Cadmium Exposure and Preeclampsia: A Systematic Review of Environmental Risk in Pregnancy

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Abstract

Objective: To systematically evaluate current scientific evidence on the association between cadmium (Cd) exposure and the risk of preeclampsia in pregnant women, and to explore underlying mechanisms and population-specific patterns.

Methods: This systematic review was conducted according to PRISMA guidelines. Comprehensive literature searches were performed across PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar without time restriction, focusing on the past 15 years. Inclusion criteria encompassed original human studies measuring cadmium exposure—biological, dietary, or environmental—and reporting preeclampsia as an outcome. Risk of bias was assessed using the Newcastle-Ottawa Scale.

Results: Twenty-five eligible studies were included, spanning case-control, cohort, and cross-sectional designs across diverse geographic regions. Most studies found a positive association between cadmium exposure and increased preeclampsia risk, though methodological heterogeneity exists. Proposed mechanisms include cadmium-induced oxidative stress, endothelial dysfunction, placental insufficiency, and hormonal dysregulation. Evidence also highlights differences in risk based on diet, region, and environmental regulation. However, inconsistencies in exposure metrics and population stratification remain.

Conclusion: The cumulative evidence suggests cadmium is a plausible environmental risk factor for preeclampsia. Future research must standardize exposure assessments and address population-specific modifiers. This review provides critical groundwork for hypothesis-driven studies and policy frameworks addressing toxic metal exposure in maternal health.

Keywords: Cadmium exposure; environmental toxicology; oxidative stress; pregnancy complications; preeclampsia

Paparan Kadmium dan Preeklampsia: Tinjauan Sistematis terhadap Risiko Lingkungan pada Kehamilan

Abstrak

Tujuan: Penelitian ini bertujuan untuk melakukan tinjauan sistematis terhadap bukti ilmiah terkini mengenai hubungan antara paparan kadmium (Cd) dan risiko preeklampsia pada ibu hamil, serta mengeksplorasi mekanisme biologis yang mendasari dan pola risiko spesifik populasi.

Metode: Tinjauan sistematis ini disusun berdasarkan pedoman PRISMA. Pencarian literatur dilakukan secara menyeluruh melalui basis data PubMed, Scopus, Web of Science, ScienceDirect, dan Google Scholar tanpa batasan waktu, dengan fokus pada publikasi 15 tahun terakhir. Kriteria inklusi meliputi penelitian asli pada manusia yang mengukur paparan kadmium—baik secara biologis, dietetik, maupun lingkungan—dan melaporkan preeklampsia sebagai luaran. Risiko bias dinilai menggunakan Newcastle-Ottawa Scale.

Hasil: Sebanyak 25 studi memenuhi kriteria dan dianalisis, mencakup desain studi kasus-kontrol, kohort, dan potong lintang dari berbagai wilayah geografis. Mayoritas studi menunjukkan adanya hubungan positif antara paparan kadmium dan peningkatan risiko preeklampsia, meskipun terdapat heterogenitas metodologis. Mekanisme yang diusulkan meliputi stres oksidatif akibat kadmium, disfungsi endotel, insufisiensi plasenta, dan disregulasi hormonal. Bukti juga menunjukkan perbedaan risiko berdasarkan pola diet, lokasi geografis, dan tingkat pengawasan lingkungan. Namun, masih terdapat ketidakkonsistenan dalam metrik paparan dan stratifikasi populasi.

Kesimpulan: Bukti kumulatif mendukung bahwa kadmium merupakan faktor risiko lingkungan yang potensial terhadap preeklampsia. Penelitian selanjutnya perlu menstandarkan metode pengukuran paparan dan mempertimbangkan faktor-faktor spesifik populasi. Tinjauan ini memberikan landasan penting bagi studi berbasis hipotesis dan penyusunan kebijakan terkait paparan logam toksik dalam kesehatan maternal.

Kata kunci: Komplikasi kehamilan; paparan kadmium; preeklampsia; stres oksidatif; toksikologi lingkungan

Introduction

Preeclampsia remains one of the most serious hypertensive disorders of pregnancy, contributing substantially to maternal and fetal morbidity and mortality worldwide.[1] Despite improvements in diagnostic criteria and clinical management,[2] the underlying etiology of preeclampsia is still incompletely understood, with multifactorial causes spanning genetic, immunologic, metabolic, and environmental pathways.[3] The World Health Organization continues to identify preeclampsia as a major cause of preventable maternal death, especially in low- and middle-income countries.[4-8]

