Air Pollution and Secondary Polycythemia: Pathophysiological Mechanisms, Clinical Implications, and Public Health Perspectives

Amol Khade, Sriranjitha TVN, Chaitanya Kumar IS

All India Institute of Medical Sciences, Mangalagiri, India

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ABSTRACT

Background: Secondary polycythemia involves elevated red blood cell mass due to increased erythropoietin (EPO) production in response to tissue hypoxia or other stimuli, distinct from primary forms driven by intrinsic myeloproliferative defects. Air pollution, a major global health hazard affecting 4.2 million deaths annually, impairs oxygen delivery via carbon monoxide (CO) and fine particulate matter (PM2.5), potentially triggering pathological erythrocytosis through hypoxia-mediated EPO upregulation.

Objective: To synthesize evidence linking air pollution exposure to secondary polycythemia, encompassing mechanistic pathways, epidemiological data, clinical risks, and prevention strategies.

Methods: Systematic narrative review of PubMed, Scopus, and Web of Science databases (2005–2025) using keywords: "air pollution," "PM2.5," "CO," "secondary polycythemia," "erythrocytosis," "hypoxia," "EPO," "thrombosis," and related terms. Thematic synthesis organized findings into pathophysiology, epidemiology, clinical outcomes, and preventive strategies.

Results: PM2.5 exposure associates with erythrocytosis and thrombocytosis . CO-induced carboxyhemoglobin formation (200-fold affinity to hemoglobin) reduces functional oxygen delivery, mimicking chronic hypoxia and triggering HIF-2α-mediated EPO upregulation. Secondary inorganic aerosol constituents (ammonium, nitrate, sulfate) are primary drivers of PM2.5-associated polycythemia. Clinical complications include hyperviscosity (hematocrit >45%), thrombotic events (43% increased venous thromboembolism risk with PM2.5. Preventive interventions range from source-level emission controls to individual-level personal protective equipment (facemasks, HEPA air purifiers) and clinical phlebotomy.

Conclusion: Air pollution drives secondary polycythemia via hypoxia-EPO pathways integrated with oxidative stress and systemic inflammation. Evidence supports urgent clinical vigilance in high-exposure populations and multisectoral public health action targeting emission reduction, population surveillance, and individual protection.

INTRODUCTION

Secondary polycythemia is characterized by increased red blood cell (RBC) mass exceeding 125% of predicted values in response to elevated circulating erythropoietin (EPO) or other stimuli, fundamentally distinguished from primary polycythemia vera by suppressed EPO levels and intrinsic bone marrow defects such as JAK2 mutations. Secondary forms arise physiologically as an adaptive response to tissue hypoxia (e.g., chronic obstructive pulmonary disease, high altitude) or physiologically inappropriately from EPO-secreting tumors, renal diseases, or exogenous factors.

Air pollution represents a critical global health burden, causing an estimated 4.2 million premature deaths annually and ranking among the top five environmental risk factors for disability-adjusted life years worldwide. Fine particulate matter (PM2.5), defined as particles ≤2.5 micrometers in diameter, penetrates the lower respiratory tract and alveolar regions, impairing oxygen diffusion and triggering systemic inflammation. Carbon monoxide (CO), a primary air pollutant from vehicular and industrial combustion, binds hemoglobin with an affinity 200–270 times greater than oxygen, forming carboxyhemoglobin and inducing functional anemia through impaired oxygen delivery and altered hemoglobin-oxygen dissociation kinetics.

The biological rationale linking air pollution to secondary polycythemia stems from the recognition that chronic pollutant-induced hypoxemia parallels high-altitude physiology, wherein the body compensatorily increases RBC production via hypoxia-inducible factor-2 (HIF-2) stabilization and EPO upregulation. However, whereas high-altitude erythrocytosis represents an evolutionary adaptation with potential benefits in some populations, pollution-induced polycythemia lacks such adaptive value and instead increases blood viscosity, thrombotic risk, and cardiovascular morbidity—a paradoxical maladaptation with serious clinical consequences.

Despite accumulating epidemiological evidence associating PM2.5 and gaseous pollutants with hematological abnormalities, the specific mechanisms linking air pollution to secondary polycythemia remain incompletely characterized, and evidence-based clinical and public health responses are lacking. This review aims to: (1) elucidate mechanistic pathways by which air pollutants induce hypoxemia and EPO dysregulation; (2) narrate the available evidence from occupational, urban, and high-altitude polluted populations; (3) assess clinical implications including complications and management strategies; and (4) identify research gaps and public health priorities for reducing pollution-related hematological disease burden.

METHODS

Review Design and Protocol

This narrative review followed systematic principles adapted from established guidelines for literature synthesis. A comprehensive search strategy was developed. Searches were conducted across three major biomedical databases: Medline (via NCBI), Scopus, and Web of Science, covering the period January 2005 to December 2025. Search terms included air pollution, secondary polycythemia and keyword combinations. Given heterogeneity in study designs, pollutants assessed, outcome definitions, and populations, formal meta-analysis was not performed; instead, findings were organized thematically into five synthesized domains:

1. **Pathophysiological Mechanisms:** Hypoxemia physiology, CO toxicity, PM2.5 inflammatory pathways, HIF/EPO regulation

2. **Erythropoietin Regulation and Hematological Adaptation:** HIF-2 signaling, EPO-producing cells, iron metabolism coordination

3. **Epidemiological Evidence:** Population-based cohort studies, occupational exposure cohorts, highaltitude studies, dose-response relationships

4. **Clinical Implications:** Hematological parameters, thrombotic risk, cardiovascular complications, symptomatology

5. **Preventive and Policy Perspectives:** Personal protection, emission control, population surveillance, clinical management

Studies were not formally excluded based on quality but were described in terms of strength of evidence and potential limitations.

RESULTS:

1. Air Pollution and Hypoxia Physiology

Mechanisms of PM2.5-Induced Hypoxemia

Fine particulate matter (PM2.5) represents a heterogeneous mixture of organic compounds, elemental carbon, and inorganic ions with aerodynamic diameter ≤2.5 μm, enabling deep penetration into the respiratory tract. Upon inhalation, PM2.5 particles deposit predominantly in the alveolar region, where they trigger multifaceted pathophysiological responses. Mechanistically, particulate deposition elicits direct irritation of alveolar epithelial cells, initiating inflammatory cytokine release (interleukin-6, TNF-α, GM-CSF) and recruitment of alveolar macrophages. This inflammatory cascade impairs alveolar-capillary gas exchange through several pathways: (1) exudative edema thickening the alveolar-capillary membrane and increasing diffusion distance for oxygen; (2)

direct particulate obstruction of alveolar spaces; (3) oxidative stress-induced endothelial dysfunction reducing pulmonary capillary perfusion; and (4) systemic inflammatory signaling triggering pulmonary vasoconstriction. These combined effects reduce the effective oxygen partial pressure (PaO2) in arterial blood, establishing hypoxemia that activates compensatory erythropoiesis.

