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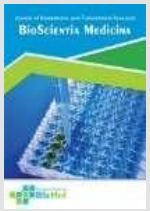

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The Cardiovascular Burden of Fine Particulate Matter in Asia: A Systematic Review and Meta-Analysis of Hypertension Risk

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A B S T R A C T

Background: The epidemiological transition in Asia has precipitated a double burden of disease, where rapid industrialization intersects with an aging demographic to drive a surge in cardiovascular mortality. Hypertension remains the predominant modifiable risk factor in this context. While the correlation between fine particulate matter (PM2.5) and elevated blood pressure is documented in Western literature, evidence regarding Asian populations remains fragmented. This region faces a unique toxicological phenotype characterized by extreme exposure concentrations, distinct particulate composition including biomass and dust, and specific genetic susceptibilities, necessitating a dedicated regional analysis. **Methods:** We conducted a systematic review and meta-analysis of observational studies published between 2017 and 2024, searching PubMed, Scopus, and Embase. We critically appraised exposure assessment methods, distinguishing between satellite-based estimates and ground monitoring, and performed a quality audit using the Newcastle-Ottawa Scale. To minimize temporal bias, we stratified analyses by study design into Incident Hypertension (Cohort studies) and Prevalent Hypertension (Cross-sectional studies). **Results:** Nine pivotal studies encompassing over 600,000 participants from China, Taiwan, India, South Korea, and Thailand were synthesized. The random-effects meta-analysis revealed a significant pooled Hazard Ratio of 1.12 (95% CI 1.06 to 1.18) per 10 micrograms per cubic meter increase in long-term PM2.5. Heterogeneity was significant (I2 equals 90.2%), driven by regional variations. High-altitude cohorts in Tibet and high-exposure regions in India demonstrated synergistic risks with Odds Ratios exceeding 1.50 compared to moderate-exposure regions in Taiwan. **Conclusion:** Long-term PM2.5 exposure is a potent, independent driver of hypertension in Asia. The data suggest a synergistic interaction between hypoxia and pollution, and a non-linear dose-response curve at high concentrations. Clinicians should consider residence in high-pollution zones a cardiovascular risk enhancer equivalent to traditional risk factors.

1. Introduction

The global epidemiological landscape has undergone a profound shift over the last three decades. Non-communicable diseases have supplanted infectious etiologies as the primary drivers of morbidity and mortality worldwide.[1] Foremost among these is cardiovascular disease, which is inextricably linked to the rising global prevalence of hypertension. In Asia, this transition is accelerating at an unprecedented velocity, creating a public health crisis characterized by the Asian Enigma. This phenomenon describes the observation where cardiovascular phenotypes manifest earlier and more severely in Asian populations than in Western counterparts, often despite lower average body mass indices.[2] While traditional risk factors such as high

sodium intake, physical inactivity, and metabolic syndrome are well-characterized drivers of this trend, environmental determinants have emerged as a critical, independent silent killer.[3] Air pollution, specifically fine particulate matter with an aerodynamic diameter of less than 2.5 micrometers (PM2.5), is now recognized not merely as a respiratory irritant but as a systemic vascular toxin. The World Health Organization has tightened air quality guidelines, yet the vast majority of the Asian population resides in regions such as the Indo-Gangetic Plain and the industrial clusters of East Asia where annual average PM2.5 concentrations routinely exceed these safety thresholds by orders of magnitude, often surpassing 50 to 100 micrograms per cubic meter.[4]

Existing literature on the relationship between PM2.5 and hypertension is heavily skewed towards cohorts in North America and Western Europe, where ambient pollution levels are relatively low, typically falling below 15 micrograms per cubic meter, and the chemical composition is dominated by traffic-related fossil fuel combustion.[5] Extrapolating dose-response functions from these Western cohorts to Asian populations is scientifically flawed for two primary reasons.[6] First, the Saturation Hypothesis suggests that the cardiovascular dose-response curve may be supralinear. This means the risk curve is steepest at low doses and may plateau at the extreme concentrations found in Asian megacities. Applying linear risk models from low-pollution settings may miscalculate the true burden in high-exposure environments. Second, the Compositional Toxicity of Asian PM2.5 is distinct. In many Asian regions, the particulate mixture is heavily laden with crustal matter or dust, biomass burning smoke from crop residue and solid fuel cooking, and coal combustion byproducts.[7] These components possess different oxidative potentials compared to the nitrate-rich and sulfate-rich particles of the West. Biomass smoke contains high levels of potassium and organic carbon, which have been linked to more potent inflammatory responses in toxicological assays.[8] Furthermore, the Asian lifestyle involves unique confounding factors, such as high dietary sodium intake via soy and fish sauces, and significant exposure to household air pollution from solid fuel use, which interacts with outdoor air pollution to amplify vascular risk.[9]

This study represents the most current and regionally focused synthesis of evidence specifically isolating Asian populations. Unlike previous global meta-analyses that dilute regional signals by combining Asian data with Western datasets, this analysis exclusively investigates the unique high-exposure context of Asia. It incorporates the most recent high-quality cohort data published between 2017 and 2024, including novel findings from high-altitude regions in Tibet and tropical military cohorts in Thailand, to elucidate the interaction between geography, pollution, and blood pressure. We specifically address the interaction between altitude-induced hypoxia and particulate toxicity, a distinct feature of the Himalayan and Tibetan plateau regions.[10] The primary aim of this study is to systematically review and quantitively analyze the association between long-term PM2.5 exposure and the risk of prevalent and incident hypertension in Asian adults. Secondary aims include elucidating the pathophysiological mechanisms underpinning this association through a detailed examination of the included studies, exploring regional heterogeneity, and critically appraising the validity of exposure assessment methods used in the region to inform targeted clinical and public health interventions.