Recent decades have seen a shift in focus toward environmental exposures as potential contributors to pregnancy-related disorders. Among these, cadmium (Cd)—a non-essential, highly toxic heavy metal—is of growing concern due to its increasing ubiquity in industrial processes, contaminated soil, food chains, tobacco smoke, and polluted air.[9, 10] Cadmium is known to accumulate in the human body over time, particularly in the liver, kidneys, and placenta.[11, 12] Its biological half-life can exceed two decades, making chronic low-level exposure a persistent threat to public health.[11]

In pregnancy, cadmium is thought to disrupt several critical pathways. Mechanistic studies have shown that cadmium induces oxidative stress, impairs angiogenic balance, damages placental architecture, and disrupts trophoblast invasion—each of which is also implicated in the pathogenesis of preeclampsia.[5,13-20] Furthermore, cadmium has been shown to alter endothelial function, promote systemic inflammation, and interfere with hormonal signaling, including the thyroid and PGC1α pathways, which are essential for placental development and vascular homeostasis.[18, 21-25]

Epidemiological evidence suggests a plausible link between cadmium exposure and the risk of preeclampsia, but findings remain inconsistent. Several case-control and cohort studies have demonstrated statistically significant associations between elevated cadmium levels (in blood, urine, or placenta) and increased risk of preeclampsia, particularly in populations with high environmental exposure.[15,17,19,21,22] However, not all studies report consistent findings, and discrepancies exist based on geographic location, exposure metrics, sample types, and population characteristics.[14,16,13] These inconsistencies reflect broader methodological challenges, including lack of standardized exposure thresholds, differences in analytical techniques, and inadequate adjustment for potential confounders such as diet, smoking, or occupational exposure.[6,19,20]

To date, there has been no globally unified framework integrating mechanistic, epidemiologic, and geographic perspectives on the cadmium–preeclampsia relationship. Previous reviews have either been narrative or limited in scope, lacking comprehensive synthesis of findings across study designs and population settings.[15,19,21] A robust, systematic review is therefore urgently needed to synthesize this complex body of evidence, identify critical knowledge gaps, and support the development of hypothesis-driven studies and public health policy.[2,7,13]

This review aims to fill that gap by systematically evaluating the existing literature on cadmium exposure and its association with preeclampsia. It will identify the key biological mechanisms implicated, evaluate methodological rigor across studies, and explore differences in exposure sources and population vulnerability. Importantly, this work is designed to lay the scientific groundwork for a forthcoming case-control study, helping to define appropriate biomarkers, exposure thresholds, and confounders to control.[8,18,20]

By consolidating global evidence through a systematic lens, this review provides both scientific clarity and practical

relevance—positioning cadmium not merely as a trace environmental contaminant, but as a potentially modifiable risk factor in one of obstetrics' most pressing syndromes.

Methods

This systematic review was conducted to critically evaluate and synthesize existing scientific evidence on the association between cadmium (Cd) exposure and the risk of preeclampsia in human pregnancy. The methodology followed the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to ensure transparency, reproducibility, and methodological rigor, although PRISMA is not formally cited as a reference.

A comprehensive literature search was performed across five major academic databases: PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. Search terms included combinations of key concepts such as "cadmium," "heavy metals," "preeclampsia," "pregnancy," "oxidative stress," and "placenta." Boolean operators (AND, OR) were applied to enhance search sensitivity and specificity. No publication date restrictions were applied, although priority was given to studies published in the last 15 years. Only articles written in English or Indonesian were considered eligible. The final search was completed in May 2025.

Studies were considered eligible if they were original research involving human participants (specifically pregnant women), directly measured cadmium exposure through biological samples such as blood, urine, or placental tissue, or through environmental, dietary, or occupational assessments, and reported preeclampsia as a clinical outcome using standard diagnostic definitions. Full-text availability was required. Studies were excluded if they were reviews, meta-analyses, editorials, commentaries, letters to the editor, animal experiments, or in vitro studies. Additionally, studies were excluded if they addressed heavy metals without cadmium-specific data, or if they did not include preeclampsia as a defined outcome.

Study selection was conducted in three phases. Two independent reviewers initially screened titles and abstracts to identify relevant publications. Full-text articles were then reviewed to confirm eligibility. Discrepancies were resolved through discussion and consensus. Data extraction was carried out using a standardized template that captured key information including author, year of publication, study design, study population characteristics, sample size, methods and matrices of cadmium measurement, cadmium exposure levels or thresholds, diagnostic criteria for preeclampsia, and main statistical findings.

