Review Article

Narrative review: environmental pollutants and essential hypertension—role of epigenetic modifiers

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Background and Objective: Hypertension remains one of the most important causes of premature death and comorbidity worldwide. Traditional risk factors associated with hypertension, including dietary patterns, physical activity, and body mass index, have been described and included in guidelines as important factors in the development of hypertension. However, epigenetic modifications secondary to exposure to environmental pollutants have not been recognized as important factors in the development of hypertension. Epigenetic modifications are reversible changes in the genomic structure that can alter gene expression and cell function without changes in nucleotide sequence. The most investigated epigenetic modification is DNA methylation at specific C-p-G points in the genome. Environmental pollutants such as inhaled particulate matter ($PM_{2.5}$), cadmium, and lead can result in alterations in DNA methylation.

Methods: This article reviews the biomedical literature (in the PubMed and Embase databases) on the relation between epigenetic modification due to exposure to environmental pollutants (mainly PM, cadmium, and lead) and the development of hypertension, as well as literature related to ongoing personalized medicine therapies to reduce exposure to environmental pollutants, hence decreasing the risk of developing hypertension.

Key Content and Findings: The review concludes that there is mounting evidence associating the development of hypertension and exposure to environmental pollutants and also describes how these factors affect epigenetics. Therapies to avoid exposure to environmental toxins include personal protection such as respiratory protective equipment, high-efficiency home air filtration, portable air cleaners and personal protective equipment. However, hypothesis on how epigenetics modifiers specifically affect the pathogenesis of hypertension needs to be further evaluated in large-scale clinical trials and other prospective studies.

Conclusions: There is mounting evidence linking environmental pollutants such as $PM_{2.5}$, lead, and cadmium as contributing factors for the development of hypertension and other cardiovascular disease (CVD), including coronary artery disease (CAD), peripheral vascular disease (PAD), and stroke.

Keywords: Environmental pollutants; cadmium; lead; hypertension (HTN); epigenetic modifications

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Introduction

Hypertension is a significant cause of premature death worldwide, increasing the risk of stroke, heart failure, coronary artery disease (CAD), and renal failure (1). Worldwide 1.13 billion people have hypertension, and nearly half (47% or 116 million) of the adult population in the United States is currently diagnosed with hypertension (2).

Essential hypertension may develop from interactions between genetic and environmental factors (3). The traditional list of risk factors associated with blood pressure (BP), including dietary patterns, physical activity, and body mass index (1), has expanded to pollutants in air, soil, and water, which have been linked to the pathogenesis of hypertensive disorders (3).

Environmental pollution is a heterogeneous mixture of particulate matter (PM), gases, chemicals, and toxic metals derived from the burning of fossil fuels such as coal, oil, and gasoline, or produced by natural processes like volcanic eruptions and smoke from wildfires. After industrialization, an increase in environmental pollutants have been detected in the composition of air, water, and soil (4-9). Most of the evidence linking environmental pollutants and cardiovascular disease (CVD) originates from the levels of inhaled PM, as well as ingested lead and cadmium (5). Once in the human body, environmental pollutants disrupt mechanisms regulating vascular function by causing direct endothelial or vascular smooth cell damage or by altering the genomic regulation of vasoactive pathways (10). This paper aims to review the association of air pollution and ingested pollutants and focus on metal contaminants, mainly cadmium and lead, as non-traditional environmental risk factors contributing to the pathogenesis and development of hypertension. A review of potential mechanisms includes epigenetic modifications as a possible link between environmental pollution and essential hypertension (*Figure 1*). We present this article in accordance with the Narrative Review reporting checklist (available at https://prpm.amegroups.com/article/view/10.21037/prpm-22-13/rc).

Methods

In January 2022, a systematic literature search was conducted by Dr. S Gaviria-Valencia and Dr. F Ujueta. Final approval of the literature was conducted by all authors. Databases used for literature review included PubMed and Embase. Selection criteria include articles specifically focus on hypertension and exposure to environmental pollutants and epigenetic modifications related with hypertension. Only studies in English were included (*Table 1*).