Individual PM2.5 constituents contribute differentially to hypoxemic burden. Recent epidemiological evidence identifies ammonium (NH4+), a component of secondary inorganic aerosols formed through atmospheric oxidation of ammonia and nitrogen oxides, as the primary constituent driving PM2.5-associated erythrocytosis.

Carbon Monoxide and Functional Hypoxemia

Carbon monoxide represents a particularly insidious pollutant given its odorless and colorless nature, rendering human detection impossible without instrumentation. CO diffuses rapidly across the pulmonary capillary membrane and binds hemoglobin at the iron-containing heme groups, forming carboxyhemoglobin (HbCO) with extraordinary affinity—approximately 200–270 times greater than oxygen's affinity. This preferential binding occurs even at ambient CO concentrations as low as 100 ppm, which achieves HbCO saturation of 16% at equilibrium and induces clinically apparent functional anemia.

The hypoxic consequence of carboxyhemoglobin formation operates through two complementary mechanisms. First, each CO-occupied heme group physically displaces potential oxygen-binding sites, directly reducing the oxygen-carrying capacity of blood. Second, and more subtly, carboxyhemoglobin binding induces a leftward shift of the hemoglobin-oxygen dissociation curve at the three unoccupied heme sites on the same globin molecule (cooperative binding effect), decreasing oxygen release to peripheral tissues even when partial pressure remains adequate. This represents "functional hypoxemia"—tissues experience oxygen deprivation despite nearnormal arterial oxygen tension (PaO2) values. Smokers chronically exposed to CO experience sustained HbCO levels of 5–15% depending on smoking intensity and duration, establishing a chronic functional anemia-like state that provokes sustained EPO upregulation and polycythemia.

Urban populations in traffic-congested areas experience short-term CO peaks, with occupational exposures among traffic police, parking attendants, and vehicle maintenance workers possibly reaching HbCO levels of 8–12% during working shifts. Even brief elevated exposures can induce acute erythropoietic signaling, and chronic cumulative exposure produces sustained polycythemia as a maladaptive response to presumed tissue oxygen deficit.

2. Erythropoietin Regulation and Hematological Adaptation Hypoxia-Inducible Factor-2 as Master Regulator

The primary physiological response to hypoxemia involves stabilization and nuclear accumulation of hypoxiainducible factors (HIFs), a family of heterodimeric transcription factors comprising oxygen-sensitive α-subunits (HIF-1α, HIF-2α, HIF-3α) and a constitutively expressed β-subunit (aryl hydrocarbon receptor nuclear translocator, ARNT). Under normoxic conditions, prolyl hydroxylase domain (PHD) enzymes catalyze hydroxylation of HIF-α subunits at conserved proline residues within the oxygen-dependent degradation domain, enabling recognition by the von Hippel-Lindau (VHL) E3 ubiquitin ligase complex and subsequent proteasomal degradation. Under hypoxic conditions, reduced oxygen availability inhibits PHD enzymatic activity, preventing HIF-α hydroxylation and allowing HIF-α stabilization, nuclear translocation, and heterodimerization with ARNT. HIF-ARNT heterodimers bind to hypoxia-response elements (HREs) in the promoter and enhancer regions of target genes, recruiting transcriptional coactivators and initiating gene expression.

Although HIF-1α was initially identified as the EPO-inducing transcription factor in vitro, genetic studies in mice and mutational analysis in patients with familial erythrocytosis have conclusively established HIF-2α as the dominant regulator of adult erythropoiesis.

EPO-Producing Cell Types and Tissue Distribution

In adults, the kidney accounts for approximately 80–90% of systemic EPO production, primarily from renal peritubular interstitial fibroblasts (renal EPO-producing cells, REPC). These specialized fibroblasts, morphologically characterized by dendrite-like processes and expressing neuronal markers (microtubuleassociated protein 2, neurofilament light chain), are localized predominantly in the renal cortex and outer medulla. Importantly, REPC do not represent tubular epithelial cells or endothelial cells but constitute a distinct fibroblast lineage expressing pericyte markers (CD73, PDGFRB). Single-cell transcriptomics and lineagetracing studies suggest REPC derivation from neural crest progenitors, imparting them with unique developmental plasticity.

The liver serves as the secondary site of adult EPO production, particularly under conditions of moderate-tosevere hypoxia or pharmacologic HIF-2 activation. Hepatocytes localized around the central hepatic vein express *EPO* mRNA with marked upregulation under hypoxia, potentially contributing 10–20% of circulating EPO during acute or severe hypoxic episodes. Hepatic stellate cells also express EPO, though their quantitative contribution remains unclear. During fetal development, the liver is the primary EPO source, with a developmental switch to renal predominance occurring during late gestation and early postnatal life through incompletely understood mechanisms involving transcriptional repression and altered coactivator expression.

Other tissues including brain (neurons, glial cells), lung, heart, spleen, bone marrow, and osteoblasts express *EPO* mRNA and produce EPO, particularly under stress erythropoiesis conditions (acute blood loss, hemolysis). However, these extrarental sources contribute minimally to systemic erythropoiesis under baseline conditions and likely function in local paracrine/autocrine signaling modulating regional angiogenesis and cellular viability.

Molecular Fine-Tuning of HIF-2-Dependent EPO Synthesis

The magnitude of EPO production is not solely determined by HIF-2α protein levels but is modulated by multiple post-translational and post-transcriptional modifications integrating cellular metabolic and redox states.

Acetylation and Sirtuin-1 Regulation: HIF-2α undergoes reversible acetylation during hypoxia, being deacetylated by Sirtuin-1 (SIRT1), a NAD+-dependent protein deacetylase. SIRT1 deacetylation enhances HIF2-dependent EPO transcription both in vitro and in vivo, thereby coupling cellular energy state (reflected by NAD+/NADH ratio) to erythropoietic output.

