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Translational Research on Household Air Pollution Exposure and Associated Health Impacts in Low- and Middle-income Countries

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An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
in Environmental Health Sciences
2021

Abstract

Translational Research on Household Air Pollution Exposure and Associated Health Impacts in Low- and Middle-income Countries

By Wenlu Ye

Nearly half of the world's population – about 3.6 billion people – are exposed to household air pollution (HAP) from burning solid fuels such as wood, animal dung, and coal for cooking and heating. HAP has been linked to numerous adverse outcomes and is also a drag on development and environment conservation, particularly in low- and middle-income countries (LMICs). Despite the growing research on HAP in public health, knowledge gaps remain in understanding 1) the levels and composition of this environmental exposure in under-researched areas/populations; 2) the health implication, i.e., the shape of exposure-response relationships to estimate the relative risk of associated diseases/subclinical impairment; and 3) the efficacy and effectiveness of clean household energy interventions, to achieve sufficient reduction in exposures and deliver desired health benefits.

Applying a translational research framework in environmental health sciences, the research presented in this dissertation contributed to these knowledge gaps by 1) characterizing the personal exposure to HAP in rural Tibetan women and children, a population with very few direct exposure measurements; 2) assessing the cross-sectional and longitudinal exposure-response relationship between HAP exposure and blood pressure in pregnant women; and 3) examine the effect of a liquified petroleum gas (LPG) stove and fuel intervention on gestation blood pressure.

Specifically, Chapter 2 of this dissertation reflects the T1 stage of the translational research framework in environmental health sciences: observation of environmental exposure. This chapter focuses on characterizing the personal exposure to HAP (i.e., $PM_{2.5}$, BC, polycyclic aromatic hydrocarbons [PAHs], and inorganic elements) from burning firewood and yak dung among women and children living in agricultural and nomadic villages of rural Tibet, China. We observed high personal HAP exposure in both women and children, particularly among those from the nomadic village where yak dung was used as a major fuel. There was also evidence of other sources, besides biomass burning, contributed to the personal $PM_{2.5}$ exposure in this region. Measurement results from this analysis questioned the commonly accepted assumption that biomass burning is the single most important source of air pollution exposure in rural Tibet. Strategies to reduce HAP exposure in this region should focus on not only the stove/fuel efficiency or ventilation but also other exposure sources and behavioral factors, such as traffic and garbage burning.

Chapter 3 explores the exposure-response relationship between HAP (i.e., $PM_{2.5}$, BC, and CO) exposure and blood pressure among pregnant women exclusively using biomass stoves and reflects the T2 stage of the translational research: understanding the health implication of environmental exposure. This study utilizes the baseline personal exposure and blood pressure measurements collected from 3190 pregnant women enrolled in the Household Air Pollution Intervention Network

(HAPIN) randomized controlled trial (RCT) at four different countries: Guatemala, India, Peru, and Rwanda. We found that the personal exposure levels in this pregnant women cohort were consistently above the recommended WHO IT-1 for annual $PM_{2.5}$ of 35 $\mu g/m^3$. Blood pressure values varied by country but were generally within normotensive ranges (93%). Trial-wide, among pregnant women with exposure in the highest quartile, we observed a significant association between BC and systolic blood pressure (SBP) and an indicative positive association between $PM_{2.5}$ and SBP. This study characterized personal exposure to three major household air pollutants in pregnant women using solid fuel in four diverse LMICs and illustrated the distribution and variability of blood pressure in pregnant women in their early pregnancy. The association analysis contributed to the limited evidence that HAP exposure may raise blood pressure among normotensive adults.

Analyses presented in Chapter 4 pertaining to the practice implication (T3) stage of the translational research framework. Work in this chapter assessed the efficacy of an LPG stove and fuel intervention to reduce HAP exposure and improve health. Specifically, an intention-to-treat (ITT) analysis was conducted to evaluate the intervention effects on blood pressure among pregnant HAPIN participants over their pregnancy. To explore the consistency with the ITT analysis and to further explore the association between HAP and gestational blood pressure, an exposure-response analysis was also conducted in Chapter 4 using repeated personal HAP exposure and blood pressure measurements. Results from this analysis showed that the LPG stove and fuel intervention led to a large reduction in the post-randomization personal exposures to $PM_{2.5}$, BC, and CO. However, the intervention showed no protective effect on gestational blood pressure in our low antenatal risk profile pregnant women cohort. Nevertheless, this study added to the limited evidence of the association between HAP exposure and blood pressure in pregnant women with repeated measurements in four LMICs and demonstrated the effect of the LPG stove and fuel intervention on reducing personal exposures to $PM_{2.5}$, BC, and CO.

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Acknowledgments

Getting a Ph.D. is long and tough journey. There are many who helped me along the way, and I want to take a moment to thank them.

First and foremost, I am extremely grateful to my advisors, Dr. Thomas F. Clasen and Dr. Eri Saikawa for their invaluable advice, continuous support and profound belief in my work and abilities during my Ph.D. study. I am particularly grateful for the projects and opportunities they brought to me and the unconditional support that allowed me to explore and pursue my interests beyond dissertation research. Their immense knowledge, experience, and visions have been constantly inspiring and encouraging me in all the time of my academic research and daily life. Without their assistance and dedication in every step of the process over the past four years, the completion of my doctoral research would not have been possible.

I would also like to extend my gratitude to my committee members, including Dr. Kalpana Balakrishnan, Dr. Ajay Pillarisetti, and Dr. Kyle Steenland. I am truly thankful to them for sharing their expertise, valuable guidance and encouragement that helped me overcome one after another challenges. Their assistance at every stage of the research project, insightful comments and suggestions, and passions for environmental health research have always inspired and motivated me.

I also grateful to all of those with whom I have had the pleasure to work over the past years. I want to thank Alexander Avramov, Lhamo, Tenpa, Kondro, Namlha and all others from the Duorang village who helped with the recruitment and sampling for the Tibet study. I also wish to thank the collaborators from the HAPIN trial: Dr. Jennifer Peel, Dr. William Checkley, Dr. Michael Johnson, Dr. Ricardo Piedrahita, Dr. Ashlinn Quinn, Dr. Maggie Clark, Dr. Dana Barr, Dr. Lance Waller, Dr. Howard Chang, Dr. Lisa Thompson, Yunyun Chen, Shirin Jabbarzadeh, Lisa Elon, Jean Wang, and Amy Lovvorn for their support in data and statistical analysis. Special thanks to the HAPIN India team: Saritha, Dr. Vigneswari Aravindalochanan, Dr. G. Thangavel, Dr. Naveen Puttaswamy, Dr. S. Sankar and many others in the field offices for their help to my India-specific analysis and taking great care of me during my visit.

Getting through my dissertation required more than academic support and I have many, many people to thank. I want to thank all EHS faculty, staff, and students (especially my "golden" cohort) for their heartful help, support and company in all means along this way. Special thanks to my MDP family – for putting up with me being distracted and missing many events. I am forever grateful for their friendship, understanding and another wonderful four years spent together in Atlanta.

Most importantly, none of this could have happened without my family. My grandparents, Yiwei Fan, Meiping Sun, Xingmin Liu and Donghua Ye, who offered encouragement and care, and set me off on the road to this Ph.D. a long time ago. To my parents, Jian Ye and Xiaoyu Fan, and cousin, Yanbin Hao – for providing with unfailing support and continuous encouragement throughout my years of study. This accomplishment would not have been possible without them.

Table of Contents

List of Figures

List of Tables

Chapter 1

Introduction

1.1 Background

In 2019, a third of the world population – around 2.6 billion people (2.2 – 3.1 billion) – lacked access to clean cooking fuels (e.g., electricity, liquified petroleum gas (LPG) and ethanol) and technologies; they relied on highly polluted open fires or simple stoves fueled by kerosene, biomass (i.e., wood, animal dung, and crop waste) and coal (IEA et al., 2021). Most of those are poor and living in low- and middle-income countries (LMICs) in Sub-Saharan Africa and Asia. They accounted for 81% of the global population without access to clean fuels and technologies between 2015 and 2019 (IEA et al., 2021).

These inefficient cooking practices and use of solid fuels in poorly ventilated houses produce high levels of household air pollution (HAP) with a wide range of health-damaging pollutants, including particulate matter with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$), black carbon (BC), and carbon monoxide (CO). The exposure to HAP is particularly high among women and young children, as they are usually responsible for the domestic work and spend the most time indoors (Bruce et al., 2015).

Worldwide, 3.8 million premature deaths in 2019 were attributable to HAP-related illnesses and the majority of the burden of disease were from LMICs (Health Effects Institute, 2020; Murray et al., 2020). Among these deaths, 27% were due to ischemic heart disease and another 27% were due to pneumonia. Other causes include chronic obstructive pulmonary disease (COPD) (20%), stoke (18%), and lung cancer (8%) (http://www.healthdata.org/gbd/2019). Mortality from ischemic heart disease and stoke are also affected by high blood pressure, a well-known risk factor that have been linked to $PM_{2.5}$ exposures (Brook et al., 2010).

Lacking access to clean household fuels and technologies also presents challenges with respect to climate change. Incomplete combustion of solid fuels impacts the climate through emissions of methane (CH_4), nitrous oxide (N_2O), CO, and BC (Goldemberg et al., 2018). As a potent short-lived climate pollutant, BC received substantial attention in recent household clean cooking energy programs, given the co-benefits of reducing BC on both climate and health (Butt et al., 2016; Serrano-Medrano et al., 2018; Tao et al., 2021).

Improving access to clean household energy contributes to development and gender equality. In many underdeveloped regions, collecting fuel takes a considerable amount of time from women and children and limits their opportunity and engagement in productive activities and education (World Health Organization, 2014). In addition, the use of these unclean household fuels introduces other safety concerns, such as burns, injuries, poisonings, and further constrains their opportunities for health and well-being. Therefore, access to clean household fuels and technologies becomes one of the top priorities among the Sustainable Development Goals (SDGs) set up in 2015 by the United Nations General Assembly to guide the international development agenda until 2030 (SDG 7). Expanding access to clean household energy also helps achieving other SDGs, such as SDG 1 (end poverty), SDG 3 (good health and welling), SDG 10 (reduce inequalities), and SDG 13 (climate actions).

Despite the substantial effects of HAP on human health, economic development and environment, the health impacts associated with HAP exposure are underestimated in calculations of the global burden of diseases, so as to the economic loss and environmental damage. The *Lancet* Commission on pollution and health (2018) highlighted the following research needs in pollution and pollution control that are particularly relevant to HAP:

- Identify and map pollution exposures particularly in low- and middle-income countries.
- Explore emerging causal links between pollution, disease, and subclinical impairment.
- Quantify the health and economic benefits of interventions against pollution and balance these benefits against the costs of interventions.

The scientific understanding of HAP exposure and its effects on health have greatly advanced during the last decade. New technologies/equipment and the increasing field measurements have enhanced our ability to understand the intensity, composition, and spatial/temporal patterns of HAP exposures (Arku et al., 2018; J. Baumgartner et al., 2011; Bruce et al., 2015; Chartier et al., 2017; Du et al., 2018; Lai et al., 2019; Ni et al., 2016). Epidemiological studies across the globe have shown that exposure to $PM_{2.5}$, BC, and CO, among the other pollutants, is associated with a wide range of diseases (Lee et al., 2020), especially the non-communicable diseases, including asthma (Brauer et al., 2007), cardiovascular diseases (Arku et al., 2018; Checkley et al., 2021; Fandiño-Del-Rio et al., 2017; Mitter Sumeet S. et al., 2016; Yu et al., 2018), Chronic obstuctive pulmonary diseases (COPD) (Siddharthan et al., 2018), and neurodevelopmental disorders and birth defects in children (Balakrishnan et al., 2018; Pope et al., 2010; Quinn et al., 2021; Thompson., et al., 2011). While field evaluations of clean cooking and household energy interventions in LMICs have demonstrated some evidence in exposure reduction and health effects, the achievable health benefits at population level remain unclear (Alexander et al., 2017, 2018; Aung et al., 2018; Balakrishnan et al., 2015a, 2015b; Dutta et al., 2017;

Johnson et al., 2019; McCracken et al., 2007; Mortimer et al., 2017; Quansah et al., 2017; Quinn et al., 2021; Romieu et al., 2009; Sharma and Jain, 2019).

Despite the growing body of evidence, there are still many gaps in our knowledge about HAP exposure and its effects on health. These gaps include: 1) HAP exposure levels and their composition in many countries and regions, especially in developing and industrializing countries; 2) health effects of a single pollutant, or a mixture of pollutants, from HAP; 3) the shape of exposure-response relationships used to estimate the relative risk of diseases or subclinical impairment associated with HAP; and 4) the efficacy and effectiveness of clean household energy interventions, refer to those that attain the $PM_{2.5}$ interim targets or guideline levels recommended in the WHO Air Quality Guidelines (2021), to achieve sufficient reduction in exposures, deliver desired health benefits and measurable indirect benefits.

The research presented in this dissertation is intended to help address these knowledge gaps by characterizing the personal HAP exposure and its effect on blood pressure in China, Guatemala, India, Peru, and Rwanda. Hypertensive disorders of pregnancy complicate up to 10% of pregnancies, and constituting one of the greatest causes of maternal and perinatal morbidity and mortality in the world (Task Force on Hypertension in Pregnancy, 2013). These complications include preeclampsia, eclampsia, stroke, the need for labor induction, and placental abruption for mothers, and preterm delivery and low birth weight for the baby, due to high blood pressure induced disruption in oxygen and nutrients supply (Callaghan et al., 2012; Creanga et al., 2014; Macdonald-Wallis et al., 2014; Task Force on Hypertension in Pregnancy, 2013). Elevated blood pressure during pregnancy has also been linked to long-term maternal and offspring consequences such as cardiovascular diseases (Lo et al., 2020). Blood pressure is constantly changing over the pregnancy. Although the hypertensive disorders of pregnancy are diagnosed after 20 weeks of gestation, both elevated blood pressure in early

pregnancy (< 20 weeks) and the blood pressure trajectory during the pregnancy have been associated with adverse perinatal and pediatric outcomes (Bakker et al., 2011; Guo et al., 2020; Iwama et al., 2020).

Specifically, this dissertation research aims to 1) characterize the personal exposure to HAP in Tibetan women and children, a population with very few direct exposure measurements; 2) assess the cross-sectional and longitudinal exposure-response relationship between HAP exposure and blood pressure in pregnant women; and 3) investigate the effect of a liquified petroleum gas (LPG) stove and fuel intervention on gestation blood pressure.

1.2 Context—Translational research

The ultimate goal of HAP research is to inform the strategies and interventions to curb HAP and prevent HAP-related adverse health effects. This dissertation applies the translational research framework to reflect this goal and to help contextualize its potential contribution to the field of HAP and household energy research.

Translational research is usually understood as the application of bench-to-bedside framework by which basic science discovery transitions to clinical treatment (Rubio et al., 2010). Kaufman and Curl, (2019) described a modified translational framework that is applicable to environmental health sciences while maintaining the basic structure underlying the original bench-to-bedside paradigm (**Figure 1.1**). The proposed translational research framework in environmental health sciences starts with scientific discovery (T1) through epidemiological or clinical observations. This discovery often involves understanding the potential for human health effects of exposure to given environmental chemicals. The practical application of this discovery evolves through an understanding of exposure-response relationships (T2) and identification of potential interventions to reduce exposure and improve health (T3). Implementation science then plays a crucial role in the development of

environmental and public health practice and policy interventions (T4). Outcome evaluation (T5) often takes the form of accountability research, as environmental health scientists work to quantify the costs and benefits of these interventions (Kaufman and Curl, 2019).

