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Baseline associations between exposure to metals and systolic and diastolic blood pressure among women in the household air pollution intervention network trial

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Abstract

Lead (Pb) and cadmium (Cd) are metals that occur naturally in the environment and are present in biomass fuels, such as wood. When these fuels are burned, they can release Pb and Cd into the air, leading to exposure through inhalation. Studies of exposure to metals and health outcomes suggest harmful impacts, including cardiovascular diseases. We assessed baseline associations between Pb and Cd concentrations in dried blood spots with systolic and diastolic blood pressure (SBP, DBP) among women in the household air pollution intervention network (HAPIN) trial. We analyzed data from three of the four HAPIN randomized controlled trial sites (Guatemala, Peru, and Rwanda), focusing on women aged 40–79 years living in households reliant on biomass cooking. Dried blood spots were analyzed for Pb and Cd exposure; SBP and DBP were measured following international guidelines. Demographic, socioeconomic, and dietary variables were collected via standardized questionnaires administered by local field staff. Statistical analyses included multivariable linear regression to examine associations between Pb and Cd, separately, and SBP and

DBP, adjusting for covariates. Additional analyses assessed effect modification by age and research site. Among 272 women, median SBP and DBP values were higher in Rwanda (116.3 mmHg, 73.0 mmHg) and Guatemala (113.3 mmHg, 68.3 mmHg) compared to Peru (106.0 mmHg, 63.3 mmHg). Pb exposure showed positive associations with both SBP and DBP. For each log-unit increase in Pb concentration, we observed increases of 2.36 mmHg SBP (95% CI 0.51, 4.20) and 1.42 mmHg DBP (95% CI 0.16, 2.67). Cd was not associated with SBP or DBP in this analysis. Pb exposure from biomass smoke inhalation may be an important risk factor for increased SBP and DBP, markers of cardiovascular disease risk.

1. Introduction

Lead (Pb) and cadmium (Cd) are metals that occur naturally in the environment and are in biomass fuels, such as wood. When burned, these fuels can release Pb and Cd into the air, leading to exposure [1]. However, dietary intake particularly via contaminated food, water, or use of lead-glazed cookware is also a significant route of exposure [2]. Although the relationship between low-dose Pb and blood pressure (BP) remains debated, some epidemiologic studies have shown associations even at subclinical exposure levels. In contrast, data on Cd are more limited and primarily from occupational settings. Investigating these metals in non-occupational populations that rely daily on burning biomass fuels for household energy needs fills a critical research gap [3, 4].

Studies on associations between exposure to these metals and health conditions suggest harmful impacts on health including cardiovascular diseases, as exposure to both Pb and Cd have been shown to be considered coronary risk factors [5]. Evidence indicates that metal levels in the body change with age due to differences in exposure sources, absorption rates, and evolving toxicokinetics over time [6]. Adults, particularly older adults, may experience chronic health effects due to long-term exposure and bioaccumulation of contaminants including metals [7]. Cd is considered a toxic pollutant due to its carcinogenic and mutagenic properties. Exposure to even low levels of Cd can affect the brain, kidneys, and heart and even result in death [8]. Biomass fuel burning is a notable source of Pb exposure in low- and middle-income countries (LMICs), where emissions from indoor stoves can accumulate in poorly ventilated spaces. In these settings, women are particularly vulnerable due to their time spent cooking indoors, making them a key population to study within the household air pollution intervention network (HAPIN) trial [9]. A systematic review identified major sources of Pb exposure as informal Pb acid battery recycling and manufacture, metal mining and processing, electronic waste, and the use of Pb as a food adulterant, primarily in spices among others [10].

There are a few suggested pathways for how Pb and Cd exposure can impact cardiovascular disease risk. Pb and Cd can lead to problems with blood coagulation [11] and can disrupt the normal functioning of blood vessels and the heart. Systolic BP (SBP) reflecting the pressure in arteries when the heart contracts, and diastolic BP (DBP) indicating the pressure between beats. Pb, for example, can interfere with the regulation of BP by affecting kidney function and the nervous system [12] while Cd may contribute to hypertension by inducing oxidative stress, impairing nitric oxide production, and causing renal tubular damage that influences blood volume regulation [13]. Exposure to these metals has been associated with an increased risk of hypertension, a major risk factor for heart attacks and strokes [14]. Chronic exposure to Pb and Cd may lead to sustained increases in BP, contributing to long-term health issues [15]. This can also result in a cycle of health decline, where hypertension exacerbates other conditions [16]. Elevated BP can serve as an early indicator of potential health impacts from environmental exposure to these heavy metals, helping in the development of preventive measures and policies [17].

Exposure to Pb has been linked to elevated BP, primarily due to its toxic effects on the cardiovascular system. Pb interferes with calcium signaling, which is crucial for maintaining vascular tone and BP regulation. It promotes oxidative stress and inflammation, leading to endothelial dysfunction and reduced nitric oxide availability, both of which impair the relaxation of blood vessels. Additionally, Pb can stimulate the sympathetic nervous system, increasing heart rate and vascular resistance. Chronic exposure may also impair kidney function, disrupting fluid and electrolyte balance, further contributing to hypertension. These combined mechanisms underscore the role of Pb and Cd exposure as a risk factor for high BP [18, 19]. While the association between Pb and BP is known, few studies have evaluated this relationship in rural LMIC settings among older women, who may be more susceptible due to older age and regular exposure to biomass smoke.

Our aim was to assess baseline associations of Pb and Cd concentrations from dried blood spots with SBP and DBP among women aged 40–79 years and to assess whether these relationships were modified by age or study site among 3 research sites (Guatemala, Peru, Rwanda) of the HAPIN trial. We hypothesized that SBP and DBP would be positively associated with higher Pb and Cd concentrations, and that older age and research site might modify the associations.

