MATERNAL HOUSEHOLD AIR POLLUTION EXPOSURES IN GUATEMALA, INDIA, PERU, AND RWANDA AS PART OF A RANDOMIZED COOKSTOVE INTERVENTION TRIAL

by

JACOB REECE KREMER

(Under the Direction of Luke Peter Naeher)

ABSTRACT

Background: The Household Air Pollution Intervention Network (HAPIN) is a randomized controlled trial that measures pregnant women and children's exposure to carbon monoxide (CO), fine particulates ($PM_{2.5}$), and black carbon (BC) with a liquified petroleum gas (LPG) intervention in Guatemala, India, Peru, and Rwanda. **Objectives:** 1) To investigate the short-term CO exposures by comparing rolling averages to World Health Organization (WHO) Air Quality Guidelines (AQGs) stratified by study arm and location, 2) build multivariable models using household questionnaire variables to try to predict CO concentrations, and 3) characterize relative exposures between pairs of pollutants and to explain observed variations in the CO:$PM_{2.5}$ and BC:$PM_{2.5}$ correlations and mass ratios. **Methods:** Implementing the Enhanced Children MicroPEM (ECM) and Lascar CO Datalogger, personal exposures from 3,195 women were investigated within the HAPIN trial. Evaluating minute-by-minute personal CO exposure we compared maximum rolling averages with established WHO AQGs to determine frequency of exceedances. Additional analyzation of 24-hour CO concentrations included over 60 time-variant and -invariant characteristics to build site-specific and HAPIN-wide multivariable models

using backwards stepwise regressions. To evaluate the strength of relationships among pollutants and HAP composition, correlations and mass ratios were evaluated between BC and $PM_{2.5}$ and between CO and $PM_{2.5}$. **Results:** Post-randomization HAPIN-wide, we observed significant reductions in the interventions arm for all mean maximum short-term personal CO exposures. In the control arm post-randomization, 4% of exposure visits exceeded a short-term CO AQG but not the 24-hour AQG. We found that the largest associations with covariates for determining CO concentrations were stove type, fuel type, and study site, while other time-invariant measures were more strongly associated than time-variant. The variation in the BC:$PM_{2.5}$ and CO:$PM_{2.5}$ ratios were almost all attributed to study arm and study site. When averaging together pollutant concentrations from the two repeated exposure visits, the Spearman Rho's improved majority of the time for HAPIN-wide comparisons. **Conclusions:** Applying three unique exposure assessment methodologies, a fuller understanding of LPG intervention stove success was evaluated in low- middle- income households that predominantly use biomass for cooking.

INDEX WORDS: Carbon monoxide (CO), Fine particulates ($PM_{2.5}$), Black carbon (BC), Household air pollution (HAP), Personal exposure monitoring, Exposure assessment

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DEDICATION

“Those who have the privilege to know have the duty to act.”

-Albert Einstein

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CHAPTER 1

INTRODUCTION

Introduction

Biomass burning within homes for cooking and heating includes dung, charcoal, wood, and agricultural waste. This burning creates harmful smoke and gases in the form of household air pollution (HAP), and thus, affordable and clean energy is included as one of the 17 United Nations Sustainable Development Goals [1]. This Sustainable Development Goal is still far from being achieved as nearly 40% of the global population still relies on solid fuels for cooking and heating [2]. This large proportion of the population exposed to HAP led to an estimated 1.8 million deaths and 60.9 million annual disability adjusted life years (DALYs) with majority of the burden in low- and middle-income countries (LMICs) [3]. To mitigate DALYs and health inequalities, the World Health Organization (WHO) has proposed a series of Air Quality Guidelines (AQGs) to reduce health effects from such pollutants. There are several classes of air pollutants that include particulates, gases, and metals, which lead to a variety of different negative outcomes. The WHO recently updated their AQGs in 2021 to set precedence over these classes of air pollutants[4]. With these updated guidelines, driven by new science, there still remain questions about how to and why we should regulate these pollutants.

Particulates range in size and composition, but fine particulates ($PM_{2.5}$) are those that are of most concern due to their ability to penetrate deep into the lung and pass through the circulatory system with ease[5]. There are several meta-analyses that have shown the respiratory

risks associated with high exposures to particulates [6–8]. With respect to respiratory outcomes, a large concern is with childhood pneumonia, which remains the leading cause of morbidity for young children outside of the neonatal period, again, mostly in LMICs [9]. One component of $PM_{2.5}$ that has drawn recent attention is black carbon (BC), which is the light absorbing fraction and known to have similar health effects as $PM_{2.5}$ [10–12]. Additionally, BC is of climate concern and there could be co-benefits of reducing BC on health and reducing climate changing chemicals[13]. Finally, carbon monoxide (CO), which is gaseous and formed during incomplete combustion, is strongly linked to cardiovascular diseases [14,15]. However, CO might not be as strongly linked to previously discussed respiratory diseases [16]. CO is still of concern due to episodic peak exposure link to cardiovascular disease (CVD) [17]. Although still not a major focus in the scope of HAP, there are also hundreds of different volatile organic compounds (VOCs) including hydrocarbons, aldehydes, and ketones which are known to have carcinogenic effects [18,19]. With all these different components of HAP and their associated health effects, there has been growing concern to reduce exposure to these pollutants in LMICs, and justification for measuring multiple pollutants within these studies.

To better understand how to improve the lives of billions of individuals, several research studies have been the foundation for investigating the link from HAP to health effects. Many meta-analyses have found that various types of interventions can reduce exposures compared to traditional open fire stoves, but there is lack of understanding how these improvements can be scaled across so many people in so many unique regions [20]. Additionally, many have agreed that improved biomass stoves, which are cheaper and easier to install and use compared to liquefied petroleum gas (LPG), offer significant benefit in reducing exposures [21]. More detail on the results and details of the previous trials can be found later in this chapter. These studies on HAP

have contributed to the push for local and international efforts to reduce the emissions from cookstoves.

There have been several attempts through both private and public sectors to help mitigate such negative health outcomes. This has included the Indian government and International Institute for Sustainable Development subsidizing LPG connections and LPG tanks to households [22]. One other major source of support is the Clean Cooking Alliance. The Clean Cooking Alliance was originally founded in 2010 by Hillary Clinton in an effort to provide clean cooking fuels and has since provided over 400 million stoves in LMICs [23]. This has far surpassed the goal of 100 million households by 2020 when the Clean Cooking Alliance was originally founded. Now the Clean Cooking Alliance has focused toward reducing emissions to help curve climate change, which includes reductions in BC and methane from biomass burning. Despite the massive improvements in the lives of millions of individuals, there is still concern that 3 billion people still use biomass stoves without definitive evidence that an LPG intervention can reduce harmful effects, especially for children under five years old. There are also still concerns about effectiveness of air pollution interventions improving the health of children, which is why there is still a need for research on the effect of intervention stoves.

While these studies and organizations provide substantial evidence about the benefits of reducing HAP, there are still major gaps concerning exposure-response and intention to treat analyses using an LPG stove as an intervention. This is where the most recent, largest, and diverse study, Household Air Pollution Intervention Network (HAPIN), can help to fill these knowledge gaps [24,25]. The HAPIN trial is unique for several reasons. First, the funding comes from both public and private sectors from The National Institutes of Health in addition and The Bill and Melinda Gates foundation. Second, this is the first concurrent multi-site randomized

controlled trial on HAP with sites in Guatemala, India, Peru, and Rwanda. Third, and most central to this dissertation, is the use of three pollutants $PM_{2.5}$, CO, and BC for exposure assessment on pregnant mothers and children. Most studies have used some combination of these three pollutants, but very rarely collect all three at all exposure visits. This extensive exposure assessment campaign is the largest of its kind and has allowed for more in-depth exposure comparisons. Finally, HAPIN has one the largest cohorts in a HAP randomized controlled trial with nearly 3,200 pregnant women and their subsequent children spilt evenly between the four sites. It has already been published that the LPG stove in HAPIN significantly reduces the $PM_{2.5}$ and CO below WHO AQGs [26]. The main phase of HAPIN has finished and has been renewed to follow a subpopulation of children until the age of five to see whether the LPG intervention during the first year of life improves development and pulmonary function later into childhood.

Purpose of Research

HAPIN is an interdisciplinary study including intervention science, biomarkers, clinical assessments, data management, and exposure assessment. Each part of HAPIN is integral toward working to a common goal of reducing the global burden of disease due to HAP. While the vast resources of HAPIN have allowed for many questions to be answered about both intentions to treat and exposure response analyses with an LPG intervention, there are opportunities to ask scientific questions that have not been able to be proposed yet. As part of the Exposure Assessment Core for HAPIN, there have been several ways that the collection of three pollutants in four study-sites on 3,200 women and children can be evaluated. These questions can be asked because of the large sample size, multiple pollutant measures, and multi-site design of HAPIN. I

have been able to leverage such advantages to expand exposure assessment knowledge within the HAP setting.

Here I discuss three main chapters that expand on one of HAPIN's main aims, to establish exposure-response relationships, by:

1) Assessing CO exposures in pregnant women by comparison with WHO AQGs for short term exposures (Chapter 2),

2) Reporting the post-birth maternal CO concentrations. As well, we aim to evaluate associations of CO concentrations with questionnaire variables. We built univariate and multivariate models to help better understand potential time-variant and time-invariant characteristics that relate to personal CO exposures (Chapter 3) and,

3) Characterizing relative exposures between pairs of pollutants and to explain observed variations in the CO:$PM_{2.5}$ and BC:$PM_{2.5}$ correlations and mass ratios. We aim to investigate the inter- and intra-variation of correlations and mass ratios of four LMICs based on study arm, stove type, and other key covariates (Chapter 4).

Outline of Dissertation

- **Chapter 1** serves as the main introduction to household air pollution, outlines the chapters of the dissertation, summarizes current and relevant literature including the three main pollutants monitored in HAPIN, summarizes previous intervention trials and their health findings, and where I see the future of exposure assessment heading.
- **Chapter 2** is a manuscript that presents the findings from a deeper exposure assessment into the real-time CO concentrations. We explore the 15-minute, 60-minute, and 8-hour rolling average CO concentrations for participants and explore how these compare with

short-term WHO AQGs. We stratify results by study site, study arm, and which WHO AQGs were exceeded.

- **Chapter 3** is a manuscript that evaluates the associations of questionnaire and household characteristics with CO. We use backwards stepwise regression models to attribute portions of variation on a HAPIN-wide and site-specific level. We also evaluate variables based on time-variant and time-invariant categories as well as considering the effect of repeated household measures. Additionally, this chapter reports the post-birth maternal CO concentrations.
- **Chapter 4** is a manuscript investigating the relations of the three primary HAPIN pollutants. This study aims to first characterize relative exposures between pairs of pollutants and to explain observed variations in the CO:$PM_{2.5}$ and BC:$PM_{2.5}$ correlations and mass ratios. We investigate correlations three different ways: the unadjusted values, the averaged by household, and by removing top percentile of points. Next, we aim to investigate the inter- and intra-variation of the mass ratios in four LMICs based on study arm, stove type, and other key covariates.
- **Chapter 5** contains a summary of this dissertation, overall thoughts and comments, and potential future work.

CHAPTER 2

LITERATURE REVIEW

This literature review summarizes 1) the global impact of HAP and the mechanisms of how pollutant exposures effect health; 2) the health impacts from exposure to three main pollutants: $PM_{2.5}$, BC, and CO; 3) the relationships and associations among these three pollutants; 4) the previous HAP trials that have been conducted and their results as it relates to health; and 5) the future of exposure assessment work with modeling and new exposure evaluation techniques.

Household Air Pollution Global Impact and Mechanisms

Reliance on biomass or solid fuels such as dung, wood, and charcoal for cooking and heating remains a global health challenge affecting nearly 3 billion people worldwide [2]. These fuels are mostly used in developing countries in Southeast Asia, Central and South America, and Sub-Saharan Africa. While the absolute number of individuals using biomass has declined by 11%, reliance on biomass still contributes to 91.4 million annual disability-adjusted life-years (DALYs) [27–29]. Even though there has been a decline in biomass usage, household air pollution (HAP) is still the second leading occupational/environmental risk factor worldwide effecting mostly women and children in low- and middle-income countries (LMICs) [27]. This is in part because women in these settings are traditionally the cooks while men are often away at work. Additionally, biomass burning occurs most frequently where fertility rates also tend to be the highest, which leads to a large number of young children being exposed to HAP early in their

life. HAP from biomass burning stoves results in a multitude of different exposures including carbon monoxide (CO), fine particulate matter (aerodynamic diameter ≤ 2.5 μm; $PM_{2.5}$), black carbon (BC), and polycyclic aromatic hydrocarbons [30,31]. High levels of exposure to these pollutants are associated with multiple adverse health outcomes including increased blood pressure, reduced birthweight, and increased acute lower respiratory infection [32–35].

The estimated number of DALYs attributed to HAP has been on the decline, but many of these risk assessment studies might not be incorporating new evidence in the HAP setting. First, there are more reports about the reduction in cognitive development later in childhood, with some even into adulthood that has widely been understudied [36,37]. These findings could indicate prolonged effects from using biomass stoves even if the exposure was early in life. Second, there are synergistic negative effects of HAP with other sectors including lack clean water and lack of food, which fundamentally arise from poverty [38,39]. The entire WASH (water, air, sanitation, hygiene) field is interrelated and it might be more difficult to gauge how one specific aspect affects human health. As Clasen and Smith 2019 describe, "…together with the continued consumption of untreated water, unsafe disposal of child feces, and inconsistent handwashing, can all leave household exposure to high levels of fine particulate and fecal pathogens that will vitiate the potential health effects that these technologies can accord" [38]. These synergies might underestimate how improving HAP would improve the lives of billions of individuals. Finally, there are other studies using only cooking fuel to estimate HAP, suggesting that previous reports underestimates around 9% of mortality and 10% of DALYs [40]. For these reasons, many studies are focused on reducing the amount of pollution individuals are exposed to. With uncertainties about the toll that HAP has taken across the globe, there is increasing research into how these

pollutants cause so many diseases, and trying to stop those mechanisms before they cause serious harm to individuals.

While the exact mechanism is unknown how these pollutants cause these health effects, there is growing evidence that pre-natal exposures to HAP can increase odds of pneumonia and growth stunting [41,42]. There is still an ongoing debate about how particulates and gases can lead to an increased incidence of bacterial or viral disease. There is a line of thought that these harmful particulates, mainly the BC fraction, are inhaled by a pregnant mother and then cross the placental barrier as one recent study showed [43]. In addition to the placental barrier, it is known that $PM_{2.5}$ as a whole can cross the alveolar barrier [44]. This can then lead to $PM_{2.5}$ being transferred to other organs including the heart, which might be reasoning for significant association with many cardiovascular diseases [45]. However, PM and BC mechanistic studies are often focused with the lens of urban air pollution. More is known about the toxicity of CO as it readily binds to hemoglobin molecules making it more difficult for blood cells to transfer oxygen throughout the body [46]. As we learn more about these mechanisms, a major goal would be to implement specific interventions that can reduce the harmful effects of HAP.

Often major risk assessments, including those from the EPA and WHO, for CO and $PM_{2.5}$ can have a focused on ambient air pollution in large urban cities [47,48]. While ambient air pollution is a large growing problem, this leaves a large knowledge gap about the risk and estimated health effects of HAP [49]. We will first summarize three of the main HAP pollutants and their health effects, $PM_{2.5}$, BC, and CO. Then, we present what previous HAP studies have found in terms of exposure reductions and health effects.

Household Air Pollution Exposures and Health

To understand why there has been so much investment from the public and private sector into reducing HAP, we must break down the components of HAP to explore the specific pollutant-health outcome pathways. A problem with using singular pollutant exposure-response is that some pollutants have different health effects than others. For example, BC and $PM_{2.5}$ can have specific health consequences including severe pneumonia which is the leading cause of death for children under 5 years-old [27]. On the other hand, acute CO exposure is commonly associated with headaches, nausea, and loss of consciousness [50]. When using exposure-response analyses it becomes more important to consider the type of pollutant evaluated with the relevant outcome pathway. In turn these pollutant-health pathways may result in different exposure-response computations. This is evident with one recent study that has shown that BC was associated with low birth weight, but $PM_{2.5}$ and CO were not associated for the same exposure-response analyses[51]. By breaking down each exposure pathway we can reveal better interpretations of pollutant exposure observed health effects.

$PM_{2.5}$

$PM_{2.5}$ as opposed to larger fraction sizes such as PM_5 or PM_{10} is more commonly used in HAP and ambient settings. The reasoning behind using the smaller particle size of $PM_{2.5}$ is because these particles are more likely to travel into and deposit on the surface of the deeper parts of the lung. PM_{10} typically does not penetrate as deeply and gets caught in the upper respiratory tract rendering it mostly inconsequential [52]. In a similar fashion, PM_{10} is not as likely to cross the alveolar barrier and move to the internal organs compared to $PM_{2.5}$ [53,54]. One study found that the smaller the particle size the stronger the relationship with childhood pneumonia[55].

This important distinction in particle aerodynamic diameter is why it is more common to study health effects associated with $PM_{2.5}$ rather than other size fractions. $PM_{2.5}$ is used in cookstove trials due the many health outcome pathways including low birth weight, childhood pneumonia, and cardiovascular diseases [56–59]. The World Health Organization (WHO) has established both interim targets (IT) and standard Air Quality Guidelines (AQGs) that have been established based on health reports (IT-1: 35 $\mu g/m^3$, IT-2: 25 $\mu g/m^3$, IT-3: 15 $\mu g/m^3$, IT-4: 10 $\mu g/m^3$, AQG: 5 $\mu g/m^3$) [4]. For those using biomass stoves, personal $PM_{2.5}$ levels can reach exceptionally high concentrations of over 400-500 $\mu g/m^3$ [60,61]. Those numbers can reach 3-5 times higher if we evaluate kitchen exposures [62,63]. Therefore, it can be difficult to reduce $PM_{2.5}$ exposures below the AQG of 5 $\mu g/m^3$. For this reason HAP studies often aim to reduce exposure below the IT-1, but this target might still be too high to see a significant reduction in health outcomes [64]. Exposure to such high levels of $PM_{2.5}$ are reason for concern, especially among older adult women and children under 5 due to their vulnerability.

Children under 5 years-old and older (>50 years-old) adult women are a priority because of the proposed $PM_{2.5}$-increased blood pressure mechanism and amount of time these individuals spend near open stoves [65]. There have been several studies in the ambient and household setting that have shown an increase in $PM_{2.5}$ can have increase blood pressure in women [58,66,67]. These studies highlight the importance of measuring $PM_{2.5}$ accurately to assess what individuals are exposure to in the HAP setting.

$PM_{2.5}$ is considered to be a gold standard for HAP exposure measurements because of the strong associations with cardiovascular disease and severe childhood pneumonia [68]. As often with gold standards, $PM_{2.5}$ is also challenging to measure accurately. The gravimetric method of capturing air pollutants on a filter has many challenges including: obtaining personal monitors

and compliance, transportation of filters to the weighing institution, and correctly calibrating and estimating concentrations from filter weights. If studies are willing to put in the monetary effort required for gravimetric $PM_{2.5}$, there can be great return on investment. However, often times real-time functionalities or proxies are used, which have been shown to not accurately assess $PM_{2.5}$ concentrations [69,70]. This large stakeholder investment to accurately measure $PM_{2.5}$ is why several studies have shown that reductions in $PM_{2.5}$ can reverse respiratory diseases such as pneumonia, cough, and wheezing [71–74]. While the whole fraction of $PM_{2.5}$ is typically a focus, there are increasing efforts to try to break down the components of $PM_{2.5}$ to further understand causes reported CVD and respiratory diseases.

Black Carbon

BC is a by-product of incomplete combustion that makes up the light-absorbing fraction of particulate matter [75]. Because of these light-absorbing properties, BC is known to contribute to global warming and polar ice melting [76–78]. Sources of BC include urban road traffic and coal fired power plants. Additionally, biomass burning accounts for around 35% of anthropogenic BC emissions, as global concentrations steadily increase [79]. As BC has gained more attention there has been a focus to determine what health effects and at what levels BC is harmful. Like $PM_{2.5}$, BC has been linked to multiple health outcomes including increase in blood pressure and low birth weight [11,80,81]. Far fewer HAP intervention stove studies have investigated BC, but those that have showed the percent reductions from interventions are similar to $PM_{2.5}$ [26,82]. Despite the known adverse health outcomes and climate impacts, there are currently no WHO guidelines on BC, and it is not regulated within the United States. The WHO has put out a “Good practice statement” for BC and elemental carbon (EC) which only states to reduces the source of BC/EC

and to take measurements for BC as there is insufficient evidence to propose an AQG [4]. BC also has more identifiable sources than $PM_{2.5}$. These specific sources include biomass burning and especially kerosene usage and, therefore, is used more frequently as an exposure metric in HAP settings [83]. Unlike $PM_{2.5}$, BC does not arise from dust and therefore when BC is detected it could be a much stronger signal of biomass combustion compared to whole $PM_{2.5}$ fraction. While this emerging pollutant is still being investigated for its human health effects, there are still many advantages to measuring BC in health effect studies.

BC might become more commonly assessed in HAP exposure studies in the future because it is an easier analytical method of concentration estimation compared with $PM_{2.5.}$ Another benefit of measuring BC in the HAP setting is to potentially see if there are different health outcomes compared to the entire $PM_{2.5}$ fractions. This is evident in a recent HAPIN publication that showed BC was associated with low birth weight but $PM_{2.5}$ was not [51]. One BC meta-analysis found that estimated health effects, including CVD and respiratory hospital emissions, were greater for BC than for either PM_{10} or $PM_{2.5}$ [12]. This could suggest that the effect of BC might be larger than that of the total particulate fraction. Alternatively, one study from China also found a similar magnitude of effect from BC as from $PM_{2.5}$ with systolic blood pressure and pulse pressure [84]. These new results are the reason for more BC exposure assessment and the mentioning to evaluate BC in the WHO guidelines. BC is best known as a climate change impactor, but growing evidence suggests that BC might be just as if not more important than the whole $PM_{2.5}$ fraction for assessing health effects related to HAP. As we learn more about this pollutant, one would expect the WHO to establish guidelines for BC.

Carbon Monoxide

CO is a colorless odorless gas that is emitted when incomplete combustion occurs. While $PM_{2.5}$, BC, and other particulates are solids that can be collected on filters, CO is often measured with colorimetric tubes or through real-time electrochemical loggers [85,86]. CO has often been used in HAP studies to estimate exposure to particulates as those are generally the more concerning pollutant. Some studies have used the real-time CO functionality in LMIC studies to compare the relationship CO between $PM_{2.5}$ [87,88]. While there are mixed interpretations on what the relationship between CO and $PM_{2.5}$ relationship are, one review shows how CO from biomass burning can be emitted at different concentrations depending on the type of biomass burned [89]. This could be important for different cultural or regional differences when selecting study sites because of the different fuel and stove types that are used around the world. The measurements of CO are often taken in 24- or 48-hour averages. However, the mechanism of toxicity of CO has led to several shorter duration guidelines to be established by the WHO [4]. These shorter duration (15 minutes- 100, 60-minutes- 35, 8-hours- 10 $\mu g/m^3$) are used for occupational exposure where individuals could be exposed to very high levels of CO for short durations. These occupational settings also include the HAP setting where fires are burned at short durations, but produce an intense peak amount of CO. HAP settings are known to be environments where short-term exposures (STE) can be important for both CO and $PM_{2.5}$ [90,91]. STE to CO is understudied despite the known differences in health effects of STE to CO and longer 24-hour averaging periods [92]. Despite these known variations, few studies have investigated the effects of STE on CO health effects and have mostly focused on ambient and vehicular emissions.

CO is of concern in most developed and developing nations as vehicle exhaust. Thus, several studies have focused on prolonged exposure to low concentrations of CO [93]. The health effects that are commonly associated with CO in these low-level ambient settings include angina, myocardial infarction, and COHb [94–96]. However, these cardiovascular diseases are understudied in HAP settings because of difficulty accurately measuring both participant cardiovascular health and exposure to HAP. CO in the HAP setting is often associated with low-birth weight and childhood pneumonia [97,98]. Some studies have found that an intervention stove could help reduce blood pressure in mothers [17] and reduce rates of childhood pneumonia [73]. CO is easier to estimate concentrations than gravimetric $PM_{2.5}$ because of the lack of need for weighing filters. However, there is growing concern that just evaluating exposure-response using a singular pollutant might not be as reliable as multipollutant modeling [99]. Individual pollutant-health pathways are helpful in understanding how to reduce pollutant concentrations, but fail to offer a holistic view of exposure that can be explored by comparing said HAP pollutants to each other.

Pollutant Relationships

The co-emission and mixtures of pollutants from HAP have generated interest about how these pollutants are related to one another. The HAP field has grown as more extensive exposure measurements and source apportionment strategies have become more prevalent. Multipollutant exposure assessment has previously been used for a variety of metrics including correlations and modeling. CO is often used as a proxy for $PM_{2.5}$ concentrations because of their positive correlation, especially for personal samples because of the ease and cost of collecting CO compared with $PM_{2.5}$ [100,101]. However, this proxy approach is not consistently validated, particularly in low emission settings [87]. CO can highly correlated to $PM_{2.5}$ [102], but other studies

have found weaker results [88,103]. This has led to fewer exposure studies using CO as the primary exposure metric due to this inconsistent relationship. Alternatively, BC and $PM_{2.5}$ correlations are becoming more frequently used and often have high correlations (R^2>0.8). One potential reasoning is that BC, unlike CO, constitutes part of $PM_{2.5}$ and can be helpful in determining the efficiency of combustion [104,105]. Another reason to use a multi-pollutant approach is to use predictive modeling for an individual's total exposure. These models can become more accurate when using one pollutant as a predictor for another pollutant[106]. Despite these strong correlations and modeling approaches, the gold-standard approach remains direct personal $PM_{2.5}$ concentrations.

Mass ratios can also be used to assess combustion efficiency and evaluate emission sources. For example, one study shows how seasonality and moisture can affect the efficiency of burning using BC:$PM_{2.5}$ mass ratios [107]. Another study has shown that the BC:$PM_{2.5}$ mass ratios from biomass burning is higher compared to that from residential coal burning [108]. These ratios help to illustrate how different stove and fuel types might affect a proportion of an individual's total exposure. However, further investigation is needed into how LPG interventions alter the BC mass ratio of $PM_{2.5}$ compared to biomass burning. Fewer such studies have evaluated CO:$PM_{2.5}$ mass ratios, but some have found that cleaner fuels reduced the mass ratios [101,109]. Pollutant mass ratios and correlations can be used for a variety of metrics that can improve how we evaluate exposure assessment.

Previous Trials

The largest most current ongoing HAP study is the Household Air Pollution Intervention Network (HAPIN). HAPIN has been heavily funded from both private and public sectors to try

to provide evidence to policy makers on the health benefits from an LPG intervention stove [24]. To understand the context and the rationale for funding such a large HAP effort, one must understand what has previously been accomplished.

There have been hundreds of HAP studies ranging from cookstove lab efficiency tests [110,111], small less than a 100 household observational studies constituting a majority of HAP studies [112–114], and large several hundred household controlled trials [115–117]. Each type of study has played a role in trying to reduce the number of individuals exposed to harmful pollutants; however, the most convincing and most robust studies remain the randomized control trial (RCT).

There have been many attempts to try to reduce health effects from biomass burning stoves. Early RCTs and observational studies used many types of improved biomass stoves. This includes the use of chimney stoves, *planchas* (a steel plate on top of a biomass stove), and increased efficiency biomass stoves [116,118,119]. These types of stoves have been shown to be effective in reducing exposures, in most cases. There is evidence that these improved stoves can reduce CO and $PM_{2.5}$ exposures by about 50% in various studies [20,120–122]. However, there are also a few studies using improved biomass stove interventions that have found non-significant differences in their reductions of exposure[61,119]. The improved biomass stove is also the most scalable in terms of cost and implementation in the developing world, which is why the first large RCT used chimney stoves as stove intervention to reduce exposures and negative health effects.

The Randomized Exposure Study of Pollution Indoors and Respiratory Effects (RESPIRE) was a RCT in Guatemala using a chimney stove intervention [122]. The chimney stove in RESPIRE was shown to reduce CO in kitchens by up to 90% and reduced maternal and child exposures by

60% and 50%, respectively [122]. Despite these large significant reductions in exposures from the chimney stove many of the exposure-response and intention to treat analyses were not statistically significant including for blood pressure, lung function, birth weight, and certain childhood pneumonia [35,73,123,124]. While non-significant, it was acknowledged that there is significant value to reducing the exposure of pregnant women in the HAP setting. The main investigators, including Kirk Smith, found that there might be a need for more substantial interventions than those that were implemented in RESPIRE. In a review [21] of improved stove invterventions the authors found a few key important strengths and limitations of using improved biomass stoves:

1. In almost every case improved biomass stove substantially reduced exposure to $PM_{2.5,}$
2. Even with this reduction, most of the studies did not reach even close to the WHO IT-1 of 35 ug/m3, and
3. The exposure-response curves derived for $PM_{2.5}$ suggest that the risk of negative health effects declines steeper at lower levels not seen for improved biomass stoves.

Additionally, it is recognized that more could possibly have been done to achieve significant results including lowering exposures further, increasing sample sizes, and implementing the intervention earlier in pregnancy. RESPIRE was the first large, randomized trial and moved the field forward and the stage for future cookstove intervention trials.

The lack of significant results from RESPIRE is further supported by two other exposure-response pieces that also suggest the use improved stoves may not get exposures low enough to reach health relevant outcomes [64,125]. Smith and Peel 2010 outline the need to reduce exposures to a lower level that is not seen currently leaving a large "gap" of knowledge about the dose-response at these levels. Similarly, Steenland et al. 2018 provided several modeled exposure-

response curves for different HAP related health effects. From these curves it can be determined that the steepest part of the slope is in the lower portion of the exposures that is not achieved with improved biomass stoves. Upon these findings it was suggested that cleaner fuel sources should be considered to try to reduce health effects. More recent studies have started to incorporate liquefied petroleum gas (LPG) as an alternative cooking method. This leads into the three next largest trials that took place in Nepal, Malawi, and Ghana.

The Nepal Cookstove Intervention Project were two randomized trials attempting to evaluate the impact of using two improved cookstoves, improved biomass and LPG [126]. The trial was focused on improving acute lower respiratory illness (ALRI) in children <36 months old, birthweight, and gestational age [126]. The exposure contrasts in the first trial (traditional vs improved biomass) for kitchen $PM_{2.5}$ averages were 1380 and 936 $\mu g/m^3$ for traditional and improved biomass stoves, respectively [127]. The second trial comparing improved biomass and LPG found kitchen $PM_{2.5}$ averages of 885 and 442 $\mu g/m^3$, respectively [127]. The authors cite lack of exposure reductions from either ambient sources or stove stacking (the use of multiple stoves in one household) as one of the main reasons for the null health outcomes for birthweight and ALRI [127]. Another limitation of this study was the lack of personal monitoring. One issue with this approach is that using area sampling has been shown to vastly overestimate a person's exposure leading to exposure misclassification [128]. The use of personal monitoring in the HAP setting is the best way to assess what individuals are exposed to, which is why the remaining highlighted studies use personal exposure monitoring.

The Cooking and Pneumonia Study (CAPS) in Malawi was a trial that used a community-level cluster RCT. CAPS used personal CO for exposure-response analysis with pneumonia, carboxyhemoglobin levels, and noncommunicable respiratory disease [129–131]. Due to

the large nature of the trial, the intervention was a cleaner-burning biomass-fueled cookstove. The results from this trial were mixed. There was no association with pneumonia and carboxyhemoglobin levels, but an associated effect of CO and noncommunicable respiratory diseases, including tuberculosis [129–131]. However, this trial cites that other sources of air pollution may have impacted the results and contributed to some of the null findings. Others have found similar results about the impact of ambient air pollution reaching indoor environments and vice versa [132,133]. The CAPS study also discusses that CO might not be the most appropriate way to measure exposures in this setting and the need to reevaluate the cleaner-burning biomass cookstoves as an appropriate intervention.

The Ghana Randomized Air Pollution and Health Study (GRAPHS) which had two treatment arms an LPG stove and a fan-assisted biomass burning cookstove with over 1,400 total households [116]. Unlike the chimney stove in RESPIRE, GRAPHS found very minimal reductions in exposure to CO with their BioLite improved biomass stove, however, they found large reductions of around 47% from traditional to LPG stoves [134]. However, one of the limitations of this trial was the primary use of CO, which may not be as reliable of a proxy as previously thought. While CO has many negative health effects, many trials rely on CO because of the easier exposure measurements compared with the gold-standard of $PM_{2.5}$. The personal CO exposure-response analyses found significant health outcomes including blood pressure in pregnant women [17]. The GRAPHS study allowed researchers to finally start addressing how cleaner burning fuels can positively affect health outcomes and thus the remainder of the trials we discuss are LPG interventions. Additionally, there have been anecdotal, at this point, reports of neurological development improvements in children under 5 that had an intervention LPG stove during the first year of life compared to the traditional stove arm.

Finally, the sister study of HAPIN, Cardiopulmonary outcomes and Household Air Pollution (CHAP) was undertaken in the same study location in Peru as HAPIN, Puno. Puno is a unique study location and adds to the portability of LPG stove interventions. Puno is situated over 3,800 meters above sea level. This altitude can be lead to different combustion properties that may ultimately lead to different health effects at such altitudes [135–137]. CHAP found similar reductions in CO as GRAPHs with an LPG stove, but this study also included $PM_{2.5}$ and BC and found that exposure for BC, $PM_{2.5}$, and CO were all reduced below respective WHO standards, if available [82]. The intention to treat analyses found no effect on blood pressure, lung function, or respiratory symptoms from the LPG intervention [138]. The authors state that this could be due to a short-term (one-year) intervention implementation period that may not have been long enough to reverse such health effects, in addition to, the smaller sample size of only 90 intervention participants. However, this trial did show that the implementation of an LPG stove can be used to reduce HAP in a variety of settings globally.

All these studies were instrumental in the funding of the largest most intensive HAP study to date, the Household Air Pollution Intervention Network (HAPIN). HAPIN is a randomized controlled trial (RCT) of 3,200 households that are evenly split between control biomass stoves and an LPG intervention stove. HAPIN not only collected exposure data but also biomarker samples on all participants [24,139,140]. The 3,200 households were evenly split amongst four LMICs in Guatemala, India, Peru, and Rwanda totaling 800 houses per site and 400 in each study arm. The three main aims of HAPIN are (1) determine the effect of LPG stove and fuel intervention on health, (2) evaluate exposure-response using BC, PM2.5, and CO, and (3) evaluate the extent of biomarkers and health effects and their association with exposure or study arm [24]. The main health outcomes of interest include low birth weight, severe pneumonia, growth

stunting in the child, and high blood pressure in the pregnant woman/ mother. While HAPIN data processing is still ongoing, some early results on newborn babies give insight into this large RCT. For exposure-response with BC, $PM_{2.5}$, and CO only BC was significantly associated with low-birth [51]. For intention to treat analyses, no significant findings were found for low birth weight study-wide or by individual site [141]. The authors state that potential null effects could be due to insufficient exposure reductions. Even though the LPG stove did reduce below the IT-1 for $PM_{2.5}$, there were very few households below the WHO AQG of 5 ug/m3. They also state there might be a need for earlier implementation of the LPG intervention. There was a near significant difference between those that got the intervention less than 18 weeks into gestation and those after with increased birth weight. This might indicate the need to implement the LPG stove earlier into pregnancy.

One other alternative for many limited health effects throughout these studies is concern over LPG as an intervention. More recent investigation into LPG has shown it to emit NO_2 and methane gases as it burns [142]. These gases are currently being explored into how they could affect human health. One study has estimated that in the United States ~13% of current childhood asthma can be attributed to gas stove use [143]. While LPG has been shown to potentially have health consequences, the alternative of biomass is known to be worse for human health. Ultimately, the goal is to reduce the harmful health effects and there are a growing number of new strategies to reduce the costs of exposure measurements.

Future of Exposure Assessment

With the large number of trials that have occurred there is now a shift in the exposure assessment field to attempt to do more measurements on tighter budgets. HAPIN might be the

last multi-site large RCT that occurs in the HAP field for some time, but the knowledge from HAPIN can be used to inform smaller-scale studies. This can be done with the growing use of statistical modeling to estimate a person's exposure. Exposure assessment can be a very expensive and challenging undertaking, and if modeling approaches can be used as a proxy for a person's actual exposure it can be beneficial to smaller less funded exposure campaigns.