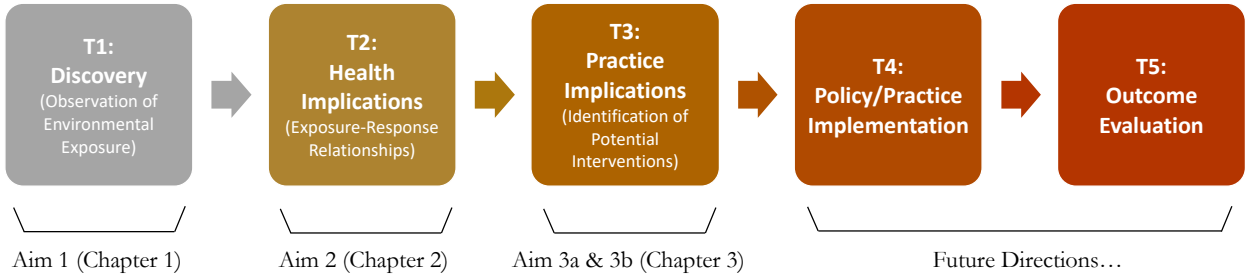


Figure 1.1 Environmental Health Sciences in a Translational Research Framework and dissertation aims (chapters), diagram adapted from Kaufman and Curl, (2019).

Aim 1 (Chapter 2) of this dissertation reflects the T1 stage of the Translational Research Framework in environmental health sciences. This study aim focuses on characterizing the personal exposure to HAP (i.e., $PM_{2.5}$, BC, polycyclic aromatic hydrocarbons [PAHs], and elements) form burning biomass fuels among women and children living agricultural and nomadic villages of rural Tibet, China. **Aim 2** (Chapter 3) explores the exposure-response relationship between HAP (i.e., $PM_{2.5}$, BC, and CO) and blood pressure among pregnant women exclusively using the biomass stoves and fuels and reflects T2 stage of the translational research: understanding the health implication of an environmental exposure. **Aim 2** utilizes the baseline personal exposure and blood pressure measurements collected from approximately 3200 pregnant women enrolled in the Household Air Pollution Intervention Network (HAPIN) trial at four different LMICs: Guatemala, India, Peru, and Rwanda. **Aim 3** (Chapter 4) assesses the efficacy of an LPG stove and fuel intervention to reduce HAP exposure and improve health. Specifically, an intention-to-treat (ITT) analysis was conducted in **Aim 3a** (Chapter 4) to evaluate the intervention effects on blood pressure among pregnant HAPIN participants over their pregnancy. To 1) explore the consistency with the ITT analysis, 2) assess the extent to which exposure

misclassification might limit the ability to detect the intervention effects, and 3) further explore the association between HAP and gestational blood pressure, an exposure-response analysis was conducted in **Aim 3b** (Chapter 4) using repeated personal HAP exposure and blood pressure measurements. Together, the **Aim 3** analyses pertain to the practice implication (T3) stage of translational research framework.

1.3 Review of Literature

1.3.1 Household air pollution exposure in Tibet

It is estimated that 41% - 75% of the rural households in China rely on solid fuels (biomass and coal) (Chen et al., 2016; Duan et al., 2014; Hou et al., 2017). In the Tibetan region, due to the traditional lifestyle and limited access to clean fuel, the percentage of household relying on solid biomass fuels (wood and yak dung) was more than 70% (Gao et al., 2009; Hu et al., 2016; Wang, 2009; Xiao et al., 2015). Despite this high consumption and potential adverse health effects due to HAP from incomplete combustion, studies that measure the personal exposure to HAP and associated health effects are extremely scarce among the Tibetan households.

Several HAP related studies have been conducted in Nam Co, central Tibet. Kang et al. (2009) measured the indoor concentrations of total suspended particles (TSP) and toxic elements, including cadmium (Cd), arsenic (As), and lead (Pb) from burning yak dung in nomadic tents. The daily indoor concentrations were 3160, 3.16, 35.00 and 81.39 $\mu g/m^3$ for TSP, Cd, As, and Pb, respectively (Kang, Li, Wang, Zhang, & Cong, 2009). In addition, Gao et al. (2009) monitored $PM_{2.5}$ concentrations in multiple microenvironments, burning different fuels for cooking and heating. The daily average $PM_{2.5}$ concentrations in kitchen, living room, bedroom, and yard were 134.9, 103.6, 76.1, and 78.3 $\mu g/m^3$, respectively (Gao et al., 2009). Their study also found that using solid biomass fuels in kitchen resulted

in higher HAP than using methane and the daily average $PM_{2.5}$ concentrations in kitchen with dung cake, fuel wood and methane use were 117.4, 271.1, and 47.0 μg/m^3, respectively (Gao et al., 2009). Li et al. (2012a) collected $PM_{2.5}$ and TSP samples from four nomadic tents using open stoves and yak dung and characterized the particle-bound trace metals and PAHs. The study suggested that the average trace metal concentrations were much higher than those of the ambient air and mean concentrations of total 13 PAHs and Benzo(a)pyrene (BaP) within tents were 5372.5 and 364.8 ng/m^3, respectively (Li et al., 2012). Li et al. (2012b) measured personal exposures to $PM_{2.5}$ and indoor CO concentrations from nine nomadic tents using traditional open/chimney stoves and yak dung in the Nam Co and Anduo regions. Results showed that 24-hour average concentrations of $PM_{2.5}$ and CO in tents with open stoves were 1.42 and 6.69 mg/m^3, respectively, and they were significantly higher than those in tents with chimney stoves at 0.14 and 0.12 mg/m^3, respectively (Li et al., 2012). More recently, Xiao et al. (2015) conducted real-time concentration measurements for $PM_{2.5}$ and BC emitted by burning yak dung from households with different living conditions and stove types. The measurements showed the hourly average $PM_{2.5}$ and BC concentrations during the study period ranged from 56.5 μg/m^3 to 1,280 μg/m^3 and from 0.67 μg/m^3 to 19.1 μg/m^3, respectively.

In other areas of the Tibetan Plateau, Hu et al. (2016) measured 4-hour indoor (330.7 μg/m^3) and outdoor (29.1 μg/m^3) $PM_{2.5}$ concentrations from eight residential homes, using cast-iron multi-pot stove fueled with yak dung in seven pastoral or agro-pastoral regions (Hu et al., 2016). Ni et al. (2016) and Carter et al. (2016) conducted a baseline assessment for an energy intervention on the eastern Tibetan Plateau among Han and Qiang minority villages by measuring 48-hour personal exposure to $PM_{2.5}$ and CO, 48-hour indoor concentrations of $PM_{2.5}$, CO, nitric oxide (NO), and nitrogen dioxide (NO_2), and outdoor concentrations of $PM_{2.5}$ in both winter and summer. The personal 48-hour geometric mean exposure to $PM_{2.5}$ was 80 μg/m^3 in summer and 169 μg/m^3 in winter, with similar seasonal differences for indoor $PM_{2.5}$ concentrations at 101 μg/m^3 in summer and 252 μg/m^3 in winter

(Carter et al., 2016; Ni et al., 2016). More than twice larger exposures and the indoor concentrations in winter may be due to the increase in the mean daily hours of combustion activity (from 5.4 hours/day in summer to 8.9 hours/day in winter) and the decrease in the effective air-exchange rate (from 18.1/h in summer to 15.2/h in winter) (Carter et al., 2016). The ambient $PM_{2.5}$ level was relatively higher in summer (27.0 $\mu g/m^3$), compared to that in winter (18.5 $\mu g/m^3$) (Carter et al., 2016).

Among these previously conducted studies, the majority measured only the indoor concentrations of household air pollutants, rather than personal exposures, which are more relevant for quantifying health effects. Also, most of the HAP measurements in Tibetan households were conducted in traditional nomadic tents with yak dung being the dominant household fuel. With the development of local economy and infrastructure (e.g., roads and hydropower), lifestyle in the Tibetan community has undergone significant changes, including engaging in more diverse livelihoods (e.g., migrant worker, rural tourism, caterpillar fungus business) and increased access to electricity, private vehicles, and highways. These factors are very likely to impact the local ambient/household air qualities, and personal exposure levels/patterns. However, the characterization of HAP and personal exposure under these new contexts is scarce. Although children are generally more susceptible to the adverse effects of HAP, no measurements have been conducted among Tibetan children. Concentrations of various chemical components of PM (e.g., PAHs and chemical elements) are also not adequately quantified, although they may have stronger association with certain health outcomes (Secrest et al., 2017). Filling these gaps are critical in furthering our understanding of HAP and personal exposure characteristics, as well as their potential environmental health impacts in Tibet.

1.3.2 Household air pollution and blood pressure among pregnant women

Although there have been many biological and epidemiological studies supporting the hypothesis that HAP exposure elevates blood pressure outcomes, controversial relationships have been found

between burning solid fuels and gestational blood pressure in field studies. Wylie et al. (2015) showed that wood user was one-third less likely to have postpartum blood pressure (blood pressure can return to antepartum values following delivery) in the hypertensive range compared with women in central east India cooking in primarily with gas although this difference did not reach statistical significance. It remains plausible that biomass smoke might protect against the development of gestational hypertension or preeclampsia. The combustion byproduct of tobacco and biomass fuels are quite similar, and cigarette smoking during pregnancy has been consistently associated with a significantly reduced risk for preeclampsia with a pooled OR of 0.51 [95% CI: 0.37, 0.63] reported in meta-analysis (Castles et al., 1999).

In another study conducted in India, Agrawal and Yamamoto (2015) found women living in households using biomass and solid fuels had two times higher likelihood of reporting preeclampsia/eclampsia symptoms than do those living in households using cleaner fuels (OR = 2.21; 95%: 1.26–3.87; p = 0.006), the trend remained after controlling for the effects of a number of potentially confounding factors. Similarly, in Ghana, a significant positive association was found between CO exposure and DBP: on average, each 1 ppm increase in CO exposure was associated with 0.43 mmHg higher DBP [0.01, 0.86] (Quinn et al., 2016). A non-significant positive trend was also observed for SBP (Quinn et al., 2016). In an RCT of an ethanol cookstove intervention conducted in pregnant Nigeria women, Alexander et al. (2017) reported that at the last visit, mean DBP was 2.8 mm Hg higher in control subjects than in ethanol users (3.6 mm Hg higher in control subjects than in ethanol users among preintervention kerosene users). 6.4% of control subjects were hypertensive versus 1.9% of ethanol users (p = 0.051), and among preintervention kerosene users, 8.8% of control subjects were hypertensive compared with 1.8% of ethanol users (p = 0.029) (Alexander et al., 2017a).

The relationship between HAP exposure and blood pressure in non-pregnant adult women also showed great variability by geographic location, pollutant type, fuel and stove type, age, and body mass index (BMI). A longitudinal evaluation of a household energy package on blood pressure in Sichuan, China, showed that women who did not receive the energy package had greater mean decreases in brachial SBP (−4.1 mmHg, 95% CI: −7.3, −0.9) and DBP (−2.0 mmHg, 95%CI −3.6, −0.5) compared with women who received the package (SBP: −2.7 mmHg, 95%CI: −5.0, −0.4; DBP: −0.3 mmHg, 95%CI: −1.4, 0.8) resulting in slightly positive but not statistically significant difference-in-differences effect estimates of 1.3 mmHg (95%CI: −2.5, 5.2) and 1.7 mmHg (95%CI: −0.3, 3.6), respectively. Similar trends were found for central blood pressure, central pulse pressure, and arterial stiffness (Clark et al., 2019). Another study conducted in the same province of China found that among women aged ≥50 years, increased $PM_{2.5}$ exposure was associated with higher SBP (brachial: 3.5 mmHg (p = 0.05); central: 4.4 mmHg (p=0.005)) and DBP (central: 1.3 mmHg (p=0.10)), higher pulse pressure (peripheral: 2.5 mm Hg (P=0.05); central: 2.9 mm Hg (P=0.008)). The association were inconsistent in the direction and the effects were not statistically significant among younger women (Baumgartner et al., 2018). Two more studies conducted in Yunnan, China, all observed elevated blood pressure with increase of exposure. Specifically, Baumgartner et al. (2014) found that BC had the strongest association with SBP (4.3 mmHg; P < 0.001) than PM mass and water-soluble organic mass and the effect of BC on SBP was almost three times greater in women living near the highway (6.2 mmHg, 95% CI: 3.6 to 8.9 vs. 2.6 mmHg, 95% CI: 0.1 to 5.2). The same research team also reported that a 1-log-$\mu g/m^3$ increase in $PM_{2.5}$ exposure was associated with 2.2 mmHg higher SBP (95% CI: 0.8, 3.7; p-value = 0.003) and 0.5 mmHg higher DBP (95% CI: –0.4, 1.3; p-value = 0.31) among all women and the estimated effects were varied by age group (Baumgartner et al., 2011).

The association between HAP exposure and blood pressure has also been assessed in several other countries. In Honduras, Young et al. (2019) observed an association between kitchen $PM_{2.5}$ concentration: one unit increase in log transformed kitchen $PM_{2.5}$ concentration was associated with 2.5 mmHg (95% CI, 0.7-4.3) increase in SBP; results were stronger among women of 40 years or older (5.2 mmHg, 95% CI, 2.3-8.1). However, they did not observe similar association between personal $PM_{2.5}$ exposure and blood pressure. In Pakistan, an evaluation of short-term health effects and exposure reduction for an improve cookstove intervention among rural women found moderate elevation in SBP and DBP with increase in exposure levels, however, none of these association reached traditional statistical significance (Jamali et al., 2017). An assessment of a biogas fuel intervention among women in rural Nepal reported the use of biogas was associated with 9.8 mmHg lower SBP (95% CI: -20.4 to 0.8) and 6.5 mmHg lower DBP (95% CI: -12.2 to -0.8) compared to firewood users among women >50 years of age. These effects, however, were not identified in younger women aged 30–50 years (Neupane et al., 2015). Decrease in SBP was also observed in indigenous Bolivian women after the introduction of an improved cookstove intervention. The mean SBP decreased from 114.5 $\pm$ 13.0 to 109.0 $\pm$ 10.4 mmHg, (p-value = 0.01) after the improved cookstove intervention; suggestive decreases were also seen in DBP (p-value = 0.05) (Alexander et al., 2015). In Nicaragua, Clark et al. (2013) investigated the impact of a cleaner-burning cookstove intervention on blood pressure in rural Nicaraguan women and found that, although substantial reductions in blood pressure were not observed among the entire population, a 5.9 mmHg reduction (95% CI: -11.3, -0.4) in SBP was observed among women aged 40 or more years and a 4.6 mmHg reduction (95% CI: -10.0, 0.8) was observed among obese women. An earlier chimney stove intervention RCT conducted in Guatemala showed that after adjusting for age, body mass index, an asset index, smoking, secondhand tobacco smoke, apparent temperature, season, day of week, time of day, and a random subject intercept, the

improved stove intervention was associated with 3.7 mm Hg lower SBP (95% CI, –8.1 to 0.6) and 3.0 mm Hg lower DBP (95% CI, –5.7 to –0.4) compared with controls (McCracken. et al., 2007).

Additionally, two studies conducted in India that assessed the association between HAP exposure and blood pressure in adult women, through either introduction of cookstove and fuel interventions or comparison between women using traditional and clean cooking fuels. Aung et al. (2018) assessed the effect of a climate-financed cookstove in rural India and observed a lower SBP (−2.0 mmHg, 95% CI: −4.5, 0.5) and DBP (−1.1 mmHg, 95% CI: −2.9, 0.6) among exclusive users of the intervention stove, although confidence intervals included zero. A panel study of the acute effects of personal exposure to HAP on ambulatory blood pressure in rural Indian women showed that interquartile range increases in BC were associated with changes in SBP from -0.4 mmHg (95% CI: -2.3, 1.5) to 1.9 mmHg (95% CI: -0.8, 4.7), with associations increasing in magnitude as BC values were assessed over greater time periods preceding blood pressure measurement. However, the interquartile range increases in BC were associated with small decreases in diastolic blood pressure from -0.9 mmHg (95% CI: -1.7, -0.1) to -0.4 mmHg (95% CI: -1.6, 0.8) (Norris et al., 2016).