2. Materials and methods

2.1. Study site and population

This paper analyzed data from the HAPIN trial from 3 of the 4 countries (Guatemala, Peru, and Rwanda, excluding India), which has been described in detail by Clasen *et al* [20]. Briefly, the HAPIN trial was a randomized controlled trial to investigate the effect of a liquefied petroleum gas cookstove and fuel intervention on exposure to household air pollution and health. For this analysis, we assessed the association of Pb and Cd exposure on BP in women residing with pregnant women enrolled in the HAPIN trial. This analysis included non-pregnant adult female participants at baseline (before households were randomly assigned to intervention or control arms, stratified by country) in the HAPIN trial research sites (Guatemala, Peru and Rwanda). Personal exposures to metals and health outcomes were obtained from 272 adult women aged 40–79 years (confirmed by government-issued identification card when possible) who resided in the same households as an enrolled pregnant woman in the HAPIN trial across study sites, provided they did not meet any of the following exclusion criteria: currently smoking cigarettes or other tobacco products, or planning to permanently move out of their current household in the next 12 months. Households were included in the study if they self-reported primarily using biomass fuels for cooking [21].

The study sites were selected because solid biomass was the primary source of fuel for a large proportion of the population. The study participants in Guatemala were characterized by the use of chimney stoves and open fires; 97% used wood fuel and cooked mainly indoors [22]. In Peru, study participants came from rural households that regularly cooked using traditional biomass (usually dung mixed with straw) burning stoves [23]. In Rwanda, 80.4% of the population relied on wood or wood-based products for cooking, which was typically done on traditional open stoves in poorly ventilated kitchens, in addition to the traditional three stone fires (62.6%) or clay brazier stove (34.6%) fueled with wood (89.9%) or charcoal (8.1%) and cooking indoors (71.9%) [24].

2.2. Clinical biomarkers and BP measurements

Following recruiting and informed consent, qualified fieldworkers visited the families at the start of the study to do baseline questionnaires and other evaluations. Dried blood spots were collected immediately after 24 h household air pollution exposure measurements using a GE Whatman 903 Protein Saver Card and a BD contact-activated 2.0 mm lancet. Technicians performed finger-stick punctures on participants' non-dominant hand, cleaning the site with 70% isopropanol to ensure sample integrity. Blood was collected by gently massaging the hand to promote flow, without squeezing, and drops were allowed to fall naturally onto the filter paper. After drying at room temperature for 24–48 h, the blood spots were stored in biospecimen bags with desiccants and humidity indicator cards at -20°C , shipped on dry ice, and analyzed at Emory University. Invalid spots were marked to guide lab processing, and valid spots were carefully selected for analysis.

At Emory University, dried blood spot samples from Guatemala, Rwanda, and Peru were analyzed using inductively coupled plasma mass spectrometry after digestion with nitric acid. A range of quality controls, including laboratory blanks and reference materials, was used to ensure accuracy. Samples were standardized for blood volume and analyzed for elements such as Pb and Cd, with strict quality control measures in place. For the potassium standardization of Pb and Cd concentrations, each metal value was multiplied by 4 mmol ml^{-1} and then divided by the individual's specific potassium value: $(\text{metal} \times 4)/\text{K}^{+}$.

BP measurements were recorded using an Omron HEM-907XL monitor, with three measurements taken after ensuring participants had not smoked, consumed alcohol or caffeine, or cooked with biomass in the last 30 min [20]. Further details on materials and methods for the clinical biomarkers from dried blood spots and BP collection can be found in supplemental materials.

2.3. Other variables

Qualified fieldworkers visited the households at the beginning of the study to conduct baseline surveys and other assessments after recruitment and informed consent. Interviews and surveys were conducted in the participant's native language by research assistants. This baseline visit included a survey covering

a range of topics like cooking behaviors, household composition, socioeconomic status (SES) and demographic information like age in years that was confirmed by national ID card, education which was self-reported and split into no formal education; primary or secondary incomplete; and secondary, college or university categories. Women self-reported exposure to secondhand tobacco (yes/no) and alcohol consumption (yes/no, number of days and drinks per day in the past 30 d as continuous variables). We determined dietary diversity using the Minimum Dietary Diversity for Women (MDD-W) indicator, which is based on ten food groups (Food insecurity experience scale, measuring food insecurity through people's experience FAO 360 2016). Diet diversity was considered low if the participant had consumed less than four of the ten food groups over the previous 30 d ($MDD-W < 4$), medium if they had consumed four or five food groups ($4 \leq MDD-W \leq 5$), and high if they had consumed more than five ($MDD-W > 5$). Food insecurity was assessed by the use Food Insecurity Experience Scale, developed by the Food and Agriculture Organization of the United Nations, www.fao.org/3/as583e/as583e.pdf.

Material items were selected as useful indicators of SES by other HAPIN investigators to be used across all publications. SES items included color TV, radio, mobile phone, bank account, and bicycle (yes/no per item).

We measured weight and height in duplicate using seca 876 electronic scales and seca 213 stadiometer platforms (seca GmbH & Co. KG., Hamburg, Germany), respectively. If the weight or height measurements differed by more than 0.5 kg or 1 cm, respectively, we collected a third measurement and the two closest readings were averaged. We computed BMI as the ratio between weight and height-squared (kg m^{-2}).