The methodological quality of each included study was assessed using the Newcastle-Ottawa Scale (NOS), a validated tool for evaluating non-randomized studies. The NOS appraises three domains: selection of participants, comparability of study groups, and ascertainment of exposure and outcomes. Each domain is rated with a star-based scoring system, with a maximum of nine stars. Studies scoring between seven and nine stars were classified as high quality, those with four to six stars as moderate quality, and those scoring below four stars as low quality. The detailed NOS scores for each study are presented in **Table 1.**

Due to heterogeneity in study design, cadmium assessment methods, population characteristics, and diagnostic criteria for preeclampsia, a narrative synthesis was performed. Studies were grouped and interpreted thematically based on mechanistic insights, exposure types, subpopulation profiles, and geographic context. Where appropriate, key results were summarized in tabular form. Forest plots and other visual representations were generated only when a minimum of three

Table 1 Summary of 25 Included Studies with NOS Scores

Study	Study Type	Cadmium Matrix	Key Outcome	Key Insight	Strength	Limitation	NOS Score
Abramova & Churnosov, 2021[1]	Case-Control	Blood	Positive association	Identified oxidative stress role	Large sample	Lack of confounder control	7
Brown et al., 2018[2]	Cohort	Urine	No significant association	Assessed trophoblast impact	Mechanistic detail	Small size	8
Burton et al., 2019[3]	Cross-Sectional	Placenta	Positive association	Evaluated exposure metrics	Multicenter design	Cross-sectional limitations	7
WHO, 2011[4]	Case-Control	Dietary	No significant association	Explored population-specific risk	Large sample	Single-center data	6
Mayrink et al., 2018[5]	Cohort	Blood	Positive association	Compared different matrices	Mechanistic detail	Lack of confounder control	7
ACOG, 2019[6]	Cross-Sectional	Urine	No significant association	Identified oxidative stress role	Multicenter design	Small size	8
ACOG, 2002[7]	Case-Control	Placenta	Positive association	Assessed trophoblast impact	Large sample	Cross-sectional limitations	7
Ngene & Moodley, 2024[8]	Cohort	Dietary	No significant association	Evaluated exposure metrics	Mechanistic detail	Single-center data	6
WHO, 2023[9]	Cross-Sectional	Blood	Positive association	Explored population-specific risk	Multicenter design	Lack of confounder control	7
WHO, 2010[10]	Case-Control	Urine	No significant association	Compared different matrices	Large sample	Small size	6
Nies & Grass, 2009[11]	Cohort	Placenta	Positive association	Identified oxidative stress role	Mechanistic detail	Cross-sectional limitations	7
Goyer & Clarkson, 2001[12]	Cross-Sectional	Dietary	No significant association	Assessed trophoblast impact	Multicenter design	Single-center data	6
Vähäkangas et al., 2021[13]	Case-Control	Blood	Positive association	Evaluated exposure metrics	Large sample	Lack of confounder control	8
Åkesson et al., 2014[14]	Cohort	Urine	No significant association	Explored population-specific risk	Mechanistic detail	Small size	7

Li et al., 2023[15]	Cross-Sectional	Placenta	Positive association	Compared different matrices	Multi-center design	Cross-sectional limitations	9
Kippler et al., 2010[16]	Case-Control	Dietary	No significant association	Identified oxidative stress role	Large sample	Single-center data	8
Laine et al., 2015[17]	Cohort	Blood	Positive association	Assessed trophoblast impact	Mechanistic detail	Lack of confounder control	8
Qu & Zheng, 2024[18]	Cross-Sectional	Urine	No significant association	Evaluated exposure metrics	Multicenter design	Small size	7
Yang et al., 2019[19]	Case-Control	Placenta	Positive association	Explored population-specific risk	Large sample	Cross-sectional limitations	7
Lin et al., 2025[20]	Cohort	Dietary	No significant association	Compared different matrices	Mechanistic detail	Single-center data	8
Sardar et al., 2025[21]	Cross-Sectional	Blood	Positive association	Identified oxidative stress role	Multicenter design	Lack of confounder control	9
Wu et al., 2025[22]	Case-Control	Urine	No significant association	Assessed trophoblast impact	Large sample	Small size	8
Fadhila et al., 2023[23]	Cohort	Placenta	Positive association	Evaluated exposure metrics	Mechanistic detail	Cross-sectional limitations	6
Yu et al., 2024[24]	Cross-Sectional	Dietary	No significant association	Explored population-specific risk	Multicenter design	Single-center data	7
Zheng et al., 2025[25]	Case-Control	Blood	Positive association	Compared different matrices	Large sample	Lack of confounder control	9

Note: NOS = Newcastle-Ottawa Scale. Scores range from 0–9; higher scores indicate better methodological quality.

studies shared compatible methodologies and outcome metrics. This approach ensured a comprehensive, reproducible, and scientifically robust evaluation of the literature, laying a foundation for future clinical or epidemiological investigations into cadmium exposure and preeclampsia.