Environmental contaminants and epigenetics

Epigenetic modifications are reversible changes in the genomic structure that can alter gene expression and cell function without changes in nucleotide sequence (11).

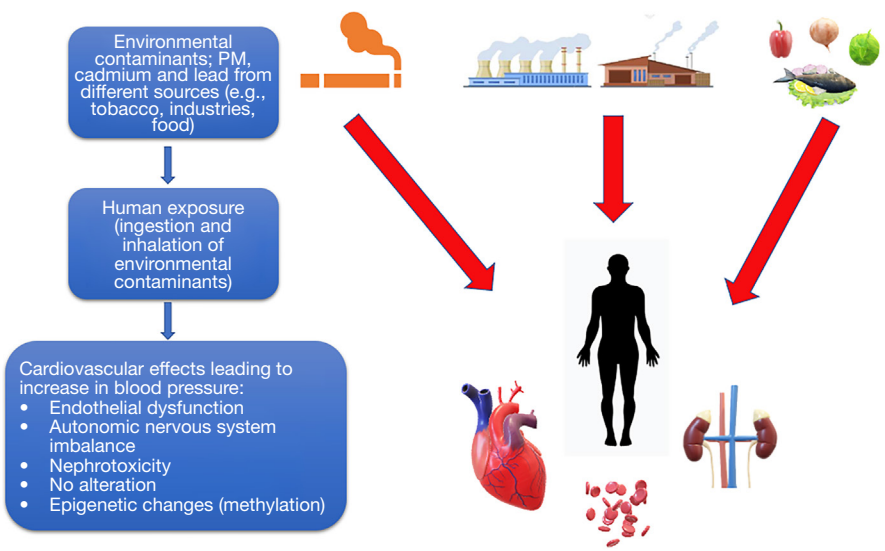

Figure 1 Illustration of environmental exposure to contaminants and its effect on human physiology leading to hypertension. PM, pollutant matter; NO, nitric oxide.

Table 1 The search strategy summary

Items	Specification
Date of search	January 15th, 2022
Databases and other sources searched	PubMed, Embase
Search terms used	Hypertension, epigenetic modifications, cadmium, lead, pollutant matter, environmental pollutants
Timeframe	From 2001 to 2021
Inclusion criteria	English literature only
Selection process	F Ujueta and S Gaviria-Valencia conducted systematic literature search and final approval was conducted by all authors

Table 2 DNA methylation outcomes and cadmium exposure

Year	Reference	Country	Size (n)	Findings
2020	Domingo-Relloso, *et al.* (18)	USA	2,325	Cadmium is a mediator of the association between smoking and differential DNA hypermethylation at specific sites (PRSS23, AHRR, F2RL3, RARA, 2q37.1).
2014	Sanders *et al.* (19)	USA	17	Hypermethylation of genes related to lipid metabolism, cell death, tissue morphology and gene expression were observed
2014	Tellez-Plaza *et al.* (20)	USA	48	Increase of methylation and hydroxy methylation. In cross-sectional analyses, the odds ratios of methylated and hydroxy methylated DNA were 1.56 (95% CI: 0.95–2.57) and 1.76 (95% CI: 1.07–2.88), respectively
2012	Hossain *et al.* (21)	Argentina	202	Hypomethylation of *LINE-1* and *DNMT3B*
2013	Zhang *et al.* (22)	China	81	Hypermethylation of *RASAL1* and *KLOTHO*
2013	Tajuddin *et al.* (23)	Spain	659	Hypomethylation of *LINE-1*

CI, confidence interval.

Epigenetic mechanisms are now thought to be central mediators of the body's adaptation to environmental stimuli such as environmental pollutants (12). There are three mechanisms involved in epigenetic modification after exposure to environmental pollutants: (I) DNA methylation, (II) histone modifications, and (III) non-coding RNAs (13). However, most studies focus on DNA methylation. Evidence about histone modification and non-coding RNAs remains scarce or inconsistent (14). DNA methylation consists of a methyl group added to the 5' position of cytosine residues by DNA methyltransferases, resulting in 5-methylcytosine (15). DNA methylation in gene promoters acts as a repressor of gene expression, whereas the decrease in DNA methylation may favor gene expression and is frequently observed in cancer cells (16). DNA methylation can be measured in specific genomic locations or globally (overall methylation state of the genome) (17).

