to recapitulate the multifactorial exposure environments experienced by humans or the background of age-related immune senescence, limiting the clinical translation of mechanistic findings.

Effective management of comorbidity relies on early identification. However, the currently proposed biomarkers or predictive models remain mostly candidate directions rather than mature clinical solutions. IL-6, a key inflammatory mediator, has shown potential diagnostic and prognostic monitoring value for lung cancer and CVDs in studies, and theoretically could also serve as a predictor for lung cancer–CVD comorbidity, but its specificity is extremely low [188, 189]. 1-OHP has long been widely used to assess exposure to PAHs. 8-OHdG is a classic product of oxidative damage caused by ROS and is suitable as a risk assessment marker [190]. There have been many studies on epigenetic alterations and exosomes, however, most of these findings remain at the mechanistic level, and evidence for their clinical application is very limited. Some studies have confirmed their potential as biomarkers and therapeutic targets. For example, miR-21 has a dual role in promoting both cancer and vascular injury, and its expression is upregulated upon exposure to air pollution. It has shown good diagnostic performance in trials for lung cancer and CVD, making it a potential biomarker [191, 192].

It is noteworthy that the limited specificity of individual circulating biomarkers may be particularly pronounced in older adults and patients with multiple comorbidities. These populations commonly exhibit inflammaging, metabolic dysregulation, age-related oxidative stress, and exposure to various environmental or lifestyle factors, all of which can generate substantial background signals that interfere with biomarker detection. In this context, the major challenge for the early prediction and clinical translation of comorbidity risk is not simply to identify more powerful biomarkers, but rather to distinguish pollution-related biological perturbations from nonspecific systemic inflammation or oxidative stress. Such discrimination is unlikely to be achieved by any single circulating molecule. A more promising strategy may involve integrating multiple biomarkers or multi-omics profiles that capture distinct pathological processes involved in air pollution-related disease progression. At a minimum, such an approach should encompass two complementary dimensions. The first is the exposure profile, including the intensity, composition, and temporal pattern of air pollution exposure. The second is the biological response profile, including inflammation, oxidative stress, vascular injury, epigenomic alterations, and extracellular vesicle characteristics as potential domains [193]. For example, the lung immune prognostic index (LIPI), composed of routine clinical indicators, can be assessed before treatment. This index reflects the baseline host inflammatory status and has been shown in a meta-analysis to have prognostic predictive value in NSCLC patients receiving immunotherapy [194]. Building on this, combining pretreatment LIPI with air pollution exposure indicators and biomarkers of oxidative stress and vascular injury, together with longitudinal assessment of changes in these parameters, may help facilitate risk stratification and aid in distinguishing treatment-related cardiovascular events.

Emerging disease risk prediction models also provide methodological insights into the potential for clinical translation. For example, Jiang *et al*. developed the UKB-MDRMF model, which integrates multiple types of information, including environmental factors, to enable joint disease prediction and risk stratification across multiple conditions, demonstrating the methodological feasibility of comorbidity prediction models [195]. However, further improvement in the accuracy of air pollution-related comorbidity prediction will require more targeted incorporation of both exposure characteristics and shared pathogenic mechanisms, such as inflammation, oxidative stress, and DNA methylation patterns, as predictive factors. This may facilitate a shift from identifying disease-associated biomarkers alone toward pollution-attributable risk stratification, thereby enhancing the potential clinical utility of such approaches, particularly in older adults and individuals with multiple comorbidities.

The management of CVDs associated with lung cancer treatment typically involves adjusting the anticancer regimen based on the patient's cardiovascular status during therapy. In contrast, comorbidities induced by air pollution require balancing the treatment of both chronic conditions from the outset, with an emphasis on cardiovascular risk monitoring throughout the entire course of lung cancer care.

Currently, drug development targeting air pollution-induced cardiopulmonary injury remains largely focused on anti-inflammatory and antioxidant strategies, and is still in animal experiments or

preclinical exploratory stages. There is a substantial gap in clinical application evidence, and extensive research is needed to evaluate benefits and risks and to expand indications. The classic antidiabetic drug metformin has been found in mouse models to inhibit systemic and pulmonary inflammation, reduce oxidative stress levels, and effectively alleviate $PM_{2.5}$-induced lung injury and cardiac dysfunction [196]. In randomized controlled trials involving patients with atherosclerosis, treatment with the anti-inflammatory drug canakinumab to inhibit the IL-1β inflammatory pathway appeared to reduce the incidence of lung cancer and lung cancer mortality [197]. However, a subsequent phase III clinical trial indicated that canakinumab did not improve progression-free survival or overall survival in patients with lung cancer [198]. Therefore, current evidence does not support the use of canakinumab for the treatment of lung cancer, although its potential role in preventing comorbidities may warrant further investigation.

