Indoor Air Pollution and Pulmonary Inflammation: Investigating the Associations Between Fine Particulate Matter Exposure and Vascular Dysfunction in Chronic Respiratory Diseases

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Abstract

Fine particulate matter ($PM_{2.5}$) in indoor environments is a persistent exposure in chronic respiratory disease, yet the pathway from inhaled particles to vascular dysfunction remains difficult to characterize because pulmonary inflammation, endothelial activation, medication use, and indoor source dynamics are tightly interwoven. This manuscript develops a methodological and analytical framework for examining whether short-term indoor $PM_{2.5}$ exposure is associated with vascular dysfunction in adults with chronic respiratory disease, and whether pulmonary inflammatory responses act as an intermediate process rather than as a parallel marker of exposure. The contribution is an integrated exposure–dose–mediation design that links indoor concentration reconstruction, deposited dose reconstruction, distributed-lag inflammatory modeling, endothelial endpoint modeling, and bias analysis within a single inferential structure. The framework specifies how source strength, air exchange, penetration, deposition, and time–activity behavior determine indoor $PM_{2.5}$; how inhaled dose differs from fixed-site concentration; and how mediation and measurement-error assumptions alter interpretation of vascular endpoints. Analytical assessment indicates that vascular associations are most defensible when exposure is represented as a time-resolved dose, inflammatory mediators are measured repeatedly, and negative-control and sensitivity analyses are used to separate pulmonary inflammatory processes from direct particle effects. The framework supports more reproducible studies of indoor air pollution and vascular risk in chronic respiratory disease and clarifies the boundary between mechanistic reasoning and observed evidence.

Keywords

indoor $PM_{2.5}$; chronic obstructive pulmonary disease; endothelial function; pulmonary inflammation; exposure reconstruction; causal mediation

1. Introduction

Indoor air pollution is a major component of personal exposure to fine particulate matter, particularly for people who spend long periods indoors because of respiratory symptoms, frailty, or home-based care [1]. Indoor $PM_{2.5}$ is not a simple reflection of outdoor concentration. Particle infiltration, indoor combustion, cooking, cleaning, resuspension, air-exchange behavior, and deposition loss create a distinct exposure profile that can vary sharply

across rooms and hours [2]. Time–activity patterns further determine whether an outdoor or indoor concentration measured at a fixed monitor represents the air actually inhaled by a person with chronic respiratory disease [3]. These features matter because $PM_{2.5}$ is associated with respiratory morbidity and cardiovascular risk at low and moderate concentrations, and the evidence base does not support treating indoor exposures as a minor or interchangeable subset of ambient pollution [4,5].

The biological plausibility of a pulmonary-to-vascular pathway is substantial. Inhaled particles can activate alveolar macrophages and airway epithelial cells, increase oxidative stress, and promote cytokine release, with downstream effects on circulating inflammatory markers, endothelial activation, and vasomotor function [6–8]. Human exposure studies have shown that combustion-related particles can produce rapid changes in vascular function and fibrinolytic balance, although the magnitude and persistence of these changes depend on particle composition, exposure dose, and host factors [7,8]. Epidemiological work has also linked particulate exposure to systemic inflammation and endothelial dysfunction, but the temporal structure is often inferred from sparse repeated measures rather than from a dose reconstruction that reflects indoor source dynamics [9,10]. The pulmonary origin of systemic signals is supported by evidence that particle deposition in the lung can initiate inflammatory cascades that propagate to the circulation, yet the same signals can be influenced by infection, obesity, renal function, and medication [11].

Chronic respiratory diseases add a further layer of complexity. In chronic obstructive pulmonary disease and related conditions, baseline inflammation, impaired gas exchange, comorbidities, and inhaled corticosteroid or bronchodilator use can alter both exposure patterns and vascular endpoints [12,13]. A short-term COPD study reported associations between particulate exposures and biomarkers of systemic inflammation and endothelial activation, which supports the relevance of acute inflammatory and endothelial responses in this population [14]. Endothelial function is an attractive integrative endpoint because it reflects nitric oxide bioavailability, oxidative stress, and vascular repair processes that are plausibly influenced by particle-induced inflammation [15]. However, intervention and panel studies also show that vascular responses can occur rapidly after combustion exposure, raising the possibility of pathways that are not fully captured by measured pulmonary inflammation [16,17].

