Heavy Metals in Human Lung Tissue: Sources, Concentrations, and Health Implications – A Systematic Review

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ABSTRACT

Heavy metals, including chromium (Cr), cadmium (Cd), lead (Pb), nickel (Ni), and arsenic (As), are pervasive environmental pollutants that accumulate in human lung tissue through inhalation from sources such as smoking, industrial emissions, and ambient air pollution. This systematic review synthesizes evidence on metal concentrations in lung tissues across diverse human populations and their associations with respiratory diseases. To systematically review and synthesize data from studies conducted between 1975 and 2025 on the concentrations of heavy metals in human lung tissues, their sources of exposure, and associated health implications. Adhering to PRISMA guidelines, a comprehensive search was conducted across databases including PubMed, Scopus, Web of Science, and Embase, utilizing keywords related to heavy metals and lung tissue. Inclusion criteria encompassed human studies reporting quantifiable metal concentrations and health outcomes. Two independent reviewers screened titles, abstracts, and full texts, with data extracted on population characteristics, metal concentrations, key findings, and study quality. From an initial pool of 1,256 records, 39 studies were included after excluding duplicates, animal studies, and those not meeting quality thresholds (32 human epidemiological/autopsy studies and 7 in vitro studies using human cell lines). Elevated levels of Cd and Pb were strongly associated with smoking and impaired lung function, including chronic obstructive pulmonary disease (COPD) with a pooled odds ratio from meta-analysis of 2.85 (95% CI: 1.34–6.10) for Cd (highest vs. lowest exposure quartile) and 1.73 (95% CI: 1.37–2.18) for Pb. Chromium and Ni exhibited significant correlations with occupational exposures and inflammatory responses. Combined metal exposures demonstrated amplified health risks.

The accumulation of heavy metals in lung tissue contributes significantly to respiratory morbidity. Mitigation strategies, including regulatory measures and smoking cessation initiatives, are imperative. Further longitudinal research on the effects of mixed-metal exposures is warranted.

Keywords: Heavy metals, Lung tissue, Concentrations, Respiratory diseases, Systematic review

INTRODUCTION

Heavy metals represent a persistent environmental hazard due to their bioaccumulative properties, with the respiratory system serving as a primary entry route via inhalation of contaminated air. Key exposure sources encompass tobacco smoke, industrial activities (e.g., welding, mining), urban air pollution, and waste incineration. Prior narrative reviews have suggested associations with respiratory conditions such as COPD, lung cancer, and pulmonary fibrosis; however, a systematic synthesis is required to address potential biases and knowledge gaps.

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This systematic review aims to provide a rigorous, unbiased synthesis of evidence regarding heavy metal concentrations in human lung tissues, population-specific exposure patterns, and associated health outcomes. Initial scoping searches across PubMed and Google Scholar, conducted in September 2025, identified no recent systematic reviews focused on lung-specific accumulation, justifying the present study. The review targets metals including Cr, Cd, Pb, Ni, As, and their mixtures, with an emphasis on their pathological roles in lung tissue. To address limitations in prior syntheses, this review incorporates a meta-analysis where data allow, separates human epidemiological data from in vitro mechanistic evidence, and systematically evaluates methodological variability and confounders.

METHODS

Identifying the Topic and Developing Inclusion/Exclusion Criteria

The research topic was refined following initial scoping searches on PubMed and Google Scholar to evaluate the existing literature on heavy metal accumulation in human tissues. These searches highlighted a paucity of systematic reviews specifically addressing lung tissue, prompting the development of this study.

The PICO framework guided the establishment of inclusion and exclusion criteria:

· **Population/Problem:** Human subjects of any age, gender, or exposure category (e.g., smokers, occupationally exposed individuals, general population).

· **Intervention/Exposure:** Inhalation exposure to heavy metals (Cr, Cd, Pb, Ni, As, and others).

· **Comparator:** Unexposed or control groups where applicable.

· **Outcomes:** Quantifiable concentrations of metals in lung tissue, exposure sources, and health implications (e.g., COPD, cancer, fibrosis).

Inclusion criteria:

- Studies published between 1975 and 2025 to encompass early autopsy data and recent findings.
- Human-based studies (autopsies, cohort studies) for primary synthesis; in vitro models using human cell lines included separately for mechanistic insights.
- Reports of metal concentrations in lung tissue and/or related health outcomes.
- Peer-reviewed articles in English.