Furthermore, antioxidant-based interventions targeting oxidative stress present a well-recognized paradox in respiratory oncology. Although antioxidants are theoretically expected to be beneficial, randomized controlled trials have shown that supplementation with exogenous antioxidants, such as β-carotene and vitamin E, can paradoxically increase lung cancer incidence in high-risk populations, including smokers, and has also been associated with an increased risk of cardiovascular mortality [199, 200]. Preclinical studies have further demonstrated that, in KRAS-mutant mouse models of lung cancer, antioxidants such as N-acetylcysteine and vitamin E can promote lung cancer cell proliferation by reducing oxidative stress and suppressing p53 expression [201]. In addition, antioxidant supplementation may promote lung cancer cell metastasis by stabilizing the transcription factor BACH1 and activating glycolysis [202]. Therefore, nonspecific systemic antioxidant supplementation is not recommended as a routine intervention for lung cancer–CVD comorbidity. In particular, indiscriminate antioxidant use should be avoided in high-risk populations.

Based on the shared molecular pathways induced by air pollution that we have summarized, including chronic inflammation, oxidative stress, epigenetic alterations, organ crosstalk, and microbial dysbiosis, from a theoretical perspective, some specific pathways such as IL-6, TNF-α, IL-17/23, MMP-9/12, NF-κB signaling, ROS generation pathways, and gut microbiota dysbiosis may represent potential candidates for therapeutic investigation in air pollution-related lung cancer–CVD comorbidity. Given the antioxidant paradox and the potential risk that antioxidant supplementation may promote the survival and metastasis of tumor cells, interventions targeting ROS should no longer rely on the indiscriminate use of broad-spectrum exogenous antioxidants, but should instead further explore the selective modulation of specific redox signaling pathways. However, to date, no studies have confirmed that targeting these pathways can simultaneously improve clinical outcomes for both diseases, particularly in the context of air pollution exposure.

7. Clinical and public health implications

Regarding air pollution, there are currently well-established recommended measures that may simultaneously reduce the comorbidity burden of lung cancer and CVD, thereby achieving dual health benefits. At the individual level, promoting the use of indoor air purifiers, wearing filtering masks during high-pollution weather, and adopting clean energy stoves can effectively reduce individual exposure risks [203]. Effective source control and policy interventions include establishing low-emission zones, expanding urban green spaces, optimizing urban planning to enhance atmospheric circulation, timely issuing air quality forecasts and warnings, and implementing strict emission controls on industry and vehicles [204].

Several targeted interventions show great promise in the prevention and management of comorbidity but have not yet been incorporated into routine practice: in high-risk residential areas, such as the Wumeng Mountain region with a high prevalence of familial lung cancer, northeastern China where both lung cancer and CVDs are highly prevalent, and heavily polluted regions, there is an urgent need for continuous environmental monitoring and early warnings, along with the use of more precise exposure assessment methods, such as equipping study subjects with personal exposure monitors. High-risk populations should be encouraged to participate in joint screening programs for lung cancer and CVD, especially those with genetic susceptibility. For instance, a single low-dose chest CT scan can simultaneously detect lung nodules and preliminarily assess coronary artery calcification (CAC), offering the potential for early joint screening of lung cancer and CVDs [205]. However, in real-world clinical practice, lung nodule screening itself carries risks of false-positive findings and overdiagnosis. Incidentally detected CAC may prompt additional imaging, specialist referrals, or even invasive investigations, thereby increasing the burden on patients and the consumption of healthcare resources. To date, there is insufficient evidence that incorporating CAC assessment into low-dose CT for lung cancer screening

further reduces all-cause mortality. In addition, standardized reporting criteria, indications for further investigations, and subsequent management pathways for incidentally detected CAC remain insufficiently established. These challenges need to be addressed before this approach can be routinely implemented in clinical practice. Furthermore, tracking the incidence of comorbidities through community health records and improving data on these conditions in these regions is essential.

To translate key research findings into clinical practice in the future, prospective cohort studies in high-exposure populations are needed to systematically track the incidence of comorbidity. Further investigations should also explore the potential value of anti-inflammatory drugs, selective redox pathway modulators, or microbiota-modulating interventions in reducing the risk of air pollution-related comorbidity. It is necessary to leverage multi-omics technologies to further identify biomarkers with high sensitivity and specificity, and to incorporate shared pathogenic mechanisms into comorbidity prediction models, thereby supporting early warning of disease.

In summary, addressing comorbidities under air pollution exposure requires integrating public health policies with clinical diagnosis and treatment, shifting from a linear mindset focused on single diseases and single factors to a systems thinking approach centered on comorbidities and multiple factors, thereby alleviating the burden of comorbidities.