We determined level of physical activity using the Global Physical Activity Questionnaire (GPAQ), which collects information on both vigorous and moderate-intensity activity in three settings: at work, traveling to and from places, and in recreational activities, as well as sedentary behavior (Global Physical Activity Questionnaire, WHO 2012). From the GPAQ data, we calculated energy consumption based on Metabolic Equivalents (METs), where one MET is defined as the energy cost of sitting quietly and is equivalent to $1 \text{ kcal kg}^{-1} \text{ h}^{-1}$. Since caloric consumption is an estimated four times as high when moderately active and eight times as high when vigorously active, we calculated overall energy expenditure by assigning four METs to the time spent in moderate activities and eight METs to the time spent in vigorous activities (WHO STEPwise approach to NCD risk factor surveillance). We reported this estimated physical activity as MET-minutes per day.

2.4. Statistical analysis

Data were managed and analyzed using R version 4.3.3 (R Foundation for Statistical Computing) and RStudio [20]. Initially, 314 non-pregnant adult women who lived in the same household as an enrolled pregnant woman were included. For data cleaning, we removed those with missing BP values ($n = 6$), those who reported taking high BP medicine ($n = 33$), and those who had missing Pb and Cd values ($n = 3$). The final dataset for analysis included 272 women with valid Pb and Cd measures and BP endpoints.

We calculated descriptive statistics for exposure, demographic, SES and other potential confounders. We used a directed acyclic graph (DAG) to help inform which covariates to investigate and which to consider for analysis (supplemental figure 1). Detailed exploratory data analysis assessed counts and frequencies for categorical variables, and mean, standard deviation (SD), median, Q1–Q3, and min–max of continuous variables for BP outcomes (SBP and DBP), Pb and Cd exposures, and all other covariates. We used diagnostic plots of simple linear regression models for Pb and Cd measures and BP to see if the Pb and Cd measures needed to be natural log-transformed to meet the assumptions of linear regression. We highlighted covariates that lacked any variation in responses and considered creating new categories (binning) if necessary or dropping these covariates.

We used covariates from the DAG and assessed associations with SBP and DBP and Pb and Cd in crude (i.e. unadjusted) linear regression models. We explored how these covariates were correlated with one another to assess for potentially strong correlations.

We built multivariable linear regression models with women's SBP and DBP as separate outcomes and Pb and Cd as separate exposures, Pb was modeled using both untransformed and log-transformed values, while Cd was modeled untransformed, as it met linear modeling assumptions. We included *a priori* confounders (i.e. age) and potential confounders (SES and other indicators of SES, e.g. education, household assets, dietary diversity, and food insecurity). Since BMI may be a mediator (supplemental figure 1), we considered models with BMI in the primary analysis and excluded BMI as an adjusted variable in sensitivity analyses. As an additional sensitivity analysis to assess potential nonlinear associations and facilitate interpretability, Pb and Cd concentrations were categorized into quartiles based on

their 0th, 25th, 50th, 75th, and 100th percentiles, labeled as Q1 (lowest, set as reference) through Q4 (highest).

Finally, we assessed effect modification in the adjusted linear regression models by adding an interaction term between the Pb and Cd exposure variables and age (median cutoff: <51 vs ≥ 51 years) and by research site (Guatemala, Peru and Rwanda).

2.5. Ethical considerations

The study protocol has been reviewed and approved by institutional review boards or Ethics Committees at Emory University (00089799), Johns Hopkins University (00007403), Universidad del Valle de Guatemala (146-08-2016) and Guatemalan Ministry of Health National Ethics Committee (11-2016), Asociación Benefica PRISMA (CE0443.18), the London School of Hygiene and Tropical Medicine (11664-5) and the Rwandan National Ethics Committee (No.853/RNEC/2016), and Washington University in St. Louis (201611159). The study has been registered with ClinicalTrials.gov (Identifier NCT02944682).

Written informed consent for all study procedures was obtained by a trained local fieldworker in the native language. The study employed standard methods for protecting the confidentiality and privacy of participants. For illiterate participants, the consent form was read and the consent process done in the presence of a witness. All participants were given a copy of the consent form for their personal records.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the participants are shown in table 1 for those analyzed with Pb and Cd measures ($n = 272$). The majority of metals data were from Peru (44%) and Guatemala (43%) with 13% from Rwanda. The average age of participants was 52.3 (SD 7.6) years. There was a notable prevalence of overweight and obesity ($n = 174$, 65%) among the participants. The educational level was generally low with 77% ($n = 203$) having no formal education or primary school incomplete (table 1).

Almost all participants had mobile phones (94%), while a half of them had radios (59%) and color tv (49%) and fewer had bicycles (31%) and a bank (30%) account. The data from this study suggested that a substantial proportion of the sample faced challenges related to both food insecurity and dietary diversity. Over half of the sample reported were food insecure with mild (36%) or moderate to severe (17%) levels. Additionally, dietary diversity was low for half the sample, indicating limited access to a variety of foods (table 1). The results also indicate that out of the total sample population, 16 individuals (6%) reported being exposed to secondhand tobacco smoke. Participants spent a substantial amount of physical exertion, as indicated by 1086 average METs per day (SD 1030), although the large SD and the wide range of values (from 0 to 6,171 METs per day) reveal significant variation in exercise habits among individuals. Most participants self-reported zero or minimal alcohol consumption in the past 30 d (98% zero to 2 alcoholic drinks).

The BP summary results (table 2) and boxplots of SBP and DBP by research site (figures 1 and 2) display BP values among the study participants. SBP and DBP pressure varied slightly across sites. For SBP, the median (25th, 75th percentiles) was 113.3 mmHg (104.7, 121.0) in Guatemala, 106.0 mmHg (100.0, 113.3) in Peru, and 116.3 mmHg (106.2, 124.3) in Rwanda. For DBP, the median (25th, 75th percentiles) was 68.3 mmHg (62.0, 75.0) in Guatemala, 63.3 mmHg (57.7, 69.3) in Peru, and 73.0 mmHg (64.3, 75.7) in Rwanda. Across all research sites, the overall median (25th, 75th percentiles) was 109.2 mmHg (102.6, 119.3) for SBP and 66.2 mmHg (61.0, 73.0) for DBP. Rwanda and Guatemala generally had higher BP levels compared to Peru.