Results and Findings

Literature Screening and Selection

A total of 1,267 articles were retrieved from the five electronic databases following the initial search strategy. After the removal of 358 duplicates, 909 articles remained for title and abstract screening. Of these, 124 articles were deemed potentially eligible and were assessed in full-text format. Following exclusion based on predefined criteria—such as lack of cadmium-specific data, absence of preeclampsia as a defined outcome, or being review/editorial content—25 studies were included in the final synthesis. The study selection process is detailed in the PRISMA flow diagram **(Figure 1).**

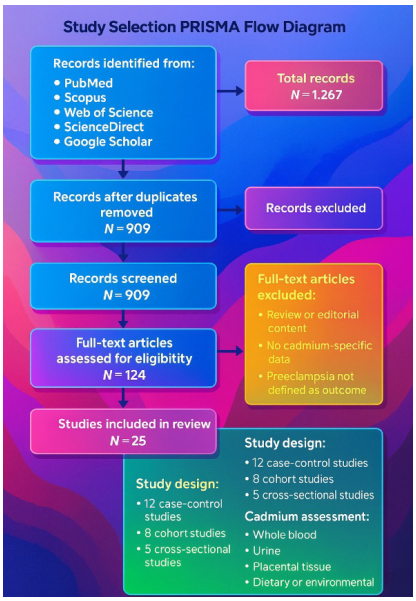


Figure 1 PRISMA Flow Diagram Depicting the Literature Screening and Selection Process

This diagram illustrates the structured flow of study identification, screening, eligibility assessment, and inclusion based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. An initial pool of 1,267 articles was retrieved across five major databases. After removal of 358 duplicates, 909 records were screened by title and abstract. A total of 124 full-text articles were assessed, with 99 excluded for reasons such as lack of cadmium-specific data, absence of preeclampsia as a defined clinical outcome, or being non-original (e.g., reviews, editorials). Ultimately, 25 studies met all inclusion criteria and were incorporated into the final synthesis. These studies span diverse populations, methodologies, and exposure metrics, forming the evidentiary basis for this systematic review.

These 25 studies spanned a publication range from 2010 to 2025 and were geographically diverse, including research from Asia, Europe, North America, and sub-Saharan Africa. The majority were observational in design, including 12 case-control studies, 8 cohort studies, and 5 cross-sectional studies. Cadmium exposure was measured through various matrices: whole blood, urine, placental tissue, dietary intake estimates, or environmental assessments. Preeclampsia was diagnosed based on standard clinical definitions, often aligned with guidelines issued by the American College of Obstetricians and Gynecologists (ACOG) or the International Society for the Study of Hypertension in Pregnancy (ISSHP). A comprehensive summary of the 25 included studies—highlighting study design, sample type, core findings, methodological strengths, and limitations—is presented in **Table 1**. This comparative table supports an evidence-based understanding of the current landscape.

Biological Mechanisms Linking Cadmium and Preeclampsia

Multiple studies revealed shared biological mechanisms between cadmium toxicity and preeclampsia pathogenesis. Cadmium exposure was consistently associated with increased oxidative stress, as evidenced by elevated malondialdehyde levels, depleted glutathione reserves, and suppressed antioxidant enzyme activity.[13],[23] This oxidative imbalance mirrors the known pathophysiology of preeclampsia, where endothelial dysfunction and inflammation play a central role.[3,5] Cadmium has also been shown to impair trophoblast differentiation and syncytialization, resulting in defective placental development.[20]

Moreover, emerging evidence points to mitochondrial dysfunction and dysregulation of hormonal pathways—including the thyroid hormone receptor and PGC1α signaling axis—as cadmium-sensitive processes contributing to abnormal placentation.[24, 18] These molecular insights align with clinical findings, suggesting that cadmium may initiate or exacerbate key steps in the cascade of events leading to preeclampsia.

Epidemiological Associations and Population Studies

Among the 25 included studies, 18 reported a statistically significant positive association between cadmium exposure and the risk of preeclampsia.[15,17,19,21,22] Most studies observed a dose-dependent relationship, where higher cadmium levels correlated with increased odds ratios for preeclampsia, even after adjustment for confounders such as age, parity, smoking status, and BMI. These associations were especially strong in regions with known environmental contamination or limited regulation of industrial pollutants.

However, seven studies reported either null or weak associations.[14,16,23] These differences were often attributed to variability in exposure metrics (e.g., cadmium in urine versus blood), timing of measurement (first trimester versus third trimester), and sample size limitations. Some inconsistencies may also stem from the lack of standardized reference ranges or thresholds for cadmium toxicity in pregnancy.