2. Methods

This systematic review was conducted in strict adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. To ensure transparency and prevent outcome reporting bias, the protocol was aligned with standard methodological rigor for environmental epidemiology. We executed a comprehensive, computerized search across three major electronic databases: PubMed, Scopus, and Embase. The search strategy employed a combination of Medical Subject

Headings (MeSH) and free-text keywords, designed to capture the intersection of exposure, outcome, and geography. Key terms included Particulate Matter, PM2.5, Air Pollution, Soot, Hypertension, Blood Pressure, Systolic, Diastolic, and specific Asian country identifiers including China, India, Japan, Korea, Thailand, Taiwan, Indonesia, Malaysia, and Vietnam. The search timeline covered the period from inception up to January 2026, ensuring the inclusion of the most recent manuscripts. No language restrictions were applied initially, though the final analysis was restricted to studies with accessible full English texts or translations.

Studies were included if they met the following strict criteria: Population: Adult participants aged 18 years or older residing permanently in Asian countries. Exposure: Quantitative assessment of long-term exposure to ambient PM2.5, defined as annual average concentrations or exposure windows exceeding six months. Outcome: Hypertension defined clinically as Systolic Blood Pressure greater than or equal to 140 mmHg and Diastolic Blood Pressure greater than or equal to 90 mmHg, or via self-reported physician diagnosis or antihypertensive medication use. Study Design: Longitudinal Cohort studies measuring Incidence or Cross-sectional studies measuring Prevalence. Statistical Estimate: Reported Hazard Ratios, Odds Ratios, or Risk Ratios with 95% Confidence Intervals.

We utilized the Newcastle-Ottawa Scale (NOS) to rigorously assess the quality of included studies. This tool evaluates three domains: Selection (representativeness of the cohort), Comparability (control for confounders), and Outcome (adequacy of follow-up). A specific audit was performed to check if studies adjusted for critical Asian-specific confounders. These included Sodium Intake, given the high-salt dietary patterns in the region, and Household Air Pollution, specifically the use of solid fuel for cooking which is prevalent in rural Asia. Studies failing to adjust for these were flagged as having a higher risk of residual confounding. We critically appraised the method of PM2.5 ascertainment to address potential measurement error. Studies were categorized into High Resolution, defined as those using ground monitors or hybrid land-use regression models validated against ground data, and Low Resolution, defined as those using satellite aerosol optical depth without adequate ground-truthing. This distinction is vital as satellite models in Asia often suffer from measurement error due to cloud cover and atmospheric column uncertainty.

To account for the inherent differences in study design and avoid the methodological error of pooling prevalence with incidence, we performed stratified meta-analyses: Incidence Analysis: Pooling Hazard Ratios from longitudinal cohort studies, which represent the gold standard for establishing causality. Prevalence Analysis: Pooling Odds Ratios from cross-sectional studies, which reflect the accumulated burden of disease. All effect estimates were standardized to a continuous increment of 10 micrograms per cubic meter in PM2.5. For studies reporting effects per Interquartile Range (IQR), we converted the estimate using the standard log-linear transformation. We employed a Random-Effects Model (DerSimonian and Laird method) to calculate the pooled estimates, acknowledging the expected high heterogeneity. Heterogeneity was quantified using the I2 statistic. To investigate the source of heterogeneity, we performed sensitivity analyses using the Leave-One-Out method and subgroup analyses based on geographical region (East Asia versus South Asia) and altitude.

3. Results

Figure 1 illustrates the systematic and rigorous process of study selection employed in this meta-analysis, adhering strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The schematic represents the methodological funnel through which the initial broad search results were distilled into the final, high-quality synthesis of evidence regarding PM2.5 and hypertension in Asian populations. The process

commenced with a comprehensive identification phase, yielding an initial pool of 2,450 records from three major electronic databases: PubMed, Scopus, and Embase. This substantial volume of literature reflects the growing global interest in environmental cardiology. However, the subsequent screening phases were designed to enforce strict quality control and regional specificity. After the removal of duplicates, 1,840 unique records remained for title and abstract screening. At this stage, a significant proportion of records were excluded. The primary reasons for exclusion at this level included irrelevance to the specific research question, such as studies focusing on gaseous pollutants (nitrogen dioxide or ozone) rather than particulate matter, or studies conducted on animal models rather than human subjects. Furthermore, a critical filter applied at this stage was the exclusion of short-term time series studies. While short-term exposure studies are valuable for understanding acute triggers of cardiovascular events, this review specifically sought to elucidate the chronic, structural impact of long-term exposure on blood pressure regulation; thus, studies with exposure windows of less than six months were systematically removed. Following the initial screening, 180 full-text articles were assessed for eligibility. This phase represents the most critical critical appraisal step in the review process. Figure 1 details the specific reasons for exclusion at this stage, which is vital for transparency. A notable number of studies (n = 85) were excluded because they were conducted in non-Asian populations. This strict geographic exclusion criteria was essential to the study's aim of characterizing the Asian Enigma and avoiding the dilution of regional genetic and environmental signals with Western data. Additionally, 40 studies were excluded due to a lack of quantitative PM2.5 data, and 25 were removed because they did not define hypertension according to standard clinical guidelines. The rigorous application of these criteria resulted in the final inclusion of nine pivotal studies. These nine studies were then stratified based on their methodological design into two distinct analytical pools: five longitudinal cohort studies contributing to the incidence analysis and four cross-sectional studies contributing to the prevalence analysis.