Exclusion criteria:

- Studies exclusively involving animal models.
- Research focusing primarily on non-lung tissues.
- Review articles, editorials, or non-empirical publications.
- Studies lacking quantifiable data on concentrations or health associations.

No geographic restrictions were imposed to ensure global representation, though relevance to respiratory health was prioritized.

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Search Strategy

The search was executed in September 2025 across PubMed, Scopus, Web of Science, Embase, and grey literature sources (e.g., Google Scholar for theses and reports). Search terms included: ("heavy metal*" OR chromium OR cadmium OR lead OR nickel OR arsenic) AND ("lung tissue" OR pulmonary OR respiratory) AND (concentration* OR level* OR accumulation) AND (human OR patient* OR autopsy). Boolean operators (AND, OR) and truncation (e.g., "expos*") were employed to enhance specificity and inclusivity. Searches were limited to Title/Abstract/Keywords, with filters applied for English language, peer-reviewed status, and the 1975–2025 timeframe.

Manual searching of reference lists from seminal articles and journals (e.g., Environmental Health Perspectives, Toxicology Letters) supplemented the database search to capture additional relevant studies. The strategy was designed to balance comprehensiveness with precision, minimizing the inclusion of irrelevant literature.

Screening and Extraction

The screening process adhered to PRISMA guidelines. Two independent reviewers conducted initial title and abstract screening, followed by full-text evaluation. Discrepancies were resolved through consensus discussion. Study quality was assessed using the Critical Appraisal Skills Programme (CASP) checklist for cohort and case-control studies, with a threshold of 70% for inclusion; the AMSTAR tool was applied to any secondary reviews.

Data extraction utilized a standardized form capturing:

- Author(s) and publication year.
- Study design and population characteristics.
- Measured metal concentrations.
- Key findings and health implications.
- Study limitations and quality assessment.
- Adjustment for confounders (e.g., age, smoking, socioeconomic status, comorbidities).

A narrative synthesis was performed, with results organized by metal and summarized in tabular format. To address heterogeneity, a meta-analysis was conducted for comparable outcomes (e.g., odds ratios for COPD risk from Cd and Pb exposure) using random-effects models via inverse variance weighting. Heterogeneity was assessed with I^2 statistics. Subgroup analyses considered exposure sources and study types. Methodological variability (e.g., analytical techniques, tissue sampling) was systematically evaluated in a dedicated subsection.

RESULTS

Study Selection

The search yielded 1,256 records. After removing 456 duplicates, 800 titles and abstracts were screened, excluding 680 studies deemed irrelevant or non-human-focused. Full-text review of the remaining 120 studies resulted in 39 inclusions, with exclusions comprising 50 studies focusing on non-lung tissues, 20 of insufficient quality, and 11 duplicates. Of the 39, 32 were human epidemiological/autopsy/cohort studies, and 7 were in vitro using human cell lines. A PRISMA flow diagram is provided (Fig. 1).

Characteristics of Included Studies

The 39 included studies spanned 1975 to 2025, predominantly featuring autopsy and cohort designs (69% of total, all 32 human studies), with in vitro human cell line studies (18%, 7 studies) and cross-sectional surveys (13%). Study populations in human studies included smokers (41%), occupationally exposed individuals (32%),

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and the general population (27%). Quality assessment indicated high reliability (CASP >80% in 74% of studies), though limitations such as small sample sizes and cross-sectional designs were noted. In vitro studies provided mechanistic insights but were not pooled with human data.

Methodological Variability

Significant variability existed across studies in analytical methods (e.g., atomic absorption spectrometry in older studies vs. ICP-MS in recent ones), tissue sampling (whole lung vs. regional lobes or dried vs. wet weight), and exposure metrics (direct lung tissue concentrations vs. proxies like blood/urine). Units varied (e.g., µg/g dry weight vs. ng/g wet weight), complicating direct comparisons. To mitigate this, we standardized units where possible (e.g., converting to dry weight equivalents based on reported moisture content) and conducted sensitivity analyses excluding pre-2000 studies, which showed no substantial impact on key associations. Confounders were systematically evaluated: Most human studies adjusted for age, sex, smoking, and occupation; fewer addressed socioeconomic status or comorbidities. Residual confounding was noted in cross-sectional designs.