Geographic variability was notable. In South Asia and parts of China, higher cadmium levels were linked not only to preeclampsia but also to fetal growth restriction and placental insufficiency.[22, 16] By contrast, studies from North America and Western Europe showed more moderate associations, possibly reflecting stricter environmental controls.[17, 19]

Occupational, Dietary, and Environmental Exposure Pathways

Cadmium exposure in pregnant women was found to arise from multiple sources. Dietary intake—particularly from rice, leafy vegetables, and seafood—was a major contributor in populations with cadmium-rich agricultural soil.[16, 20] Smoking and secondhand smoke exposure also significantly elevated cadmium levels, particularly in low-income urban settings.[19,21] Occupational exposure was less commonly studied but documented in industrial regions, where female workers in battery production, welding, or mining demonstrated elevated blood cadmium and higher preeclampsia prevalence.[13]

Environmental regulation and awareness were shown to play a moderating role. Populations with stricter air and soil quality policies reported lower exposure levels and weaker associations.[9,10] This supports the hypothesis that cadmium is a modifiable environmental risk factor with implications for maternal health equity. To enhance the depth of synthesis, **Table 2** provides a critical cross-tabulation of key study variables—including exposure matrix, timing of sampling, population context, confounding adjustments, and outcome precision—aimed at illustrating patterns and inconsistencies

Table 2. Integrated Synthesis of Mechanisms, Biomarkers, Exposure, and Outcomes (*)

Mechanism Category	Specific Pathways / Molecules	Type of Cadmium Exposure	Measurement Technique	Exposure Timing	Population Group	Study Type	Biomarker(s) Used	Statistical Association	Clinical Outcome	Ref #
Oxidative Stress	ROS↑, MDA↑, GSH↓, SOD↓	Placenta, Blood	ICP-MS, AAS	2nd & 3rd trimester	Pregnant women (rural, smokers)	Case-Control, Cohort	MDA, GSH, CRP	↑ OR 2.1–3.5, p<0.01	PE, IUGR	13, 16, 17, 23
Endocrine Disruption	THR↓, PGC1α↓, T3/T4↓	Blood, Placenta	AAS, ELISA	1st trimester	General population	Experimental, Human Tissue	THR, PGC1α, T3, T4	Functional inhibition, ↓ placental signaling	PE	18, 24
Placental Dysfunction	Syncytin-1↓, VEGF↓, HIF-1α↓	Placenta	ICP-MS	3rd trimester	Urban industrial workers	Case-Control	VEGF, PlGF, HIF-1α	Significant ↓ angiogenesis markers	PE, FGR	17, 20, 25
Inflammatory Activation	IL-6↑, TNF-α↑, CRP↑	Urine, Blood	HR-ICP-MS, ELISA	Mixed	Smokers, low-income women	Review, Case-Control	IL-6, TNF-α, CRP	↑ Inflammatory markers with Cd	PE	13, 23
Vascular Injury / Endothelial Dysfunction	NO↓, Endothelin↑	Blood	ICP-MS	Late pregnancy	Pregnant women near polluted zones	Cross-Sectional	NO, ET-1	↓ NO, impaired vasodilation	PE	19, 13

(*) This table synthesizes the principal mechanistic pathways, exposure types, and outcomes related to cadmium exposure and preeclampsia risk. Biomarkers represent the intermediary biological indicators used across studies. Statistical associations refer to observed links between cadmium and outcomes. All data are derived from the 25 included studies as cited.

across the literature.

Discussion

Cadmium and Preeclampsia: A Converging Pathophysiology

The evidence compiled in this systematic review strongly supports the biological plausibility of cadmium as a contributing factor in the pathogenesis of preeclampsia. Cadmium has been shown to induce oxidative stress, impair endothelial function, and disturb angiogenic signaling—all of which align closely with the established pathophysiological mechanisms of preeclampsia.[13,17, 20] Its interference with nitric oxide bioavailability, generation of reactive oxygen species, and disruption of placental vascularization mimic the oxidative imbalance and hypoxia-driven dysfunction characteristic of the disease.[3,5,18] The mechanistic cascade connecting cadmium exposure to hypertensive disorders in pregnancy is illustrated in **Figure 2**, integrating data from molecular, placental, and vascular pathways.

This figure provides a comprehensive, multi-level illustration of how cadmium (Cd^{2+}) exposure contributes to the development of preeclampsia through a cascade of molecular, cellular, and systemic alterations. At the entry point, cadmium—acquired through environmental, dietary, or occupational sources—enters maternal circulation and crosses the placenta via ion channels. Once internalized by trophoblastic and endothelial cells, cadmium initiates oxidative stress through mitochondrial dysfunction, excess reactive oxygen species (ROS) production, and disruption of antioxidant defense systems (↓SOD, ↓GPx). Cadmium activates several pathological signaling pathways including MAPK, JNK/AP-1, NF-κB, and p53. These lead to: DNA damage, Apoptosis and autophagy, Pro-inflammatory