1.3.3 Interventions to reduce household air pollution exposure and improve health

HAP exposures has been linked to a wide range of adverse health effects, including respiratory, cardiovascular (Aung et al., 2018; Chakraborty and Mondal, 2018), and reproductive (Balakrishnan et al., 2018) outcomes. Evidence of these links are generated by various studies conducted worldwide, comparing the households using traditional biomass fuels/stoves and improved biomass cookstoves or cleaner fuels/stoves (e.g. biogas, electricity and Liquefied Petroleum Gas [LPG]) (Aung et al., 2018; Chakraborty et al., 2014; Chakraborty and Mondal, 2018; Hanna et al., 2016; Johnson et al., 2019; Mazumder et al., 2019; Pathak et al., 2019; Sharma and Jain, 2019).

However, mixed results have been reported. Several reasons may contribute to these inconsistencies: 1) promoted improved biomass cookstoves may not be efficient enough to reduce personal exposure to HAP; 2) the use of traditional cookstove alongside the improved or clean cookstoves/fuel interventions (stacking); 3) other indoor/outdoor sources that might have contributed to the personal exposures (Jack et al., 2015; Romieu et al., 2009; Smith et al., 2011). These explanations were also confirmed by the exposure measurement results. Although a large percentage of HAP reductions were observed, post-intervention microenvironment $PM_{2.5}$ concentrations were still much over the WHO interim target-1 (IT-1) annual average level of 35 $\mu g/m^3$ (Balakrishnan et al., 2015a; Chengappa et al., 2007; Dutta et al., 2007; Muralidharan et al., 2015; Sambandam et al., 2015). A fundamental issue was that the stove designs did not reduce emissions, but focused on fuel efficiency and, at best moved the smoke outside, where it still caused exposures (Landrigan et al., 2018). These field studies highlight the needs for a wide adoption and an exclusive use of clean household fuels (e.g. LPG), in order to achieve meaningful health gain (Bruce et al., 2015; Mazumder et al., 2019; Pathak et al., 2019).

In addition, most of the studies examining the effects of household fuel/cookstove interventions were observational. Yet, these observational designs have the inherent difficulty to minimize the confounding from the association between HAP exposure and health outcomes (Smith et al., 2011), and they are less capable for causal inference compared to experimental designs such as randomized controlled trials (RCTs).

Several field clean cooking intervention RCTs have been reported to date. The RESPIRE (Randomized Exposure Study of Pollution Indoors and Respiratory Effects) trial conducted in Guatemala found that the CO levels were significantly lower among the intervention (improved cookstove with a chimney) group, however, the exposure reduction achieved with these stoves did not significantly reduce the primary outcome of physician-diagnosed pneumonia for 518 children

younger than 18 months (Smith et al., 2011, 2010). The Cooking and Pneumonia Study (CAPS) conducted in Malawi collected data in 10543 children from 8470 households across 150 community-level clusters also reported no effect of the intervention (two cleaner-burning, biomass-fueled cookstoves with a solar charger) on the primary outcome of WHO Integrated Management of Childhood Illness–defined pneumonia in an ITT analysis (Mortimer et al., 2017; Mortimer and Balmes, 2018). Similarly, in rural Mexico, Romieu et al. (2009) compared the respiratory health of 552 women randomly assigned to use an improved biomass stove with chimney (Patsari Stove) versus traditional open fire and found no statistically significant effects in the ITT analyses.

More recently, Alexander and colleagues reported findings of a randomized controlled trial in Nigeria to determine the impact of an ethanol-fueled stove on pregnancy outcomes (Alexander et al., 2017a, 2018b). There was no significant effect of the intervention on SBP, but an observed effect on DBP with unclear clinical relevance (Alexander et al., 2017a; Mortimer and Balmes, 2018). This study also found that the difference in birthweight was statistically significant only after covariate adjustment and no significant differences in exposure levels between the two treatment arms were detected (Alexander et al., 2018b). There is another RTC on clean cooking interventions in Nepal (Tielsch et al., 2014). The full trial report is awaited, however several respiratory, birth and obstetric outcomes that have been reported in papers/abstracts showed no statistically significant effect in the intervention compared with the control group (Tielsch et al., 2016). The recently released ITT analysis results from a cluster RCT of cookstove interventions (Jack et al., 2015) concluded that neither prenatally-introduced LPG nor improved biomass cookstoves improved birth weight or reduced severe pneumonia risk in the first 12 months of life. They hypothesized that it was due to lower-than-expected exposure reductions in the intervention arms (Jack et al., 2021). In the exposure-response analysis, Quinn et al. (2021) observed effects of CO on birth weight, birth length, and gestational age that were modified by placental malarial status. Negative associations were seen in above outcomes

with increased CO exposures among infants from pregnancies without evidence of placental malaria; these associations were not observed in pregnancies with evidence of placental malaria (Quinn et al., 2021a).

The use of LPG in LMICsis likely to increase in the near future driven by several government initiatives (Asante et al., 2018; Bruce et al., 2018; Goldemberg et al., 2018; Gould and Urpelainen, 2018; Pillarisetti et al., 2019; Quinn et al., 2018; Srinivasan and Carattini, 2020). However, there has been no multi-country field trials with LPG stoves, likely the cleanest scalable intervention in LMICs. Rigorous evidence is needed to understand the potential of exclusive use of LPG in reducing HAP exposure and improving health to inform policies and interventions at all levels, especially for countries with large number of populations relying on biomass solid fuels and bearing the most health burden.

Chapter 2

Household Air Pollution and Personal Exposure from Burning Firewood and Yak Dung in Summer in the Eastern Tibetan Plateau

2.1 Background

Globally, 2.8 billion people still depend on solid fuel for cooking and heating (World Health Organization, 2014). Incomplete combustion of solid fuels results in high levels of household air pollution (HAP), including $PM_{2.5}$, carbon monoxide (CO), black carbon (BC), as well as polycyclic aromatic hydrocarbons (PAHs). The latest Global Burden of Disease (GBD) study estimated that more than 1.6 million deaths in 2017 were attributable to HAP exposure from solid fuels (Stanaway et al., 2018). Studies have shown that HAP, particularly $PM_{2.5}$ exposure is associated with a wide range of health effects, including low birth weight (Pope et al., 2010), chronic obstructive pulmonary disease (COPD) (Kurmi et al., 2010), and ischemic heart disease (IHD), among others (Chen and Liao, 2018; Lee et al., 2012; McCracken et al., 2007). The GBD study estimated that approximately 0.82 million annual premature deaths were attributable to HAP in China in 2010. A more recent study showed that solid fuel use, for both cooking and heating, was significantly associated with increased risks of cardiovascular and all-cause mortality (Yu et al., 2018).

Due to the traditional life style and the availability and affordability of fuels, solid biomass fuels (wood and yak dung) contribute to more than 70% of the household energy consumption in the Tibetan region, among which yak dung accounted for 53% (Gao et al., 2009; Hu et al., 2016; Wang, 2009; Xiao

et al., 2015). Evidence have shown strong associations between household solid biomass fuel use and local/regional air quality (Liu et al., 2008), human health, as well as climate change (Lacey and Henze, 2015). As women in Tibet are usually responsible for cooking, collecting fuels and caring children at home, they are disproportionally affected by the adverse social and health impacts linked to HAP exposure from the solid fuel use.

Despite the widespread solid fuel use and its potential health effects, studies that directly measure the personal exposure to $PM_{2.5}$ and its chemical components are scarce in Tibetan households, most previous studies focused on measuring the indoor HAP concentrations. A study conducted in Nam Co (central Tibet) measured indoor total suspended particles (TSP) and toxic elements, including cadmium (Cd), arsenic (As), and lead (Pb) from burning yak dung in nomadic tents (Kang et al., 2009). The daily indoor concentrations for TSP, Cd, As, and Pb were 3160, 3.16, 35.00 and 81.39 $\mu g/m^3$, respectively (Kang et al., 2009). Another study conducted in central Tibet reported daily average $PM_{2.5}$ concentrations in kitchen, living room, bedroom, and yard to be 134.9, 103.6, 76.1, and 78.3 $\mu g/m^3$, respectively (Gao et al., 2009). Their study also found that using solid biomass fuels in kitchen resulted in higher HAP than using methane and the daily average $PM_{2.5}$ concentrations in kitchen using dung cake, fuel wood and methane use were 117.4, 271.1, and 47.0 $\mu g/m^3$, respectively (Gao et al., 2009). Li et al. (2012a) characterized the particle-bound PAHs from $PM_{2.5}$ and TSP samples collected in four nomadic tents using open stoves and yak dung in Nam Co. The average concentrations of total 13 PAHs and Benzo(a)pyrene (BaP) within tents were 5372.5 and 364.8 ng/m^3 (Li et al., 2012a). The team also measured personal exposures to $PM_{2.5}$ and indoor CO concentrations from nine nomadic tents using traditional open/chimney stoves burning yak dung in the Nam Co and Anduo regions. Results showed that 24-hour average concentrations of $PM_{2.5}$ and CO in tents with open stoves were 1420 and 6690 $g/\mu m^3$, respectively, and they were ten and fifty-six times higher than those in tents with chimney stoves, respectively (Li et al., 2012b). More recently, Xiao et al. (2015) conducted real-

time concentration measurements for $PM_{2.5}$ and BC emitted by burning yak dung from households with different living conditions and stove types. The hourly average $PM_{2.5}$ and BC concentrations during their study period ranged from 56.5 to 1,280 $\mu g/m^3$ and from 0.67 to 19.1 $\mu g/m^3$, respectively. In other regions of the Tibetan Plateau, Hu et al. (2016) measured 4-hour indoor (330.7 $\mu g/m^3$) and outdoor (29.1 $\mu g/m^3$) $PM_{2.5}$ concentrations from eight residential homes, using cast-iron multi-pot stove fueled with yak dung in seven pastoral or agro-pastoral regions (Hu et al., 2016). Ni et al. (2016) and Carter et al. (2016) conducted an assessment on the eastern Tibetan Plateau among Han and Qiang minority villages regarding personal exposure to $PM_{2.5}$ and CO, indoor concentrations of $PM_{2.5}$, CO, nitric oxide (NO), and nitrogen dioxide (NO_2), and outdoor concentrations of $PM_{2.5}$ in both winter and summer. The personal 48-hour geometric mean exposure to $PM_{2.5}$ was 80 $\mu g/m^3$ in summer and 169 $\mu g/m^3$ in winter, with similar seasonal differences for indoor $PM_{2.5}$ concentrations at 101 $\mu g/m^3$ in summer and 252 $\mu g/m^3$ in winter (Carter et al., 2016; Ni et al., 2016).

Although these studies conducted in Tibet have measured the HAP concentrations and personal exposures in houses with different structures, stoves, fuel types by different seasons, knowledge gaps remain. Though personal exposures are more relevant in quantifying the health effects, very few HAP studies have measured personal exposure. Moreover, most of the existing HAP measurements in Tibet were conducted in traditional nomadic tents with yak dung being the dominant fuel. Yet, with the development of local economy and infrastructure (e.g. roads and hydropower), life in the Tibetan community is undergoing several transitions, including engaging in more diverse livelihoods (e.g. migrant worker, rural tourism, caterpillar fungus business) and increased access to electricity, private vehicles, and highways (Sclar and Saikawa, 2019). These factors are likely to contribute more and more to the local ambient/household air qualities, and personal exposure levels/patterns. However, the characterization of HAP and personal exposure under these new contexts is scarce. In addition, although children are generally more susceptible to the adverse effects of HAP, no measurements

have been conducted with Tibetan children. Concentrations of various chemical components of PM (e.g. PAHs and chemical elements) are also insufficiently quantified, though they may have stronger association with certain health outcomes (Secrest et al., 2017). These knowledge gaps motivated this preliminary/hypothesis-generating study to further our understanding of personal HAP exposure levels and potential health effects in Tibet.

In this study, we recruited households from villages located in the Eastern Tibetan Plateau living in different type of houses and using diverse stoves/fuels. We collected information on demographics, stoves, and fuels, cooking behaviors, lifestyles, and self-reported health concerns. We measured 24-hour personal exposure to $PM_{2.5}$, indoor kitchen BC concentrations, as well as particle-bound PAH and inorganic elemental concentrations. In addition, fasting urine samples were collected, matched with the personal exposure data, to assess internal exposure and health effects, and to identify potential biomarkers of exposure and health effects. The biospecimen analysis results will be reported elsewhere. Here, we focus on the HAP exposure measurement results, which include 1) the sources, composition, indoor concentrations, and personal exposures of $PM_{2.5}$ and BC in Tibetan households across different village, stove, fuel types and sub-populations; and 2) the correlation and significance of potential HAP exposure determinants in this region.

2.2 Methods

2.2.1 Study location

Field samplings were conducted in two townships, Pengbuxi and Gonggashan, in the Ganzi Tibetan Autonomous Prefecture (30.05° N, 101.96° E, 3500m a.s.l.) during July and August in 2016 (**Figure 1, Top**). Ganzi is located in the transition zone between the mountainous region of western Sichuan Basin and the southeastern Tibetan Plateau. The main income sources include farming barleys and

caterpillar fungus business for Pengbuxi residents and yak herding and caterpillar fungus business for Gonggashan residents.

In Pengbuxi, residents live in traditional Tibetan style houses made by wood and stone. In Gonggashan, in addition to a similar traditional Tibetan house, people also own a tent, or a portable dwelling made by fabric, steel and plastic panel in the pastoral area as temporary residence during summer grazing season (May to August). Most of the traditional Tibetan style houses and all tents/portable dwellings have only one room without separation of a kitchen, living room and a bedroom. Traditional Tibetan-style cast-iron stoves with chimneys are pervasively used for in-room cooking and heating in both townships (**Supplementary Figure 1**). Majority of the households in Pengbuxi also own a secondary stove, usually a simplified traditional stove or an open stove, placed in the yard or barn to warm fodder and water for livestock during cold days. Firewood is the primary fuel used in Pengbuxi, where free forestry resources are accessible. In contrast, yak dung is the primary fuel for Gonggashan residents, as they own many more yaks and the higher altitude of the pastoral area only grows shrubs, which is reported as the secondary fuel for many Gonggashan households. Based on these distinct characteristics, we hereafter refer to Pengbuxi and Gonggashan township as agricultural and nomadic village, respectively.

2.2.2 Field survey

A household survey was administered to collect information on demographics, daily time-activity patterns, household fuel/stove characteristics, cooking behavior, awareness/knowledge of HAP exposure and associated health effects and major health concerns. Snowball sampling method was used to recruit participants. In this preliminary/hypothesis-generating assessment, the sample size was determined by reviewing the sample sizes of other studies with similar purposes, research budget, and the variations in the stove/fuel use in our study site according to our community contacts. In total, 24

households were interviewed from agricultural (n = 14) and nomadic (n = 10) villages. This study was approved by Emory University Institutional Review Board and the study design, sampling procedure and compensation strategy were thoroughly reviewed and developed together with field staff and community contacts. Oral consents were obtained from each of the participants or their custodians before enrolling the study. Eligible participants were informed of the objectives, processes, schedules, time commitment, incentives, benefits, and risks of this study. Following informed consent, survey questions were read and explained to consenting participants and the responses were recorded, coded, and analyzed. All surveys took place in the first visit of each household before any other samplings were conducted. Several local community members assisted in transportation and translation between Mandarin and Tibetan. Survey questions are included in the **Supplementary Information**.