Environmental pollutants such as cadmium and lead can result in alterations of DNA methylation. Some of the most relevant studies demonstrating the relationship between exposure to PM, lead, cadmium, and DNA methylation are depicted in *Tables 2-4*.

Epigenetic modifications and hypertension

Genetic factors explain up to 50% of the BP variation among individuals in the general population (32). Susceptible genetic variants that favor the hypertensive phenotype have been identified in genome-wide studies (33). However, the individual contribution of these variants to BP levels is minimal (10). Lately, it has been recognized that environmental factors could lead to hypertension by inducing epigenetic modifications (34). For instance, the reduction of DNA methylation of several candidate

Table 3 DNA methylation outcomes and lead exposure

Year	Reference	Country	Size (n)	Findings
2010	Wright *et al.* (24)	USA	679	Hypomethylation of *LINE-1*
2012	Hanna *et al.* (25)	USA	24	Reduced methylation was detected in the *COL1A2* promoter with higher exposure to lead
2013	Tajuddin *et al.* (23)	Spain	659	Hypomethylation of *LINE-1*
2013	Li *et al.* (26)	China	91	Pb exposure significantly decreased the level of *LINE-1* methylation

Table 4 DNA methylation outcomes and PM exposure

Year	Reference	Country	Size (n)	Findings
2016	Breton *et al.* (27)	USA	392	Hypermethylation of *LINE-1* and *AluYb8*
2019	Zhou *et al.* (28)	China	568	Increase of SOD2 (promoter of methylation)
2018	He *et al.* (29)	China	527	Hypermethylation of H19 and H19 DMR
2013	Bellavia *et al.* (30)	USA	15	Hypomethylation of *TLR4* and *Alu*
2018	Tobaldini *et al.* (31)	Italy	12	Hypermethylation of INF gamma

DMR, differential methylation region; INF, interferon; PM, particulate matter; TLR4, toll-like-receptor 4.

genes for hypertension affecting renal (*ARHGAP24*, *OSR1*, *SLC22A7*, *TBX2*) and vascular smooth muscle cell function (*IGFBP3*, *KCNK3*, *PDE3A*, *PRDM6*) have been associated with the severity of hypertension (11). Moreover, hypomethylation of genes involved in cortisol regulation, the renin-angiotensin-aldosterone system, and the expression of membrane cotransporters such as Na^+-K^+-2Cl, have been associated with increasing the risk of hypertension (35).

Inflammation and essential hypertension

Long-term inflammation has been shown to be associated with hypertension (36). Reactive oxygen species (ROS) are produced during inflammation, causing oxidative stress and endothelial disruption by decreasing the production of nitric oxide (NO). The main mechanism of NO is to regulate vascular tone by vasodilation. Therefore, NO decrease leads to impairment in vasodilation, causing an increase in peripheral vascular resistance (37). Levels of systemic inflammatory markers have been associated with the risk of hypertension. In experimental studies, the degree of activation of TNF-α has been positively and significantly associated with systolic (SBP) and diastolic (DBP) BP (38). Similar to ROS, activation of the tumor necrosis factor α (TNF-α) system results in decreased bioavailability of NO and leads to endothelial dysfunction and elevated BP (39). TNF-α antagonists have been shown to improve endothelial function in a model of aged animals. Studies in humans, however, have not been described to date (40).

Air pollutants and hypertension

The vast majority of the world population inhales air that exceeds the World Health Organization (WHO) guideline limits for levels of pollutants (41). It is estimated that 4.2 million annual deaths are secondary to exposure to outdoor air pollution and 2.9 million additional deaths to household air pollution (41). The PM found in air pollution is broadly categorized by aerodynamic diameter: PM_{10}, which are inhaled particles with diameters of 10 microns or less, PM_5, and $PM_{2.5}$, which are fine particles with diameters up to 5 and 2.5 microns, respectively (42). $PM_{2.5}$ is considered the most toxic, due to its capability to travel deep into the lungs, activate neural receptors, and translocate directly into the bloodstream (43).