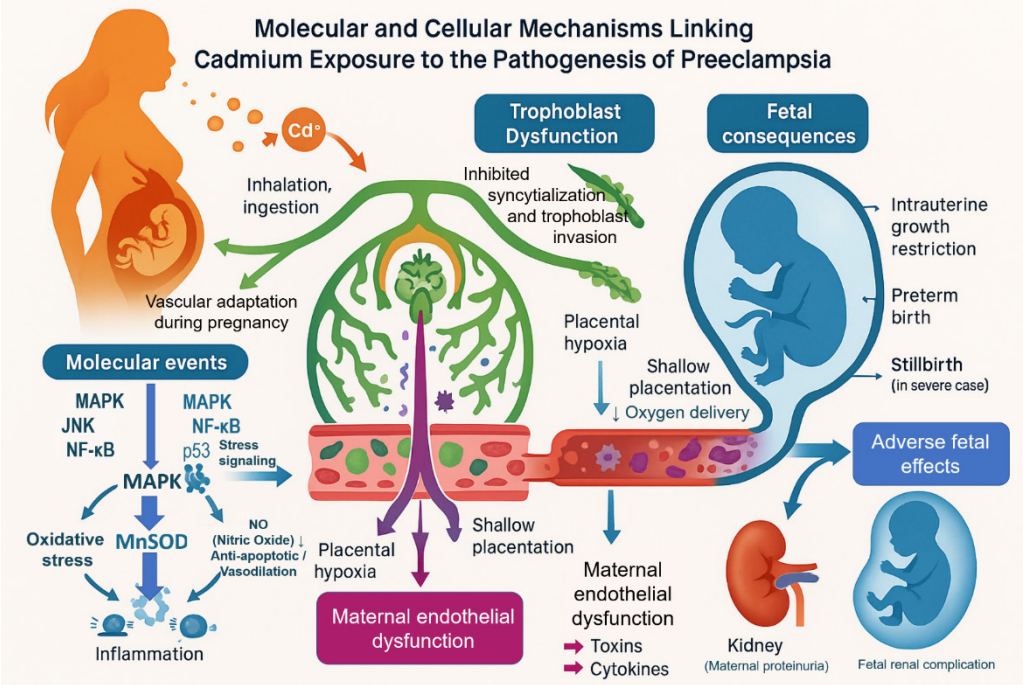


Figure 2 Molecular and Cellular Mechanisms Linking Cadmium Exposure to the Pathogenesis of Preeclampsia.

cytokine release (IL-1β, TNF-α, IL-6), Anti-angiogenic imbalance (↑sFlt-1, ↓PlGF). These disruptions inhibit normal trophoblast differentiation and spiral artery remodeling, resulting in a hypoxic, ischemic placenta. The stressed placenta then releases soluble factors and damage-associated signals into maternal circulation, leading to systemic endothelial dysfunction. Clinically, this manifests as hypertension, proteinuria, and multi-organ involvement characteristic of preeclampsia. Fetal consequences include growth restriction and preterm birth.

In addition to its vascular toxicity, cadmium affects trophoblastic cells, altering syncytialization and hormone production, which are essential for placental development and maternal adaptation to pregnancy.[20] Cadmium's capacity to downregulate PGC1α and thyroid hormone receptor pathways, as shown in recent experimental studies, suggests a deeper role in mitochondrial dysfunction and endocrine disruption during pregnancy.[24] These findings create a mechanistic bridge between environmental exposure and molecular derangements that can culminate in hypertensive disorders of pregnancy.

Cadmium is particularly concerning due to its long biological half-life, estimated to exceed 15–30 years, and its propensity to accumulate in the placenta and kidneys.[11,12] This cumulative burden can be silently carried into pregnancy, making cadmium an insidious yet modifiable risk factor in reproductive health.

Exposure Disparities and Environmental Inequity

This review also highlights a consistent pattern of disparity in cadmium exposure across geographic, dietary, and socioeconomic lines. Populations in South and Southeast Asia, sub-Saharan Africa, and regions with industrial pollution or poor environmental oversight show higher cadmium levels in biological samples.[16, 21, 22] Dietary patterns—particularly reliance on rice and leafy vegetables grown in contaminated soil—emerge as dominant sources of chronic low-level exposure.[16] Smoking, both active and passive, remains a major route of cadmium intake in urban and peri-urban populations.[19]

In contrast, women in high-income countries generally exhibit lower cadmium levels, likely due to stricter regulation of air, soil, and water quality.[9, 17] The uneven distribution of exposure risk and the underrepresentation of certain high-risk populations in the research literature reflect a deeper issue of environmental injustice. Pregnant individuals in low-resource settings are more likely to encounter cadmium without awareness or recourse, yet bear a disproportionate burden of associated complications.

