THESIS

ASSOCIATION BETWEEN EXPOSURE TO CADMIUM AND LEAD DURING GESTATION AND ADVERSE BIRTH OUTCOMES IN THE HOUSEHOLD AIR POLLUTION INTERVENTION NETWORK (HAPIN) TRIAL

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ABSTRACT

ASSOCIATION BETWEEN EXPOSURE TO CADMIUM AND LEAD DURING GESTATION AND ADVERSE BIRTH OUTCOMES IN THE HOUSEHOLD AIR POLLUTION INTERVENTION NETWORK (HAPIN) TRIAL

Low- and middle-income countries (LMICs) are particularly vulnerable to the adverse effects of metal exposure. These countries' rapid industrialization coupled with population growth, result in substantial environmental exposures, which many governments have limited capacity to formally regulate. Even when regulations exist, many governments have a limited capacity to enforce those regulations. Additionally, LMICs bear a disproportionate burden of adverse birth outcomes, including low birth weight and preterm birth, which carry long-term health implications such as increased risk of chronic diseases, developmental delays, and mortality. Several studies have examined the association between metals and adverse birth outcomes such as low birth weight and preterm births. Specifically, despite the low number of studies, cadmium has been consistently linked to lower birth weights, smaller sizes for gestational age, and reduced head circumference. However, the association between lead exposure and birth outcomes shows inconsistent results. This inconsistency in findings, along with the low number of studies overall, especially in LMICs, regarding lead has prompted further investigation in our current study.

Here we utilized data from the Household Air Pollution Intervention Network (HAPIN) trial, a randomized controlled trial conducted in rural areas of Guatemala, Peru, Rwanda, and India. The HAPIN trial evaluated the impact of replacing biomass stoves with liquefied

petroleum gas stoves on various health outcomes, including infant birth weight among 3200 participants. The participants in the current analysis included pregnant women with a live singleton birth with exposure and birth data (n=2396). Maternal exposure to cadmium and lead were evaluated by analyzing dried blood spots using inductively coupled mass spectrometry. Blood spots were collected at baseline (9 - <20 weeks gestational age) and 32-36 weeks gestational age; we also evaluated the average of these two measurements. Birth weight was measured using a digital infant scale, with low birth weight defined as <2500 grams, and gestational age at birth was determined using screening data and ultrasonography, with preterm birth defined as <37 weeks.

We utilized linear regression for birth weight and gestational age, logistic regression for dichotomous low birth weight, and Cox proportional hazards model for preterm birth. The models accounted for infant sex, maternal age, nulliparity, body mass index, maternal hemoglobin, mother's dietary diversity, food insecurity, tobacco smoking in the household, and study arm. We assessed effect modification by study location, sex, and study arm by including an interaction term.

In sensitivity analyses, we included study location, household assets, maternal education in the models; replaced values below the limits of detection (LOD) with LOD/$\sqrt{2}$, and evaluated metal concentrations standardized by potassium levels. We also excluded maternal hemoglobin from the main model.

The mean birth weight was 3,020 (standard deviation [SD]=445.5) grams, and 10.3% of all births were classified as low birth weight. The mean gestational age was 39.5 weeks (SD=1.7 weeks), and 5.2% of the births were preterm. The median lead concentration across the time points was 1.4 µg/dL (IQR: 0.9 – 2.2 µg/dL), and the median cadmium concentration was 1.0

ng/mL (IQR: 0.7 – 1.4 ng/mL), values comparable to those found in other studies. Overall, the results did not indicate a consistent or strong association between lead or cadmium and adverse birth outcomes. Baseline cadmium levels showed a modest increase in the odds ratio for low birth weight (OR per IQR increase: 1.2, 95% CI: 0.97 to 1.47). Sensitivity analyses closely aligned with the main findings. All the results for effect modification did not indicate differences in the strata.

The study found a suggestive, but inconsistent evidence between exposure to cadmium and low birth weight. This study has some limitations. There is potential for non-differential measurement error due to the hematocrit effect, which alters the estimated spot volume based on participants' hematocrit levels. A sensitivity analysis using potassium standardized metal concentrations partially addressed this, but individual hematocrit variability can still bias the observed association towards the null, with a moderate magnitude. The probability of the bias is moderate. The chromatographic effect, which can cause variations in concentration due to the interaction between blood and the analyte with the filter paper, was also partially addressed using internal standards, blanks, calibration samples, quality controls, and reference materials. This potential bias is of low probability and magnitude, biasing the observed association toward the null. Confounding bias was considered a concern due to incomplete adjustment for covariates like seasonal variation, which can affect metal exposure and birth outcomes. Sensitivity analyses supported the main model findings, suggesting a low probability and magnitude of confounding bias, which could bias the observed association towards or away from the null. Despite residual confounding concerns linked to socio-economic indicators like assets and diet diversity, the sensitivity analyses did not deviate from the main model findings, indicating a small probability and magnitude of the bias, which would bias the observed association in either direction.

The study had several strengths including a large sample size compared to previous studies, especially those in LMICs and it was conducted in three distinct rural LMIC settings, which, to the best of our knowledge, had not been done before. This study's strength lies in its large sample size of 2,152 participants with complete data, enhancing its statistical robustness and addressing the common issue of small sample sizes and missing data in prior LMIC research. Additionally, its unique examination across three distinct rural LMIC settings provides valuable insights into the regional variations affecting the outcomes studied.

Future steps include using whole blood samples instead of dried blood spots (DBS) and measuring exposure at multiple time points, particularly at birth via the umbilical cord, could yield more accurate concentrations. It is also recommended that subsequent studies employ better socio-economic indicators to reduce residual confounding effects. Expanding the geographical scope of the study to include a broader range of urban areas within the HAPIN countries would improve the generalizability of the findings. Additionally, future research should consider analyzing the effects of metal mixtures to better replicate real-world environmental conditions and interactions. The results are generally consistent with existing limited data indicating no evidence of an association between lead and adverse birth outcomes and a potential association between higher cadmium exposure during pregnancy with increased risk of low birth weight.

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Chapter 1 - Introduction and Literature Review

Metals like cadmium and lead are naturally occurring elements in the Earth's crust that are shiny, ductile, and malleable (Mosher & Kelter, 2023). While metals are a part of the natural environment, anthropogenic activities have increased their levels in the environment, leading to increased exposure through air, water, and food (Balali-Mood et al., 2021). Exposure to metals is associated with various health issues such as kidney failure, elevated blood pressure, cancer, neurocognitive, neuropsychiatric, respiratory, and cardiovascular disorders (Balali-Mood et al., 2021).

Lead exposure in humans primarily occurs through ingestion or inhalation, leading to its absorption. It inhibits key enzymes such as delta-aminolevulinic acid dehydratase (ALAD) and glutathione reductase (GR), which triggers the release of free radicals (Nekeety et al., 2009; Wu et al., 2016). Lead's inhibition of GR reduces the availability of glutathione, a vital antioxidant, impairing the cell's ability to protect itself from oxidative stress (Wu et al., 2016). By acting on ALAD, lead increases delta-ALAD levels, promoting the formation of reactive oxygen species (ROS), which can lead to DNA and lipid damage (Ahamed et al., 2005; Wu et al., 2016). This is particularly concerning during pregnancy, as ROS can inhibit the Ca^{2+} placental transporter polycystin-2 in trophoblast membranes, potentially affecting placental function (Aouache et al., 2018). Furthermore, placental membrane disruption may trigger the onset of labor, potentially leading to preterm birth (Duhig et al., 2016). Lead also displaces essential elements like zinc, disrupting DNA binding and possibly affecting gene expression (Wu et al., 2016). This can have serious implications because a meta-analysis revealed a significant correlation between maternal zinc levels and birth weight (Atazadegan et al., 2022).

Cadmium exposure primarily occurs through skin contact, ingestion, or inhalation (Wu et al., 2016). It binds to metallothionein to form complexes that accumulate in organs like the liver, lungs, and kidneys due to inadequate excretion mechanisms (Jomova & Valko; Wu et al., 2016). While cadmium does not directly generate free radicals, it induces the production of nitric oxide, superoxide, and hydroxyl radicals (Waisberg et al., 2003; Wu et al., 2016). This mechanism involves cadmium displacing iron and copper from proteins, thereby allowing these metals to participate in oxidative stress (Wätjen & Beyersmann, 2004; Wu et al., 2016). During pregnancy, ROS can inhibit the placental transporter polycystin-2, compromising placental function (Aouache et al., 2018). Additionally, cadmium can cause placental necrosis, hinder trophoblastic growth, and alter nutrient transfer (Rani et al., 2014).

The adverse effects of exposure to metals on the environment are a global concern (Balali-Mood et al., 2021), and it is a problem that disproportionately impacts low- and middle-income countries (LMICs) (Heng et al., 2022). People in these countries are particularly vulnerable to the effects of metals, as LMICs are experiencing rapid industrialization and population growth, coupled with governments that have limited capacity to enforce regulations (Dowling et al., 2017).

The aforementioned scenario can be clearly seen in La Oroya, Peru, which was home to a metallurgical complex from 1922 to 2009 that mined and smelted heavy metals. Reuer et al. (2012) studied five locations located between 1 to 26 km from the complex, observing surface soil, drinking water, and indoor dust concentrations. The study revealed that all five locations had high levels of cadmium and lead in their soil, dust, and water. Similarly, mining in Guatemala has also led to high metal exposure levels. Basu et al. (2010) studied four field sites, three adjacent or downstream to the Marlin Mine, and one upstream. They collected samples of

hair, blood, urine, communal drinking water, and surface soil. Cadmium levels were similar across all sites, while lead levels increased with distance from the mine. Echoing these findings, in Rwanda, both the mining sector and artisanal and small-scale mining had severe environmental impacts. Muhire et al. (2021) collected water, soil, and vegetation from five mining sites near the Gishwati forest and compared them to a nearby site that was not mined. They found high levels of lead and cadmium in the water and soil of the mining sites.

Environmental pollution is not the only public health problem that LMICs face. Another public health issue that disproportionally affects LMICs is that of low birth weight, defined as birth weight less than 2500g, which puts low birth weight newborns at higher risk of morbidity and stunting in childhood, and in the long term, it increases the risk of adult-onset chronic conditions like cardiovascular disease (Blencowe et al., 2019; Fall, 2013). Similarly, preterm birth disproportionately affects LMICs and can increase mortality and morbidity of the preterm children (Ohuma et al., 2023; Saigal & Doyle, 2008).

To exemplify the issue of adverse birth outcomes in LMICs, in the 2019-2020 Rwanda Demographic and Health Survey, it was found that 7% of children with known birth weights were low birth weight. For home deliveries, the mothers' estimates were used to determine the children's size. According to the mothers, approximately 3% of births were very small, 15% were smaller than average, and the rest were estimated to be average or larger than average. Notably, the prevalence of low birth weight was slightly higher in rural settings, 7.1%, compared to urban settings, 6.2% (National Institute of Statistics of Rwanda - NISR et al., 2021). In Guatemala, another LMIC country, a study found that the prevalence of low birth weight among women enrolled in Madres Sanas, a program associated with the Center for Human Development in Southwest Trifinio, Guatemala, was 13.8%, which was higher than the national average of 10.9%

(S Himes et al., 2022). Finally, in Peru, another LMIC country, a pooled analysis of births between 2012 and 2019 from the national birth registry revealed important trends. The study found that the lowest mean birth weight was in the Highlands (2,954 grams in 2019), which is a rural and poor region, while the highest mean birth weight was in the Coast (3,516 g in 2019). However, the prevalence of low birth weight decreased from 6.9% in 2012 to 6.2% in 2019 (Carrillo-Larco et al., 2021). Looking at the overall trend, as of 2020, countries like Rwanda, Peru, and Guatemala have shown very little improvement in preterm birth rates from 2010 (Ohuma et al., 2023). The same is true for the rate of low birth weight in Rwanda and Guatemala during the same time period (Ohuma et al., 2023).

Studies that investigated the association between metals exposure and adverse birth outcomes fall into two broad categories. The first category comprises studies that look at individual metals, and the second category consists of studies that examine metal mixtures.

For instance, cadmium is notably implicated in numerous studies with adverse birth outcomes. Wai et al. (2017) examined the association between urinary cadmium and low birth weight in a cohort of 419 mother-infant pairs in Ayeyarwady Division, Myanmar, and found that the adjusted model had an OR of 1.10 (95% CI: 1.02–1.19) per 1 µg/g increase in creatinine-adjusted urinary cadmium. Barn et al. (2019) observed a 95 g (95% CI: 34, 155 g) decrease in birth weight associated with a doubling of blood cadmium levels from roughly 0.15 to 0.29 µg/L in 374 mother-child pairs in Ulaanbaatar, Mongolia. These findings are further supported by Kippler et al. (2012), who found a negative association between maternal urinary cadmium and birth weight, with a coefficient of -31.0 g (95% CI: -59, -2.8 g) and head circumference, with a coefficient of -0.15 cm (95% CI: -0.27, -0.026 cm), per 1 µg/L increase in urinary cadmium in a rural Bangladeshi cohort of 1616. However, the association was only found in girls, who had a

birth weight coefficient of -44.9 g (95% CI: -82.5, -7.3 g) and a head circumference coefficient of -0.26 cm (95% CI: -0.43, -0.088 cm) per 1 µg/L increase in urinary cadmium. In contrast, boys had a birth weight coefficient of -17.0 g (95% CI: -59.4, 25.4 g) and a head circumference coefficient of -0.051 cm (95% CI: -0.23, 0.13 cm) per 1 µg/L increase in urinary cadmium.

In a cohort of 1027 mother-infant pairs in Durham, North Carolina, Johnston et al. (2014) found that infants born to mothers with high blood cadmium levels (>0.50 µg/L) were more likely to be smaller for their gestational age, with an OR of 1.72 (95% CI: 1.1, 2.68) compared to those with low cadmium levels (≤2.8 µg/L). However, they did not find an association with low birth weight, as it had an OR of 1.07 (95% CI: 0.67, 1.73). The same was true for preterm birth, which had an OR of 1.17 (95% CI: 0.74, 1.87). Al-Saleh et al. (2014), examining a cohort of 1578 mother-infant pairs from Saudi Arabia, found a significant relationship between umbilical cord cadmium concentration and low birth weight, with an adjusted OR of 2.026 (95% CI: 1.148–3.575) per 1 µg/L increase in cadmium. However, a significant association was not found when adjusting for gestational age, as it resulted in an OR of 1.549 (95% CI: 0.807–2.973) per 1 µg/L increase in cadmium. However, a significant association was found when excluding preterm births, as it resulted in an OR of 1.634 (95% CI: 1.098–2.43) per 1 µg/L increase in cadmium. Finally, Lee et al. (2021) did not find an association between log-transformed cadmium and birth weight, which had a coefficient of 2.15 g (95% CI: -42.43, 46.73 g), but found significant associations with birth length, which had a coefficient of -0.31 cm (95% CI: -0.60, -0.01 cm) per IQR increase in log-transformed cord blood cadmium concentration in a cohort of 1088 mother-infant pairs in Bangladesh.