Many studies have attempted different methods for determining the best ways to explore proxying exposure. One such recent study attempted to use a Bluetooth logger in the monitoring vest on a child to estimate exposure based on the location of the child and proxied to the nearest exposure monitor performed well (R^2=.83) compared to direct exposures [144]. These indirect assessments are useful when direct personal monitoring cannot be achieved on children due to their inability to carry instruments. However, this approach still requires the use of multiple area personal measures, which can be burdensome. Using modeling and machine learning personal $PM_{2.5}$ exposure in the HAP setting has been difficult to understand with some studies finding low (R^2< 0.5) correlations and poor estimates of exposure [145,146]. However, there have been other studies that have found better correlations using kitchen or other microenvironmental data [106,147]. Microenvironmental data (i.e., kitchens, secondary rooms) is easier to collect than personal data and does not require the participant to wear any exposure equipment. In Table 1.2 there is a comparison of R^2 values for different modeling data that have previously be conducted with their predictors. As part of this modeling, it can also be incorporated how many repeated exposure visits are necessary to accurately assess what average daily exposure is [148].

Ultimately, these modeled estimates can make extrapolated global risk and exposure assessments more accurate than previous. One such study was able to estimate country-level HAP exposures in 106 countries by using global database models [59]. One potential use for these

large-scale estimations could be to use where limited data is collected, therefore, helping to better estimate the burden of HAP in global estimations [149]. Conversely, some say that direct personal exposure metrics are still necessary to avoid to exposure misclassification and are still a necessary part of the HAP assessments [128]. With the growing number of tools and analytic techniques, there is potential for the exposure assessment field to be less reliant on direct measurements. These models are helping move toward the use of indirect measurements complemented with questionnaire variables.

Summary

Previous trials have shown mixed results about the benefits of interventions. Although some trials have found null results, there has been a continued effort to reduce the number of people in developing countries using biomass stoves. This includes efforts from the Indian government which has subsidized up to 12 LPG tanks per household per year. Additionally, the founding of the Clean Cooking Alliance in 2010 has since granted access to more than 400 million people worldwide. The trajectory of HAP field is encouraging as the reliance on solid fuels for cooking and heating declines around the world.

Table 1.2 Different studies that have modeled exposures and the predictor inputs used for model with model fit.

Selected Studies Predictors of Exposure			
Outcome	**Predictors**	**R^2**	**Reference**
Personal $PM_{2.5}$	Indirect $PM_{2.5}$	0.81	Liao et al., 2019[144]
Personal $PM_{2.5}$	Time-invariant	0.30-0.50	Sanchez et al., 2020[145]
Personal $PM_{2.5}$	Kitchen exposure factors	0.26-0.31	Hill et al., 2019[146]
Personal $PM_{2.5}$	Survey-type data, microenvironmental $PM_{2.5}$	0.53	Johnson et al., 2020[106]
Personal $PM_{2.5}$	Kitchen $PM_{2.5}$	0.58	Baumgartner et al., 2011 [147]
Personal $PM_{2.5}$	Stove type, time-variant	0.57	Clark et al., 2010[113]
Indoor 1-h max CO	Stove type, kitchen volume, stove use, wall with eave space	0.86	Clark et al., 2010[113]
Personal CO	Fuel type, season, other PM sources	0.44	Dionisio et al., 2012 [150]

CHAPTER 3

EVALUATION OF SHORT-TERM PERSONAL MATERNAL CARBON MONOXIDE (CO) EXPOSURE ASSESSMENT IN GUATEMALA, PERU, INDIA, AND RWANDA AS PART OF THE HOUSEHOLD AIR POLLUTION INTERVENTION NETWORK (HAPIN) TRIAL[1]

[1] Jacob R. Kremer, Michael Johnson, Lance A. Waller, Ajay Pillarisetti, Wenlu Ye, Ricardo Piedrahita, Devan Campbell, Katherine A. Kearns, Erick Mollinedo, Maggie L. Clark, Kendra Williams, Lindsay J. Underhill, Jiantong (Jean) Wang, John P. McCracken, Anaité Díaz-Artiga, Florien Ndagijimana, Ephrem Dusabimana, Kyle Steenland, Ghislaine Rosa, Kalpana Balakrishnan, Lisa M. Thompson, Laura Nicolaou, William Checkley, Jennifer L. Peel, Thomas F.Clasen, Luke P. Naeher, and HAPIN Investigators. To be submitted to *Journal of Exposure Science & Environmental Epidemiology*

Abstract

Background: A growing body of studies measure real-time household air pollution (HAP) exposures with most using integrated or averaged measurements of CO. Often these studies reduce time-resolved data collected over 24 to 72 hours into daily metrics, with limited efforts to understand the role of peak exposures or quantification of exceedances of short-term exposure over World Health Organization Air Quality Guidelines (WHO-AQG), which could have differential health endpoints compared to the 24-hour AQG. We build on earlier HAPIN trial findings that used 24-hour averages and investigate participant short-term exposures to CO.

Methods: As part of the exposure assessment conducted in the HAPIN trial, we measured pregnant mothers' CO exposures using the Lascar CO-USB for 24-hours at one-minute intervals. First, we calculated short-term exposure levels using rolling averages based on the WHO AQGs (15-minute: 87.3 ppm; 60-minute: 30.6 ppm; 8-hour: 8.7 ppm). Second, we identified participant exceedances of WHO AQGs by using the maximum short-term level for each exposure visit. Third, we investigated if participants exceeded any of the short-term exposure AQGs but not the 24-hour WHO AQG or Interim-Target 1 AQG (IT-1) of 3.5 and 6.1 ppm, respectively. Finally, we examined the correlations between the maximum STE level and corresponding 24-hour averages.

Results: We used 2155, 2077, 1654, and 2057 valid measures in Guatemala, India, Peru, and Rwanda, respectively. At baseline (pre-randomization), we saw no differences between arms for exceedances of short-term exposure AQGs. Post-randomization, in the control arm for each AQGs (15- and, 60-minute and, 8-, 24-, and 24-hour IT-1), the percent exceedances of AQG were 2.0, 4.6, 6.8, 10.0, and 3.0% for Guatemala; 10.0, 14.0, 11.2, 14.0, and 6.0% for India;

10.9, 16.8, 14.8, 15.8, and 8.3% for Peru; and 8.4, 13.5, 11.3, 11.3, and 6.2% for Rwanda. Households exceeding the AQG limits in the intervention arm were 0.1, 0.6, 0.8, 1.6, and 0.6% for Guatemala; 0.2, 0.5, 0.9, 2.3, and 0.6% for India; 1.9, 4.9, 3.5, 4.3, and 1.4% for Peru; and 0.6, 1.8, 1.7, 2.0, and 0.3% for Rwanda. In the control arm, there were 4.0% of participant visits that exceeded a short-term exposure AQG but did not exceed the 24-hour AQG, which was lower in the intervention arm of 0.8%. HAPIN-wide post-randomization, exposure visit maximum short-term exposures had moderate to high correlations (ρ) with the overall visit 24-hour averages (15-minute [0.83], 60-minute [0.89], 8-hour [0.96]).

Conclusions: We used real-time CO data to examine short-term exposure AQG exceedances, finding lower AQG exceedances in the intervention arm, and a wide range of AQG exceedances between the four study sites. In the LPG intervention group, we do not miss many short-term exceedances when only using the 24-hour AQG. However, in the traditional stove group, we found a larger significant proportion of households that would miss a short-term AQG if using only the time resolved 24-hour average.

Introduction

Reliance on solid fuels such as dung, wood, and charcoal for cooking and heating remains a global health challenge affecting nearly 3 billion people worldwide[150]. In 2019, the majority of the yearly 91.4 million disability-adjusted life-years lost from the resulting household air pollution (HAP) were in low- and middle-income countries (LMICs) [27]. HAP from biomass stoves contains a large number of combustion byproducts, including carbon monoxide (CO). CO is often associated with low birth weight [97,98], high blood pressure [151], and growth stunting [152].

Exposures are measured in randomized controlled trials (RCT) to estimate the impact of interventions, in contrast to a control group, on pollutant concentrations and for exposure-response analyses. There have been several household energy intervention trials that have used CO 24- or 48-hour average concentrations in exposure-response analyses [122,126,127,134]. While some trials found increased maternal blood pressure[17] and pneumonia[73,153] associated with CO exposure in exposure-response analyses, many other trials have found null associations for severe pneumonia[130], low birth weight[35,51,127], and blood pressure[138]. Some of the null associations might be attributed to small sample size[35,73], small exposure reductions[127], or LPG use in control arms[138]. However, one other reasoning could be that CO exposure-assessment often fails to consider more acute (≤ 8 hours) exposures to CO.

Due to the episodic nature of CO emissions and exposures, there are several reasons acute CO exposure events might be relevant in HAP studies. First, certain combustion activities such as lighting, cooking, or smoldering fires only occur for a few hours of the day but could be diluted in 24-hour averages when there are no biomass burning activities. Second, the World Health Organization (WHO) has outlined several short-term exposure (STE) air quality guidelines (AQGs) (15-minute: 87.3 ppm; 60-minute: 30.6 ppm; 8-hour: 8.7 ppm) that are associated with adverse health impacts including angina, ischemic heart disease, and myocardial infarction[4,48,154,155]. These studies and guidelines highlight the need for acute STE CO monitoring compared to the 24-hour AQG (3.5 ppm) and interim target-1 (IT-1, 6.1 ppm) used as an intermediate goal in highly polluted areas. Finally, previous studies have shown that CO peaks in kitchen measurements can exceed the 8-hour 8.7ppm WHO guideline 60% of the time in wood heated homes[156]. Some additional studies used maximum 1-hour CO to address peak levels; however, these studies used either kitchen measures[92,112,157] or largely focused on 24-hour

averages [158]. Although STE to CO in episodic HAP environments is shown to exceed health-relevant WHO guidelines, there are just a few limited studies that have investigated frequencies of such guideline exceedances.

As part of The Household Air Pollution Intervention Network (HAPIN), we build on these studies by using time-resolved personal exposure measures to explore acute real-time CO exposures. HAPIN measured exposure to CO 8,574 times among 3,200 participants, one of the largest exposure monitoring undertakings to date[24,140]. Along with the updated 2021 24-hour and 24-hour IT-1 guidelines, we investigate all STE WHO AQGs HAPIN-wide, study site-specific, and by arm. We expand earlier HAPIN findings using 24-hour averages [159] and investigate participant STE CO exposures to determine previously uncaptured WHO guideline exceedances.

Methods

Study Design

HAPIN was a randomized controlled trial (RCT) of 3,200 households evenly split between control households using primarily biomass stoves and intervention households using primarily LPG stoves in Guatemala, India, Peru, and Rwanda with informed consent and ethics approval (NCT02944682). The study population was pregnant mothers in their second trimester followed until the child was one-years old. Although the trial followed the child until they were one year old, this paper focuses on data collected during the pregnancy period. Previous publications detail the overall objectives, design, and aims of the HAPIN study [24], along with exposure assessment[140] and biomarker [139] methodologies.

Exposure Assessment Measurements

We measured personal 24-hour CO exposures of the pregnant mother at <20 weeks gestation (baseline measurement, pre-randomization), 24-26 weeks gestation, and 32-36 weeks gestation. Lascar CO-USB Dataloggers (Lascar Electronics, Erie, PA) and $PM_{2.5}$ samplers on the mothers were collocated in specially designed aprons or vests that held the monitors near the breathing zone of the participant [140]. Overall daily average exposure assessment and exposure response, and intention to treat analyses have been previously published[51,141,159].

The Lascar CO-USB Datalogger uses an electrochemical sensor to measure CO from 0-300 ppm with a limit of detection estimated to be 1 ppm. The Lascar was set to log every 30 or 60 seconds during each exposure visit with a resolution of 0.5 ppm. Lascars were calibrated using span gas monthly[140]. Further visual inspection was performed on the real-time traces of all CO files to remove unrealistic monitor files following a protocol similar to previous trials[134].

The Lascar logs in parts per million (ppm); WHO AQGs are reported in mg/m^3. To convert AQGs from mg/m^3 to ppm we used the following equation, with a conversion factor of 1 mg/m^3 = 0.858 ppm for CO [4]:

$$Equation\ 1:\ AQG(ppm) = (24.04(L) * AQG(mg/m^3))/28.01\ (g/mol),$$

where 24.04 is the volume in liters occupied by a mole of air at 20°C and 1 ATM, and 28.01 is the molecular weight of CO.

The gas constant of 24.04, conversion factor, and WHO AQGs are assumed to be at 20°C and at 1 ATM. Due to the varying study site elevations and temperatures in HAPIN, WHO

guidelines have been adjusted using Equation 2 for each study site specifically similar to Kephart et al. 2021:

$$Equation\ 2:\ \ AQG_{adj}\ (ppm) = 22.41\ (L) * \frac{C° + 273\ (C°)}{273\ (C°)} * \frac{1013\ (hPa)}{hPa} * \frac{AQG\ (mg/m3)}{28.01\ (g/mol)}$$

where 22.41 is 1 mol of gas at 0 °C and 1 atm and 28.01 is the molar mass of CO. All adjusted AQGs are presented in Table 3.1 °C is the average temperature in Celsius and hPa is the average pressure in hectopascals of each study site. Standard guidelines are those presented in the updated WHO 2021 AQGs [160].

Real-Time Determination and Statistical Analysis

If the Lascar logged at less than 1-minute intervals (e.g., every 30 seconds), we first calculated 1-minute averages. Following, centered rolling averages were estimated for the three STE WHO AQGs (15-minute, 60-minute, and 8-hour) at each logged minute. For example, the 15-minute average at 12:35:00 would be an average of the CO concentrations in the 15 minutes between 12:28:00 and 12:43:00 (Figure 3.1). We took the maximum STE for each exposure visit to determine if the participants were in exceedance of any of the WHO AQGs. To quantify durations of exceedances, we calculated the number of minutes above each guideline averaged together by study site and arm. To determine how many of the WHO AQGs the participants exceeded, each exposure visit was categorized as none, one, two, three, four, or all the WHO AQGs exceeded (i.e., 15 minutes, 1 hour, 8 hours, 24-hour AQG, 24-hour IT-1). Further, we evaluate non-independence of repeated measures by investigating how many times each household exceeded each AQG over the three repeated exposure visits. Finally, we subdivided

these exceedances where participants exceeded one of the <24-hour AQGs but not the 24-hour AQG.

We used two-sample tests of proportions to determine differences in percent exceedances of WHO AQGs between study arms stratified by pre- and post-randomization and study sites. Independent two-sample t-tests compared differences in maximum rolling average means between study arms.

We also averaged hourly concentrations to explore temporal patterns of CO concentrations. Minute concentrations were grouped and averaged by hour of the day and then stratified by study site and study arm for statistical analyses. For example, all measures between 06:00-06:59 were categorized into hour 6. An hour was excluded if there were fewer than 45 minutes available within that given hour. Independent two-sample t-tests compared mean hourly concentrations between study arms. Within the strata of arm, study site, and hour (i.e., Guatemala 06:00 intervention arm vs Guatemala 06:00 control arm), we had 96 hourly comparisons, and we used Bonferroni multiple comparisons to adjust p-values from 0.05 to 0.05/96= 0.0005.

We used Pearson correlations to determine how well STEs followed overall 24-h averages. We assessed the strength of relationships between the maximum time weighted averages for the 15-minute, 60-minute, and 8-hour with the overall 24-hour averages from the same household visit. We further investigated 24-hour averages with STEs using a simple linear regression model adjusting for study site and report the R^2 to determine fit.

Results

We used 7,943 valid CO measures from data that have previously been published and described how valid measures were determined based on runtime and visual inspection [159]. Guatemala, India, Peru, and Rwanda had 2155, 2077, 1654, and 2057 valid CO measures, respectively. Mean (SD) 24-hour post-randomization CO exposures in the control arm were 1.81 (2.15), 1.93 (3.48), 3.39 (6.54), and 2.12 (3.46) for Guatemala, India, Peru, and Rwanda, respectively, as previously reported. In the intervention arm post-randomization, mean (SD) 24-hour CO exposures were 0.51 (1.02), 0.41 (1.16), 1.31 (2.26), and 0.63 (1.08) ppm for Guatemala, India, Peru, and Rwanda, respectively[159].

WHO AQG Exceedances

Percentages of exceedances based on the maximum time-weighted average for each guideline (15-minute, 60-minute, and 8-hour) are outlined in Table 3.2, Figures 3.3-3.5, and 3.S2-3.S3. HAPIN-wide pregnancy visits post-randomization, the most frequently exceeded AQGs for the respective control and intervention arm were the 24-hour (12.5% [n_{exceed}= 316] control vs. 2.4% [n_{exceed}= 61] intervention); 60-minute (11.8% [n_{exceed}= 299] control vs. 1.7% [n_{exceed}= 43] intervention); and 8-hour (10.7% [n_{exceed}= 270] control vs. 1.7% [n_{exceed}= 42] intervention) time weighted averages. The fewest exceedances occurred for the 15-minute (7.55% [n_{exceed}= 190] control vs. 0.6% [n_{exceed}= 16] intervention); and 24-hour IT-1 (5.7% [n_{exceed}= 143] control vs. 0.7% [n_{exceed}= 17] intervention) AQGs in the control and intervention arm, respectively. When stratified by study site in the control arm, Guatemala had the fewest exceedances for any guideline at 5.3% followed by Peru (13.3%), India (11.0%), and Rwanda

(10.1%). The intervention arm had reduced absolute differences by country for average percent exceedance of any guideline (Guatemala= 0.7%, India= 0.9%, Peru= 3.2%, Rwanda= 1.3%). HAPIN-wide and site-specific, the intervention arm had significantly lower ($p<0.001$) percentages of participants exceeding each of the WHO AQGs.

Most participants at pregnancy in the intervention arm post-randomization (96.8%) did not exceed any of the 5 different WHO AQGs (15- and, 60-minute and, 8-, 24-, and 24-hour IT-1), and the distribution of the number of AGQs exceeded was distributed as 1.3%, 1.0%, 0.3%, 0.3%, and 0.3% exceeding 1-5 AGQs. The majority of the control arm participants (83.5%) also did not exceed any AQGs, with 4.4%, 3.3%, 2.4%, 1.8%, and 4.6% exceeding 1-5 AQGs, respectively. Of the 416 exceedances, the most common AQG combinations exceeded were all five AQGs (27.9%), only the 24-hour (13.7%), and only the 60-minute (10.3%).

During the post-randomization pregnancy period, some households did not exceed the 24-hour guideline, but did exceed at least one of the 15-minute, 60-minute, or 8-hour AQGs. One hundred (4.0%) and 21 (0.8%) of the control and intervention arm visits, respectively, exceeded one or more of the <24-hour guidelines but did not exceed the 24-hour AQG (Figure 3.S4). Of those 100 and 21 individual visits there were 99 (6.7%) and 20 (1.4%) unique households. Those numbers increased when evaluating visits under the 24-hour IT-1 AQG and exceeding at least one of the 15-minute, 60-minute, or 8-hour AQGs to 216 (8.5%) and 46 (1.8%) in the control and intervention arm, respectively (Figure 3.S5). Of those visits there were 200 (13.6%) and 45 (3.1%) unique households that fit in those exceedance categories. Finally, we observed very few households experiencing the same exceedances over the three visits (Figure 3.S6).

Hourly Averages

When stratified by study site, none of the baseline hours mean CO concentrations pre-randomization were significantly different between arms. For both arms when hourly averages were stratified by study site, they were highest during typical cooking times 07:00-10:00 and 17:00-20:00 (Figure 3.2). In the control arm post-randomization, the largest hourly averages HAPIN-wide were 5.08 (18:00), 4.61 (07:00), and 4.54 (08:00) ppm compared to the largest averages in the intervention arm of 1.24 (18:00), 1.17 (10:00), 1.10 (11:00) ppm. HAPIN-wide post-randomization, the temporal pattern of CO concentrations was not as apparent in the intervention arm compared to the control arm, with hourly averages ranging from 0.28 to 1.24 ppm and from 0.28 to 5.08 ppm, respectively. There were only 9 hours where the intervention arm post-randomization had a slightly larger CO average. However, these differences were small, ranging from 0.01 to 0.11 ppm, and occurred only during the late-night hours (from 00:00 to 03:00). Among these, only one hour (03:00 in Rwanda) showed a statistically significant difference (0.30 ppm in the intervention arm vs. 0.20 ppm in the control arm; p=0.037), but this difference did not prove significant if using Bonferroni multiple comparison corrections.

The three largest hourly means by study site and study arm were all in the control arm in Peru 7.75 (18:00) ppm, 7.51 (07:00) ppm, and 7.32 (08:00) ppm. The top three hourly CO exposures by country in the intervention arm were also all in Peru with averages of 3.47 (18:00) ppm, 2.42 (06:00) ppm, and 2.37 (19:00) ppm. As shown in Figure 3.2, Guatemala had a prominent mid-day peak in the control arm with highest exposures in between breakfast and dinner meals despite having lowest overall concentrations, which could be due to a common time to cook tortillas. India had two very clear peaks at breakfast (06:00-10:00) and dinner (16:00-20:00). Peru has peak CO concentrations that started in the morning around 07:00 and slowly

declined steadily until around 18:00 when a clear dinner time peak occurred. Finally, in Rwanda there was a weaker signal at late breakfast hours at 9:00 and a much stronger hourly peak pattern starting around 16:00 for the typical dinner time peaks.

Amount of time above WHO AQGs

Breakdowns for the quantity of time above the 15-minute, 60-minute, and 8-hour guidelines by study site and AQG are provided in Table 3.3. Similar to the exceedance percentages, the HAPIN-wide and study site specific average number of minutes above the AQGs were significantly larger ($p<0.001$) in the control arm than the intervention arm for each WHO AQG. The intervention arm had an average of 6.5 minutes above any guideline while the control group spent approximately 33.0 minutes above any guideline (26.5 minutes less in intervention arm, 95% CI= 24.4, 28.6). The countries with the most minutes exceeding any WHO standards in both arms combined post-randomization were Peru (33.3 minutes) and Rwanda (19.4 minutes), while the least were in Guatemala (14.0 minutes) and India (15.8 minutes). Finally, for both arms post-randomization HAPIN-wide average number of minutes above the guidelines were 2.6, 9.2, and 47.3 minutes for the 15-minute, 60-minute, and 8-hour AQGs, respectively (Table 3.3).

Correlations

Post-randomization, HAPIN-wide Pearson correlations were strong between the 15-minute ($\rho= 0.83$), 60-minute ($\rho= 0.89$), and 8-hour ($\rho= 0.96$) maximum time weighted averages

and the 24-hour averages (Figure 3.6). Using a simple linear model adjusting for study site we found most of the variation in the 24-hour averages could be explained using the maximum 15-minute (R^2= 0.68), 60-minute (R^2= 0.78), and 8-hour (R^2=0.93) time weighted averages.

Discussion

Exposure Assessment Implications

After a deeper investigation of the CO maternal exposures in HAPIN, we found reductions from an LPG stove were similar for 15-minute, 1-hour, and 8-hour exposures [159]. The control arm had clear peaks during typical cooking times at breakfast and dinner both at baseline and during the post-randomization pregnancy period, while the intervention arm had unclear and more sporadic hourly averages post-randomization. While the patterns in the control arm were very clear, the lack of high temporal hourly averages in the intervention arm at point cooking times indicate that there are little to no CO emissions from LPG stoves [110]. In addition to differences in ventilation, the different exposure patterns observed between the study sites could be due to either cultural and/or culinary differences[91,161]. For example, LPG users in Puno, Peru households have been previously found to frequently cook a third mid-day meal [117]. In some cases, there were minor peaks during dinner time in Peru in the intervention arm, but most of the time there were no discernible or identifiable CO peak exposures. These minor elevations are mostly seen in the means, but the medians in the intervention arm remain lower than the limit of detection of 1 ppm for the Lascar instrument[162]. Measured CO in the intervention group might be attributed to other nearby biomass burning or stove stacking. However, the low intervention averages and medians align with the observed high adherence to the LPG stove [163] and suggest

that there were limited CO exposures from outside sources (i.e., roadways or neighboring biomass stoves) [164].

The hourly averages also highlight a key exposure assessment dilemma; 24-hour measurements may miss critical peak CO exposure times. We consistently found that the hours between 07:00-10:00 and 17:00-20:00 contribute most to participants' overall exposure. If monitoring ends up part of missing that critical CO peak window it could lead to potential exposure misclassification [100]. For example, if a field staff member drops off equipment at 10:00 and returns the next day at 08:00 and stops the monitor, the integrated average could underestimate the true concentration, despite meeting minimum acceptable runtimes.

We found that the intervention arm had a significantly reduced percentage of participants that exceeded WHO guidelines both on a stratified and combined study site grouping compared to control arm participants. Regardless of hour of day, study site, or AQG, the LPG stove significantly reduced CO exposures among intervention participants compared to controls. We found that average peak 60-minute concentrations (~20 ppm) were similar to other studies in the control arm but were about three-quarters less in the intervention arm (5.4ppm) [92,112].

Effect of Peak CO Exposures

AQG exceedances varied significantly between the different study sites. In arm-wide comparisons, Peru had the highest percentage and number of minutes above the WHO guidelines for all durations followed by Rwanda and India. Puno, Peru is nearly 4,000 meters above sea level, which could have potential impacts on how participants heat their house in the cold

environment, combustion properties of biomass, and the density of CO in the air[137,165]. Previous studies from Puno have adjusted the WHO guidelines for NO_2 to account for air density; however, despite making similar adjustments for CO in our study, we still found that Peru had a significantly higher level of exceedances than the other study sites[159,162,166]. Not only could these increased CO concentrations warrant concern, but it has also been shown that CO more readily binds to hemoglobin molecules (COHb) at higher altitudes, which could have negative health consequences [136,137]. Conversely, Guatemala had less than a quarter of exceedances as Peru. This variability in exceedances highlights the need for multisite exposure studies because this trend is reversed when compared to $PM_{2.5}$ 24-hour averages [159].

We found that there is the potential for missing guideline exceedances for CO when only using the 24-hour averages. Over 6% and 13% of control arm exposure households were below the 24-hour or 24-hour IT-1 WHO AQGs, but exceeded the 15-minute, 60-minute, and/or 8-hour AQG values. This could imply that if only using 24-hour guideline there could be missed relationships with CO STE events and angina, ischemic heart disease, and myocardial infarction [48,154,155,160]. STE to CO have been shown to be differential from that of a 24-hour as seen in a similar study[92]. Alternatively, the correlations between the maximum averaging times were very strong for both HAPIN-wide and site-specific level comparisons, which might indicate that we would not expect many differences in health models that use different CO metrics. If the shorter exposures are good predictors of the 24-hour average, then we might expect the 24-hour average to have strong relationships with STE health related outcomes because of the strong STE- 24-hour associations.

Future studies may consider exposure response analyses to determine if exceedance of the STE AQGs have any differential health impacts compared to exceedances of the 24-hour

AQGs on the participants' blood pressure, birthweight, or childhood pneumonia. We do have reason to believe that there would not be any significant changes from previously published CO exposure-response [51] because of the high correlations between the STE averages and the overall 24-hour averages. Additionally, exposure-response with birthweight and childhood pneumonia, common HAP study outcomes, might not be as helpful because these outcomes are not necessarily those that could be associated with STE to CO (which include angina, myocardial infarction, and COHb [14,95,96]). One further analysis that could be done is the combined effect of altitude and CO on the birthweight of children that has been shown to have a potential synergistic effect [167].

Limitations

While HAPIN is one of the largest environmental health randomized controlled trials conducted to date, there are some key limitations to keep in mind. First, we use only data from pregnant women, which has limited our findings to just maternal personal STE. Not examining the child or any of the area monitoring that was also conducted as part of HAPIN did not allow us to corroborate our results nor help determine if children are more susceptible to peak CO events compared to the mother. These future analyses could be important because there might be differential behavior patterns as the pregnant mother may not cook as frequently after the child is born.

Second, the Lascar was calibrated monthly with span gas; however, field performance of monitors varied. The site-specific duplicate correlations from CO analyses (ρ= 0.43-0.67) were fair [159]. The lack of instrument reliability could lead to greater exposure misclassification for CO

impacting the accuracy results reported here. For example, if the monitor does not detect a peak CO, there could be underestimation of the true number of exceedances of STE AQGs. This could also be a part of why there is often a lack of reliable correlations between CO and $PM_{2.5}$ [87].

Finally, there are other ways to determine peak CO. While the categorical yes/no AQG exceedance variable might not be the best way to interpret peak exposure, giving context to the exposure reductions in peak CO helps underscore the potential health benefits from an LPG intervention. The WHO AQGs made ideal comparisons with already established health relevant guidelines and time weighted averages. However, there are other possible ways to define peak exposures, including using percentiles for each exposure visit.

Conclusion

The LPG intervention successfully reduced participant STE to CO in all study sites despite large disparities in site-specific STE WHO AQG exceedances in the control arm. Future HAP studies monitoring CO, especially those using the 24-hour IT-1 as a guideline, might consider investigating peak exposures with relevant health outcomes to capture the 4-8% of misclassified biomass-using homes when using only the 24-hour AQGs.

Tables and Figures

Table 3.1 The adjusted AQGs based on study site average elevation and temperature.

Altitude and Temperature Adjusted WHO Guidelines and Observed Measurements for Five Study Sites in HAPIN

	Temperature (C°)	Pressure (hPa)	15-minute (ppm)	60-minute (ppm)	8-hour (ppm)	24-hour IT1 (ppm)	24-hour (ppm)
Standard	20°	1013	87.3	30.6	8.7	6.1	3.5
Guatemala	17°	870	99.0	34.6	9.9	6.9	4.0
India: Nagapattinam	29°	1012	88.6	31.0	8.9	6.2	3.6
India: Villupuram	29°	1005	89.2	31.2	8.9	6.2	3.6
Peru	10°	620	134.4	47.0	13.4	9.4	5.3
Rwanda	20°	843	103.2	36.1	10.3	7.2	4.1

Table 3.2 Median post-intervention CO exposures in the control and intervention arm alongside number and percentage of households in exceedance of AQGs. Percentages in the 24-hour column refer to exceedances of the 24-hour AQG. ppm= parts per million; AQG= air quality guideline; IT-1= interim-target 1.

HAPIN Maternal Post-Randomization Median Maximum Rolling Averages (ppm) (N exceeding AQG, Percent Exceeding AQG)							
15-minute (ppm)		60-minute (ppm)		8-hour (ppm)		24-hour (ppm)	
Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
14.7 (14, 2.0%)	3.3 (1, 0.1%)	8.7 (32, 4.6%)	1.9 (4, 0.6%)	2.6 (47, 6.8%)	0.4 (6, 0.9%)	1.2 (69, 10.0%)	0.2 (11, 1.6%)
99.0		34.6		9.9		6.1 (IT-1); 4.0 (AQG)	
8.8 (13, 4.1%)	1.9 (0, 0%)	4.9 (21, 6.6%)	0.9 (2, 0.7%)	1.2 (18, 5.7%)	0.2 (4, 1.3%)	0.5 (25, 7.9%)	0.1 (13, 4.2%)
88.6		31.0		8.9		6.2 (IT-1); 4.0 (AQG)	
19.4 (54, 15.2%)	1.2 (1, 0.3%)	11.2 (73, 20.6%)	0.5 (1, 0.3%)	2.5 (57, 16.1%)	0.1 (2, 0.6%)	1.1 (69, 19.4%)	0.0 (2, 0.6%)
89.2		31.2		8.9		6.2 (IT-1); 4.0 (AQG)	
26.8 (52, 10.8%)	12.9 (10, 1.9%)	14.3 (81, 16.8%)	6.1 (25, 4.9%)	3.4 (71, 14.8%)	1.4 (18, 3.5%)	1.3 (76, 15.8%)	0.6 (22, 4.3%)
134.4		47.0		13.4		9.4 (IT-1); 3.6 (AQG)	
21.3 (57, 8.4%)	4.1 (4, 0.6%)	10.1 (92, 13.5%)	2.1 (11, 1.7%)	2.3 (77, 11.3%)	0.5 (12, 1.8%)	1.0 (77, 11.3%)	0.2 (13, 2.0%)
103.2		36.1		10.3		7.2 (IT-1); 4.1 (AQG)	
17.7 (190, 7.5%)	**3.9 (16 0.6%)**	**9.3 (299, 11.8%)**	**2.0 (43, 1.7%)**	**2.4 (270, 10.7%)**	**0.4 (42, 1.7%)**	**1.1 (316, 12.5%)**	**0.2 (61, 2.4%)**

Table 3.3 Post-randomization, mean (SD) of the number of minutes above WHO AQGs for HAPIN-wide and individual study sites.

HAPIN Maternal Mean (SD) Number of Minutes Above WHO AQGs Post-Randomization				
IRC	**Arm**	**15-Minute**	**60-Minute**	**8-Hour**
HAPIN-wide	**Control (n= 2524)**	4.9 (23.3)	16.2 (53.4)	77.9 (124.4)
	Intervention (n= 2542)	0.46 (5.8)	2.3 (18.8)	16.7 (64.1)
Guatemala	**Control (n= 691)**	0.9 (7.8)	4.9 (24.0)	69.3 (119.5)
	Intervention (n= 707)	0.1 (1.8)	0.6 (9.3)	9.1 (59.5)
India: Nagapattinam	**Control (n= 317)**	1.9 (13.8)	7.4 (34.7)	35.5 (79.6)
	Intervention (n= 307)	0.0 (0.0)	1.8 (31.3)	10.7 (68.1)
India: Villupuram	**Control (n= 355)**	6.0 (21.8)	22.7 (62.0)	93.3 (133.2)
	Intervention (n= 353)	0.1 (1.4)	0.4 (7.6)	5.1 (30.9)
Peru	**Control (n= 481)**	10.7 (37.7)	30.7 (74.0)	107.1 (144.6)
	Intervention (n= 514)	1.7 (11.2)	7.1 (27.2)	45.7 (91.9)
Rwanda	**Control (n= 680)**	5.5 (24.1)	18.2 (56.9)	77.9 (120.0)
	Intervention (n= 661)	0.3 (5.1)	1.6 (13.5)	11.4 (44.0)

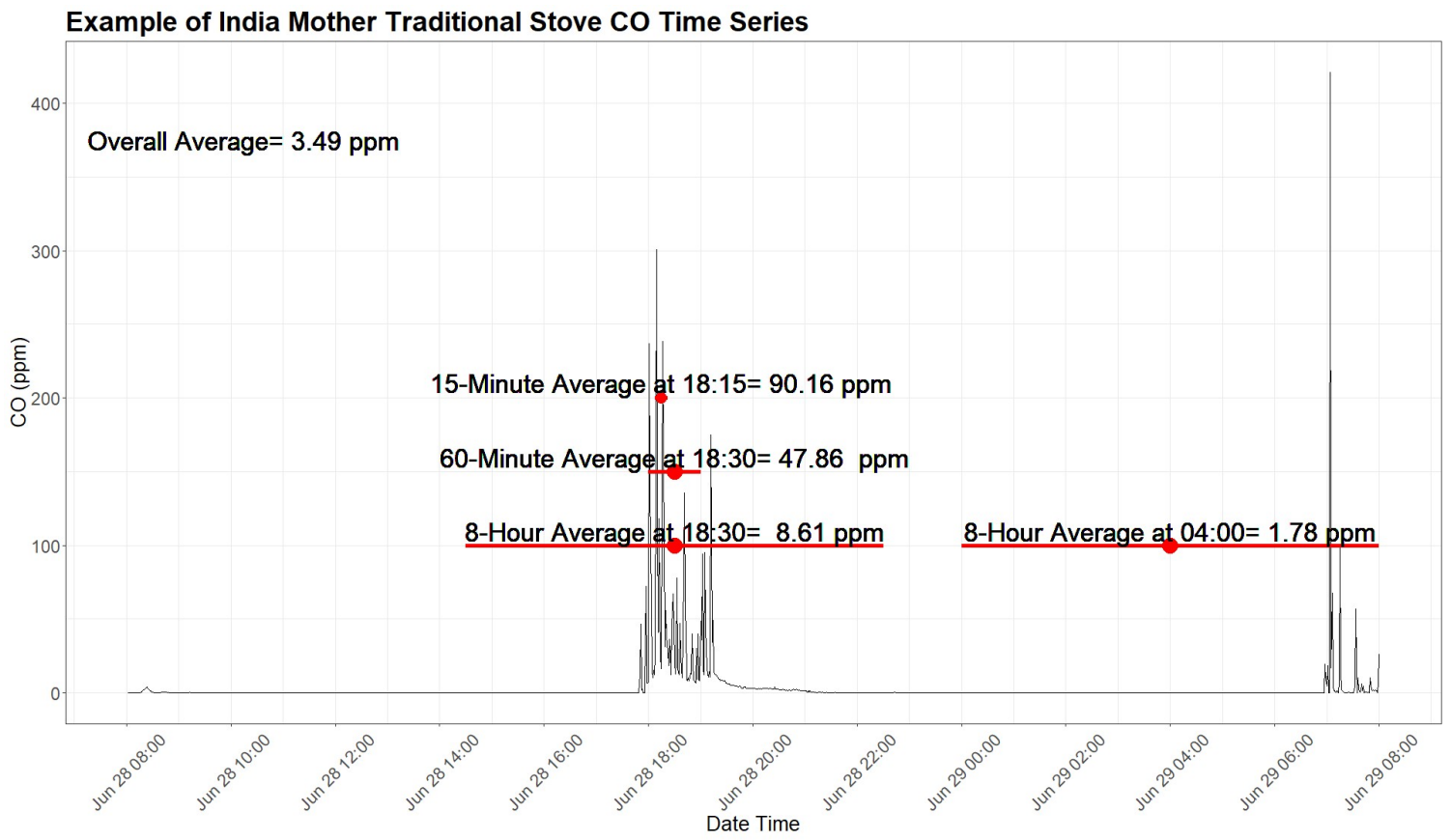

Fig 3.1 An example CO time series on an Indian mother at baseline. Red lines indicate the minutes included in respective averages at red points.