8. Conclusion

Air pollution not only increases the risks of lung cancer and CVD individually, but may also create a shared biological and epidemiological environment that promotes the co-occurrence and mutual aggravation of these two diseases. $PM_{2.5}$ and NO_2 are the most extensively studied pollutants and currently have the strongest evidence suggesting a potential role in promoting lung cancer–CVD comorbidity. Other common pollutants also have some mechanistic and epidemiological support; however, validation from cohort studies remains limited, and findings across studies are not entirely consistent. It should be emphasized that the current evidence mainly supports the biological plausibility and epidemiological possibility that air pollution contributes to lung cancer–CVD comorbidity, while direct evidence is still needed to establish causality. With regard to susceptible populations, individuals of lower socioeconomic status, older age, and those with a genetic predisposition to lung cancer or CVD may represent high-risk groups for comorbidity. Mechanistically, the most well-established pathways involve systemic inflammation, oxidative stress, and tumor-promoting angiogenesis. Organ crosstalk, exosome-mediated signaling, and microbiota dysbiosis, particularly gut microbiota dysbiosis, represent promising mechanisms but require further validation and integration into clinical practice. Future studies are strongly encouraged to investigate the risk of CVD associated with air pollution exposure in lung cancer cohorts, particularly in highly polluted regions or areas with a high incidence of lung cancer, and to conduct prospective cohort studies using comorbidity as a predefined endpoint. In addition, the shared pathogenic pathways underlying these two diseases require further validation, targeted interventions should be explored, and precision strategies for air pollution control and disease prevention should be developed to effectively reduce the overall disease burden.

Abbreviations

AF: Atrial Fibrillation
ACE: Angiotensin Converting Enzyme
BaP: Benzo[a]pyrene
α-SMA: α-Smooth Muscle Actin
CAC: Coronary Artery Calcification
CO: Carbon Monoxide
CVD: Cardiovascular Disease
COL1A1: Type I Collagen
cMSCs: Cardiac Mesenchymal Stromal Cells
CD36: Macrophage Scavenger Receptor CD36
DNMT: DNA Methyltransferase
CRP: C-Reactive Protein
DALYs: Disability-Adjusted Life Years
GPBAR1 (TGR5): G protein-Coupled Bile Acid Receptor 1
GR: Glucocorticoid Receptor
GzmB: Granzyme B
EGFR: Epidermal Growth Factor Receptor
EMT: Epithelial–Mesenchymal Transition
FOXP3: Forkhead Box Protein P3
HPA axis: Hypothalamic-Pituitary-Adrenal Axis
HDAC: Histone Deacetylase
HF: Heart Failure
HR: Hazard Ratio
IL: Interleukin
IQR: Interquartile Range
ID2: Inhibitor of DNA Binding 2
IFN-γ: Interferon-γ
LPS: Lipopolysaccharide
LC: Lung Cancer
LIPI: Lung Immune Prognostic Index
mtROS: Mitochondrial Reactive Oxygen Species
MMP: Matrix Metalloproteinases
NF-κB: Nuclear Factor-κB
NLRP3: NOD-like Receptor Family Pyrin

Domain Containing 3
NO_2: Nitrogen Dioxide
NSCLC: Non-Small Cell Lung Cancer
ox-LDL: Oxidized Low-Density Lipoprotein
O_3: Ozone
PAHs: Polycyclic Aromatic Hydrocarbons
PDE4DIP: Phosphodiesterase 4D Interacting Protein
PM: Particulate Matter
ROS: Reactive Oxygen Species
RR: Relative Risk
SBAs: Secondary Bile Acids
SCFAs: Short-Chain Fatty Acids
SO_2: Sulfur Dioxide
CD40LG: Soluble CD40 Ligand
SIRT3: Sirtuin 3
SOD2: Superoxide Dismutase 2
TMAO: Trimethylamine N-Oxide
TLR4: Toll-Like Receptor 4
TRPV1/A1: Transient Receptor Potential Vanilloid 1 / Ankyrin 1
TRAP: Traffic-Related Air Pollution
TNF: Tumor Necrosis Factor
VOCs: Volatile Organic Compounds

Supplementary Material

Literature search strategy for this review and the epidemiological evidence for the incidence rates of lung cancer and CVDs associated with air pollution. https://www.medsci.org/v23p3822s1.pdf

Acknowledgements

Funding

This work was supported by the National Natural Science Foundation of China (Nos. 82060426, 82272980, and 82360562); the Yunnan Provincial Key Research and Development Program (No. 202403AC100015); the First-Class Discipline Team Construction Project of Kunming Medical University for the Environmental, Genetic, and Lung Cancer Pathogenesis Research Team (Nos. 2024XKTDPY07); the First-Class Discipline Team Construction Project of Kunming Medical University (No. 2024XKTDYS07); the Yunnan Provincial Chest Tumor Prevention and Treatment Research Innovation Team (No. 202405AS350015); the Yunnan Provincial Medical Academic Leader Program (No. D-2025006); the Medical and Health Talent Project of the Yunnan "Xingdian Talent Support Program" (No. XDYC-YLWS-2025-0083); and the Development of Precision Prevention and Full-Cycle Intelligent Management System for Regionally High-Incidence Lung Cancer in Yunnan (No. 202303AC100203).

Author contributions

Y C contributed to conceptualization and funding acquisition; K Y supervised the whole study and contributed to funding acquisition. H Y was responsible for writing the original draft and formal analysis; P L participated in writing the original draft, data curation and literature screening; J Z and D S were involved in visualization and data curation; all authors contributed to writing – review & editing and approved the final manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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