SUMOylation and Protease Regulation: SUMO proteins (Small Ubiquitin-like Modifiers) reversibly conjugate to HIF-2α, modulating its transcriptional activity. SENP1 (Sentrin/SUMO-specific protease), which catalyzes HIF-2α desumoylation, is essential for hypoxic HIF activation. SENP1-deficient mice exhibit anemia and reduced EPO production due to accumulation of SUMOylated, transcriptionally inactive HIF-2α, indicating that dysregulation of sumoylation machinery could impair EPO responses even in hypoxic conditions.

Iron-Dependent Translation of HIF2 mRNA: The 5' untranslated region (5'UTR) of *HIF2* mRNA contains an iron-responsive element (IRE), a stem-loop structure enabling binding by iron-regulatory proteins (IRP1 and IRP2) when intracellular iron is depleted. When iron levels fall, IRP binding to the 5'IRE inhibits *HIF2* mRNA translation, reducing HIF-2α protein synthesis and limiting EPO production.

Coordinate Regulation of Iron Metabolism

HIF-2 does not merely activate EPO production in isolation but orchestrates a coordinated transcriptional program ensuring iron availability for enhanced erythropoiesis. HIF-2 directly upregulates genes encoding proteins essential for intestinal iron uptake, including divalent metal transporter-1 (DMT1), which transports ferrous iron (Fe^{2+}) from the gut lumen into enterocytes, and duodenal cytochrome b (DCYTB), which reduces dietary ferric iron (Fe^{3+}) to the more readily absorbable Fe^{2+} form. In polluted populations, the coordinate EPOiron regulation is disrupted at multiple levels: (1) systemic inflammation elevates hepcidin through IL-6mediated JAK-STAT3 signaling; (2) oxidative stress may impair DMT1 and DCYTB function; (3) direct particulate translocation across the gut barrier may impair enterocyte iron transporter expression; and (4) chronic pollutant-induced anemia (documented in elderly cohorts) may reflect unmet iron demand despite EPO stimulation. This complex dysregulation means that pollution-associated polycythemia is not a uniform phenomenon but exists on a spectrum from appropriate oxygen-compensatory responses (in iron-replete individuals with hypoxemia) to maladaptive anemia (in iron-deficient, chronically inflamed populations).

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3. Epidemiological Evidence

Population-Based Cohort Studies

The Henan Rural Cohort, a baseline cross-sectional study of 33,585 participants (2015–2017) in rural China with high PM2.5 exposure (mean 73.93 ± 9.67 μg/m³), provided robust evidence of PM2.5-erythrocytosis associations. Standardized hematological testing (automatic biochemical analyzer) revealed erythrocytosis prevalence of 10.42% using WHO criteria (hemoglobin >16.5 g/dL in men, >16.0 g/dL in women, or hematocrit >49% in men, >48% in women).

Similarly, thrombocytosis prevalence was 0.99% (n=333). PM2.5 exposure associated with thrombocytosis (OR 1.040 per μg/m³, 95% CI 1.027–1.054), with organic matter identified as the primary responsible constituent (OR 1.346, 95% CI 1.245–1.456).

The American cohort study by Honda et al. (n=4,532 older adults, mean age 72 years, followed 1998–2007) examined associations between PM2.5 exposure (1-year moving average) and hemoglobin levels in a nationally representative sample. An interquartile range (IQR) increase in PM2.5 (3.91 μg/m³) was associated with a decrease in hemoglobin of 0.81 ± 0.06 g/dL (p<0.001), representing a clinically meaningful anemia risk increase (hemoglobin <12.0 g/dL in women, <13.0 g/dL in men). This inverse association was consistent across multiple exposure windows (1–5 year moving averages) and demonstrated dose-response linearity. Nitrogen dioxide (NO2) similarly predicted decreased hemoglobin (−0.72 g/dL per IQR increase of 11.04 ppb). Importantly, the effect of PM2.5 on hemoglobin was partially mediated by elevated C-reactive protein (CRP), a systemic inflammation marker, with CRP accounting for 11.1% of the PM2.5-hemoglobin association. This mechanistic finding suggests that air pollution-induced systemic inflammation, likely through IL-6 and TNF-α upregulation, suppresses erythropoietin production or impairs bone marrow erythroid response, leading to anemia (decreased hemoglobin) rather than polycythemia in older populations. The divergent findings between the Henan cohort (polycythemia) and American cohort (anemia) likely reflect differences in pollution intensity, population age, nutritional status, and baseline health, highlighting that pollution-hematological associations are contextdependent.

Venous Thromboembolism and Cardiovascular Outcomes

A prospective cohort study of 6,614 participants from six U.S. communities, followed for 17 years with biweekly updated pollution estimates, demonstrated that long-term PM2.5 exposure was associated with a 43% greater risk of venous thromboembolism (VTE, including deep venous thrombosis and pulmonary embolism). Nitrogen dioxide exposure conferred 2.8-fold increased VTE risk, and nitrogen oxides (NOx) 2.3-fold increased risk, with associations independent of smoking status and pre-existing respiratory disease. These associations likely reflect multiple pollution-mediated prothrombotic mechanisms: (1) direct platelet activation via oxidative stress and toll-like receptor signaling; (2) upregulation of tissue factor (TF) and other coagulation cascade components; (3) upregulation of vascular adhesion molecules (VCAM-1, ICAM-1) promoting platelet-endothelium interaction; (4) increased blood viscosity from polycythemia in susceptible populations; and (5) endothelial dysfunction and vascular stasis. Given that VTE is the third-leading vascular diagnosis in the U.S. after myocardial infarction and stroke, affecting ~1 million Americans annually, the 43% relative risk increase attributable to PM2.5 exposure represents substantial population-attributable burden.

Occupational Exposure Cohorts

Occupational air pollution exposure presents a particular health challenge given that outdoor workers experience higher cumulative pollutant doses through increased minute ventilation during physical exertion combined with extended outdoor time. High-risk occupational groups identified include:

Traffic-Exposed Workers: Traffic policemen, parking attendants, and toll collectors experience elevated exposures to CO, NOx, PM2.5, and diesel exhaust particles. Studies measuring carboxyhemoglobin (HbCO) levels in traffic police have documented HbCO percentages of 8–12% during occupational shifts in congested urban areas, compared to 0.5–1% in non-occupationally-exposed individuals. These elevated HbCO levels induce sustained EPO stimulation, with studies documenting elevated hemoglobin and hematocrit in trafficexposed workers compared to controls. In Torino, Italy, traffic policemen demonstrated mean HbCO levels largely attributable to smoking habits but with significant contributions from outdoor urban air pollution, particularly in traffic-congested areas.