The baseline statistical summaries of Pb and Cd are presented in supplemental table 1 and supplemental figures 2 and 3 as box-and-whisker plots. In brief, Pb concentrations ($\mu\text{g dl}^{-1}$) were as follows: Guatemala: 117 samples, Median = 1.49, 25th percentile = 0.938, 75th percentile = 2.42, Peru: 121 samples, Median = 1.19, 25th percentile = 0.880, 75th percentile = 1.99, and Rwanda: 34 samples, Median = 1.47, 25th percentile = 0.937, 75th percentile = 2.79. Cd concentrations (ng ml^{-1}) were as follows: Guatemala: 117 samples, Median = 0.993, 25th percentile = 0.709, 75th percentile = 1.25, Peru: 121 samples, Median = 1.05, 25th percentile = 0.775, 75th percentile = 1.42, and Rwanda: 34 samples, Median = 1.03, 25th percentile = 0.728, 75th percentile = 1.30. Overall, Pb and Cd concentrations did not show much variation between research sites.

3.2. Results from adjusted linear regression models

Table 3 shows the primary model results of adjusted associations between SBP and DBP and the concentrations of two metals as exposures, Pb and Cd. There was a statistically significant positive association

Table 1. Baseline characteristics among adult women with valid Pb and Cd measures, Guatemala, Peru, and Rwanda ($N = 272$).