The central problem is therefore not whether $PM_{2.5}$ can be associated with vascular measures, but how to construct an inferential design that distinguishes a pulmonary inflammatory pathway from confounding and from direct or non-inflammatory particle effects when exposure is indoors, intermittent, and person-specific. This manuscript addresses that problem by developing a methodological framework for studies of indoor $PM_{2.5}$, pulmonary inflammation, and vascular dysfunction in chronic respiratory disease. The contribution is not an empirical estimate of effect. It is a connected analytical design that specifies exposure reconstruction, dose calculation, distributed-lag modeling, mediation analysis, and measurement-error sensitivity in a form that can be implemented with repeated biomarker and endothelial measurements. The framework is intended to make explicit where mechanistic claims are warranted and where observed associations remain compatible with alternative structures.

2. Conceptual Model and Research Question

The research question is whether short-term indoor $PM_{2.5}$ exposure is associated with vascular dysfunction in adults with chronic respiratory disease, and whether pulmonary

inflammation mediates that association after accounting for indoor source patterns, time–activity behavior, disease severity, and medication use. A defensible model must represent four linked domains. The first is the indoor exposure system: outdoor concentration, penetration, air exchange, indoor sources, deposition, and occupant behavior jointly determine the concentration field. The second is the inhaled dose: ventilation rate, exposure duration, and deposition fraction convert concentration into a biologically relevant mass delivered to the respiratory tract. The third is the pulmonary inflammatory response: epithelial and macrophage activation, cytokine release, and systemic inflammatory markers form a candidate mediating pathway. The fourth is the vascular endpoint: brachial artery flow-mediated dilation, reactive hyperemia index, augmentation index, blood pressure variability, or circulating endothelial activation markers may be used, but each captures a different aspect of vascular function.

The conceptual model treats pulmonary inflammation as a candidate mediator rather than as a surrogate for exposure. This distinction is important because a biomarker such as C-reactive protein or interleukin-6 can rise in response to infection, adiposity, renal dysfunction, or medication changes unrelated to $PM_{2.5}$. If the study design does not separate exposure timing from mediator timing, an inflammatory marker may appear to mediate a vascular association when it is actually a consequence of the same upstream confounder. The model therefore requires repeated measures ordered in time: indoor $PM_{2.5}$ should be measured or reconstructed before the inflammatory marker, and the inflammatory marker should be measured before the vascular endpoint when mediation is being evaluated. Cross-sectional measurement of all three domains can describe correlation but cannot support a temporal mediation claim.

A second design principle is that vascular endpoints should be interpreted as integrated physiological states rather than as direct measures of endothelial inflammation. Flow-mediated dilation depends on shear stress, nitric oxide bioavailability, smooth muscle responsiveness, and operator technique. Reactive hyperemia index depends on peripheral microvascular function. Circulating endothelial markers reflect endothelial activation and injury but are not equivalent to vasomotor function. The framework therefore treats vascular endpoints as a family of related but noninterchangeable outcomes and requires that the chosen endpoint be specified before analysis. This prevents selective interpretation of whichever vascular measure shows the strongest association.

3. Methodological Framework

3.1 Indoor $PM_{2.5}$ Exposure Reconstruction

Indoor concentration should be represented as a dynamic quantity rather than as a single household average. At steady state, with constant outdoor concentration, air exchange, penetration, deposition, and indoor source strength, the indoor concentration can be written as a mass-balance expression:

$$C_in = \frac{\left(aPC_out + \frac{S}{V}\right)}{(a+k)}$$

Here C_in is the indoor $PM_{2.5}$ concentration, a is the air-exchange rate, P is the particle penetration factor, C_out is the outdoor concentration, S is the indoor source emission rate, V is the room volume, and k is the deposition loss rate. The expression is not a substitute for time-resolved measurement, but it clarifies why two homes with the same outdoor

concentration can have very different indoor exposures. A high air-exchange rate increases the contribution of outdoor particles and reduces the concentration effect of indoor sources. A low air-exchange rate allows indoor sources to accumulate, while deposition removes particles at a rate that depends on particle size and surface characteristics. Cooking, candle burning, incense, cleaning, and resuspension can create short peaks that are poorly represented by daily averages.

For study design, the mass-balance formulation supports a hybrid measurement strategy. Fixed-site indoor monitors can capture temporal variation, but they must be placed to represent the breathing zone and must record source events. Outdoor monitors can provide a boundary condition when indoor–outdoor ratios are estimated, but they cannot replace indoor measurements in homes with strong indoor sources. Time–activity diaries and occupancy sensors can identify periods when the participant is in the same room as the monitor. If direct indoor monitoring is not feasible, the model can be used to structure a prediction model with measured air-exchange proxies, source indicators, and outdoor concentration, but the resulting exposure estimate should be treated as an input with known error rather than as a gold-standard measurement.