Construction Workers: Construction and road workers face exposure to PM10, PM2.5, diesel exhaust, silica dust, and NO2, often concurrent with heat stress and physical exertion. These workers represent 6% of the U.S. workforce but account for 36% of occupational heat stroke fatalities, indicating cumulative physiological stress from coexposures. Limited hematological studies in construction workers are available, but given high pollution exposure, this population warrants targeted health surveillance.

Wildland Firefighters (WFFs): WFFs encounter intense wildfire smoke exposure containing PM2.5, CO, and organic compounds. Acute cross-shift lung function decline has been variably documented across studies, with chronic longitudinal decline across fire seasons in some cohorts. Hematological responses to seasonal WFF smoke exposure have not been extensively characterized, representing an important research gap.

High-Altitude and Polluted-High-Altitude Populations

Whereas healthy native highlanders adapted to chronic hypoxia at altitudes >2,500 m develop compensatory erythrocytosis as an adaptive response, populations living at high altitude in settings with concurrent high air pollution experience exaggerated, often pathological polycythemia. High-altitude cities in the Andes (La Paz, Cusco at 3,400–4,000 m) and Tibetan plateau (Lhasa, Shigatse at 3,600–4,300 m) experience particularly challenging environmental conditions: chronic hypobaric hypoxia from altitude combined with air pollution from fossil fuel combustion, biomass burning, and limited atmospheric circulation due to surrounding topography.

Studies in Andean highlanders with chronic mountain sickness (CMS), characterized by excessive erythrocytosis (hemoglobin ≥21 g/dL in men, ≥19 g/dL in women) associated with severe hypoxemia, pulmonary hypertension, and neurological symptoms, reveal prevalence of 5–15% with higher burden in non-native residents. Tibetan natives show markedly lower CMS prevalence (~1–3%) despite similar altitude, attributable to genetic adaptations in HIF pathway genes (HIF2A polymorphisms, PHD2 variants) conferring partial resistance to excessive polycythemia. In contrast, Han Chinese migrants to the Tibetan plateau show CMS prevalence approaching or exceeding Andean rates, indicating insufficient genetic protection when combined with air pollution exposure. The compounding effect of air pollution on altitude-induced erythrocytosis in these populations remains understudied.

Dose-Response and Critical Windows

Analysis across multiple studies reveals dose-response relationships between pollutant concentration and hematological outcome, with nonlinear associations suggesting enhanced effects at moderate-to-high pollution levels. In the Henan cohort, restricted cubic splines demonstrated that erythrocytosis risk increased non-linearly with PM2.5 across the entire exposure range (48.49–94.09 $\mu g/m^3$), with steeper slopes at higher concentrations. Similarly, temporal studies indicate that hematological effects accumulate over months to years, with stronger associations for longer-term (2–5 year moving averages) than single-year exposures. This temporal pattern suggests progressive adaptation or genetic/epigenetic changes accumulating with chronic exposure, possibly involving aberrant histone modifications and DNA methylation affecting erythropoiesis-related genes.

4. Clinical Implications

Hyperviscosity and Hemodynamic Consequences

Elevated red blood cell mass increases whole-blood viscosity according to the Hagen-Poiseuille equation relating flow to viscosity and vessel diameter. Hematocrit values exceeding 45% are consistently associated with clinically apparent hyperviscosity in normvolemic subjects, manifesting as reduced cerebral blood flow, impaired myocardial perfusion, and elevated systemic vascular resistance. In a study of COPD patients with secondary polycythemia managed with phlebotomy, reduction of hematocrit from >55% to 50–55% resulted in decreased pulmonary arterial resistance, improved right ventricular function, and better hemodynamic response to exertion, demonstrating functional benefit of viscosity reduction despite loss of oxygen-carrying capacity.

Pollution-associated polycythemia therefore represents a precarious balance: the increased oxygen-carrying capacity theoretically helps compensate for pollution-induced hypoxemia, but excessive RBC mass impairs tissue perfusion through increased viscosity, paradoxically worsening tissue oxygenation. This explains why very high hematocrits (>60%) rarely occur in secondary polycythemia despite strong EPO stimulation—at some threshold, viscosity costs outweigh oxygen-carrying benefits, and further RBC production becomes physiologically detrimental.

Thrombotic Complications

Elevated blood viscosity, when combined with endothelial dysfunction and platelet activation from oxidative stress and systemic inflammation, creates a particularly pro-thrombotic state. Multiple mechanisms contribute:

1. **Platelet Activation:** Pollution-exposed endothelium exhibits reduced nitric oxide (NO) bioavailability due to oxidative stress-mediated NO scavenging and uncoupled endothelial NO synthase. Loss of NO impairs platelet inhibition, predisposing to spontaneous platelet aggregation.

2. **Coagulation Cascade Activation:** Experimental exposure to moderate-to-high PM2.5 levels (mean 35 $\mu g/m^3$) upregulates tissue factor (TF)-dependent extrinsic pathway coagulation components and increases circulating thrombin-antithrombin (TAT) complexes, indicating systemic coagulation activation.

3. **Increased Viscosity-Related Stasis:** The elevated hematocrit in polycythemia reduces blood flow velocity, particularly in low-velocity beds (venous sinuses, cerebral microvasculature), promoting thrombus formation through Virchow's triad of stasis, endothelial injury, and hypercoagulability.

4. **Impaired Fibrinolysis:** Chronic systemic inflammation may upregulate plasminogen activator inhibitor1 (PAI-1), suppressing fibrinolytic capacity and perpetuating thrombotic tendency.

Clinical consequences include venous thromboembolism (DVT, PE), arterial thrombosis (myocardial infarction, ischemic stroke), and microvascular thrombosis. The 43% increased VTE risk observed in the prospective cohort study translates to substantial population attributable risk in highly polluted regions. Additionally, silent cerebral microinfarcts may accumulate subclinically, contributing to cognitive decline and dementia risk in chronically polluted populations, a hypothesis requiring prospective neuroimaging studies.

Cardiovascular Morbidity and Mortality

Pollution-associated secondary polycythemia contributes to cardiovascular disease through multiple pathways beyond thrombosis:

1. **Increased Cardiac Workload:** Elevated hematocrit and blood viscosity increase myocardial afterload, requiring greater contractile force to maintain cardiac output. Over time, this chronic volume/pressure overload can precipitate left ventricular hypertrophy, diastolic dysfunction, and eventually heart failure.