Numerous studies have demonstrated that exposure to $PM_{2.5}$ increases the risk of adverse cardiovascular outcomes (6-8,44,45). The proposed mechanisms contributing to adverse cardiovascular outcomes are endothelial dysfunction, atherosclerosis, systemic inflammation, autonomic imbalance, plaque vulnerability, enhanced thrombosis-coagulation, and elevated BP (5). The most common cardiovascular effects include acute myocardial

infarction (MI), cerebrovascular disease, heart failure, cardiac arrhythmias, and hypertension (46-49).

Short and long-term exposure to ambient pollutants is associated with hypertension (50-54). Studies have demonstrated short-term exposure to elevations of PM by 10 microns can lead to an increase of 1 to 3 mmHg of BP over subsequent days (<8 days) (55). A recent meta-analysis combining data from 20 original studies totaling approximately 468,212 individuals found that the prevalence of hypertension was associated with long-term exposure to $PM_{2.5}$ [odds ratio (OR) =1.05; 95% confidence interval (CI): 1.01–1.09] (56). Additionally, two large clinical trial studies conducted in South Korea (n=10,459), and in six U.S. cities (n=5,112) also supported the association between $PM_{2.5}$ and hypertension. Interestingly, they found that a history of hypertension and longer duration of exposure to PM were strongly associated with an increase in BP (57-59). The previous studies suggested a dose-response relationship between air pollution and the degree of hypertension.

Substantial evidence illustrates three non-mutually exclusive mechanisms by which both short and long-term exposure to air pollutants might affect BP (5). These mechanisms include (I) autonomic nervous system (ANS) imbalance favoring sympathetic over parasympathetic tone, (II) direct damage of the vascular endothelium by particles capable of translocating across the alveolar membrane, then gaining access to the bloodstream and triggering an inflammatory cascade (60), and (III) the generation and release of endogenous pro-inflammatory cytokines from various sources (mainly pulmonary cells) which may alter the vascular hemodynamics (51).

The ANS imbalance is primarily involved in the short-term exposure to $PM_{2.5}$, which triggers an acute response causing a rapid and transitory increase in BP (5). After inhalation of $PM_{2.5}$, pulmonary receptors (TRPA1, TRPV1, and P2X) are activated, leading to a blunting of the cardiovascular parasympathetic response and favoring sympathetic activity (61). Numerous controlled studies in humans have shown changes in heart rate variability and BP, suggesting a predominance of sympathetic activity. For instance, Brook *et al.* reported a trend of borderline significance with both SBP and DBP increasing per 10 min of exposure during the inhalation of $PM_{2.5}$, when compared with changes while breathing filtered air in 32 healthy exposed adults. These findings, although underpowered, may suggest ANS imbalance as a plausible mechanism for the hypertensive response (62). Evidence for long-term exposure and ANS activation is limited to animal studies, however. One study found that 6-month exposure to $PM_{2.5}$ in mice led to an elevation in both BP and heart rate due to increased sympathetic activity (63).

Damage to vascular endothelium, resulting in release of cytokines and pro-inflammatory markers, has been associated with long-term exposure to $PM_{2.5}$ and chronic elevations in BP (51). Studies on human cell cultures and animals, showed that endothelial dysfunction caused by PM exposure is primarily explained by vascular inflammation and oxidative stress. After the inhalation of $PM_{2.5}$ for several weeks, NO synthase is inhibited resulting in a rapid reduction of NO, which is known to play an essential role in regulating vessel tone and structure (64). Deposition of PM in the lungs triggers activation of NADPH oxidase causing stimulation of the bone marrow by alveolar macrophages and subsequent inflammatory response with the release of acute-phase proteins, such as interleukin (IL)-1b, IL-6, tumor necrosis factor alpha, fibrinogen, C-reactive protein (CRP), circulating soluble adhesion molecules and white blood cells, eventually resulting in a decrease of NO (65,66). Additionally, experimental and observational studies have demonstrated the release of potent endogenous vasoconstrictor mediators (e.g., endothelin) in the circulation following exposure to air pollutants (67).