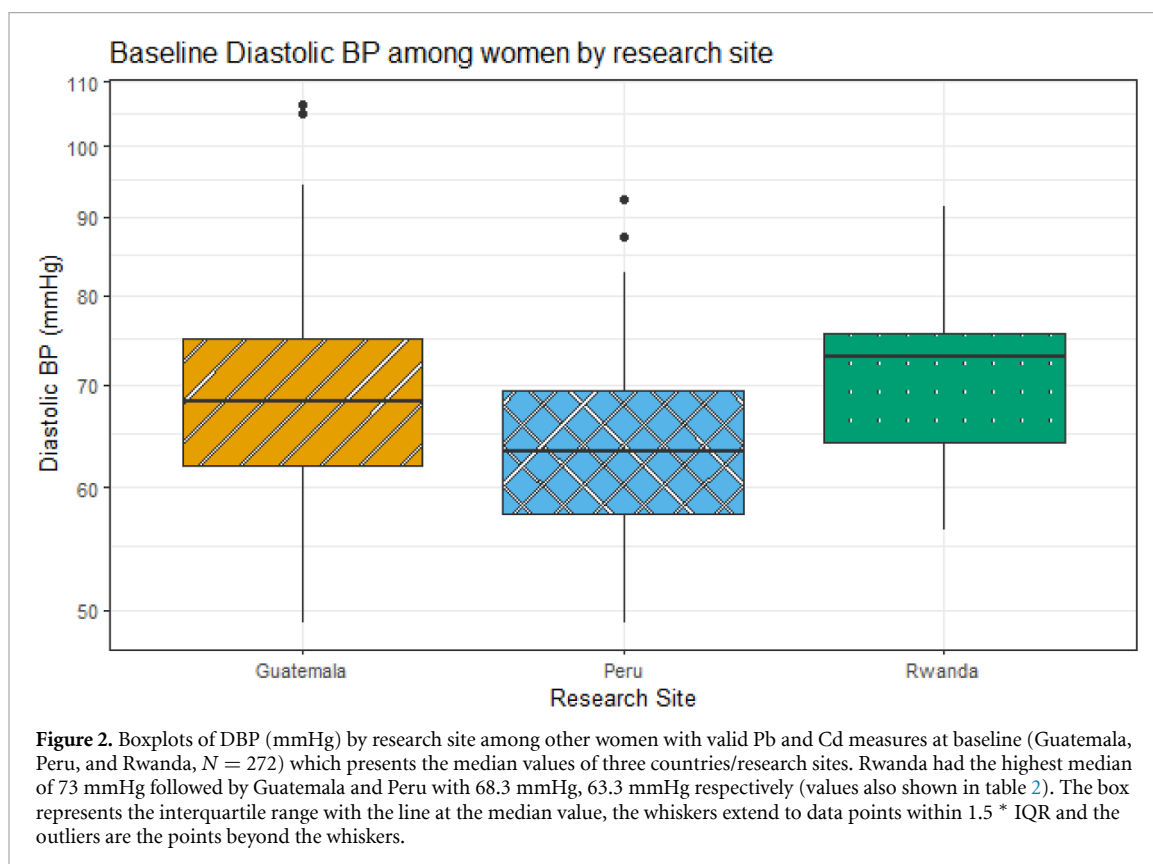
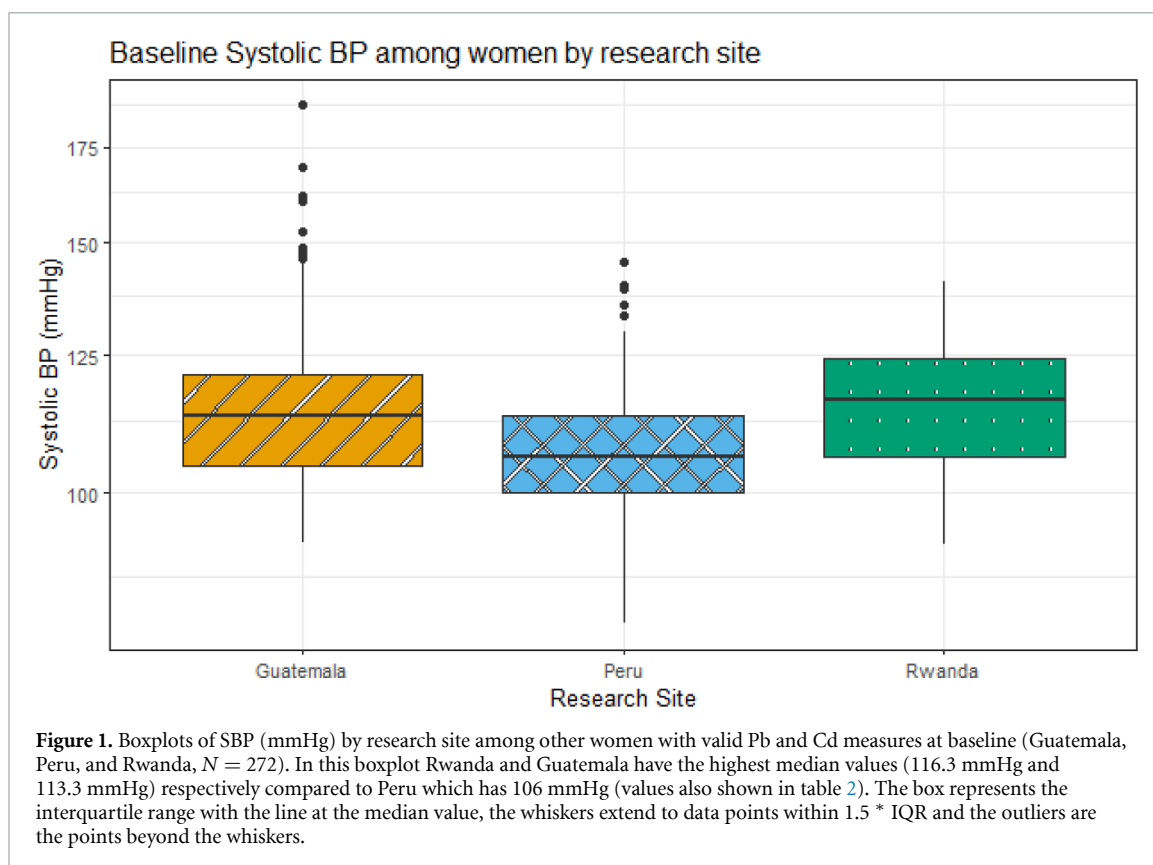
Variable	Mean (SD); min–max or n (%)
Research sites	
Guatemala	117 (43%)
Peru	121 (44%)
Rwanda	34 (13%)
Age at baseline (years)	52.3 (7.6); 40.1–73.8
Age at median cutoff, binary (years)	
Aged <51	134 (49%)
Aged ≥ 51	138 (51%)
BMI (continuous, kg m^{-2})	26.8 (4.7); 15.4–39.2
BMI, binary version	
Underweight, normal	94 (35%)
Overweight, obese	174 (65%)
Hypertension status, stage 1 (SBP ≥ 130 mmHg and/or DBP ≥ 80 mmHg)	37 (14%)
Color TV	132 (49%)
Radio	161 (59%)
Mobile phone	257 (94%)
Bank account	82 (30%)
Bicycle	85 (31%)
METs per day of physical activity	1086 (1030); 0–6171
Food insecurity	
None	127 (48%)
Mild	95 (36%)
Moderate/severe	45 (17%)
Dietary diversity	
Low	137 (50%)
Medium	102 (38%)
High	33 (12%)
Education 2-levels	203 (77%) 61 (23%)
No formal education or primary school incomplete	
Primary school complete, secondary school incomplete, Secondary school complete or vocational or some college or university	
Exposure to secondhand tobacco smoke	16 (6%)
Alcohol consumption in the past 30 d	266 (98%)
0–2 drinks	2 (1%)
3 or more drinks	4 (1%)
Unreported	

Table 2. Summary of SBP and DBP (mmHg) among adult women with valid Pb and Cd measures at baseline visit per research site, HAPIN (Guatemala, Peru, Rwanda) $N = 272$.

	N	Mean (SD)	Median	25th, 75th percentiles	Min–max
Systolic BP (mmHg)					
All research sites	272	112.2 (14.5)	109.2	102.6, 119.3	81.0–187.3
Guatemala	117	115.9 (16.6)	113.3	104.7, 121.0	92.3–187.3
Peru	121	107.4 (11.4)	106.0	100.0, 113.3	81.0–145.3
Rwanda	34	116.2 (12.03)	116.3	106.2, 124.3	92.0–140.7
Diastolic BP (mmHg)					
All research sites	272	67.3 (9.6)	66.2	61.0, 73.0	49.0–106.3
Guatemala	117	69.2 (10.0)	68.3	62.0, 75.0	49.0–106.3
Peru	121	64.1 (8.5)	63.3	57.7, 69.3	49.0–92.3
Rwanda	34	71.8 (8.5)	73.0	64.3, 75.7	56.3–91.3

between Pb exposure (log-transformed and not transformed) and SBP and DBP. The strongest association was observed as a 1-unit increase in log Pb value with an associated SBP increase by 2.36 mmHg (95% CI 0.51, 4.20). The adjusted associations between Cd exposure and SBP and DBP included the null value (table 3). Overall, results suggested that exposure to Pb, but not Cd, was associated with increases in both systolic and diastolic BPs in the studied sample (table 3).