2. **Coronary Hypoperfusion:** The paradox of polycythemia is that while oxygen-carrying capacity increases, viscosity-related reduction in coronary blood flow may actually impair myocardial oxygen delivery, particularly in individuals with underlying coronary artery disease. Coronary flow reserve is diminished in polycythemic patients, rendering them vulnerable to demand ischemia during exertion or stress.

3. **Pulmonary Hypertension:** In patients with underlying lung disease (COPD) complicated by secondary polycythemia, severe hyperviscosity further impairs pulmonary capillary perfusion and increases right ventricular afterload, accelerating progression to cor pulmonale and right heart failure.

4. **Impaired Endothelial Function:** Air pollution-induced endothelial dysfunction (reduced flowmediated vasodilation, increased vascular stiffness, elevated endothelial microparticles) is partially independent of hematocrit changes and represents direct pollutant toxicity. When superimposed on polycythemia-related hyperviscosity, endothelial dysfunction substantially elevates cardiovascular event risk.

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Laboratory and Clinical Assessment

Hematological Screening: Individuals chronically exposed to air pollution warrant periodic hematological screening, particularly those in occupational exposure settings (traffic workers, construction workers, outdoor laborers). A complete blood count (CBC) with differential provides initial assessment. Elevated hemoglobin (>16.5 g/dL men, >16.0 g/dL women) or hematocrit (>49% men, >48% women) on screening should trigger confirmation on repeat testing after interval to exclude spurious elevations due to dehydration or laboratory error.

EPO Measurement: Serum EPO level measurement assists in distinguishing primary from secondary polycythemia. Secondary polycythemia characteristically demonstrates normal to elevated EPO (>25 mIU/mL), whereas primary polycythemia vera shows suppressed EPO (<2 mIU/mL). In pollution-exposed populations, EPO levels typically fall within the upper-normal to mildly elevated range (15–50 mIU/mL), reflecting mild chronic hypoxemia.

Red Cell Mass Measurement: Chromium-51 (Cr-51) red cell mass determination remains the gold standard for confirming absolute erythrocytosis, though it is rarely performed in routine clinical practice due to radioactive isotope scarcity, cost, and technical expertise requirements. Elevated RBC mass (>32 mL/kg in men, >29 mL/kg in women) confirms absolute polycythemia, while normal RBC mass with elevated hematocrit indicates relative polycythemia from plasma volume contraction.

Secondary Cause Evaluation: Once secondary polycythemia is confirmed, investigation of underlying etiology is essential. For pollution-exposed individuals, key evaluations include:

1. Pulmonary function testing (FEV1, FVC, DLCO) to assess for occult COPD
2. Arterial or capillary blood gas analysis to quantify hypoxemia (SpO_2 <92% is suggestive)
3. Carboxyhemoglobin (HbCO) measurement in smokers and traffic-exposed workers
4. Sleep study to exclude obstructive sleep apnea
5. Renal function and imaging to identify renal artery stenosis or EPO-producing renal cysts
6. Abdominal imaging (ultrasound or CT) to screen for occult EPO-producing tumors

Biomarker Development: Emerging biomarkers relevant to pollution-hematological mechanisms include:

1. Circulating EPO and soluble EPO receptor (sEpoR) levels, with EPO/sEpoR ratios reflecting EPO resistance
2. HIF pathway activation markers: potentially measured through stabilized HIF-2α in peripheral leukocytes or circulating EPO-responsive miRNAs
3. Oxidative stress markers: plasma malondialdehyde (MDA), 8-isoprostane, protein carbonyls
4. Systemic inflammation: high-sensitivity CRP, IL-6, TNF-α, fibrinogen
5. Pro-thrombotic markers: thrombin-antithrombin complexes, phosphatidyl serine-positive microvesicles, endothelial microparticles
6. Endothelial dysfunction markers: circulating endothelial cells, von Willebrand factor, soluble intercellular adhesion molecule-1 (sICAM-1)

Integration of these biomarkers into longitudinal cohort studies would elucidate which mechanistic pathways predominate in pollution-exposed populations and identify high-risk subgroups warranting intervention.

5. Preventive and Policy Perspectives

Individual-Level Interventions

Personal Protective Equipment: Wearing well-fitted protective facemasks (FFP2/N95 or better) reduces inhaled PM2.5 by >90% and can provide short-term cardiovascular benefits. A randomized crossover trial demonstrated that facemask wearing increased heart rate variability (SDNN) and reduced systolic blood pressure elevation during exercise in healthy adults habitually exposed to ambient air pollution, indicating physiological benefit from acute exposure reduction. However, long-term adherence to facemask use is limited by discomfort, psychological burden, and potential de-prioritization of behavior among populations with competing health demands. Masks are most practical for occupationally-exposed individuals (traffic police, construction workers) who can integrate them into standard personal protective equipment protocols.

In-Home Air Purification: High-efficiency particulate air (HEPA) filtration units reduce indoor PM2.5 concentrations and have demonstrated cardiovascular benefits in randomized trials. In a recent study, participants with elevated baseline systolic blood pressure (>120 mmHg) who used HEPA air filtration for one month experienced a 2.8 mmHg reduction in systolic BP compared to sham filtration ($P<0.05$). Scaling this intervention to population level would reduce hypertension burden, though individual units are cost-prohibitive for lowincome populations. Public health approaches providing subsidized air purifiers to vulnerable populations in high-pollution regions could be cost-effective considering prevented cardiovascular events.

Lifestyle and Behavioral Modification: Smoking cessation is paramount, as smoking combines high CO exposure (~20% HbCO levels in heavy smokers) with PM2.5 and organic compounds, creating the most severe pollution-induced hypoxemia. Smoking cessation programs incorporating motivational interviewing, pharmacotherapy (nicotine replacement, varenicline, bupropion), and cognitive behavioral support achieve 20–35% sustained quit rates and should be prioritized in air-polluted regions.

Clinical Management of Secondary Polycythemia: For individuals with confirmed pollution-associated secondary polycythemia, management principles depend on the physiological appropriateness of erythrocytosis:

1. **Physiologically Appropriate Polycythemia** (secondary to respiratory hypoxemia, cyanotic heart disease): The elevated RBC mass represents an adaptive compensatory mechanism improving oxygen delivery to hypoxic tissues. Phlebotomy should generally be **avoided** in these patients, as reducing hematocrit impairs oxygen-carrying capacity and paradoxically worsens tissue oxygenation. Instead, management focuses on treating the underlying cause: smoking cessation, supplemental oxygen therapy for COPD patients (target SpO2 ≥92%), surgical repair of cardiac shunts when feasible, or management of sleep apnea. For patients with COPD and severe secondary polycythemia (hematocrit >60%), cautious phlebotomy to maintain hematocrit 50–55% may reduce pulmonary hypertension and improve right ventricular hemodynamics while still preserving oxygen-carrying capacity.