2.2.3 Exposure and indoor concentration sampling instruments and sampling strategy

$PM_{2.5}$ concentrations were measured for 24 hours with MicroPEM (RTI International, Research Triangle Park [RTP], NC), a wearable PM personal exposure monitor (Chartier et al., 2017). The MicroPEM collects both real-time and gravimetric $PM_{2.5}$ concentrations with gold-standard integrated filter (Cho et al., 2016). The laser-based light scattering nephelometer collects real-time PM concentration data at every ten seconds resolution and at the flowrate of 0.4 L/min (Cho et al., 2016). The MicroPEM also collects PM on a 25mm PTFE filter for gravimetric and chemical speciation analyses (Cho et al., 2016). The instruments were calibrated once before starting each measurement with MicroPEM Docking Station software (RTI International, RTP, NC) (Cho et al., 2016). The average daily temperature was between 9 C° and 22 C° in Ganzi and the average daily precipitation was 7.5 mm (https://www.ncdc.noaa.gov/data-access/land-based-station-data) over the sampling period. 24-hour integrated personal $PM_{2.5}$ exposures were measured in agricultural (n = 26) and nomadic (n = 20) villages. MicroPEM was distributed to voluntary participants, usually the primary

adult cook and a child in each household, whenever it was possible. MicroPEM was placed in a wearable crossbody pouch and carried by each participant to approximate the breathing zone without disturbing daily activities. Participants were instructed to wear the instrument, while conducting their daily routines and place the instrument next to them (within 1 m) when sleeping or showering. Instruments were given and started, measuring right after the household survey, and retrieved during the second household visit after at least 24 hours.

Kitchen area BC concentrations were measured by a Model AE51 microAeth Black Carbon aerosol monitor (Aethlabs, Inc., range: 0 - 1 mg/m^3, resolution: 0.001 mg/m^3) at 50 mL/min flow rate (Xiao et al., 2015). Due to the limited number of instrument and battery life, eight 24-hour BC measurements were completed over the sampling period in agricultural (n = 5) and nomadic (n = 3) households. During sampling, microAeth was placed on the shelves, open closets, or other safe locations in the kitchen at around 0.5 m above the ground to approximate the exposure environment of stove users without interrupting their cooking activities. MicroAeth was set up and retrieved at about the same time as MicroPEM for each household visit.

2.2.4 Exposure and indoor concentration data processing and chemical speciation analysis

Real-time personal $PM_{2.5}$ concentrations were processed with MicroPEM Docking Station software (RTI International, RTP, NC) at ten-second intervals and were calibrated with corresponding gravimetric filter measurements. All filters were pre- and post-weighed at RTI International (RTP, NC), using a microbalance (Mettler Toledo UMX2) housed in a temperature and humidity controlled environmental chamber (21°C, 35% RH). The filters were subsequently analyzed for black carbon in RTI-proprietary integrating sphere via optical transmittance method. Following post-weighing and BC measurements, filters were stored in a -20°C freezer until compositional analysis. Detailed filter

weighing process and quality assurance (QA) measures are presented in **Supplementary Information**. Real-time kitchen area BC concentrations were sampled at one-minute intervals and processed with microAeth online data processing software (AethLabs, San Francisco, CA). Smoothing was conducted for BC real-time data with local polynomial regression by every seven points.

Two different subsets of the filters in MicroPEM were used to assess the composition and mass of each "EPA 16-PAHs" (n = 12) and 33 inorganic elements (n = 11) by gas chromatography–mass spectrometry (GC-MS) (Agilent 6890/5975) and energy-dispersive X-ray fluorescence spectroscopy (EDXRF) (ARL™ QUANT'X EDXRF Spectrometer, Thermo Scientific), respectively. Details on sample preparation, analysis and QA measures are included in **Supplementary Information.**

2.2.5 Statistical analysis

Descriptive statistics were performed for household survey results, 24-hour average $PM_{2.5}$, PAHs, and inorganic element exposures, and kitchen area BC concentrations. Peak, correlation, and daily variation of real-time $PM_{2.5}$ and BC were also summarized. Potential determinant of $PM_{2.5}$ personal exposure was identified and examined using regression analysis. $PM_{2.5}$ concentrations were log transformed (natural log) to account for their skewed distribution and to improve normality and variance homogeneity. Univariate and multiple linear regression analyses were performed to explore the roles of household survey variables as predictors of individual $PM_{2.5}$ exposures. Univariate linear regression results were examined first to identify variables that are significantly associated with personal $PM_{2.5}$ exposures. Then, a multiple linear regression model was fitted to assess which characteristics together best explain the personal exposure to $PM_{2.5}$. Any characteristic that was significant at $\alpha < 0.02$ in the univariate analysis was included in the multiple linear regression model. The final multivariable model for personal $PM_{2.5}$ exposures includes all variables remained significant ($p < 0.05$) after forward, backward, and stepwise selection procedures. Regression diagnostic

procedures were also performed to ensure that none of the model assumptions were violated. All analyses were performed using R software (version 3.6.0).

2.3 Results

2.3.1 Survey results

Key characteristics related to HAP exposure from household survey are summarized in **Table 2.1**. Complete survey results can be found in **Supplementary Table A1**. We enrolled 24 households from agricultural (n = 14) and nomadic (n = 10) village. The average household size was six and four in agricultural and nomadic villages, respectively. The nomadic village household size was smaller as it only reflected the number of family members lived in their temporary dwelling during the summer grazing season. Among the 24 households, 37.5% (n = 9) had one or more active smokers at home. The average annual income was $5,155 and $3,102 in agricultural and nomadic villages, respectively. People who were responsible for cooking and other housework generally spent 16 hours/day at home in both village types in summer and spent more than 20 hours/day at home in winter. Children spent similar time indoors when we conducted measurements, as they were not attending school in the summer.

In agricultural village, 100% (n = 14) of surveyed households owned more than one stove. Besides the traditional Tibetan-style cast-iron chimney stove as the primary cooking and heating stove, families may also own in-room electric stoves and/or simplified traditional stoves or open stoves to warm fodder and water for livestock during cold days. In contrast, most of the nomadic households had only one smaller size traditional Tibetan-style stove with a chimney in their temporal dwelling. Stoves are mainly used for cooking and boiling water, plus heating in the cold weather. The average stove age in agricultural village was seven years, while it was four years in the nomadic village. Several nomadic

households reported that stoves and chimneys were easily broken when migrating between their temporary dwellings in the pasturing area and permanent houses in the village, and therefore replaced more frequently. Agricultural households reported to operate the primary cooking stoves 5.3 hours/day in summer and 9.6 hours/day in winter, whereas nomadic households reported to operate the primary stove 7.1 hours/day in summer.

In the agricultural village, firewood (n = 12, 86%) and electricity (n = 2, 14%) were reported as the primary fuels for cooking and heating, while yak dung was the secondary fuel (n = 12, 86%). In the nomadic village, firewood (n = 5, 50%) and yak dung (n = 5, 50%) were equally reported as the primary fuels for cooking and heating. For those that used firewood in the nomadic village answered yak dung as the secondary fuel and vice versa. Despite this self-reported household fuel use proportions, we observed more yak dung use in the nomadic village as both primary and secondary fuels than in the agricultural village. The fuel use difference in the two villages may be due to the altitude, which is correlated to temperature and heating needs, as well as the accessibility of wood/yak dung, utility and transportation infrastructure.

Most of the surveyed households (n = 22, 92%) were not aware of or not sure about the adverse health effects related to HAP exposure because of indoor biomass burning. Participants from two households in agricultural village (14%) reported of being told by their doctors that smoke can cause negative health impacts, mainly respiratory diseases, during their hospital visits. Members in 11 households (46%) reported that they have never experienced any discomfort when using stoves, while the rest (n = 13, 54%) reported some discomfort, including cough, eye/nose irritation, headache, and dizziness, especially when making the fire or when smoke was too strong. Despite the low awareness of health effects and a limited reported discomfort, respiratory diseases remained the primary (n = 4,

29%) self-reported health concern in the agricultural village. Among the nomadic households, rheumatism and joint pain were the major (n = 9, 90%) health concerns.

Table 2.1 Summary of key characteristics related to HAP exposure

	Agricultural Village	**Nomadic Village**	**Total**
Participant demographics	(n = 14)	(n = 10)	(n = 24)
Number of Household members, mean (SD)	6.07 (2.20)	3.90 (1.37)	5.17 (2.16)
Active smoker, n (%)	6 (43%)	3 (10%)	9 (37.5%)
Time spent at home (hours), mean (SD)	18.3 (2.6)	N/A	N/A
Summer	16.1 (3.8)	15.7 (1.6)	15.9 (3.1)
Winter	20.4 (2.7)	N/A	N/A
Stove, fuel, and cooking behavior			
Households with more than one stove, n (%)	14 (100%)	1 (10%)	15 (62.5%)
Households with type of stove, n (%)			
Traditional chimney stove (in-house)	14 (100%)	10 (100%)	24 (100%)
Electric stove (heating wire, in-house)	9 (64.3%)	0 (0%)	9 (37.5%)
Traditional stove for livestock (outdoor)	5 (35.7%)	0 (0%)	5 (20.8%)
Open fire for livestock (outdoor)	4 (28.6%)	0 (0%)	3 (12.5%)
Gas stove	0 (0%)	1 (10%)	1 (4%)
Main stove age (years), mean (SD)	7 (4.16)	4 (1.93)	5 (3.66)
Daily operation time (hours), mean (SD)	7.5 (3.7)	N/A	N/A
Summer	5.3 (2.6)	7.1 (1.3)	6 (2.3)
Winter	9.6 (5.2)	N/A	N/A
Primary cooking fuel, n (%)			
Electricity	2 (14%)	0 (0%)	2 (8%)
Firewood	12 (86%)	5 (50%)	17 (71%)
Yak dung	0 (0%)	5 (50%)	5 (21%)

Note:
Firewood = wood and shrub

2.3.2 Air quality measurement results

We conducted 46 integrated personal $PM_{2.5}$ exposure measurements. The overall mean waking-hour wearing compliance (WWC) (%) was 66% and it was similar across agricultural (65%) and nomadic villages (67%), as well as child (65%) and adult (66%). Among all, two measurements were flagged due to the broken inlet and filter, respectively. Additionally, two filters were suspected to be swapped

and one real-time data file was accidentally deleted. These samples were excluded from the analysis. Ultimately, 41 nephelometric and 42 gravimetric $PM_{2.5}$ personal exposure measurements were included in analyses. All real-time measurements were corrected by their corresponding filter-based measurements.

Figure 2.1 (bottom) is the violin plot of 24-hour average personal $PM_{2.5}$ exposures (n = 42) by: (a) village type; (b) primary household fuel type; (c) population group; and d) the presence of active smoker(s) at home. The daily average personal $PM_{2.5}$ exposures ranged from 8.86 to 865 $\mu g/m^3$. The geometric mean (95% CI) of all daily $PM_{2.5}$ exposures was 74.3 (53.6, 103) $\mu g/m^3$; and 35.3 (28.4, 44.0) $\mu g/m^3$ and 200 (143, 281) $\mu g/m^3$ in agricultural and nomadic village, respectively. The geometric mean (95% CI) of $PM_{2.5}$ exposures for primary adult cooks was 91.0 (60.0, 138) $\mu g/m^3$ and for children was 49.6 (29.6, 83.1) $\mu g/m^3$. The geometric mean of daily $PM_{2.5}$ exposures (95% CI) by primary household fuel types were 32.6 (19.6, 54.3) $\mu g/m^3$, 61.0 (42.3, 88.0) $\mu g/m^3$ and 202 (104, 394) $\mu g/m^3$ for electricity, firewood, and yak dung, respectively. Student's t-test displayed a statistically significant difference in personal $PM_{2.5}$ exposures by village type ($p < 0.001$) and by primary household fuel type (yak dung vs. firewood, yak dung vs. electricity, but not for firewood vs. electricity) ($p < 0.05$).

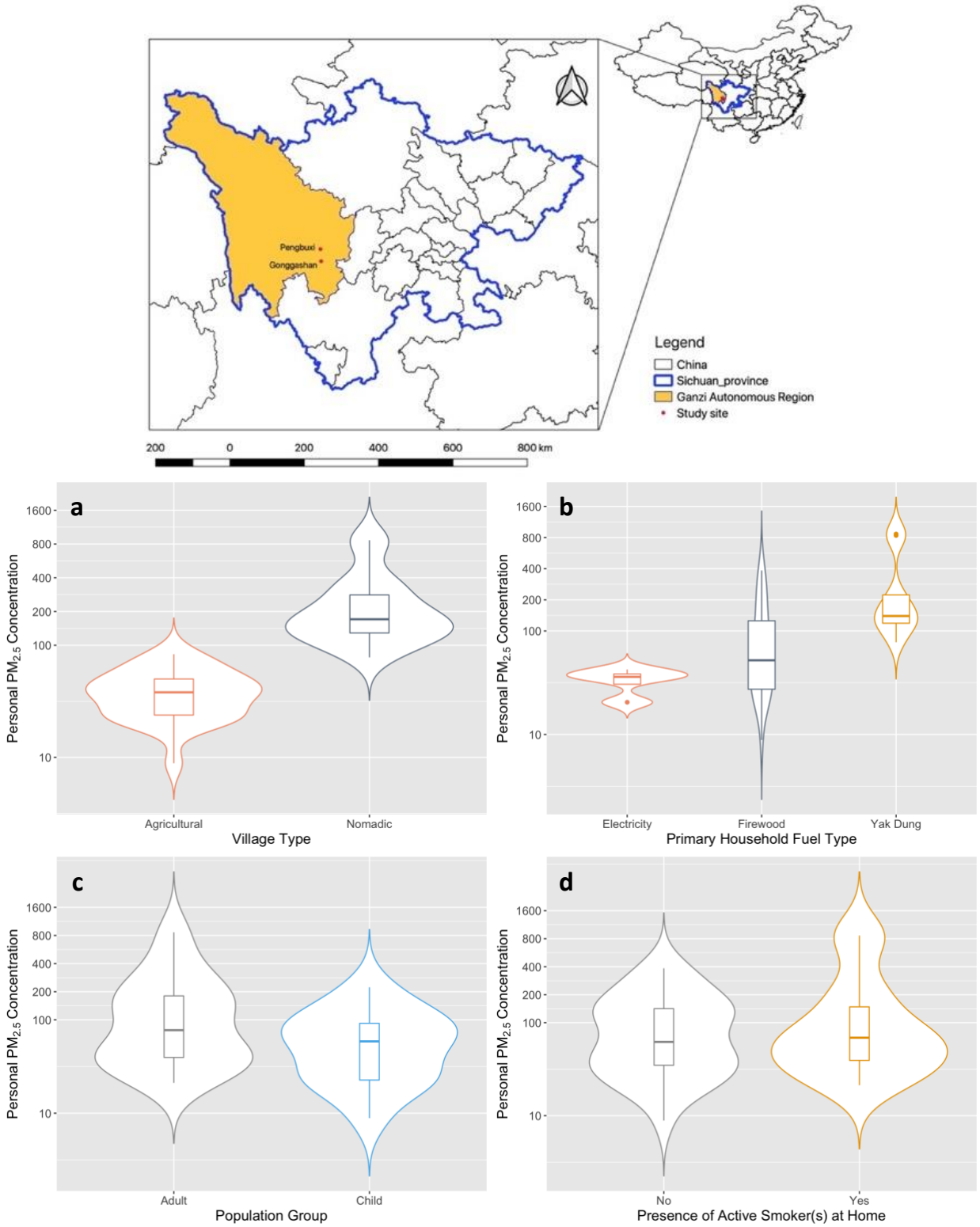


Figure 2.1 (Top) Map of study sites in Pengbuxi (agricultural village) and Gonggashan townships (nomadic village) of Ganzi Tibetan Autonomous Prefecture, China. (Bottom)Violin plot of personal exposure to $PM_{2.5}$ by a) village type; b) primary household fuel type; c) population group; and d) presence of active smoker(s) at home ($\mu g/m^3$)

Figure 2.2 shows the boxplot of the 41 filter-corrected real-time personal $PM_{2.5}$ hourly-average exposures. **Supplementary Table A2** also summarizes the mean, SD, and total sampling time of these exposure measurements. The high hourly-average concentration (> 170 $\mu g/m^3$) time periods were 7:00 – 10:00, 11:00 – 13:00, and 18:00 – 20:00, which aligned well with observed and self-reported cooking times and reaffirmed that cooking is a major source of high $PM_{2.5}$ exposure in our sampled households. The hourly-average $PM_{2.5}$ personal exposures in the nomadic village showed greater fluctuation than those in the agricultural village. The exposure levels were higher in the nomadic village across all reported cooking time windows; however, the exposure levels were higher in the agricultural village during the night when stoves were not in use (**Figure 2.2**). These different diurnal patterns indicated that other factors such as sources other than solid fuels burning and ventilation conditions may also contribute to the $PM_{2.5}$ personal exposure.