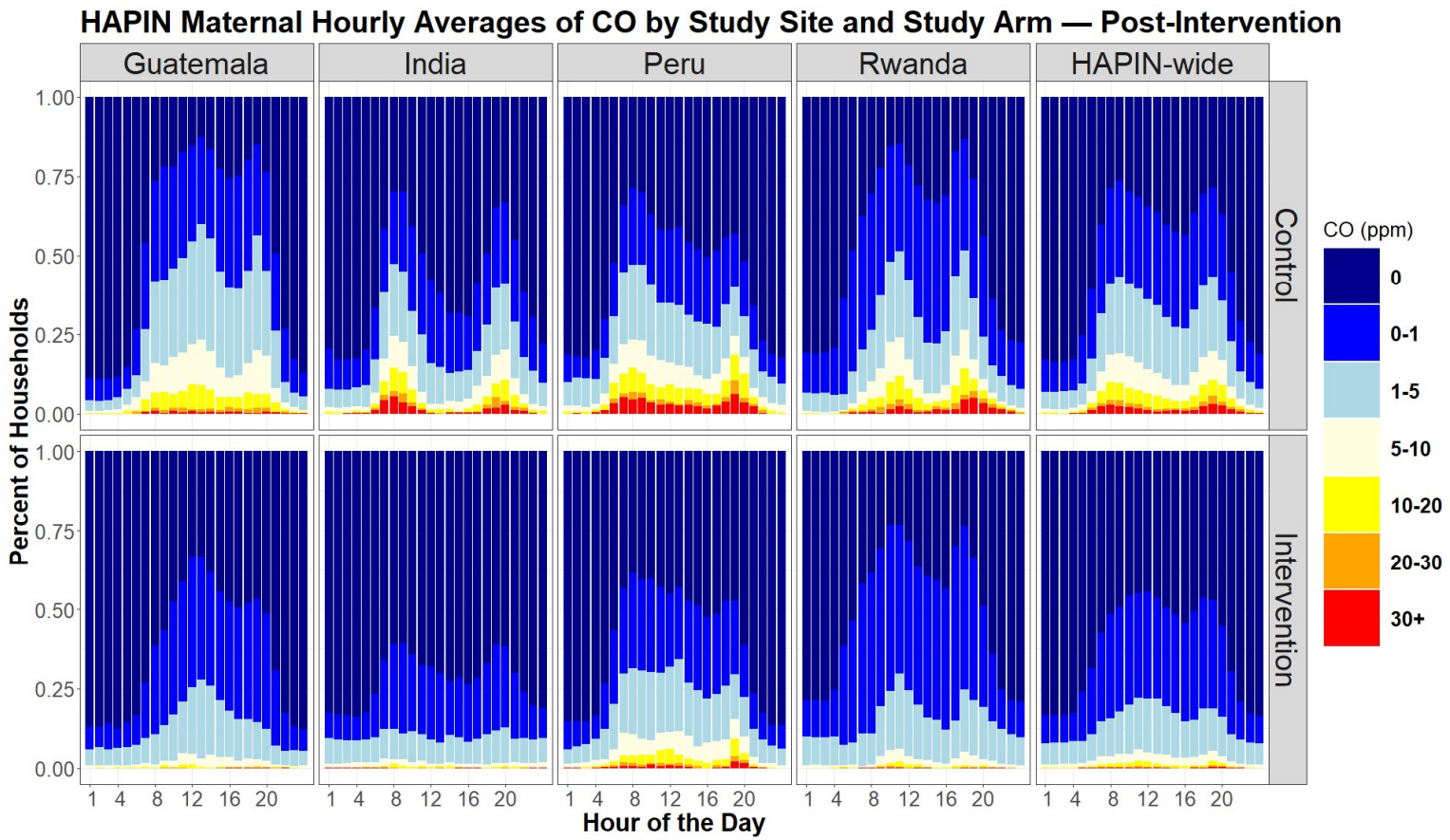

Fig 3.2 The percent of households in categorized hourly CO averages post-randomization. For example, the '6' in Guatemala refers to average CO exposures from 06:00-06:59 for all households in Guatemala and the sky-blue color refers to the percentage of those households that are between 1-5 ppm.

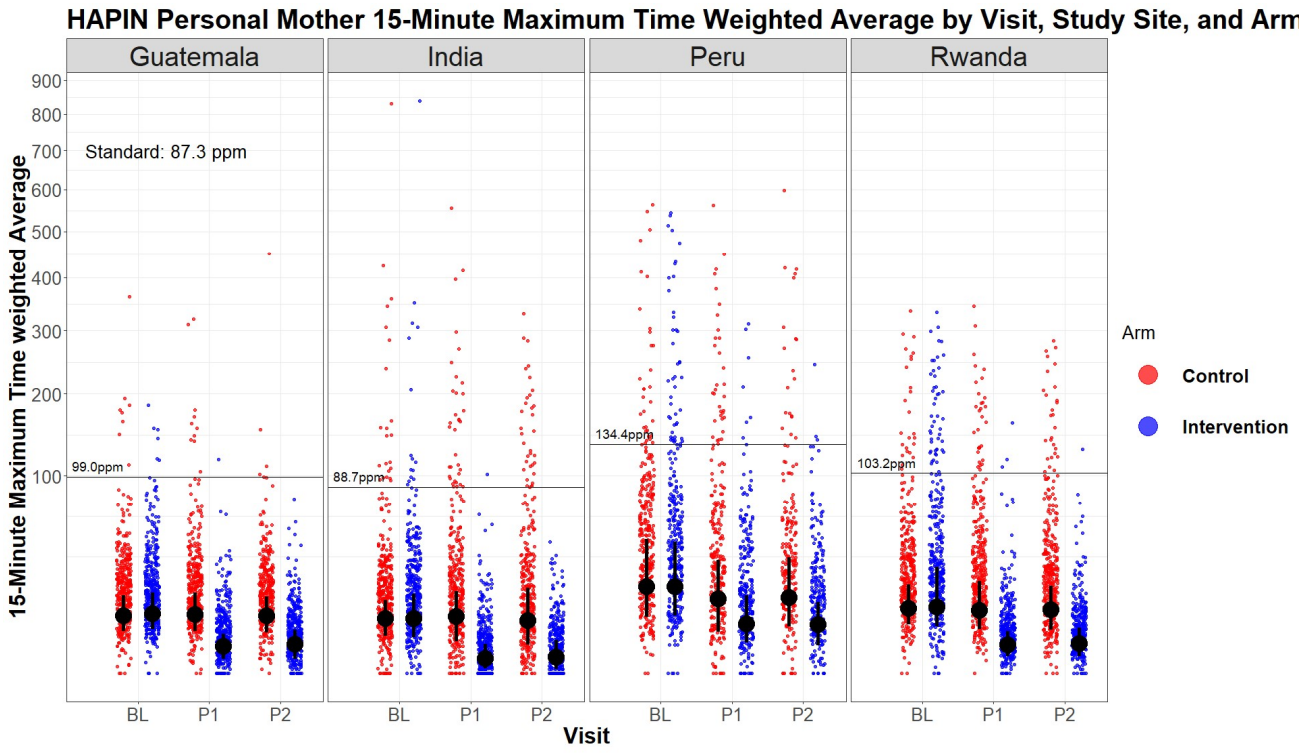

Fig 3.3 Maximum rolling averages for 15-minute intervals at each exposure visit. The horizontal black lines are altitude and temperature adjusted WHO AQGs. Large points correspond to the median and the tails are the first and third quartile. BL (<20 weeks gestation) is the baseline pre-randomization visit; P1(24-26 weeks gestation) and P2 (32-36 weeks gestations) are the two follow-up post-randomization visits that occurred during pregnancy.

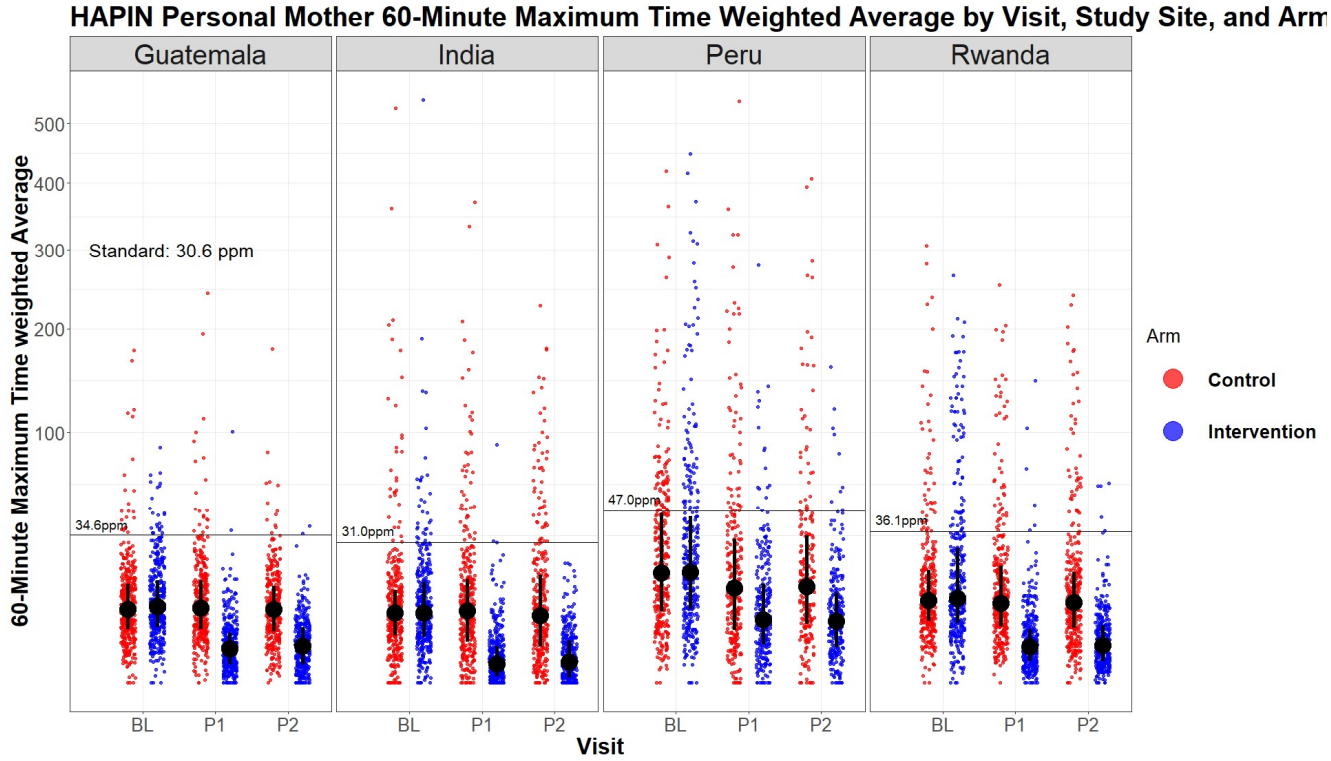

Fig 3.4 Maximum rolling averages for 60-minute intervals at each exposure visit. The horizontal black lines are altitude and temperature adjusted WHO AQGs. Large points correspond to the median and the tails are the first and third quartile. BL (<20 weeks gestation) is the baseline pre-randomization visit; P1(24-26 weeks gestation) and P2 (32-36 weeks gestations) are the two follow-up post-randomization visits that occurred during pregnancy.

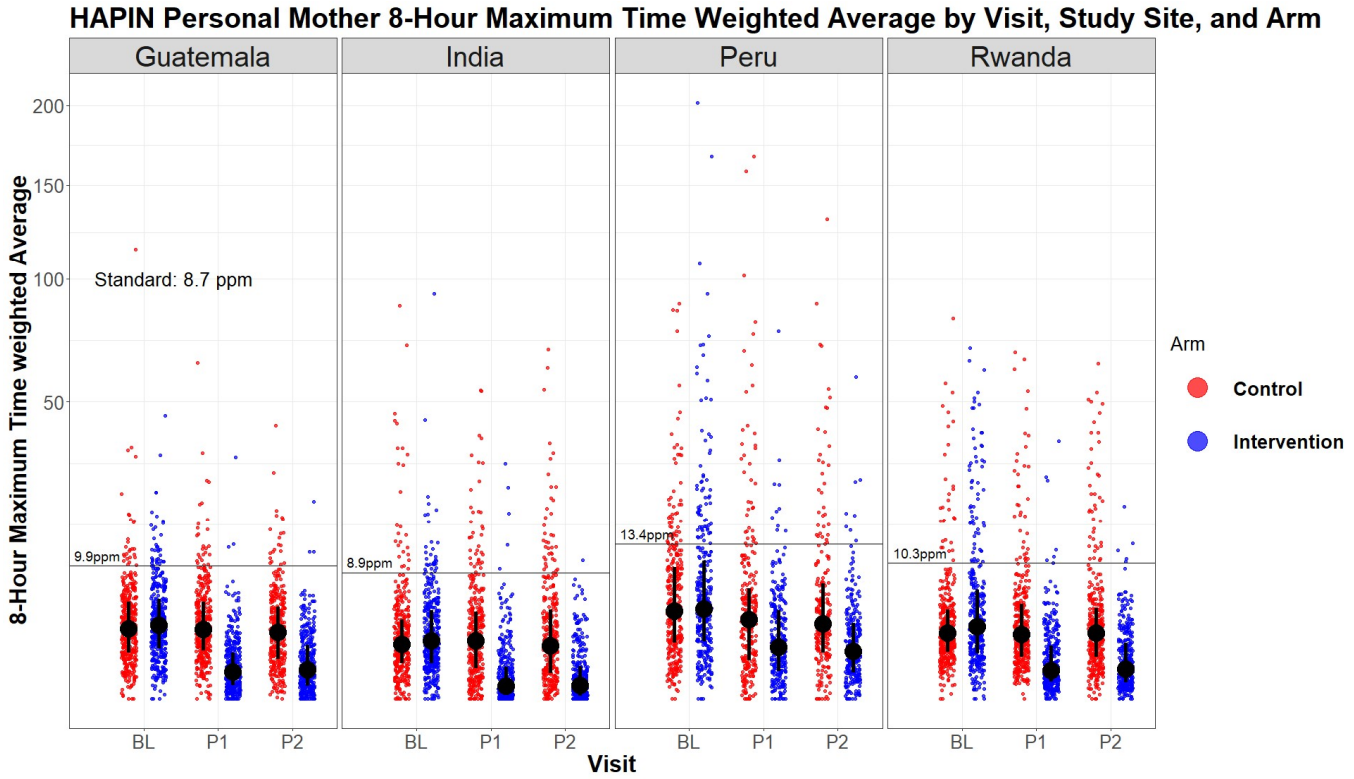

Fig 3.5 Maximum rolling averages for 8-hour (bottom) intervals at each exposure visit. The horizontal black lines are altitude and temperature adjusted WHO AQGs. Large points correspond to the median and the tails are the first and third quartile. BL (<20 weeks gestation) is the baseline pre-randomization visit; P1(24-26 weeks gestation) and P2 (32-36 weeks gestations) are the two follow-up post-randomization visits that occurred during pregnancy.

Fig 3.6 Pearson Correlations, scatter plots, and histograms for both HAPIN-wide and by study site for each of the time weighted averages (15-minute, 60-minute, 8-hour, and 24-hour).

Supplemental Figures

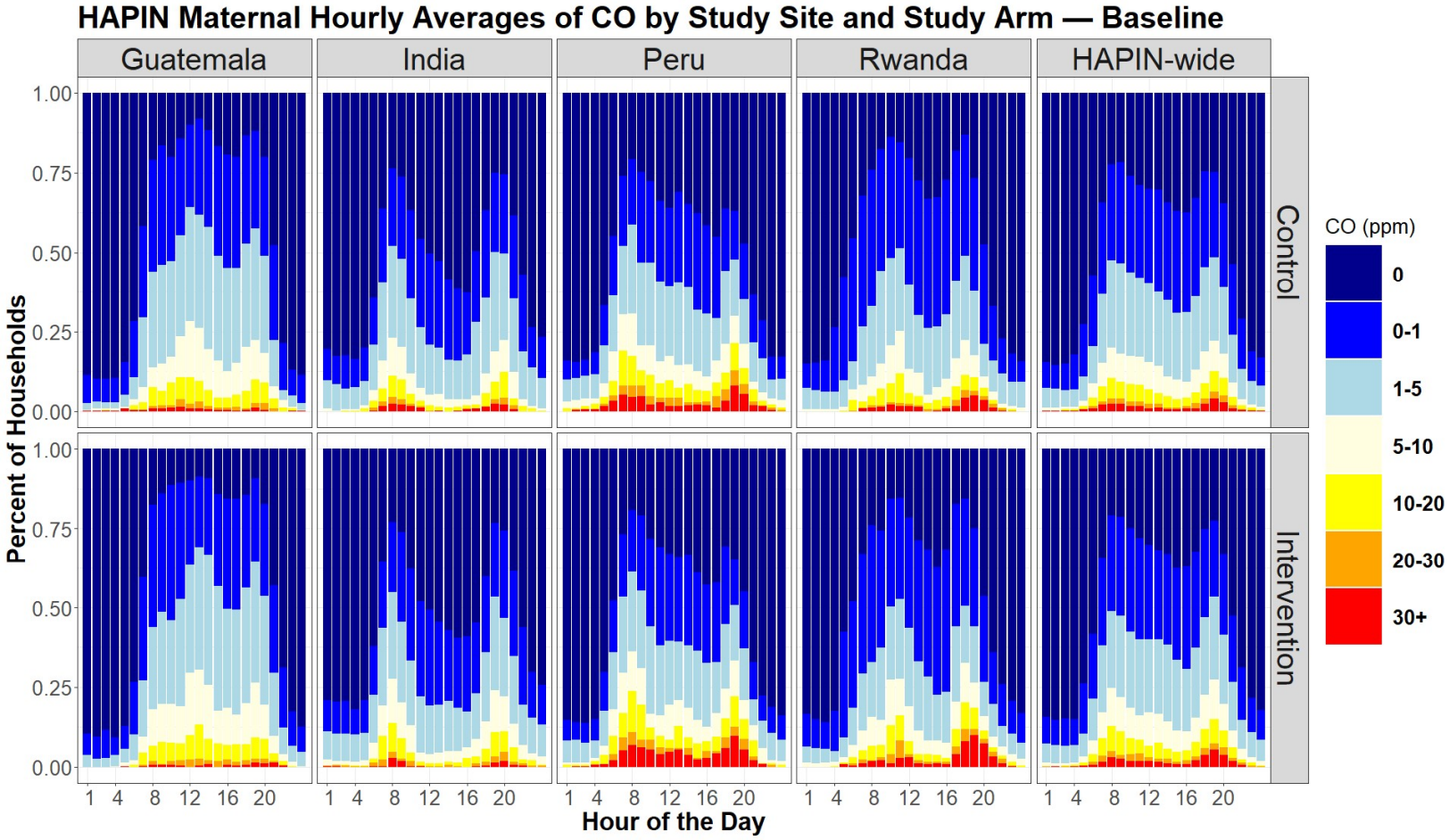

Fig S3.1 The percent of households categorized by hourly CO averages pre-randomization.

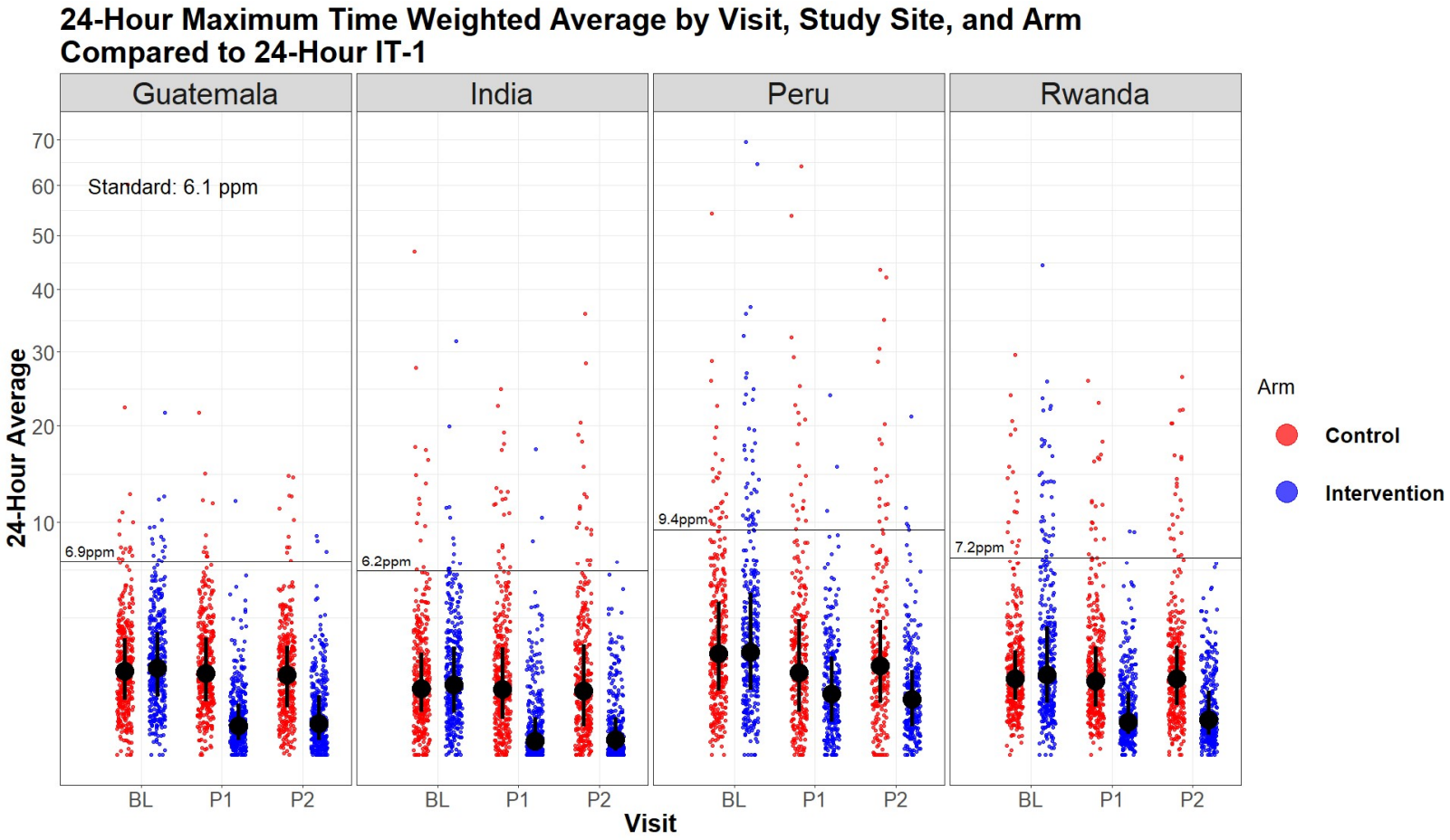

Fig 3.S2 Show the maximum rolling averages for the 24-hour averages compared to the 24-hour IT-1 at each exposure visit. The horizontal black lines are altitude and temperature adjusted WHO AQGs. Large points correspond to the median and the tails are the first and third quartile. BL (<20 weeks gestation) is the baseline pre-randomization visit; P1(24-26 weeks gestation) and P2 (32-36 weeks gestations) are the two follow-up post-randomization visits that occurred during pregnancy.

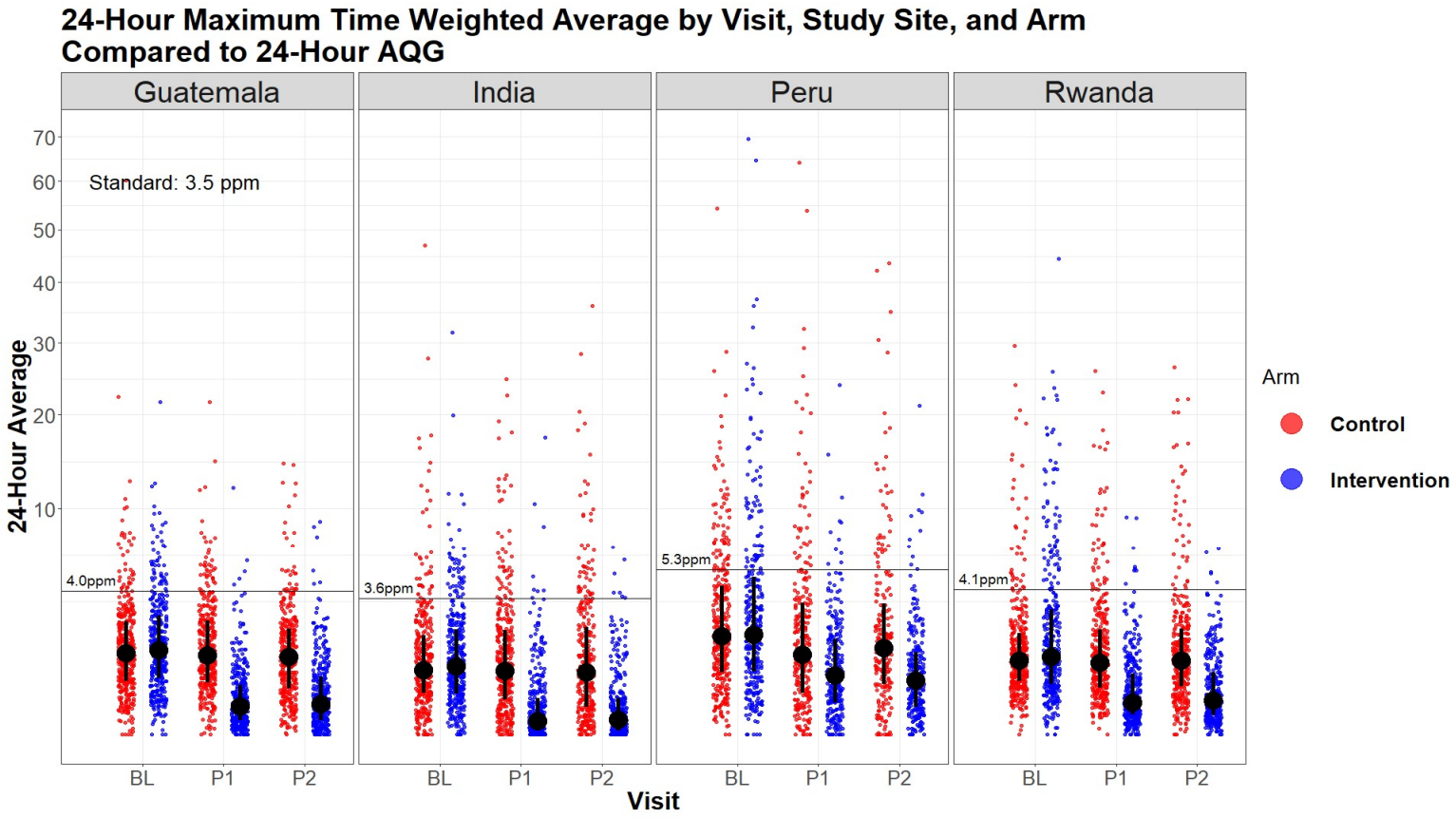

Fig 3.S3 Show the maximum rolling averages for the 24-hour averages compared to the 24-Hour AQG at each exposure visit. The horizontal black lines are altitude and temperature adjusted WHO AQGs. Large points correspond to the median and the tails are the first and third quartile. BL (<20 weeks gestation) is the baseline pre-randomization visit; P1(24-26 weeks gestation) and P2 (32-36 weeks gestations) are the two follow-up post-randomization visits that occurred during pregnancy.

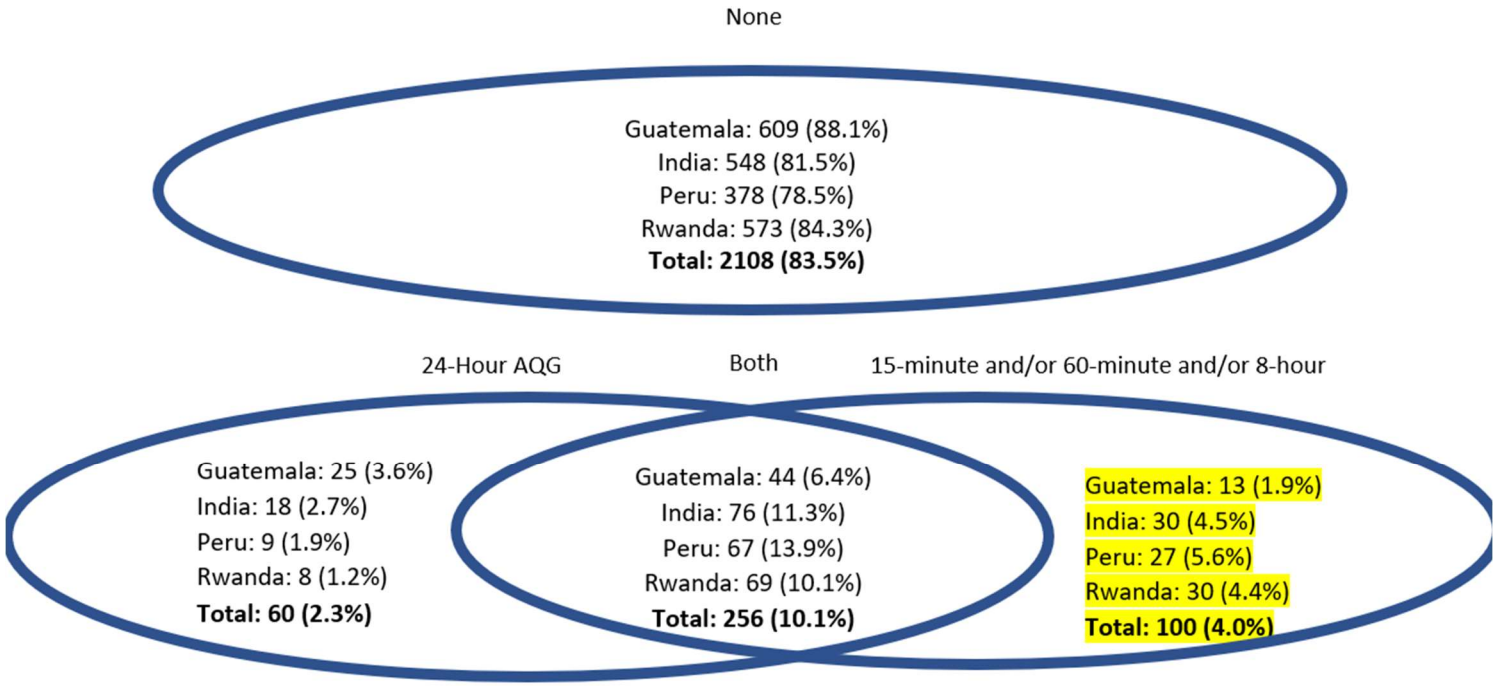

Fig 3.S4 Categorizing control arm post-randomization exceedances by over no guidelines, over only the 24-hour guideline, over both the 24-hour and a short term (≤ 8 hours) guideline, or over only a short-term guideline. Note the values in the lower right as exceedances that might not be captured using just the 24-hour guideline.

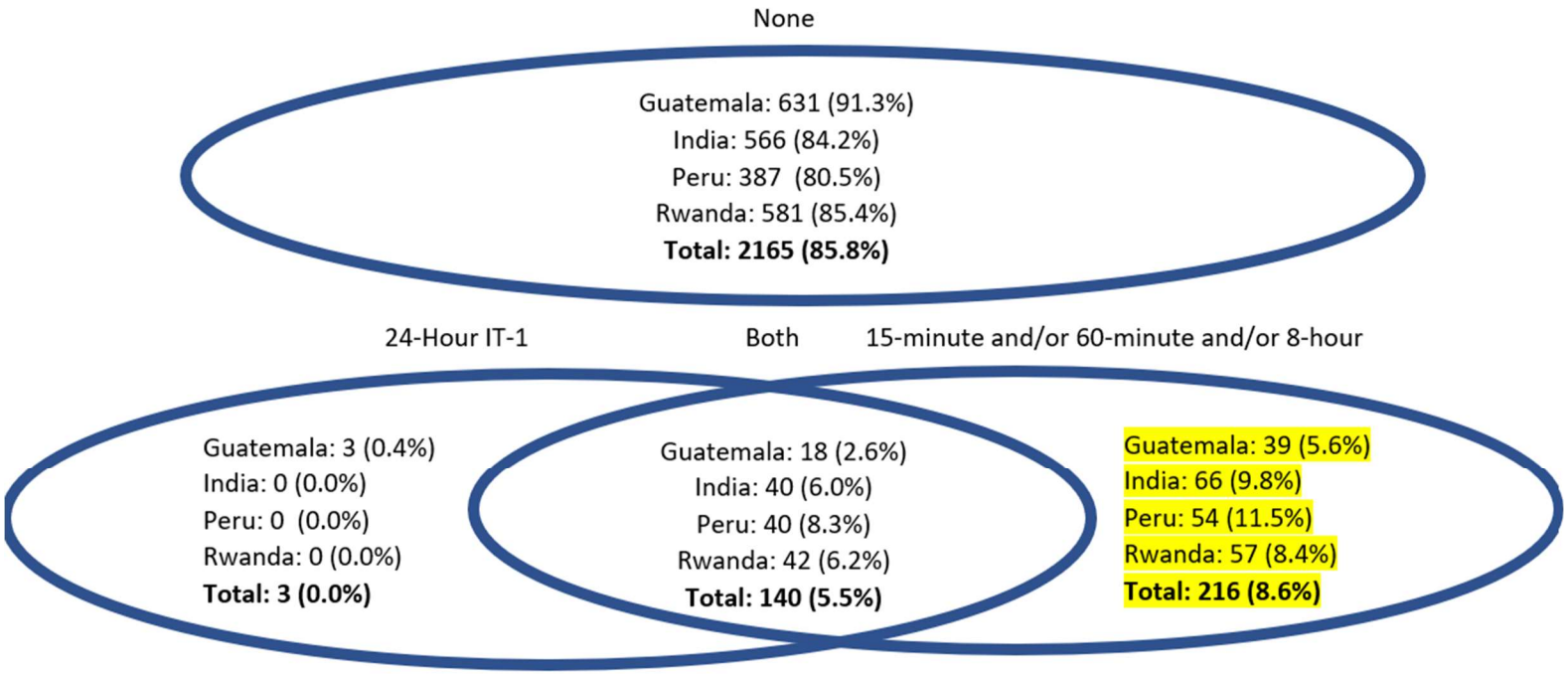

Fig 3.S5 Categorizing control arm post- randomization exceedances by over no guidelines, over only the 24-hour guideline, over both the 24-hour Interim Target-1 and a short term (≤ 8 hours) guideline, or over only a short-term guideline.