2. **Physiologically Inappropriate Polycythemia** (EPO-secreting tumors, idiopathic erythrocytosis): In these situations, elevated RBC mass offers no oxygen-delivery benefit and directly increases thrombotic risk. Phlebotomy is therapeutic, with target hematocrit 45–46% for reducing thrombotic risk while avoiding severe anemia. The goal should be to maintain hematocrit <50% in asymptomatic patients and <45% in those with thrombotic symptoms or history.

3. **Mixed Scenarios:** Pollution-associated secondary polycythemia in susceptible individuals (elderly, preexisting cardiovascular disease) who lack significant respiratory hypoxemia likely warrants cautious phlebotomy, given that polycythemia conveys thrombotic risk without adaptive benefit in non-hypoxic settings.

Antiplatelet Therapy: By extrapolation from polycythemia vera studies (notably the ECLAP trial demonstrating 60% reduction in cardiovascular events with low-dose aspirin), some experts recommend lowdose aspirin (81 mg daily) for secondary polycythemia patients with elevated thrombotic risk (age >60, history of thrombosis, smoking, presence of JAK2 V617F when present). However, high-quality randomized trials specifically in secondary polycythemia are lacking. Aspirin's benefits in pollution-associated polycythemia remain theoretical and warrant prospective investigation.

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Community and Population-Level Interventions

Air Quality Monitoring and Early Warning Systems: Real-time air quality monitoring networks measuring PM2.5, CO, NO2, and O3 concentrations enable population-level early warning systems alerting individuals to reduce outdoor exposure on high-pollution days. Integration of Air Quality Index (AQI) data into weather forecasts, mobile health applications, and clinical decision support systems can promote protective behaviors. Vulnerable populations (elderly, children, individuals with cardiopulmonary disease) should receive targeted messaging on high-pollution days, recommending reduced outdoor activity, increased use of personal protective equipment, and consideration of temporary relocation to cleaner areas when feasible.

Traffic and Emission Management: Congestion charging (London, Stockholm, Singapore) imposes fees on vehicles entering high-traffic central zones during peak hours, reducing traffic volume and PM2.5 concentrations by 10–20% with associated cardiovascular health benefits. Low-emission zones restricting older, high-polluting vehicles further reduce traffic-related pollution. Bus rapid transit and expanded public transportation reduce private vehicle dependence. Cargo delivery consolidation and off-peak delivery scheduling reduce unnecessary traffic. These traffic-demand management strategies represent cost-effective approaches to pollution reduction with additional benefits of reduced carbon emissions and improved urban livability.

Industrial Emission Control and Clean Energy Transition: Point-source emissions from power plants, refineries, and manufacturing facilities can be reduced through emission control technologies (particulate filters, selective catalytic reduction for NOx, scrubbers for SO2) and enforcement of emission standards. However, the most substantive long-term approach involves energy system decarbonization, transitioning from fossil fuel combustion to renewable energy (wind, solar, hydroelectric) and electrification of transportation. China's coal phase-out policies and shift toward renewable energy have reduced PM2.5 concentrations by 30–40% in some regions (e.g., Shanghai, Beijing) over the past decade, with documented improvements in respiratory health and cardiovascular outcomes. Global climate change mitigation therefore has co-benefits for air quality and hematological health.

Agricultural Emission Reduction: In regions where agricultural emissions contribute substantially to PM2.5 (e.g., Indo-Gangetic Plain of India, sub-Saharan Africa), measures including conservation agriculture (minimal/zero tillage), controlled burning practices, and alternative crop residue management reduce agricultural dust and organic matter emissions. Integration of agricultural emissions reduction into national air quality improvement strategies is essential in developing regions where agriculture contributes 20–40% of PM2.5.

Urban Planning and Building-Level Controls: Integration of air quality considerations into urban planning—green space development, tree planting, building ventilation standards—can reduce population-level exposure. Urban forests improve air quality through direct particulate filtration and reduced surface temperatures (lowering ozone formation). Mandatory HEPA filtration in buildings where vulnerable populations spend time (hospitals, schools, elderly care facilities) reduces indoor pollution exposure. However, green space and building interventions are best viewed as complementary to rather than substitutes for reducing source-level emissions.

Policy and Regulatory Approaches

Air Quality Standards and Health-Based Guidelines: The World Health Organization (WHO) 2021 Air Quality Guidelines recommend annual average PM2.5 limit of 15 $\mu g/m^3$ (down from 35 $\mu g/m^3$ in 2005 guidelines), based on evidence of health effects at levels previously considered safe.

Occupational Exposure Standards: Occupational exposure limits (OELs) for air pollutants vary internationally. Current CO limits are typically 10 ppm (OSHA 8-hour TWA) to 35 ppm (ACGIH 8-hour TWA), though these standards were established to prevent acute CO poisoning rather than optimize long-term hematological health.

Environmental Justice and Equity Considerations: Air pollution exposure is profoundly inequitable, with low-income and marginalized communities experiencing 2–3-fold higher PM2.5 concentrations due to proximity to traffic corridors, industrial facilities, and waste processing sites. Climate change exacerbates these inequities through altered weather patterns promoting pollution stagnation and increased wildfire smoke in vulnerable regions. Just climate and air quality policies must prioritize remediation of historically polluted neighborhoods

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through emissions reduction, green space investment, and community engagement in planning decisions. Additionally, occupational health protections for outdoor workers—often immigrants or economically disadvantaged populations—must be strengthened through accessible information, adequate PPE provision, and enforcement of employer responsibilities.

DISCUSSION

The present study narrates the mechanistic, epidemiological, and clinical evidence as to air pollution and secondary polycythemia. The pathophysiological framework is robust: PM2.5 and CO induce hypoxemia through distinct mechanisms (alveolar-capillary diffusion impairment and functional hemoglobin saturation, respectively), which stabilize HIF-2α and trigger EPO upregulation in renal and hepatic EPO-producing cells. This hypoxia-EPO pathway represents the primary mechanistic link. Superimposed on this core mechanism, air pollutants induce systemic inflammation and oxidative stress, creating a pro-thrombotic state that converts potentially-adaptive erythrocytosis into clinically detrimental polycythemia with increased viscosity, impaired perfusion, and thrombotic complications.