Alterations of DNA methylation after PM exposure could affect several biological mechanisms involved with inflammatory, vasoactive, and oxidative pathways (68). For instance, short-term exposure to PM resulted in hypo-methylation of several specific genes involved with vascular reactivity including nitric-oxide-synthase-3 (NOS3), endothelin-1 (EDN1), and endogenous thrombin potential. A small crossover trial suggested that short-term exposure to concentrated ambient particles decreased the methylation of *Alu*, *LINE-1* and toll-like-receptor 4 (*TLR4*) genes. The decrease in *Alu* and *TLR4* methylation was weakly associated with higher DBP (β-standardized =0.41, P=0.04; and β-standardized =0.84, P=0.02, respectively) (30).

Cadmium and hypertension

Numerous epidemiologic studies have found a positive association between elevated blood and urinary cadmium levels and hypertension (69-71). A Korean study of 958 men and 944 women who participated in the 2005 Korean National Health and Nutrition Examination Survey (KNHANES) demonstrated that higher serum cadmium levels were significantly associated with increased BP (OR =1.51; 95% CI: 1.13–2.05, P<0.01) (69). Franceschini *et al.* studied

the relationship of urinary cadmium with BP among 3,714 middle-aged American Indian participants of the Strong Heart Study and reported that elevated urinary cadmium was significantly associated with a higher SBP (P=0.002) and DBP (P=0.004) (70).

One of the potential mechanisms by which cadmium causes hypertension is nephrotoxicity (72). After cadmium enters the body, it is filtered by the kidneys and reabsorbed in the proximal tubules resulting in tubular injury, sodium retention, and volume overload leading to nephrotoxicity and renal dysfunction, potentially contributing to hypertension (73). The renal injury is explained by the accumulation of cadmium-metallothionein complex (Cd-MT) in the kidney (73). After its filtration from the blood, Cd-MT is reabsorbed in the proximal tubule, enters the renal cells, and is then separated from metallothionein in the lysosomes. Unbound cadmium directly results in damage to renal cells (74).

Other proposed mechanisms by which cadmium is involved in hypertension include alteration of NO production, direct injury to the vascular endothelium, disruption of calcium (Ca^{2+}) channels, and interference with intracellular signaling of Ca^{2+} (75). Cadmium affects NO functioning by impairing phosphorylation of endothelial NO synthase, resulting in a decrease in NO and peripheral vasoconstriction (76). It has been shown that direct contact of cadmium with the endothelium results in loss of barrier integrity, and alteration in permeability leading to inflammation and hypoxia (77). Cadmium is a potent inhibitor of the plasma membrane Ca^{2+} ATPase pump resulting in decreased response to evoked Ca^{2+} signaling which is involved in the process of BP homeostasis through vascular tone control (78).

Although epigenetic and genetic effects of cadmium have been commonly implicated in carcinogenesis, an association with cardiovascular-related health outcomes has also been proposed. For instance, an epigenome-wide association study on active and former smokers demonstrated that cadmium causes DNA methylation in different sites essential for endothelial cell differentiation, thus contributing to vascular flow alterations and atherosclerosis (79-81). Additionally, cadmium may disrupt the regulation of transcription factors involved in pro-inflammatory, oxidative stress, NO metabolism, and endothelial cell transcription; all potential mechanisms involved in the pathogenesis of vascular damage, leading to BP changes (82).

Lead and hypertension

Epidemiologic research on the association of lead and cardiovascular effects has primarily focused on lead's effect on BP (83-85). The association between lead exposure and hypertension has been identified since the 19th century. In modern times, the association was established with results obtained from experimental animals chronically exposed to elevated lead concentrations, followed by occupational studies in humans who had elevated lead levels (86). A meta-analysis combining data from 31 studies, with a total of 58,518 subjects, assessed the association between BP and blood lead levels, concluding that a doubling of the blood lead concentration is associated with an increase of 1 mmHg in SBP and 0.6 mmHg in DBP (87,88).