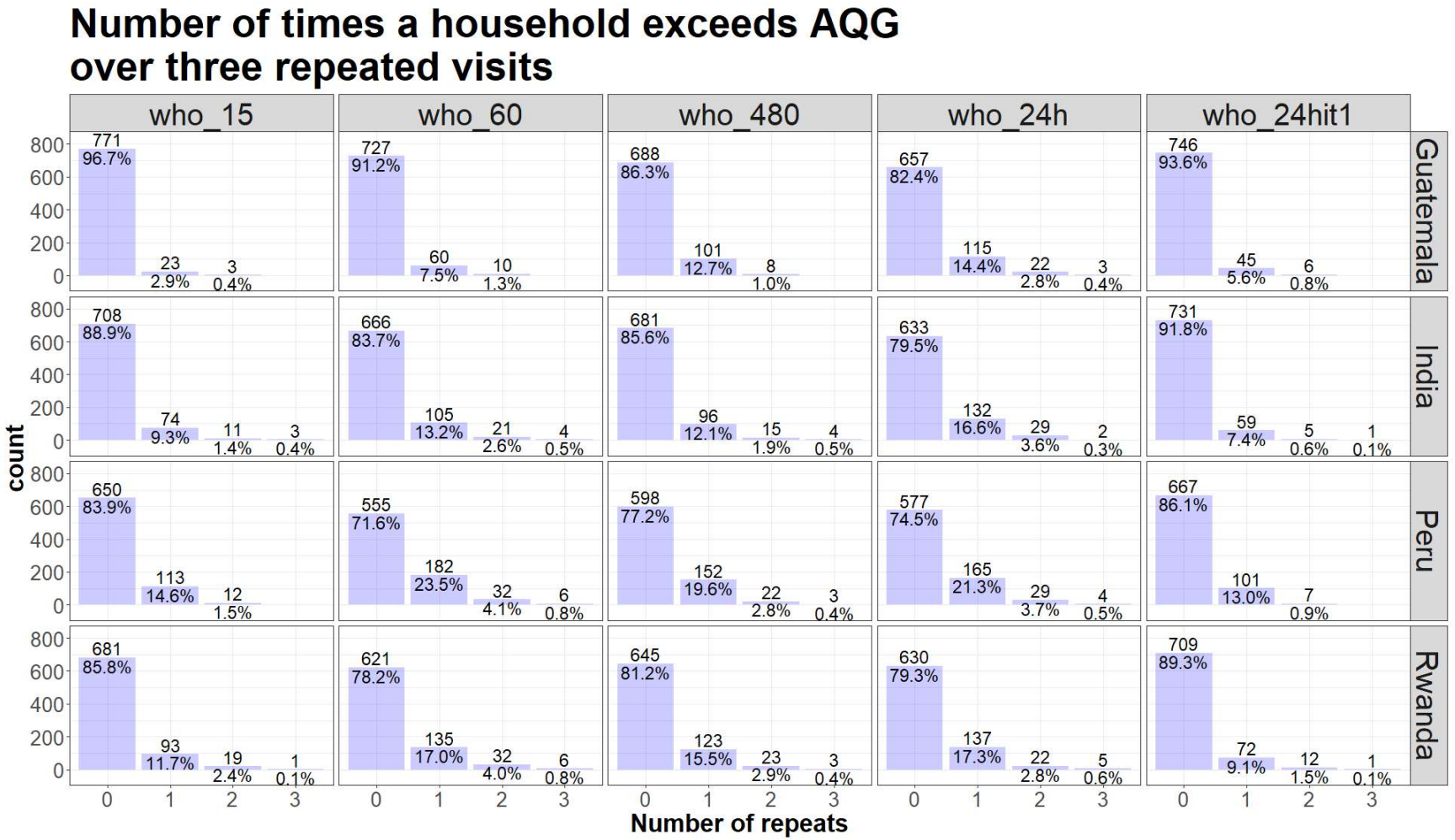

Fig 3.S6 How often a HAPIN participant exceeded the same guideline over the three repeated exposure visits.

CHAPTER 4

MODELING AND ESTIMATING CARBON MONOXIDE EXPOSURE IN GUATEMALA, INDIA, PERU, AND RWANDA IN THE HOUSEHOLD AIR POLLUTION INTERVENTION NETWORK TRIAL[2]

[2] Jacob R. Kremer, Michael Johnson, Lance A. Waller, Ajay Pillarisetti, Wenlu Ye, Ricardo Piedrahita, Devan Campbell, Katherine A. Kearns, Erick Mollinedo, Maggie L. Clark, Kendra Williams, Lindsay J. Underhill, Jiantong (Jean) Wang, John P. McCracken, Anaité Díaz-Artiga, Florien Ndagijimana, Ephrem Dusabimana, Kyle Steenland, Ghislaine Rosa, Kalpana Balakrishnan, Lisa M. Thompson, Laura Nicolaou, William Checkley, Jennifer L. Peel, Thomas F.Clasen, Luke P. Naeher, and HAPIN Investigators. To be submitted to *Indoor Air*

Abstract

Background*:* Several attempts to model exposure to household air pollution, including carbon monoxide (CO), have had varying success. One area that has not been explored much is variability between study site model fit, and how larger number of covariates input into such models perform. Household Air Pollution Intervention Network's (HAPIN) is a randomized controlled trial assessing the effect of an intervention liquefied petroleum gas (LPG) stove in Guatemala, India, Peru, and Rwanda. We aim to evaluate predictive validity of models for maternal CO exposure in HAPIN, based on subject and household characteristics. Then using these models, we evaluate fit from modeled CO concentrations.

Methods: Using six maternal exposure visits on 3,200 participants and over 60 covariates of interest, we perform backwards stepwise regression for both HAPIN-wide and site-specific models. We estimate association with time-variant and time-invariant separately. To evaluate the repeatability of six exposure visits, we added a unique household identifier as a random intercept and use intra-class correlations to calculate how repeatable CO measurements are within a household.

Results: We found backwards selection models accounted for 12-30% of the variation in 11,353 personal maternal CO measures depending on the study site, with Guatemala and India having the strongest performing models and our overall HAPIN-wide model with R^2=0.25. Time-invariant measures such as kitchen dimensions, stove number, and water source were more strongly associated with CO than time-variant measures such as stove usage variables and other sources of smoke. Finally, we find that intra-class correlation of our HAPIN-wide model to be

0.111 and 0.137, 0.147, 0.157, and 0.128 for Guatemala, India, Peru, and Rwanda-specific models, respectively.

Conclusion: Consistent with previous similar studies presented in the literature, model performance was not strong. We recommend that future studies with a large number of covariates use backward selection approaches to find novel results that may not previously be considered. However, when fewer variables are collected implementing a different modeling approach due to potential spurious results of the approach here.

Introduction

There are more than 3 billion people worldwide that use solid fuels such as wood, dung, agricultural waste, and charcoal to cook and heat in their homes[2]. The resulting household air pollution (HAP) is still a leading risk factor in the Global Burden of Disease with 2.3 million premature deaths and 91.5 million annual disability-adjusted life years (DALYs), ranking second in occupational risk factors worldwide[27]. These DALYs are in part a result of large exposures to carbon monoxide (CO) and fine particulates ($PM_{2.5}$) among other biomass-burning pollutants. The use of solid fuels and exposure to HAP pollutants is positively associated with multiple health effects including pneumonia, chronic obstructive pulmonary disease, still birth, and tuberculosis, which is why it is so critical to try to reduce such exposures[3].

CO is commonly associated with angina, myocardial infarction, and all cause hospital admissions; however, these cardiovascular diseases are understudied in HAP settings[94–96]. CO in the HAP setting is often associated with low-birth weight [97,98]. Therefore, CO is often studied for exposure-response relationships in intervention trials. Some studies have found that an intervention stove, such as improved biomass or liquefied petroleum gas (LPG) stoves, could

help reduce CO enough to see significant reductions in blood pressure in women [17] and pneumonia in children [73]. Despite the importance of measuring HAP CO concentrations there are still many gaps in terms of cost of instrumentation, field personnel, number of exposure measurements needed on a single individual, and accuracy of CO monitors [128,168]. Therefore, it has become more common to start estimating and modeling HAP exposures by using questionnaire, household, and cooking characteristics. However, there is still a need to explore what factors contribute to an individual's exposure to CO.

Exposure to CO has been difficult to model due to the many factors such as cooking fuels, kitchen dimensions, and other sources of indoor smoke that contribute to an individual's exposure to HAP. Studies have previously used linear regressions to establish relationships between CO exposure and seasonality, fuel type, kitchen dimensions, air exchange rates, and cooking behavior to be associated with CO exposure [169,170]. Using modeling and machine learning personal CO and $PM_{2.5}$ exposure in the HAP setting has been difficult to understand with some studies finding low ($R^2 < 0.5$) correlations and poor estimates of exposure [145,146,171]. However, some other studies have found better correlations using kitchen or other microenvironmental data to estimate personal exposures to HAP [106,172]. Microenvironmental data are easier to collect than personal data and does not require the participant to wear any exposure equipment. However, only evaluating the microenvironments does not account for the movement of an individual throughout the house. Hence, there is still much uncertainty with how to best model and how to use modeled CO concentrations, which is where the Household Air Pollution Intervention Network (HAPIN), an extensive multi-country trial, can fill these knowledge gaps.

The HAPIN randomized controlled trial used extensive CO, $PM_{2.5}$, and black carbon monitoring on nearly 3,200 pregnant women and their children in Guatemala, India, Peru, and

Rwanda [24]. In this trial it was shown that the LPG stove intervention package drastically and significantly reduced exposures to all measured pollutants, including CO [26]. Here we report the post-birth maternal personal CO exposures for the second half of the HAPIN trial. We also aim to leverage the pre-birth and post-birth maternal CO dataset and the extensive questionnaire variables to build univariate and multivariate models to help find the strongest associations with these questionnaire variables.

Methods

Study Design and Population

HAPIN is a randomized controlled trial assessing the efficacy of an LPG stove intervention package on health outcomes in pregnant mothers and children compared to the control arm using primarily traditional biomass stoves. Previous publications detail the overall objectives, design, and aims throughout the HAPIN study[24], along with exposure assessment [25] methodology. Briefly, 3,200 households were split evenly in four intervention research centers (IRCs), Guatemala, India, Peru, and Rwanda for a total of 800 houses per IRC, 400 in each study arm. Study sites are rural communities with low ambient air pollution to reduce bias from other sources of pollution beyond the cookstove.

CO Collection Methods

There were six 24-hour exposure visits for the mothers one at baseline where all participants used their traditional stove, two during pregnancy at 24-26 weeks gestation and 32-36 weeks gestation, and three when the child was <3 months, about 6 months, and about 12 months[25]. CO was measured using the Lascar CO-USB Datalogger (Lascar Electronics, Erie,

PA) using integrated real-time measures. The Lascar logged every 60 seconds for 24-hours with a resolution of 0.5 ppm ranging from 0-300 ppm. Lascars were checked for validity monthly using span gas. Lascars were placed in specially designed aprons or vests for the monitor to be in the breathing zone. Previous methodologies on data filtering and cleaning based on runtimes and flagged files are reported in Johnson et al. 2022. Here we consider only maternal exposures.

Survey Collection

Questionnaire data were taken by trained exposure field technicians at the setup of equipment during exposure visits, which can be found in the data repository for this manuscript. Time-invariant survey data such as kitchen dimensions, open windows/doors, and socioeconomic information like toilet type and electricity availability were taken at the baseline visit only. Time-variant data such as stove hour usage, purpose for stove usage, and other sources of smoke were taken at each exposure visit because of uniqueness to each visit. If any of the time-variant factors were missing, then we chose to fill data in with the previous visit results to be as data inclusive as possible.

Because fuel type and stove type are inherently linked and correlated with one another this causes a violation of collinearity in our models. To account for this, we ran models for both terms included and when using either just fuel or stove type. The best performing model with just one of the two variables was selected for final multivariable analysis and for comparison when both terms were included.

Statistical Methods

Means of CO were computed with the six maternal exposure visits stratified by IRC, exposure visit, and treatment arm. To handle CO values that are 0's for modeling we add a small insignificant value (0.01) to all CO concentrations to compute natural log on all observations. We used medians (interquartile range), means (standard deviation), and ranges for descriptive statistics stratified by stove type, fuel type, and any variable that was significantly associated with CO in the HAPIN-wide multivariable regression.

We consider three methods for handling low (<1ppm) values. First, the removal of any CO concentrations that are 0ppm. This approach was deemed unnecessary because of the similarity to the full model and keeps around 6% of potentially discarded data. Second, we consider dropping all values below the limit of detection of 1 ppm. We did not use this approach because of the large subset of data that would be excluded, ~60%. Third, we consider substituting all limit of detection values with $1\text{ppm}/2^{0.5} = 0.707$, a common utility for limit of detection values, but one that is inherently flawed with the large percentage of CO concentrations below limit of detection[173]. Thus, we chose not to implement this method and include all original values in our model.

For univariate analyses we ran both IRC-specific models in addition to the HAPIN-wide models. For HAPIN-wide models we include IRC as a fixed effect in the following equation where:

$$EQ1: y_{ij} = \mu + IRC_{ij} + \beta_{ij} + \epsilon_{ij}$$

- y_{ij} is the natural log transformed CO concentration in ppm for individual *i* in household *j,*
- μ is the intercept of the slope,

- IRC_{ij} is the study site that the participant belongs to,
- β_{ij} is the parameter of interest, and
- $\epsilon_{ij}$is the error term for the model.

For IRC-specific models, we stratify by IRC effect. For all fitted models, we report marginal R^2 for how much additional variation that parameter estimates and the percent change from a specified reference group for each variable. We selected Guatemala as the reference for all IRC comparisons based on alphabetical order.

Backwards selection was used for the multivariate model to include the largest number of significant covariates for further interpretation. This technique is implemented as a starting point to find potentially unique questionnaire variable associations that might not be included in a forward selection type model. The previously mentioned 63 variables were inserted into the backwards selection. These methods are implemented for both HAPIN-wide and IRC-specific models where IRC is a fixed effect in the HAPIN-wide approach. Backwards selection requires complete case analysis; therefore, we removed observations with any missing questionnaire values. Implementing this method removed 12, 17, 12, and 8 variables from the Guatemala, India, Peru, and Rwanda IRC-specific models, respectively. Following the final model building stage, we predict CO concentrations from the multivariate model to calculate means, medians, root mean square error (RMSE), and R^2 for our predicted CO concentrations for both HAPIN-wide and IRC-specific results.

Our final approach was to assess the effect of repeated household measurements. This was done by adding a random intercept for the unique household number to the final multivariable regression model. We report adjusted intra-class correlation to determine how well repeated measures explain variation.

Results

We started with 13623 valid CO measures, with 3896, 3860, 2433, and 3434 in Guatemala, India, Peru, and Rwanda, respectively. Means (standard deviation), medians (inter-quartile ranges), and ranges by study site, randomization period, and arm are presented in Table 4.1. As previously reported, we show a percent reduction in the CO means in the intervention arm of 76% HAPIN-wide. However, for our HAPIN-wide modelling results we use 11353 valid CO measures, with 3573, 3594, 1682, and 2504 in Guatemala, India, Peru, and Rwanda, respectively due to missingness in one of the 63 variables used in our regression analyses. Despite this missingness, CO means of the two datasets HAPIN-wide were not significantly different (p=0.07).

Univariate Exposure Contrasts

In the univariate stratifications there were only a few significant variables that were associated with CO exposures. The three most critical variables being IRC, fuel type, and stove type. With reference to Guatemala those in Peru had significantly higher percent change in CO ppm [115%, (95% CI: 95, 137)] compared to a significant reduction in India [-40%, (95% CI: -45,-35)], and no significant change in Rwanda [3%, (95% CI: -6, 12)]. With reference to the LPG stove we found that the Imbabura stove used in Rwanda had that largest percent change [1367%, (95% CI: 1131, 1647)] and open fires still had a large percent increase of 620% (95% CI: 464, 818). With reference to LPG fuel, we find that charcoal use had a 1242% increase (95% CI: 1012, 1521), wood with a 444% increase (95% CI: 409, 481), and cow dung with a 167% increase (95% CI: 131,208) in personal CO concentrations (Table 4.S1). Other variables that gave moderate associations were number of stoves, smoke reported from another kitchen, and

kitchen dimensions. Compared to using one stove, using two or more stoves resulted in a 150% increase (95% CI: 124, 178) in CO exposures. When the field technician reported smoke from another kitchen outside the home there was a 49% increase (95% CI: 27, 74) in CO exposures compared to when it was not reported. Finally, for every one-meter increase in maximum height and minimum height of the kitchen resulted in an 8 (95% CI: -11, -4) and 5% (95% CI: -8, -1) reduction in respective exposure to CO.

Regression Analysis

When comparing the fuel vs stove type models, we found that the stove type model performed best and at a similar level to when both variables were included (R^2_{Stove}=0.249, R^2_{Fuel}=0.239, R^2_{Bot} =0.255). Therefore, we chose to just use stove type models for our HAPIN-wide and IRC-specific models. HAPIN-wide Ns were reduced by around 16% due to missingness of questionnaire variables, to 11353 available data points. The largest source of variation in our HAPIN-wide model was stove type. When compared to an LPG stove and adjusting for other variables, we found 1.2, 2.7, 1.7, 2.2, and 1.1 ppm increase in CO exposures for the chimney, Imbabura, open biomass, other (electric, portable, rocket), and Rondereza stoves, respectively (Table 4.2). Compared to piped water there were 0.8, 0.7, and 0.2 ppm increase in CO exposures for other, rainwater, and unprotected dug well water sources; however, there a was a non-significant decrease of 1.1 and 0.3 ppm for packaged water that was sachet and bottled, respectively. When investigating water sources further, there was a 0.1 ppm increase from using the primary stove for drinking water compared to not using the stove for drinking water. There were 0.1ppm reductions for both permeable roof and permeable wall material compared to impermeable roof and wall material. Other variables that were significantly

associated with a 0.3, 0.2, and 0.1ppm increases in CO were outside smoke from another kitchen, having a smokey kitchen, and having two or more stoves, respectively. However, there were others that were significantly associated with 0.6, 0.6, and 0.1ppm decrease in CO from 1 meter increase in max kitchen height, outdoor vehicular smoke, and having electricity, respectively (Table 4.2).

We found varying degrees of fit in our IRC-specific multivariable models with R^2= 0.30, 0.30, 0.12, and 0.23 for Guatemala, India, Peru, and Rwanda, respectively (Table 4.3, Fig 4.1-4.3, Fig S4.1-4.9). The only variable that was selected across all four IRC-specific multivariable models was stove type. However, using the stove for roasting meats, kitchen length, kitchen maximum height, wall material, and stove use hours were significant in three of the four study sites. Many of variables unique to just one study site were time-variant, including other sources of indoor and outdoor smoke, or unique to IRC variables such as Rondereza stoves in Rwanda. The IRC-specific models RMSE also varied where Peru had the largest error (RMSE=6.71), while Guatemala had the smallest error (RMSE=2.97) (Table 4.3).

When we added the random effect of repeated household measurements, we calculated adjusted intra-class correlation HAPIN-wide of 0.111. For each IRC we found intra-class correlation coefficients of 0.137, 0.147, 0.157, and 0.128 for Guatemala, India, Peru, and Rwanda, respectively.

Discussion

We evaluated the factors that were associated with personal CO exposures, finding that beyond IRC and stove type and/or fuel type there was little variation that could be explained by other variables. The massive undertaking of collecting over 13,000 individual CO data points

allows for deeper comparison of questionnaire variables than any that have previously been conducted for a HAP study. Beyond the main sources of variation, in HAPIN-wide models most of the significant and largest associated variables were time-invariant. These associations could indicate that survey data based on daily exposures might not be as significant as those related to kitchen dimensions, roof and wall material, and number of stoves. One unique aspect of our study was finding the potential link between exposure to CO and water sources. It has already been proposed how water quality and air quality are linked, but this paper provides further evidence that an improvement in water quality can potentially lead to reductions in HAP [38,174]. Now we find more evidence with specific water sources where those drinking packaged water have lower CO exposures than those who needed to use their stove for boiling drinking water like unprotected dug well water. We also found that having electricity, another socioeconomic factor, to be associated with lower CO concentrations. These water, sanitation, hygiene, and air sectors of health have become inextricably linked to one another and these results further uphold such potential connections. However, despite these potential sector links the results here are very limited and show just modest changes in CO concentrations from these other socioeconomic factors.

The usage of four different study sites allows for insight into how well models perform in different settings where altitude, cultural, and behavioral differences can potentially impact model performance. We found that there were a few key variables that were significant across at least three of the study sites. However, this also shows how building such models can result in a high degree of variability in estimates and fit from different study locations. This model variability could also be attributed to different reductions in pollutants from the LPG interventions across different study sites [21,175]. Not only did the IRC-specific models' fit vary, but

also the HAPIN-wide model varied significantly from the IRC-specific results. While an LPG intervention stove can reduce CO exposures, the degree to which CO exposures are reduced and the factors related to CO exposure are not uniform from site to site. This is corroborated with the differences in the CO concentrations among the IRCs where Guatemala has nearly a quarter of the concentrations as that of Peru. This inter-site comparison has helped understand the portability of such models in other environments and to help provide more clarity on different underlying factors in different study locations. Another source of variability included finding low ICC values. This indicates that CO exposure varies widely from exposure visit to visit, which is to be expected based on previous studies [148,176] .

When compared to other similar HAP studies we found similar weak R^2, and we find this for similar reasons. The multivariate models were more accurate for estimations of modeled median CO concentrations, but had poor accuracy for modeled standard deviations [145]. This was likely a result of the strength of association between CO and IRC and fuel type and/or stove type and weak associations with other covariates. These associations resulted in large 'peaks' that are evident in Figures 3.S9-12 with very small standard deviations. These peaks are mostly driven by study site and stove type effect, making it difficult to interpret how other selected variables influence the models.

We found that the variables that were selected via a backwards selection were also similar to other studies using other methodologies, including significant associations with fuel type, roof/wall material, number of open windows, and kitchen volume [112,162,177]. These results suggest that despite the backwards selection approach taken here we ended with similar results that other approaches have shown. This gives more validity to our modelling approach, which could be considered for future applications when a large number (>50) of household

characteristics and questionnaire variables are collected to avoid cumbersome univariate analyses.

All model selections and decisions will also have limitations and our study is no exception. Due to the usage of the backwards selection approach, we lost around 13% of our dataset. Despite these missing points, upon further investigation the differences in the mean CO exposures were not significant (p=0.07) between the two datasets HAPIN-wide and when stratified by IRC and study arm. However, we are unable to determine if any of our associations change between the two datasets because of the backwards selection approach. Additionally, the large number of variables input into the models in combination with backwards selection can result in irrelevant or weakly correlated variables in the model. Ultimately, these varaibles can be deemed as spurious and ignored in the final interpretations. However, we believe the models here had few such spurious results due to logical trends and associations. Additionally, this the methods here are backed by other studies that have shown forward selection resulting in similar model variable selections [106,128]. Another limitation of our HAPIN-wide models is the large number of covariates that were selected making some findings difficult to interpret with so many other variables to be adjusted for. Despite this limitation, our main results are unaffected by these weakly correlated variables and provide unique associations that may not have been found using just a univariate approach. We found that the backwards selection approach might be helpful in determining interesting findings, but ultimately should be used in situations when large amounts covariates are present due to the many possible models that would need to be run.

One of the other major limitations of our CO exposure model is the low 24-hour averages in our study. The Lascar is not designed to handle such low concentrations, and with an limit of detection of 1ppm can reduce the accuracy of our 24-hour averages [25,162]. However, the 24-hour

average may not be the best representation of an individual's CO concentration and could have instead used a 1-hour maximum CO concentration to better understand peak CO exposures, which we suggest for future interpretations of CO.

Conclusions

We found backward selection models accounted for 12-30% of the variation in 11,353 personal maternal CO measures. The variables that explained the most variation were the key time-invariant variables of study location and fuel type and/or stove type. Time-invariant measures such as kitchen dimensions, stove number, and water source were more strongly associated with CO than time-variant measures such as what the stove was used for and other sources of indoor/outdoor smoke.

Tables and Figures

Table 4.1a Shows the number of CO measurements stratified by variable category, the percentage of time those variables appear, and the median (interquartile range), mean (standard deviation), and range for those CO concentration stratifications.

Univariate analyses of maternal HAPIN CO concentrations (Two pages)

Variable	N	(%)	Median (IQR)	Mean (SD)	Range
Overall	13830	100%	0.6 (0.1-1.8)	1.7 (3.7)	0-98.5
IRC					
Guatemala	3934	28%	0.5(0.1,1.6)	1.2(2.1)	0-60.2
India	3914	28%	0.3(0.0,1.3)	1.3(2.9)	0-47.8
Peru	2428	18%	1.2(0.3,3.3)	3.1(6.1)	0-98.5
Rwanda	3500	25%	0.5(0.1,1.6)	1.6(3.4)	0-50.5
Stove Type					
Open fire	6077	45%	1.0 (0.3-2.5)	2.4 (4.3)	0-98.5
LPG	5665	42%	0.2 (0.0-0.7	0.8 (2.2)	0-70.0
Chimney	625	5%	0.7 (0.2-1.8)	1.5 (3.4)	0-64.2
Rondereza	585	4%	0.5 (0.2-1.2)	1.1 (1.8)	0-20.9
Imbabura	464	3%	2.7 (0.9-6.7)	5.2 (6.8)	0-50.5
Other	207	2%	1.1 (0.5- 2.6)	2.4 (4.1)	0-27.6
Wall Material					
Impermeable	10286	74%	0.6(0.1,1.8)	1.6(3.6)	0-98.5
Permeable	2031	15%	0.5(0.1,1.6)	1.5(3.5)	0-71.8
NA	1513	11%	0.8(0.2,2.1)	2.1(4.5)	0-64.6
Roof Material					
Impermeable	10077	73%	0.6(0.1,1.7)	1.6(3.6)	0-98.5
Permeable	2308	17%	0.5(0.1,1.6)	1.6(3.5)	0-37
NA	1445	10%	0.8(0.2,2.1)	2.1(4.5)	0-64.6
Number of stoves					
One	12366	89%	0.5 (0.1-1.6)	1.5 (3.4)	0-71.8
Two or more	1462	11%	1.4 (0.5-3.0)	2.7 (5.3)	0-98.5
NA	2	0%	6.0 (3.0-8.9)	6.0 (8.4)	0-11.9
Fuel Type					
Wood	6164	45%	0.9(0.3,2.1)	1.7(3.2)	0-98.5
LPG	5499	40%	0.1(0,0.7)	0.8(2.2)	0-70
Cow dung	1213	9%	1.7(0.5,4.2)	3.7(6.5)	0-71.8
NA	501	4%	1.0(0.2,2.9)	2.8(5.8)	0-64.2
Charcoal	391	3%	2.6(0.7,6.6)	5.0(6.8)	0-50.5
Agricultural waste	26	0%	0.6(0.3,1.3)	0.9(0.8)	0-2.8
Electricity	5	0%	0.8(0.2,1.3)	0.8(0.7)	0-1.5

Grass/shrubs	22	0%	0.5(0.3,1.1)	1.3(2.3)	0-10.7
Other	9	0%	0.9(0.3,3.6)	1.9(2.1)	0.1-5
Indoor Smoke from another Kitchen					
No	13683	99%	0.6(0.1,1.7)	1.7(3.7)	0-98.5
Yes	147	1%	0.8(0.2,2)	1.6(2.6)	0-25.2
Water source					
Piped water-Public tap/standpipe	3943	29%	0.4(0.0,1.3)	1.4(3)	0-47.8
Piped water to yard/plot	3012	22%	0.6(0.1,1.9)	1.8(3.7)	0-69.5
Unprotected dug well	1177	9%	0.8(0.2,2.2)	2.1(4.5)	0-64.6
Protected spring	1045	8%	0.6(0.1,1.6)	1.4(2.4)	0-37
Piped water to neighbor	841	6%	0.6(0.1,1.9)	1.8(3.3)	0-36.6
Protected dug well	804	6%	0.8(0.1,2.4)	2.5(6.2)	0-98.5
Piped water into dwelling	769	6%	0.5(0.1,1.7)	1.4(2.5)	0-28.7
Tube Well/Borehole	644	5%	0.6(0.1,1.7)	1.5(2.9)	0-35.9
NA	391	3%	0.6(0.1,2.3)	2.1(5.2)	0-64.2
Water kiosk	329	2%	0.7(0.1,1.8)	2.2(5.2)	0-50.5
Unprotected spring	310	2%	0.7(0.2,1.8)	1.4(2.3)	0-22.3
Surface water	135	1%	0.6(0.2,2.1)	1.7(3.4)	0-26.2
Tanker-truck	79	1%	0.9(0.1,2.6)	2.4(4.7)	0-35.6
Other	57	0%	1.1(0.4,2.5)	2(2.4)	0-12.1
Packaged water: Bottled water	42	0%	0.1(0.0,1.2)	0.9(1.6)	0-6.9
Rainwater	26	0%	1.1(0.6,2.6)	3.7(7.9)	0.1-36.6
Cart with small tank	18	0%	0.1(0,0.7)	0.8(1.7)	0-7
Packaged water: Sachet water	1	0%	0.8(0.8,0.8)	0.8(NA)	0.8-0.8
Uses a mosquito coil					
No	13207	97%	0.6(0.1,1.8)	1.7(3.7)	0-98.5
Yes	415	3%	0.5(0.1,1.4)	1.2(2.2)	0-17.2
Has Electricity					
NA	8870	65%	0.4(0.1,1.5)	1.4(3.2)	0-98.5
Yes	3931	29%	0.8(0.2,2.4)	2.2(4.7)	0-71.8
No	822	6%	0.9(0.3,2.1)	1.9(3)	0-36
Stove used for drinking water					
No	8332	61%	0.5(0.1,1.6)	1.5(3.1)	0-69.5
Yes	5291	39%	0.7(0.1,2.1)	2.0(4.4)	0-98.5

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Table 4.1b Maternal CO concentrations stratified by tertiles of kitchen dimensions and study site. Shown are the percentages, medians (interquartile ranges), means (standard deviations), and ranges for those CO concentration stratifications.

Maternal HAPIN CO concentrations stratified by kitchen dimensions										
Minimum Kitchen Height						**Maximum Kitchen Height**					
HAPIN-wide						**HAPIN-wide**					
Tertile (cm)	N	(%)	Median (IQR)	Mean (SD)	Range	**Tertile (cm)**	N	(%)	Median (IQR)	Mean (SD)	Range
(2,186]	4558	33%	0.6(0.1,1.8)	1.7(4.1)	0-98.5	**(85,240]**	4497	33%	0.7(0.1,2.1)	1.9(4.1)	0-98.5
(186,227]	4648	34%	0.7(0.1,1.9)	1.7(3.5)	0-70	**(240,285]**	4701	35%	0.6(0.1,1.8)	1.6(3.2)	0-60.2
(227,2283]	4412	32%	0.5(0.1,1.5)	1.6(3.5)	0-64.6	**(285,2685]**	4424	32%	0.4(0.1,1.4)	1.5(3.6)	0-70
Guatemala						**Guatemala**					
(2,198]	1306	34%	0.7(0.2,2)	1.5(2.1)	0-23	**(166,240]**	1361	35%	0.7(0.2,2.1)	1.5(2.2)	0-23
(198,223]	1301	33%	0.6(0.1,1.6)	1.2(2.4)	0-60.2	**(240,268]**	1262	32%	0.6(0.1,1.6)	1.2(2.5)	0-60.2
(223,312]	1284	33%	0.4(0.1,1.2)	1(1.7)	0-21.7	**(268,367]**	1271	33%	0.4(0.1,1.2)	0.9(1.4)	0-14.8
India						**India**					
(23,134]	1281	33%	0.3(0,1.3)	1.2(2.8)	0-46.9	**(85,236]**	1298	34%	0.4(0,1.5)	1.4(3.2)	0-46.9
(134,184]	1316	34%	0.3(0,1.4)	1.3(3.1)	0-47.8	**(236,304]**	1290	33%	0.4(0,1.5)	1.4(3.2)	0-47.8
(184,1322]	1262	33%	0.4(0,1.4)	1.3(2.8)	0-32.8	**(304,820]**	1271	33%	0.2(0,1.2)	1(2.1)	0-32.8
Peru						**Peru**					
(35,183]	811	33%	1.2(0.3,3.2)	3.2(6.7)	0-98.5	**(108,217]**	811	33%	1.2(0.3,3.2)	3.1(6.5)	0-98.5
(183,215]	818	34%	1.2(0.3,3.4)	2.8(4.7)	0-69.5	**(217,265]**	829	34%	1.1(0.3,3.2)	2.9(5.3)	0-69.5
(215,2283]	794	33%	1.1(0.2,3.1)	3.2(6.8)	0-70	**(265,2685]**	792	33%	1.2(0.3,3.5)	3.3(6.5)	0-70
Rwanda						**Rwanda**					
(102,227]	1139	33%	0.6(0.2,1.6)	1.6(3.3)	0-50.5	**(112,261]**	1137	33%	0.6(0.2,1.6)	1.6(3.5)	0-50.5
(227,265]	1172	34%	0.6(0.1,1.6)	1.6(3.3)	0-44.4	**(261,300]**	1216	35%	0.6(0.1,1.7)	1.5(3)	0-36.6
(265,422]	1122	33%	0.4(0.1,1.5)	1.6(3.5)	0-32.9	**(300,2220]**	1080	31%	0.4(0.1,1.4)	1.6(3.6)	0-44.4

Table 4.2 Fixed effects from backwards selection multivariable model. Reference groups specified in paratheses if applicable with N's (%), effect estimates, and p-values.

Fixed effect multivariate model for maternal CO concentrations (two pages)

Term	N (%)	Estimate	P- value
(Intercept)	---	-3.75	<0.001
Study Site (ref= Guatemala)	3573 (31%)		
India	3594 (32%)	-0.31	<0.001
Peru	1682 (15%)	0.91	<0.001
Rwanda	2504 (22%)	-0.13	0.107
Stove Type (ref= LPG)	4649 (41%)		
Open	5165 (45%)	1.74	<0.001
Chimney	591 (5%)	1.18	<0.001
Rondereza	448 (4%)	1.07	<0.001
Imbabura	309 (3%)	2.66	<0.001
Other	144 (1%)	2.19	<0.001
Outside smoke from another kitchen (ref=no smoke)	537 (5%)	0.30	<0.001
Indoor smoke from another kitchen (ref=no smoke)	113 (1%)	0.28	0.091
Stove used to cook (ref=not used)	11349 (100%)	2.00	0.021
Stove used for drinking water (ref= not used)	1184 (10%)	0.11	0.046
Max height of kitchen per 1 meter	11353 (100%)	-0.06	0.03
Minimum height of kitchen per 1 meter	11353 (100%)	0.08	0.042

Permeable wall material, like reed/thatch/mesh (ref= impermeable)	1887 (17%)	-0.14	0.005
Permeable roof material, like reed/thatch/mesh (ref= impermeable)	2096 (82%)	-0.13	0.01
Each additional window	11353 (100%)	-0.01	<0.001
Each additional stove hour	11353 (100%)	0.02	0.076
Used two or more stoves (ref= used one stove)	1189 (10%)	0.13	0.026
Has electricity (ref=no electricity)	9443 (83%)	-0.11	0.035
Used a mosquito coil (no use)	382 (3%)	0.15	0.112
Water source (ref= Piped water- Public tap)	3419 (30%)		
Piped water to yard/plot	2681 (24%)	0.08	0.204
Unprotected dug well	1063 (9%)	0.22	0.001
Protected spring	836 (7%)	0.07	0.349
Piped water to neighbor	688 (6%)	0.14	0.088
Piped water into dwelling	656 (6%)	-0.04	0.68
Protected dug well	632 (6%)	0	0.989
Water kiosk	267 (2%)	0.11	0.13
Unprotected spring	265 (2%)	0.21	0.064
Unprotected spring	265 (2%)	0.21	0.064
Surface water	90 (1%)	0.03	0.860
Packaged water: Bottled water	33 (0%)	-0.34	0.272
Rainwater	22 (0%)	0.72	0.051
Cart with small tank	18 (0%)	-0.73	0.074

Table 4.3 Measured CO exposures compared to modeled exposures from fixed effects model. RMSE= root mean square error, SD= standard deviation.