In sensitivity analyses (table 4), we explored the exposures of Pb and Cd in quartiles, rather than as continuous variables. We observed a statistically significant positive associations Pb and SBP in a



dose-response pattern, particularly in the highest quartile (Q4 vs Q1: 5.67 mmHg; 95% CI: 0.81, 10.52). This dose-response pattern supports a potential hypertensive effect of Pb exposure. For Pb and DBP, results were in the hypothesized direction with DBP increasing with increasing quartiles of Pb concentrations, however, the 95% CI included the null value. No consistent or statistically significant associations

Table 3. Primary results: adjusted associations between outcomes of systolic and diastolic BP and exposures of Pb and Cd concentrations (K+ standardized)^a.

Outcomes	Metals exposures	N	Adjusted estimate (mmHg)	95% CI
Systolic BP	Pb (natural log-transformed, K+ standardized)	256	2.36	0.51, 4.20
Systolic BP	Pb (untransformed, K+ standardized)	256	1.03	0.93, 2.00
Systolic BP	Cd (untransformed, K+ standardized)	256	−0.30	−4.18, 3.58
Diastolic BP	Pb (natural log-transformed, K+ standardized)	256	1.42	0.16, 2.67
Diastolic BP	Pb (untransformed, K+ standardized)	256	0.61	−0.02, 1.25
Diastolic BP	Cd (untransformed, K+ standardized)	256	0.59	−2.04, 3.22

^a Adjusted for: age, 5 household assets (color TV, radio, mobile phone, bank account, bicycle), food insecurity, education, diet diversity, secondhand smoke exposure, physical activity (METs/day), and BMI (kg m^{-2}).

Table 4. Quartile results: adjusted associations between outcomes of systolic and diastolic BP and exposures of Pb and Cd concentrations as quartiles (K+ standardized, untransformed)^a.

Outcomes	Metals exposures	N	Adjusted estimate (mmHg)	95% CI
Systolic BP	Pb (untransformed, K+ standardized)	256		
	Q1	65	Reference	
	Q2	63	4.02	−0.83, 8.86
	Q3	64	5.52	0.66, 10.38
	Q4	64	5.67	0.81, 10.52
Systolic BP	Cd (untransformed, K+ standardized)	256		
	Q1	65	Reference	
	Q2	64	−4.52	−9.55, 0.50
	Q3	63	−1.34	−6.36, 3.68
	Q4	64	−2.07	−7.02, 2.87
Diastolic BP	Pb (untransformed, K+ standardized)	256		
	Q1	65	Reference	
	Q2	63	1.47	−1.85, 4.78
	Q3	64	2.50	−0.83, 5.82
	Q4	64	2.71	−0.62, 6.03
Diastolic BP	Cd (untransformed, K+ standardized)	256		
	Q1	65	Reference	Reference
	Q2	64	−1.85	−5.26, 1.57
	Q3	63	0.55	−2.87, 3.96
	Q4	64	−0.11	−3.47, 3.26

^a Adjusted for: age, 5 household assets (color TV, radio, mobile phone, bank account, bicycle), food insecurity, education, diet diversity, secondhand smoke exposure, physical activity (METs/day), and BMI (kg m^{-2}).

Table 5. Sensitivity analysis results: adjusted associations between outcomes of systolic and diastolic BP and exposures of Pb and Cd concentrations (K+ standardized), excluding BMI^a.

Outcomes	Metals exposures	N	Adjusted estimate (mmHg)	95% CI
Systolic BP	Pb (natural log-transformed, K+ standardized)	260	2.32	0.43, 4.21
Systolic BP	Pb (untransformed, K+ standardized)	260	0.99	0.03, 1.95
Systolic BP	Cd (untransformed, K+ standardized)	260	1.06	−2.86, 4.98
Diastolic BP	Pb (natural log-transformed, K+ standardized)	260	1.42	0.15, 2.70
Diastolic BP	Pb (untransformed, K+ standardized)	260	0.60	−0.05, 1.24
Diastolic BP	Cd (untransformed, K+ standardized)	260	1.43	−1.20, 4.06

^a Adjusted for: age, 5 household assets (color TV, radio, mobile phone, bank account, bicycle), food insecurity, education, diet diversity, secondhand smoke exposure, physical activity (METs/day).

were found between Cd levels and either SBP or DBP when considering Cd in quartiles. Overall, these findings were generally consistent with the primary models.

The sensitivity analysis (table 5) presents the adjusted associations between BP (both systolic and diastolic) and the concentrations of Pb and Cd, without adjustment for BMI. The association between Pb

Table 6. Effect modification models. Adjusted associations between outcomes of systolic and diastolic BP and exposures of Pb and Cd concentrations (K+ standardized), interactions with age and research site^a.

Personal exposures	<i>N</i>	Adjusted mean difference (mmHg) (95% CI)	<i>p</i> -value for interaction
Log-transformed Pb with SBP			
Age <51 years	128	1.25 (−1.43, 3.92)	0.26
Age ≥51 years	128	3.37 (0.81, 5.93)	
Guatemala	106	3.71 (0.43, 6.99)	0.43
Peru	116	1.06 (−1.33, 3.45)	
Rwanda	34	2.64 (−2.36, 7.63)	
Log-transformed Pb with DBP			
Age <51 years	128	1.60 (−0.22, 3.42)	0.78
Age ≥51 years	128	1.25 (−0.50, 2.99)	
Guatemala	106	1.51 (−0.69, 3.71)	0.94
Peru	116	1.02 (−0.58, 2.62)	
Rwanda	34	1.06 (−2.28, 4.41)	
Untransformed Cd with SBP			
Age <51 years	128	0.73 (−4.89, 6.36)	0.61
Age ≥51 years	128	−1.28 (−6.64, 4.07)	
Guatemala	106	−1.14 (−6.95, 4.67)	0.44
Peru	116	−0.67 (−6.12, 4.79)	
Rwanda	34	6.93 (−4.34, 18.20)	
Untransformed Cd with DBP			
Age <51 years	128	0.33 (−3.49, 4.14)	0.86
Age ≥51 years	128	0.78 (−2.85, 4.41)	
Guatemala	106	0.12 (−3.76, 3.99)	0.77
Peru	116	0.76 (−2.88, 4.40)	
Rwanda	34	3.26 (−4.27, 10.78)	