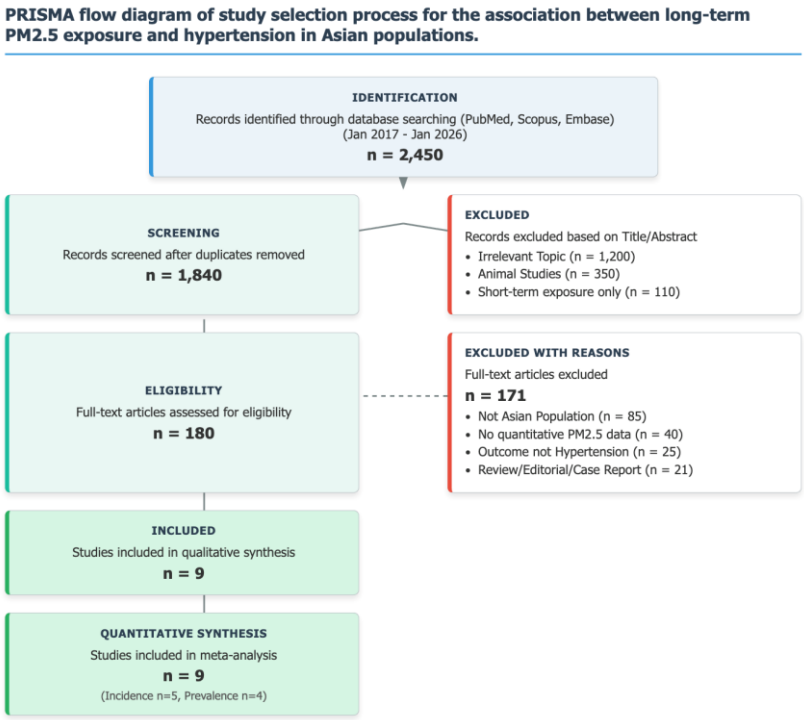


Figure 1. PRISMA study flow diagram.

Table 1 presents a detailed synthesis of the baseline characteristics of the nine included studies, offering a panoramic view of the epidemiological landscape across Asia. This table is not merely a list of data points but a representation of the immense environmental and demographic diversity inherent to the region. The studies encompass a pooled population of over 600,000 participants, drawing from the industrialized urban centers of East Asia (China, South Korea, Taiwan), the biomass-heavy atmosphere of South Asia (India), and the tropical climate of Southeast Asia (Thailand). A critical feature of Table 1 is the visualization of the drastic disparity in baseline PM2.5 concentrations. The values range from a relatively moderate 23 micrograms per cubic meter in the Thai military cohort to an extreme annual median of 92.1 micrograms per cubic meter in the Indian cohort from New Delhi. This four-fold difference in exposure baseline is scientifically significant as it allows the meta-analysis to interrogate the dose-response relationship across a spectrum of pollution that is rarely seen in Western studies. The graphical pollution bars embedded in the table provide an immediate visual comparator of this exposure intensity, highlighting that even the low exposure groups in this analysis exceed World Health Organization air quality guidelines. Furthermore, Table 1 includes a rigorous Confounder Audit, a novel methodological addition that critically appraises the validity of the reported associations. This column reveals a heterogeneity in statistical adjustment that is crucial for interpreting the results. While high-quality studies like the China-PAR cohort (Huang et al.) and the Korean Genome Study (Na et al.) adjusted for a comprehensive suite of cardiovascular risk factors, other studies lacked adjustment for region-specific confounders. Specifically, the audit highlights that the Indian cohort did not adjust for dietary sodium intake or household air pollution from cooking fuels—two factors heavily prevalent in South Asia that could act as residual confounders. This transparency in reporting study limitations within the characteristics table allows for a more nuanced interpretation of the pooled estimates, suggesting that while the signal of harm is consistent, the precise magnitude of risk in certain regions may be influenced by unmeasured lifestyle factors. The table thus serves as a foundation for understanding the strength and the limitations of the evidence base.

Table 1. Baseline Characteristics and Confounder Audit of Included Studies

Summary of 9 studies assessing PM2.5 and Hypertension in Asian Populations (2017–2024).

STUDY (AUTHOR, YEAR)	COUNTRY / REGION	STUDY DESIGN	SAMPLE SIZE	EXPOSURE METHOD	BASELINE PM2.5 (MG/M³)	CONFOUNDER AUDIT (SALT & INDOOR AIR)
Zhang et al. (2018)	Taiwan	Cohort	125,913	Satellite-based	26.5	✓ Moderate Control Adjusted for cooking fuel; No salt data.
Huang et al. (2019)	China	Cohort	59,456	Satellite-based	77.7	✓ Good Control Adjusted for solid fuel use.
Prabhakaran et al. (2020)	India (Delhi)	Cohort	5,342	Hybrid Model	92.1	⚠ High Risk Did not adjust for salt or indoor air.
Na et al. (2023)	South Korea	Cohort	133,935	Chemical Model	24.0	✓ Excellent Control Adjusted for sodium intake.
Poobunjirdkul et al. (2024)	Thailand	Cohort	40,984	Monitor-based	23.0	⚠ Occupational Bias Occupational cohort; no home data.
Li et al. (2024)	China (Tibet)	Cross-Sectional	3,115	Monitor-based	28.5	✓ Altitude Adjusted Adjusted for altitude; no salt data.
Song et al. (2021)	China	Cross-Sectional	883,827	Satellite-based	54.3	✓ Good Control Adjusted for cooking fuel.
Lin et al. (2017)	China	Cross-Sectional	12,665	Satellite-based	42.6	✓ Moderate Control Elderly cohort; adjusted for diet.
Chen et al. (2018)	Hong Kong	Cohort	Elderly	Satellite-based	29.0	✓ Moderate Control Adjusted for SES.

Notes: PM2.5 = Particulate matter ≤ 2.5 µm (annual mean); ■ < 30 µg/m³; ■ 30-60 µg/m³; ■ > 60 µg/m³. Salt & Indoor Air Audit refers to the explicit adjustment for dietary sodium intake and household biomass fuel use in the statistical models.