Perfomance of HAPIN-wide and site-specific backwards selection models

		Measured Exposure (ppm)			**Modeled Exposure (ppm)**			**Model Statistics**	
Site	N	Median	Mean	SD	Median	Mean	SD	RMSE (ppm)	R^2
HAPIN-wide	11,353	0.54	1.59	3.48	0.43	0.59	0.61	4.19	0.25
Guatemala	3,573	0.55	1.25	2.15	0.47	0.60	0.52	2.97	0.30
India	3,594	0.34	1.28	2.81	0.45	0.41	0.35	3.81	0.29
Peru	1,682	1.24	3.08	6.00	1.01	1.05	0.64	6.71	0.10
Rwanda	2,504	0.49	1.50	3.34	0.35	0.60	0.83	3.95	0.22

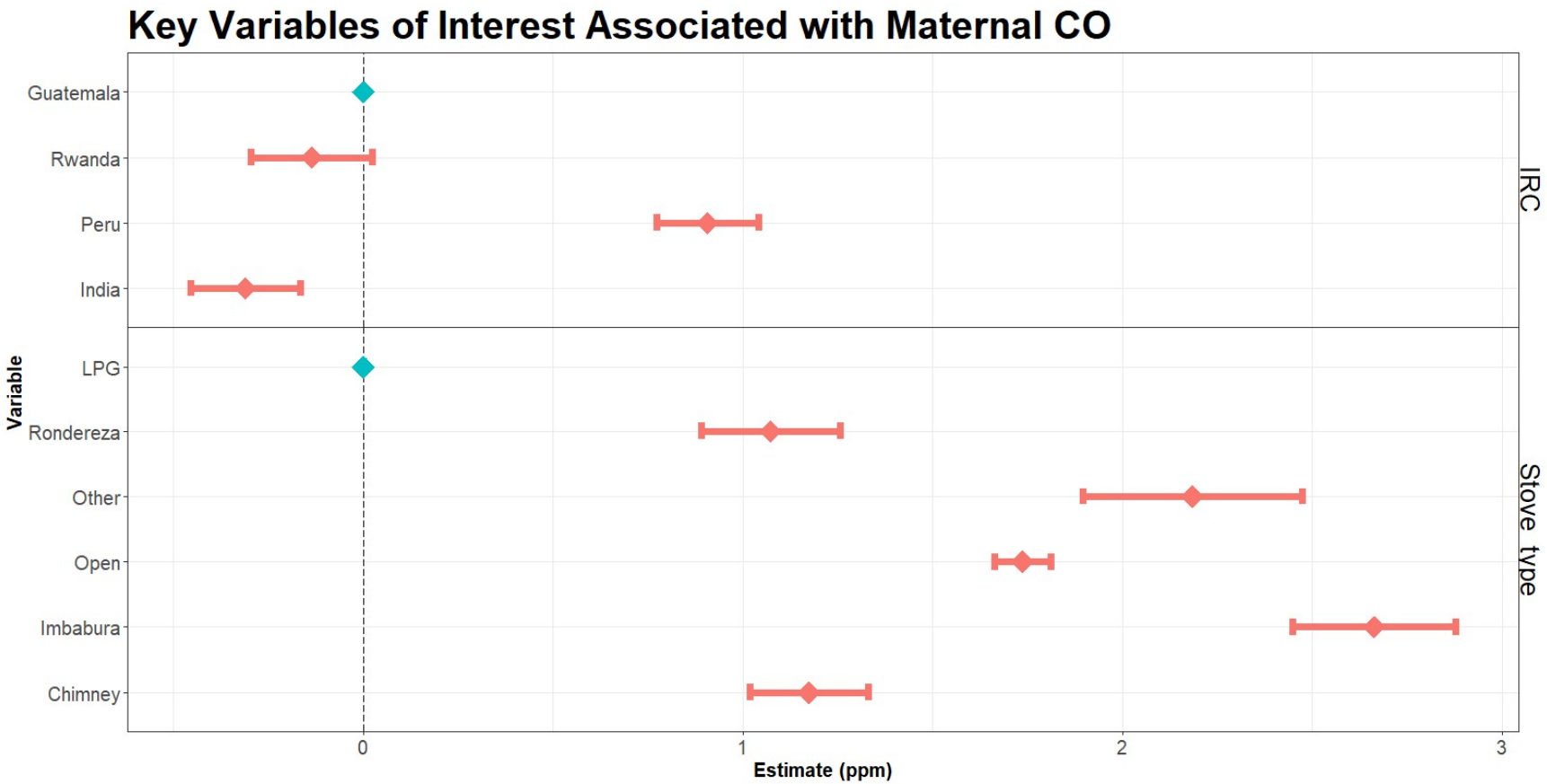

Fig 4.1 Forest plots of effect estimates (ppm) with 95% CI for HAPIN-wide multivariable mixed-effects model for key variables. Reference groups are blue diamonds.

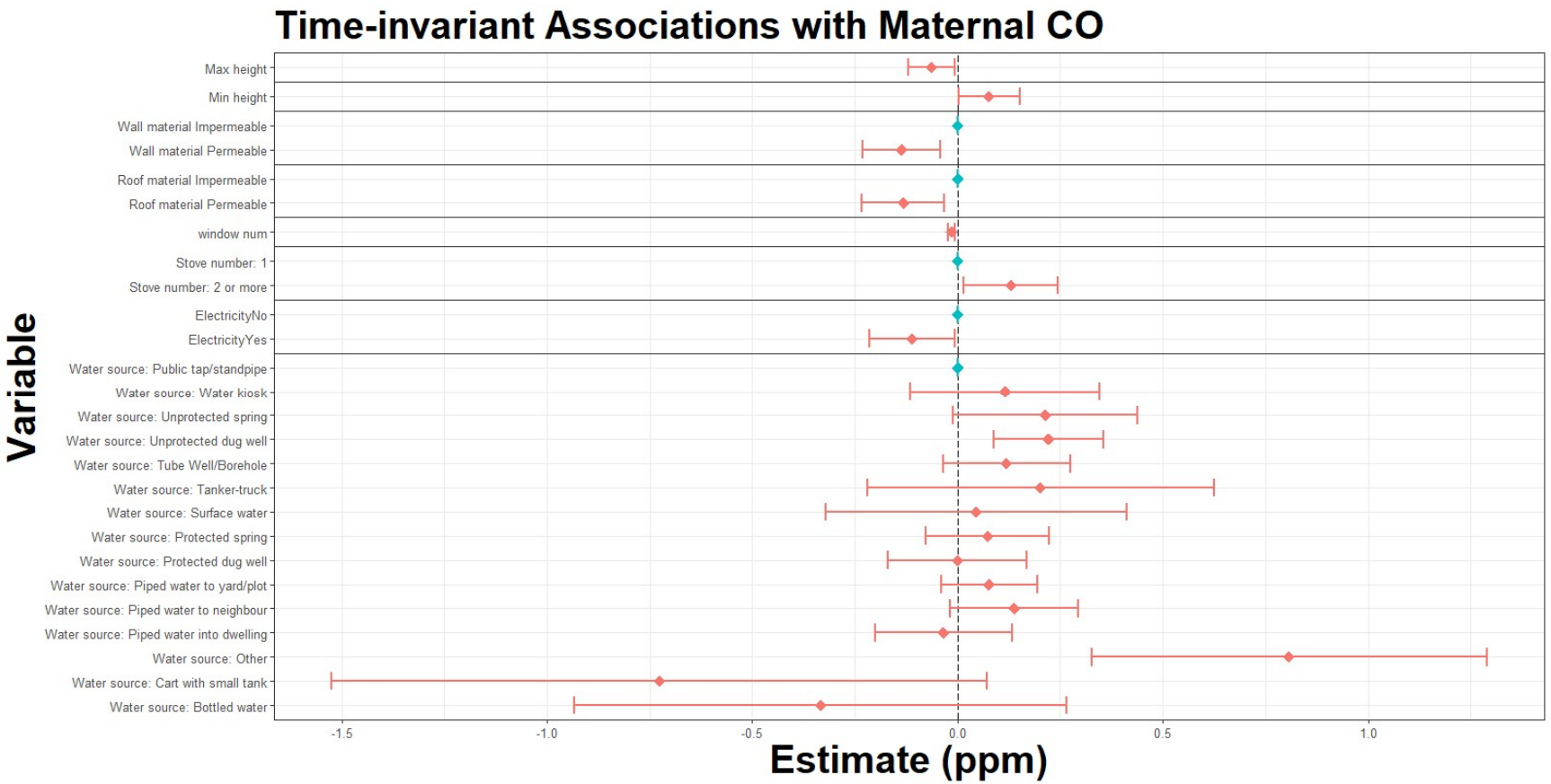

Fig 4.2 Forest plots of effect estimates (ppm) with 95% CI for HAPIN-wide multivariable mixed-effects model for time-invariant variables. Reference groups are blue diamonds.

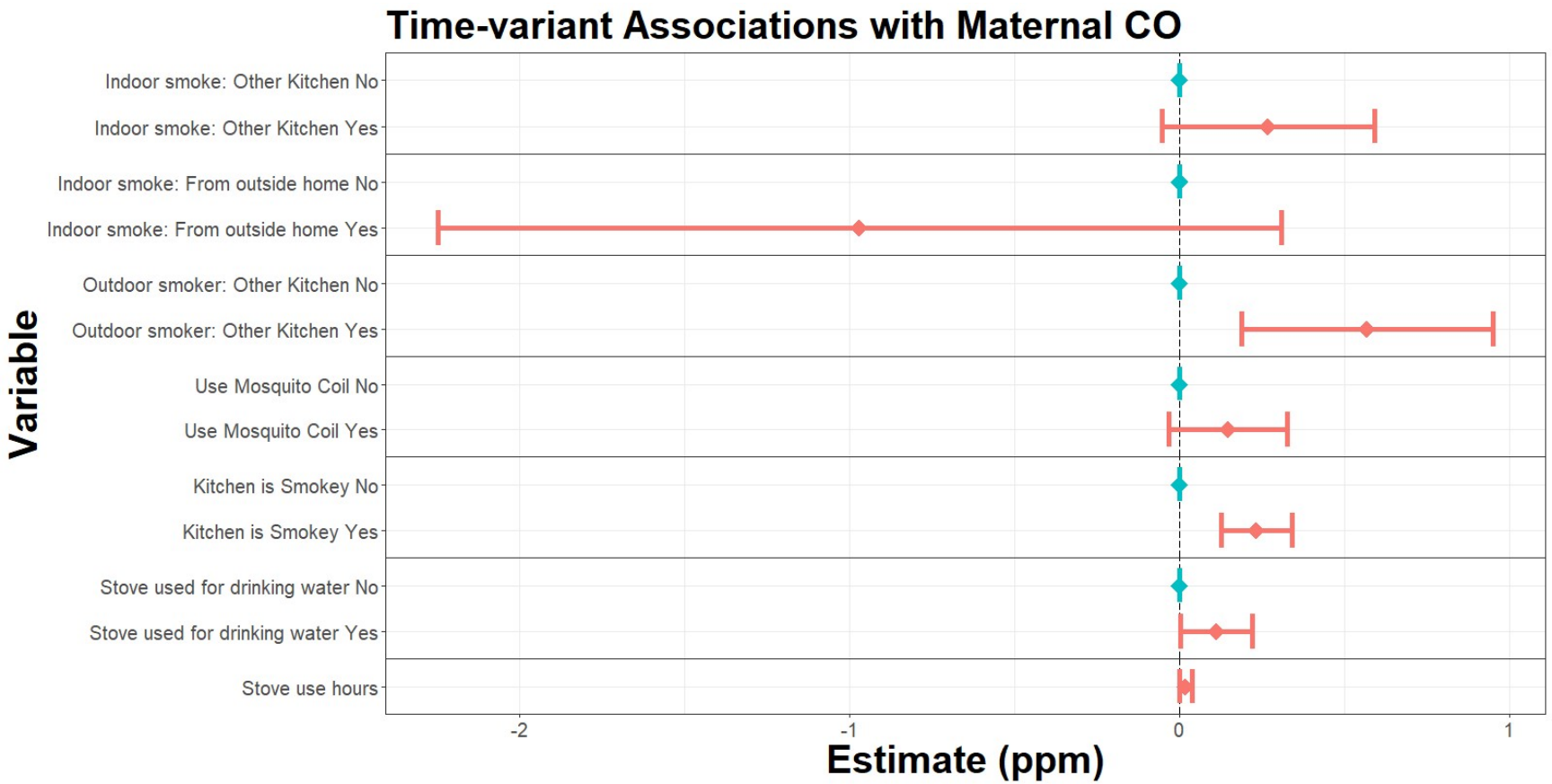

Fig 4.3 Forest plots of effect estimates (ppm) with 95% CI for HAPIN-wide multivariable mixed-effects model for time-variant variables. Reference groups are blue diamonds.

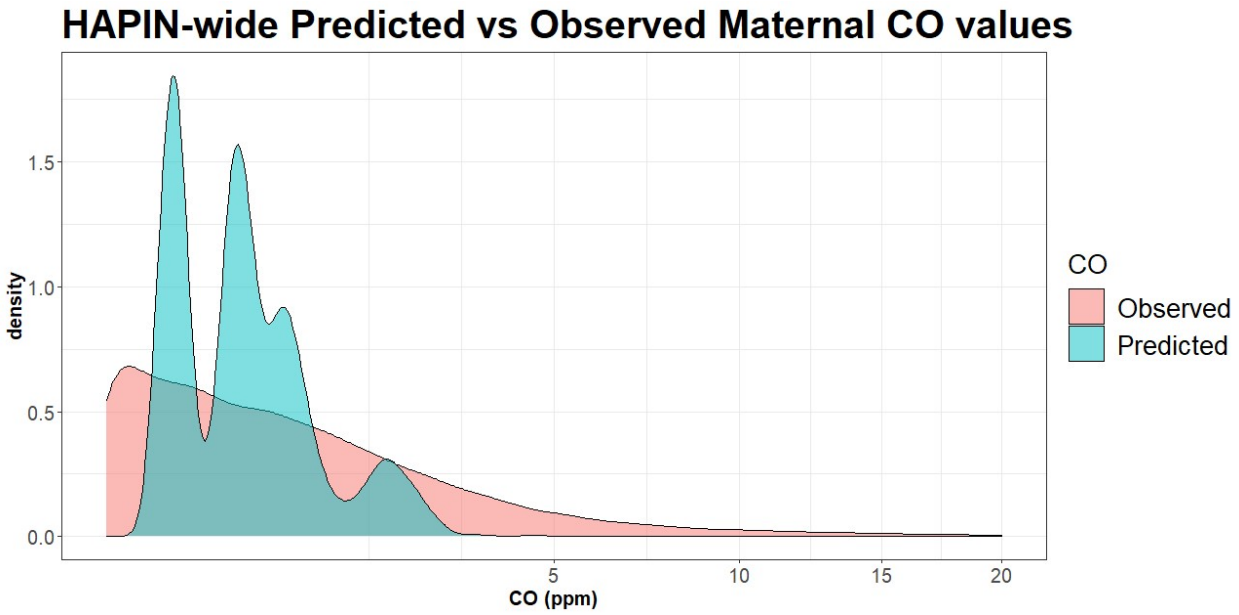

Fig 4.4 Predicted (blue) and observed (red) CO concentration distributions HAPIN-wide using mixed-effect backward selection model.

Supplemental Tables and Figures

Table 4.S1 Univariate changes in percent CO concentrations (95% CI) HAPIN-wide and site-specific. Marginal R^2 of effect is also presented in bold.

Univariate analysis of variables with HAPIN maternal CO concentrations (3 pages)

	HAPIN-wide		**Guatemala**		**India**		**Peru**		**Rwanda**	
Characteristic	%change in Personal CO	R2 or sample size	%change in Personal CO	R2 or sample size	%change in Personal CO	R2 or sample size	%change in Personal CO	R2 or sample size	%change in Personal CO	R2 or sample size
Study Site		**0.05**	---	---	---	---	---	---	---	---
Guatemala	Ref	3934	---	---	---	---	---	---	---	---
India	-40 (-45, -35)	3914	---	---	---	---	---	---	---	---
Peru	115 (95,137)	2482	---	---	---	---	---	---	---	---
Rwanda	3 (-6,12)	3500	---	---	---	---	---	---	---	---
Primary Stove Type		**0.23**		**0.25**		**0.27**		**0.08**		**0.18**
LPG	Ref	5665	Ref	1547	Ref	1581	Ref	1221	Ref	1316
Chimney	199 (158,247)	625	222 (176, 275)	535	-16 (-83, 315)	5	272 (149, 455)	85	---	---
Imbabura	1367 (1131,1647)	464	---	---	---	---	---	---	1002 (822, 1218)	464
Open	433 (400, 468)	6077	608 (537,687)	1805	822 (720, 937)	2224	178 (140, 223)	1122	174 (138, 216)	926
Other	620 (464, 818)	207	136 (-14,552)	9	2501 (1457, 4246)	50	-45 (-89, 173)	5	354 (239, 508)	143
Rondereza	186 (144,236)	585	---	---	---	---	---	---	115 (83, 154)	585
Primary Fuel Type		**0.22**		**0.24**		**0.27**		**0.05**		**0.15**
LPG	Ref	5415	Ref	1573	Ref	1572	Ref	925	Ref	1345
Charcoal	1242 (1012, 1521)	387	---	---	---	---	---	---	868 (698, 1075)	387
Cow Dung	167 (131, 208)	1169	---	---	---	---	132 (97, 171)	1169	---	---
Other	218 (106, 393)	62	211 (28, 659)	12	---	---	72 (-49, 477)	9	161 (53, 344)	41

Wood	444 (409, 481)	6023	497 (440, 561)	2210	826 (723, 943)	2170	109 (53, 186)	155	191 (157, 230)	1488
Number of Doors		**0.05**		**0**		**0**		**0**		**0**
Each additional door	-9 (-14, -3)	12379	-3 (-11,7)	3781	-18 (-27,-8)	3827	2 (-13,20)	1971	-14 (-32,8)	2800
Number of Windows		**0.04**		**0**		**0**		**0**		**0**
Each additional window	-1 (-2, 0)	12379	-1 (-2,0)	3781	6 (1, 12)	3827	3 (-3, 9)	1971	1 (-4, 6)	2800
Number of Stoves		**0.06**		**0.08**		**0**		**0.01**		**0.01**
One	Ref	12366	Ref	3139	Ref	3873	Ref	1955	Ref	3399
Two or more	150 (124,178)	1462	260 (215, 312)	795	104 (6,293)	41	41 (18,70)	525	179 (93,302)	101
Has electricity		**0.05**		**0.00**		**0**		**0**		**0**
No	Ref	2423	Ref	376	Ref	104	Ref	118	Ref	1825
Yes	-14 (-23,-6)	10987	-13 (-28, 5)	3522	-10 (-41,36)	3782	4 (-27,49)	2173	-18 (-28,-7)	1510
Max height		**0.05**		**0.02**		**0**		**0**		**0**
each additional 100 cm	-8 (-11,-4)	12302	-48 (-56,-39)	3934	-16 (-24,-9)	3914	1 (-4, 6)	2482	-7 (-16, 3)	3500
Min Height		**0.05**		**0.01**		**0**		**0**		**0**
each additional 100 cm	-5 (-8,-1)	12302	-34 (-44,-23)	3934	-11 (-18,-4)	3914	0 (-4,4)	2482	-10 (-21, 2)	3500
Stove Hours		**0.05**		**0.00**		**0.05**		**0.01**		**0**
Each additional hour used	10 (8, 12)	13623	3 (0, 5)	3896	53 (44, 62)	3860	10 (5, 17)	2433	8 (3, 12)	3434
Wall material		**0.04**		**0**		**0**		**0**		**0**
Impermeable	Ref	10089	Ref	3253	Ref	2450	Ref	1738	Ref	2648
Permeable	3 (-7, 14)	1988	6 (-11, 27)	455	2 (-11, 18)	1276	-8 (-31,22)	186	29 (-17, 100)	71
Roof material		**0.04**		**0**		**0**		**0**		**0**
Impermeable	Ref	9893	Ref	3569	Ref	2203	Ref	1421	Ref	2700
Permeable	-3 (-12,7)	2246	-6 (-29, 25)	158	-3 (-15, 12)	1556	-3 (-20, 18)	500	-2 (-49, 88)	32
Kitchen is smokey		**0.05**		**0**		**0**		**0**		**0**
No	Ref	12242	Ref	3163	Ref	3743	Ref	2301	Ref	3035
Yes	20 (8, 34)	1381	9 (-6, 26)	733	30 (-12, 92)	117	2 (-27, 43)	132	47 (21, 79)	399

Use Mosquito Coil		**0.05**		**0**		**0**		**0**		**0**
No	Ref	13208	Ref	3549	Ref	3549	Ref	2408	Ref	3415
Yes	10 (-10, 33)	415	14 (-28, 80)	60	9 (-15, 39)	311	-11 (-58, 88)	25	52 (-34, 253)	19
Vehicular Smoke from outside		**0.05**		**0**				**0**		**0**
No	Ref	13570	Ref	3894	Ref	3860	Ref	2431	Ref	3385
Yes	-22 (-53, 32)	53	77 (-85, 2032)	2	---	0	-91 (-99, 22)	2	-17 (-51, 41)	49
Outdoor smoke from another kitchen outside		**0.05**		**0**		**0**		**0**		**0.01**
No	Ref	12994	Ref	3536	Ref	3831	Ref	2423	Ref	3204
Yes	49 (27, 74)	629	34 (11, 63)	360	-18 (-62, 80)	29	58 (-51, 415)	10	87 (46, 139)	230
Indoor smoke from outside the house		**0.05**		**0**				**0**		**0**
No	Ref	13614	Ref	3893	Ref	3860	Ref	2431	Ref	3430
Yes	-63 (-89,32)	9	-84 (-98, 25)	3	---	0	-40 (-96, 732)	2	-46 (-91,240)	4
Stove used for drinking water		**0.05**		**0**		**0**		**0**		**0**
No	Ref	1355	Ref	131	Ref	344	Ref	87	Ref	793
Yes	8 (-3, 21)	11172	31 (-4, 80)	3582	-5 (-25, 20)	3288	18 (-21, 77)	2007	10 (-5, 28)	2295
Stove used for cooking		**0.05**				**0**		**0**		**0**
No	Ref	5	Ref	0	Ref	1	Ref	1	Ref	3
Yes	228 (-40, 1687)	13618	---	3896	63 (879, 10602)	3859	8589 (110,359169)	2432	39 (-83, 1051)	3431

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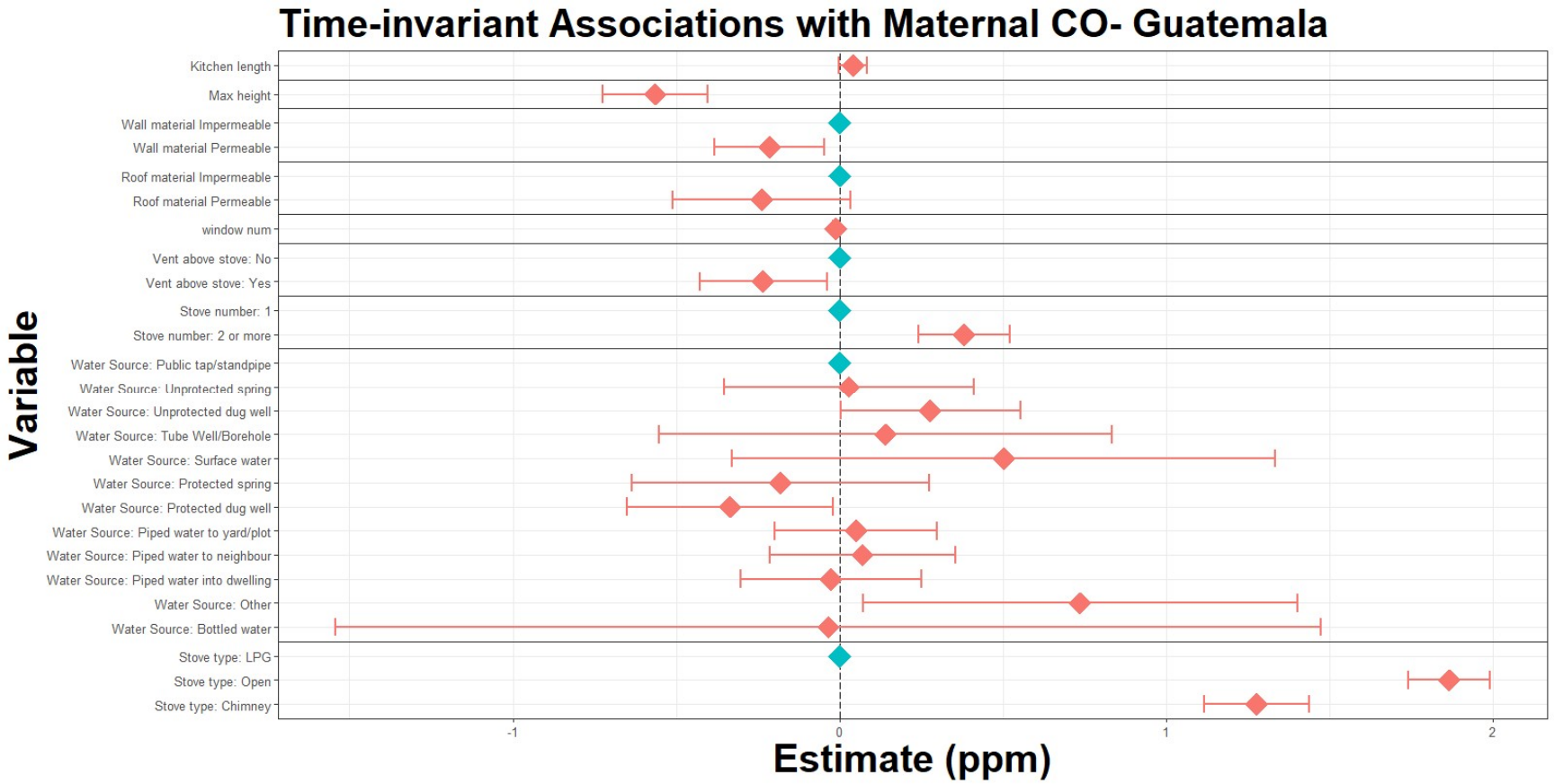

Fig 4.S1 Forest plots of effect estimates (ppm) with 95% CI for Guatemala multivariable fixed-effects model for time-invariant variables. Reference groups are blue diamonds.

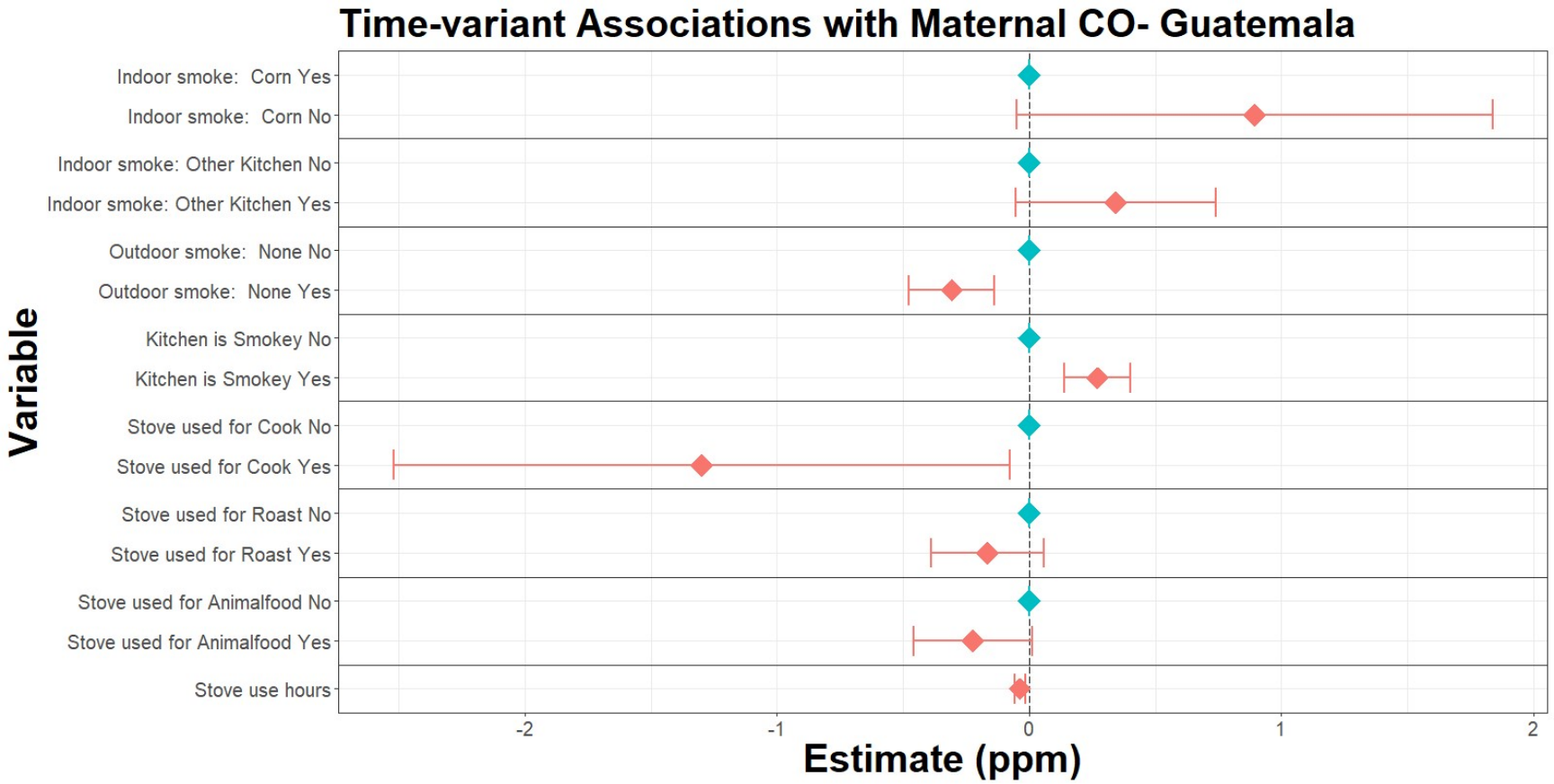

Fig 4.S2 Forest plots of effect estimates (ppm) with 95% CI for Guatemala multivariable fixed-effects model for time-variant variables. Reference groups are blue diamonds.

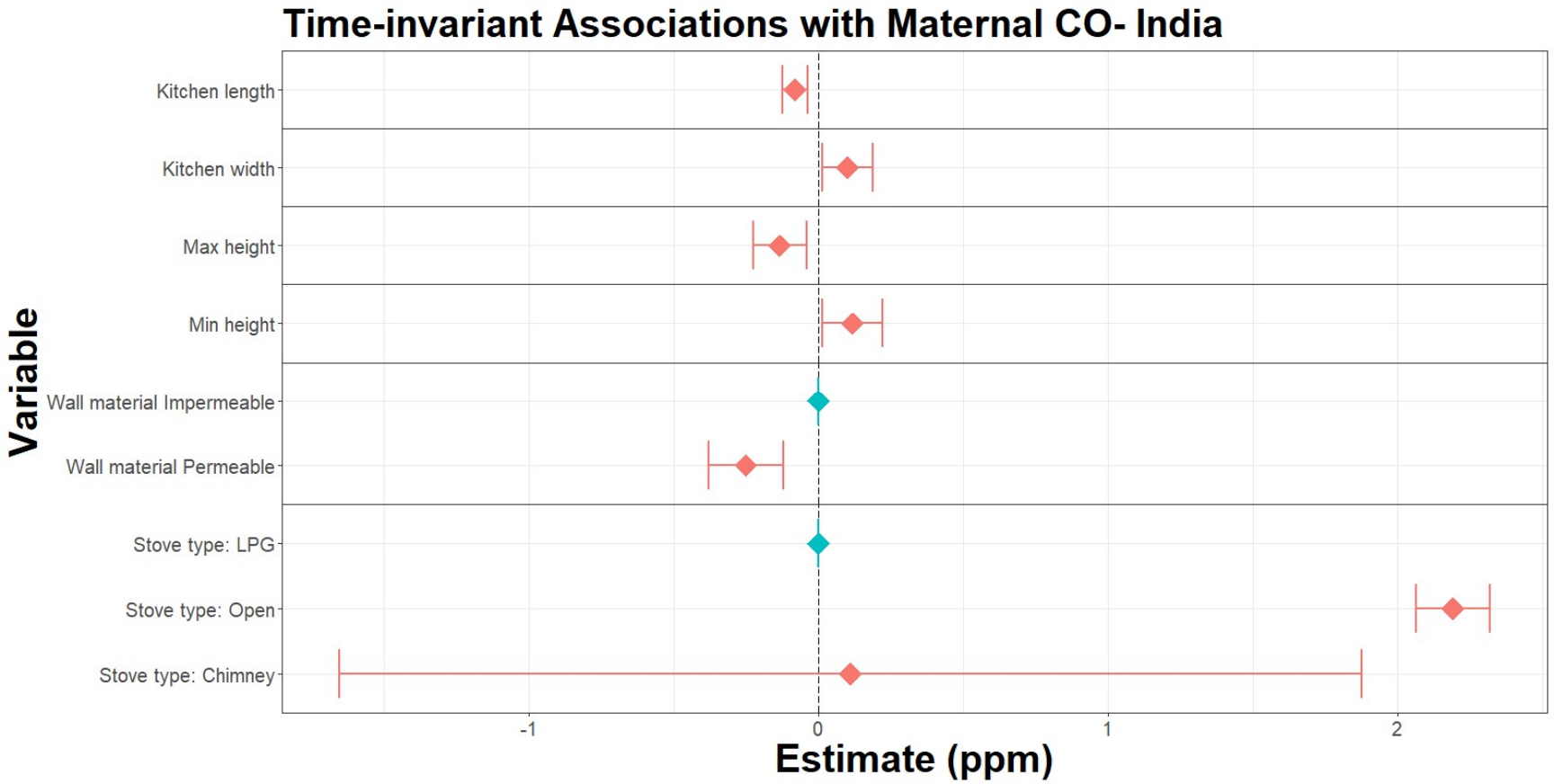

Fig 4.S3 Forest plots of effect estimates (ppm) with 95% CI for India multivariable fixed-effects model for time-invariant variables. Reference groups are blue diamonds.