In eight of the sampled households, we concurrently measured kitchen area BC concentrations. Characteristics of these households and measurement results are summarized in **Table 2.2.** The daily-average personal $PM_{2.5}$ exposures in these eight households (n = 15) were 68.6 ± 46.7$\mu g/m^3$ and ranged from 20.5 to 148 $\mu g/m^3$. The observed daily average kitchen-area BC concentrations ranged from 0.673 to 15.1 $\mu g/m^3$ with a mean of 4.90 ± 5.01 $\mu g/m^3$. Time-series plots of overlaid real-time personal $PM_{2.5}$ and kitchen BC concentrations from selected households are included in the **Supplementary Figure A2**. Generally, the concentration peaks were well aligned with self-reported indoor and cooking time. However, the correlation between personal $PM_{2.5}$ and kitchen area BC was relatively low and showed great variability across different households (Range: 0.002 - 0.77) (**Table 2.2**). This relatively low correlation may result from various factors that could have an impact on personal exposure, e.g., daily activities, proximity to road and garbage burning site etc.

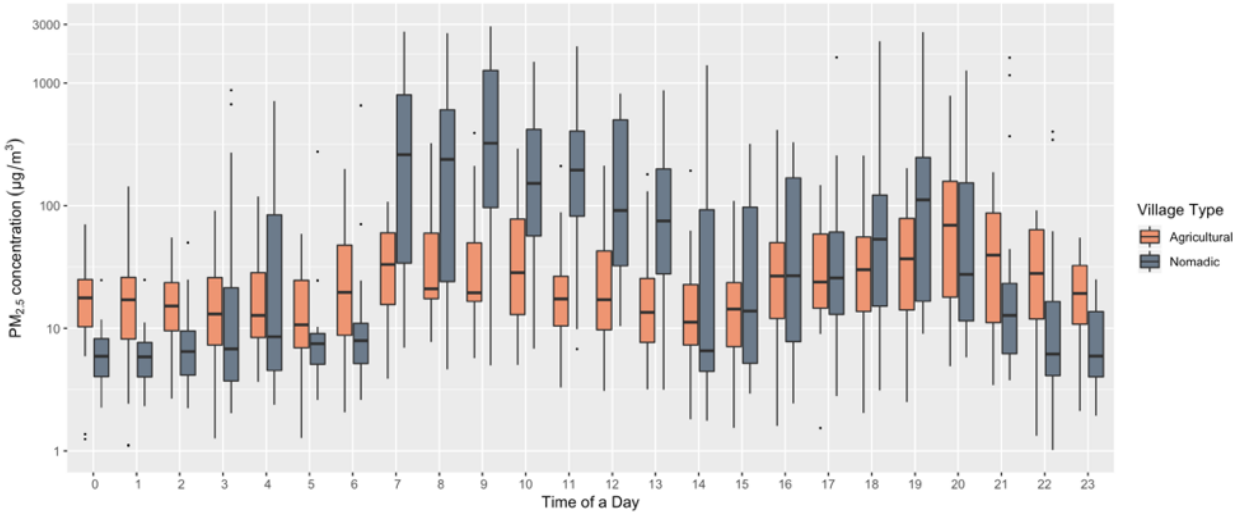


Figure 2.2 Boxplot of filter-corrected real-time mean $PM_{2.5}$ concentration by hour in agricultural and nomadic villages ($\mu g/m^3$)

The real-time monitoring also allowed us to examine the minute-level personal $PM_{2.5}$ exposure and kitchen area concentrations. The range of minute-level exposure by HAP type, subpopulation group and fuel type are summarized in **Supplementary Table A3**. We found that nomadic households had much higher minute level $PM_{2.5}$ personal exposures and kitchen BC concentrations compared to agricultural households. The $PM_{2.5}$ exposure and BC concentration short-term peaks were 2 – 16 times and 3 – 55 times higher in nomadic households. The highest minute-level $PM_{2.5}$ (8.10 mg/m^3) and BC (559 $\mu g/m^3$) exposures/concentrations were found in household primarily burning yak dung.

Using the integrated filters of MicroPEM, we examined $BC/PM_{2.5}$ mass ratios (n = 41). The average mass ratio was 0.24 and ranged from 0.03 to 0.67. **Supplementary Figure A3** shows the filter-based $BC/PM_{2.5}$ mass ratio for all 41 effective samples compared against the previously reported maximum mean level. **Table 2.2** lists the filter-based $BC/PM_{2.5}$ mass ratios from the eight households, where personal exposure to $PM_{2.5}$ and kitchen area BC were concurrently measured.

Furthermore, we identified the BC peak concentration events based on real-time kitchen BC monitoring to further understand the cooking activities. A peak concentration event is defined as

constantly high concentrations (> 75 percentiles) lasting for more than 10 minutes. Details on peak concentration events are summarized in **Table 2.2**. Households relying on firewood and yak dung had similar number and duration of peak concentration events and both were greater than those primarily using electricity.

Table 2.2 Summary of $PM_{2.5}$ and BC observational data in eight households.

	1	2	3	4	5	6	7	8
Village type	A	A	A	A	A	N	N	N
House type	House	House	House	House	House	Portable	Portable	Portable
Primary fuel	Electricity	Firewood	Firewood	Firewood	Firewood	Firewood	Yak dung	Yak dung
Active smoker	No	Yes	No	Yes	Yes	No	No	Yes
24 h personal $PM_{2.5}$ exposure ($\mu g/m^3$)	42.5 (adult) 20.5 (child)	40.3 (adult) 83.2 (child)	37.2 (adult) 34.9 (adult)	49.3 (adult) 38.9 (child)	24.7 (adult) 27.4 (child)	148 (adult) 125 (adult)	139 (adult) 140 (child)	77 (adult)
24 h Avg. kitchen BC concentration ($\mu g/m^3$)	2.70	4.00	0.673	0.746	1.04	6.37	15.1	8.60
Minute-level 24 h personal $PM_{2.5}$ and kitchen BC correlation coefficient	0.02 (adult) 0.09 (child)	0.14 (adult) 0.35 (child)	-0.002 (adult) -0.002 (adult)	0.64 (adult) 0.64 (child)	0.28 (adult) 0.51 (child)	0.29 (adult) 0.44 (adult)	0.77 (adult) 0.64 (child)	0.66 (adult)
24 h Avg. filter-based BC/ $PM_{2.5}$ mass ratio	0.12 (adult) 0.20 (child)	0.14 (adult) 0.08 (child)	0.21 (adult) 0.11 (adult)	0.10 (adult) 0.11 (child)	0.13 (adult) 0.10 (child)	0.09 (adult) 0.10 (child)	0.62 (adult) 0.56 (child)	0.26 (adult)
# of kitchen BC peak concentration event	3	6	9	8	6	11	11	10
Total length of peak BC concentration events	153	376	333	385	360	360	355	328
Avg. minutes of peak BC concentration events	51	62.7	37	48.1	60	32.7	32.3	32.8

Note:

A: Agricultural village; N: Nomadic village

Particle-bound PAHs on filters were examined (n = 12) and the daily mean concentrations of total 15 PAHs with good recovery were 292 ± 364 ng/m^3 and ranged between 53.3 and 1129 ng/m^3. The daily mean total 15 PAH concentrations were much higher in the nomadic village (480 ± 450 ng/m^3) than in the agricultural village (105 ± 72.6 ng/m^3) and this might be due to the more yak dung burning in the nomadic village than in the agricultural village. More of the semi-volatile PAHs (4-ring) would occur during yak dung combustion, where temperatures are lower than in wood fires.

Among the 15 detected PAHs, benzo(a)pyrene (BaP) showed the highest overall average concentration (53.3 ± 64.0 ng/m^3) and fluorene showed the lowest overall average concentration (1.80 ± 0.88 ng/m^3). The daily mean BaP personal exposure ranged from 9.37 to 192 ng/m^3 and were all significantly higher than the daily BaP concentration limit in China's 2002 National Indoor Air Quality Standard of 1.0 ng/m^3. **Figure 2.3** shows the mean and SD of the 15 PAH concentrations by village type. Among these, concentrations for dibenzo(al)pyrene and dibenzo(ah)pyrene were significantly higher in the nomadic village (t-test, $p < 0.05$). In addition, personal $PM_{2.5}$ concentration exposure was highly correlated to the total 15 PAH concentrations ($r = 0.92$, p-value < 0.001).

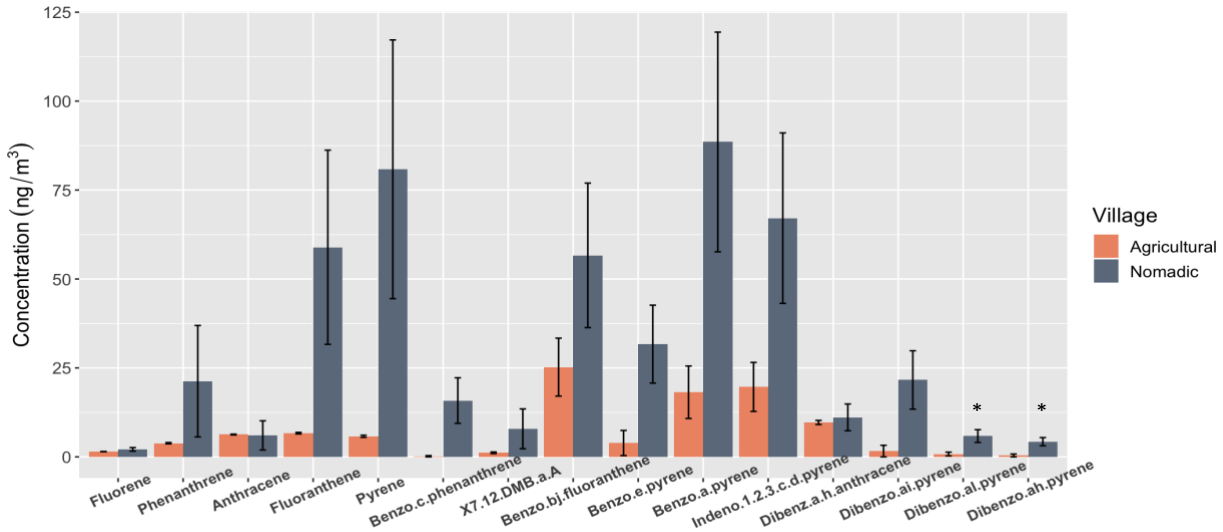


Figure 2.3 Bar plot of 15 PAH mean concentrations by village type (ng/m^3). Error bar indicates 1 SD. * indicates significant difference in PAH concentration by village type

We analyzed 33 inorganic element mass concentrations obtained from $PM_{2.5}$ filters (n = 11) placed in MicroPEM (**Supplementary Table A4**). 24 elements had at least one measurement above the minimal detectable limit (MDL) of applied analytical techniques. Among these, Al, Ba, Br, Ca, Cl, Cs, Fe, K, Mn, Na, P, S, Si, Ti and Zn were present in all 11 samples; Cr, Mg, Ni, Rb and V were present in ten samples. **Figure 2.4** presents the mean and SD of all 33 examined element concentrations by the village type. Al, Cl, S, and V showed significantly different concentration between the two villages (t-test, $p < 0.05$).

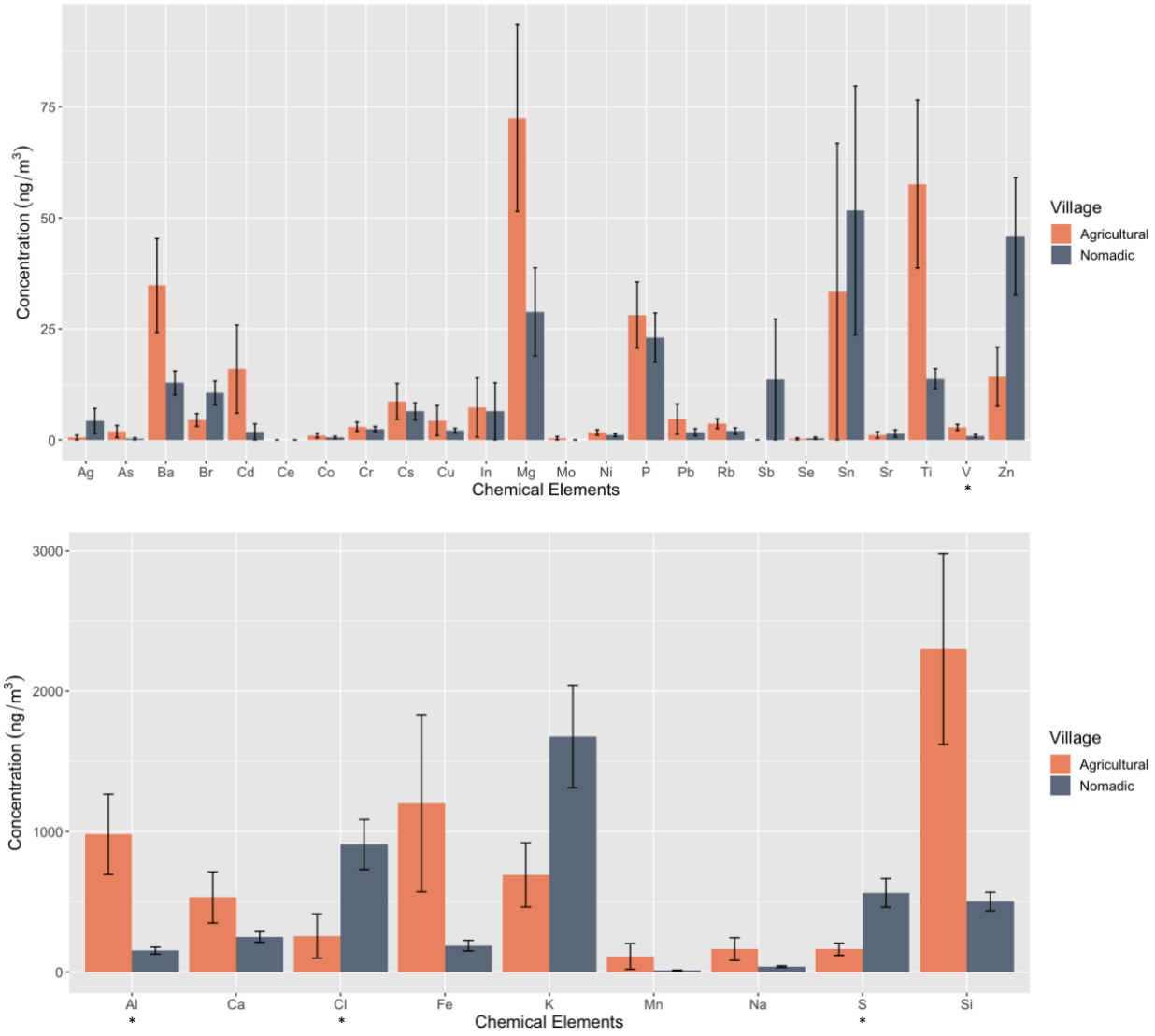


Figure 2.4 Bar plot of element concentrations by village. Error bars indicate 1 SD. Top: mean concentrations lower than 50 ng/m^3; Bottom: mean concentrations higher than 50 ng/m^3. *Element concentrations significantly different by village type ($p<0.05$)

2.3.3 Statistical analysis results

Personal $PM_{2.5}$ exposure was significantly higher in nomadic households and all identified exposure determinants in univariate analyses were also related to the village type (**Supplementary Table A5**). Household size is smaller in nomadic village due to the temporary residency in summer and thus it was negatively associated with higher level of $PM_{2.5}$ exposure. Annual household income is lower in the nomadic village and thus it was also negatively associated with the level of $PM_{2.5}$ exposure. Households with multiple stoves tend to have lower levels of $PM_{2.5}$ exposure because most of households that owned more than one stove were from agricultural village, while only one household in the nomadic village did. The secondary stoves in the agricultural village were usually electric or animal fodder stoves, located outside of the house and it may help reduce the usage of the more polluted primary stove in the kitchen. The age of the main stove and chimney were lower in the nomadic village, as discussed earlier, and thus they were negatively associated with $PM_{2.5}$ exposure. Yak dung was significantly associated with higher levels of $PM_{2.5}$ exposure, but firewood was not, when electricity was set as the reference group.