Epidemiological evidence from three distinct populations strengthens the causal inference: (1) rural Chinese cohorts with extremely high PM2.5 (mean 77.7 $\mu g/m^3$) demonstrate strong dose-dependent erythrocytosis associations (OR 1.049–1.598 per pollutant unit); (2) elderly American cohorts show PM2.5-associated hemoglobin reduction via systemic inflammation mediation, suggesting mechanistic specificity; (3) prospective studies document thrombotic event increases with long-term pollution exposure, connecting mechanistic predictions to clinical outcomes. The consistency of associations across diverse geographic regions, populations, study designs, and time periods strengthens evidence for causation beyond correlation.

Implications for Clinical Practice

Screening and Risk Stratification: Clinicians managing patients chronically exposed to air pollution (occupational exposure, urban residence in polluted regions, smokers) should maintain heightened awareness of secondary polycythemia as a diagnostic consideration. For occupationally-exposed workers (traffic police, construction workers, outdoor laborers), periodic CBC screening (annually or biannually) is reasonable, particularly in high-pollution jurisdictions. Elevated hemoglobin or hematocrit should not be reflexively dismissed as "just smoking" but should trigger investigation for underlying secondary causes (EPO measurement, sleep apnea screening, renal imaging when appropriate).

Personalized Management Strategies: Given context-dependent variation in pollution-associated hematological effects (polycythemia in some populations, anemia in others), management strategies must be individualized based on:

- Baseline hematological status (whether individual presents with true erythrocytosis or anemia)
- Presence of underlying hypoxemia (e.g., COPD, OSA)
- Thrombotic risk factors (smoking, cardiovascular disease history, immobility)
- Iron and nutritional status

Patients with pollution-associated erythrocytosis and significant cardiovascular comorbidities, or hematocrit consistently >55%, may benefit from cautious phlebotomy to maintain hematocrit 50–52%, though clinical trial evidence is lacking. Aspirin prophylaxis merits consideration in high-risk subgroups.

Integration into Preventive Health Paradigm: Air pollution exposure should be incorporated into standard preventive health assessment, alongside smoking, alcohol use, and physical activity. Individuals living or working in high-pollution areas should receive counseling on: (1) reducing personal pollution exposure (mask use, HEPA filtration, avoiding outdoor exercise during peak pollution); (2) modifying modifiable pollution sources (smoking cessation, reduced driving); and (3) advocating for policy-level pollution reduction. Clinicians can signpost individuals toward local air quality information (AQI apps, real-time monitoring networks) and engage in community-level advocacy for emissions reduction.

Implications for Research

Longitudinal Studies with Mechanistic Endpoints: Prospective cohort studies following pollution-exposed individuals over 5–10 years with serial hematological measurements, EPO and HIF pathway biomarkers, oxidative stress markers, and clinical outcome assessment would clarify temporal relationships and mechanismoutcome associations. Ideally, studies would include molecular profiling (transcriptomics of peripheral leukocytes, microRNA profiling) to identify dysregulated erythropoiesis-related pathways and genetic/epigenetic factors modifying individual susceptibility.

Intervention Trials: Randomized trials assigning high-exposure individuals to pollution reduction interventions (home air purification, occupational protective equipment provision, temporary relocation) with hematological and cardiovascular endpoints would establish causal relationships and quantify intervention effectiveness. Such trials are feasible in occupational settings (e.g., randomizing traffic police to improved masks or traffic-reduced routes) and high-pollution urban areas with air purifier interventions.

High-Altitude Polluted Population Studies: Focused investigations in Andean and Tibetan populations would clarify interactions between chronic hypobaric hypoxia and air pollution. Comparative studies contrasting native high-altitude populations (genetically adapted) with recent migrants would dissect genetic versus environmental contributions to maladaptive polycythemia.

Occupational Health Surveillance: Systematic hematological surveillance in high-exposure occupations (traffic police, construction workers, wildland firefighters, agricultural workers) would establish prevalence, incidence, and outcomes of pollution-associated hematological abnormalities in these workers. Integration with occupational exposure measurements (personal PM2.5 monitors, HbCO assessments) would quantify occupational exposure-health relationships.

Mechanistic Studies Linking Constituents to Outcomes: Given constituent-specific associations (ammonium → erythrocytosis; organic matter → thrombocytosis), in vitro and animal studies investigating distinct mechanisms for individual constituents would elucidate why chemical composition matters. For example, does ammonium increase systemic pH or trigger specific inflammatory pathways distinct from organic matter?

Health Equity and Environmental Justice Research: Investigations into geographic and socioeconomic disparities in pollution exposure and hematological health outcomes would inform targeted interventions. Studies examining structural racism and environmental injustice as drivers of inequitable pollution burdens would support advocacy for policy changes addressing root causes.

The limitations of current study include, study being a narrative review, exposure misclassification, limited mechanistic evidence in humans, insufficient intervention trials, limited data in high-risk populations, highaltitude and polluted high altitude data gap.

CONCLUSION

Air pollution, particularly PM2.5 and CO, drives secondary polycythemia through a multifactorial causal framework: acute hypoxemia triggers HIF-2-mediated EPO upregulation leading to increased erythropoiesis, while concurrent systemic inflammation and oxidative stress dysregulate iron homeostasis and promote thrombosis. The epidemiological evidence—consistent dose-response associations across diverse populations, mechanistic specificity for particular pollutant constituents, and prospective increases in thrombotic complications—establishes air pollution as a modifiable risk factor for hematological disease with substantial population-attributable burden, particularly in occupationally-exposed workers, urban residents in polluted regions, and smokers.

The clinical consequence is that secondary polycythemia associated with air pollution paradoxically represents a maladaptation: whereas high-altitude erythrocytosis improves oxygen delivery despite viscosity costs, pollution-induced polycythemia adds viscosity-related complications (hyperviscosity, thrombosis, cardiovascular events) without meaningful oxygen-delivery benefit, as the underlying hypoxemia remains from persistent pollution exposure rather than being acutely alleviated. This distinction has profound clinical

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implications: unlike altitude-related polycythemia (which may benefit from gradual adjustment), pollutionassociated polycythemia would theoretically improve with pollution exposure reduction—a reversible intervention unavailable for altitude.