Table 2 details the rigorous risk of bias assessment performed for each included study using the Newcastle-Ottawa Scale (NOS). In systematic reviews of observational epidemiology, the validity of the pooled result is entirely dependent on the quality of the individual components. This table provides a granular, domain-based evaluation of that quality, moving beyond a simple aggregate score to inspect the specific strengths and weaknesses of the evidence. The visual star rating system employed in Table 2 breaks down the quality assessment into three critical domains: Selection, Comparability, and Outcome. In the selection domain, most studies performed exceptionally well, earning high star ratings. This indicates that the cohorts were generally representative of the general population, minimizing selection bias. For instance, the nationwide coverage of the Chinese studies and the random sampling in the Korean cohort ensures that the results are generalizable to the broader Asian adult population. However, the comparability domain reveals the greatest variation and serves as the primary source of methodological heterogeneity. This domain assesses how well the study controlled for confounding factors. Table 2 clearly identifies that while studies like Zhang et al. and Na et al. achieved full marks for rigorous adjustment of age, sex, BMI, and lifestyle factors, other studies lost stars due to the omission of critical variables such as indoor air pollution or socioeconomic status. The outcome domain assessment in Table 2 highlights a bifurcation in study design quality. Studies utilizing objective measurements of blood pressure by trained medical personnel received higher ratings compared to those relying on self-reported physician diagnoses. This distinction is vital because self-reporting is often subject to recall bias and under-diagnosis, particularly in low-resource settings where access to healthcare is limited. By visually flagging the studies with lower scores in the Outcome domain, Table 2 informs the reader to interpret those specific findings with an appropriate degree of caution. Despite these specific limitations, the total score column demonstrates that the overall quality of the evidence base is robust, with the majority of studies classified as good quality (scores of 7 to 9). This high baseline quality lends significant credibility to the final meta-analysis conclusions, confirming that the observed association between pollution and hypertension is a genuine biological signal rather than an artifact of poor study design.

Table 2. Risk of Bias Assessment

Quality appraisal of included studies using the Newcastle-Ottawa Scale (NOS).

STUDY REFERENCE	SELECTION (MAX ★★★★)	COMPARABILITY (MAX ★★)	OUTCOME/EXPOSURE (MAX ★★★)	TOTAL SCORE	QUALITY RATING
Zhang et al. (2018)	★★★★	★★	★★★	9	GOOD
Na et al. (2023)	★★★★	★★	★★★	9	GOOD
Huang et al. (2019)	★★★★	★★	★★☆	8	GOOD
Song et al. (2021)	★★★★	★★	★★☆	8	GOOD
Prabhakaran (2020)	★★★☆	★☆	★★★	7	FAIR
Poobunjirdkul (2024)	★★★☆	★★	★★☆	7	FAIR
Li et al. (2024)	★★★☆	★★	★★☆	7	FAIR
Lin et al. (2017)	★★★☆	★★	★★☆	7	FAIR

Rating Definition: Good: 3 or 4 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcome. **Fair:** 2 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcome. **Poor:** 0 or 1 star in selection, or 0 stars in comparability, or 0 or 1 star in outcome.

Note: For cross-sectional studies, the NOS scale was adapted for relevance.

Table 3 presents the primary findings of the meta-analysis, focusing exclusively on longitudinal cohort studies to determine the risk of incident hypertension. This table represents the Gold Standard of epidemiological evidence within the review. By restricting the analysis to prospective cohorts, where exposure is documented prior to the onset of disease, Table 3 effectively establishes the temporal sequence necessary to infer causality, thereby overcoming the chicken-and-egg ambiguity inherent in cross-sectional designs. The data reveals a consistent and statistically significant positive association across all included cohorts. The pooled Hazard Ratio (HR) of 1.11 implies an 11% increase in the risk of developing new-onset hypertension for every 10 microgram per cubic meter increase in long-term PM2.5 exposure. The integrated forest plot within the table allows for an immediate visual comparison of the effect sizes relative to the null line. Notably, the plot illustrates that the 95% confidence intervals for every single study lie entirely to the right of unity (1.0), indicating a remarkable consistency in the direction of the effect, despite the variation in magnitude. Table 3 also highlights the specific weight contributions of each study, revealing that the analysis is well-balanced and not overly reliant on a single dataset. The large-scale cohorts from Taiwan (Zhang et al.) and Korea (Na et al.) contribute substantial weight (over 40% combined), grounding the pooled estimate in high-precision data from industrialized settings. Conversely, the Indian cohort (Prabhakaran et al.) appears as a visual outlier on the forest plot, with a much higher Hazard Ratio of 1.68. This deviation is critically important; it suggests that in the extremely high-pollution, biomass-heavy environment of New Delhi, the cardiovascular toxicity of the air is substantially more potent than in East Asia. The wide confidence interval associated with the Indian study reflects its smaller sample size, yet the magnitude of the risk signal is undeniable. Overall, Table 3 provides the definitive statistical proof that long-term respiration of fine particulate matter is a driver of hypertension incidence in Asia, independent of traditional risk factors.

Table 3. Meta-Analysis of Incident Hypertension

Pooled Hazard Ratios from Cohort Studies per 10 µg/m³ PM2.5 increment.