Potential mechanisms of the hypertensive effect of environmental lead include reductions in renal function, enhanced oxidative stress, stimulation of the renin-angiotensin system, down-regulation of NO soluble guanylate cyclase, and desensitization of beta-adrenergic receptors (89-93), which lead to an increase in vascular tone and peripheral vascular resistance. Using experimental animals and *in vitro* laboratory techniques (cultured endothelial cells, vascular smooth muscle cells, isolated tissues), numerous studies have explored that lead promotes the production of ROS and oxidative stress by participation in the formation of hydroxide (OH^-) and hydroxyl radical ($OH\cdot$) by a reaction between iron (II) (Fe^{2+}) and hydrogen peroxide (H_2O_2) reactions (94). Moreover, ROS inactivates vasoactive hormones and factors, including endothelium-derived relaxation factors, leading to an increase in vascular tone. Chronic lead exposure also decreases NO production, increases NO inactivation, downregulates soluble guanylate cyclase, and reduces cyclic guanosine monophosphate (cGMP) production by promoting oxidative stress (95). A decrease in cGMP causes activation of intracellular Ca^{2+} signaling increasing cytosolic Ca^{2+} concentrations in vascular smooth muscle cells, thus, heightening arterial pressure and systemic vascular resistance (93). An inverse association between blood lead and estimated glomerular filtration rate has been observed at blood lead levels >5 µg/dL in general population studies, which suggests that lead causes a reduction in renal function that might contribute to hypertension (89,90).

Epigenetic alterations associated with lead exposure can result in hypertension by increasing oxidative stress pathways (96). Lead results in an increase of ROS production which may deplete glutathione (GSH), a

sulfhydryl antioxidant associated with the dampening of free radicals. Glutathione-S-transferase (GST) is an essential antioxidant enzyme involved in the conjugation of GSH-lead detoxification. Polymorphisms of the GST enzyme have been associated with higher risk of lead-induced hypertension. Lee *et al.* found that GST-theta 1 (GSTT1) positive allele polymorphism was strongly associated with hypertension in lead-exposed Korean male factory workers (97).

Water pollutants and hypertension

Exposure to contaminated water with arsenic is associated with the development of hypertension (98). Arsenic is naturally present in the groundwater of several countries, and it is highly toxic for the human body affecting multiple organs, including the cardiovascular system. People are exposed to elevated levels of inorganic arsenic through drinking contaminated water, using contaminated water in food preparation, and irrigation of food crops (99). Some small studies have demonstrated a significant association of hypertension after exposure to arsenic-contaminated water. Xu *et al.* found a significant association of arsenic levels with high BP in a study of 150 participants from India exposed to contaminated water (100). The pathophysiologic mechanisms by which arsenic causes hypertension include enhanced myosin light-chain phosphorylation and an increase in calcium sensitization in medium and small blood vessels (101).

Proposed therapies for air pollutants and toxic metals

To the present date, no large-scale randomized controlled clinical trial addressing clinical end-points on air pollution exposure prevention strategies exists despite the growing evidence suggesting that reductions in $PM_{2.5}$ levels can result in health benefits to the population (42). In 2010, the American Heart Association addressed the risk of air pollution exposure, specifically addressing $PM_{2.5}$, but provided few recommendations to prevent exposure because of the lack of large-scale clinical studies (102). In 2019 the National Heart, Lung, and Blood Institute, Environmental Protection Agency (EPA), National Institute of Environmental Health Sciences, and Centers for Disease Control and Prevention proposed personal-level and building-level interventions to decrease household and outdoor air pollution for use in large-scale clinical trials (42).

Personalized medicine therapies to mitigate the effects of environmental pollutants on hypertension

Personal-level interventions to protect against $PM_{2.5}$ include lifestyle modifications and personal protection such as respiratory protective equipment, high-efficiency home air filtration, and portable air cleaners (PAC) (103). Respiratory equipment such as gauze, cotton, surgical, and cloth face mask have not shown to effectively reduce $PM_{2.5}$ exposure; thus, are not recommended in the prevention of air pollution. However, other forms of personal protective equipment (PPE) such as respirator face masks (e.g., N95 mask) have been validated and are specifically designed to filter 95% of particles, including $PM_{2.5}$ (42). The benefits on cardiovascular risk including hypertension have not been elucidated. Thus, short- and long-term studies are needed to further explore PPE and cardiovascular benefits.