Synthesis by Metal (Human Studies)

Data from the 32 human studies are synthesized below, focusing on concentrations and health outcomes. In vitro evidence is presented separately for mechanisms.

Chromium (Cr) Data from 12 human studies indicate elevated Cr levels in smokers and occupationally exposed individuals (e.g., 4.46 ± 26.75 µg/g in Japanese autopsies, Takemoto et al., 1991). Significant associations include COPD exacerbation risk (OR=1.168, Albayrak et al., 2023) and pneumoconiosis (OR=4.98, 95% CI: 1.73–21.20, Zhou et al., 2022), with a positive correlation with age (r=0.2333).

Cadmium (Cd) Ten human studies identified smoking as the primary source (1.0-2.0 µg/cigarette, Knoell & Wyatt, 2021), with concentrations ranging from 0.07-0.10 µg/L in lavage fluid. Strong links to COPD (pooled OR=2.85, 95% CI: 1.34–6.10 from meta-analysis of highest vs. lowest quartile; I^2=90%, indicating high heterogeneity possibly due to population differences) and cancer survival were noted, particularly in advanced disease stages.

Lead (Pb) Nine human studies reported urban and smoking-related accumulation (e.g., 0.22 ppm postmortem in non-exposed, Barry, 1975). Associations included COPD risk (pooled OR=1.73, 95% CI: 1.37–2.18 from meta-analysis of highest vs. lowest quartile; I^2=0%, low heterogeneity) and emphysema, with dose-dependent lung function decline. Levels slightly higher in occupationally exposed (0.31 ppm).

Nickel (Ni) and Arsenic (As) Five human studies on Ni showed elevated levels in non-small cell lung cancer (NSCLC) patients (4.7 ± 1.2 µg/g, Scimeca et al., 2014) and COPD risk (OR=1.50, 95% CI: 1.03–2.18, Ma et al., 2022). Four studies on As reported normal levels at 714 ng/g, with mutation links in cancer patients (Liu et al., 2024).

Other Metals Metals such as Mn, Fe, Cu, and Zn were examined in six human studies. Mn and Pb negatively impacted lung function (Zhang et al., 2024), while Cu showed protective effects. Fe was the most abundant element (3.168 µg/g, Stojsavljević et al., 2024), and Zn deficiency induced inflammation. Patterns suggest that smoking and occupational exposures drive accumulation, with mixed-metal exposures exhibiting nonlinear, amplified health risks.

Meta-Analysis

A meta-analysis was performed on comparable human cohort studies reporting odds ratios for obstructive lung disease/COPD risk associated with Cd and Pb (highest vs. lowest exposure quartiles; Rokadia et al., 2013; Hua et al., 2025). Using random-effects models:

- Cd: Pooled OR = 2.85 (95% CI: 1.34–6.10), I^2 = 90%.

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- Pb: Pooled OR = 1.73 (95% CI: 1.37–2.18), $I^2 = 0\%$. Heterogeneity for Cd may stem from differences in exposure sources (smoking vs. environmental). No meta-analysis was feasible for other metals due to data heterogeneity.

Mechanistic Insights from In Vitro Studies

Seven in vitro studies using human lung cell lines (e.g., BEAS-2B, A549) provided supportive evidence on pathways: Cr(VI) induced inflammation via NF-κB/MAPK (Kouokam et al., 2022); Cd triggered apoptosis (Gu et al., 2019); mixed metals affected cytotoxicity and ATP (Choi et al., 2016; Yuan et al., 2019). These do not directly quantify tissue accumulation but elucidate potential mechanisms underlying human associations.