Lead exposure during pregnancy has also been studied, but the findings are less consistent compared to cadmium. Wai et al. (2017) found no significant relationship between

urinary lead concentrations and low birth weight in the adjusted model, which had an OR of 0.76 (95% CI: 0.57–1.03) per 1 µg/g increase in creatinine-adjusted urinary lead. Similar results were seen for preterm birth for the adjusted model, which had an OR of 0.98 (95% CI: 0.89–1.07) per 1 µg/g increase in creatinine-adjusted urinary lead. Similarly, Sweberath Misser et al. (2022) examined the association between blood lead levels (<3.5 µg/dL as the reference, and ≥ 3.5 µg/dL) and found an OR of 1.38 (95% CI: 0.40–4.79) in the adjusted model among 380 mother-infant pairs in Suriname. Regarding the association between lead and low birth weight, the Chi-squared test yielded a value of 0.974 with a p-value of 0.333.

In contrast, Cheng et al. (2017) investigated the relationship between lead exposure during pregnancy and preterm birth among 7299 mother-infant pairs in Hubei, China using creatinine-adjusted maternal urinary lead concentrations. In the highest tertile (>4.06 µg/g), they found an OR of 1.75 (95% CI: 1.30–2.36) in the adjusted model compared to the lowest tertile (≤2.29 µg/g). They also reported that women in this highest tertile had an adjusted gestational age in days of -0.58 (95% CI: -1.06, -0.11) compared to the lowest tertile. In contrast, Jelliffe-Pawlowski et al. (2006) found a non-significant increase of 1.6 g (SE: 3.4) in the adjusted model for pregnant women with max lead levels (≥10 µg/dL) in a 262 mother-infant pairs in California. However, the author did find a significant decrease of -0.3 days (SE: 0.1) for total gestational age for women with max lead levels. Finally, Lee et al. (2021) did not find an association between birth weight and lead exposure, with a change of 20.68 g (95% CI: -78.43, 37.08 g) per IQR increase in log-transformed cord blood lead concentration.

Wai et al. (2017) also investigated the association between creatinine-adjusted urinary arsenic concentrations and adverse birth outcomes, and found an OR of 0.99 (95% CI: 0.99–1.00) in the adjusted model for low birth weight per 1 µg/g increase in creatinine-adjusted

urinary arsenic. For the preterm birth models, the adjusted model yielded an OR of 1.00 (95% CI: 0.99–1.00) per 1 µg/g increase in creatinine-adjusted urinary arsenic. In contrast, Rahman et al. (2009) found that average urinary arsenic was associated with a decrease 1.68 g (SE=0.62) in the adjusted model per 1 µg/L increase in average urinary arsenic among a 1,578 mother-infant pairs in Matlab, Bangladesh. Finally, Lee et al. (2021) found no association between the log blood concentration of arsenic and birth weight (14.71 g [95% CI: -19.05, 51.36]), birth length (0.11 cm [95% CI: -0.12, 0.34]), or head circumference (-0.08 cm [95% CI: -0.19, 0.03]) per IQR increase log-transformed arsenic levels.

Vigeh et al. (2018) examined the impact of mercury exposure in 334 mother-child pairs in Tokyo, Japan, finding that higher prenatal mercury levels were present in umbilical cord blood compared to maternal blood, indicating significant placental transfer. In an adjusted birth weight model, the study reported a standardized beta coefficient of -0.170 for $\log_{10}$ blood mercury in the first trimester, with a p-value of 0.006. In contrast, Sweberath Misser et al. (2022) studied prenatal mercury exposure and found no significant association between mercury levels ≥3.5 µg/L (<3.5 µg/L as the reference) and stillbirth (Chi-squared: 2.472, p-value = 0.134), preterm birth (Chi-squared: 0.254, p-value = 0.648), low birth weight (Chi-squared: 2.270, p-value = 0.144), or Apgar scores <7 (Chi-squared: 1.284, p-value = 0.337) compared to the reference of <3.5 µg/L. They also examined manganese levels (≥13.0 µg/L) and found no association with stillbirth (Chi-squared: 2.402, p-value = 0.195), preterm birth (Chi-squared: 2.684, p-value = 0.117), low birth weight (Chi-squared: 0.764, p-value = 0.408), or Apgar scores <7 (Chi-squared: 1.038, p-value = 0.333) compared to reference values (≥13.0 µg/L). Finally, Lee et al. (2021) identified a significant association between log-transformed umbilical cord manganese

concentrations and birth weight, finding a coefficient of -29.32 g (95% CI: -58.36, -0.29 g) per IQR increase log-transformed manganese levels.

Recent research has begun to explore the relationship between metal mixtures and birth outcomes, recognizing that real-world exposures often involve multiple metals simultaneously. Berky et al. (2023) assessed the impact of a mix of minerals (zinc, magnesium, calcium, selenium, and iron) and toxic metals (lead, mercury, arsenic, and cadmium) on birth outcomes in a 198 mother-child pairs in Peru. They found that a 1% increase in maternal blood lead levels, accounted for by creating latent variables for maternal and fetal metal environments that included the aforementioned metals, shortened gestational age by 0.05 days (beta = -0.75; 95% CI: -1.51, -0.13). This potentially reduces gestational age by 3.6 days and birth weight by 76.5 grams if blood lead levels reach the 5 µg/dL threshold. This suggests that the combined effects of multiple metals can differ from those of individual metals. Similarly, Howe et al. (2020) used Bayesian kernel machine regression to investigate relationships between several metals (cadmium, cobalt, mercury, nickel, molybdenum, lead, antimony, tin, and thallium) and birth weight for gestational age in a California cohort of 262 mother-infant pairs. Mercury and nickel had the highest posterior inclusion probabilities (PIPs) of 0.40 and 0.35, respectively. Mercury had an inverse linear relationship with birth weight for gestational age, while nickel showed a positive association at low to moderate concentrations. Lee et al. (2021) investigated a mixture of arsenic, cadmium, manganese, and lead, finding significant decreases in birth length when all four metal concentrations were ≥ 60th percentile and a decrease in head circumference when all four were ≥ 55th percentile. Lastly, Michael et al. (2022) found chromium and thallium to be inversely associated with birth weight, with PIPs of 0.757 and 0.646, respectively in a 975

mother-infant pairs in Israel. Cadmium, with a PIP of 0.350, had a negative association with birth weight, while lead, with a PIP of 0.434, showed a positive relationship with birth weight.

To address the gaps in the literature, we evaluated the association between exposure to cadmium and lead during gestation and birth outcomes, including birth weight, low birth weight, gestational age at birth, and preterm birth. We hypothesized that exposure to cadmium and lead during gestation is inversely associated with birth weight and gestational age at birth and positively associated with low birth weight and preterm birth.

As the research shows, there are a still conflicting results about what metals are associated with adverse birth outcomes. We will leverage data from the Household Air Pollution Intervention Network (HAPIN) trial to address this gap. The HAPIN trial is a randomized controlled trial conducted in rural areas in Guatemala, India, Peru, and Rwanda, evaluating the effects of a liquefied petroleum gas stove and fuel intervention on biomass users during pregnancy and early childhood. The trial has four primary outcomes: infant birth weight, growth stunting in infants, severe pneumonia in infants, and systolic blood pressure in women living in the same household as pregnant women (Clasen et al., 2022). Leveraging dried blood spots (DBS) collected from the pregnant women at baseline (<20 weeks gestation) and 32-36 weeks gestation, the impact of exposure to cadmium and lead during pregnancy on birth outcomes in rural regions of LMICs was evaluated. The data on metals were not available for India; hence, we focused on the 2,396 enrolled and randomized participants from the three remaining countries.

To summarize, there are gaps in understanding the impact of lead and cadmium exposure during gestation and birth outcomes in rural settings of LMICs. Hence, by addressing these gaps, public health can better understand the effects of cadmium and lead exposure in vulnerable

populations, which aids in the development of targeted interventions, improved health outcomes, and public health policy that limits exposure to these metals. Small health improvements at a population level can have significant benefits for public health (Rose, 2001), making this research essential.

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Chapter 2 - Association Between Exposure to Cadmium and Lead During Gestation and Adverse Birth Outcomes in the Household Air Pollution Intervention Network (HAPIN) Trial

Summary

Background

Metals exposure is a global problem linked to negative health outcomes, including adverse birth outcomes. Limited data exists on metal exposure and adverse birth outcomes, especially in LMICs, with studies consistently finding associations with cadmium, while those on lead show more inconsistent results.

Methods

This study used data from the Household Air Pollution Intervention Network (HAPIN) trial to assess the association between exposure to cadmium and lead during gestation and birth weight, low birth weight, gestational age, and preterm birth, adjusting for relevant covariates. The study had a total of 2,396 participants from Guatemala (n=800), Peru (n=798), and Rwanda (n=798). There were 2,152 mother-infant pairs with complete data included in the birth weight analyses and 2,191 mother-infant pairs with complete data included in the gestational age analyses.

Results

The mean birth weight was 3,020 ± 446 g (median = 3,020, IQR: 2,743–3,300), with 10.3% classified as low birth weight, and the mean gestational age was 39.5 ± 1.7 weeks (median = 39.6, IQR: 38.7–40.4), with 5.2% preterm births. Median lead and cadmium concentrations were 1.4 µg/dL (IQR: 0.9–2.2) and 1.0 ng/mL (IQR: 0.7–1.4), respectively, which align with other studies on LMIC cohorts. The results did not generally indicate an association between lead or cadmium exposure and adverse birth outcomes, though baseline cadmium exposure

showed a modest increase in the odds of low birth weight (OR: 1.2 per IQR increase, 95% CI: 0.97–1.47). Sensitivity analyses supported these findings, and there was no evident effect modification by intervention, sex, or study location.

Discussion

In line with previous literature, this study found a suggestive yet inconsistent association between cadmium and low birth weight. Despite potential limitations such as non-differential exposure misclassification and confounding, the study's robust methodology and large sample size provide valuable insights. However, the observed inconsistencies in the findings indicate the need for cautious interpretation. This study contributes to our understanding of how metal exposure may affect birth outcomes in rural LMIC settings, though further research is necessary to clarify these relationships. Further research should explore the association between metals and adverse birth outcomes using whole blood or urine samples as well metals mixtures.

Introduction

Metals such as cadmium and lead are abundant in the Earth's crust (Mosher & Kelter, 2023). However, human activities have significantly elevated their environmental levels, posing health risks through exposure via air, water, and food sources (Balali-Mood et al., 2021). The adverse health effects associated with metal exposure range from kidney failure to neurocognitive disorders (Balali-Mood et al., 2021).

Exposure to these metals commonly occurs through multiple routes, including skin contact, ingestion, and inhalation (Jomova and Valko, 2011; Nekeety et al., 2009; Wu et al., 2016). Lead exposure, for example, can lead to the formation of harmful reactive oxygen species (ROS), while cadmium accumulates in vital organs, generating oxidative stress (Ahamed et al., 2005; Jomova and Valko, 2011; Wu et al., 2016).

The global concern regarding the harmful effects of metal exposure is particularly pronounced in low- and middle-income countries (LMICs), where rapid industrialization, population growth, and limited governmental capacity for formal regulation and enforcement create substantial environmental exposures (Heng et al., 2022) (Dowling et al., 2017). LMICs such as Peru, Guatemala, and Rwanda, with poorly regulated mining industries, face heightened risks of metal exposure (Basu et al., 2010; Muhire et al., 2021; Reuer et al., 2012).

Furthermore, LMICs bear a disproportionate burden of adverse birth outcomes such as low birth weight and preterm birth, which have long-term health implications (Blencowe et al., 2019; Fall, 2013; Ohuma et al., 2023; Saigal & Doyle, 2008). Cadmium has been consistently linked to lower birth weights, smaller sizes for gestational age, and reduced head circumference (Al-Saleh et al., 2014; Barn et al., 2019; Johnston et al., 2014; Kippler et al., 2012; Wai et al., 2017). However, the association between lead exposure and birth outcomes shows inconsistent results, with some studies finding an association (Cheng et al., 2017; Lee et al., 2021; Sweberath Misser et al., 2022; Wai et al., 2017). This inconsistency in findings regarding lead has prompted further investigation in our current study. To address this research gap, the Household Air Pollution Intervention Network (HAPIN) trial data presents a unique opportunity to investigate the association between cadmium and lead exposure during gestation with adverse birth outcomes in rural LMIC settings.

Methods

Study Design and Population

We investigated the association between cadmium and lead exposure during gestation and birth outcomes, including birth weight, low birth weight, gestational age at birth, and preterm birth, across three locations within the HAPIN trial: Jalapa, Guatemala; Puno, Peru; and Eastern

Province, Rwanda. Full details about the trial can be found elsewhere (Barr et al., 2020; Clasen et al., 2020; Clasen et al., 2022). Briefly, The HAPIN trial is a randomized controlled trial conducted in rural areas in Jalapa, Guatemala; Tamil Nadu, India; Puno, Peru; and Eastern Province, Rwanda, evaluating the effects of a liquefied petroleum gas stove and fuel intervention on biomass users during pregnancy and early childhood. The trial has four primary outcomes: infant birth weight, growth stunting in infants, severe pneumonia in infants, and systolic blood pressure in women living in the same household as pregnant women (Clasen et al., 2022). Participants were recruited between 9 and < 20 weeks gestation, and data collection occurred at baseline, 32-36 weeks gestation, and birth. All participants provided informed consent; the HAPIN study protocols were reviewed and approved by the institutional review boards or ethics committees of Emory University, Johns Hopkins University, Universidad del Valle de Guatemala, Asociación Benéfica PRISMA, the London School of Hygiene and Tropical Medicine, and Washington University in St. Louis, the Guatemalan Ministry of Health National Ethics Committee, and the Rwandan National Ethics Committee. This analysis included 2,396 pregnant women: 800 from Guatemala, 798 from Rwanda, and 798 from Peru; participants from the India location of the HAPIN trial were not included because we do not have data on lead and cadmium for those participants.