3.2 Inhaled Dose and Pulmonary Inflammatory Load

Concentration alone does not determine the dose delivered to the respiratory tract. The inhaled dose for participant i over a measurement period can be represented as:

$$D_i \;=\; f_dep \int VE_i(t)\; C_in(t)\; dt$$

Here D_i is the deposited dose, f_dep is the deposition fraction for the relevant particle size distribution and breathing pattern, VE_i(t) is the minute ventilation, and C_in(t) is the indoor concentration at time t. The integral is taken over the exposure window of interest. This expression is analytically important because a person with chronic respiratory disease may have altered breathing frequency, tidal volume, and deposition patterns. Exercise, speaking, and respiratory exacerbation can increase ventilation and therefore dose even if concentration is unchanged. The deposition fraction is not a fixed constant; it depends on particle size, hygroscopic growth, airway geometry, and breathing route. For a methodological framework, f_dep should be specified as an assumption or estimated from published deposition models, and sensitivity to that assumption should be reported.

The dose formulation also clarifies why time-resolved exposure is preferable to daily average concentration. A one-hour cooking peak may contribute disproportionately to deposited dose if it coincides with high ventilation. Conversely, a long period of low concentration may be more important for cumulative inflammatory load than a brief peak. The choice of averaging window should therefore be tied to the biological process being studied. If the outcome is endothelial function measured on the same day, short lags are plausible. If the outcome is a circulating inflammatory marker with a half-life of hours to days, a distributed-lag structure may be more appropriate than a single exposure average.

3.3 Distributed-Lag Inflammatory Modeling

Pulmonary and systemic inflammatory responses are unlikely to be confined to a single time point. A distributed-lag model allows the association between dose and an inflammatory marker to vary across exposure lags while adjusting for covariates:

$$E[Y_t \mid D] \;=\; \beta 0 \;+\; \sum (s = 0\ to\ L)\; \beta_s\; D_(t - s) \;+\; \gamma\,^{T} X_t$$

Here Y_t is the inflammatory marker at time t, D_(t-s) is the dose at lag s, L is the maximum lag, β_s is the lag-specific coefficient, X_t is a vector of covariates, and γ is the corresponding coefficient vector. The model is a specification, not a fitted result. Its value is that it forces the analyst to state the exposure window, the lag structure, and the covariate set before interpreting mediation. If the inflammatory marker is measured repeatedly, within-person correlation should be modeled explicitly. If the marker is measured only once, the lag structure cannot be identified and the analysis should be framed as an association rather than as a temporal pathway.

The model also provides a way to examine whether the inflammatory response is sensitive to source composition. A cooking-related indoor peak may contain different particle chemistry from outdoor infiltration, and the inflammatory response may depend on metals, organic compounds, or ultrafine particle fraction. The distributed-lag coefficients should not be interpreted as universal biological constants. They are study-specific estimates that depend on the exposure reconstruction, the biomarker assay, and the population. The framework therefore recommends reporting lag-specific estimates with uncertainty intervals and conducting sensitivity analyses across plausible lag windows.

3.4 Vascular Endpoint and Mediation Model

To examine mediation, the inflammatory marker and the vascular endpoint should be represented in a structural model with explicit temporal ordering. A simple linear formulation for the mediator is:

$$I_i = \alpha 0 + \alpha_D D_i + \alpha_X {}^{T} X_i + \varepsilon_i$$

and for the vascular endpoint:

$$Y_i = \theta 0 + \theta_D D_i + \theta_I I_i + \theta_X {}^{T} X_i + \eta_i$$

Here I_i is the inflammatory mediator, Y_i is the vascular endpoint, D_i is the deposited dose, X_i is the covariate vector, ε_i and η_i are residual terms, and the α and θ parameters describe the exposure–mediator and exposure–outcome relationships conditional on the mediator. The total effect of dose on the vascular endpoint can be decomposed as:

$$TE = \theta_D + \theta_I \alpha_D$$

where TE is the total effect, θ_D is the direct effect not operating through the measured mediator, θ_I is the mediator–outcome association, and α_D is the exposure–mediator association. This decomposition is valid only under strong assumptions: no unmeasured exposure–outcome confounding, no unmeasured mediator–outcome confounding, no exposure-induced confounding of the mediator–outcome relationship, and correct model specification [18]. These assumptions are unlikely to hold exactly in observational indoor air pollution research. The decomposition is therefore best treated as a structured sensitivity analysis rather than as proof that pulmonary inflammation explains the vascular association.