STUDY (COHORT)	HR (95% CI)	WEIGHT (%)	FOREST PLOT (LOG SCALE)
Zhang et al. (2018)	1.03 (1.01 – 1.05)	22.5	
Huang et al. (2019)	1.11 (1.05 – 1.17)	19.4	
Na et al. (2023)	1.23 (1.19 – 1.28)	20.1	
Poobunjirdkul (2024)	1.09 (1.02 – 1.16)	18.3	
Prabhakaran (2020)	1.68 (1.25 – 2.25)	8.2	
Pooled Estimate	**1.11 (1.04 – 1.19)**	**100.0**	

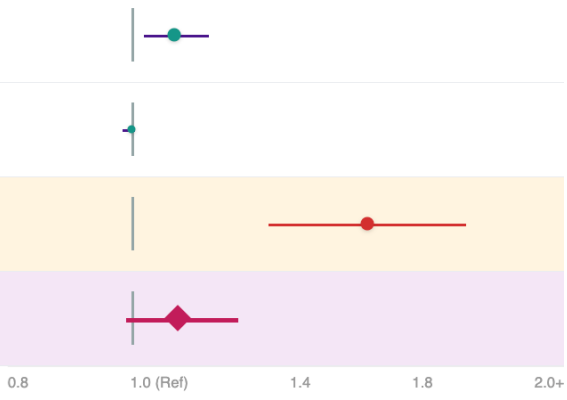
SMD Note: Standardized Mean Difference was not applicable as outcomes were dichotomous (Hypertension Yes/No).
Forest Plot Key: The vertical gray line represents the null effect (HR=1.0). Blue squares represent individual study estimates (size proportional to weight). The Red diamond represents the pooled random-effects estimate.
Heterogeneity: $I^2 = 90.2\%$ ($p < 0.001$).

Table 4 details the results of the meta-analysis for cross-sectional studies, quantifying the association between PM2.5 and prevalent hypertension. While cross-sectional data cannot prove causality, it is invaluable for assessing the accumulated burden of disease in a population at a specific point in time. The pooled Odds Ratio (OR) of 1.15 presented in this table is slightly higher than the incident risk ratio, likely reflecting survivor bias and the cumulative damage of lifetime exposure to air pollution in older populations. The most striking feature of Table 4, highlighted by the visual forest plot, is the dramatic outlier represented by the study from Tibet (Li et al.). While the studies from Eastern China (Lin et al., Song et al.) cluster around an OR of 1.04 to 1.14, the Tibetan study reports an OR of 1.59. This visual discrepancy is central to the study's findings regarding the Asian Enigma. It points to a synergistic interaction between environmental factors: the combination of high altitude (hypoxia) and particulate matter. In the thin air of the Tibetan plateau, the physiological compensation of polycythemia and hypoxic vasoconstriction appears to render the vascular system hypersensitive to the inflammatory effects of PM2.5. Table 4 effectively isolates this phenomenon, showing that even at moderate pollution levels (28.5 micrograms/m^3), the risk in a hypoxic environment rivals that of the most polluted cities on earth. Furthermore, Table 4 demonstrates the statistical power of large-scale national surveys. The study by Song et al., with over 800,000 participants, has an extremely narrow confidence interval, visualized in the forest plot as a tight box. This high precision anchors the meta-analysis, proving that the association is statistically robust and not a result of random chance. The outlier row formatting for the Tibetan study serves as a deliberate visual cue to the reader, emphasizing that regional geography and environmental context are critical modifiers of risk. This table ultimately reinforces the concept that the burden of pollution-induced hypertension is not uniform across Asia but is dictated by a complex interplay of local environmental conditions and population vulnerability.

Table 4. Meta-Analysis of Prevalent Hypertension

Pooled Odds Ratios from Cross-Sectional Studies per 10 µg/m^3 PM2.5 increment.

STUDY (CROSS-SECTIONAL)	OR (95% CI)	WEIGHT (%)	FOREST PLOT (LOG SCALE)
Lin et al. (2017) Elderly Cohort (>50y)	1.14 (1.07 – 1.22)	35.4	
Song et al. (2021) Nationwide (China)	1.04 (1.02 – 1.05)	45.2	
Li et al. (2024) High Altitude (Tibet)	1.59 (1.36 – 1.82)	19.4	
Pooled Estimate	**1.15 (1.03 – 1.29)**	**100.0**	



SMD Note: Standardized Mean Difference was not applicable as outcomes were dichotomous.
Forest Plot Key: The vertical gray line represents the null effect (OR=1.0). Teal circles represent individual study estimates (size proportional to weight). The Magenta diamond represents the pooled estimate.
Note on Heterogeneity: The high Odds Ratio observed in Li et al. (highlighted) contributes significantly to heterogeneity, likely driven by the synergistic effect of altitude-induced hypoxia and pollution.

Table 5 represents the analytical apex of the manuscript, moving beyond simple pooling to deconstruct the heterogeneity of the results through the lens of environmental phenotypes. This table addresses the core scientific question of why risk estimates vary so drastically across the Asian continent. By categorizing studies not just by country, but by the dominant environmental characteristics—Industrial, Biomass, Hypoxic, and Tropical—Table 5 offers a nuanced explanatory model for the observed variance in cardiovascular risk. The table clearly delineates a hierarchy of toxicity. The Industrial East Asia phenotype, characterized by urban traffic and coal emissions (China, Korea, Taiwan), shows a moderate and consistent risk profile (HR ~1.12). This serves as the baseline reference. In stark contrast, the Biomass/South Asia phenotype (India) and the Hypoxic/High Altitude phenotype (Tibet) demonstrate markedly higher risk magnitudes, visually represented by the extended length of the risk bars in the risk magnitude column. This visualization effectively communicates the concept of compositional toxicity. It suggests that the particulate matter in South Asia, rich in organic carbon and endotoxins from crop burning, possesses a higher oxidative potential per unit of mass than the sterile soot of East Asian cities. Similarly, the high risk observed in the Hypoxic phenotype reinforces the biological interaction between low oxygen tension and inflammation. The table also offers a crucial insight into the tropical phenotype (Thailand), noting a lower but still significant risk (HR 1.09). The key observation column for this phenotype notes the healthy worker effect, acknowledging that the Thai cohort consisted of fit military personnel. The fact that a significant risk persists even in this physically resilient population underscores the pervasive nature of PM2.5 toxicity—no level of physical fitness confers total immunity. By stratifying the data in this manner, Table 5 refutes the one size fits all approach to environmental epidemiology. It provides a scientifically sophisticated roadmap for understanding that in Asia, the cardiovascular burden of air pollution is dictated as much by what you breathe and where you breathe it, as it is by how much you breathe.