Exposure to Lead and Cadmium During Pregnancy

The study examined maternal cadmium and lead concentrations at baseline, 32-36 weeks gestations, and the average of these two measurements. Maternal dried blood samples were collected following HAPIN protocols (Barr et al., 2020). First, fingers were sterilized with an alcohol wipe and pricked, ensuring the removal of the first drop of blood. Five blood spots were then collected and left to dry at room temperature for a minimum of 24 hours. Subsequently, the dried blood spots were securely packaged in zip-top bags containing desiccant packets and

shipped from the HAPIN countries to the Biomarker Core at Emory University. Upon arrival, the dried blood spots were soaked in 200 µL phosphate-buffered saline (PBS) to release the dried blood. The samples underwent digestion using nitric acid on a heater block at 90°C for one hour to break down molecular components. Following digestion, the matrix was diluted with buffer and injected into an inductively coupled plasma mass spectrometer (ICP-MS). Multiple isotopes of each metal were monitored to ensure the reliability of results, with yttrium being employed as an internal standard to facilitate accurate measurements.

Additionally, each DBS card served as its own blank by finding a part of the card that did not contain blood and punching a blood spot-sized portion. Furthermore, each analytic run included three extra laboratory blanks, calibration samples, NIST reference material SRM 1643f, and two levels of quality control samples. Finally, spectral interferences were addressed by utilizing internal standards and a dynamic collision reaction cell to remove them.

The limits of detection for cadmium were 0.1 ng/mL and 0.001 µg/dL for lead, with relative standard deviations of 4% and 7%, respectively. Additionally, the NIST SRM recoveries were 99 (SD: 3) and 101 (SD: 4), for cadmium and lead, respectively. In the primary analyses, the instrument-provided values were utilized. In sensitivity analyses, values below the limit of detection (LOD) were replaced with the LOD/$\sqrt{2}$. Specifically, for baseline data, 14 (0.59%) cadmium values and 1 (0.4%) lead value were replaced. At 32-36 weeks gestation, 102 (4.29%) cadmium values and 1 (0.4%) lead value were replaced.

Birth Outcomes

The study assessed several birth outcomes, including birth weight, low birth weight, gestational age at birth, and preterm birth. Birth weight measurements were obtained within 24 hours of delivery for infants assessed at healthcare facilities (Clasen et al., 2020). Trained field

workers or nurses utilized the Seca 334 mobile digital baby scale to measure birth weight, either with infants unclothed or wearing pre-weighed clothing. Duplicate measurements were recorded to the nearest 10 grams, and in cases where discrepancies exceeded 10 grams, a third measurement was taken, with the two closest measurements being averaged. In instances where immediate birth weight measurement was not feasible, often due to logistical constraints such as coronavirus disease 2019 restrictions or neonatal admittance to intensive care units, birth weights provided by the healthcare facility were utilized. Low birth weight was defined as birth weight <2500 grams. Gestational age at birth was estimated based on gestational age at recruitment and further corroborated by ultrasonography. Preterm birth was defined as birth at <37 weeks of gestational age (Clasen et al., 2020; Clasen et al., 2022).

Statistical Analyses

Linear regression was used for analyzing birth weight and gestational age at birth, while logistic regression was used for assessing low birth weight. A Cox proportional hazards model was utilized for analyzing preterm birth, as the data is available and it has greater statistical power to detect exposure effects compared to logistic regression. All linear and logistic regression analyses were done using the "stats" R package and the cox proportional hazard analyses used the "survival" package using R version 4.3.1. The analysis used measurements of lead and cadmium at baseline (<20 weeks) and at 32-36 weeks gestation, as well as the average of the two measurements. For the gestational age and preterm birth analyses, only baseline metal measurements were considered, without adjustment for study arm, since earlier births are more likely to be missing values for the exposure, which is not missing at random since the availability of data may be dependent on the outcome. Hence, this would likely result in selection bias. Covariates were determined a priori based on literature and directed acyclic graphs. The covariates included infant sex, maternal age

(<20, 20-24, 25-29, 30-35), nulliparity, body mass index, maternal hemoglobin, mother's minimum dietary diversity during the previous month using an adapted version of the Food and Agriculture Organization Minimum Diet Diversity for Women (MDD-W) (low [<4], medium [4-5], high [>5]), food insecurity using the Food and Agriculture Organization Food Insecurity Experience Scale (FIES) (food secure [0], mild [1,2,3], moderate [4,5,6]/severe [7,8] (combined)), whether someone in the household smoked tobacco, and study arm. The study arm was not included in models evaluating the baseline time point analysis of birth weight and low birth weight because the participants had not yet been assigned to a study arm.

Potential effect modification by infant sex, study site, and study arm was examined by including an interaction term. Sensitivity analyses further adjusted for study location, household assets, maternal education, replacing values below the LOD with LOD/$\sqrt{2}$, and excluding hemoglobin from the main analysis. Additionally, a sensitivity analysis was also conducted using metal values standardized to 4 mmol/mL potassium. Participants with missing exposure, outcome, or covariate values were excluded from the analysis.

Results

There were 2,152 participants with complete covariate and exposure data for birth weight, with 733 participants in Guatemala, 687 from Peru, and 732 from Rwanda (Table 1). Among the original 2,396 participants (Table S1), 151 (6.3%) were missing birth weight data (Table S2) while 19 (0.79%) were missing exposure data (all participant either had both exposure data, or were missing both) (Table S3). There are other covariates with higher number of missing data including 110 (4.6%) missing values for infant sex and 42 (1.75%) for household food insecurity score (Table S1). Examining the characteristics by study location, it becomes apparent that maternal age, household food insecurity score, diet diversity score, maternal

education, and assets owned were different among study locations, with Peru having the most favorable results in those categories (Table 1).

There were 2,191 participants with complete covariate and exposure data for gestational age at birth with 752 participants from Guatemala, 697 from Peru, and 742 from Rwanda (Table S4). Among the original 2,396 participants, 110 (4.6%) were missing birth gestational age at birth data (Table S2). Examining the characteristics by study location, it becomes apparent that maternal age, household food insecurity score, diet diversity score, maternal education, and assets owned differed, with Peru having the most favorable results in those categories (Table S4). The participants included in the final analyses for birth weight and gestational age at birth had similar characteristics (Table 1, Table S4).

The mean birth weight for the participants included in the birth weight analyses was 3,020 ± 446 g (median: 3,020 g, IQR: 2,742–3,300 g). Out of the 2,152 births, 221 were classified as low birth weight, representing 10.3% of all births. There were differences in birth weight and low birth weight percentages between study locations. For instance, Peru had the highest birth weight at 3,184 ± 408 g (median: 3,200 g, IQR: 2,934 – 3,458 g) and the lowest percentage of low birth weight at 4.2%. In contrast, Guatemala had the lowest birth weight at 2,866 ± 428 g (median: 2,870 g, IQR: 2,604 – 3,143 g) and the highest percentage of low birth weight at 16.6% (Table S5, Figure 1). The mean gestational age at birth among the 2,191 participants was 39.5 ± 1.7 weeks (median: 39.6 weeks, IQR: 38.7–40.4 weeks), with preterm births comprising 5.2% of the total, with little variation between study locations (Table S5, Figure 1).

For the participants included in the birth weight analyses, the median cadmium concentration was 1.0 ng/mL (IQR: 0.7–1.3 ng/mL) with a mean of 1.0 ± 0.4 ng/mL, and the

median lead concentration was 1.4 µg/dL (IQR: 0.9–2.1 µg/dL) with a mean of 2.1 ± 2.1 µg/dL. By 32–36 weeks gestation, the median cadmium concentration remained at 1.0 ng/mL (IQR: 0.5–1.5 ng/mL) with a mean of 1.1 ± 0.7 ng/mL. Similarly, the median lead concentration during this period was 1.4 µg/dL (IQR: 0.9–2.3 µg/dL) with a mean of 2.1 ± 2.4 µg/dL. The median values for average cadmium and lead concentrations were 1.0 ng/mL (IQR: 0.7–1.4 ng/mL) with a mean of 1.1 ± 0.5 ng/mL, and 1.4 µg/dL (IQR: 0.9–2.2 µg/dL) with a mean of 2.1 ± 2.2 µg/dL (Table S6). The distribution of maternal metal concentrations was similar across study locations and across participants included in the gestational age analyses and all participants with exposure data (Table S3, Table S7, Figure 2, Figure S1).

Analysis of birth weight models at baseline, 32-36 weeks gestation, and average cadmium dried blood concentrations indicated a decrease of 6.2 grams (95% CI: -31.36, 19.06), an increase of 16.2 grams (95% CI: -8.19, 40.61), and an increase of 10.5 grams (95% CI: -15.59, 36.66), respectively, per IQR increase (Table 2). Birth weight models evaluating baseline, 32-36 weeks gestation, and average lead dried blood concentrations showed increases of 8.5 grams (95% CI: -1.48, 18.44), 6.8 grams (95% CI: -3.84, 17.42), and 7.8 grams (95% CI: -2.46, 17.97), respectively, per IQR increase. Furthermore, the analysis of gestational age at birth and baseline cadmium concentrations has shown that an IQR increase was associated with a 0.02 week (95% CI: -0.12, 0.07) decrease in gestational age at birth. The analysis of gestational age at birth and baseline lead concentrations has shown that an IQR increase was associated with a 0.03 week (95% CI: -0.12, 0.07) increase in gestational age at birth (Table 2).

Low birth weight models at baseline, 32-36 weeks gestation, and average cadmium dried blood concentrations yielded odds ratios (OR) of 1.2 (95% CI: 0.97, 1.47), 1.0 (95% CI: 0.81, 1.21), and 1.1 (95% CI: 0.87, 1.32), respectively, per IQR increase (Table 2). Conversely,

models under baseline, 32-36 weeks gestation, and average lead dried blood concentrations resulted in ORs of 1.0 (95% CI: 0.92, 1.09), 1.0 (95% CI: 0.93, 1.11), and 1.0 (95% CI: 0.93, 1.10), respectively, per IQR increase (Table 2). For preterm birth, the model baseline cadmium dried blood concentration resulted in a hazard ratio (HR) of 1.0 (95% CI: 0.77, 1.30), whereas the baseline lead dried blood concentration model showed an HR of 1.0 (95% CI: 0.89, 1.10).

The sensitivity analyses did not reveal any substantial differences in the main results of the study (Tables S8, S9, S10, S11, S12, and S13). Additionally, there was no evident effect modification based on study location, infant sex, or study arm (Tables S14, S15, S16, and S17). The exposure-quartile analysis did not show any discernible trends and did not yield a significant p-value for linear trends (Table S18).

Discussion

The results suggest an association for cadmium and adverse birth outcomes at baseline, but the results for 32-36 weeks are equally suggestive in the opposite direction. Sensitivity analyses closely aligned with the main findings. These findings support existing literature as previous research, though limited, has found a consistent association between cadmium exposure and adverse birth outcomes while the association between lead and adverse birth outcomes has been inconsistent. For instance, a study on a Myanmar population found that higher maternal creatinine-adjusted urinary cadmium concentrations were associated with low birth weight in newborns, as shown in the adjusted model, which had an OR of 1.10 (95% CI: 1.01–1.21) per 1 µg/g increase in creatinine-adjusted urinary cadmium (Wai et al., 2017). A study in Ulaanbaatar, Mongolia, also observed a 95-gram (95% CI: 34–155 grams) decrease in birth weight linked to a doubling of blood cadmium levels from approximately 0.15 to 0.29 µg/L (Barn et al., 2019). In contrast, in a Suriname study population, the association between blood lead levels (<3.5 µg/dL

as the reference and ≥ 3.5 µg/dL) was found to have an OR of 1.38 (95% CI: 0.40–4.79) in the adjusted model (Sweberath Misser et al., 2022). In another study that investigated the relationship between lead exposure during pregnancy and preterm birth, creatinine-adjusted maternal urinary lead concentrations in the highest tertile (>4.06 µg/g) were linked to an OR of 1.75 (95% CI: 1.30–2.36) in the adjusted model compared to the lowest tertile (≤2.29 µg/g). Furthermore, women in this highest tertile had an adjusted gestational age (days) of -0.58 (95% CI: -1.06, -0.11) in the adjusted model compared to the lowest tertile (Cheng et al., 2017). Hence, understanding how lead and cadmium exposure impacts birth outcomes is crucial, given the large number of the global population exposed to these metals (Doccioli et al., 2024; Ericson et al., 2021).

Exposure to lead in humans typically occurs through ingestion or inhalation, leading to its absorption into the body (Nekeety et al., 2009; Wu et al., 2016). Lead inhibits two crucial enzymes, delta-aminolevulinic acid dehydratase (ALAD) and glutathione reductase (GR), which triggers the release of free radicals in the body (Wu et al., 2016). By disrupting GR, responsible for recycling oxidized glutathione (GSSG) to reduced glutathione (GSH), lead reduces the availability of GSH—a vital antioxidant that protects cells from oxidative damage (Wu et al., 2016). GSH also supports the function of antioxidant enzymes like glutathione peroxidases, glyoxalases, and glutathione S-transferases (Wu et al., 2016). Additionally, lead acts on ALAD, increasing delta-ALAD levels, which promotes the formation of reactive oxygen species (ROS) (Ahamed et al., 2005; Wu et al., 2016). This is concerning as ROS can oxidize nitric oxide in vascular endothelial cells, forming peroxynitrite (ONOO-), which causes DNA and lipid damage (Wu et al., 2016). In pregnancies, ROS can inhibit the Ca^{2+} placental transporter polycystin-2 in trophoblast membranes, potentially impacting placental function (Aouache et al., 2018).

Furthermore, disruption of the placental membrane is thought to trigger labor, potentially causing preterm birth (Duhig et al., 2016). Lead can also displace elements such as zinc in proteins, disrupting their DNA binding and potentially altering gene expression (Wu et al., 2016). This is problematic because a recent meta-analysis has found a significant pooled correlation (r: 0.09, 95% CI: 0.04 to 0.15) with significant heterogeneity (I^2% = 63) between maternal blood zinc concentrations and birth weight (Atazadegan et al., 2022).