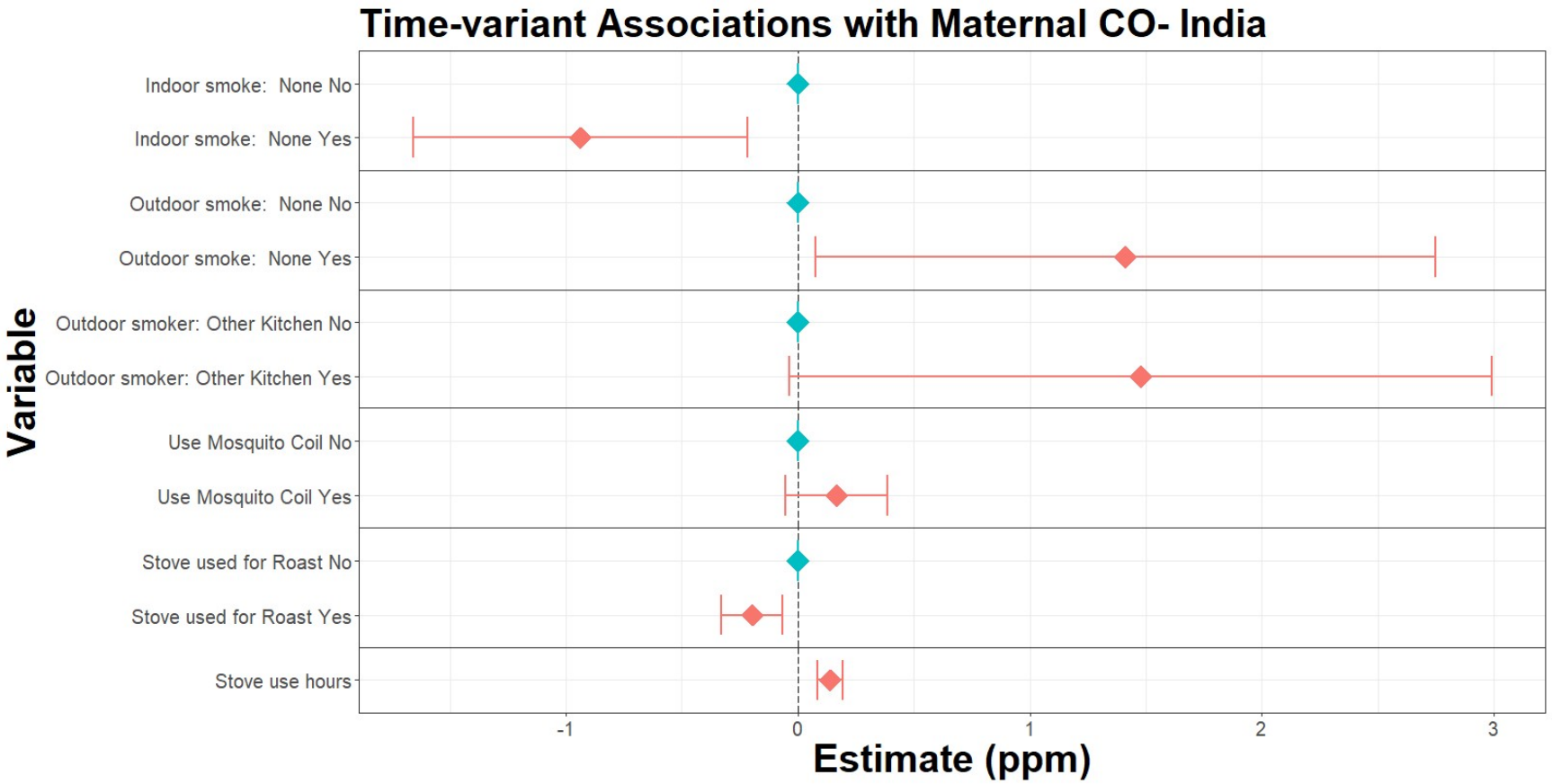

Fig 4.S4 Forest plots of effect estimates (ppm) with 95% CI for India multivariable fixed-effects model for time-variant variables. Reference groups are blue diamonds.

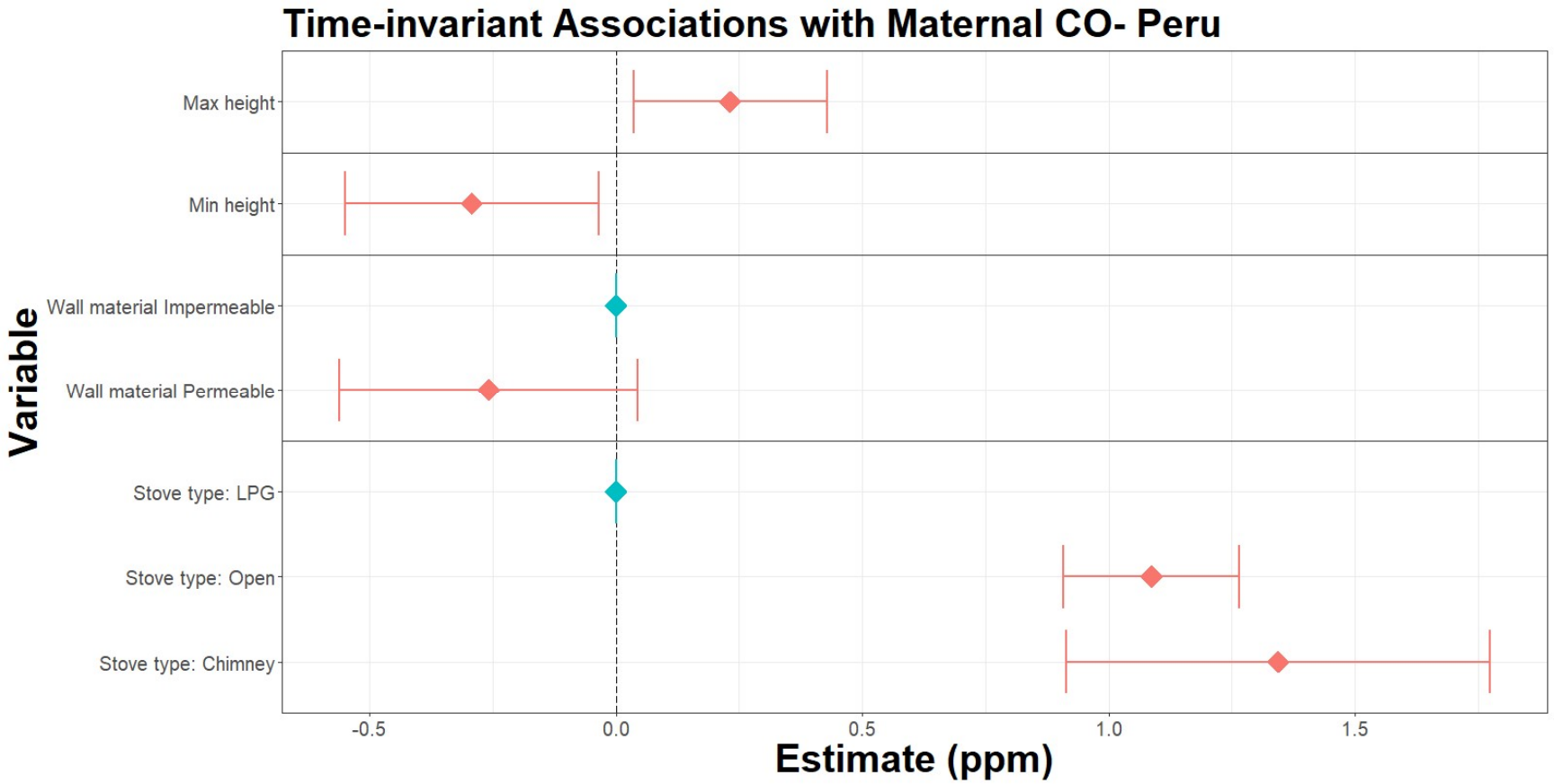

Fig 4.S5 Forest plots of effect estimates (ppm) with 95% CI for Peru multivariable fixed-effects model for time-invariant variables. Reference groups are blue diamonds.

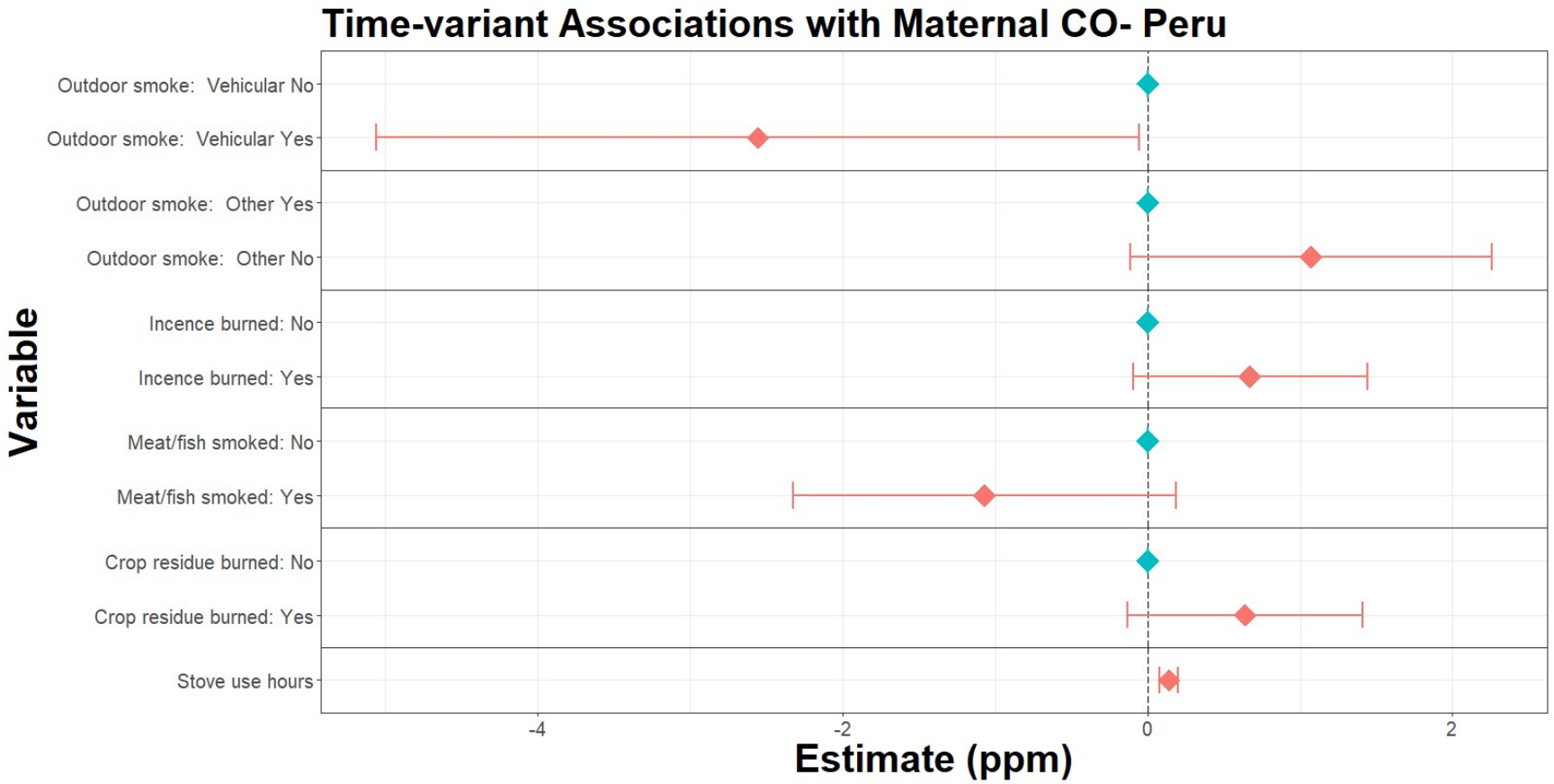

Fig 4.S6 Forest plots of effect estimates (ppm) with 95% CI for Peru multivariable fixed-effects model for time-variant variables. Reference groups are blue diamonds.

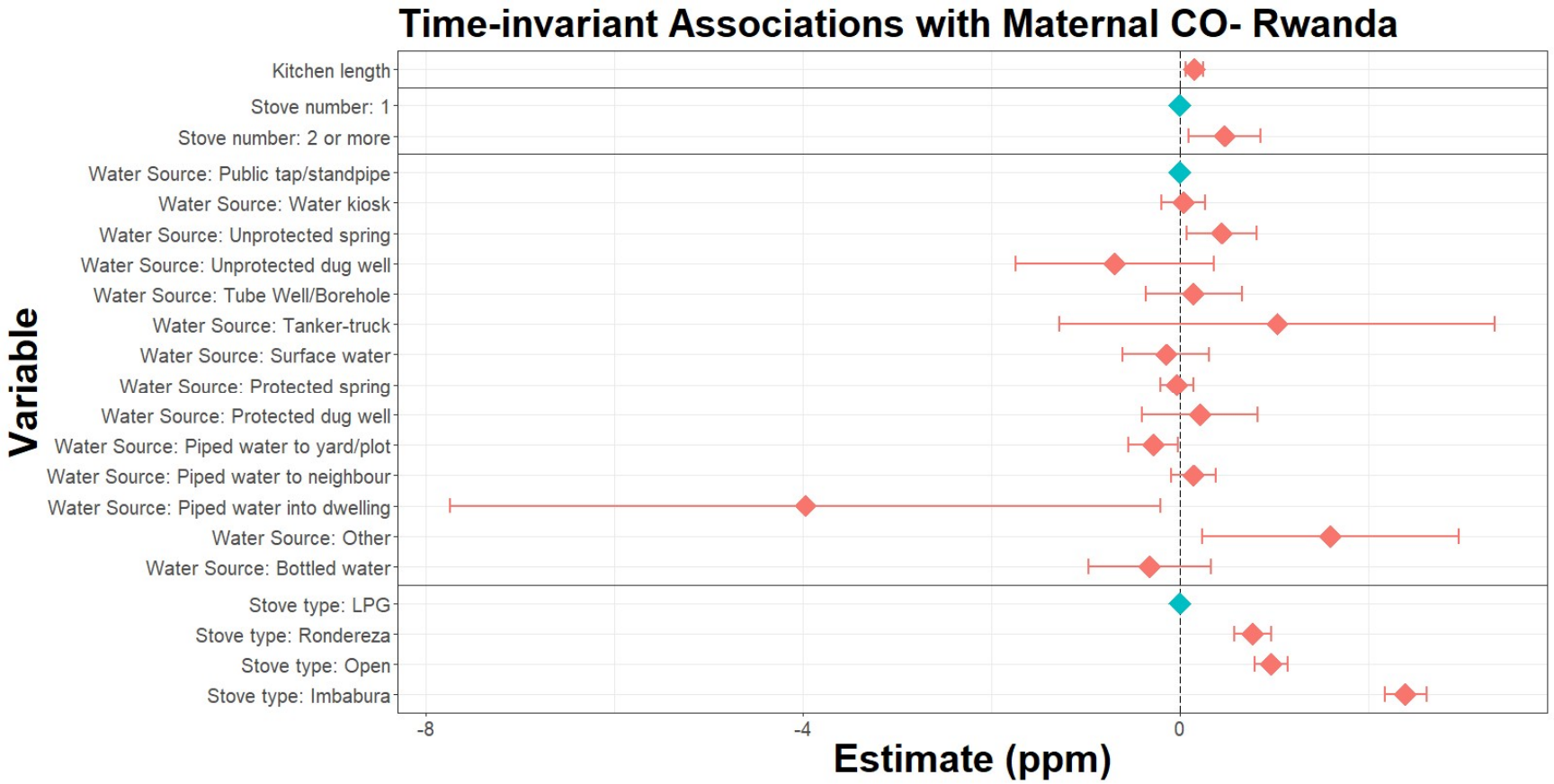

Fig 4.S7 Forest plots of effect estimates (ppm) with 95% CI for Rwanda multivariable fixed-effects model for time-invariant variables. Reference groups are blue diamonds.

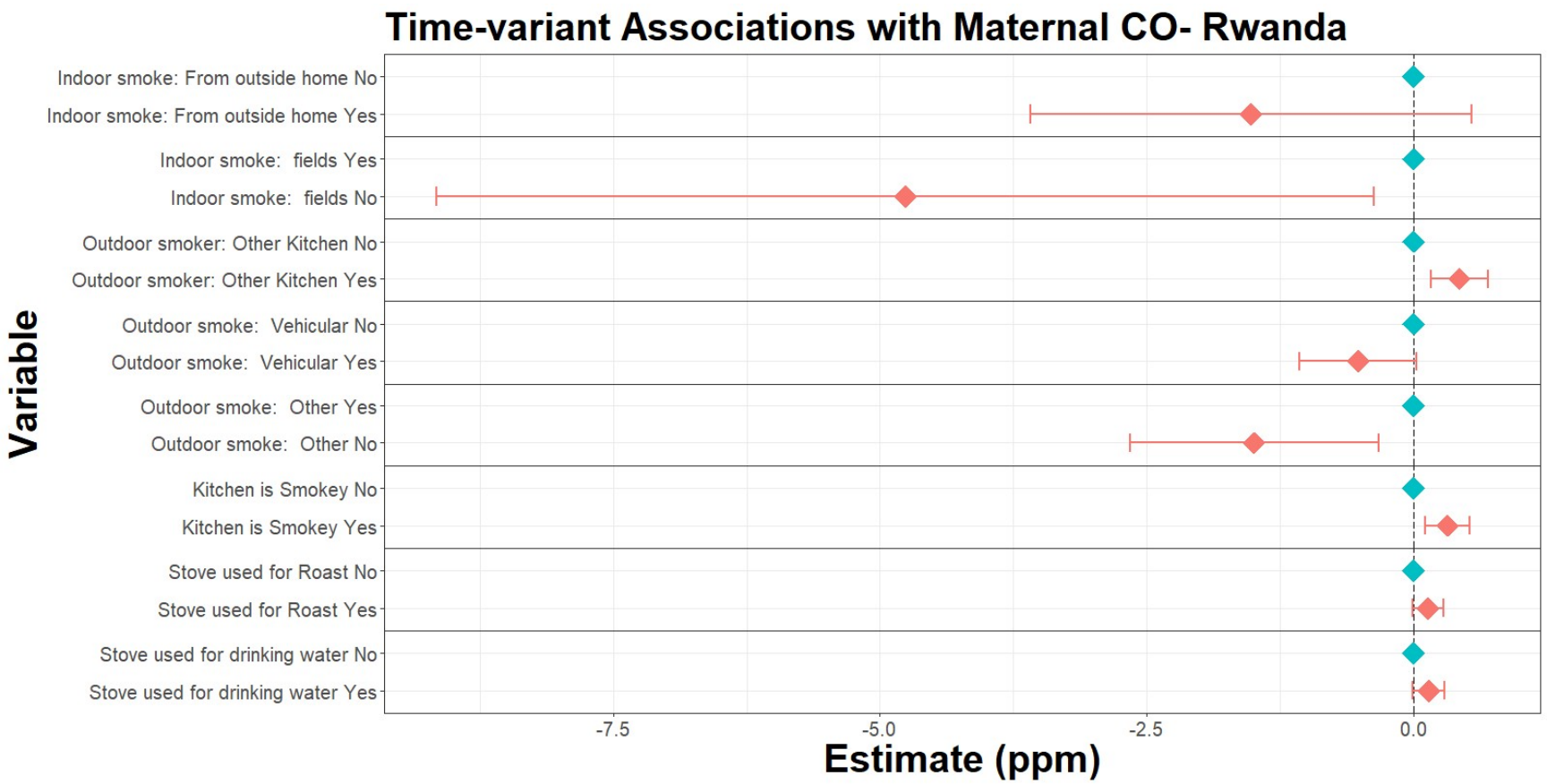

Fig 4.S8 Forest plots of effect estimates (ppm) with 95% CI for Rwanda multivariable fixed-effects model for time-variant variables. Reference groups are blue diamonds.

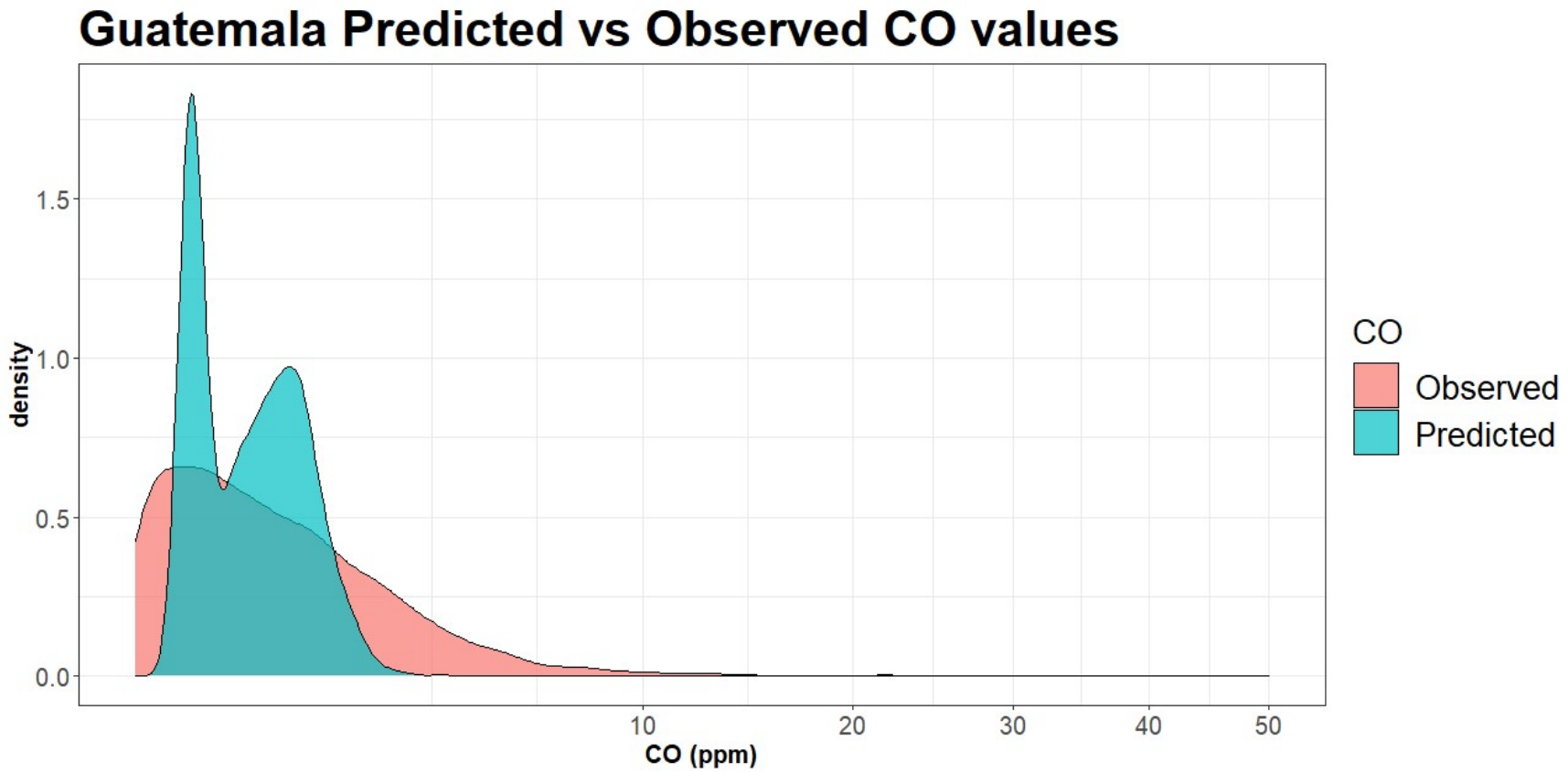

Fig 4.S9 Predicted (blue) and observed (red) CO concentration distributions for Guatemala using site-specific backwards selection model.

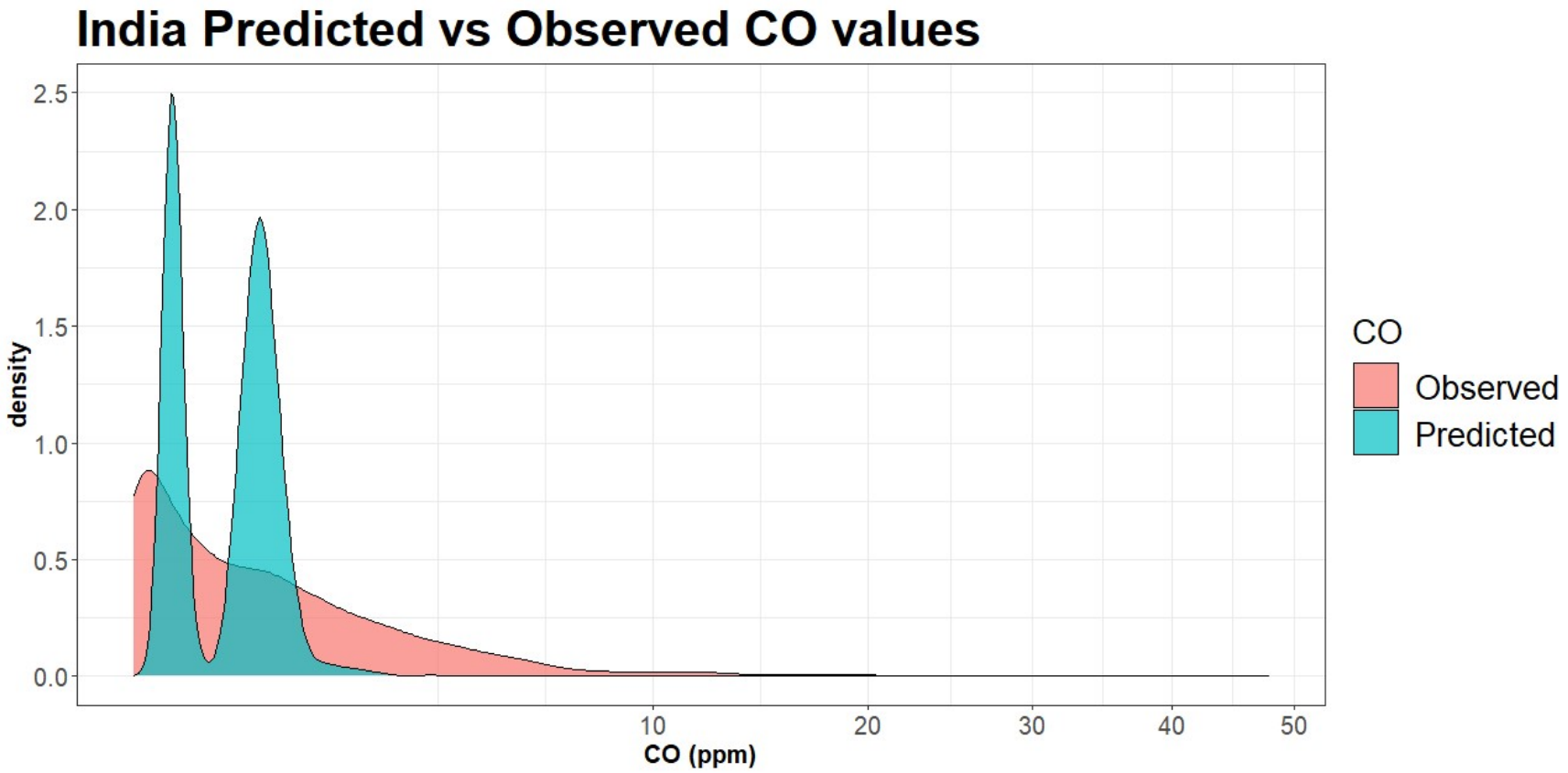

Fig 4.S10 Predicted (blue) and observed (red) CO concentration distributions for India using site-specific backwards selection model.

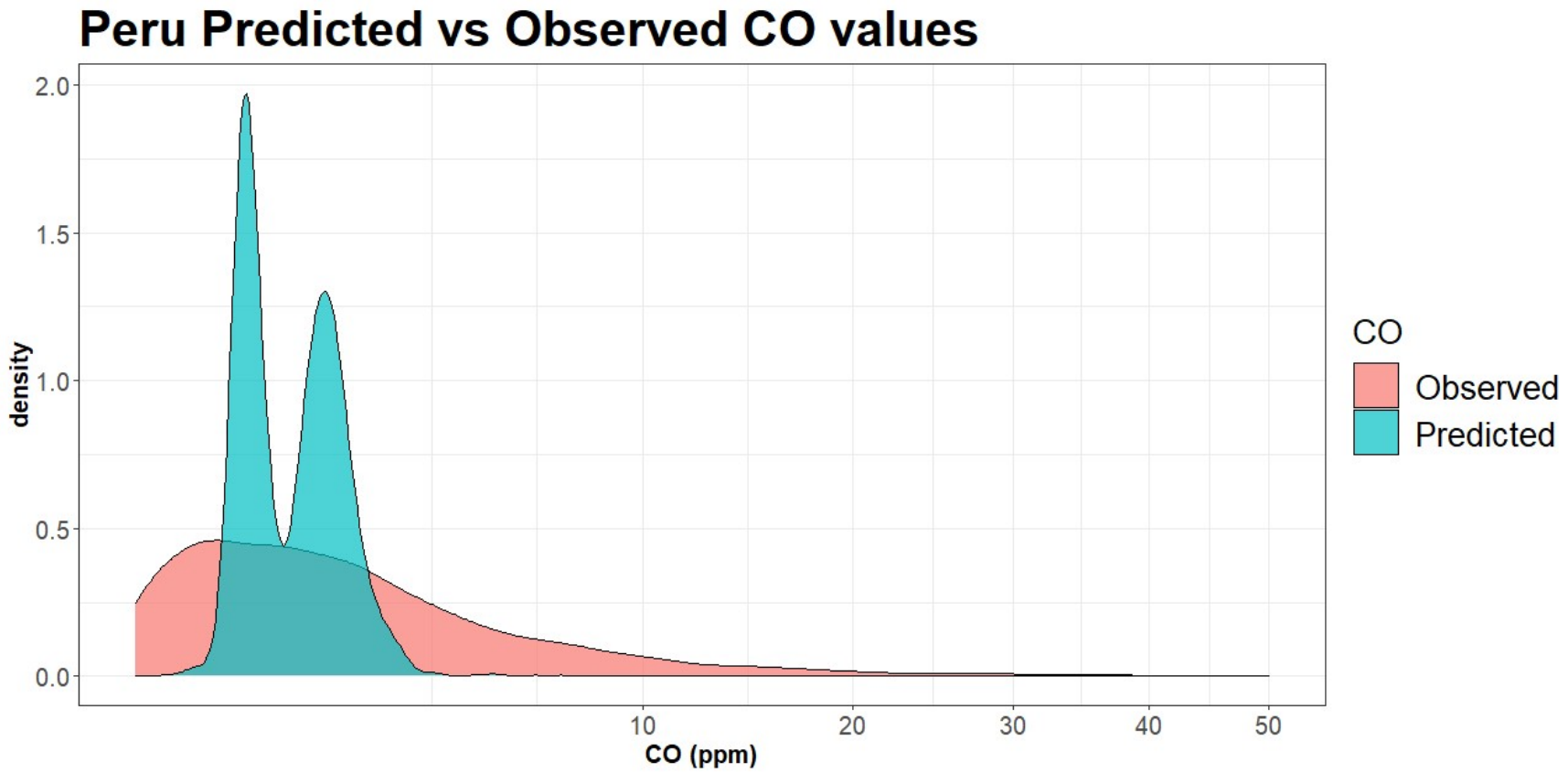

Fig 4.S11 Predicted (blue) and observed (red) CO concentration distributions for Peru using site-specific backwards selection model.

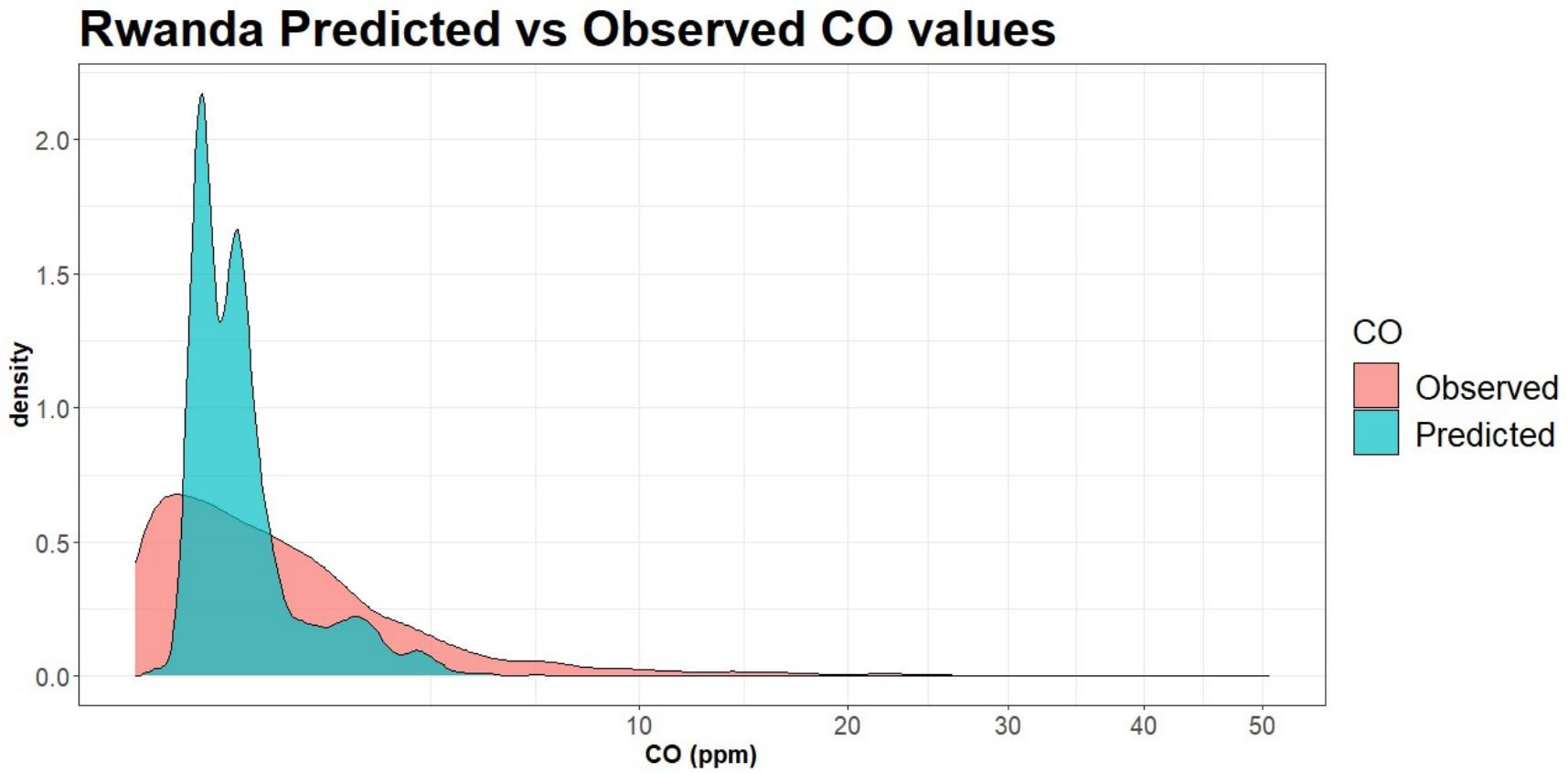

Fig 4.S12 Predicted (blue) and observed (red) CO concentration distributions for Rwanda using site-specific backwards selection model.

CHAPTER 5

RELATIONSHIPS OF PERSONAL EXPOSURES TO FINE PARTICULATE MATTER ($PM_{2.5}$), CARBON MONOXIDE (CO), AND BLACK CARBON (BC) AMONG PREGNANT WOMEN IN GUATEMALA, INDIA, PERU, AND RWANDA AS PART OF THE HOUSEHOLD AIR POLLUTION INTERVENTION NETWORK (HAPIN) TRIAL[3]

[3] Jacob R. Kremer, Michael Johnson, Lance A. Waller, Ajay Pillarisetti, Wenlu Ye, Ricardo Piedrahita, Devan Campbell, Katherine A. Kearns, Erick Mollinedo, Maggie L. Clark, Kendra Williams, Lindsay J. Underhill, Jiantong (Jean) Wang, John P. McCracken, Anaité Díaz-Artiga, Florien Ndagijimana, Ephrem Dusabimana, Kyle Steenland, Ghislaine Rosa, Kalpana Balakrishnan, Lisa M. Thompson, Laura Nicolaou, William Checkley, Jennifer L. Peel, Thomas F.Clasen, Luke P. Naeher, and HAPIN Investigators. To be submitted to *Journal of Exposure Science & Environmental Epidemiology*

Abstract

Background: Household air pollution (HAP) exposure assessment is often evaluated using a singular pollutant approach. However, HAP is a mixture of pollutants that results in various health effects. Because of these specific health-pollutant pathways, there is growing interest in looking at how multipollutant relationships and correlations differ between biomass and cleaner burning stoves.

Methods: Within the randomized controlled HAPIN trial, we investigated fine particulate matter ($PM_{2.5}$), carbon monoxide (CO), and black carbon (BC) concentrations in 3,195 households split evenly between traditional and LPG intervention stoves in Guatemala, India, Peru, Rwanda over one baseline and two post-randomization exposure visits. We estimate three types of correlations among pollutants: an unadjusted Pearson's R^2, averaged concentrations by household visit, and removal of the top 5 percentile of points. Wilcoxon Rank-Sum were used to test for differences in CO:$PM_{2.5}$ and BC:$PM_{2.5}$ mass ratio stratifying by study sites and study arms. Additionally, we used linear regressions to compute partial correlations to attribute proportions of additional variation in mass ratios to questionnaire variables, such as other sources of smoke, fuel type, and stove type.