In a multivariable linear regression analysis of $PM_{2.5}$ personal exposure, covariates that remained significant in all three variable selection procedures (forward, backward, and stepwise) were village type and chimney age. As expected, being in nomadic village is positively associated with higher level of $PM_{2.5}$ exposure. The age of chimney was negatively related to the $PM_{2.5}$ exposure from the reason mentioned above. The R^2 was 0.697, when adjusted for the number of predictors in the model (**Table**

2.3). The results also suggested that personal $PM_{2.5}$ exposure in nomadic households would be five times higher compared to that in agricultural households.

Table 2.3. Multivariable linear regression outcome [a.]

Covariates	β Coefficient (Standard Error)	P value	R^2
(Intercept)	3.86 (0.20)	< 0.001	0.712
Village type (ref. Agricultural village)			
Nomadic village	1.59 (0.20)	< 0.001	**Adjusted R^2**
Chimney age	-0.05 (0.03)	0.07	0.697

[a.] Modeled on natural log scale

2.4 Discussion

In this study, we measured 24-hour integrated personal exposure to multiple household air pollutants and kitchen area BC concentrations. To our knowledge, this is one of the most comprehensive HAP measurements conducted in the Tibetan region and the first exposure assessment performed on both women and children. The exposure levels in nomadic village were comparable to previous measurements in the same region and season (Carter et al., 2016; Hu et al., 2016; Li et al., 2012a, 2012b; Ni et al., 2016; Xiao et al., 2015), although, the exposure levels in agricultural village were much lower. This result indicated great heterogeneity in the personal HAP exposures of the Tibetan community. Factors contributing to the high exposure levels in the nomadic village may include poor ventilation of temporary housing, inefficient combustion resulting from higher moisture content in yak dung or shrubs due to frequent rain in the summer, and poorer conditions of the stoves/chimney.

Personal $PM_{2.5}$ exposures from present study were not significantly different between the primary adult cooks and children. Although children were not involved in cooking activities as much, the non-separated kitchen leads to a similar exposure level between adults and children. Our result is supported by another study conducted in rural Yunnan that found similar overall levels of exposure between

adults and children (J. Baumgartner et al., 2011). We also did not observe significant HAP exposure differences between households with and without active smoker(s). Several households reported that smokers usually smoked outside of the house/tent; other households mentioned that smokers (all males) typically worked outside and spent little time indoors during the day. These may explain the nondifferential HAP exposures between homes with and without smokers.

Studies conducted in other areas of rural China, mainly north/northeast China (e.g. Hebei, Shanxi) and southwest China (e.g. Yunnan, Sichuan), showed that the personal exposure to $PM_{2.5}$ ranged from around 30 to 600 $\mu g/m^3$, depending on fuel and stove types, cooking behaviors, sampling seasons and locations among other factors (Du et al., 2018). The overall geometric mean of personal $PM_{2.5}$ exposure for north/northeast rural residents in winter and summer were 359 and 121 $\mu g/m^3$; while for southwest residents in winter and other seasons were 160 and 69 $\mu g/m^3$, respectively (Du et al., 2018). These results are comparable to what we observed.

Generally, personal exposure levels from this study were higher than the WHO interim annual $PM_{2.5}$ target (IT-1) for household air pollution at 35 $\mu g/m^3$, China's 2012 NAAQS for annual $PM_{2.5}$ at 35 $\mu g/m^3$ and 24-hour $PM_{2.5}$ at 75 $\mu g/m^3$, as well as and the United States Environmental Protection Agency (USEPA) annual primary ambient air quality standard for $PM_{2.5}$ at 12 $\mu g/m^3$ and 24-hour $PM_{2.5}$ at 35 $\mu g/m^3$. These high HAP exposures may imply great health risks in the region.

The observed mean $\pm$ SD of 24-hour kitchen area BC concentrations were 1.83 $\pm$ 1.47 $\mu g/m^3$ in the agricultural village ($n = 5$) and 10.0 $\pm$ 4.53 $\mu g/m^3$ in the nomadic village ($n = 3$). Shan et al. (2014) also measured kitchen area BC in Sichuan province, although their study was conducted in fall, among households using wood as the primary fuel. They reported the geometric mean of kitchen BC at 3.5 $\mu g/m^3$ (range: 0.7–11.8). Secrest et al. (2016) measured personal exposure to BC for rural women in

Sichuan during the summer and reported similar geometric mean BC exposure at 3.42 μg/m^3 (range: 1.47–7.77). These results were comparable to what we observed in the firewood using households.

BC/$PM_{2.5}$ mass ratio from personal filter samples provides information on fuel combustion (Xiao et al., 2015), particulate chemical composition and health implications. In our analysis, the average BC/$PM_{2.5}$ mass ratio was 0.24 and ranged from 0.03 to 0.67. Our results show similarities with other studies conducted in India, Nepal, and northern China (Garland et al., 2017; Li et al., 2009; Soneja et al., 2015) but it is much higher than the previously-reported ratios in central Tibet at 0.013 (range: 0.006 - 0.028), where 83% of the households were using yak dung exclusively (Xiao et al., 2015). The average BC/$PM_{2.5}$ mass ratio indicates the average contributions of BC to $PM_{2.5}$ mass and it is related to various combustion conditions, which vary by stove types, human activities (e.g. cooking and fuel adding etc.), fuel moisture contents, air supply, heat transfer rate, and ventilation due to chimney/house structures (MacCarty et al., 2010; Xiao et al., 2015). We observed a low to moderate correlations between minute level personal $PM_{2.5}$ exposure and kitchen area BC concentration (range: -0.002 – 0.77). Similar observations have been reported by previous studies in Sichuan (Shan et al., 2014) and Yunnan (J. Baumgartner et al., 2011), indicating that participants were not always at home and other combustion or non-combustion sources might have influenced the personal exposures.

Of the subset of 12 filters analyzed for 15 PAHs, the daily mean concentration was 292 ± 364 ng/m^3 and ranged between 53.5 and 1129 ng/m^3. We also observed much higher total PAH concentrations in the nomadic village than in the agricultural village. One explanation is that nomadic households used more yak dung than in agricultural households. Large amounts of PAHs could be produced during the slow burning of yak dung with a high moisture content at lower temperatures. Secrest et al. (2017) also found that household burning dung and crop residues resulted in higher PAH mass concentrations than wood and coal and suggested burning animal dung may pose a greater health risk

than other fuels. Among the PAH personal exposure measurements in China, Lin et al., (2016) reported comparable particulate total PAH_{15} exposures for wood gasifier stove users in Hubei, (central China) at 310 ± 326 ng/m^3. Another study conducted in rural Hebei (north China) reported higher particulate phase total PAH_{15} exposure for both cook (1,610 ± 980 ng/m^3) and non-cook (684 ± 258 ng/m^3), using biomass stoves during winter (Ding et al., 2012). Factors contributing to the variability of PAH concentration include seasons (heating vs non-heating seasons), indoor ventilation conditions, fuel types, measurement types (e.g., personal, microenvironment), cooking methods (e.g. frying, roasting, boiling), combustion conditions, fuel moisture contents, as well as outdoor and other PAH sources etc. As we measured in a non-heating season, when cookstoves were solely used for preparing food, the PAH exposures were slightly lower.

The average daily personal exposure to BaP from this study (53.3 ± 64.0 ng/m^3) was significantly higher than the concentration limit for BaP in China's National Air Quality Standard for indoor air at 1.0 ng/m^3 and for ambient air at 2.5 ng/m^3. Ding et al., (2012) reported BaP exposure for cooks using biomass in Hebei (north China) at 190 ± 150 ng/m^3 in winter and 1.2 ± 0.77 ng/m^3 in summer. Lin et al. (2016) reported particulate BaP exposure for wood gasifier stove users in Hubei (central China) at 27.1 ± 34.7 ng/m^3 in winter. In Yunnan (southwest China), Downward et al., (2014) assessed the particle-bound BaP exposure for households using wood (66.6 ng/m^3) and plant (95.6 ng/m^3). These studies suggest that BaP exposure vary by season, geographic location, household fuel types and whether a person was engaged in cooking activities. Although our BaP measurement result lies in the middle of previously observed values in households burning biomass, it was still 25 – 50 times higher than the national standard and should be concerned regarding the potential health effects.

Lastly, identified high concentration elements in our analysis also showed great variability by village type. Four metals – Al, Cl, S, and V – were significantly different between agricultural and nomadic

village. The highest five concentrations were for elements Si, Fe Al, K, and Ca in the agricultural village, and K, Cl, S, Si and Ca in the nomadic village. Elements Si, Fe, Al, Ca and Ti are usually considered as tracers for road dust generated from vehicles emissions, tire/brake wear debris and road abrasion (Liu et al., 2016; Tullio et al., 2008; Yu et al., 2013). The element Ca may originate from construction dust and V is related to human activities, such as vehicle exhaust (Liu et al., 2016). Therefore, the high concentrations for Si, Fe, Al, and Ca in the agricultural village may be explained by highway traffic nearby. Biomass (wood) burning is characterized by high concentration of K and S (Hedberg et al., 2002; Ryu et al., 2007; Yu et al., 2013). The high K and S levels form both villages aligned with the observation that wood and shrubs were commonly used in sampled households. Additionally, Sb and Cl are typical element markers for garbage burning emissions (Jayarathne et al., 2018). The relatively higher concentrations of Sb and Cl in the nomadic village indicated a possibility of indoor garbage burning. This is further supported by our observation that there was no solid waste management facility in the nomadic village and burning garbage at home was one of the few viable options and therefore commonly conducted. Very few studies have measured personal exposure or indoor concentrations of particle-bound elements in rural China. One study in rural Sichuan (southwest China) reported mean personal exposure to Zn was 103 ng/m^3 (range: 22.2 – 403 ng/m^3) and to Pb was 76.1 ng/m^3 (range: 5.54 – 570 ng/m^3) (Secrest et al., 2016; 2017). Another study conducted in Henan (north China) measured mass concentration of As, Pb, Zn, Cd, Cu, Ni and Mn by different locations, various household energy sources and in different seasons (Wu et al., 2015). They reported that Zn, Pb and Mn were the most abundant elements in $PM_{2.5}$. In our analysis, concentrations for As, Pb, Zn, Cd, Cu, Ni and Mn were all much higher than their samples collected from the most polluted coal-burning households in winter (Wu et al., 2015). Li et al. (2012a) reported concentrations of As, Bi, Co, Cs, Cu, and Pb in $PM_{2.5}$ from Tibetan tents in the pastoral area of southern Tibetan Plateau using yak dung

exclusively. The concentrations of these trace metals were all higher compared to ours, suggesting that burning yak dung exclusively could be more hazardous than other household solid fuel mixes.

2.5 Conclusion

Our findings show that HAP exposures in Tibetan households is pervasively high and requires immediate actions to mitigate the potential adverse health impacts. Moreover, our study questions the commonly accepted assumption that biomass burning was the single most important source of air pollution exposure in rural Tibet as the ambient air is deemed to be the cleanest in this area. As the local infrastructure and economy develops, "new" sources such as traffic, road/construction dusts and garbage burning could contribute more and more to personal HAP exposure, especially when stoves are not in use. Strategies to reduce air pollution exposure and associated health effects in this region should, therefore, consider not only improving the stove/fuel efficiency and room ventilation, but also identifying and managing other pollution sources and behavioral factors, such as indoor garbage burning. Additionally, the awareness of HAP exposure and associated health effects was very low among our sampled households. Environmental health education programs are equally important and should be implemented to strengthen the internal motivation for positive changes.

Chapter 3

Baseline associations between household air pollution and maternal blood pressure in the Household Air Pollution Intervention Network (HAPIN) multi-country randomized controlled trial

3.1 Background

Approximately 49% of the global population – about 3.8 billion people – burn solid fuels (including coal, wood, charcoal, dung, and crop residues, among others) as an energy source for cooking and heating (Health Effects Institute, 2020). These practices result in the release of high concentrations of air pollutants, resulting in exposure that often exceeds WHO air pollution guidelines (Johnson et al., 2011; Johnson and Chiang, 2015). Household air pollution (HAP) generated from the incomplete combustion of these fuels in traditional stoves contributes to a large burden of ill health – between 1.6 and 4 million deaths per year from causes including diabetes, respiratory, and cardiovascular diseases (CVD) (Landrigan et al., 2018; Murray et al., 2020).

Numerous pollutants are released during the combustion of solid fuels (Naeher et al., 2007; Northcross et al., 2012); the most well studied are (A) particulate matter with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$) and (B) carbon monoxide (CO) (Shupler et al., 2018). These pollutants have been associated with changes in blood pressure – a known risk factor for cardiovascular disease – in

association with exposure to ambient air pollution (Yang et al., 2018) and specifically among households using solid fuels (Alexander et al., 2015; Arku et al., 2018; Baumgartner et al., 2011, 2018, 2014; Clark et al., 2013). The exact mechanisms by which air pollution impacts blood pressure are unknown; it is hypothesized that pulmonary and systemic oxidative stress, inflammation, and disturbances of the cardiac autonomic nervous system may contribute to the observed effects (Brook et al., 2010, 2009, 2004).

While several studies have evaluated the relationship between solid fuel use and blood pressure, only a small number have measured personal exposure to HAP constituents. Most have focused on comparing biomass versus clean fuel users as a proxy for exposure (Agrawal and Yamamoto, 2015; Lee et al., 2012; Painschab et al., 2013; Wylie et al., 2015; Yan et al., 2016). Several studies have evaluated interventions that reduce HAP exposure and their impacts on blood pressure (Alexander et al., 2015; Clark et al., 2013; McCracken. et al., 2007). However, few have evaluated the impact of HAP on blood pressure during pregnancy (Alexander et al., 2017; Quinn et al., 2017, 2016; Thompson. et al., 2011). Blood pressure changes during pregnancy are well documented: during normal pregnancy, changes in blood volume and cardiac output result in decreased systolic and diastolic blood pressure in early pregnancy, followed by elevated blood pressure and a return to normal, pre-pregnancy levels at approximately 20 weeks' gestation (Ayala et al., 1997; Hermida et al., 2000). Elevated blood pressure complicates an estimate of 3-10% of pregnancies worldwide (Steegers et al., 2010) and contributes to 30,000 maternal deaths annually (von Dadelszen and Magee, 2016).

As part of the Household Air Pollution Intervention Network (HAPIN) multi-country randomized controlled trial (RCT), we are evaluating the impact of a clean fuel and stove intervention during pregnancy on birth weight, growth, and severe pneumonia in children and blood pressure in older adult women over ~18 months of follow-up. As secondary measures, we assessed, among other things,

personal exposures of pregnant HAPIN participants to $PM_{2.5}$, BC, and CO and their blood pressure at various time points throughout the trial (Clasen et al., 2020; Johnson. et al., 2020). Prior to randomization and intervention delivery, we collected baseline data on participants and their households and measured their systolic blood pressure (SBP) and diastolic blood pressure (DBP). We also assessed their personal exposures to household air pollutants. In this paper, we report associations of HAP (i.e., $PM_{2.5}$, BC, and CO) exposures and gestational blood pressure at baseline.

3.2 Methods

3.2.1 Study design, location, and population

This analysis includes 3195 pregnant women enrolled between 2016 and 2018 at the four international research centers (IRCs) of the HAPIN trial at baseline: Guatemala (N = 800), India (N = 799), Peru (N = 798), and Rwanda (N = 798). Details about the study design and locations are provided elsewhere (Clasen et al., 2020). The four IRCs selected span a range of characteristics expected to influence intervention effects, including altitude, population density, cooking practices, baseline pollution levels, and sources of pollution other than cooking (Clasen et al., 2020).