Similarly, human exposure to cadmium primarily occurs through skin contact, ingestion, or inhalation (Wu et al., 2016). Once cadmium enters the body, it binds to metallothionein, forming cadmium-metallothionein complexes that accumulate in organs like the liver, lungs, kidneys, and pancreas due to the lack of effective excretion mechanisms (Jomova and Valko; Wu et al., 2016). These complexes disrupt the cellular thiol redox balance, contributing to oxidative stress (Wu et al., 2016). Although cadmium itself does not generate free radicals, it induces the production of nitric oxide, superoxide, and hydroxyl radicals (Waisberg et al., 2003; Wu et al., 2016). This mechanism involves cadmium displacing iron and copper from cytoplasmic and membrane proteins, freeing these metals to participate in oxidative stress via the Fenton reaction (Wätjen & Beyersmann, 2004; Wu et al., 2016). The ROS can potentially impact placental function by inhibitinting the Ca^{2+} placental transporter polycystin-2 in trophoblast membranes (Aouache et al., 2018). Cadmium has also been shown to cause placental necrosis, retard trophoblastic outgrowth, and alter nutrient handling in the placenta (Rani et al., 2014).

Within our study, the potential presence of non-differential measurement error of the exposure warrants consideration, particularly given the inherent limitations of DBS in measuring metal values. The two main potential sources of non-differential measurement error in DBS measurements are the chromatographic effect and the hematocrit effect. The chromatographic

effect, which occurs from the interaction of blood and/or the analyte with the filter paper, can cause significant differences in concentrations measured in different punches. This has been addressed in the methods through various steps. First, each DBS card served as its own blank by finding a part of the card that did not contain blood and punching a blood spot sized. Furthermore, three additional laboratory blanks, calibration samples, NIST reference material SRM 1643f, and two levels of quality control samples were used per analytic run. In addition to the internal standards used, spectral interreference with a dynamic collision reaction cell were removed. Finally, all samples were blank subtracted. Given the methods, the probability and magnitude of the bias is likely to be low and towards the null.

In terms of addressing the hematocrit effect, which alters the volume estimate of the spot, a sensitivity analysis using metal values standardized to 4 mmol/mL potassium to correct for volume discrepancies did not show substantial deviations from the main findings. However, given the nature of the hematocrit effect and the variability of hematocrit amongst individuals due to reasons like age, sex, pathological conditions, nutritional status, and pregnancy (Daousani et al., 2019), the potassium standardization may not be sufficient in addressing the bias; hence, the probability and magnitude of the bias is likely to be moderate and towards the null. Finally, another limitation is that of the dried blood spots measurements not being representative of the true exposure. However, conducting two measurements helped address this limitation to some extent, thus; given that this is classic error, the probability and magnitude of the bias is low and towards the null.

Furthermore, confounding bias emerges as another significant concern. Certain covariates essential for understanding the relationship between metal exposure and birth outcomes may not have been comprehensively adjusted for in our analysis. For instance, seasonal variation may

contribute to increased exposure to metals due to changes in activities and could also be linked to birth outcomes through seasonal illnesses or nutritional variations. However, the robustness of our findings is supported by sensitivity analyses, which produced results consistent with those of the main model. This suggests that while these biases are acknowledged, they are unlikely to alter the overall conclusions of our study. Therefore, the probability and magnitude of confounding bias are low, and it is likely to cause shifts in the observed association either toward or away from the null.

Additionally, the potential for residual confounding warrants acknowledgment in this study. Some variables, such as owned assets, food insecurity, dietary diversity, and maternal education, serve as imperfect indicators of socio-economic status. These variables can influence the observed relationships, complicating the interpretation of findings. Despite this concern, sensitivity analyses did not reveal substantial deviations from the main models' findings, providing reassurance about the robustness of the conclusions. Thus, the probability and magnitude of bias are likely small, and it may shift the observed association either toward or away from the null.

The primary strength of this study lies in its substantial sample size, which stands in stark contrast to previous research, particularly those conducted in LMICs, which often suffered from small population sizes and significant amounts of missing data, particularly concerning covariates (Barn et al., 2019; Cheng et al., 2017; Sewberath Misser et al. 2022; Wai et al, 2017). By contrast, this study included 2,152 participants with complete exposure, outcome, and covariate data, thereby bolstering its statistical robustness. A further strength of the study lies in its unique geographical scope. To the best of our knowledge, no prior research has explored similar interventions or phenomena across three distinct rural LMIC settings: Jalapa, Guatemala;

Puno, Peru; and Eastern Province, Rwanda. This multifaceted approach not only enhances the study's breadth but also offers valuable insights into the contextual variations and similarities that may influence the outcomes under investigation.

Given the primarily null associations observed between cadmium and lead exposure and adverse birth outcomes, future research should delve deeper into these relationships using whole blood or urine samples to address the inherent limitations of DBS. Additionally, measuring the exposure at multiple time points, including at birth via the umbilical cord, could provide more accurate exposure assessments. Future studies should also use more accurate socio-economic indicators to reduce residual confounding. Furthermore, expanding the geographical scope to include more urban areas across HAPIN countries would enhance the generalizability of the findings. Finally, analyzing the effects of metal mixtures would better replicate real-world environmental conditions and interactions.

Conclusion

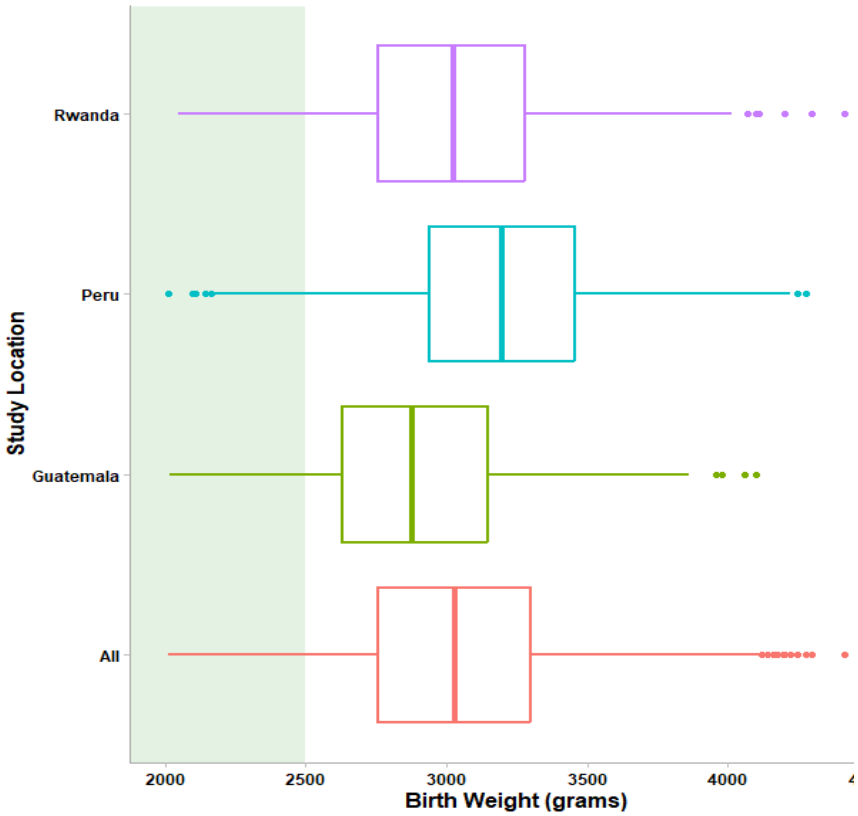
The results of the study support the existing literature on the association between lead and adverse birth outcomes; however, the findings for cadmium do not align with current literature. Future studies should utilize more accurate exposure measurements, either through whole blood or urine samples. Finally, analyzing metal mixtures would help replicate real-world environmental conditions and interactions.

Table 1. Baseline maternal characteristics by study location and overall.
Data are n (%) or median (IQR). Descriptive statistics are based on the number of pregnant women included in the birth weight and low birth weight analyses.

	Study Location			Overall
	Guatemala, N = 733	Peru, N = 687	Rwanda, N = 732	N = 2,152
Study Arm				
Control	367 / 733 (50%)	332 / 687 (48%)	372 / 732 (51%)	1,071 / 2,152 (50%)
Intervention	366 / 733 (50%)	355 / 687 (52%)	360 / 732 (49%)	1,081 / 2,152 (50%)
Age				
<20	114 / 733 (16%)	86 / 687 (13%)	44 / 732 (6.0%)	244 / 2,152 (11%)
20-24	297 / 733 (41%)	248 / 687 (36%)	182 / 732 (25%)	727 / 2,152 (34%)
25-29	212 / 733 (29%)	221 / 687 (32%)	275 / 732 (38%)	708 / 2,152 (33%)
30-35	110 / 733 (15%)	132 / 687 (19%)	231 / 732 (32%)	473 / 2,152 (22%)
Sex				
Female	356 / 733 (49%)	339 / 687 (49%)	357 / 732 (49%)	1,052 / 2,152 (49%)
Male	377 / 733 (51%)	348 / 687 (51%)	375 / 732 (51%)	1,100 / 2,152 (51%)
Nulliparity	206 / 733 (28%)	259 / 687 (38%)	211 / 732 (29%)	676 / 2,152 (31%)
Body Mass Index kg/m²	23.3 (21.5 - 25.5)	25.8 (23.6 - 28.2)	22.8 (21.1 - 25.1)	23.8 (21.8 - 26.3)
Hemoglobin Level g/dl	12.8 (12.2 - 13.4)	14.3 (13.5 - 15.1)	12.5 (11.6 - 13.5)	13.2 (12.3 - 14.1)
Someone in the Household Smokes	39 / 733 (5.3%)	7 / 687 (1.0%)	26 / 732 (3.6%)	72 / 2,152 (3.3%)
Household Food Insecurity Score				

None (0)	412 / 733 (56%)	363 / 687 (53%)	275 / 732 (38%)	1,050 / 2,152 (49%)
Mild (1-3)	236 / 733 (32%)	239 / 687 (35%)	211 / 732 (29%)	686 / 2,152 (32%)
Moderate/Severe (4-8)	85 / 733 (12%)	85 / 687 (12%)	246 / 732 (34%)	416 / 2,152 (19%)
Diet Diversity Score				
Low	498 / 733 (68%)	65 / 687 (9.5%)	494 / 732 (67%)	1,057 / 2,152 (49%)
Medium	205 / 733 (28%)	378 / 687 (55%)	204 / 732 (28%)	787 / 2,152 (37%)
High	30 / 733 (4.1%)	244 / 687 (36%)	34 / 732 (4.6%)	308 / 2,152 (14%)
Maternal Education				
No formal education or Primary school incomplete	351 / 733 (48%)	29 / 687 (4.2%)	313 / 732 (43%)	693 / 2,152 (32%)
Primary school complete or Secondary school incomplete	285 / 733 (39%)	211 / 687 (31%)	289 / 732 (39%)	785 / 2,152 (36%)
Secondary school complete or Vocational or Some college or university	97 / 733 (13%)	447 / 687 (65%)	130 / 732 (18%)	674 / 2,152 (31%)
Owns Household Assets				
Color Television	330 / 733 (45%)	439 / 687 (64%)	92 / 732 (13%)	861 / 2,152 (40%)
Radio	278 / 733 (38%)	508 / 687 (74%)	406 / 732 (55%)	1,192 / 2,152 (55%)
Mobile Phone	671 / 733 (92%)	662 / 687 (96%)	576 / 732 (79%)	1,909 / 2,152 (89%)
Bicycle	89 / 733 (12%)	257 / 687 (37%)	224 / 732 (31%)	570 / 2,152 (26%)
Bank Account	179 / 733 (24%)	161 / 687 (23%)	212 / 732 (29%)	552 / 2,152 (26%)

A)



B)

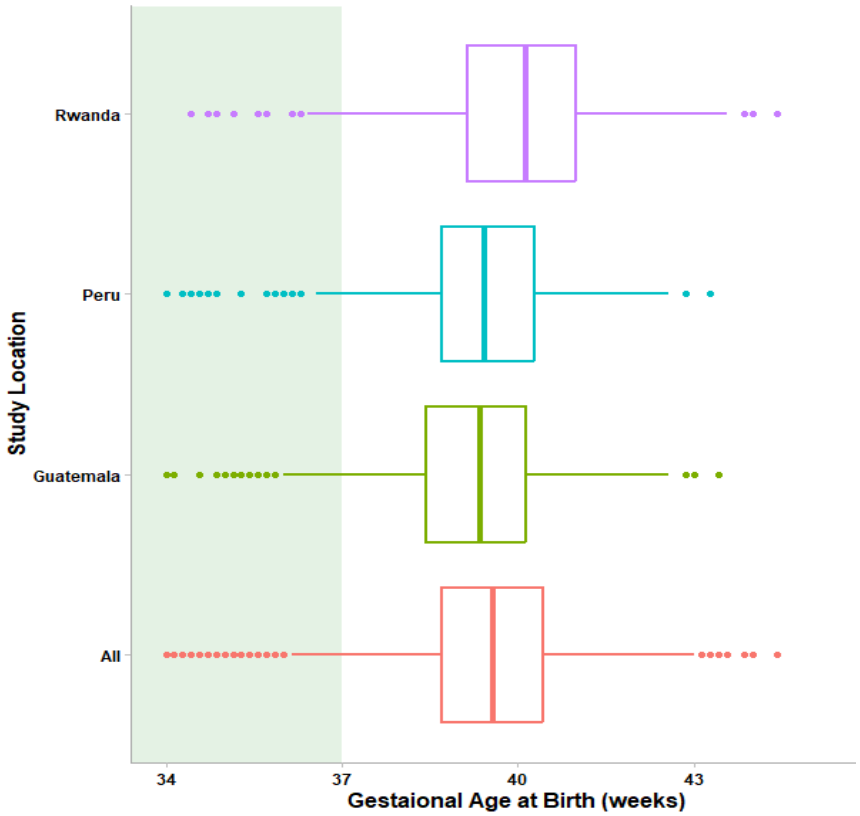
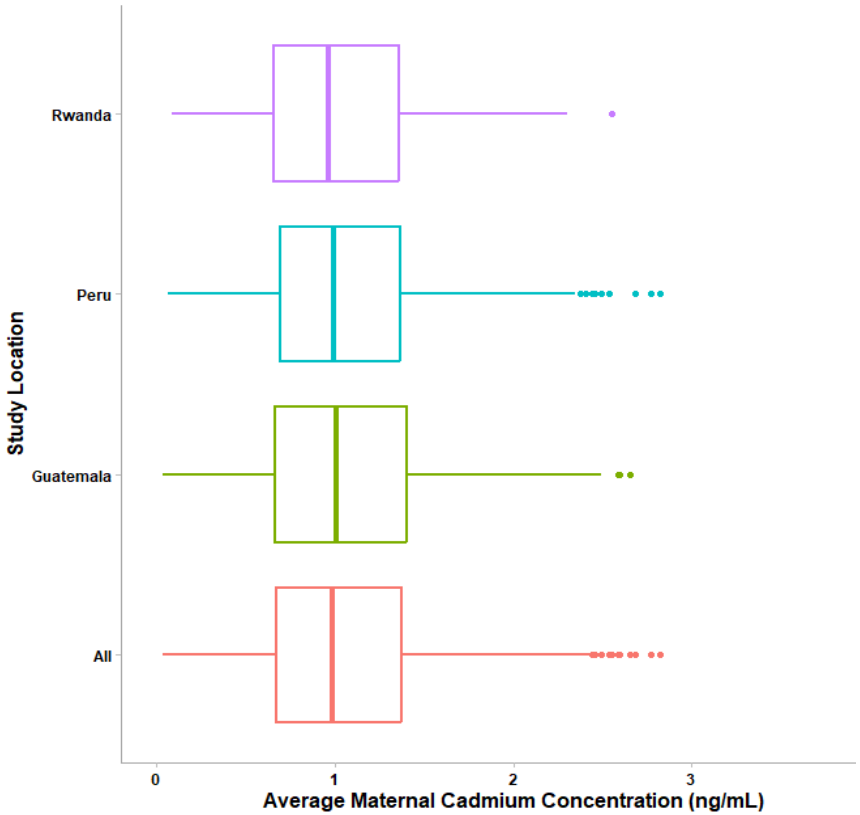


Figure 1: Distribution of (A) birth weight and (B) gestational age at birth by study location and overall.
In panel A, the shaded area indicates low birth weight (<2500 g). In panel B, the shaded area indicates preterm births (<37 weeks). The birth weight boxplot contains 195 data points outside of the scale range, while the gestational age boxplot contains 135 data points outside the scale range.