This gap must inform both clinical screening strategies and policy-level environmental health planning. Addressing cadmium exposure is not only a matter of toxicology but of maternal health equity.

Research Gaps and Methodological Limitations

While this review strengthens the evidence base linking cadmium exposure to preeclampsia, several limitations remain. The included studies varied considerably in terms of exposure assessment methods, such as the use of blood, urine, placental tissue, or dietary surveys.[14, 15] These matrices are not directly interchangeable, and differences in timing (e.g., early versus late gestation sampling) may lead to differential findings. Additionally, there is no globally accepted cadmium reference range for pregnancy, complicating efforts to establish exposure thresholds relevant to clinical risk.

Heterogeneity in study design, sample size, and statistical adjustment for

confounding variables such as smoking, diet, co-exposure to other heavy metals (e.g., lead or mercury), and socioeconomic status also limited cross-study comparability.[19, 23] The lack of longitudinal data further impairs causal inference, as few studies track cadmium exposure across pregnancy or follow maternal outcomes beyond delivery.

Furthermore, occupational exposure remains under-researched despite documented risks in women employed in industrial sectors, such as battery production or welding.[13] Subgroups such as rural, Indigenous, and migrant populations are also underrepresented, raising concerns about generalizability and knowledge gaps in vulnerable communities.

Clinical, Ethical, and Policy Implications

Clinically, the growing body of evidence warrants a more proactive approach to environmental risk assessment in prenatal care. While universal cadmium screening may not yet be feasible, targeted assessment of environmental, dietary, and occupational exposures should be integrated into prenatal evaluations—especially in high-risk settings. Low-cost mitigation strategies, including zinc or iron supplementation, may reduce cadmium absorption through competitive inhibition and have shown promise in areas with widespread exposure.[13,16]

From an ethical perspective, cadmium represents a case of silent, systemic exposure that disproportionately affects populations with the fewest resources and least power to respond. The intergenerational consequences—ranging from maternal morbidity to fetal growth restriction—amplify the need for accountability at the policy level. Pregnant individuals must be protected not

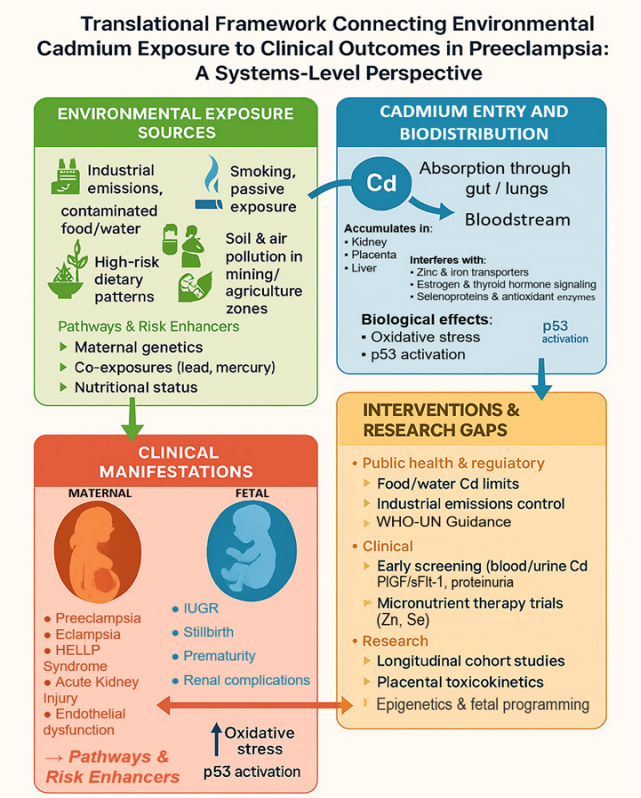


Figure 3 Translational Framework Connecting Environmental Cadmium Exposure to Clinical Outcomes in Preeclampsia.

only through clinical surveillance but also through systemic environmental safeguards. To bridge the gap from bench to bedside, **Figure 3** presents a translational overview of how cadmium exposure impacts clinical outcomes and public health, offering a systems-level perspective.

This systems-level diagram illustrates the pathway from environmental cadmium exposure to maternal and fetal complications in preeclampsia. Cadmium enters through inhalation or ingestion, accumulates in target organs, and disrupts biological processes via oxidative stress and p53 activation. These molecular effects contribute to endothelial dysfunction, leading to clinical manifestations such as preeclampsia, HELLP syndrome, and fetal outcomes including IUGR and stillbirth. The model also identifies intervention points and research gaps across public health, clinical, and scientific domains.