Indoor air $PM_{2.5}$ concentrations can be reduced with high-efficiency air filtration systems in the air conditioning of cars and homes. In Taipei, Taiwan, a study by Chuang *et al.* demonstrated that one year of active filtration reduced indoor $PM_{2.5}$ by nearly one-half (104). A longer-term randomized crossover study by Chuang *et al.* recruited 200 healthy homemakers who were randomly assigned to air filtration or control intervention for one year. The study demonstrated that air filtration reduced $PM_{2.5}$ and this led to a decrease in SBP and DBP, of 3.76% and 2.66% respectively, compared with the control group ($P<0.05$) (105).

In controlled clinical trials, portable air cleaners provided some degree of protection by reducing $PM_{2.5}$ as much as 50% to 65%, but removal rates depend on room ventilation, size, and flow rate of cleaning. A small randomized, double-blind crossover intervention study demonstrated that short-term use of portable air purifiers systems reduced personal $PM_{2.5}$ exposures and SBP (106). However, this type of personal-level intervention needs to be studied in a large-scale clinical trial to evaluate its effect on cardiovascular outcomes (42).

Cadmium and lead are divalent cations. They persist in the body for decades because of the body's inability to actively eliminate them. Both cadmium and lead, therefore, may cause chronic damage to multiple tissues (107). Ethylene diamine tetraacetic acid and its salts (edetate disodium, edetate calcium disodium) are chelators with a high affinity for divalent cations such as cadmium and lead (108). Currently, edetate disodium is approved by the Food and Drug Administration (FDA) for lead poisoning

because of its ability to bind lead and excrete it in urine. Multiple studies have demonstrated that the administration of edetate disodium increases urinary excretion of toxic metals, including cadmium and lead (109,110). A study by Arenas *et al.*, revealed that administration of a single 3-gram infusion of edetate disodium in patients with a history of MI resulted in an increase of 71% in the total urinary level of metals compared to baseline with a substantial effect on lead (3,835% increase) and cadmium (633% increase) (111).

The largest and only interventional environmental study demonstrating improvement in cardiovascular outcomes with edetate disodium therapy is the Trial to Assess Chelation Therapy (TACT). This large-scale study was a randomized, double-blind, placebo-controlled, 2×2 factorial clinical trial testing the risks and potential benefit of 40 infusions of edetate disodium-based chelation solution compared with a placebo in 1,708 post-MI participants followed for 5 years. This trial demonstrated an 18% reduction (P=0.035) in a combined primary endpoint of death, MI, stroke, coronary revascularization, or hospitalization for angina. The benefit was more substantial in patients with a history of diabetes with a 41% relative reduction in risk of combined cardiovascular endpoint (P<0.001) and a 43% reduction in all-cause mortality (P=0.01) (112,113). It is unclear whether lead and cadmium chelation can reduce the risk of hypertension since this was not evaluated in TACT. Furthermore, the effect of chelation therapy reversing the epigenetic modifications induced by lead and cadmium is unknown.

Highlights

Scientific evidence about the relation of hypertension and epigenetic modification secondary to exposure to environmental pollutants increases rapidly. Incremental scientific evidence emphasizes the need for large-scale clinical trials to demonstrate the important role of environmental pollutants in the development of hypertension, but help to identify new factors in the pathogenesis of this important disease.

Limitations

Literature about the association between exposure to environmental pollutants (lead, cadmium and pollutant matter) and epigenetic modifications leading to the development of hypertension was limited to small and mid-scale prospective studies. Additionally, the most of the P values did not show a significant association.

Conclusions

There is mounting evidence linking environmental pollutants such as $PM_{2.5}$, lead, and cadmium as contributing factors for the development of hypertension and other CVD, including CAD, peripheral vascular disease (PAD), and stroke. Once in the body, pollutants can disrupt normal biological processes directly or by inducing epigenetic modifications that could result in human disease. Epigenetic effects may be a link between environmental exposure and the development of hypertension. This hypothesis needs to be further evaluated.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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