Results: We analyzed a total of 7,673, 7,165, and 7,650 personal exposure $PM_{2.5}$, BC, and CO observations, respectively. HAPIN-wide post-randomization, correlations between CO and $PM_{2.5}$ were higher for the biomass arm (0.47) than the LPG arm (0.05). HAPIN-wide post-randomization, BC and $PM_{2.5}$ correlations were strong in both biomass (0.80) and LPG (0.66) arms. We also found that averaging concentrations from repeated household visits had the strongest correlations between pollutants in the intervention and control arms, respectively (CO:$PM_{2.5}$- 0.012 (intervention) , 0.422 (control); BC:$PM_{2.5}$- 0.685, 0.850). Median CO:$PM_{2.5}$

mass ratios were lower in the intervention group compared to the control group at each study site and there was large intra-site variation by site (Guatemala= 12 (control) vs 7 (intervention); Rwanda= 11 vs 7; Peru= 35 vs 32; India= 11 vs 1). Most of the mass ratio variation between pollutants was attributable to site and arm differences, and kerosene use, roasting meats, and fuel type used as explanatory variables.

Conclusion: This study demonstrates the importance of considering multipollutant correlations and highlights how variable correlations among pollutants can be between biomass and cleaner burning stoves. Additionally, the significant differences in mass ratios emphasize the role of site-specific and arm-specific factors in HAP exposure assessment.

Introduction

Globally, nearly 3 billion people still rely on solid fuels including wood, dung, charcoal, and other plant material for cooking and heating [2]. Often these fuels are inefficiently burned in poorly ventilated environments resulting in household air pollution (HAP) exposure to fine particulate matter (aerodynamic diameter ≤ 2.5 μm; $PM_{2.5}$), carbon monoxide (CO), and black carbon (BC) [30,31]. HAP ranks in the top ten overall and second in occupational/ environmental risk factors for disability adjusted life years with majority of the burden in low- and middle-income countries (LMICs) [27]. High levels of exposure to these pollutants is associated with multiple adverse health outcomes including increased blood pressure, reduced birthweight, and increased incidence of acute lower respiratory infection [32–35]. Much of the investigation into health effects is done with one pollutant and one outcome of interest. So, while exposure-assessment and exposure-response often focus on individual HAP pollutants, comparisons of co-emissions are far less investigated.

For various reasons, many HAP studies opt to use single pollutant exposure measures, which only allows for one pollutant exposure-response analyses [99]. Singular pollutant exposure-response could be misleading as some HAP pollutants might have different health effects because of the nature of the pollutant. For example, BC can have specific health consequences, including the ability to penetrate the placental barrier during pregnancy [43]. On the other hand, CO is commonly associated with cardiovascular effects such as blood pressure, angina, and myocardial infarction [17,154,178]. In turn these pollutant-health pathways may result in different exposure-response computations. Different pathways are exemplified with one recent study that has shown that BC was associated with low birth weight, but $PM_{2.5}$ and CO were not significantly associated for pollutant exposure-response analyses for low birth weight [51]. Similarly, another study found that BC was more strongly associated with asthma attacks than the total $PM_{2.5}$ fraction [179]. A BC meta-analysis found that estimated health effects were greater for BC than for either PM_{10} or $PM_{2.5}$ suggesting that the effect of BC might be larger than that of the total particulate fraction [12]. The exposure-response differences between pollutants leads to questions about what the effect of interventions are on co-emission of pollutants.

This potential exposure misrepresentation has led to many studies using multipollutant exposure assessment for a variety of metrics including correlations and modeling. CO is often used as a proxy to determine $PM_{2.5}$ concentrations because of their positive correlation, especially for personal samples because of the ease and cost of collecting CO compared with $PM_{2.5}$ [100,101]. However, this proxy approach is not consistently validated, particularly in low emission settings [175]. BC and $PM_{2.5}$ correlations are becoming more frequently used and often have high ($R^2 > 0.7$) correlations as BC, unlike CO, constitutes a part of $PM_{2.5}$ [104,105].

Another way that pollutant relationships can be evaluated is by computing mass ratios. Mass ratios can help determine sources of smoke and combustions efficiency, as one previous study has shown that the BC:$PM_{2.5}$ mass ratios from biomass burning is higher compared to that from residential coal burning [108]. However, further investigation is needed into how LPG interventions alter the BC mass ratio of $PM_{2.5}$ compared to biomass burning. Fewer such studies have evaluated CO:$PM_{2.5}$ mass ratios, but some have found that cleaner fuels reduced these mass ratios [101,109]. CO:$PM_{2.5}$ mass ratios might also be important for HAP interventions using LPG as methane and NO_2 are known to be emitted from such stoves while emitting close to no $PM_{2.5}$ [142]. To help ensure that CO is also not being co-emitted with other gases, CO:$PM_{2.5}$ mass ratios can be used to evaluate multi-pollutant reductions simultaneously. To address how correlations and mass ratios can be used to evaluate LPG intervention success, we leverage one of the largest HAP exposure assessment campaigns monitoring CO, BC, and $PM_{2.5}$. This study aims to leverage 3,195 households in the HAPIN randomized trial in Guatemala, India, Peru, and Rwanda to explore how mass ratios and correlations of pollutants vary for traditional versus LPG stoves.

This study aims to characterize relative exposures between pairs of pollutants and to explain observed variations in the CO:$PM_{2.5}$ and BC:$PM_{2.5}$ correlations and mass ratios. Our study also aims to investigate the inter- and intra-variation of the mass rations in four LMICs based on study arm, stove type, and other key covariates within the large multi-country Household Air Pollution Intervention Network (HAPIN) trial.

Methods

Study Design

HAPIN is a randomized controlled trial (RCT) assessing the efficacy of a liquified petroleum gas (LPG) stove intervention on health outcomes in pregnant mothers and children compared to traditional biomass stoves. Previous publications detail the overall objectives, design, and aims throughout the HAPIN study [24], along with exposure assessment [140] and biomarker [139] methodology. Briefly, 3,200 households were split evenly in four LMIC intervention research centers (IRCs) (Peru, Guatemala, Rwanda, India) for a total of 800 houses per IRC, 400 in each study arm. One main aim of HAPIN is to determine the effect of an LPG stove and continuous supply of LPG fuel intervention on health outcomes of pregnant mothers and their children using exposure-response curves.

$PM_{2.5}$ Sampling Methods

$PM_{2.5}$ was measured using filter-based gravimetric methods with the Enhanced Children's microPEM (ECM, RTI International, Durham, North Carolina), a robust and lightweight monitor [180]. Participants wore specially designed vests or aprons to accommodate the ECM along with other exposure monitoring equipment and the inlet was placed in the breathing zone of the participant. 15mm Teflon filters housed in the ECMs were placed at 6 visits (one at baseline prior to randomization, two at pregnancy, and three post-partem) on the mothers and simultaneously in the cooking area at designated exposure visit detailed in Johnson et al. 2022. Flow rate for the ECM was 0.3 L/minute for the 24-hour exposure monitoring period. Filters were cold chain transported to respective weighing institutions. For the Guatemala, Rwanda, and Peru study sites, the filters were weighed at University of Georgia, and the India site were

weighed at Sri Ramachandra Institute of Higher Education and Research. Weighing (Sartorius Cubis, Göttingen, Germany) was conducted in best accordance with the EPA weighing protocol. If a filter was damaged, then the ECM real-time light scattering nephelometric concentration was used as the concentration for that individual.

CO Sampling Methods

CO was measured using the Lascar CO-USB Datalogger (Lascar Electronics, Erie, PA) using integrated real-time measures. The Lascar logged every 60 seconds for 24-hours with a resolution of 0.25 ppm ranging from 0-300 ppm. Lascars were calibrated using span gas monthly. Further, visual inspection was performed on the real-time traces of all CO files to remove artifactual monitor files with protocol similar to previous trials [134]. Lascars were collocated on mothers, children (at the three birth exposure visits), and kitchens with the ECMs at the same time points for $PM_{2.5}$ collection. For CO:$PM_{2.5}$ mass ratios CO was converted from parts per million to $\mu g/m^3$ using the following equation where 28.01 is the molecular weight of CO and 0.0409 is the gas constant:

$$CO(ug/m^3) = 28.01\ (g/mol) * 0.0409 * CO(ppm).$$

BC Sampling Methods

BC was collected with filter-based methods with the same filter and protocol as $PM_{2.5}$ collection. After the filters were weighed, BC was estimated with the SootScan OT-21 transmissometer (Magee Scientific, Berkeley, CA). Infrared light at 880nm was passed through the filter to obtain attenuation values on the filter. Using previously published methodology attenuation was converted to a BC concentration [181,182].

Statistical Analysis

We used just the first three visits pre-birth for the following analyses in alignment with previous HAPIN publications [26,141]. CO:$PM_{2.5}$ and BC:$PM_{2.5}$ correlations and ratios were explored stratified by treatment arm, IRC, and visit round for pregnant mother personal exposures. We report medians that were used for CO:$PM_{2.5}$ and BC:$PM_{2.5}$ mass ratios because of right-skewed data. We used Wilcoxon Rank-Sum Test to test mass ratio medians between study sites and treatment arms. We report three post-randomization Spearman Rho's to summarize fit of our linear regressions. First, we report similar correlations to Johnson et al. 2022 supplementary figures with unadjusted data. Second, we investigate CO:$PM_{2.5}$ and BC:$PM_{2.5}$ correlations when averaging post-randomization repeated visits together. Finally, we investigate these correlations by removing extremely extremely high (95^{th} percentile and above) values of both pollutants in the correlation to see if removing influencing points improves correlations.

To evaluate other sources of variation in mass ratio, we used linear mixed modeling to estimate associations with other potential predictors including stove use factors, fuel type, stove type, and other sources of air pollution. This was done by using IRC as a fixed effect, followed by univariately examining questionnaire variables. Unique individual household identifiers were added as a random effect accounting for the multiple participant measurements. Only linear univariate analyses were considered as a starting point for understanding variations in relative abundance. To examine how absolute values influence the ratio we examine the percentiles of $PM_{2.5}$ and BC individually within the mass ratio. All analyses were performed using R version 4.1.3.

Results

Our results included 7,165 valid BC, 7,673 valid $PM_{2.5}$, 7,650 valid CO measures. The post-randomization absolute concentrations are reported in Table 5.1 and are consistent with Johnson et al. 2022 showing large percentage decreases upon the implementation of the LPG intervention.

BC:$PM_{2.5}$

Using Wilcoxon Rank Sum tests, none of the baseline BC:$PM_{2.5}$ mass ratio medians were significantly different between treatment arms ($p>0.05$) both for site-specific and HAPIN-wide comparisons. When comparing between the two post-randomization visits by study site and arm, the only significant decrease was in the India intervention arm ($p<0.001$, estimate= -0.02, CI= -0.03, -0.01) from the first to the second follow-up visit. BC:$PM_{2.5}$ ratios in the other study sites and arms were all not significantly different ($p>0.05$). Post-randomization, BC:$PM_{2.5}$ ratios stratified by study site and treatment arm were 0.04 units larger in the intervention ($p<0.001$) in Guatemala, 0.03 units larger in the control ($p<0.001$) in India, 0.03 units larger in the control in Peru ($p<0.001$), and not statistically significant in Rwanda ($p=0.500$). HAPIN-wide, there was no significant ($p=0.057$) difference between the arms for BC:$PM_{2.5}$ mass ratios. The individual BC:$PM_{2.5}$ mass ratios, n's, and medians are further described in Figure 5.1.

Based on Figure 5.3, $PM_{2.5}$ was more strongly dependent in determining the BC:$PM_{2.5}$ ratios with lower $PM_{2.5}$ values generally leading to larger BC:$PM_{2.5}$ ratios. Alternatively, this trend is less clear in the BC percentiles where lower BC values do not equate to higher or lower mass ratios.

Building on the supplementary figures in Johnson et al. 2022, BC:$PM_{2.5}$ Spearman Rho's were generally strong in both traditional and intervention arms, respectively (Guatemala= 0.69 [traditional], 0.73 [intervention]; India= 0.78, 0.61; Peru= 0.87, 0.45; Rwanda= 0.82, 0.72; HAPIN-wide= 0.66, 0.80) (Table 4.2). Upon averaging together repeated measures, correlations improved for most (9/15) of the strata and all of the HAPIN-wide comparisons. However, we found removing the lowest and highest 5th percentile of points did not improve any of the BC:$PM_{2.5}$ correlations.

After adjusting for IRC and repeated household measures, we found only a few significant covariates that were associated with the BC:$PM_{2.5}$ mass ratios (Table 5.3). Those who used cow dung as their primary fuel source compared to wood had on average 3.6% higher BC:$PM_{2.5}$ ratios. We found that participants who used their stove for light and heating had significantly lower BC:$PM_{2.5}$ ratios 2% and 3%, respectively. Those that used the stove for multiple meals and who kerosene for purposes other than cooking, mainly in India and Rwanda, saw on average a significant 2% and 5% increase in BC:$PM_{2.5}$ ratios, respectively. No other indoor or outdoor sources of smoke were found to be significantly associated with BC:$PM_{2.5}$ ratios.

CO:$PM_{2.5}$

Three large outliers, two in India and one in Peru, were kept in the analyses to keep this dataset consistent with those previously published on this exposure dataset [159]. CO:$PM_{2.5}$ mass ratios did not significantly ($p>.05$) change after the removal of those outliers.

Using Wilcoxon Rank Sum tests, Rwanda was significantly different in the pre-randomization CO:$PM_{2.5}$ mass ratios where the intervention arm was 2.59 units lower than the

control arm. The remaining site-specific and HAPIN-wide comparisons were not significantly different between treatment arms ($p>0.05$), pre-randomization. When comparing between the two post-randomization visits by study site and treatment arm none of the visits were significantly different ($p>0.05$). Post-randomization CO:$PM_{2.5}$ ratios stratified by study site were 3.54 units larger in the control (95% CI: 2.40, 4.60, $p<0.001$) in Guatemala, 5.49 units larger in the control (4.33, 6.46, $p<0.001$) in India, and 5.49 units larger in the control in Rwanda ($p=0.500$), but not significantly different in Peru ($p=0.311$). HAPIN-wide, there was a 4.17 higher CO:$PM_{2.5}$ mass ratio in the control arm by 4.17 units (3.49, 4.85, $p<0.001$). The individual CO:$PM_{2.5}$ mass ratios, n's, and medians are further described in Figure 4.2. Evaluating the variation in the CO:$PM_{2.5}$ ratios found study site making up the largest proportion of the variation (Fig 4.1). Additionally, CO is strongly dependent in determining the CO:$PM_{2.5}$ ratios where larger CO values generally lead to larger CO:$PM_{2.5}$ mass ratios (Fig 4.4), though this trend is less clear for $PM_{2.5}$ percentile concentrations.

Continuing the investigation of supplementary figures in Johnson et al. 2022, CO:$PM_{2.5}$ Spearman Rho's were stronger in the control than LPG arms, respectively (Guatemala= 0.65 [control], 0.17 [intervention]; India= 0.65, 0.16 Peru= 0.49, 0.06; Rwanda= 0.28, 0.15). When we averaged repeated measures together, about half of the correlations improved from the original correlations (7/15), including the HAPIN-wide correlations for both arms. Like the BC:$PM_{2.5}$ correlations, removing the bottom and top 5^{th} percentile of values there were no improvements in the correlations.

After adjusting for country effects and repeated household measures, we found a few significant covariates that were associated with CO:$PM_{2.5}$ mass ratios (Table 4.3). Those using charcoal, primarily in Rwanda, on average had 82.9 higher CO:$PM_{2.5}$ units than those using

wood, while cow dung users, exclusively used in Peru, were 13.6 units lower compared to wood. Those that used their stove for roasting saw a decrease of 11.4 in the CO:$PM_{2.5}$ ratio. No other indoor or outdoor sources of smoke were found to be significant covariates for these ratios.

Discussion

The CO:$PM_{2.5}$ correlations indicate that there are certain scenarios where CO could proxy $PM_{2.5}$ with moderate correlations, particularly areas with higher pollution. Our HAPIN-wide Spearman Rho correlation value of 0.42 is comparable to similar correlations found in a similar meta-analysis [175]. We did find that there was improvement when using repeated measures and might improve more if there were more than just the two post-randomization visits to compare [183]. However, we found that low mean $PM_{2.5}$ concentration averages in the intervention arm (25.8-43.8 $\mu g/m^3$ for four sites) might lead to the reduced Spearman Rho's of a HAPIN-wide CO:$PM_{2.5}$ ρ= 0.051. Our results show that CO can be somewhat linearly related in settings where there is a wide range of exposure values for both CO and $PM_{2.5}$, which is not seen in the intervention arm.

We found that mean CO:$PM_{2.5}$ ratios consistently decreased when the intervention stove was put into place, except in Rwanda. This may offer some insight into why CO is being reduced by higher percentages than $PM_{2.5}$ with an LPG intervention. LPG is known to emit very low (<1g) CO, the lowest of any fuel-based cooking method, leading to very low personal exposures (<1ppm) [110,134]. However, $PM_{2.5}$ might not equivalently decrease because often $PM_{2.5}$ can come from external sources such as organics from food being cooked and ambient $PM_{2.5}$ from nearby cookstoves and traffic [184]. Based on our results we show that CO is being reduced from LPG in large portions compared with $PM_{2.5}$, which confirms that CO is not a pollutant of concern when

using LPG stoves. The mass ratios presented here are consistent with those found in the literature of around 10 depending on fuel source and study site [101,109,185]. This is consistent with the findings that fuel source and specific stove uses are significantly associated to the CO:$PM_{2.5}$ mass ratio. In contrast to some studies, study site accounted for the largest portion of variation in these ratios particularly in Peru. One potential reasoning for the large ratios in Peru might be due to higher elevation in combination with cooler climates than the other three study sites. Peru also had the lowest $PM_{2.5}$ exposures and the highest CO exposures, which could also be reasoning for such large CO:$PM_{2.5}$ mass ratios compared with the other sites.

BC:$PM_{2.5}$ correlations were very strong and stable between treatment arms, which could be expected as these pollutants are co-emitted from biomass burning. Both the HAPIN-wide intervention (ρ=0.66) and control (ρ= 0.84) BC:$PM_{2.5}$ correlations were stronger than those for CO:$PM_{2.5}$. BC is largely cheaper and easier to measure than $PM_{2.5}$ and could be a better proxy for $PM_{2.5}$ than CO in cases where $PM_{2.5}$ cannot be practically measured or might be missing. HAPIN-wide correlations were also stronger when households were averaged together indicating how repeat measures are critical when performing exposure assessment campaigns.

The BC:$PM_{2.5}$ ratios gave varied results depending on the study site with significant decreases in Peru and India, a significant increase in Guatemala, and no difference in Rwanda from traditional to LPG users. One potential reasoning for some these site specific results could be ambient sources of $PM_{2.5}$ that do not contribute to BC exposure such as crustal or dust signals. Dust can occur in sub-Saharan countries such as Rwanda contributing to potential non-significant differences in the mass ratios. One of the potential reasons for the larger BC proportion in intervention homes in Guatemala could be outside sources such as traffic, where BC is often found in high proportions of the $PM_{2.5}$ fraction [186]. The increased BC:$PM_{2.5}$ ratio in

Guatemala has also been seen previously in other studies reporting larger ratios in intervention households than in control [187,188]. While we found that there was no effect of the stove type in the global analyses for the BC:$PM_{2.5}$ ratio, this could indicate that the LPG stove significantly reduces the BC and $PM_{2.5}$ concentrations in approximately equivalent proportions. LPG stoves have been shown to greatly reduce BC and $PM_{2.5}$, but this is the first study, to our knowledge, to report that proportional declines are relatively equal. It is still important to note that although the BC:$PM_{2.5}$ ratio did not decline, the absolute $PM_{2.5}$ and BC both significantly declined in the LPG study arm[26].

We found that aside from the effect of study site, fuel type and stove type were most influential in our regressions predicting ratios of CO:$PM_{2.5}$. Burning charcoal and cow dung was differentially larger for the CO:$PM_{2.5}$ mass ratios compared to that from burning wood. These fuel sources may have chemical components that release more CO than wood, which would increase these mass ratios. The use of kerosene lamps was expected to significantly increase the BC:$PM_{2.5}$ ratio as kerosene has been shown to emit extremely large amounts of BC as a fraction $PM_{2.5}$, upwards of 23% [189]. The one covariate we found that was significant for both the CO: $PM_{2.5}$ and BC:$PM_{2.5}$ ratios was using the stove for roasting. In both cases the ratios were significantly lower if the stove was used for roasting. This might indicate that there is a greater $PM_{2.5}$ contribution from roasting activities including organics from food.

Similar to other studies, we report CO in the HAP setting as generally not a good predictor of $PM_{2.5}$ for LPG users [175,177]. These results contribute to the growing evidence that CO is not a reliable surrogate for $PM_{2.5}$, particularly when using real time electrochemical monitors that struggle to monitor CO accurately and reliably at low levels seen in LPG households. However, we did see that BC is much more strongly associated with $PM_{2.5}$. If there were

instances where a $PM_{2.5}$ measurement was missing and a proxy was to be used, we suggest using a valid BC measurement over the use of a CO measurement in this scenario.

This study aimed to describe ratios of the three main pollutants for the HAPIN trial and make univariate linear models to better understand relative abundance of $PM_{2.5}$ with CO and BC concentrations, and to better understand how the components of woodsmoke are related to each other.

There were three central limitations of this study. First, we do not assess how correlations between kitchen and personal monitoring compare. This would be useful as microenvironmental exposure has been shown to be another proxy option that was not considered here [144]. Second, the low 24-hour CO averages in combination with lower resolution monitors impacted our ability to finely examine the relationships between CO and $PM_{2.5}$. Despite insutrument reliability concerns, the correlations and ratios still align with has previously been reported. Finally, we did not build multivariable models for our modeling approach. For the purposes of this study, we just explore univariate models as a starting point to assess potential association and to simplify modeling results. We believe that building a multivariable model would have limited interpretability when evaluating mass ratios.

Conclusion

In this study a more consistent and stronger relationship between BC and $PM_{2.5}$ was evaluated than the CO and $PM_{2.5}$ relationship in the HAP setting. Along with overall study site effects, we found that stove type and fuel type influence pollutant correlations and mass ratios most.

Tables Figures

Table 5.1 Adapted from Johnson et al. 2022 of absolute HAPIN personal pregnant mother exposures, post-randomization. Presented are N's, means (SD), and medians.

Absolute concentrations of HAPIN personal pregnant mother exposures									
	$PM_{2.5}$ (ug/m3)			BC (ug/m3)			CO (ppm)		
	N	Mean (SD)	Median	N	Mean (SD)	Median	N	Mean (SD)	Median
Guatemala Control	656	129 (108)	94.4	640	12.1 (6.88)	11.4	659	1.82 (2.17)	1.19
Guatemala Intervention	691	32.3 (35.6)	23.4	685	4.94 (6.40)	2.77	674	0.52 (1.04)	0.16
India Control	595	106 (119)	67.4	581	11.4 (11.3)	8.67	659	1.94 (3.51)	0.77
India Intervention	607	37.9 (39.3)	26.4	594	3.85 (6.26)	2.27	643	0.39 (1.11)	0.04
Peru Control	488	65.7 (114)	28.6	447	8.57 (11.9)	4.07	461	3.40 (6.60)	1.34
Peru Intervention	553	24.2 (55.1)	14.6	510	1.95 (1.48)	1.58	494	1.31(2.25)	0.64
Rwanda Control	650	104 (95.6)	79.6	598	11.5 (9.09)	10.2	641	2.17 (3.55)	1.04
Rwanda Intervention	610	44.0 (46.3)	31.9	571	5.37 (4.97)	4.08	612	0.65 (1.11)	0.21
HAPIN Control	2389	103 (111)	70.8	2266	11.1 (9.86)	9.64	2420	2.25 (4.07)	1.06
HAPIN Intervention	2461	34.8 (44.7)	23.9	2360	4.12 (5.45)	2.77	2423	0.68 (1.44)	0.18

Table 5.2 Post-randomization BC and $PM_{2.5}$ Spearman Rho's using three methods: unadjusted, averaging of the two post-randomization concentrations, and removal of the 95th percentile and above for each pollutant. Highlighted values are the strongest correlations of the three methods.

Spearman Rho's for CO:$PM_{2.5}$ and BC:$PM_{2.5}$ using three different strategies

		CO:$PM_{2.5}$			BC:$PM_{2.5}$		
	Arm	Original	HHID Averaged	Below 95th percentiles	Original	HHID Averaged	Below 95th percentiles
Guatemala	Control	0.657	0.704	0.585	0.704	0.706	0.659
	Intervention	0.166	0.134	0.125	0.729	0.772	0.702
	Both	0.602	0.637	0.574	0.873	0.886	0.880
India	Control	0.645	0.625	0.600	0.792	0.781	0.713
	Intervention	0.160	0.115	0.083	0.608	0.633	0.507
	Both	0.544	0.558	0.493	0.800	0.816	0.747
Peru	Control	0.489	0.483	0.355	0.843	0.836	0.839
	Intervention	0.063	0.130	0.053	0.454	0.414	0.325
	Both	0.336	0.395	0.235	0.706	0.708	0.630
Rwanda	Control	0.275	0.210	0.260	0.812	0.807	0.782
	Intervention	0.148	0.156	0.046	0.719	0.711	0.677
	Both	0.404	0.394	0.296	0.854	0.854	0.836
HAPIN-wide	Control	0.469	0.443	0.418	0.812	0.814	0.776
	Intervention	0.051	0.012	0.009	0.657	0.685	0.645
	Both	0.421	0.422	0.351	0.840	0.850	0.835

Table 5.3 Significant covariates for BC: $PM_{2.5}$ mass ratios with n's. * is significant at p<.05 ** is significant at p<.001.

Significant covariated for a mixed effect BC:$PM_{2.5}$ ratio model		
Variables	HAPIN-wide N	Global BC:$PM_{2.5}$ Beta
Household Characteristics		
Fuel Type (Wood ref)	3900	*ref*
Cow Dung	1024	0.036**
Behavior Characteristics		
Stove used for light (no ref)	5404	*ref*
Yes	60	-0.023*
Stove used for heat (no ref)	5359	*ref*
Yes	105	-0.034**
Stove used for multiple meals (no ref)	3600	*ref*
Yes	1864	0.015**
Stove used for roasting meats (no ref)	2373	*ref*
Yes	2944	0.011**
Use kerosene (not for cooking) (ref no)	5188	*ref*
Yes	276	0.045**

Table 5.4 Significant covariates for CO:$PM_{2.5}$ mass ratios with n's. * is significant at p<.05 ** is significant at p<.001.

Significant univariate for a mixed effect CO:$PM_{2.5}$ ratio model		
Variables	HAPIN-wide N	HAPIN-wide CO:PM Beta
Household Characteristics		
Fuel Type (Wood ref)	3900	*ref*
Charcoal	333	82.9
Cow Dung	1024	-13.6
Behavior Characteristics		
Stove used for roasting (no ref)	2373	*ref*
Yes	2944	11.4**

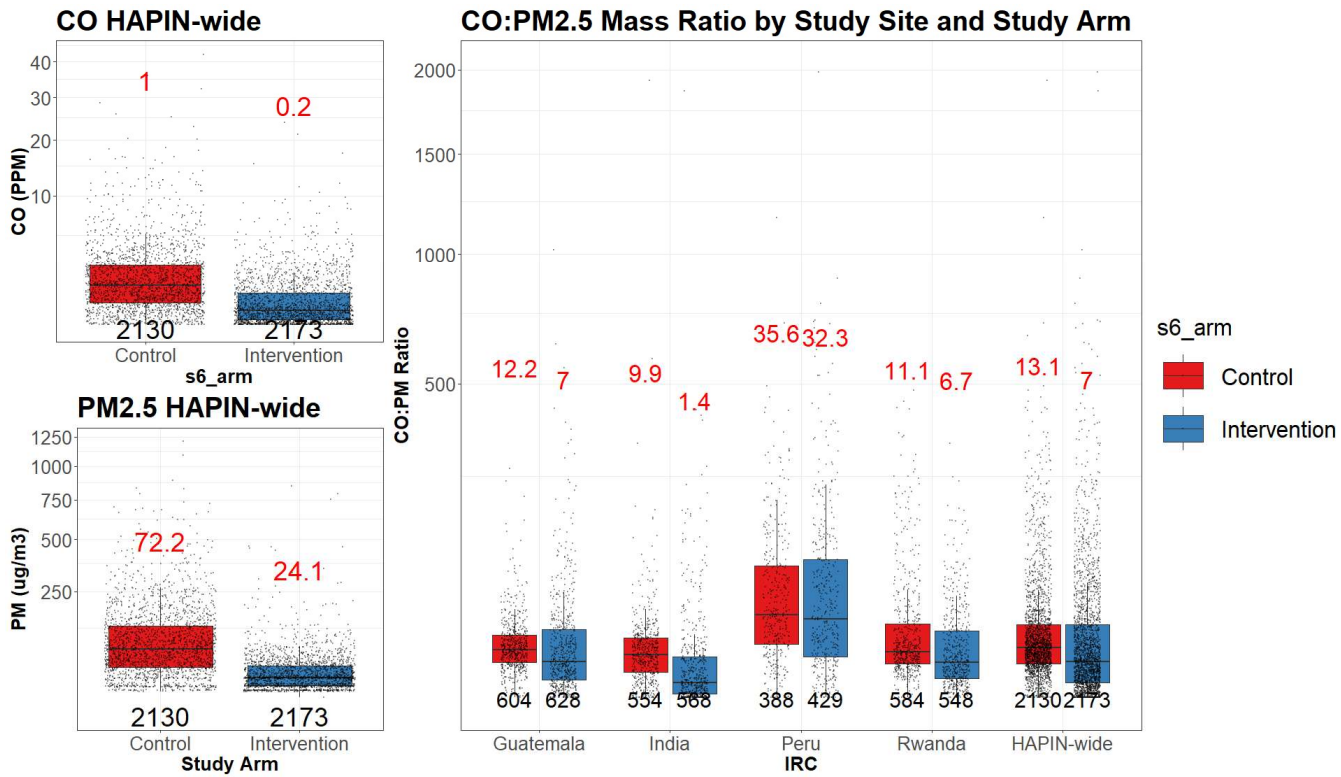

Figure 5.1 Post-randomization absolute CO concentrations (upper left), absolute $PM_{2.5}$ concentrations (lower left), and CO:PM ratios with medians (red) and N's (black) for pregnant mother exposures in the HAPIN trial.

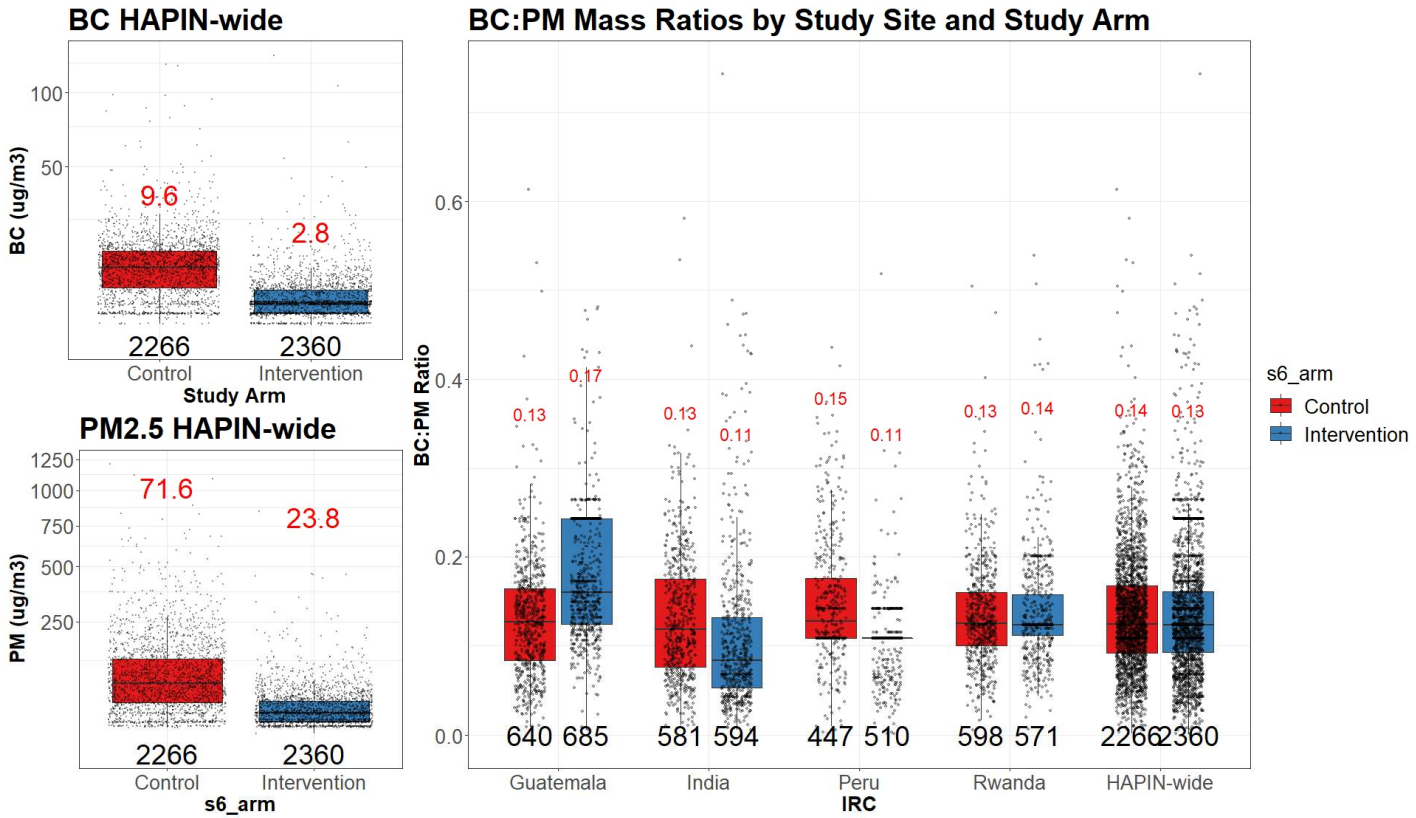

Figure 5.2 Post-randomization absolute BC concentrations (upper left), absolute $PM_{2.5}$ concentrations (lower left), and BC:PM ratios with medians (red) and N's (black) for pregnant mother exposures in the HAPIN trial.

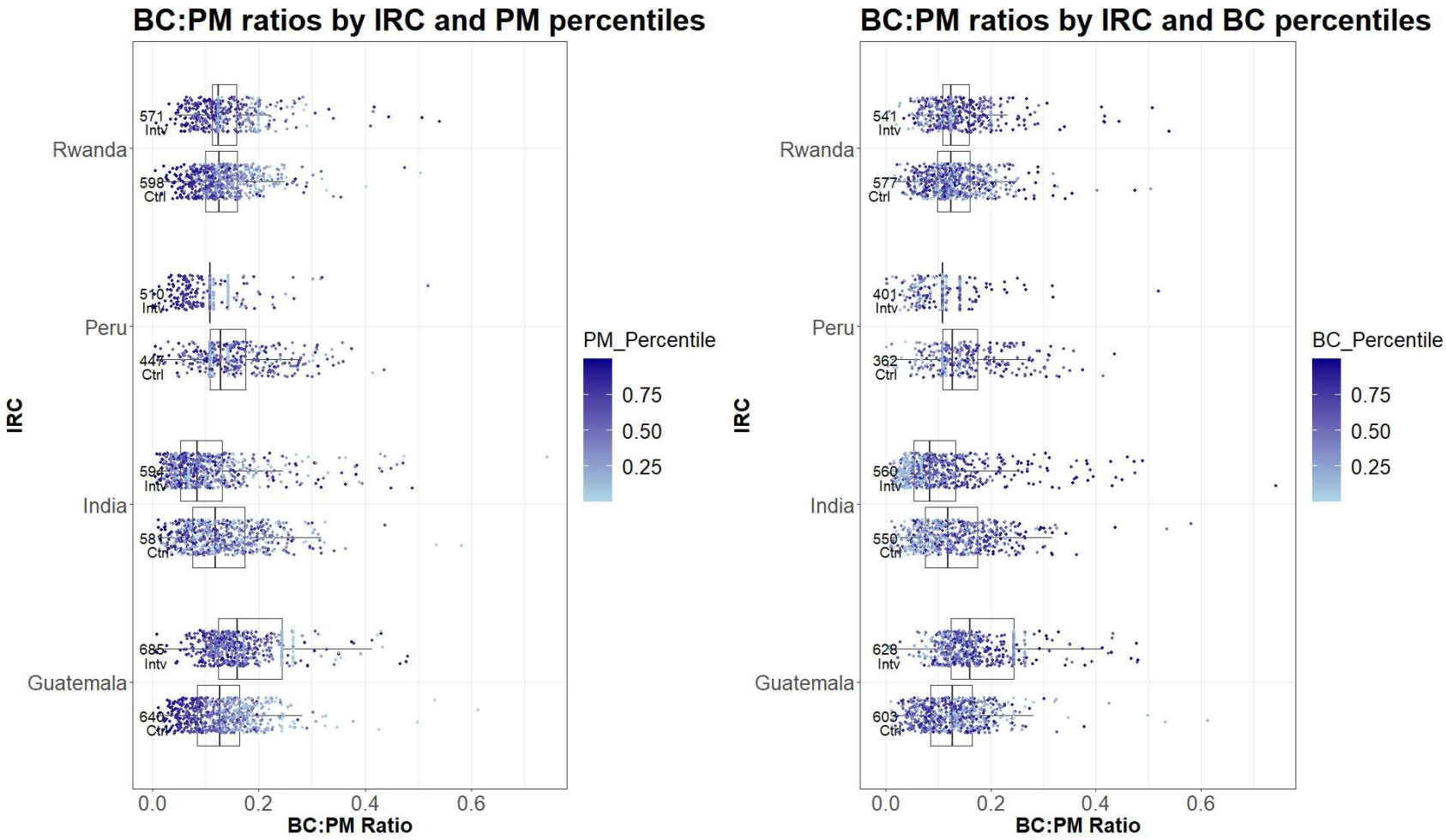

Figure 5.3 Post-randomization BC:$PM_{2.5}$ mass ratios with points filled by the percentile of $PM_{2.5}$ (left) and BC (right) concentrations grouped by IRC and stove type. $PM_{2.5}$ visually appears to be influencing the BC:$PM_{2.5}$ ratio more than BC.