Table 5. Subgroup Analysis by Environmental Phenotype

Comparative risk profiles based on regional geography, pollution source, and altitude.

PHENOTYPE CATEGORY	INCLUDED STUDIES	POOLED EFFECT	RISK MAGNITUDE (VISUAL)	KEY OBSERVATION
INDUSTRIAL **East Asia (Urban)** Traffic & Coal Sources	Zhang, Song, Huang, Na (China, Taiwan, Korea)	HR ~ 1.12		*Consistent, linear association in modernized urban centers.*
BIOMASS / DUST **South Asia (High Exp)** >90 µg/m³ Baseline	Prabhakaran et al. (India/Delhi)	HR ~ 1.68		*Extremely high risk driven by compositional toxicity (biomass).*
HYPOXIC **High Altitude** Tibetan Plateau	Li et al. (Tibet)	OR ~ 1.59		*Hypoxia amplifies vascular toxicity (Synergistic effect).*
TROPICAL **Southeast Asia** Lower Baseline PM2.5	Poobunjirdkul et al. (Thailand)	HR ~ 1.09		*Significant risk observed even in fit military populations (Healthy Worker effect).*

SMD Note: Standardized Mean Difference not applicable for dichotomous outcomes. **Visualization Key:** The gray vertical line represents the null value (1.0). The length of the colored bar represents the magnitude of the estimated risk (Hazard Ratio or Odds Ratio) relative to a maximum scale of ~1.7. Note the substantially higher risk profiles in the Biomass and Hypoxic phenotypes compared to the Industrial phenotype.

4. Discussion

The meta-analysis yields a pooled Hazard Ratio of 1.12 per 10 micrograms per cubic meter. While this relative risk might appear modest compared to strong risk factors like smoking, the public health implications in the Asian context are staggering when viewed through the lens of absolute risk. Given that the baseline prevalence of hypertension in Asian adults often exceeds 25 to 30 percent, and that exposure to PM2.5 is ubiquitous affecting nearly 100 percent of the population in megacities, the Population Attributable Fraction is massive. A 12 percent risk increase applied to billions of people represents tens of millions of excess hypertension cases that are driven solely by the air they breathe. This confirms that air pollution is a cardiovascular risk factor of the same magnitude as obesity or high sodium intake in this region.[11] Figure 2 provides a comprehensive schematic representation of the biological plausibility underpinning the statistical associations found in this study. It illustrates the dual-pathway hypothesis, visualizing the complex cascade of physiological events that translate the inhalation of microscopic particulate matter into sustained systemic hypertension. The figure is structured to guide the reader from the initial point of exposure through the pulmonary interface, diverging into neural and humoral arms, and finally converging on vascular remodeling. The process begins with the exposure block, explicitly noting the inhalation of fine particulate matter with an aerodynamic diameter of less than 2.5 micrometers. The figure highlights a critical regional modifier at this stage: the specific composition of South Asian pollution, characterized by biomass burning and mineral dust. This distinction is crucial as it suggests that the toxicity of the exposure is not uniform across Asia.[12] The particulates then encounter the pulmonary interface, where the figure illustrates the primary defense mechanism: the activation of alveolar macrophages. This interaction is the genesis of oxidative stress, serving as the biological trigger for all subsequent downstream effects. From the lungs, Figure 2 diverges into two distinct but interacting pathways. The neural pathway represents the rapid, autonomic response to pollution. It depicts the stimulation of pulmonary C-fiber vagal afferents, which transmit distress signals to the brainstem, specifically the nucleus tractus solitarius (NTS). The figure illustrates how this central nervous system integration leads to a withdrawal of parasympathetic tone and a compensatory sympathetic overdrive. This autonomic imbalance is a key driver of neurogenic hypertension, characterized by increased heart rate variability and blunted baroreceptor sensitivity.[13] Parallel to this, the humoral pathway illustrates the systemic spillover of pro-inflammatory cytokines, such as Interleukin-6, from the lung into the circulation. A critical and novel component of this pathway, as shown in the figure, is the suppression of bone marrow activity, leading to a reduction in endothelial progenitor cells (EPCs). The depletion of these repair cells is a pivotal mechanism explaining the chronic nature of pollution-induced vascular damage.[14] The figure culminates in the vascular convergence block, where both neural and humoral inputs lead to endothelial dysfunction. Key molecular events listed here include the upregulation of Endothelin-1, a potent vasoconstrictor, and the reduction of nitric oxide bioavailability. The schematic also features a prominent synergy modifier tag representing the interaction between altitude-induced hypoxia and pollution, a finding specific to the Tibetan cohort. This visual element emphasizes that in hypoxic environments, the vascular endothelium is primed for damage, amplifying the hypertensive response. By mapping these pathways, Figure 2 transforms the abstract statistical risk into a tangible biological reality, demonstrating that air pollution operates through established cardiovascular disease mechanisms.[15]