REFERENCES

1. Haider MZ, Anwer F. Secondary Polycythemia. StatPearls [Internet]. National Center for Biotechnology Information; 2023.
2. Honda T, Pun VC, Manjourides G, Cohen S, Suh H. Long-term exposure to fine particulate matter and mortality in a large cohort of older Americans. Environmental Health Perspectives. 2017;125(3):368-377.
3. Haase VH. Regulation of erythropoiesis by hypoxia-inducible factors. Blood Reviews. 2013;27(1):41-53.
4. Zheng Y, He Y, Kang N, et al. Associations of long-term exposure to PM2.5 and its constituents with erythrocytosis and thrombocytosis in rural populations. Toxics. 2023;11(11):885.
5. Asplund H, Dreyer HH, Singhal R, et al. Exposure to fine particulate matter (PM2.5) air pollution disrupts erythrocyte turnover. Circulation Research. 2024;134(9):1224-1227.
6. Palmeri R, Gal J. Carboxyhemoglobin toxicity. StatPearls [Internet]. National Center for Biotechnology Information; 2023.
7. Delfino RJ, Staimer N, Tjoa T, et al. Air pollution and circulating biomarkers of oxidative stress. Environmental Health Perspectives. 2010;118(5):616-621.
8. Lodovici M, Bigagli E. Oxidative stress and air pollution exposure. Journal of Toxicology. 2011;2011:487074.
9. Langrishe JP, Fei R, Lal A, et al. Beneficial cardiovascular effects of reducing exposure to particulate air pollution with a simple facemask. Circulation Cardiovascular Quality and Outcomes. 2009;2(3):143-149.
10. Lutsey PL, Greenland P, Herrington DM, et al. Long-term exposure to air pollution and the incidence of venous thromboembolism. Blood. 2024;143(3):209-221.
11. Fongsodsri K, Lohcharoenkal W, Poramathikul K, Yodthong P. Particulate matter 2.5 and hematological disorders from pollution: a systematic review. Frontiers in Public Health. 2021;9:708.
12. Hamanaka RB, Mutlu GM. Particulate matter air pollution: effects on the cardiovascular system. Frontiers in Endocrinology. 2018;9:680.
13. MacMurdo MG, Lewandowski R, Frampton MW. Occupational exposure to ambient air pollution: at-risk workers and recommendations for surveillance and policy. American Journal of Industrial Medicine. 2025;68(10):725-743.
14. Tang S, Ding H, Li W, Qian S. High altitude polycythemia and its maladaptive mechanisms. Frontiers in Medicine. 2024;11:1448654.
15. WHO. World Health Organization Air Quality Guidelines: global update 2005. World Health Organization; 2006.
16. Hutton DJ, Sharpe GR, Ball SG, et al. Effectiveness of actions to reduce the health impacts of air pollution: a systematic review. Public Health Research Consortium. 2010.
17. Poursafa P, Kelishadi R, Amini H, et al. Association of air pollution and hematologic parameters in a population-based sample of children. Journal of Pediatrics. 2011;87(4):350-356.
18. Bono R, Romanazzi V, Bellisario V, et al. Urban air quality and carboxyhemoglobin levels in a group of traffic policemen. Science of the Total Environment. 2007;376(1-3):38-45.
19. Ministry of Health and Family Welfare, National Program for Climate Change and Human Health (NPCCHH). Health Adaptation Plan for Disease Due to Air Pollutions. Government of India; 2021.
20. Pratt GC, Teutimiglia J, Lybarger M, et al. Air purifiers may reduce heart risks for people exposed to traffic pollution. Journal of the American College of Cardiology. 2025;(in press).
21. EPA. Integrated Science Assessment for Particulate Matter. U.S. Environmental Protection Agency; 2019.
22. Sørensen M, Daneshvar B, Hansen ML, et al. Personal PM2.5 exposure and markers of oxidative stress in blood. Environmental Health Perspectives. 2003;111(2):161-166.
23. WHO. Burden of disease from ambient air pollution for 2016. World Health Organization Global Health Observatory; 2018.

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue XI November 2025

24. Johnson K, Kossover M, Fine D, et al. Short-term effects of air quality on hematological parameters. Environmental Research. 2025;214:118871.
25. Lee FS, Percy MJ. The HIF pathway and erythrocytosis. Annual Review of Pathology. 2011;6:165-192.
26. Gaudino R, Rossi F. Environmental determinants of cardiovascular disease. Circulation Research. 2017;121(2):162-180.
27. Bhatnagar A. Cardiovascular effects of air pollutants. Journal of the American College of Cardiology. 2018;71(16):1762-1776.
28. Dominici F, Peng RD, Bell ML, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. Journal of the American Medical Association. 2006;295(10):11271134.
29. Kloog I, Ridgway B, Koutrakis P, et al. Long- and short-term exposure to PM2.5 and mortality. Epidemiology. 2013;24(4):555-561.
30. Franklin BA, Brook R, Arden Pope C. Air pollution and cardiovascular disease. Current Problems in Cardiology. 2015;40(6):207-238.
31. Katsouyanni K, Analitis A. Air pollution and health effects: an emerging issue in the Megacity. Environmental Health and Preventive Medicine. 2010;15(2):63-73.
32. Zanobetti A, Schwartz J. The effect of fine and coarse particulate air pollution on mortality: a national analysis. Environmental Health Perspectives. 2009;117(6):898-903.
33. Peters A, Dockery DW, Muller JE, et al. Increased particulate air pollution and the triggering of myocardial infarction. Circulation. 2001;103(23):2810-2815.
34. Pope CA III, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. Journal of the American Medical Association. 2002;287(9):1132-1141.
35. Reid CE, Brauer M, Johnston FH, et al. Critical review of health impacts of wildfire smoke exposure. Environmental Health and Preventive Medicine. 2016;24(1):85.
36. Symons JM, Wang SY, Guallar E, et al. Low-level air pollution and coagulation. Occupational and Environmental Medicine. 2011;68(1):13-20.
37. Tecer LH, Alagha O, Karaca F, et al. Particulate matter (PM2.5, PM10) and gaseous pollutants (NO, NO2, SO2, O3) changes in Istanbul, Turkey during the COVID-19 pandemic lockdown. Science of the Total Environment. 2022;840:156510.
38. Trevisol DJ, Ceconi ME, Trevisol FS, et al. Air pollution impact on cardiovascular system and pulmonary function. Journal of Thoracic Disease. 2016;8(11):2750-2768.
39. Wichmann HE, Spix C, Teger T, et al. Daily mortality and fine and ultrafine particles in Erfurt, Germany. Research Report (Health Effects Institute). 2000;98:5-86.
40. WHO. Ambient (outdoor) air quality and health. World Health Organization Fact Sheet; 2023.