A)



B)

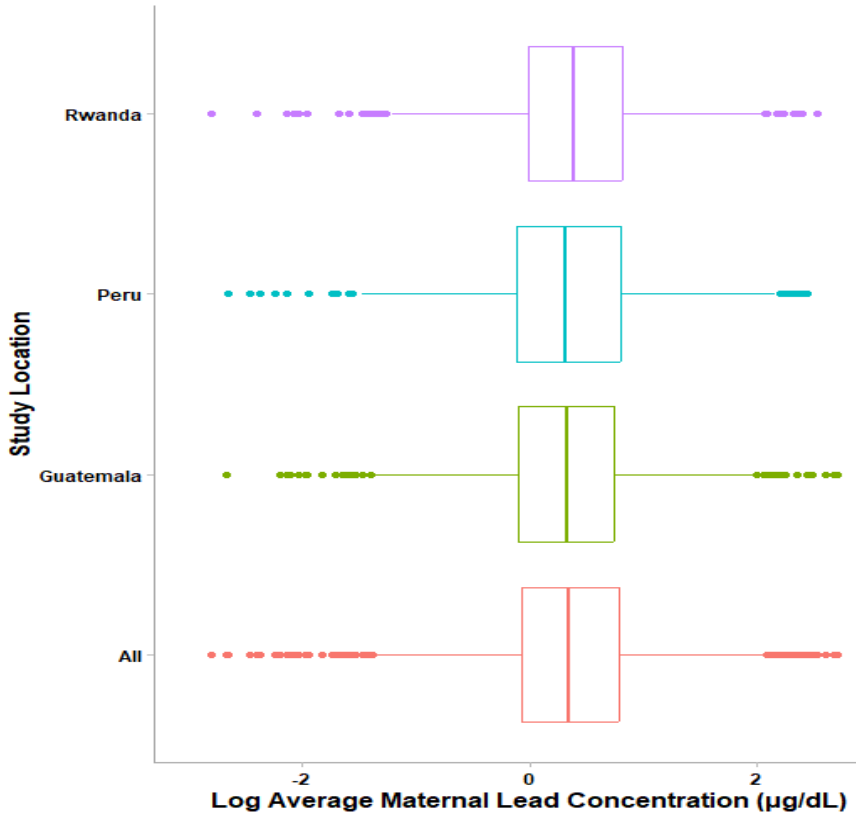


Figure 2: Distribution of (A) average maternal cadmium concentration and (B) average maternal lead concentration by study location and overall.

The average maternal cadmium concentration boxplot contains 19 data points outside of the scale range, while the log average maternal lead concentration boxplot contains 24 data points outside of the scale range.

Table 2: Estimated associations between lead and cadmium exposure during pregnancy (interquartile range) and adverse birth outcomes.
Birth weight, gestational age at birth, low birth weight, and preterm births per interquartile range increase in cadmium or lead concentration.
CI: Confidence interval. Some values are NA because it was not appropriate to run them as it would result in selection bias. Models adjusted for infant sex, maternal age, nulliparity, body mass index, maternal hemoglobin, mother's minimum dietary diversity during the previous month using an adapted version of the FAO Minimum Diet Diversity for Women, food insecurity using the FAO Food Insecurity Experience Scale, and whether someone smoke tobacco. Study arm was adjusted for in 32-36 weeks gestation and average models. Baseline refers to the pre-intervention period.

	Cadmium			**Lead**		
	Baseline (9 to < 20 weeks): IQR: 0.58	32-36 weeks gestation: IQR: 0.99	Average of Baseline and 32-36 weeks: IQR: 0.71	Baseline (9 to < 20 weeks): IQR: 1.20	32-36 weeks gestation: IQR: 1.44	Average of Baseline and 32-36 weeks: IQR: 1.27
Birth Weight (Beta coefficient, 95% CI)	-6.2 grams (-31.36, 19.06)	16.2 grams (-8.19, 40.61)	10.5 grams (-15.59, 36.66)	8.5 grams (-1.48, 18.44)	6.8 grams (-3.84, 17.42)	7.8 grams (-2.46, 17.97)
Gestational Age at Birth (Beta coefficient, 95% CI)	-0.02 weeks (-0.12, 0.07)	NA	NA	0.03 weeks (-0.01, 0.07)	NA	NA
Low Birth Weight (odds ratio, 95% CI)	1.20 (0.97, 1.47)	0.99 (0.81, 1.20)	1.07 (0.87, 1.32)	1.01 (0.92, 1.09)	1.02 (0.93, 1.11)	1.02 (0.93, 1.10)
Preterm Birth (hazard ratio, 95% CI)	1.00 (0.77, 1.30)	NA	NA	0.99 (0.89, 1.10)	NA	NA

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Appendix

Table S1. Baseline maternal characteristics by study location and overall.
Data are presented as n (%) or median (IQR). Descriptive statistics are based on the total number of participants.

Characteristic	Study Location			Overall
	Guatemala, N = 800	Peru, N = 798	Rwanda, N = 798	N = 2,396
Study Arm				
Control	400 / 800 (50%)	402 / 798 (50%)	404 / 798 (51%)	1,206 / 2,396 (50%)
Intervention	400 / 800 (50%)	396 / 798 (50%)	394 / 798 (49%)	1,190 / 2,396 (50%)
Age				
<20	122 / 800 (15%)	99 / 798 (12%)	49 / 798 (6.1%)	270 / 2,396 (11%)
20-24	324 / 800 (41%)	286 / 798 (36%)	203 / 798 (25%)	813 / 2,396 (34%)
25-29	231 / 800 (29%)	257 / 798 (32%)	299 / 798 (37%)	787 / 2,396 (33%)
30-35	123 / 800 (15%)	156 / 798 (20%)	247 / 798 (31%)	526 / 2,396 (22%)
Sex				
Female	373 / 770 (48%)	373 / 743 (50%)	370 / 773 (48%)	1,116 / 2,286 (49%)
Male	397 / 770 (52%)	370 / 743 (50%)	403 / 773 (52%)	1,170 / 2,286 (51%)
Missing	30	55	25	110
Nulliparity	227 / 800 (28%)	310 / 794 (39%)	232 / 796 (29%)	769 / 2,390 (32%)
Missing	0	4	2	6
Body Mass Index kg/m^2	23.3 (21.5 - 25.5)	25.6 (23.5 - 28.2)	22.8 (21.1 - 25.0)	23.8 (21.8 - 26.3)
Missing	5	10	4	19
Hemoglobin Level g/dl	12.8 (12.2 - 13.5)	14.3 (13.5 - 15.1)	12.5 (11.6 - 13.5)	13.2 (12.3 - 14.2)
Missing	3	19	8	30
Someone in the Household Smokes	44 / 800 (5.5%)	7 / 796 (0.9%)	30 / 796 (3.8%)	81 / 2,392 (3.4%)
Missing	0	2	2	4
Household Food Insecurity Score				
None (0)	440 / 790 (56%)	412 / 786 (52%)	296 / 778 (38%)	1,148 / 2,354 (49%)
Mild (1-3)	255 / 790 (32%)	274 / 786 (35%)	221 / 778 (28%)	750 / 2,354 (32%)
Moderate/Severe (4-8)	95 / 790 (12%)	100 / 786 (13%)	261 / 778 (34%)	456 / 2,354 (19%)
Missing	10	12	20	42
Diet Diversity Score				

Low	547 / 799 (68%)	87 / 798 (11%)	541 / 797 (68%)	1,175 / 2,394 (49%)
Medium	219 / 799 (27%)	437 / 798 (55%)	219 / 797 (27%)	875 / 2,394 (37%)
High	33 / 799 (4.1%)	274 / 798 (34%)	37 / 797 (4.6%)	344 / 2,394 (14%)
Missing	1	0	1	2
Maternal Education				
No formal education or Primary school incomplete	381 / 800 (48%)	35 / 797 (4.4%)	338 / 798 (42%)	754 / 2,395 (31%)
Primary school complete or Secondary school incomplete	312 / 800 (39%)	234 / 797 (29%)	318 / 798 (40%)	864 / 2,395 (36%)
Secondary school complete or Vocational or Some college or university	107 / 800 (13%)	528 / 797 (66%)	142 / 798 (18%)	777 / 2,395 (32%)
Missing	0	1	0	1
Owns Household Assets				
Color Television	357 / 800 (45%)	507 / 798 (64%)	101 / 798 (13%)	965 / 2,396 (40%)
Radio	304 / 800 (38%)	593 / 798 (74%)	449 / 798 (56%)	1,346 / 2,396 (56%)
Mobile Phone	731 / 800 (91%)	766 / 798 (96%)	631 / 798 (79%)	2,128 / 2,396 (89%)
Bicycle	98 / 800 (12%)	309 / 798 (39%)	246 / 798 (31%)	653 / 2,396 (27%)
Bank Account	197 / 800 (25%)	180 / 798 (23%)	232 / 798 (29%)	609 / 2,396 (25%)

Table S2. Overall and country-specific outcome characteristics.
Data are presented as n (%) or mean ± standard deviation, and median (interquartile range). Descriptive outcome data are provided by IRC and overall for all participants. Low birth weight is defined as a birth weight below 2,500 grams. Preterm birth is defined as a birth occurring before 37 weeks of gestational age.

	Guatemala, N = 751	Peru, N = 731	Rwanda, N = 763	Overall, N = 2,245
Birth weight - in grams	2,862.1 ± 428.3; 2,863.3 (2,603.3-3,141.3)	3,180.3 ± 409.2; 3,200.0 (2,930.0 - 3,455.0)	3,021.9 ± 437.8; 3,015.0 (2,750.0 - 3,280.0)	3,020.0 ± 444.5; 3,020.0 (2,745.0 - 3,300.0)
Low Birth Weight	125 / 751 (17%)	32 / 731 (4.4%)	72 / 763 (9.4%)	229 / 2,245 (10%)
	Guatemala, N = 770	**Peru, N = 743**	**Rwanda, N = 773**	**Overall, N = 2,286**
Gestational Age at Birth - in weeks	39.1 ±1.6; 39.3 (38.4 - 40.1)	39.3 ± 1.4; 39.4 (38.7 - 40.2)	39.9 ± 1.9; 40.0 (39.1 - 41.0)	39.4 ± 1.7; 39.6 (38.7 - 40.4)
Preterm Birth	50 / 770 (6.5%)	36 / 743 (4.8%)	36 / 773 (4.7%)	122 / 2,286 (5.3%)

Table S3. Overall and country-specific exposure characteristics.
Data are presented as median (interquartile range) and mean ± standard deviation. Descriptive outcome data are provided by IRC and overall for all. Baseline refers to the pre-intervention period (9 to less than 20 weeks gestational age). 32-36 weeks refers to 32-36 weeks of gestational age. The average represents the mean of the baseline and 32-36 weeks gestational age values.

	Guatemala, N = 798	Peru, N = 785	Rwanda, N = 794	Overall, N = 2,377
Lead: Baseline - µg/dL	1.3 (0.9 - 2.0); 2.0 ± 2.3	1.4 (0.9 - 2.2); 2.1 ± 2.7	1.5 (1.0 - 2.2); 2.1 ± 2.0	1.4 (0.9 - 2.1); 2.1 ± 2.3
Cadmium: Baseline - ng/mL	1.0 (0.7 - 1.3); 1.0 ± 0.4	1.0 (0.7 - 1.3); 1.0 ± 0.4	1.0 (0.7 - 1.3); 1.0 ± 0.4	1.0 (0.7 - 1.3); 1.0 ± 0.4
Lead: 32-36 weeks - µg/dL	1.4 (0.9 - 2.2); 2.1 ± 2.7	1.4 (0.9 - 2.4); 2.1 ± 2.5	1.5 (0.9 - 2.3); 2.1 ± 2.0	1.4 (0.9 - 2.3); 2.1 ± 2.4
Cadmium: 32-36 weeks - ng/mL	1.0 (0.5 - 1.5); 1.1 ± 0.8	1.0 (0.6 - 1.5); 1.1 ± 0.7	1.0 (0.5 - 1.5); 1.1 ± 0.7	1.0 (0.5 - 1.5); 1.1 ± 0.7
Lead: Average - µg/dL	1.4 (0.9 - 2.1); 2.1 ± 2.4	1.4 (0.9 - 2.3); 2.1 ± 2.5	1.5 (1.0 - 2.3); 2.1 ± 1.9	1.4 (0.9 - 2.2); 2.1 ± 2.3
Cadmium: Average - ng/mL	1.0 (0.7 - 1.4) 1.1 ± 0.5	1.0 (0.7 - 1.4); 1.1 ± 0.5	1.0 (0.7 - 1.4); 1.0 ± 0.5	1.0 (0.7 - 1.4); 1.0 ± 0.5

Table S4. Baseline maternal characteristics by study location and overall for participants included in the gestational age at birth and preterm birth analyses.