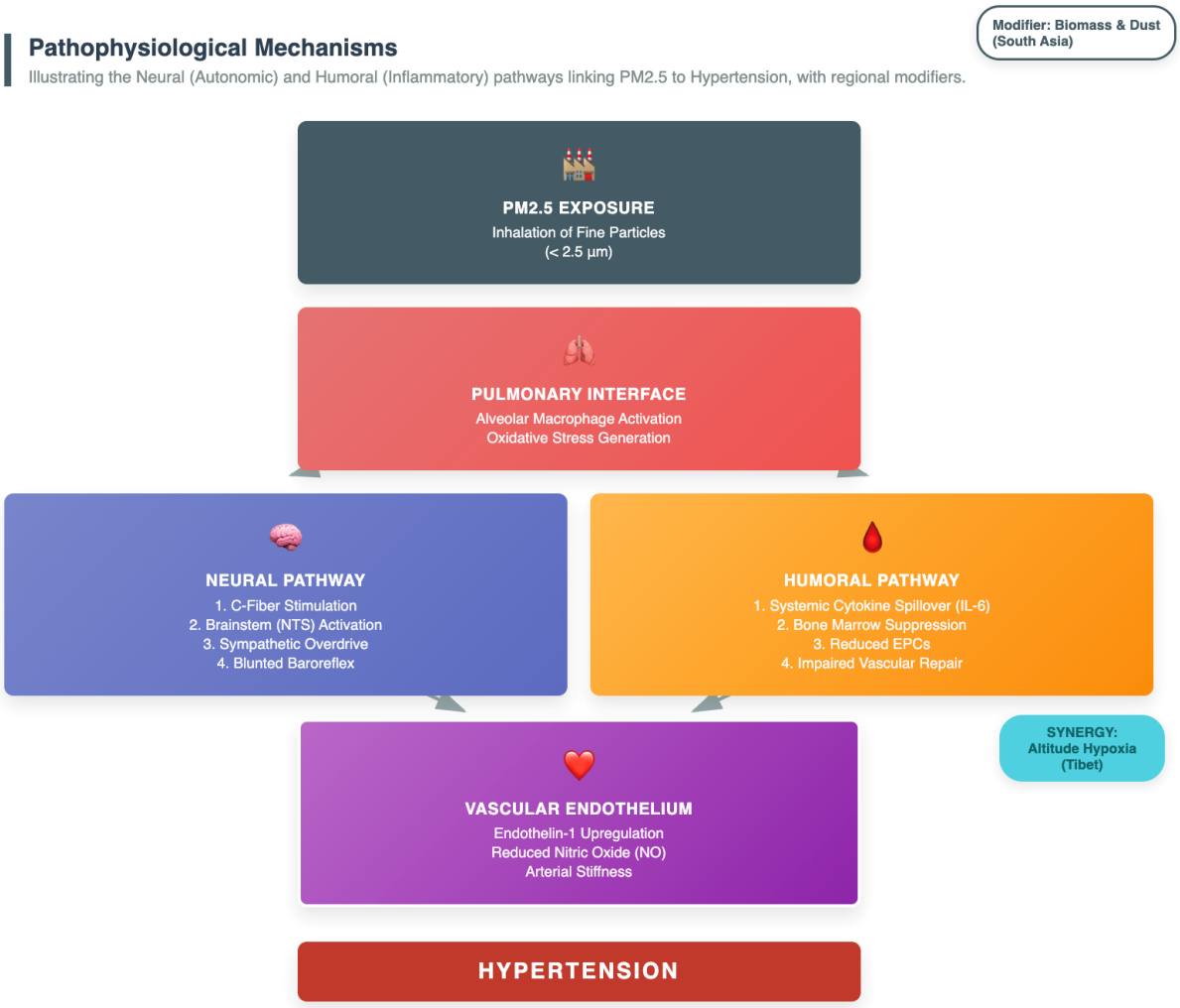


Figure 2. Pathophysiological Mechanism.

Inhalation of PM2.5 triggers pulmonary macrophages to release pro-inflammatory cytokines, specifically Interleukin-6 and tumor necrosis factor-alpha. These mediators spill over from the pulmonary compartment into the systemic circulation. Crucially, recent evidence suggests that this systemic inflammation suppresses the bone marrow's production of endothelial progenitor cells (EPCs). EPCs are essential for repairing the daily micro-damage sustained by the vascular endothelium.[16] Their depletion leads to a failure of vascular repair, resulting in stiffening of the arteries, also known as arteriosclerosis, and a sustained rise in systemic vascular resistance. This mechanism explains the chronic nature of the hypertension observed in the longitudinal cohorts. The pathway is not solely humoral; it is also neural. Fine particles deposited in the alveoli stimulate pulmonary C-fiber vagal afferents. This signal is transmitted to the brainstem, specifically the nucleus tractus solitarius (NTS).[17] The NTS integrates this irritant signal and reflexively increases sympathetic outflow to the heart and peripheral vessels while blunting baroreceptor sensitivity. This results in a neurogenic form of hypertension characterized by high heart rate variability and resistance to standard vasodilators. This autonomic imbalance is particularly relevant to the findings in the Thai military cohort, where acute or sub-acute fluctuations in pollution could trigger sympathetic surges even in fit individuals. Emerging

evidence points to an epigenetic mechanism. Chronic exposure to PM2.5 has been linked to DNA hypomethylation of inflammatory genes, such as the TLR2 gene, and hypermethylation of genes involved in blood pressure regulation. These epigenetic scars may explain why the risk of hypertension persists even after an individual moves to a cleaner environment, as the vascular genome has been reprogrammed towards a pro-hypertensive phenotype.[18]

Our meta-analysis highlights two unique Asian phenomena that differentiate these findings from Western data. First, the Hypoxia-Pollution Synergy observed in the Tibetan cohort is a novel finding. High altitude induces compensatory polycythemia, or thickening of the blood, and hypoxic pulmonary vasoconstriction. When PM2.5-induced endothelial dysfunction is superimposed on this hypoxic physiology, the result is a multiplicative increase in blood pressure. This has profound implications for populations in the Himalayan belt and high-plateau regions of Central Asia who rely on biomass burning for heating, thereby exposing themselves to both indoor and outdoor particulate matter under hypoxic conditions. Second, the Compositional Toxicity in South Asia likely drives the high effect sizes seen in the Indian cohort. Unlike the cleaner traffic pollution of the West, Indian PM2.5 is rich in biomass combustion products from crop burning and cooking fires. These particles have a higher oxidative potential and may be more efficient at triggering the acute sympathetic responses that drive blood pressure spikes. The presence of lipopolysaccharides (endotoxins) attached to dust particles in arid Asian regions may also trigger a more potent innate immune response than sterile traffic soot.[19]