^a Adjusted for: age, 5 household assets (color TV, radio, mobile phone, bank account, bicycle), food insecurity, education, diet diversity, secondhand smoke exposure, physical activity (METs d^{−1}), and BMI (kg m^{−2}).

exposure (log-transformed and untransformed) and SBP remained statistically significant after removing BMI (e.g. 2.32 mmHg (95% CI 0.43, 4.21 for log-transformed Pb). After removing BMI, there was still no statistically significant association between Cd exposure and SBP. The association between Pb exposure (log-transformed) and DBP also remained statistically significant. For a unit increase in the natural log of Pb concentration, DBP increased by 1.42 mmHg (95% CI 0.15, 2.70). After removing BMI, there remained no statistically significant association between Cd exposure and DBP. The sensitivity analyses confirmed that the associations observed between Pb exposure and increased BP were robust, regardless of the inclusion or exclusion of BMI. Cd exposure continued to show no significant association with BP changes in the adjusted models.

Table 6 shows the effect modification results from the adjusted associations between outcomes of SBP and DBP and exposures of Pb and Cd concentrations with interaction effects of exposure by age (median cutoff of <51 years and ≥51 years), and by research site (Guatemala, Peru, and Rwanda). Among women ≥51 years, there was an association with increased SBP per log-unit increase in Pb (3.37 mmHg), though the confidence interval was large as shown in table 6 (95% CI 0.81, 5.93). Given the *p*-value for interaction was 0.26, while the association between SBP and Pb appeared stronger among older women compared to younger women, the difference in effect between the two age groups was not significant, as women ≤51 years experienced no significant association between increased SBP and Pb. No other interaction models showed statistically significant interactions across age groups or countries, as all *p*-values for interaction were above 0.05 and 95% CIs included the null value.

4. Discussion

Assessing metals' exposure on SBP and DBP can provide insights into the broader implications of environmental health risks' impacts on cardiovascular disease and inform public health strategies. A persistent public health concern in LMICs is high BP, where cooking with solid biomass fuel is a prevalent practice. This produces dangerous levels of household air pollution, to which exposure can lead to significant morbidity and mortality, with air pollution accounting for nearly 1 in 6 deaths in children under 5 across Africa. Since women are most often the ones preparing meals on biomass cookstoves, they tend to have higher levels of exposure [25].

These results provided an insightful overview of the baseline characteristics of the participants, highlighting important socioeconomic, health, and lifestyle factors. These factors are likely interrelated and may exacerbate disparities in health outcomes indicating significant health and socioeconomic challenges among the participants, such as overweight/obesity (65%), food insecurity with 36% experiencing mild and 17% moderate, and low educational attainment (77%). While most participants owned mobile phones (94%), fewer had access to other assets like radios (59%), televisions (49%), bicycles (31%), or bank accounts (30%). These findings reflect varying levels of SES and suggest limited access to diverse communication tools and financial services.

These results also provided a comprehensive analysis of the associations between BP and exposure to Pb and Cd among adult women across Guatemala, Peru, and Rwanda, highlighting regional variations in BP levels among study participants, with Rwanda and Guatemala generally exhibiting higher SBP and DBP levels compared to Peru. Consistent with findings from a population-based study in India, where 95% of participants with valid baseline BP measurements were normotensive (SBP <120 mmHg and DBP <80 mmHg) [26], the majority of our participants also exhibited BP within the normotensive range. Distributions of baseline SBP and DBP by study sites are visualized in figures 1 and 2. Thirteen pregnant women (2%) were considered as at hypertension stage 1, defined as SBP between 130 and 139 mmHg or DBP between 80 and 89 mmHg. Two individuals (<1% of the participants) were categorized as overly hypertensive, defined as SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg. Compared to national biomonitoring data from NHANES, our Pb concentrations were lower overall but within ranges associated with BP increases in older adults Navas-Acien *et al* [27]. Cd levels were similar to rural populations in Asia but lower than occupational studies [28].

Pb exposure, as indicated by the median levels, showed regional disparities, with Guatemala having the highest median Pb levels, followed by Peru and Rwanda. Cd exposure, on the other hand, exhibited similar median levels across the three research sites, indicating consistent central tendencies. Pb exposure (log-transformed) showed statistically significant positive associations with both SBP and DBP, with as much as a 2.36 mmHg and 1.42 mmHg increases observed in SBP and DBP, respectively. Cd exposure, however, did not show significant associations with BP changes.

Sensitivity analyses, which excluded adjustment for BMI, confirmed the robustness of the associations between Pb exposure and BP changes. Even after excluding BMI, the positive associations remained statistically significant. Cd exposure continued to show no significant association with BP changes, even after removing BMI. Assessing the exposures as quartiles suggested a dose-response relationship with Pb's effects on SBP and DBP.

Current literature suggests that high BP is a persistent public health concern in LMICs, where environmental factors such as air pollution from biomass fuel use significantly contribute to morbidity and mortality. Previous studies have demonstrated that household air pollution, which is common in low- and middle income countries due to the use of solid biomass fuels for cooking, disproportionately affects women, who often spend more time near cookstoves. This exposure contributes to adverse health outcomes, including cardiovascular diseases. Air pollution alone accounts for nearly one in six deaths among children under five years across Africa [29–31].