The mediation formulation also clarifies why measuring a single inflammatory marker is insufficient for a strong mechanistic claim. Pulmonary inflammation is multidimensional: neutrophil recruitment, macrophage activation, epithelial cytokine release, oxidative stress, and endothelial activation are related but not interchangeable. A marker such as interleukin-6 may capture one component of the systemic response, while C-reactive protein reflects a downstream hepatic response with a different time course. If the chosen mediator is measured at the wrong time, the estimated indirect effect can be biased toward zero or can reflect

reverse causation. The design should therefore include repeated mediator measurements and should prespecify the primary mediator and the primary vascular endpoint.

3.5 Measurement Error, Confounding, and Sensitivity

Indoor exposure estimates are almost always measured with error. Instrument error, monitor placement, source-event misclassification, and the difference between fixed-site concentration and personal breathing-zone concentration can attenuate observed associations. Under classical additive measurement error, the observed coefficient is related to the true coefficient by an attenuation factor:

$$\beta_o bs = \lambda \beta_t rue, \lambda = \mathrm{Cov}\frac{(T, M)}{\mathrm{Var}}(M)$$

Here β_obs is the estimated coefficient using the observed exposure M, β_true is the coefficient for the true exposure T, and λ is the reliability ratio. If M = T + U with independent error U, then λ is less than or equal to one, and the observed association is attenuated toward the null. The formula is a diagnostic device, not a correction that can be applied without validation data. It indicates why a null vascular association in a study with poor indoor exposure measurement should not be interpreted as evidence of no biological effect. It also indicates why studies using different exposure assessment methods may produce apparently inconsistent results.

Confounding is a second major concern. Disease severity can affect both indoor exposure and vascular function: a person with more severe respiratory disease may spend more time indoors, use more combustion sources for heating, and have greater baseline endothelial dysfunction. Medication use can reduce inflammation and alter vascular tone. Outdoor temperature, humidity, and co-pollutants can affect both indoor concentration and vascular measurements. The framework recommends measuring disease severity, exacerbation history, medication class and timing, home heating and cooking fuel, ventilation behavior, and outdoor co-pollutants. Negative-control outcomes, such as a vascular measure that should not be acutely affected by pulmonary inflammation, can help identify residual confounding. Negative-control exposures, such as indoor particles from a source with low expected toxicity, can help separate source-specific effects from general particulate load.

4. Analytical Assessment

4.1 Mechanistic Plausibility and Endpoint Selection

The strongest version of the pulmonary inflammatory hypothesis requires convergence across three forms of evidence: exposure–mediator association, mediator–outcome association, and temporal ordering. Mechanistic studies support the plausibility of particle-induced oxidative stress and cytokine release, and human exposure studies show that combustion particles can alter vascular function within hours [6–8]. However, plausibility is not the same as demonstrated mediation in a given population. The vascular endpoint should be selected for its sensitivity to the hypothesized pathway. Flow-mediated dilation is sensitive to nitric oxide bioavailability and endothelial health, but it is also sensitive to operator technique, fasting state, temperature, and medication. Reactive hyperemia index is less operator-dependent but captures microvascular function rather than conduit artery function. Circulating endothelial markers are easier to measure repeatedly but may reflect systemic activation rather than local vascular function. A study that uses multiple endpoints should prespecify one primary endpoint and treat the others as secondary.

4.2 Temporal Structure and Distributed Lags

The temporal structure is a central source of inferential fragility. Indoor $PM_{2.5}$ exposure is intermittent, inflammatory markers have different half-lives, and vascular function can change rapidly after exposure. A distributed-lag model is appropriate when repeated exposure and outcome measures are available, but it requires enough observations per person to identify lag-specific effects. If the study has only a few repeated measures, a simpler predefined exposure window may be more defensible than a data-driven lag search. The analysis should not select the lag window that produces the strongest association without accounting for multiple testing. Instead, the lag window should be based on biological reasoning, prior evidence, and the sampling schedule.

The dose formulation adds another temporal consideration. A high indoor concentration during a short cooking event may produce a different inflammatory response than a sustained lower concentration. If the exposure model uses daily averages, it may obscure this distinction. If the model uses hourly data, it may introduce exposure misclassification when the participant is not in the measured room. The framework therefore recommends combining time-resolved monitoring with occupancy information and reporting the proportion of exposure variance attributable to indoor sources. This allows readers to judge whether the exposure metric is appropriate for the proposed biological lag.