Data are presented as n (%) or median (IQR). Descriptive statistics are based on the number of pregnant women included in the gestational age and preterm birth analyses.

	Study Location			Overall
	Guatemala, N = 752	Peru, N = 697	Rwanda, N = 742	N = 2,191
Study Arm				
Control	378 / 752 (50%)	338 / 697 (48%)	378 / 742 (51%)	1,094 / 2,191 (50%)
Intervention	374 / 752 (50%)	359 / 697 (52%)	364 / 742 (49%)	1,097 / 2,191 (50%)
Age				
<20	117 / 752 (16%)	86 / 697 (12%)	44 / 742 (5.9%)	247 / 2,191 (11%)
20-24	304 / 752 (40%)	250 / 697 (36%)	185 / 742 (25%)	739 / 2,191 (34%)
25-29	217 / 752 (29%)	226 / 697 (32%)	280 / 742 (38%)	723 / 2,191 (33%)
30-35	114 / 752 (15%)	135 / 697 (19%)	233 / 742 (31%)	482 / 2,191 (22%)
Sex				
Female	366 / 752 (49%)	345 / 697 (49%)	361 / 742 (49%)	1,072 / 2,191 (49%)
Male	386 / 752 (51%)	352 / 697 (51%)	381 / 742 (51%)	1,119 / 2,191 (51%)
Nulliparity	210 / 752 (28%)	260 / 697 (37%)	215 / 742 (29%)	685 / 2,191 (31%)
Body Mass Index kg/ m^2	23.3 (21.5 - 25.5)	25.8 (23.6 - 28.3)	22.8 (21.1 - 25.0)	23.8 (21.8 - 26.3)
Hemoglobin Level g/dl	12.8 (12.2 - 13.4)	14.3 (13.5 - 15.1)	12.5 (11.6 - 13.5)	13.2 (12.3 - 14.1)
Someone in the Household Smokes	40 / 752 (5.3%)	7 / 697 (1.0%)	26 / 742 (3.5%)	73 / 2,191 (3.3%)
Household Food Insecurity Score				
None (0)	421 / 752 (56%)	369 / 697 (53%)	280 / 742 (38%)	1,070 / 2,191 (49%)
Mild (1-3)	243 / 752 (32%)	242 / 697 (35%)	213 / 742 (29%)	698 / 2,191 (32%)
Moderate/Severe (4-8)	88 / 752 (12%)	86 / 697 (12%)	249 / 742 (34%)	423 / 2,191 (19%)
Diet Diversity Score				
Low	511 / 752 (68%)	65 / 697 (9.3%)	502 / 742 (68%)	1,078 / 2,191 (49%)
Medium	209 / 752 (28%)	383 / 697 (55%)	205 / 742 (28%)	797 / 2,191 (36%)
High	32 / 752 (4.3%)	249 / 697 (36%)	35 / 742 (4.7%)	316 / 2,191 (14%)
Maternal Education				

No formal education or Primary school incomplete	360 / 752 (48%)	29 / 697 (4.2%)	318 / 742 (43%)	707 / 2,191 (32%)
Primary school complete or Secondary school incomplete	293 / 752 (39%)	213 / 697 (31%)	291 / 742 (39%)	797 / 2,191 (36%)
Secondary school complete or Vocational or Some college or university	99 / 752 (13%)	455 / 697 (65%)	133 / 742 (18%)	687 / 2,191 (31%)
Own Household Assets				
Color TV	337 / 752 (45%)	444 / 697 (64%)	93 / 742 (13%)	874 / 2,191 (40%)
Radio	286 / 752 (38%)	516 / 697 (74%)	414 / 742 (56%)	1,216 / 2,191 (55%)
Mobile Phone	686 / 752 (91%)	671 / 697 (96%)	584 / 742 (79%)	1,941 / 2,191 (89%)
Bicycle	90 / 752 (12%)	261 / 697 (37%)	228 / 742 (31%)	579 / 2,191 (26%)
Bank Account	181 / 752 (24%)	162 / 697 (23%)	216 / 742 (29%)	559 / 2,191 (26%)

Table S5. Overall and country-specific outcome characteristics for participants included in birth weight, low birth weight, gestational age at birth, and preterm birth analyses.

Data are presented as n (%) or mean ± standard deviation, and median (interquartile range). Descriptive outcome data are provided by IRC and overall for participants included in birth weight, low birth weight, gestational age at birth, and preterm birth analyses. Low birth weight is defined as a birth weight below 2,500 grams. Preterm birth is defined as a birth occurring before 37 weeks of gestational age.

	Guatemala, N = 733	**Peru, N = 687**	**Rwanda, N = 732**	**Overall, N = 2,152**
Birth weight - in grams	2,865.7 ± 428.4; 2,870.0 (2,604.0 - 3,142.5)	3,184.3 ± 408.3; 3,200.0 (2,933.8 - 3,457.5)	3,021.5 ± 441.0; 3,010.0 (2,744.4 - 3,280.0)	3,020.4 ± 445.5; 3,020.0 (2,742.5 - 3,300.0)
Low Birth Weight	122 / 733 (17%)	29 / 687 (4.2%)	70 / 732 (9.6%)	221 / 2,152 (10%)
	Guatemala, N = 752	**Peru, N = 697**	**Rwanda, N = 742**	**Overall, N = 2,191**
Gestational Age at Birth - in weeks	39.1 ± 1.6; 39.3 (38.4 - 40.1)	39.3 ± 1.4; 39.4 (38.7 - 40.3)	39.9 ± 1.9; 40.0 (39.1 - 41.0)	39.5 ± 1.7; 39.6 (38.7 - 40.4)
Preterm Birth	46 / 752 (6.1%)	34 / 697 (4.9%)	34 / 742 (4.6%)	114 / 2,191 (5.2%)

Table S6. Overall and country-specific exposure characteristics for participants included in the birth weight and low birth weight analyses.

Data are presented as median (interquartile range) or mean ± standard deviation. Descriptive outcome data are provided by IRC and overall for pregnant women included in the birth weight and low birth weight analyses. Baseline refers to the pre-intervention period (9 to less than 20 weeks of intervention). 32-36 weeks refers to 32-36 weeks of gestational age. The average represents the mean of the baseline and 32-36 weeks gestational age values.

	Guatemala, N = 733	Peru, N = 687	Rwanda, N = 732	Overall, N = 2,152
Lead: Baseline - µg/dL	1.3 (0.9 - 2.0); 2.0 ± 2.3	1.4 (0.9 - 2.2); 2.0 ± 2.2	1.5 (1.0 - 2.2); 2.1 ± 2.0	1.4 (0.9 - 2.1); 2.1 ± 2.1
Cadmium: Baseline - ng/mL	1.0 (0.7 - 1.3); 1.0 ± 0.4	1.0 (0.7 - 1.3); 1.0 ± 0.4	1.0 (0.7 - 1.3); 1.0 ± 0.4	1.0 (0.7 - 1.3); 1.0 ± 0.4
Lead: 32-36 weeks - µg/dL	1.4 (0.8 - 2.2); 2.1 ± 2.7	1.4 (0.9 - 2.4); 2.1 ± 2.4	1.5 (0.9 - 2.4); 2.1 ± 2.0	1.4 (0.9 - 2.3); 2.1 ± 2.4
Cadmium: 32-36 weeks - ng/mL	1.0 (0.5 - 1.5); 1.1 ± 0.8	1.0 (0.6 - 1.5); 1.1 ± 0.7	1.0 (0.5 - 1.5); 1.1 ± 0.7	1.0 (0.5 - 1.5); 1.1 ± 0.7
Lead: Average - µg/dL	1.4 (0.9 - 2.1); 2.1 ± 2.4	1.4 (0.9 - 2.3); 2.1 ± 2.2	1.5 (1.0 - 2.2); 2.1 ± 1.9	1.4 (0.9 - 2.2); 2.1 ± 2.2
Cadmium: Average - ng/mL	1.0 (0.7 - 1.4); 1.1 ± 0.5	1.0 (0.7 - 1.4); 1.1 ± 0.5	1.0 (0.7 - 1.4); 1.0 ± 0.5	1.0 (0.7 - 1.4); 1.1 ± 0.5

Table S7. Overall and country-specific exposure characteristics for participants included in the gestational age at birth and preterm birth analyses.

Data are presented as median (interquartile range) or mean ± standard deviation. Descriptive outcome data are provided by IRC and overall for pregnant women included in the gestational age at birth and preterm birth analyses. Baseline refers to the pre-intervention period (9 to less than 20 weeks of intervention). 32-36 weeks refers to 32-36 weeks of gestational age. The average represents the mean of the baseline and 32-36 weeks gestational age values.

	Guatemala, N = 752	Peru, N = 697	Rwanda, N = 742	Overall, N = 2,191
Lead: Baseline - µg/dL	1.3 (0.9 - 2.0); 2.0 ± 2.3	1.4 (0.9 - 2.2); 2.0 ± 2.2	1.5 (1.0 - 2.2); 2.1 ± 2.0	1.4 (0.9 - 2.1); 2.1 ± 2.1
Cadmium: Baseline - ng/mL	1.0 (0.7 - 1.3); 1.0 ± 0.4	1.0 (0.7 - 1.3); 1.0 ± 0.4	1.0 (0.7 - 1.3); 1.0 ± 0.4	1.0 (0.7 - 1.3); 1.0 ± 0.4
Lead: 32-36 weeks - µg/dL	1.4 (0.8 - 2.2); 2.1 ± 2.7	1.4 (0.9 - 2.4); 2.1 ± 2.4	1.5 (0.9 - 2.4); 2.1 ± 2.0	1.4 (0.9 - 2.3); 2.1 ± 2.4
Cadmium: 32-36 weeks - ng/mL	1.0 (0.5 - 1.5); 1.1 ± 0.8	1.0 (0.6 - 1.5); 1.1 ± 0.7	1.0 (0.5 - 1.5); 1.1 ± 0.7	1.0 (0.5 - 1.5); 1.1 ± 0.7
Lead: Average - µg/dL	1.4 (0.9 - 2.1); 2.1 ± 2.4	1.4 (0.9 - 2.3); 2.1 ± 2.2	1.5 (1.0 - 2.2); 2.1 ± 1.9	1.4 (0.9 - 2.2); 2.1 ± 2.2
Cadmium: Average - ng/mL	1.0 (0.7 - 1.4); 1.1 ± 0.5	1.0 (0.7 - 1.4); 1.1 ± 0.5	1.0 (0.7 - 1.4); 1.0 ± 0.5	1.0 (0.7 - 1.4); 1.1 ± 0.5

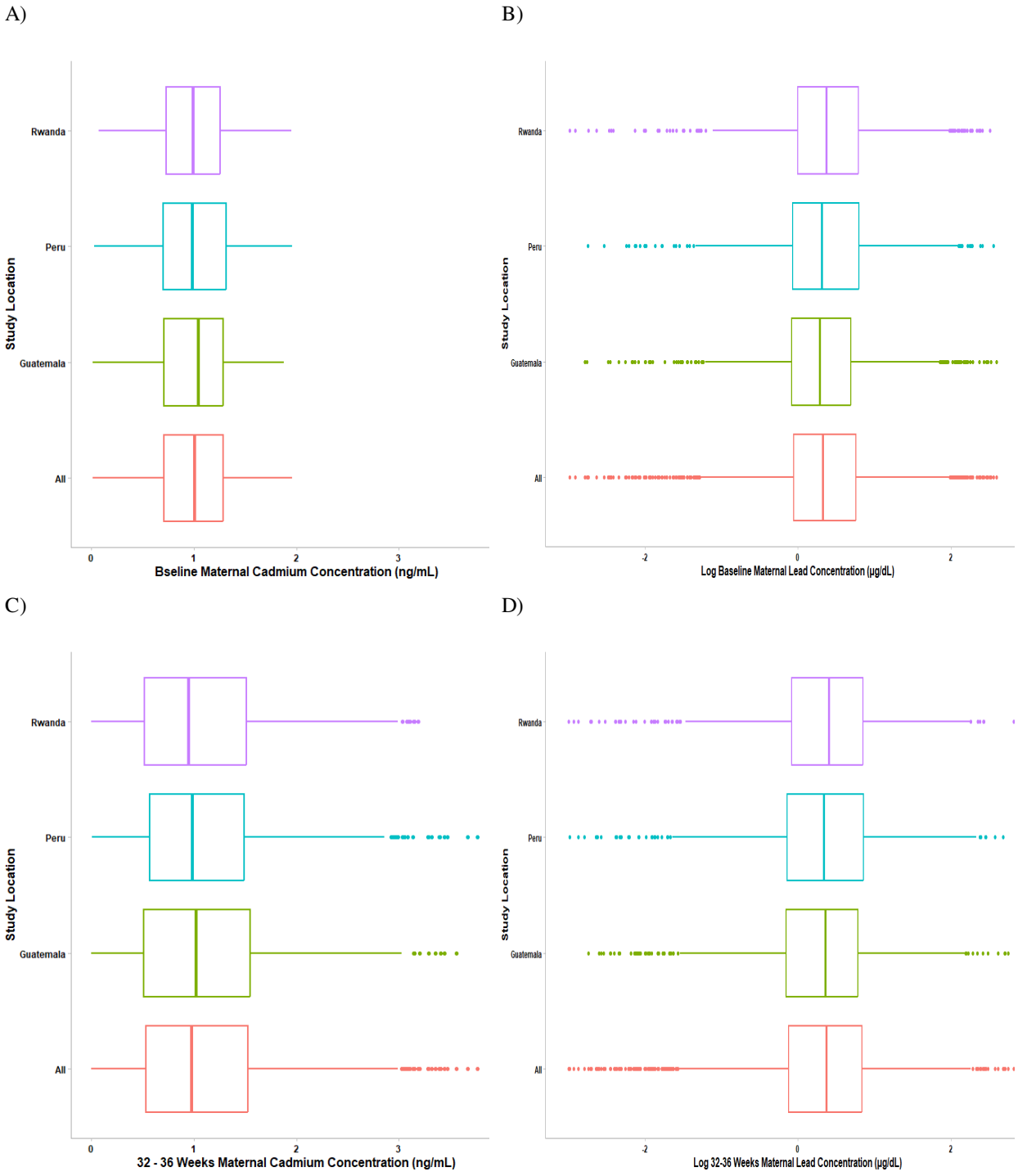

Figure S1: Distribution of (A) baseline maternal cadmium concentration, (B) baseline maternal lead concentration (C) 32-36 weeks maternal cadmium concentration, and (D) 32-36 weeks maternal lead concentration by study location and overall.