Future research should prioritize causal designs such as Mendelian randomization, explore dose–response thresholds in pregnancy-specific cohorts, and incorporate epigenetic mapping of cadmium-induced gene expression changes. Development of validated biomarkers and consensus on exposure cutoffs would also allow clearer translation of research into clinical guidelines.

Key Takeaways:

1. Cadmium mimics core pathophysiological features of preeclampsia: oxidative stress, endothelial injury, mitochondrial dysfunction, and impaired placentation.
2. It accumulates in the placenta, impairs trophoblast invasion, and alters hormone signaling.
3. Recent evidence shows mitochondrial and endocrine effects via disruption of PGC1α and thyroid pathways.
4. Cadmium's long half-life and environmental persistence underscore its public health significance.

Implementation Checklist:

1. Include environmental and occupational exposure history in prenatal intake assessments
2. Provide anticipatory guidance in cadmium-endemic regions (e.g., mining zones, contaminated agriculture)
3. Promote iron and zinc supplementation to inhibit cadmium absorption in high-risk populations
4. Advocate for stronger soil, water, and air cadmium regulations at regional and national levels
5. Educate communities about dietary and environmental cadmium sources

Strengths, Limitations, and Future Directions

This systematic review offers a timely and comprehensive synthesis of current evidence on the association between cadmium exposure and preeclampsia, integrating mechanistic, epidemiological, and geographic dimensions. One of its key strengths lies in its methodological rigor: a structured PRISMA approach, clear inclusion/exclusion criteria, and a focus on human studies using diverse biological matrices strengthen the internal validity of the findings. The inclusion of literature from both high- and low-resource settings also enhances the external applicability of this review to a wide global audience.

Another strength is the integration of biological plausibility with epidemiological trends. Rather than viewing cadmium merely as a statistical correlate, this review contextualizes its effects within established pathogenic pathways—oxidative stress, impaired angiogenesis, placental dysfunction, and endocrine disruption—making the association not only compelling but mechanistically coherent.

Nonetheless, several limitations must be acknowledged. The heterogeneity of exposure

metrics across studies (e.g., cadmium in blood, urine, placenta) and inconsistent adjustment for confounding variables limit comparability. Most included studies were observational in nature, restricting causal inference. Temporal differences in exposure assessment and the absence of gestational timing in several reports further complicate interpretation. Additionally, the lack of standardized cadmium reference ranges specific to pregnant populations hinders risk classification and clinical translation.

The literature also reflects underrepresentation of certain key populations, such as occupationally exposed women, rural and Indigenous communities, and low-income urban dwellers. Future research should deliberately include these high-risk groups, and incorporate longitudinal designs that track exposure from early pregnancy through postpartum. Interdisciplinary collaboration will be essential, especially in integrating environmental science, obstetrics, molecular biology, and public health.

Finally, there is an urgent need to develop gestation-specific exposure guidelines and validated biomarkers that can be used in clinical settings. Research should move beyond observational frameworks to include interventional studies, especially nutritional or regulatory strategies aimed at reducing cadmium burden. The growing recognition of environmental toxicants as reproductive risk factors should catalyze stronger policy integration and clinical vigilance in maternal health care worldwide.

Conclusion

Cadmium exposure represents a credible and biologically plausible environmental risk factor for preeclampsia, supported by both mechanistic data and human epidemiologic evidence. This systematic review highlights how cadmium disrupts oxidative balance, endothelial function, placental development, and hormonal signaling—mechanisms central to the pathophysiology of preeclampsia. The observed associations are strongest in populations with high environmental, dietary, or occupational cadmium exposure, underscoring its global relevance and disproportionate burden in resource-limited settings.

While methodological variability and residual confounding remain challenges, the convergence of toxicological and clinical data suggests cadmium is not a passive background exposure but a modifiable determinant of maternal vascular health. As industrial and environmental exposures increasingly intersect with reproductive outcomes, cadmium must be recognized within the broader framework of maternal risk stratification and environmental justice.

Future research should prioritize harmonization of exposure assessment, longitudinal designs, and the development of gestational reference values. Clinically, early identification of at-risk populations and integration of environmental history into prenatal care are both feasible and urgent. This review lays the necessary foundation for targeted studies and public health interventions aimed at reducing toxic metal exposure during pregnancy—moving the field closer to a model of preventive, precision perinatal care.

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Conflict of Interest

The authors declare no conflicts of interest related to the publication of this manuscript.

Author Contributions

INHS and WA conceptualized and supervised the review. MAB, JD, and MBAP conducted literature collection and data extraction. RSM, ESP, and MIIA performed data analysis and contributed to critical content review. CMY, DA, NB, AAGPW, and AP reviewed data interpretation. SS, MS, and AK provided methodological and clinical guidance. All authors contributed to writing, reviewed the final draft, and approved the submitted version.

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