4.3 Confounding by Disease Severity, Medication, and Coexposures

Chronic respiratory disease is not a homogeneous condition. COPD, asthma, bronchiectasis, and interstitial lung disease differ in baseline inflammation, airway physiology, and comorbidity profiles [12,13,20]. Disease severity can influence both exposure and outcome. For example, a patient with severe dyspnea may spend more time in a bedroom with a portable heater, increasing indoor $PM_{2.5}$ exposure while also having lower baseline vascular function. If severity is not measured well, the exposure–vascular association may be confounded. Medication is another time-varying confounder. Inhaled corticosteroids can reduce pulmonary inflammation, and bronchodilators can affect heart rate and vascular tone. The analysis should record medication changes and consider them as time-varying covariates rather than as fixed baseline characteristics.

Coexposures are also important. Indoor $PM_{2.5}$ often co-occurs with nitrogen dioxide from gas cooking, carbon monoxide from combustion, and volatile organic compounds from cleaning products. Outdoor $PM_{2.5}$, ozone, and temperature can modify the indoor concentration–response relationship. A study that attributes vascular effects to $PM_{2.5}$ without measuring co-pollutants may overstate specificity. The framework recommends measuring or estimating the most relevant co-pollutants and conducting sensitivity analyses that adjust for them. If co-pollutant data are unavailable, the interpretation should be framed in terms of indoor particulate mixture rather than $PM_{2.5}$ alone.

4.4 Boundary Conditions and Generalizability

The framework has clear boundary conditions. It is designed for short-term repeated-measures studies in adults with chronic respiratory disease. It does not estimate long-term atherosclerotic risk, and it does not replace clinical trials of filtration or source control. The mediation model assumes that the inflammatory marker is measured after exposure and before the vascular endpoint; if the timing is reversed, the decomposition is not interpretable. The measurement-error attenuation formula assumes classical error; if the error is differential with respect to outcome or disease severity, the direction of bias may be different. The dose model

assumes that the deposition fraction can be approximated from published data; if the particle size distribution is highly variable, this assumption should be tested.

Generalizability depends on the indoor source profile. A study conducted in homes with gas cooking, wood heating, or incense burning may not generalize to homes with electric cooking and mechanical ventilation. The framework therefore recommends reporting the source profile, air-exchange conditions, and participant behavior in enough detail to allow comparison across settings. It also recommends reporting the exposure contrast, because a study with a narrow indoor $PM_{2.5}$ range may have limited power to detect a vascular association even if the biological pathway is present.

5. Implications for Study Design and Clinical Interpretation

For study design, the framework supports a repeated-measures panel with three measurement layers. The first layer is time-resolved indoor $PM_{2.5}$ measurement in the breathing zone, complemented by outdoor concentration, indoor source indicators, and occupancy data. The second layer is repeated inflammatory biomarker measurement, with timing chosen to capture the expected pulmonary and systemic response. The third layer is repeated vascular measurement using a prespecified primary endpoint and standardized operator conditions. The analysis should prespecify the exposure window, lag structure, mediator, endpoint, and sensitivity analyses. This reduces the risk of selective reporting and makes the mediation claim falsifiable.

For clinical interpretation, the framework suggests that indoor $PM_{2.5}$ should be treated as a modifiable exposure in chronic respiratory disease, but not as a proven cause of vascular dysfunction in every patient. Source control, ventilation, and filtration can reduce indoor concentrations, and these interventions may be particularly relevant for patients who spend most of their time indoors. However, clinical decisions should not be based on a single inflammatory or vascular measurement. The relevant signal is a consistent pattern across exposure, mediator, and outcome with appropriate temporal ordering and sensitivity to confounding. The framework provides a way to evaluate that pattern without overstating the strength of observational evidence.

6. Conclusion

Indoor $PM_{2.5}$ exposure in chronic respiratory disease is a technically demanding exposure problem because concentration, dose, pulmonary inflammation, and vascular function vary across time and among individuals. This manuscript developed an integrated methodological framework that connects indoor mass balance, inhaled dose reconstruction, distributed-lag inflammatory modeling, mediation analysis, and measurement-error sensitivity. The framework shows why fixed-site concentration is an incomplete exposure metric, why pulmonary inflammation should be treated as a candidate mediator rather than as a proxy for exposure, and why vascular endpoints require prespecification and temporal ordering. It also identifies the assumptions that limit causal interpretation: no unmeasured confounding, correct temporal sequence, reliable mediator and outcome measurement, and adequate exposure contrast. The practical implication is that studies of indoor air pollution and vascular dysfunction in chronic respiratory disease should combine time-resolved indoor measurement with repeated biomarkers and rigorous sensitivity analysis. This design does not guarantee a causal conclusion, but it makes the difference between mechanistic reasoning and observed evidence explicit and therefore improves the reproducibility and interpretive value of future research.

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