The baseline maternal cadmium concentration boxplot contains 19 data points outside of the scale range, while the log baseline maternal lead concentration boxplot contains 33 data points outside of the scale range. The 32-36 weeks maternal cadmium concentration boxplot contains 16 data points outside of the scale range, while the log 32-36 weeks maternal lead concentration boxplot contains 40 data points outside of the scale range.

Table S8. Estimated associations between lead and cadmium exposure during pregnancy (interquartile range) and adverse birth outcomes, adjusted for household assets in addition to other variables in the main model.

Birth weight, gestational age at birth, low birth weight, and preterm births per interquartile range increase in cadmium or lead concentration. CI: Confidence interval. Some values are NA because it was not appropriate to include them due to selection bias. Models are adjusted for infant sex, maternal age, nulliparity, body mass index, maternal hemoglobin, maternal minimum dietary diversity in the previous month (using an adapted version of the FAO Minimum Diet Diversity for Women), food insecurity (using the FAO Food Insecurity Experience Scale), tobacco smoking, and assets (including color television, radio, mobile phone, bicycle, and bank account). Study arm was also adjusted for in the 32-36 weeks gestation and average models. Baseline refers to the pre-intervention period.

	Cadmium			**Lead**		
	Baseline (9 to < 20 weeks): IQR: 0.58	32-36 weeks gestation: IQR: 0.99	Average of Baseline and 32-36 weeks: IQR: 0.71	Baseline (9 to < 20 weeks): IQR: 1.20	32-36 weeks gestation: IQR: 1.44	Average of Baseline and 32-36 weeks: IQR: 1.27
Birth Weight (Beta coefficient, 95% CI)	-5.4 grams (-30.58, 19.77)	15.8 grams (-8.53, 40.19)	10.6 grams (-15.52, 36.63)	7.9 grams (-2.01, 17.89)	6.3 grams (-4.29, 16.95)	7.3 grams (-2.96, 17.46)
Gestational Age at Birth (Beta coefficient, 95% CI)	-0.02 weeks (-0.12, 0.08)	NA	NA	0.03 weeks (-0.01, 0.07)	NA	NA
Low Birth Weight (odds ratio, 95% CI)	1.20 (0.97, 1.47)	0.99 (0.81, 1.20)	1.07 (0.87, 1.32)	1.01 (0.93, 1.09)	1.03 (0.94, 1.11)	1.02 (0.93, 1.10)
Preterm Birth (hazard ratio, 95% CI)	1.00 (0.76, 1.30)	NA	NA	0.99 (0.89, 1.10)	NA	NA

Table S9. Estimated associations between lead and cadmium exposure during pregnancy (interquartile range) and adverse birth outcomes, adjusted for maternal education in addition to other variables in the main model.

Birth weight, gestational age at birth, low birth weight, and preterm births per interquartile range increase in cadmium or lead concentration. CI: Confidence interval. Some values are NA because they could not be included due to selection bias. Models are adjusted for infant sex, maternal age, nulliparity, body mass index, maternal hemoglobin, maternal minimum dietary diversity in the previous month (using an adapted version of the FAO Minimum Diet Diversity for Women), food insecurity (using the FAO Food Insecurity Experience Scale), tobacco smoking, and maternal education. Study arm was also adjusted for in the 32-36 weeks gestation and average models. Baseline refers to the pre-intervention period.

	Cadmium			**Lead**		
	Baseline (9 to < 20 weeks): IQR: 0.58	32-36 weeks gestation: IQR: 0.99	Average of Baseline and 32-36 weeks: IQR: 0.71	Baseline (9 to < 20 weeks): IQR: 1.20	32-36 weeks gestation: IQR: 1.44	Average of Baseline and 32-36 weeks: IQR: 1.27
Birth Weight (Beta coefficient, 95% CI)	-6.4 grams (-31.44, 18.73)	15.6 grams (-8.65, 39.93)	10.0 grams (-16.04, 35.96)	9.7 grams (-0.23, 19.61)	7.8 grams (-2.77, 18.39)	8.9 grams (-1.28, 19.06)
Gestational Age at Birth (Beta coefficient, 95% CI)	-0.03 weeks (-0.12, 0.07)	NA	NA	0.03 weeks (-0.01, 0.07)	NA	NA
Low Birth Weight (odds ratio, 95% CI)	1.20 (0.98, 1.48)	1.00 (0.82, 1.21)	1.08 (0.87, 1.33)	1.00 (0.91, 1.08)	1.02 (0.93, 1.10)	1.01 (0.92, 1.09)
Preterm Birth (hazard ratio, 95% CI)	1.00 (0.77, 1.30)	NA	NA	0.99 (0.89, 1.10)	NA	NA

Table S10. Estimated associations between lead and cadmium exposure during pregnancy (interquartile range) and adverse birth outcomes, adjusted for study location in addition to other variables in the main model.

Birth weight, gestational age at birth, low birth weight, and preterm births per interquartile range increase in cadmium or lead concentration. CI: Confidence interval. Some values are NA because they could not be included due to selection bias. Models are adjusted for infant sex, maternal age, nulliparity, body mass index, maternal hemoglobin, maternal minimum dietary diversity in the previous month (using an adapted version of the FAO Minimum Diet Diversity for Women), food insecurity (using the FAO Food Insecurity Experience Scale), tobacco smoking, and study location. Study arm was also adjusted for in the 32-36 weeks gestation and average models. Baseline refers to the pre-intervention period.

	Cadmium			**Lead**		
	Baseline (9 to < 20 weeks): IQR: 0.58	32-36 weeks gestation: IQR: 0.99	Average of Baseline and 32-36 weeks: IQR: 0.71	Baseline (9 to < 20 weeks): IQR: 1.20	32-36 weeks gestation: IQR: 1.44	Average of Baseline and 32-36 weeks: IQR: 1.27
Birth Weight (Beta coefficient, 95% CI)	-3.1 grams (-27.89, 21.62)	19.5 grams (-4.48, 43.42)	14.5 grams (-11.16, 40.13)	8.9 grams (-0.93, 18.63)	7.7 grams (-2.78, 18.09)	8.4 grams (-1.63, 18.43)
Gestational Age at Birth (Beta coefficient, 95% CI)	-0.02 weeks (-0.11, 0.08)	NA	NA	0.03 weeks (-0.01, 0.06)	NA	NA
Low Birth Weight (odds ratio, 95% CI)	1.18 (0.96, 1.46)	0.98 (0.80, 1.19)	1.06 (0.86, 1.30)	1.00 (0.92, 1.08)	1.02 (0.93, 1.10)	1.01 (0.93, 1.09)
Preterm Birth (hazard ratio, 95% CI)	0.99 (0.76, 1.29)	NA	NA	0.99 (0.89, 1.10)	NA	NA

Table S11. Estimated associations between lead and cadmium exposure during pregnancy (interquartile range) and adverse birth outcomes, replacing values below the limit of detection (LDO) with LOD/√2.
Birth weight, gestational age at birth, low birth weight, and preterm births per interquartile range increase in cadmium or lead concentration. CI: Confidence interval. Some values are NA because they could not be included due to selection bias. Models are adjusted for infant sex, maternal age, nulliparity, body mass index, maternal hemoglobin, maternal minimum dietary diversity in the previous month (using an adapted version of the FAO Minimum Diet Diversity for Women), food insecurity (using the FAO Food Insecurity Experience Scale), and tobacco smoking. Metal values below the limit of detection (LOD) were replaced with LOD/√2. Study arm was also adjusted for in the 32-36 weeks gestation and average models. Baseline refers to the pre-intervention period.

	Cadmium			**Lead**		
	Baseline (9 to < 20 weeks): IQR: 0.58	32-36 weeks gestation: IQR: 0.99	Average of Baseline and 32-36 weeks: IQR: 0.71	Baseline (9 to < 20 weeks): IQR: 1.20	32-36 weeks gestation: IQR: 1.44	Average of Baseline and 32-36 weeks: IQR: 1.27
Birth Weight (Beta coefficient, 95% CI)	-6.1 grams (-31.32, 19.11)	16.2 grams (-8.29, 40.60)	10.5 grams (-15.65, 36.60)	8.5 grams (-1.48, 18.44)	6.8 grams (-3.84, 17.42)	7.8 grams (-2.46, 17.97)
Gestational Age at Birth (Beta coefficient, 95% CI)	-0.02 weeks (-0.12, 0.07)	NA	NA	0.03 weeks (-0.01, 0.07)	NA	NA
Low Birth Weight (odds ratio, 95% CI)	1.20 (0.97, 1.47)	0.99 (0.81, 1.20)	1.07 (0.86, 1.32)	1.01 (0.92, 1.09)	1.02 (0.93, 1.11)	1.02 (0.93, 1.10)
Preterm Birth (hazard ratio, 95% CI)	1.00 (0.77, 1.30)	NA	NA	0.99 (0.89, 1.10)	NA	NA

Table S12. Estimated associations between lead and cadmium exposure during pregnancy (interquartile range) and adverse birth outcomes, standardized to 4 mmol/mL potassium.

Birth weight, gestational age at birth, low birth weight, and preterm births per interquartile range increase in cadmium or lead concentration. CI: Confidence interval. Some values are NA because they could not be included due to selection bias. Models are adjusted for infant sex, maternal age, nulliparity, body mass index, maternal hemoglobin, maternal minimum dietary diversity in the previous month (using an adapted version of the FAO Minimum Diet Diversity for Women), food insecurity (using the FAO Food Insecurity Experience Scale), and tobacco smoking. Metal values are standardized to 4 mmol/mL potassium. Study arm was also adjusted for in the 32-36 weeks gestation and average models. Baseline refers to the pre-intervention period.

	Cadmium			**Lead**		
	Baseline (9 to < 20 weeks): IQR: 0.67	32-36 weeks gestation: IQR: 0.99	Average of Baseline and 32-36 weeks: IQR: 0.71	Baseline (9 to < 20 weeks): IQR: 1.44	32-36 weeks gestation: IQR: 1.62	Average of Baseline and 32-36 weeks: IQR: 1.45
Birth Weight (Beta coefficient, 95% CI)	-1.5 grams (-23.17, 20.14)	13.6 grams (-7.69, 34.87)	10.9 grams (-12.18, 34.01)	8.1 grams (-1.52, 17.79)	6.5 grams (-4.2, 17.26)	7.6 grams (-2.49, 17.65)
Gestational Age at Birth (Beta coefficient, 95% CI)	-0.02 weeks (-0.12, 0.07)	NA	NA	0.03 weeks (-0.01, 0.07)	NA	NA
Low Birth Weight (odds ratio, 95% CI)	1.12 (0.94, 1.33)	0.99 (0.81, 1.20)	1.12 (0.93, 1.34)	1.01 (0.92, 1.09)	1.04 (0.95, 1.12)	1.02 (0.93, 1.11)
Preterm Birth (hazard ratio, 95% CI)	0.90 (0.71, 1.14)	NA	NA	0.94 (0.83, 1.07)	NA	NA

Table S13. Estimated associations between lead and cadmium exposure during pregnancy (interquartile range) and adverse birth outcomes, not adjusting for maternal hemoglobin.

Birth weight, gestational age at birth, low birth weight, and preterm births per interquartile range increase in cadmium or lead concentration. CI: Confidence interval. Some values are NA because they could not be included due to selection bias. Models are adjusted for infant sex, maternal age, nulliparity, body mass index, maternal minimum dietary diversity in the previous month (using an adapted version of the FAO Minimum Diet Diversity for Women), food insecurity (using the FAO Food Insecurity Experience Scale), and tobacco smoking. Hemoglobin is not included as an adjusted variable. Metal values are standardized to 4 mmol/mL potassium. Study arm was also adjusted for in the 32-36 weeks gestation and average models. Baseline refers to the pre-intervention period.

	Cadmium			**Lead**		
	Baseline (9 to < 20 weeks): IQR: 0.58	32-36 weeks gestation: IQR: 0.99	Average of Baseline and 32-36 weeks: IQR: 0.71	Baseline (9 to < 20 weeks): IQR: 1.20	32-36 weeks gestation: IQR: 1.44	Average of Baseline and 32-36 weeks: IQR: 1.27
Birth Weight (Beta coefficient, 95% CI)	-4.0 grams (-29.18, 21.17)	17.3 grams (-7.05, 41.70)	12.4 grams (-13.72, 38.46)	7.7 grams (-2.27, 17.64)	6.1 grams (-4.51, 16.75)	7.0 grams (-3.20, 17.24)
Gestational Age at Birth (Beta coefficient, 95% CI)	-0.02 weeks (-0.12, 0.08)	NA	NA	0.03 weeks (-0.01, 0.07)	NA	NA
Low Birth Weight (odds ratio, 95% CI)	1.20 (0.97, 1.47)	0.99 (0.81, 1.20)	1.07 (0.86, 1.31)	1.01 (0.92, 1.09)	1.03 (0.94, 1.11)	1.02 (0.93, 1.10)
Preterm Birth (hazard ratio, 95% CI)	1.00 (0.77, 1.30)	NA	NA	0.99 (0.89, 1.10)	NA	NA

Table S14. Estimated associations between lead and cadmium exposure during pregnancy (interquartile range) and birth weight, with effect modification by study location, infant sex, and study arm.
Birth weight per interquartile range increase in cadmium or lead concentration. CI: Confidence interval. Effect modification by study location (Guatemala, Peru, Rwanda), infant sex (female, male), and study arm (control, intervention) was tested by including an interaction term between the metal (cadmium and lead analyzed separately) and the effect modifier. Models are adjusted for infant sex, maternal age, nulliparity, body mass index, maternal hemoglobin, mother's minimum dietary diversity during the previous month using an adapted version of the FAO Minimum Diet Diversity for Women, food insecurity using the FAO Food Insecurity Experience Scale, and whether someone smokes tobacco. Study arm was adjusted for in the 32-36 weeks gestation and average models. Baseline refers to the pre-intervention period.