In Guatemala, the study sites are in the Jalapa municipality. Cooking occurs primarily indoors using wood in chimney stoves and open fires. In India, study sites are in the southern state Tamil Nadu, where traditional clay/mud stoves are fueled with wood, predominantly indoors. In Peru, study sites are spread across six rural provinces in the Department of Puno. Households rely on dung-fueled stoves for daily cooking. The study sites in Rwanda are in the Eastern Province. Most households cook indoors using (1) traditional three-stone fires or simple open stoves (known as *rondereza)* fueled with wood and (2) portable charcoal stoves (*imbabura*).

Pregnant women were eligible for enrollment into the HAPIN trial if they 1) were between 18 and <35 years of age, 2) cooked primarily with solid fuels and did not plan to switch to clean fuels predominantly in the near future, 3) lived in the study area and did not plan to move permanently in the next 12 months, 4) were between 9 and < 20 weeks of gestation with a singleton pregnancy confirmed by ultrasound, 5) continued pregnancy at the time of randomization, 6) were not current smokers, and 7) agreed to participate with informed consent (Clasen et al., 2020). Study protocols and procedures have been reviewed and approved by institutional review boards (IRBs) or Ethics Committees of Emory University (00089799), Johns Hopkins University (00007403), Sri Ramachandra Institute of Higher Education and Research (IEC-N1/16/JUL/54/49) and the Indian Council of Medical Research – Health Ministry Screening Committee (5/8/4-30/(Env)/Indo-US/2016-NCD-I), Universidad del Valle de Guatemala (146-08-2016) and Guatemalan Ministry of Health National Ethics Committee (11-2016), Asociación Beneficia PRISMA (CE2981.17), the London School of Hygiene and Tropical Medicine (11664-5), the Rwandan National Ethics Committee (No.357/RNEC/2018), and Washington University in St. Louis (201611159).

3.2.2 Measurement of personal exposure to household air pollution

Exposure measurement procedures have been published elsewhere (Johnson et al., 2020). 24-hour personal exposures to $PM_{2.5}$ and CO were measured simultaneously for all participants; BC concentrations were assessed using transmissometer after gravimetric sample collection. At exposure monitoring visits, pregnant women were instructed to wear a customized garment, with exposure instrumentation kept near the breathing zone. Participants were also asked to hang the garment on a stand and keep it nearby (within 1-2m) when sleeping, bathing, or conducting other activities during which it was not suitable to wear the monitoring equipment.

Personal exposure to $PM_{2.5}$ was monitored using the Enhanced Children's MicroPEM™ (ECM) (RTI International, Research Triangle Park, USA). The ECM is lightweight (~150g) and generates minimal noise. It measures real-time $PM_{2.5}$ concentrations at 10-second intervals using a nephelometer and simultaneously collects an integrated gravimetric sample on a 15mm PTFE filter. The instrument also records temperature, relative humidity, inlet pressure, and triaxial accelerometry. Twenty-four-hour gravimetric samples were collected for each participant; changes in pre- and post-sampling filter mass were assessed using 1-μg resolution microbalances (Sartorius Cubis, MSA6.6s-000-DF, Göttingen, Germany) at labs at the University of Georgia (for samples collected in Guatemala, Peru, and Rwanda) and Sri Ramachandra Institute for Higher Education and Research (for samples collected in India). Detailed methods and validity criteria are reported elsewhere (Johnson et al, submitted). When a gravimetric sample was deemed invalid, due to missing or damaged filters or flow faults, the nephelometer data from the ECM instrument was used to estimate the instrument-specific nephelometric $PM_{2.5}$ concentrations normalized to field-based filters. Quality control and assurance, duplicates, and instrument wearing compliance are documented in Johnson et al, (submitted).

24-hour BC concentrations were estimated from $PM_{2.5}$ filter samples using SootScan Model OT21 Optical Transmissometers (Magee Scientific, USA). BC depositions were estimated per Garland et al. (2017). Personal CO exposure was measured by Lascar EL-USB-300 (Lascar Electronics, USA). Lascar is the size of a large pen (125 x 26.4 x 26.4mm, 42g) and logged CO concentrations at 1-minute intervals. Details for CO and BC data quality assurance and instrument calibration are reported in Johnson et al. (2020).

3.2.3 Measurement of blood pressure

At the baseline health assessment visit for the study, a nurse or trained field worker measured resting blood pressure in the right arm of the pregnant women in triplicate (with at least 2 minutes between

measurements) using an automatic monitor (model HEM-907XL; Omron®). Before starting the measurement, the participant was instructed to sit on a chair in a quiet room for 5 min with legs uncrossed, their back supported by the chair, and their arm supported on a table. The pregnant woman also confirmed that she had not smoked, consumed alcohol, or caffeinated beverages (coffee, tea, or Coca-Cola), or cooked using biomass in the past 30 minutes. If she had done any of those activities in the 30 minutes prior to the measurement, she would be asked to refrain from doing these activities for 30 minutes before proceeding with the measurements.

In analyses, the average of all three BP measurements was used. A participant with a measured SBP ≥ 140 mmHg and/or a DBP ≥ 90 mmHg was checked again during the same visit. If the same result was observed on two measurements, the participant was referred to the nearest health center or hospital to receive age-appropriate treatment. If a participant had SBP < 80 mmHg or a DBP < 40 mmHg, she would also be referred to the nearest health center or hospital.

3.2.4 Questionnaires and other measurements

During the baseline visit, questionnaires were administered by trained field works in the local language to obtain information on households' demographic and socioeconomic status based on ownership of assets (e.g., color TV, radio, mobile phone, bicycle, bank account, etc.); stove and energy use patterns; kitchen configuration(s); other exposure sources (e.g., environmental tobacco smoke; incense and garbage burning, etc.); self-reported medical/gynecological history and medication use; and lifestyle behaviors (i.e., physical activity, diet diversity, food insecurity, and alcohol/tobacco consumption). Questionnaires were tested prior to implementation. Baseline maternal weights (seca 876/874 scales; Seca) and heights (seca 213 stadiometer; Seca) were measured in duplicate. Gestational age at the blood pressure measurement visit was calculated by using the ultrasound-estimated gestational age at

screening plus the difference in days between the screening date and the blood pressure measurement date.

3.2.5 Statistical analysis

We used univariate and multivariable regression models to investigate the association between personal exposure to $PM_{2.5}$/BC/CO and gestational SBP and DBP. We evaluated correlations between pollutants (Spearman's ρ). Model assumptions were verified using routine regression diagnostics.

Because we hypothesized that there may be nonlinear relationships between HAP exposure and BP, we utilized Generalized Additive Models (GAMs) with default thin plate regression splines with 2, 3, and 4 degrees of freedom and restricted maximum likelihood estimation to model smooth functions of exposure. We compared GAMs, linear models, and loglinear models through visual inspection and a comparison of Akaike Information Criterion (AIC; an estimate of goodness of fit; a lower AIC indicates a better fit to the data). Based on these assessments, we report our main results for $PM_{2.5}$/BC/CO and SBP/DBP relationships using linear models with both natural log-transformed and categorical (in quartiles) exposure terms.

Covariates included in the final adjusted models were either chosen *a priori* as known confounders from the literature or were identified as potential confounders guided by a DAG (**Figure S1**). They were included if they changed the estimate of $PM_{2.5}$/BC/CO exposure by more than 10%. Covariates selected *a priori* were gestational age, BMI, nulliparity, and IRC. Nulliparity is defined as zero pregnancies reaching 20 weeks and 0 days of gestation or beyond; miscarriages can have occurred in a woman who is nulliparous. Variables evaluated as potential confounders included maternal age, mother's highest level of education, socioeconomic status (a wealth index calculated based on a group

of household assets or ownership of specific assets), physical activity, date (weekday vs. weekend) and time (morning vs. afternoon) of the blood pressure measurement, household food insecurity score, mother's minimum diet diversity, exposure to environmental tobacco smoke, and month of the blood pressure measurement (to account for potential seasonality).

Potential effect modification by BMI, physical activity, and exposure to environmental tobacco smoke was assessed using multiplicative interaction terms between these factors and $PM_{2.5}$/BC/CO exposure variables in adjusted models.

We conducted multiple sensitivity analyses. We ran separate models for $PM_{2.5}$ and BC given their correlations (Spearman's $\rho = 0.79$). CO was moderately associated with $PM_{2.5}$ (Spearman's $\rho = 0.47$) and BC (Spearman's $\rho = 0.42$). Therefore, in addition to single pollutant models, we also conducted multi-pollutant models that contain exposure terms for both $PM_{2.5}$ and CO or both BC and CO as one sensitivity analysis. Additionally, to control potential clustering within each IRC, we fit mixed effects models with an individual IRC random intercept. We evaluated variance components from the mixed effects models to estimate the intraclass correlation coefficient (the ICC, or fraction of variance explained by between IRC differences). We compared fixed versus mixed effects model findings. We evaluated whether our results changed after excluding the highest 1% and 5% exposure measurements given that few data points were collected at these very high values and corresponding confidence intervals were wide.

All statistical modeling was using R version 4.0.3. GAMs were fitted using the `mcgv` package (Wood, 2021). Mixed effects models were fitted with the `lme4` package (Bates *et al.*, 2015).

3.3 Results

3.3.1 Participant characteristics

Five pregnant women were taking antihypertensive medication at baseline, and they were excluded from all analyses. The association analyses were restricted to individuals with both valid exposure and blood pressure measurements. After excluding the five participants on antihypertensive medication at baseline, the remaining 3,190 pregnant women comprise our analytical population (**Table 3.1**). The average maternal age of this cohort was 25.4 years (range 18-35), and the mean gestational age was 15.4 (range 8.43 – 24.9) weeks (**Figure B2**). More than half (59%) of the participants were normal/healthy weight; 30% of the participants were considered overweight or obese. 1228 (38%) of the pregnant women were nulliparous. About two-third of the women (2150, 67%) had completed at least primary education, and more than half (57%) were employed outside the household. Very few participants reported a history of hypertension (<1%), or diabetes (<1%) at the baseline health assessment. 82% of the pregnant women were the primary cooks of their family, and 10% reported that one or more smokers lived in their household.

Table 3.1 Baseline characteristics of pregnant women participating in the HAPIN Trial[1]

Characteristic	**Guatemala** N = 800	**India** N = 799	**Peru** N = 798	**Rwanda** N = 793	**All** N = 3190
Maternal characteristics					
Maternal age, Mean (SD) [Range]	24.7 (4.44) [18.0, 34.9]	24.0 (3.79) [18.1, 34.8]	25.5 (4.49) [18.0, 35.0]	27.3 (4.41) [18.1, 34.9]	25.4 (4.46) [18.0, 35.0]
Gestational age (weeks), Mean (SD) [Range]	14.3 (3.06) [8.43, 21.3]	16.1 (3.04) [9.57, 24.9]	15.2 (3.31) [9.00, 22.7]	15.5 (2.79) [9.71, 21.7]	15.4 (3.13) [8.43, 24.9]
BMI, Mean (SD) [Range]	23.8 (3.32) [16.4, 44.2]	19.7 (3.18) [13.3, 37.6]	26.0 (3.63) [17.9, 39.6]	23.4 (3.38) [16.6, 42.7]	23.2 (4.07) [13.3, 44.2]
BMI categories, N (%)					
Underweight (<18.5)	11 (1%)	308 (39%)	1 (<1%)	13 (2%)	333 (10%)
Normal/Healthy Weight (18.5 – 24.9)	543 (68%)	434 (54%)	330 (41%)	573 (72%)	1880 (59%)
Overweight (25.0 – 29.9)	205 (26%)	50 (6%)	341 (43%)	166 (21%)	762 (24%)
Obesity (≥30.0)	36 (5%)	7 (1%)	116 (15%)	37 (5%)	196 (6%)
Missing	5 (<1%)	0	10 (1%)	4 (1%)	19 (1%)

Nulliparous, N (%)					
Yes	227 (28%)	459 (57%)	310 (39%)	232 (29%)	1228 (38%)
No	573 (72%)	340 (43%)	484 (61%)	559 (70%)	1956 (61%)
Missing	0	0	4 (1%)	2 (<1%)	6 (<1%)
History of preterm birth, N (%)	19 (2%)	12 (2%)	36 (5%)	24 (3%)	91 (3%)
History of spontaneous abortion, N (%)	123 (15%)	84 (11%)	84 (11%)	131 (17%)	422 (13%)
History of stillborn, N (%)	35 (4%)	15 (2%)	13 (2%)	37 (5%)	100 (3%)
History of hypertension, N (%)	7 (1%)	0	3 (<1%)	5 (<1%)	15 (<1%)
History of diabetes, N (%)	1 (<1%)	0	1 (<1%)	3 (<1%)	5 (<1%)
Mother's education level, N (%)					
No formal education or Primary school incomplete	381 (48%)	285 (36%)	35 (4%)	338 (43%)	1039 (33%)
Primary school complete or Secondary school incomplete	312 (39%)	227 (28%)	234 (29%)	316 (40%)	1089 (34%)
Secondary school complete or Vocational or Some college or university	107 (13%)	287 (36%)	528 (66%)	139 (18%)	1061 (33%)
Missing	0	0	1 (1%)	0	1 (<1%)
Mother's occupation, N (%)					
Agriculture	6 (1%)	338 (42%)	513 (64%)	540 (68%)	1397 (44%)
Commercial	17 (2%)	4 (1%)	111 (14%)	135 (17%)	267 (8%)
Household	746 (93%)	432 (54%)	132 (17%)	56 (7%)	1366 (43%)
Other	31 (4%)	25 (3%)	42 (5%)	62 (8%)	160 (5%)
Physical activities (total MET[2] min/day), Mean (SD)					
Quartile 1	67.1 (60.6)	109 (48.1)	136 (70.1)	109 (68.3)	81.9 (63.1)
Quartile 2	419 (149)	517 (195)	567 (174)	514 (164)	496 (182)
Quartile 3	1011 (180)	1076 (157)	1151 (177)	1118 (179)	1110 (176)
Quartile 4	2288 (735)	2258 (706)	2365 (655)	2485 (812)	2401 (727)
Household characteristics					
Household size, Mean (SD) [Range]	5.2 (2.6) [2, 18]	3.8 (1.5) [1, 10]	4.6 (1.8) [2, 12]	3.5 (1.5) [1, 10]	4.2 (2.0) [1, 18]
Household wealth at national quintiles, N (%)					
1 (lowest)	603 (75%)	179 (22%)	618 (77%)	88 (11%)	1488 (47%)
2	117 (15%)	401 (50%)	120 (15%)	181 (23%)	819 (26%)
3	66 (8%)	176 (22%)	55 (7%)	172 (22%)	469 (15%)
4	14 (2%)	43 (5%)	5 (1%)	237 (30%)	299 (9%)
5 (highest)	0	0	0	115 (15%)	115 (4%)
Household primary fuel, N (%)					
Charcoal	0	0	0	193 (24%)	193 (6%)
Cow dung	0	0	697 (87%)	0	697 (22%)
Wood	793 (99%)	799 (100%)	90 (11%)	580 (73%)	2262 (71%)
Other	3 (<1%)	0	10 (1%)	18 (2%)	31 (1%)
Missing	4 (<1%)	0	1 (<1%)	2 (<1%)	7 (<1%)
Household primary cook, N (%)					
Pregnant women	676 (85%)	757 (95%)	455 (57%)	732 (92%)	2620 (82%)
Others in the household	123 (15%)	42 (5%)	342 (43%)	59 (7%)	566 (18%)

Missing	1 (<1%)	0	1 (<1%)	2 (<1%)	4 (<1%)
Someone in the household smokes, N (%)					
Yes	44 (5%)	253 (32%)	7 (1%)	30 (4%)	334 (10%)
No	756 (95%)	546 (68%)	789 (99%)	761 (96%)	2852 (89%)
Missing	0	0	2 (<1%)	2 (<1%)	4 (<1%)

Note:

[1] 5 pregnant women on antihypertensive medication are excluded.