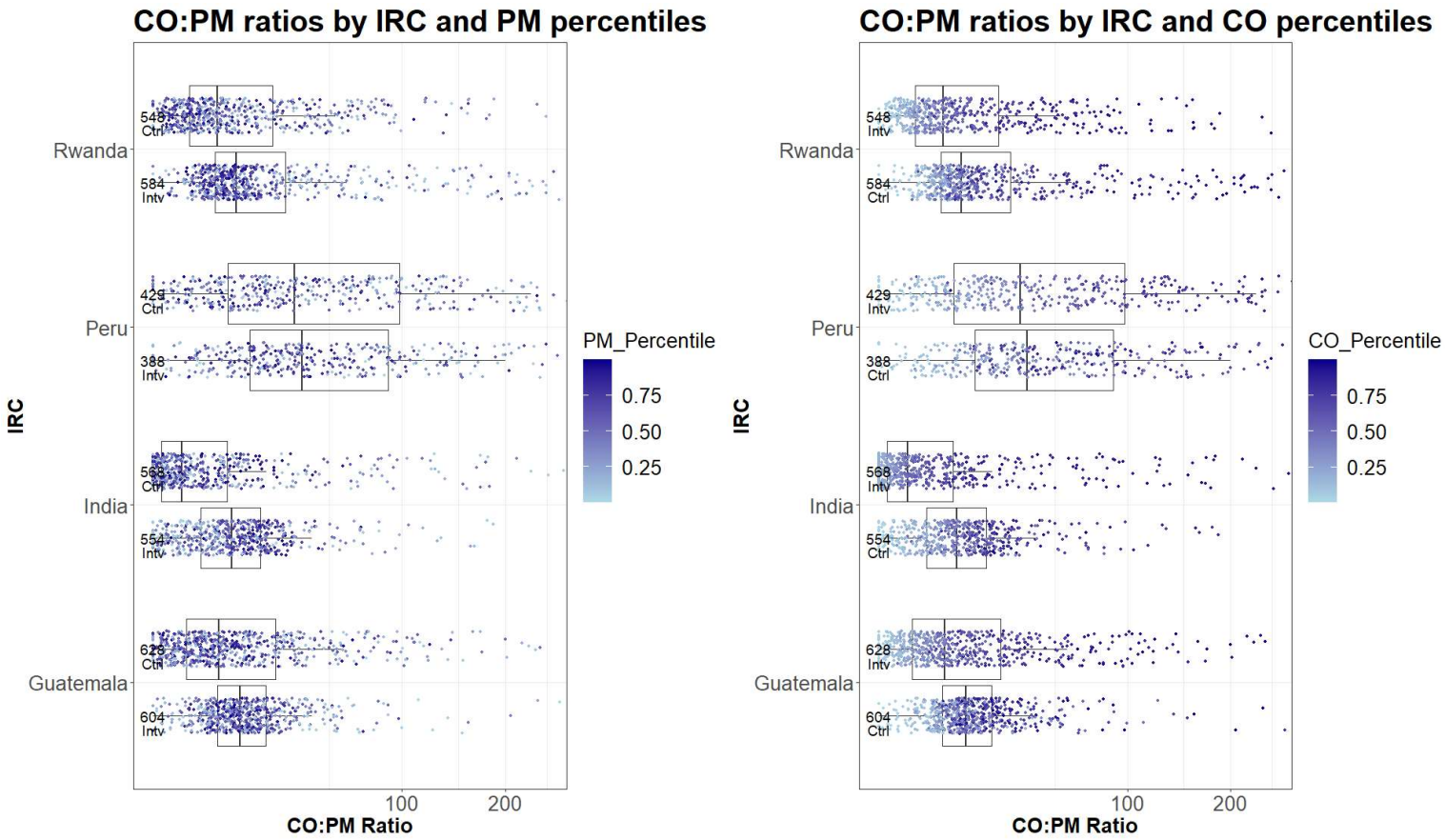

Figure 5.4 Post-randomization CO:$PM_{2.5}$ mass ratios with points filled by the percentile of $PM_{2.5}$ (left) and CO (right) concentrations grouped by IRC and stove type. Guatemala selected to further zoom in on color gradients (following page). Very clear relationship of larger CO percentile and larger CO:$PM_{2.5}$ ratio.

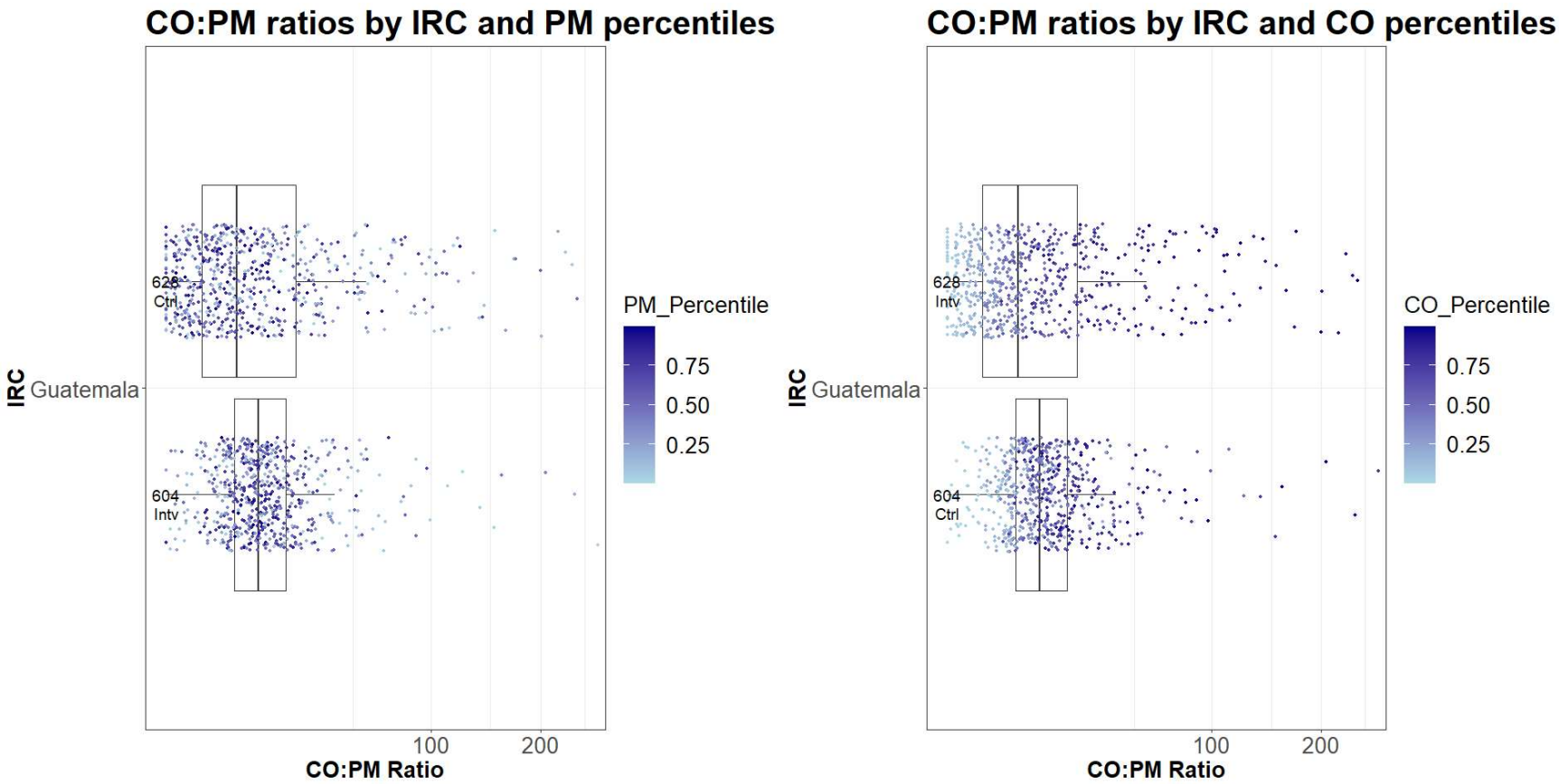

Figure 5.4a Guatemala post-randomization CO:$PM_{2.5}$ mass ratios with points filled by the percentile of $PM_{2.5}$ (left) and CO (right) concentrations grouped by stove type.

Supplemental Tables and Figures

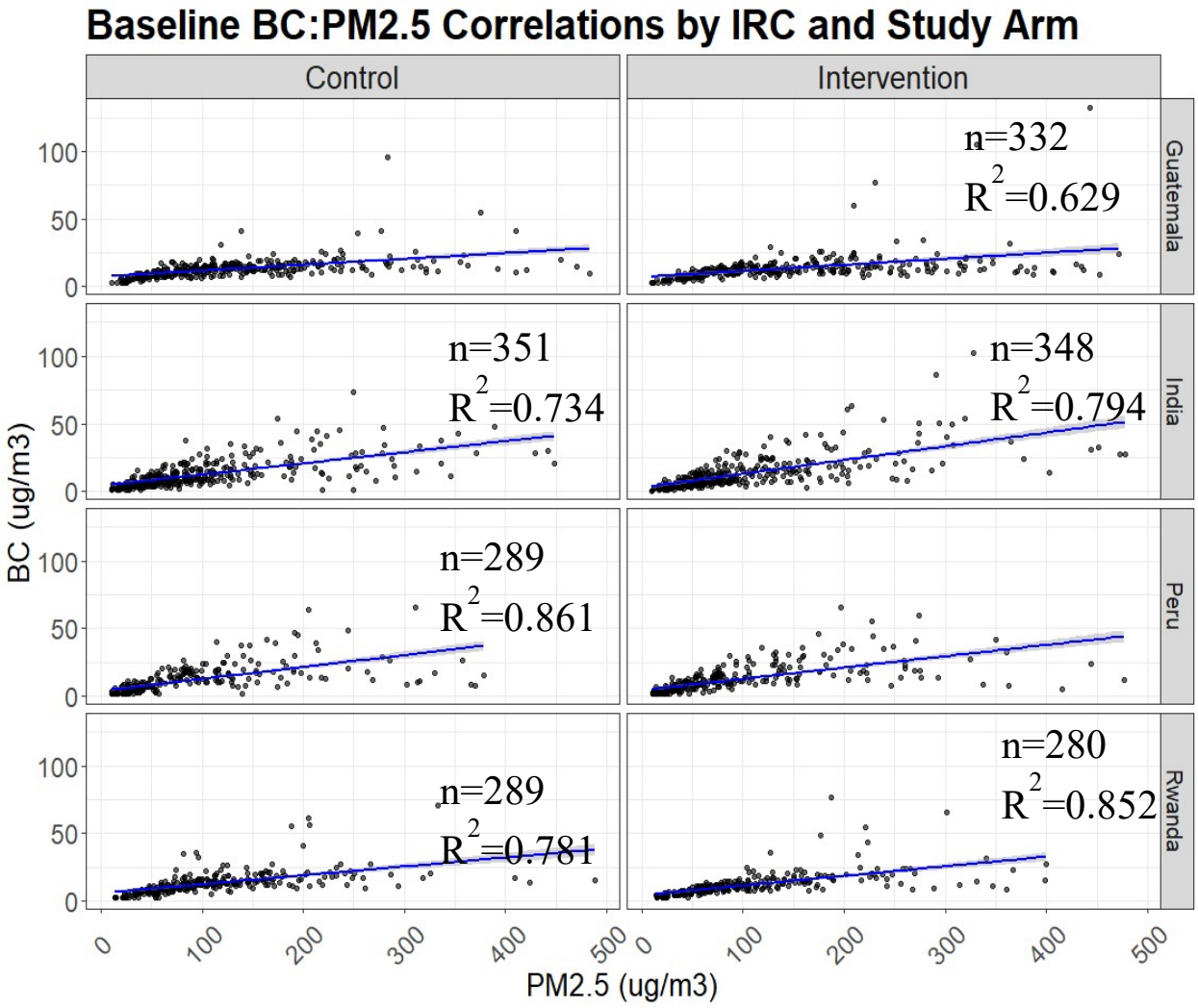

Fig 5.S1 The baseline correlations between $PM_{2.5}$ and BC, blue line indicates the linear best fit with 95% CI.

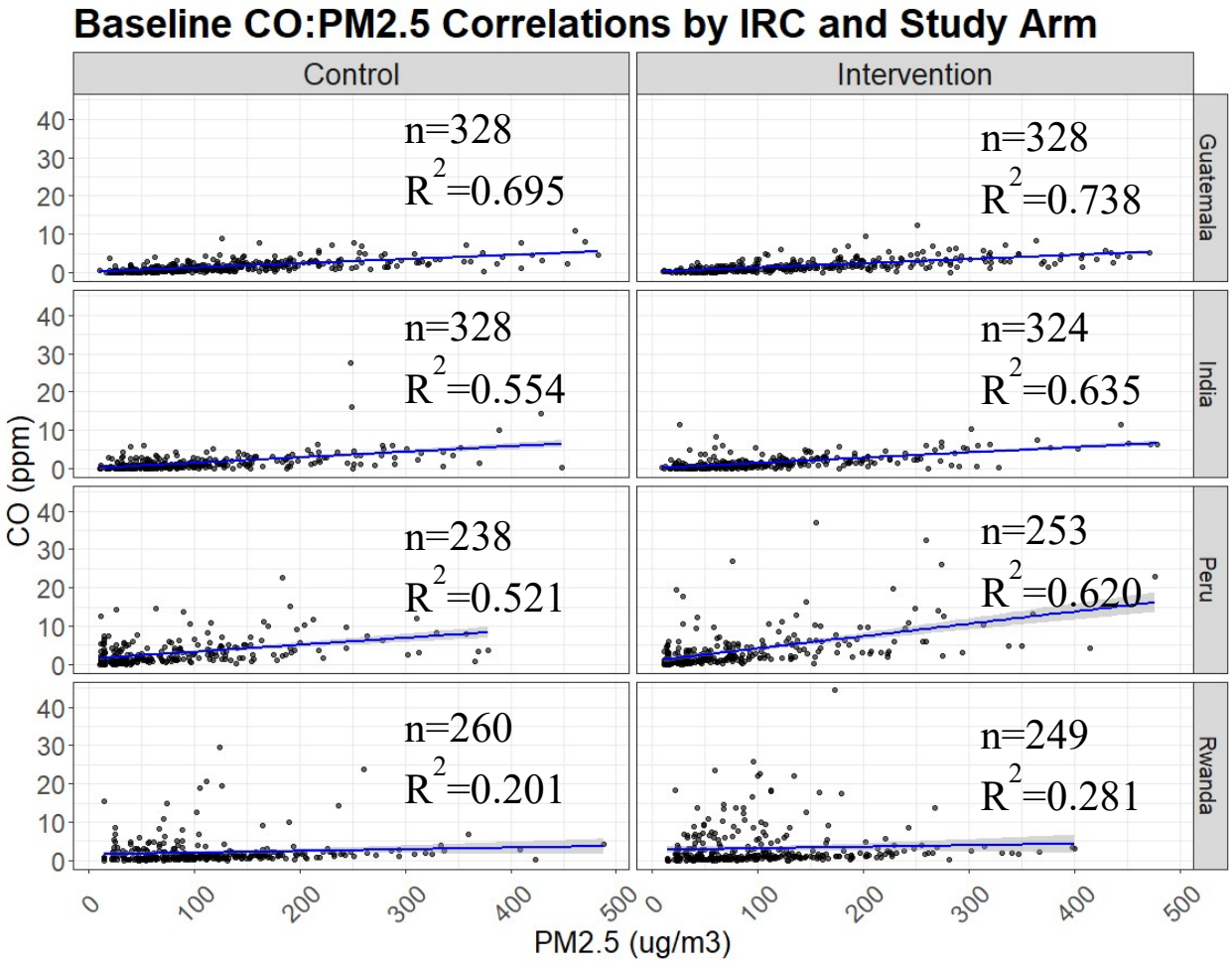

Fig 5.S2 The baseline correlations between $PM_{2.5}$ and CO, blue line indicates the linear best fit with 95% CI.

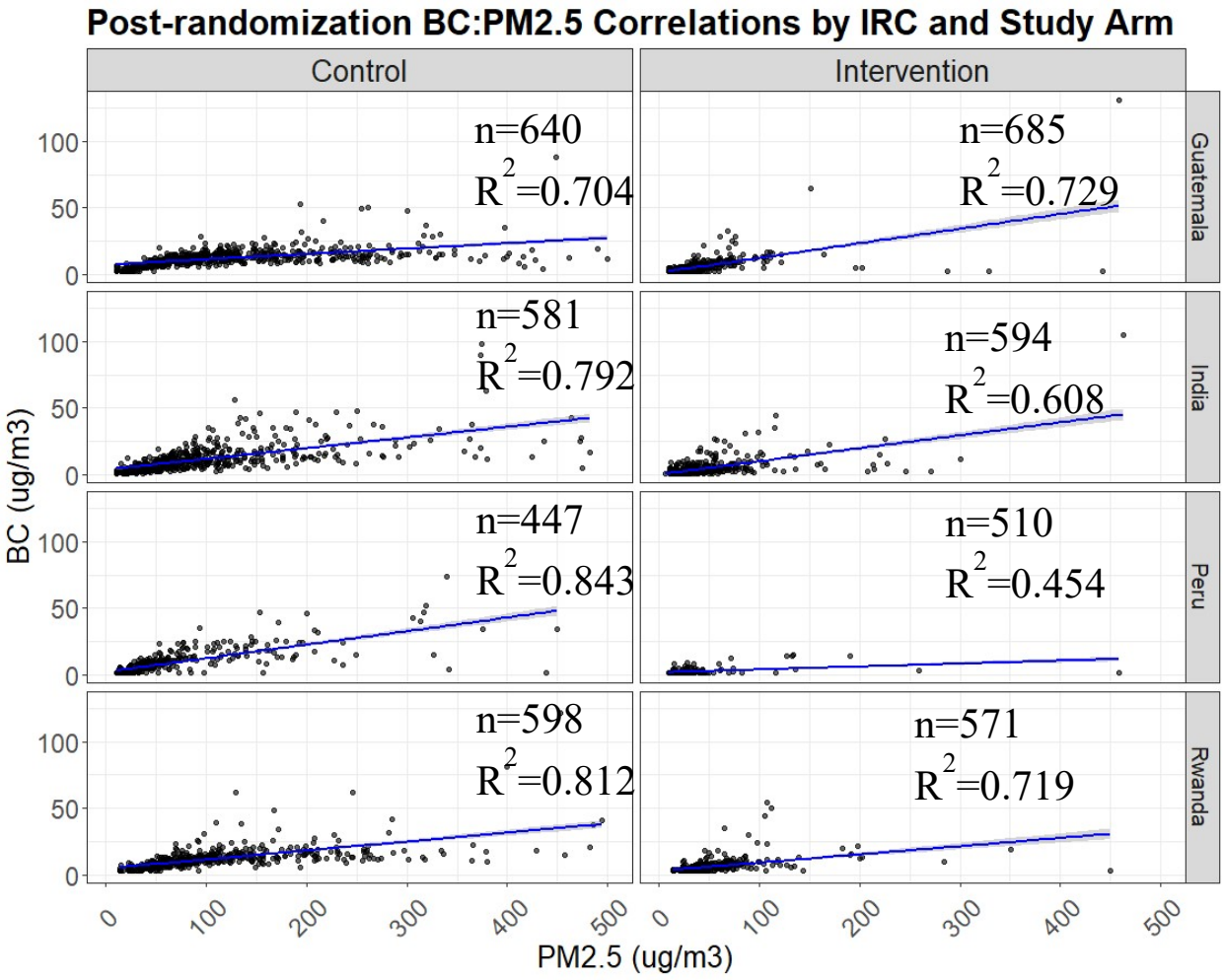

Fig 5.S3 The post-randomization correlations between $PM_{2.5}$ and BC, blue line indicates the linear best fit with 95% CI.

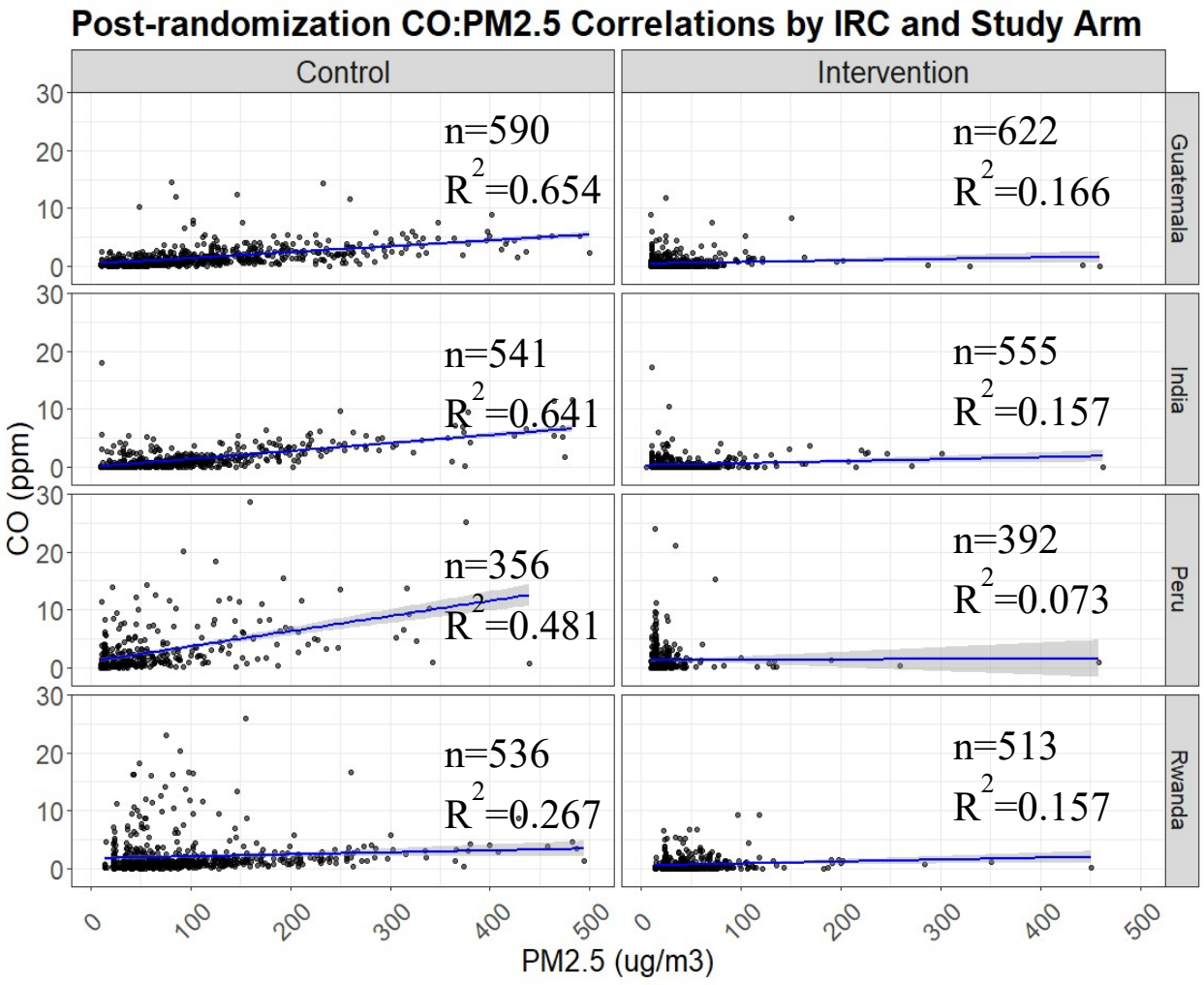

Fig 5.S4 The post-randomization correlations between $PM_{2.5}$ and CO, blue line indicates the linear best fit with 95% CI.

CHAPTER 6

SUMMARY, CONCLUSIONS, AND FUTURE RESEARCH

Summary

While there has been a declining proportion of individuals using solid fuels for cooking, there are still over 3 billion individuals worldwide that still use these high polluting fuels [2]. Much of the burden is placed on mothers and children who are often the individuals in closest contact to fires used for cooking and heating [27]. The most commonly measured pollutants in this setting are CO, BC, and $PM_{2.5}$ because of their known connection to several health effects including pneumonia, low birth weight, and high blood pressure [9,97,190]. To help address this global issue there have been several intervention trials implementing a variety of different cookstoves to reduce exposure to such pollutants. The most recent trial, HAPIN, is the largest and has the advantage of using four study sites in Guatemala, India, Peru, and Rwanda. The LPG intervention package has been shown to reduce exposures to these three pollutants, and as part of this dissertation we investigate the many other ways to look at exposure assessment to help support one of HAPIN's main aims of establishing exposure-response curves [26].

The first manuscript is a deeper investigation into CO concentrations by leveraging the real time functionality of the Lascar to assess AQG exceedances to the short-term air quality guidelines set by the WHO. The WHO has set short-term guidelines to protect from potentially harmful health effects such as low-birth weight, angina, and CVD[17,151,178]. We used maximum rolling averages of CO and compared AQGs for exceedances based on temperature and altitude for site-specific comparisons. Additionally, we consider how short-term exposures compare to

the 24-hour AQG. We found that there were significantly more exceedances for the 15-mintue, 60-minute, and 8-hour AQGs ($p<0.001$) in the control arm than the intervention arm, post-randomization HAPIN-wide. We also found Peru had the largest number of exceedances over any of the other sites and Guatemala had the fewest exceedances. Using hourly averages, there were clear temporal patterns in all four study sites. The highest CO peaks were in early morning breakfast hours (06:00-10:00) and evening dinner cooking times (05:00-08:00). There were about 4% of exposure visits and 14% of unique households where an individual exceeded either the 15-mintue, 60-minute, and 8-hour AQG but not the 24-hour AQG. These findings are important for future exposure work and understanding the role of peak exposures in the HAP setting. There are also potentially missed health effects missed from only looking at exposure-response curves with only the 24-hour averages. Future work should consider trying to link maximum time weighted averages with health effects of interest.

The second manuscript is another deeper investigation into CO, but this time through understanding the significance of other household characteristics for predicting CO. Modeling performance of HAP has varied in success with the strongest performing models using microenvironmental approaches to exposure [106,145,146]. However, few modeling approaches have used a multi-site and as in-depth questionnaire approach as HAPIN. We perform backwards selection with a targeted kitchen sink approach for both HAPIN-wide and site-specific models. We also investigate univariate associations to further explain variation seen for maternal CO exposures. Finally, we look at the effect of repeated household visits by adding a household identifier as a random effect. We found HAPIN-wide $R^2= 0.25$ with site specific $R^2= 0.30$, 0.30, 0.12, and 0.23 for Guatemala, India, Peru, and Rwanda, respectively. Most of the variation was accounted for by either study site or stove-type effects. Other associated factors were mainly

time-invariant including factors such as number of stoves, kitchen dimensions, and water source with a few time-variant factors associated such as cooking hours and stove usage variables. When investigating the effect of the repeated household measures we calculated adjusted intra-class correlation to be 0.111, HAPIN-wide. For each site we found intra-class correlation coefficients of 0.137, 0.147, 0.157, and 0.128 for Guatemala, India, Peru, and Rwanda, respectively. Our modeling results suggest that most of the CO variation could not be explained by other household factors but have similar fit to what other studies have previously found for models based solely on household factors and questionnaire variables.

The third and final manuscript discusses yet another aspect of exposure assessment with correlations and ratios of the three pollutants collected in HAPIN, CO, BC, and $PM_{2.5}$. Studies that have previously conducted correlations between pollutants found varying success with CO:$PM_{2.5}$ and strong correlations between BC:$PM_{2.5}$ [87,105]. We find correlations between pairs of pollutants with a linear mixed effect model for all values and when we average values by household. We also look at the ratio of CO:$PM_{2.5}$ and BC:$PM_{2.5}$ to evaluate how a decrease in $PM_{2.5}$ proportionally affects CO and BC. We found that averaging repeated household visits produced the strongest correlations between pollutants in the intervention and control arms, respectively, compared to non-averaged correlations (CO:$PM_{2.5}$- 0.012, 0.422; BC:$PM_{2.5}$- 0.685, 0.850). Median CO:$PM_{2.5}$ mass ratios were reduced significantly different ($p<0.001$) comparing traditional and intervention arms, respectively (Guatemala= 12 [intervention], 7 [control]; Rwanda= 11, 7; Peru= 35, 32; India= 11, 1). However, we saw post-randomization BC:$PM_{2.5}$ ratios were 0.04 larger in the intervention ($p<0.001$) in Guatemala, 0.03 larger in the control ($p<0.001$) in India, 0.03 larger in the control in Peru ($p<0.001$), and no statistical significance in

Rwanda (p=0.500). We found, like other studies, that there is a more consistent relationship between BC and $PM_{2.5}$ than CO and $PM_{2.5}$ in the HAP setting.

Overall, these unique exposure methodologies bring better understanding of maternal exposure to HAP and how LPG stoves reduce exposure to harmful pollutants. Future studies can use these methodologies to improve exposure assessment and help protect women and children around the world.

Conclusions

We found through this dissertation that there are more ways to evaluate reductions in exposure from an LPG stove. HAPIN has benefited from such intensive monitoring that it has allowed questions presented here to be answered for the first time and offers insight into novel approaches to exposure assessment.

Our evaluation of real-time CO shows how sometimes there were households that exceeded a short-term AQG but not the 24-hour, highlighting potential exposure misclassification. However, studies that use the 24-hour IT-1 should be cautious about the impact of short-term peaks as there could be missed exceedances for short-term AQGs not captured only using the 24-hour IT-1. These short-term exposures might have differential health effects compared with the 24-hour average. One insight from this study was how CO concentrations over 24-hours are low regardless of study arm. Therefore, it can be difficult to reasonably perform exposure-response analyses when CO exposure contrasts are marginal. We would suggest that future studies consider using a maximum 60-minute and 8-hour concentrations due to the wider range of exposure contrasts when using an intervention stove.

Modeling CO has continued to be a challenge in the HAP setting without the use of microenvironmental measurements. We did find that there were several time-variant and time-invariant measures that would be most helpful to measure in future studies. Despite our novel approach to creating a backwards selection kitchen-sink type approach, we find similar low R^2 values to other studies. Additionally, we find that intra-class correlation coefficients were very low indicating that the predictive ability of CO cannot be extrapolated to a participant's entire exposure. Our approach also corroborated the potential for co-benefits of installing LPG stoves with safe drinking water. Hopefully future HAP studies can learn from our approach and use different modelling methodologies when there are a large number of variables collected on participants.

Finally, we find that when looking at correlations and ratios of pollutants there might be benefits to using an averaged by household method for correlating pollutants if using a proxy method for exposure assessment, particularly with CO:$PM_{2.5}$. We also found that despite previous studies finding variability in the CO:$PM_{2.5}$ correlations that in highly polluted settings there were stronger correlations in the intervention arm compared to the control arm. The variations in the ratios between study sites we find are the result of nearly equivalent percent reductions in both BC and $PM_{2.5}$. When we looked at the percentiles of each pollutant within the ratio, we found that $PM_{2.5}$ was the main influencing factor in the ratios for the BC:$PM_{2.5}$ ratio. There is still much work to be done to further understand how pollutant mass ratios might affect health as BC is becoming more prevalent in exposure assessment studies in the HAP setting.

Future Research

With the size, multi-site, and wide exposure assessment within HAPIN there are several questions that remain to be answered. Exposure assessment is a costly and time-intensive part of intervention HAP trials that often have many flaws. However, HAPIN has taken great lengths to have accurate monitoring and has continued to follow a subset of children until their fifth birthday. There is already evidence from the GRAPHS study that there could be differences in cognitive development at age 5 from the one-year intervention, despite returning to traditional stoves following the trial. These new insights are why HAPIN has continued to monitor these children. I believe it could be beneficial to use short-term peaks of both $PM_{2.5}$ and CO to evaluate what these children are exposed to. Therefore, we also plan to investigate these short-term CO exposures for the second half of the trial and beyond. We are also working with HAPIN epidemiologist to see how these short-term peaks are associated with risk of low birthweight. If results are stronger for the short-term exposure this could be an indication for future studies to use these short-term measurements instead of the 24-hour averages. We also plan to look at children for the sites that placed Lascars on the children to see differences in exposure to the mother and if there could be valid proxies from mother to child.

Some of the modeling results were underwhelming, but we can use what was learned from our approach to build on it for future work. This can include incorporating other pollutants in our model to see if we can make improvements and try other modeling strategies. As machine learning becomes more prominently used, I would also like to attempt to use that method to try to model CO concentrations. Another potential idea would be to see if the short-term peak exposures (i.e., maximum 15-minute, 60-minute, and 8-hour) can be modeled with more precision than that of the 24-hour average. There are so many ways to model, but we think that

future work on modeling can help studies when there are fewer exposure measurements or when attempting to proxy $PM_{2.5}$ or CO with questionnaire variables. However, there is little consensus on how to properly implement these models. In the future it would not be surprising to see models be substituted for actual exposure assessment as the cost savings would be enormous if models could somewhat accurately estimate exposures.

Finally, there is more room for improvement in how correlations can be used for future work. With so many pollutants being evaluated, it can be difficult to parse which pollutants are most attributed to health effects. We suggest future work where pollutant ratios be used in health effects studies where both BC and $PM_{2.5}$ are at high levels. This can potentially show differences of how composition of wood smoke can lead to different health outcomes. However, there is still much to be understood about how to properly interpret these pollutant ratios. As more literature comes out about LPG health effects using ratios to understand the effects of lower emitting stove could be useful. For example, LPG is known to not emit much if any CO so if the CO:$PM_{2.5}$ ratio is smaller, then there might be other sources of CO or other byproducts from LPG burning.

Working on these projects has made me appreciate how challenging but rewarding it can be with so many different team members on the HAPIN project. A study like HAPIN might never occur again, so it has been an extraordinary experience to be part of something this large and to be able to step foot at the sites themselves to see how large trials operate. This interdisciplinary team has taught me everything from epidemiology to biomarkers to biostatistics and has “added so many tools to my toolbox”. I have had an amazing and unique experience working alongside the top environmental scientists in the field and have been able to say that I have helped change the world for the better. In the future I see myself contributing to similar studies with the knowledge I have gain and to also apply these skills in other occupational and

risk assessment situations. I hope to continue making progress in the field of environmental health to improve the lives of others and use my knowledge to help others try to do the same.

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