Prior research has also established a link between metal exposure and BP changes. For instance, a study in the United States that assessed associations of blood Pb, Cd, and mercury with resistant hypertension among adults in National Health and Nutrition Examination Survey, 1999–2018 showed that BP increased with higher concentrations of certain metals, including Pb (per 1 $\mu\text{g dl}^{-1}$ increase in blood Pb concentration, the proportion of resistant hypertension increased by 16% [adjusted odds ratio, 1.16; 95% confidence interval (CI) 1.01–1.32]). This study adds to the existing body of knowledge by examining the associations between BP and metal exposure in diverse geographical regions, namely Guatemala, Peru, and Rwanda [32]. Positive associations were also observed between exposure to metals and age, BMI and DBP in a study conducted in Peru [33]. In Korea a study found significant associations of blood Cd and Pb with higher hypertension prevalence and there was a significant interaction between blood Cd and physical activity on hypertension risk [34].

These findings also align with several previous studies showing a link between Pb exposure and increased BP. For instance, Navas-Acien *et al.* using NHANES data, observed that even low levels of Pb exposure were associated with higher SBP and DBP in older adults [27]. Similarly, Kaufman *et al* reported elevated BP among adults with increased Pb levels, suggesting that Pb may influence vascular resistance and endothelial function [35]. However, it is essential to report that some other studies that did not observe similar effects, which helps contextualize the results and strengthen the interpretation: Staessen *et al* in a European cohort found no consistent association between blood Pb concentrations and BP in normotensive adults, suggesting that the effect may depend on existing hypertensive status or other modifying factors [36]. Furthermore, the lack of significant findings for Cd in our study is consistent with Tellez-Plaza *et al* [37], who reported only a weak or non-significant relationship between urinary Cd and hypertension when adjusting for smoking and other confounders. This may reflect the complex biological mechanisms of Cd, where it accumulates in the kidneys and may impact BP only at higher, occupational exposure levels or through indirect mechanisms like kidney damage which is in line with our null findings for Cd [37].

These findings underscore the importance of understanding regional variations in BP levels and metal exposure for targeted public health interventions. The regional differences in Pb and Cd levels, as well as BP, are notable. Rwanda and Guatemala had higher median Pb levels and BP measures compared to Peru. These differences could be due to several factors: environmental sources, such as residual leaded gasoline, industrial emissions, or poorly regulated waste disposal, dietary habits, where food grown in contaminated soil or stored in certain containers could lead to higher exposure and nutritional deficiencies (e.g. calcium or iron), which may enhance Pb absorption and toxicity.

Moreover, this study highlights socioeconomic and health disparities among the participants: high rates of overweight/obesity, food insecurity, and low education—all of which may compound vulnerability to environmental toxins. When stratified by age, women ≥ 51 years exhibited a stronger association between Pb exposure and SBP, which is supported by a study which found that age may amplify the vascular effects of Pb due to cumulative exposure or age-related endothelial dysfunction [38]. Yet, interaction analyses by research site and age in our study did not reach statistical significance, suggesting that more granular or longitudinal data may be necessary to detect nuanced effects. The significant associations between Pb exposure and BP emphasize the need for policies and interventions aimed at reducing Pb exposure, especially in regions with high levels of exposure. Further research and monitoring are needed to better understand the mechanisms underlying the observed associations and to inform evidence-based interventions for preventing and managing hypertension and related cardiovascular diseases. Further research should employ longitudinal designs to assess causality, incorporate biological markers of oxidative stress and kidney function, explore gene-environment interactions that may explain individual susceptibility and evaluate the effectiveness of interventions (e.g. improved cookstoves, soil remediation, dietary supplements) in reducing metal exposure and mitigating cardiovascular risks.

4.1. Strengths and limitations

This study was limited by its cross-sectional design, which restricts causal inference. Furthermore, the relatively small sample size from Rwanda ($n = 34$) may have limited the power to detect region-specific interactions. Laboratory analyses of Pb and Cd were performed using dried blood spots rather than venous blood. Although this approach is acceptable, the concentration estimates derived may be less precise than those obtained from whole blood measurements. Biomarker data was only available at one time point, and additional biomarkers like urinary Cd or bone Pb were not assessed. While data were collected to estimate dietary intake, full exposure data from other sources of metals, such as ingestion of contaminated foods or exposure to other sources, was not assessed. Although Pb may act as a toxicant, in certain settings, it may also function as an indicator of air pollution exposure from biomass combustion. Future work may consider Pb as a potential mediator in this pathway. Several strengths are important to note, including the multi-country design, detailed adjustment for confounders, and robust sensitivity analyses.

5. Conclusions

Adjusted associations between SBP and DBP and Pb concentrations showed statistically significant positive associations, even after adjusting for various factors. The sensitivity analyses further confirmed the robustness of the observed associations between Pb exposure and increased BP, with a potential dose-response effect. In summary, these findings highlight potential implications for public health interventions, particularly in areas where people rely on biomass fuel to meet household energy needs,

and further research into the determinants of BP variations across different geographical contexts. Additionally, the associations between Pb exposure and increased BP warrant attention and may have implications for environmental and occupational health policies.

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This paper was submitted on behalf of the *HAPIN* investigators.

Data availability statement

No new data were created or analysed in this study.

Conflict of interest

All authors declare no conflict of interest.

Statement of data sharing

Deidentified data associated with the paper has been deposited in Emory's Dataverse data repository [39]. Dataverse is widely accessible and provides long-term access to the public and to related research communities.

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