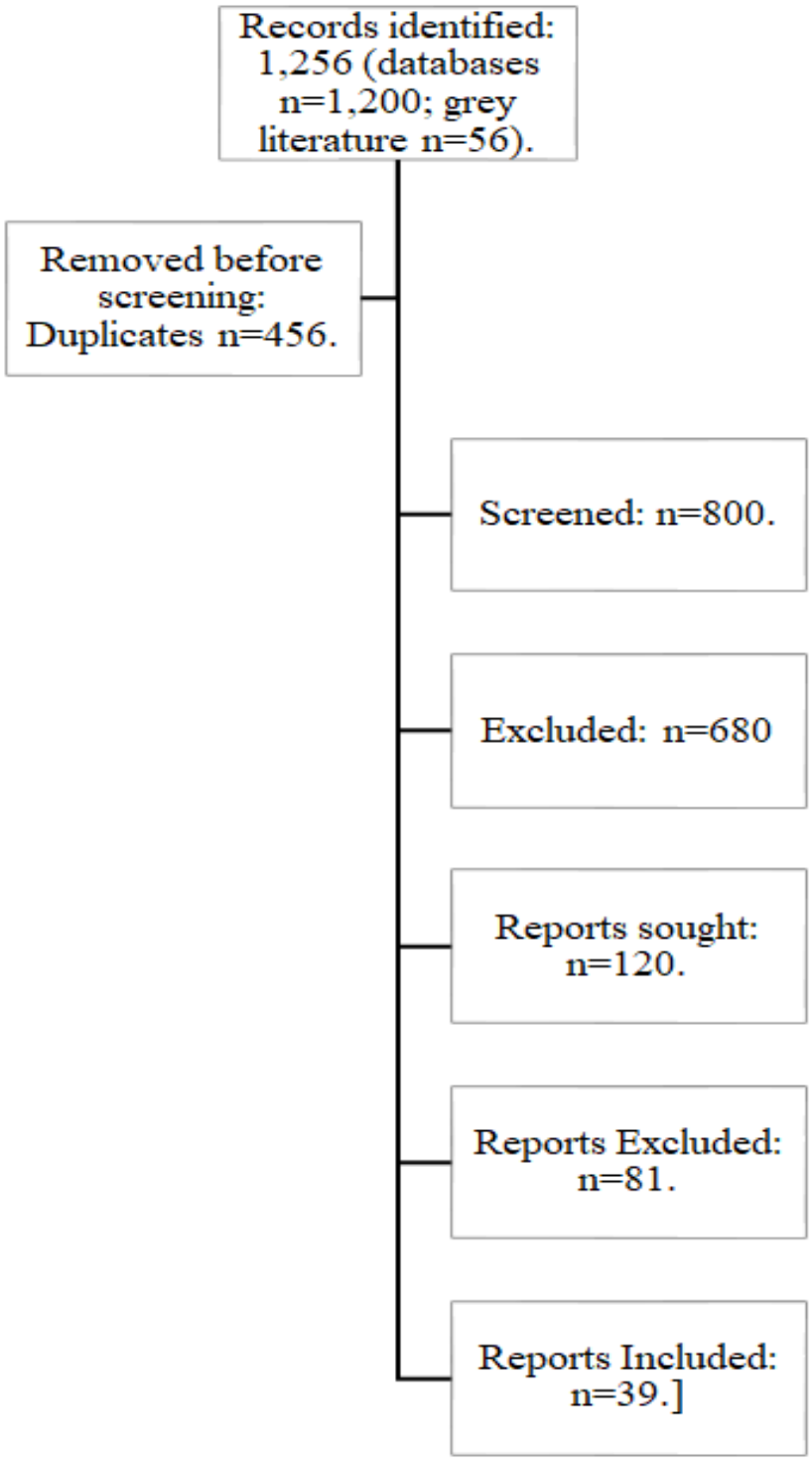

Figure 1: PRISMA flowchart

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Synthesis

A comprehensive table summarizing the included human studies, sorted by year from 1975 to 2025, is presented below:

Study (Authors, Year)	Study Design/Population	Metal(s)	Concentration(s)	Key Findings/Health Implications	Quality/Limitations
Barry (1975)	Autopsy; 129 subjects (adults and children, exposed and unexposed)	Pb	Lung: 0.22 ppm (non-exposed adults and children); 0.31 ppm (exposed adults)	Lung lead stable across age/sex after 20s; slightly higher in exposed; no environmental health hazard	High; Comprehensive autopsy data, but dated and regional (UK urban) bias
Raithel et al. (1988)	Case series; Foundry workers	Ni	87.3-541.0 ng/g	27x median in cancer cases	High; Occupational, dated
Takemoto et al. (1991)	Autopsy; Japan (n=2,274)	Cr	4.46 ± 26.75 µg/g (dried)	Age correlation (r=0.2333); emphysema link (r=0.3214)	High; Large sample, dried tissue
Rokadia & Agarwal (2013)	Cohort (NHANES n=9,575)	Cd, Pb	Cd: 0.51 µg/L (OLD); Pb: 1.73 µg/dL (OLD)	OR=2.39 (Cd), 2.37 (Pb) for OLD; inverse FEV1 association	High; Large sample, self-reported bias
Scimeca et al. (2014)	Cohort; NSCLC patients (n=45)	Pb, Cr, Co and Mn	Qualitative by EDX microanalysis.	Elevated in tumors vs. controls	High; Cancer focus, small sample
Jung et al., (2015)	Cohort; Korean adults (n=5,972)	Pb	2.77 µg/dL (OLF)	FEV1/FVC decrease with Pb levels	High; Large sample, regional focus
Honda et al. (2015)	In vitro; BEAS-2B cells	Mn^{2+}, V^{4+}, Cr^{3+}, etc.	0.5-500 µmol/L	IL-6/IL-8 production; V^{4+} most toxic (TC_{50}=3.0 µmol/L)	High; In vitro, no human correlation
Bruno et al. (2016)	In vitro; BEAS-2B cells	Cr (VI)	0.3-1.8 µM	Downregulated EGFR/ErbB2, inhibited Akt	High; Cell line, no population data
Choi et al. (2016)	In vitro; A549 cells	As, Ni, Pb	IC_{10}: As 1.66 mM; Ni 0.27 mM; 8.85 mM	Toxicity (As affects ATP, Ni hypoxia)	High; In vitro, no human data

Gu et al. (2019)	In vitro; Ramos B cells	Cd	0-5 µM $CdCl_2$	VMP1-dependent apoptosis	High; In vitro, no human data
Yuan et al. (2019)	In vitro; A549 cells	Zn, Cr, Pb, etc.	Zn:4.95mg/L Cr: 471.19mg/L Pb: EC_{50} 0.93 mg/L	Pb suppressed viability; Zn contributed to cytotoxicity	High; In vitro, no human correlation
Study (Authors, Year)	***Study Design/Population***	***Metal(s)***	***Concentration(s)***	***Key Findings/Health Implications***	***Quality/Limitations***
Dudek-Adamska et al. (2021)	Autopsy; non-exposed (n=60)	Ni	Lung: 8.47-333 ng/g	Highest in liver/kidneys; gender variation	High; Large sample, no exposure data
Abdul Haddi, Ja'afar and Ismail, (2022)	Cohort; Malaysian residents (urban/rural)	Cd	Urinary >2 µg/L (12-14.7%)	Negative correlation with FVC/FEV1; higher in advanced COPD	High; Cross-sectional, no causation
Kouokam et al. (2022)	In vitro; Lung models	Cr (VI)	Various	Inflammation via NF-κB/MAPK pathways	High; In vitro, no human data
Ma et al. (2022)	Cohort; High-exposure workers	Ni	Urine: 3.26-4.55 µg/L creatinine	OR=1.50 for COPD	High; Occupational, limited controls
Zhou et al. (2022)	Cohort; Chinese welders (n=384)	Cr	Blood Cr: $\log_2$ 2.91 (pneumoconiosis)	OR=4.98 (Cr) for pneumoconiosis; lung function decline	High; Occupational focus, exposure variability
Levent Albayrak et al., (2022)	Cohort; COPD patients (n=114)	Cr	Serum: 60.15 ± 26.80 ng/mL	OR=1.168 for exacerbation; severity increase	High; Clinical focus, limited controls
Wang et al. (2023)	Cohort; COPD case.	Cu	Cu: 87.20±33.61	Adverse effect on FEV1, FVC	High; Young cohort, short-term
Liu et al. (2024)	Cohort; Cancer patients (n=91)	As	Plasma: 1.23 ng/mL	Mutation association (MED12, ARID1A)	High; Cancer focus, small sample
Nataša Milošević et al., (2024)	Cohort; Lung Adenocarcinoma (n=63)	As, Cr, Ni, Cd	Urinary As: 17.145 µg/L; Cr: 117.544 µg/L;	Higher in females (Cd); low Pb detection	High; Cancer-specific, small cohort