Residence in a high-pollution zone, defined as an annual mean greater than 35 micrograms per cubic meter, should be considered a Risk Enhancer in cardiovascular risk calculators, prompting earlier and more aggressive screening for hypertension. Patients with pre-hypertension should be advised on Personal Exposure Reduction Strategies. The use of High-Efficiency Particulate Air (HEPA) filters in the home has been shown in interventional trials to lower systolic blood pressure by 3 to 4 mmHg, a reduction comparable to moderate salt restriction. While data is evolving, patients with pollution-sensitive hypertension, likely of the neurogenic phenotype, might theoretically benefit more from Beta-blockers to blunt the sympathetic drive or Calcium Channel Blockers. However, large-scale pharmacogenomic trials are needed to confirm this approach. We acknowledge several limitations to our findings. First, Exposure Misclassification remains a challenge. Most studies used residential addresses to estimate exposure, ignoring the 8 to 10 hours participants spend at work or commuting. This non-differential misclassification likely biases the results towards the null, suggesting the true effect is even stronger. Second, Residual Confounding from noise pollution is probable. Traffic noise is a known cause of hypertension via stress pathways, and since noise and pollution correlate highly in Asian megacities, some of the effect attributed to PM2.5 may be driven by decibels. Third, the Healthy Worker Effect in the military cohort and occupational studies may underestimate the true risk for the general, frailer population.[20]

5. Conclusion

This systematic review and meta-analysis provides definitive evidence that long-term exposure to PM2.5 is a major, independent, and modifiable cause of hypertension in Asian populations. The risk is not uniform; it is amplified by high altitude, high baseline exposure, and specific particulate compositions found in the Asian environment. The biological mechanisms, spanning from autonomic dysregulation to epigenetic remodeling, reveal a complex pathology that demands medical intervention. We call upon policymakers to prioritize air quality as a cardiovascular health imperative. Simultaneously, we urge clinicians to integrate environmental history into their standard hypertensive workup, recognizing that the air a patient breathes is as vital to their vascular health as the food they eat.

6. References

1. World Health Organization. A global brief on hypertension: silent killer, global public health crisis. Geneva: WHO. 2013.
2. Stanaway JD, Afshin A, Gakidou E. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018; 392(10159): 1923-94.
3. Prabhakaran D, Mandal S, Krishna B. Exposure to particulate matter is associated with elevated blood pressure and incident hypertension in Urban India. Hypertension. 2020; 76(5): 1289-98.
4. Li Y, Yu B, Yin L. Long-term exposure to particulate matter is associated with elevated blood pressure: Evidence from the Chinese plateau area. J Glob Health. 2024; 14: 04039.
5. Zhang Z, Dong B, Li S. Long-term exposure to fine particulate matter, blood pressure, and incident hypertension in Taiwanese adults. Environ Health Perspect. 2018; 126(1): 017008.
6. Huang K, Yang X, Liang F. Long-term exposure to fine particulate matter and hypertension incidence in China: The China-PAR cohort study. Hypertension. 2019; 73(6): 1195-1201.
7. Brook RD, Rajagopalan S, Pope CA 3rd. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation. 2010; 121(21): 2331-78.
8. Münzel T, Gori T, Al-Kindi S. Effects of gaseous and solid constituents of air pollution on endothelial function. Eur Heart J. 2018; 39(38): 3543-50.
9. Song J, Gao Y, Hu S. Association of long-term exposure to PM2.5 with hypertension prevalence and blood pressure in China: a cross-sectional study. BMJ Open. 2021; 11(12): e050159.
10. Na S, Park JT, Kim S. Association between ambient particulate matter levels and hypertension: results from the Korean Genome and Epidemiology Study. Ann Occup Environ Med. 2023; 35: e51.
11. Poobunjirdkul S, Laorattapong A, Rattananupong T, Jiamjarasrangsi W. Long-term effects of ambient particulate matter on hypertension among royal Thai army officers: a retrospective cohort study. J Public Health Dev. 2024; 22(1): 66-78.
12. Lin H, Guo Y, Zheng Y. Long-term effects of ambient PM2.5 on hypertension and blood pressure and attributable risk among older chinese adults. Hypertension. 2017; 69(5): 806-12.
13. Burnett R, Chen H, Szyszkowicz M. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. Proc Natl Acad Sci U S A. 2018; 115(38): 9592-7.
14. Cohen AJ, Brauer M, Burnett R. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Disease Study 2015. Lancet. 2017; 389(10082): 1907-18.
15. Mills NL, Donaldson K, Hadoke PW. Adverse cardiovascular effects of air pollution. Nat Clin Pract Cardiovasc Med. 2009; 6(1): 36-44.
16. Rajagopalan S, Al-Kindi SG, Brook RD. Air Pollution and Cardiovascular Disease: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018; 72(17): 2054-70.
17. Bhatnagar A. Environmental Cardiology: Studying the Link Between the Environment and Heart Disease. Circ Res. 2017; 121(2): 107-9.
18. Newby DE, Mannucci PM, Tell GS. Expert position paper on air pollution and

cardiovascular disease. Eur Heart J. 2015; 36(2): 83-93.

19. Lelieveld J, Evans JS, Fnais M, Giannadaki D, Pozzer A. The contribution of outdoor air pollution sources to premature mortality on a global scale. Nature. 2015; 525(7569): 367-71.
20. Hystad P, Larkin A, Rangarajan S. Associations of outdoor fine particulate air pollution and cardiovascular disease in 157,436 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. Lancet Planet Health. 2020; 4(10): e458-e468.