	Cadmium			**Lead**		
	Baseline (9 to < 20 weeks): IQR: 0.58	32-36 weeks gestation: IQR: 0.99	Average of Baseline and 32-36 weeks: IQR: 0.71	Baseline (9 to < 20 weeks): IQR: 1.20	32-36 weeks gestation: IQR: 1.44	Average of Baseline and 32-36 weeks: IQR: 1.27
Study Location: Birth Weight (Beta coefficient, 95% CI)						
Guatemala	-21.5 grams (-64.33, 21.30)	39.5 grams (-0.04, 79.09)	24.1 grams (-18.92, 67.11)	13.7 grams (-2.16, 29.58)	9.5 grams (-6.08, 25.14)	11.7 grams (-3.92, 27.23)
Peru	5.5 grams (-54.77, 65.81)	18.2 grams (-40.32, 76.74)	16.6 grams (-45.85, 79.09)	12.1 grams (-11.19, 35.31)	14.5 grams (-9.92, 38.84)	13.2 grams (-10.26, 36.74)
Rwanda	6.8 grams (-54.25, 67.75)	-1.6 grams (-58.94, 55.84)	2.0 grams (-60.12, 64.10)	-1.2 grams (-25.35, 22.91)	-4.3 grams (-30.46, 21.88)	-2.7 grams (-27.71, 22.27)
p-value for interaction	0.59	0.37	0.78	0.43	0.41	0.43
Infant Sex: Birth Weight (Beta coefficient, 95% CI)						
Female	0.00 grams (-35.31, 35.32)	8.4 grams (-25.85, 42.55)	7.0 grams (-29.42, 43.49)	2.3 grams (-11.33, 15.93)	6.0 grams (-8.75, 20.69)	4.3 grams (-9.80, 18.39)
Male	-12.6 grams (-62.98, 37.88)	24.4 grams (-24.45, 73.19)	14.2 grams (-37.99, 66.47)	15.6 grams (-4.41, 35.53)	7.7 grams (-13.62, 29.00)	11.6 grams (-8.88, 32.08)
p-value for interaction	0.63	0.52	0.79	0.19	0.87	0.49
Study Arm: Birth Weight (Beta coefficient, 95% CI)						
Control	-7.8 grams (-44.31, 28.80)	26.3 grams (-7.84, 60.48)	18.6 grams (-18.53, 55.64)	4.6 grams (-10.51, 19.73)	6.5 grams (-10.22, 23.19)	5.7 grams (-10.13, 21.47)

Intervention	-4.0 grams (54.47, 46.47)	5.7 grams (-42.92, 54.38)	2.7 grams (-49.45, 54.79)	11.4 grams (-8.69, 31.49)	7.0 grams (-14.64, 28.64)	9.3 grams (-11.44, 29.96)
p-value for interaction	0.88	0.41	0.55	0.51	0.96	0.73

Table S15. Estimated associations between lead and cadmium exposure during pregnancy (interquartile range) and gestational age at birth, with effect modification by study location, infant sex, and study arm. Gestational age at birth per interquartile range increase in cadmium or lead concentration.
CI: Confidence interval. Effect modification by study location (Guatemala, Peru, Rwanda), infant sex (female, male), and study arm (control, intervention) was tested by including an interaction term between the metal (cadmium and lead analyzed separately) and the effect modifier. Models are adjusted for infant sex, maternal age, nulliparity, body mass index, maternal hemoglobin, mother's minimum dietary diversity during the previous month using an adapted version of the FAO Minimum Diet Diversity for Women, food insecurity using the FAO Food Insecurity Experience Scale, and whether someone smokes tobacco. Baseline refers to the pre-intervention period.

	Cadmium	**Lead**
	Baseline (9 to < 20 weeks): IQR: 0.58	Baseline (9 to < 20 weeks): IQR: 1.20
Study Location: Gestational Age at Birth (Beta coefficient, 95% CI)		
Guatemala	-0.06 weeks (-0.22, 0.11)	0.02 weeks (-0.04, 0.08)
Peru	0.09 weeks (-0.15, 0.33)	0.05 weeks (-0.05, 0.15)
Rwanda	-0.08 weeks (-0.32, 0.16)	0.02 weeks (-0.08, 0.12)
p-value for interaction	0.32	0.81
Infant Sex: Gestational Age at Birth (Beta coefficient, 95% CI)		
Female	-0.04 weeks (-0.18, 0.10)	0.04 weeks (-0.01, 0.09)
Male	-0.01 weeks (-0.21, 0.19)	0.02 weeks (-0.06, 0.10)
p-value for interaction	0.74	0.56
Study Arm: Gestational Age at Birth (Beta coefficient, 95% CI)		

Control	-0.04 weeks (-0.19, 0.10)	0.03 weeks (-0.03, 0.09)
Intervention	0.00 weeks (-0.20, 0.20)	0.02 weeks (-0.06, 0.10)
p-value for interaction	0.69	0.86

Table S16. Estimated associations between lead and cadmium exposure during pregnancy (interquartile range) and low birth weight, with effect modification by study location, infant sex, and study arm. Low birth weight per interquartile range increase in cadmium or lead concentration.

CI: Confidence interval. Effect modification by study location (Guatemala, Peru, Rwanda), infant sex (female, male), and study arm (control, intervention) was tested by including an interaction term between the metal (cadmium and lead analyzed separately) and the effect modifier. Models are adjusted for infant sex, maternal age, nulliparity, body mass index, maternal hemoglobin, mother's minimum dietary diversity during the previous month using an adapted version of the FAO Minimum Diet Diversity for Women, food insecurity using the FAO Food Insecurity Experience Scale, and whether someone smokes tobacco. Study arm was adjusted for in the 32-36 weeks gestation and average models. Baseline refers to the pre-intervention period.

	Cadmium			**Lead**		
	Baseline (9 to < 20 weeks): IQR: 0.58	32-36 weeks gestation: IQR: 0.99	Average of Baseline and 32-36 weeks: IQR: 0.71	Baseline (9 to < 20 weeks): IQR: 1.20	32-36 weeks gestation: IQR: 1.44	Average of Baseline and 32-36 weeks: IQR: 1.27
Study Location: Low Birth Weight (odds ratio, 95% CI)						
Guatemala	1.31 (0.98, 1.75)	0.95 (0.72, 1.24)	1.07 (0.80, 1.42)	1.01 (0.90, 1.12)	1.03 (0.93, 1.13)	1.03 (0.92, 1.13)
Peru	1.30 (0.72, 2.34)	1.00 (0.54, 1.84)	1.13 (0.60, 2.11)	0.95 (0.74, 1.23)	0.98 (0.76, 1.27)	0.97 (0.75, 1.25)
Rwanda	0.96 (0.60, 1.54)	1.04 (0.68, 1.60)	1.01 (0.63, 1.62)	1.00 (0.82, 1.22)	0.99 (0.80, 1.23)	1.00 (0.82, 1.22)
p-value for interaction	0.41	0.93	0.94	0.91	0.87	0.89
Infant Sex: Low Birth Weight (odds ratio, 95% CI)						
Female	1.23 (0.93, 1.63)	1.04 (0.79, 1.35)	1.13 (0.85, 1.49)	1.04 (0.93, 1.14)	1.01 (0.88, 1.12)	1.02 (0.91, 1.13)
Male	1.15 (0.76, 1.74)	0.93 (0.63, 1.38)	1.00 (0.65, 1.54)	0.96 (0.81, 1.15)	1.04 (0.87, 1.24)	1.00 (0.84, 1.19)
p-value for interaction	0.76	0.58	0.59	0.37	0.71	0.84
Study Arm: Low Birth Weight (odds ratio, 95% CI)						
Control	1.13 (0.84, 1.52)	0.85 (0.64, 1.12)	0.92 (0.68, 1.24)	1.02 (0.91, 1.14)	1.01 (0.88, 1.14)	1.02 (0.90, 1.14)

Intervention	1.26 (0.83, 1.90)	1.17 (0.79, 1.74)	1.25 (0.81, 1.92)	0.98 (0.82, 1.17)	1.03 (0.86, 1.23)	1.02 (0.85, 1.21)
p-value for interaction	0.61	0.12	0.15	0.66	0.80	0.95

Table S17. Estimated associations between lead and cadmium exposure during pregnancy (interquartile range) and preterm birth, with effect modification by study location, infant sex, and study arm. Preterm birth per interquartile range increase in cadmium or lead concentration.

CI: Confidence interval. Effect modification by study location (Guatemala, Peru, Rwanda), infant sex (female, male), and study arm (control, intervention) was tested by including an interaction term between the metal (cadmium and lead analyzed separately) and the effect modifier. Models are adjusted for infant sex, maternal age, nulliparity, body mass index, maternal hemoglobin, mother's minimum dietary diversity during the previous month using an adapted version of the FAO Minimum Diet Diversity for Women, food insecurity using the FAO Food Insecurity Experience Scale, and whether someone smokes tobacco. Study arm was adjusted for in the 32-36 weeks gestation and average models. Baseline refers to the pre-intervention period.

	Cadmium	**Lead**
	Baseline (9 to < 20 weeks): IQR: 0.58	Baseline (9 to < 20 weeks): IQR: 1.20
Study Location: Preterm Birth (hazard ratio, 95% CI)		
Guatemala	1.04 (0.68, 1.58)	1.08 (0.96, 1.22)
Peru	0.90 (0.48, 1.69)	0.96 (0.74, 1.24)
Rwanda	1.04 (0.55, 1.99)	0.83 (0.62, 1.11)
p-value for interaction	0.88	0.14
Infant Sex: Preterm Birth (hazard ratio, 95% CI)		
Female	1.06 (0.71, 1.60)	1.00 (0.86, 1.16)
Male	0.95 (0.56, 1.62)	0.98 (0.79, 1.22)
p-value for interaction	0.70	0.87
Study Arm: Preterm Birth (hazard ratio, 95% CI)		

Control	0.82 (0.56, 1.21)	0.99 (0.84, 1.16)
Intervention	1.19 (0.70, 2.01)	0.99 (0.80, 1.23)
p-value for interaction	0.18	0.96

Table S18. Estimated associations between lead and cadmium exposure during pregnancy (quartiles of exposure) and adverse birth outcomes.

Birth weight, gestational age at birth, low birth weight, and preterm births per quartile increase in cadmium or lead concentration. CI: Confidence interval. Some values are NA because they could not be included due to selection bias. Models are adjusted for infant sex, maternal age, nulliparity, body mass index, maternal hemoglobin, maternal minimum dietary diversity in the previous month (using an adapted version of the FAO Minimum Diet Diversity for Women), food insecurity (using the FAO Food Insecurity Experience Scale), and tobacco smoking. Quartiles of Exposure: Quartiles were determined based on the distribution of lead and cadmium concentrations across the study population. The lowest quartile includes values up to the 25th percentile, the second quartile is the 25th to 50th percentile, the third quartile is the 50th to 75th percentile, and the highest quartile is above the 75th percentile. Study arm was also adjusted for in the 32-36 weeks gestation and average models. Baseline refers to the pre-intervention period.

	Cadmium			**Lead**		
	Baseline (9 to < 20 weeks)	32-36 weeks gestation	Average of Baseline and 32-36 weeks	Baseline (9 to < 20 weeks)	32-36 weeks gestation	Average of Baseline and 32-36 weeks
Birth Weight (Beta coefficient, 95% CI)						
Quartile 1 (Reference)						
Quartile 2	-12.3 grams (-62.88, 38.21)	8.5 grams (-41.91, 58.87)	-9.0 grams (-59.56, 41.64)	-13.0 grams (-62.98, 36.99)	-12.5 grams (-62.70, 37.63)	-17.1 grams (-67.10, 32.95)
Quartile 3	-23.5 grams (-73.68, 38.21)	-13.5 grams (-63.76, 36.80)	-13.6 grams (-63.79, 36.57)	-7.2 grams (-57.61, 43.22)	-33.7 grams (-84.15, 16.68)	-20.8 grams (-71.08, 29.51)
Quartile 4	-7.1 grams (-57.32, 43.09)	33.1 grams (-17.29, 83.46)	14.0 grams (-36.46, 64.38)	-6.4 grams (-56.46, 43.22)	3.0 grams (-47.19, 53.25)	5.5 grams (-25.69, 14.68)
The p-value for linear trends	0.69	0.34	0.65	0.87	0.89	0.87
Gestational Age at Birth (Beta coefficient, 95% CI)						
Quartile 1 (Reference)						

Quartile 2	-0.08 weeks (-0.28, 0.12)	NA	NA	-0.01 weeks (-0.21, 0.18)	NA	NA
Quartile 3	-0.05 weeks (-0.25, 0.15)	NA	NA	0.06 weeks (-0.14, 0.26)	NA	NA
Quartile 4	-0.02 weeks (-0.22, 0.18)	NA	NA	0.1 weeks (-0.07, 0.32)	NA	NA
The p-value for linear trends	0.93	NA	NA	0.15	NA	NA
Low Birth Weight (odds ratio, 95% CI)						
Quartile 1 (Reference)						
Quartile 2	1.0 (0.68, 1.58)	0.8 (0.56, 1.26)	1.3 (0.84, 1.89)	1.3 (0.88, 1.99)	1.5 (0.97, 2.25)	1.2 (0.83, 1.88)
Quartile 3	1.1 (0.75, 1.72)	1.0 (0.66, 1.46)	1.0 (0.64, 1.48)	1.1 (0.71, 1.66)	1.6 (1.05, 2.43)	1.2 (0.78, 1.79)
Quartile 4	1.4 (0.93, 2.09)	0.9 (0.61, 1.36)	1.3 (0.83, 1.87)	1.3 (0.87, 1.98)	1.3 (0.87, 2.06)	1.3 (0.85, 1.93)
The p-value for linear trends	0.09	0.84	0.54	0.35	0.17	0.30
Preterm Birth (hazard ratio, 95% CI)						
Quartile 1 (Reference)						

Quartile 2	1.5 (0.88, 2.57)	NA	NA	1.1 (0.67, 1.85)	NA	NA
Quartile 3	1.4 (0.79, 2.33)	NA	NA	1.0 (0.57, 1.61)	NA	NA
Quartile 4	1.1 (0.63, 1.98)	NA	NA	0.9 (0.52, 1.49)	NA	NA
The p-value for linear trends	0.12	NA	NA	0.61	NA	NA