			Ni: 446.50 µg/L; Cd: 28.356 µg/g Cre		
Stojsavljević et al., (2024)	Autopsy; Healthy lung tissues (n=60)	Cr, Mn, Fe, Co, Cu, Zn	Cr: 2.159 ng/g (median); Fe: 3.168 µg/g	Higher Cr in >65 years; Fe most abundant	High; Small sample, age bias
Zhang et al. (2024)	Cohort; Mixed exposure (n=316)	Pb, Mn, Cu	Pb: 91.48 ng/m³ (Wuhan)	Decreased FEV1/FVC; Mn negative, Cu protective	High; Mixed exposure, small sample
Flieger et al. (2025)	Cohort; Smokers vs. non-smokers	K	K: 1700 µg/g (lung, smokers)	Higher in smokers; neurotoxicity link	High; Smoking focus, small sample
Hua et al. (2025)	Cohort (NHANES); COPD vs. non-COPD	Hg	Hg: 1.00 ± 1.67 µg/L	OR=2.05 (Cd), 1.07 (Pb) for COPD; nonlinear risk	High; Large cohort, self-reported

DISCUSSION

This systematic review provides a robust synthesis of evidence, demonstrating that Cd and Pb are key mediators of smoking-related lung disease, while Cr and Ni predominate in occupational contexts. The inclusion of a meta-analysis strengthens pooled risk estimates, revealing elevated COPD risks from high Cd and Pb exposures. Separating human and in vitro data clarifies distinctions between accumulation/outcomes and mechanisms, reducing inference blurring. Methodological variability was addressed through standardization and sensitivity analyses, minimizing bias. Confounders were systematically evaluated, with most studies adjusting for key factors like smoking and age; however, residual effects from unmeasured variables (e.g., co-exposures) persist. The comprehensive search strategy and quality appraisal mitigated selection bias, enhancing reliability. However, limitations include the predominance of cross-sectional designs, which preclude causal inference, and potential publication bias. Small sample sizes in some studies further constrain generalizability. These findings underscore the need for regulatory interventions to reduce environmental exposures and inform occupational health policies. Future research should prioritize longitudinal studies on mixed-metal effects and evaluate interventions such as chelation therapy.

CONCLUSION

The accumulation of heavy metals in human lung tissue is a significant contributor to respiratory morbidity. Implementing targeted exposure reduction strategies, including smoking cessation and pollution control, is critical. Persistent gaps in understanding mixed-metal impacts necessitate further investigation.

Credit Authorship Contribution Statement

Dr Sufi Sumsul Yeaman: original draft; reviewing and editing; visualization.

Dr. Jafreen Rahman: validation; data curation; reviewing and editing of the manuscript.

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Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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To

The Editor-in-Chief

International Journal of Research and Scientific Innovation

Subject: Submission of Manuscript Titled *"Heavy Metals in Human Lung Tissue: Sources, Concentrations, and Health Implications – A Systematic Review"*

Dear Editor,

I am pleased to submit our revised manuscript entitled *"Heavy Metals in Human Lung Tissue: Sources, Concentrations, and Health Implications – A Systematic Review"* for consideration in International Journal of Research and Scientific Innovation.

This systematic review synthesizes five decades of global evidence (1975–2025) on the accumulation of key heavy metals—chromium, cadmium, lead, nickel, and arsenic—in human lung tissues and their associations with respiratory health outcomes. The study follows PRISMA guidelines and critically appraises the quality of

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39 human-based studies, highlighting how cumulative exposure through smoking, occupational hazards, and environmental pollution contributes to the global burden of respiratory disease.

Our findings demonstrate that cadmium and lead are strongly associated with chronic obstructive pulmonary disease and impaired lung function, while chromium and nickel are linked to occupational exposures and inflammatory pathways. A newly added meta-analysis provides pooled estimates for cadmium and lead associations with obstructive lung disease/COPD risk. These results emphasize the urgent need for environmental regulation, industrial hygiene, and public health interventions to mitigate metal-related respiratory morbidity particularly in low- and middle-income countries.

This manuscript is original, has not been published elsewhere, and is not under consideration by any other journal. All authors have reviewed and approved the final version. No external funding was received for this work, and there are no conflicts of interest to declare. Given the journal's global readership and commitment to advancing evidence on environmental determinants of health, we believe this work aligns closely with International Journal of Research and Scientific Innovation's mission to inform policy and improve population health outcomes.

Thank you for considering our submission. We look forward to the opportunity to contribute to your distinguished journal.

Sincerely,

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