[2] MET: Metabolic equivalent of task

4.3.2 Gestational blood pressure

The mean (SD) SBP and DBP in this cohort were 104.8 (9.7) mmHg and 60.7 (7.8) mmHg (**Table 3.2, Figure B3**). Participants in Rwanda had both the highest mean SBP and DBP; on average, Peruvian participants had the lowest SBP and DBP. Based on the blood pressure classification of AHA/ACC[1] Guideline, 93% (2959) of the participants had normal blood pressure (<120/<80 mmHg) and 5% (152) had elevated blood pressure (120-129/<80 mmHg). 56 (2%) had High Blood Pressure (Stage 1) (130-139/80-89 mmHg) and very few (9, <1%) had High Blood Pressure (Stage 2) (≥140/≥90 mmHg) category.

Table 3.2 Measured blood pressure at baseline by IRC

	Guatemala N = 798	**India** N = 799	**Peru** N = 788	**Rwanda** N = 791	**All** N = 3176
SBP					
Mean, (SD)	103.9 (8.5)	104.5 (9.1)	99.6 (7.9)	111.2 (9.4)	104.8 (9.7)
[Range]	[77.7, 145]	[80.0, 142.0]	[74.0, 136.0]	[86.0, 156.0]	[74.0, 156.0]
DBP					
Mean, (SD)	59.6 (7.2)	61.5 (7.6)	57.1 (6.9)	64.8 (7.4)	60.7 (7.8)
[Range]	[38.5, 88.7]	[42.0, 95.3]	[38.0, 86.0]	[44.0, 112.0]	[38.0, 112.0]

Note:

[1] 14 missing SBP/DBP measurement at baseline: 2 in Guatemala, 10 in Peru, 2 in Rwanda

[1] American Heart Association, American College of Cardiology

3.3.3 Personal exposures to $PM_{2.5}$, BC, and CO

Of the 3190 pregnant women in our analytical population, 2818 (88%), 2536 (79%), and 2872 (90%) participants had valid personal exposure measurements to $PM_{2.5}$, BC, and CO, respectively. Distributions of $PM_{2.5}$, BC, and CO exposure by IRCs are shown in **Figure 3.1**. The median (IQR) 24-hour $PM_{2.5}$ personal exposure in this cohort is 82.9 (99.8) $\mu g/m^3$, and 82% of the participants' exposures to $PM_{2.5}$ were higher than the World Health Organization's annual interim target 1 guideline value of 35 $\mu g/m^3$. The median (IQR) of the 24-hour personal exposure to BC and CO was 10.7 (9.0) $\mu g/m^3$ and 1.2 (2.3) ppm, respectively. Descriptive summaries of exposure to $PM_{2.5}$, BC, and CO after removing the highest 1% and 5% data points are presented in **Table B1**. 95% of the $PM_{2.5}$, BC and CO exposure observations were less than 312.7 $\mu g/m^3$, 29.4 $\mu g/m^3$, and 9.0 ppm, respectively. Based on the intraclass correlation coefficient for $PM_{2.5}$ (ICC = 0.13), BC (ICC = 0.07), and CO (ICC = 0.06), we observed high within-IRC variability relative to total variability in $PM_{2.5}$/BC/CO exposures. ICCs from models excluding the highest 5% of exposures slightly increased for $PM_{2.5}$ (ICC = 0.14) and BC (ICC = 0.12) but decreased for CO (ICC = 0.04). Including covariates or log transform exposure did not change our results.

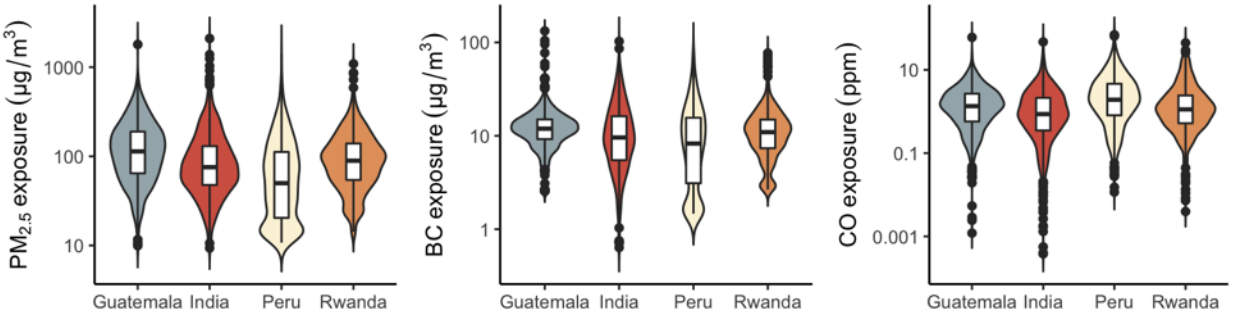


Figure 3.1 Violin plot of personal exposure to $PM_{2.5}$, BC, and CO at baseline by IRC. Y-axes are log_{10}-transformed.

Table 3.3 Measured 24-hour personal exposures to $PM_{2.5}$, BC, and CO (all valid samples) by IRC

	Guatemala	India	Peru	Rwanda	All

$PM_{2.5}$ exposure ($\mu g/m^3$)					
N (% of valid)	733 (92%)	715 (89%)	658 (82%)	712 (90%)	2818 (88%)
Median (IQR)	113.0 (125.0)	75.5 (82.2)	49.9 (91.5)	89.2 (84.8)	82.9 (99.8)
Mean [Range]	146.0 [9.9, 1799]	115.0 [9.4, 2100]	84.9 [10.7, 1400]	112 [14.2, 1090]	115.5 [9.4,2100]
BC exposure ($\mu g/m^3$)					
N (% of valid)	675 (84%)	699 (87%)	596 (75%)	566 (71%)	2536 (79%)
Median (IQR)	11.9 (5.8)	9.6 (10.7)	8.3 (12.5)	10.9 [7.6]	10.7 (9.0)
Mean [Range]	13.2 [2.6, 133.0]	12.9 [0.6, 103.0]	11.3 [1.5, 75.3]	12.3 [2.7, 76.9]	12.5 [0.6, 132.6]
CO exposure (ppm)					
N (% of valid)	757 (95%)	745 (93%)	659 (83%)	711 (90%)	2872 (90%)
Median (IQR)	1.33 (2.04)	0.83 (1.76)	8.26 (12.5)	10.9 (7.57)	1.2 (2.3)
Mean [Range]	2.03 [0, 60.2]	1.75 [0, 46.9]	11.3 [1.46, 75.3]	2.48 [0, 44.4]	2.5 [0, 69.5]

3.3.4 Associations between household air pollution and gestational blood pressure

Assessing non-linearity. The associations between SBP/DBP and covariates (i.e., gestational age, nulliparity, BMI, maternal age, mother's highest education level, household wealth index, time of the blood pressure measurement, and mother's diet diversity score) were consistent with linearity. **Figure B4** shows adjusted associations between SBP/DBP and $PM_{2.5}$/BC/CO exposures using GAMs with thin plate regression splines and 3 degrees of freedom. The visually observed nonlinear pattern – where the association flattens or changes direction at very high exposure levels – occurs in data sparse regions where confidence intervals are wide. The associations between GBP and HAP are near-linear when considering 95% of exposure samples, as indicated in red outlined boxes. We thus conclude that the relationships between GBP and HAP are consistent with linearity overall, and therefore report our results using linear, log-linear and categorical (quartiles) exposures for all exposure observations (main analysis) and then excluding the highest 1% and 5% of exposures (sensitivity analysis).

Models. Results of adjusted models including all valid exposure observations are presented in **Table 3.4**. We observed that increased exposures to BC were significantly associated with SBP in pregnant women with BC exposures in the highest quartile compared to those with BC exposures in the lowest quartile (1.21 mmHg, 95% CI: 0.22, 2.19). We also observed borderline significant association between

$PM_{2.5}$ exposure and SBP in women with exposures in the highest quartile compared to the lowest (0.93 mmHg, 95%: -0.04, 1.89, p-value = 0.059) and log transformed BC exposure and SBP (0.44 mmHg. 95% CI: -0.01, 0.89).

Non-significant increases in SBP were related to increased exposure to log transformed $PM_{2.5}$ (0.25 mmHg, 95% CI: -0.14, 0.65), and CO (0.04 mmHg, 95% CI: -0.19, 0.27). Removing the highest 1% and 5% of the exposure observations resulted in 10%-27% larger associations between log transformed $PM_{2.5}$/BC exposure and DBP. Unadjusted and minimally adjusted findings are presented in the SI (**Tables B2** and **B3**). Minimally adjusted models (randomization strata, gestational age, nulliparity, BMI) followed similar trends and did not result in substantial difference in estimates.

For $PM_{2.5}$ and BC exposures, we observed evidence that BMI modified the associations with SBP, with stronger associations among obese women (BMI $\geq$ 30) compared to women who were considered normal or healthy weight (BMI between 18.5 and 24.9). Among obese women, a 1 log $\mu g/m^3$ increase in $PM_{2.5}$ exposure was associated with 2.08 mmHg higher SBP (95% CI: 0.60, 3.57) and a 1 log $\mu g/m^3$ increase BC exposure was associated with 1.78 mmHg higher SBP (95% CI: 0.01, 3.55). We also observed a statistically significant interaction between $PM_{2.5}$ and BC exposures and physical activity levels (determined by total MET min/week in quartiles) for DBP. Compared to women with physical activity in the lowest quartile, we found stronger negative associations between $PM_{2.5}$ and BC exposures in women in the highest physical activity quartile. Among women in the most physically active group, a 1 log $\mu g/m^3$ increase in $PM_{2.5}$ exposure was associated with -1.06 mmHg DBP (95% CI: -1.94, -0.18) and a 1 log $\mu g/m^3$ increase in BC exposure was associated with -1.20 mmHg DBP (95% CI: -2.31, -0.08). The associations between air pollution and blood pressure were not modified by exposure to environmental tobacco smoke. Multipollutant models that included both

$PM_{2.5}$ and CO, or BC and CO exposure terms did not show any significant association (data not shown).

The fully adjusted mixed effect models also showed non-significant increases in SBP in relation to increase in log transformed $PM_{2.5}$ (0.21 mmHg, 95% CI: -0.19, 0.61), BC (0.4, 95% CI: -0.05, 0.86), and CO (0.05 mmHg, 95% CI: -0.18, 0.28). The negative association between DBP and increased exposures to $PM_{2.5}$ and BC preserved but are non-significant, with 1 log $\mu g/m^3$ increase in $PM_{2.5}$ and BC associated with -0.25 (95% CI: -0.57, 0.08) and -0.21 (95% CI: -0.58, 0.16) in DBP, respectively.

Table 3.4 Association between HAP exposure and gestational blood pressure at baseline. Results from fully adjusted models (all valid samples)

	Model Type	Estimate	p-value	95% CI	AIC
Systolic Blood Pressure					
$PM_{2.5}$	Linear	0.0014	0.3126	(-0.0013, 0.0041)	19988
	Log linear	0.2525	0.2091	(-0.1416, 0.6466)	19987
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.3865	0.4201	(-0.5533, 1.3262)	19987
	Quartile 3	-0.0598	0.9020	(-1.0121, 0.8925)	
	Quartile 4	0.9280	0.0590	(-0.0352, 1.8912)	
BC	Linear	0.0441	0.0094	(0.0109, 0.0774)	17944
	Log linear	0.4398	0.0580	(-0.0149, 0.8945)	17947
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.0613	0.9027	(-0.9227, 1.0454)	17947
	Quartile 3	0.6022	0.2485	(-0.4208, 1.6252)	
	Quartile 4	1.2061	0.0163	(0.2219, 2.1902)	
CO	Linear	-0.0147	0.6960	(-0.0884, 0.059)	20092
	Log linear	0.0435	0.7121	(-0.1874, 0.2744)	20092
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.1506	0.7461	(-1.0628, 0.7616)	20095
	Quartile 3	0.1836	0.6951	(-0.7345, 1.1016)	
	Quartile 4	-0.2221	0.6392	(-1.1511, 0.7068)	
Diastolic Blood Pressure					
$PM_{2.5}$	Linear	-0.0008	0.4779	(-0.003, 0.0014)	18838
	Log linear	-0.2510	0.1248	(-0.5716, 0.0696)	18836
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.3019	0.4391	(-1.067, 0.4631)	18840
	Quartile 3	-0.5809	0.1419	(-1.3562, 0.1945)	
	Quartile 4	-0.3656	0.3607	(-1.1498, 0.4186)	

BC	Linear	-0.0048	0.7287	(-0.032, 0.0224)	16928
	Log linear	-0.2135	0.2593	(-0.5846, 0.1575)	16927
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.1939	0.6362	(-0.6097, 0.9975)	16930
	Quartile 3	-0.2200	0.6057	(-1.0554, 0.6155)	
	Quartile 4	-0.2303	0.5743	(-1.034, 0.5735)	
CO	Linear	0.0310	0.3133	(-0.0293, 0.0914)	18972
	Log linear	0.0426	0.6585	(-0.1466, 0.2318)	18973
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.1348	0.7236	(-0.8823, 0.6127)	18977
	Quartile 3	-0.0915	0.8115	(-0.8438, 0.6608)	
	Quartile 4	0.0436	0.9105	(-0.7176, 0.8049)	

Note: *All models adjusted for IRC, gestational age at blood pressure measurement (weeks), nulliparity, BMI, maternal age, mother's level of education, time (morning vs. afternoon) of blood pressure measurement, mother's diet diversity.*

3.4 Discussion

As part of the HAPIN randomized controlled trial baseline measurement period, we conducted $PM_{2.5}$, BC, and CO personal exposure assessment (n = 2818, 2536, 2872, respectively) and collected gestational blood pressure during early pregnancy (n = 3176, average of 15.4 gestational weeks). Exposure levels were consistently above the recommended WHO Interim Target values for $PM_{2.5}$; blood pressure values varied by IRC but were generally within normotensive ranges (n = 2959, 93%).

Reported associations between HAP exposure and blood pressure vary. Among older, non-pregnant women (Baumgartner et al., 2011, Clark et al., 2013, McCracken. et al., 2007), evidence of an association exists between HAP exposure and SBP, DBP, or both. The comparison between older adult women and pregnant women may, however, not be appropriate due to both physiological and risk factor-related differences. Two studies (Alexander et al., 2017; Quinn et al., 2016) evaluated the impacts of HAP on gestational blood pressure and found reductions in DBP, though only one presented quantitative exposure-response evidence for carbon monoxide (Quinn et al., 2016).

Trial-wide, among pregnant women, we observed significant association between BC and SBP, as well as trends indicative of a positive exposure-dependent association between exposure to $PM_{2.5}$ and SBP. We observed evidence of a positive relationship between exposure to either $PM_{2.5}$ or BC and SBP (Table 4). Associations for CO were inconsistent. Our findings, though smaller in magnitude or inconsistent with the existing literature base, were robust across model specifications and sensitivity analyses. We observed evidence that BMI modified the associations between $PM_{2.5}$/BC and SBP. A 2.08 mmHg (95% CI: 0.60, 3.57) and 1.78 mmHg (95% CI: 0.01, 3.55) increase in SBP was observed among obese women compared to normal or healthy weight women for 1 log $\mu g/m^3$ increase in $PM_{2.5}$, and BC exposure, respectively. We also saw a statistically significant interaction between $PM_{2.5}$ and BC exposures and physical activity levels for DBP. Compared to women with physical activity in the lowest quartile, we found a 1.06 mmHg (95% CI: -1.94, -0.18), and 1.20 mmHg (95% CI: -2.31, -0.08) decrease in DBP among women in the highest physical activity quartile for 1 log $\mu g/m^3$ increase in $PM_{2.5}$, and BC exposure, respectively.

Given the paucity of data on the impact of HAP on gestational blood pressure – and the inconsistency in findings – further evaluation is needed. Recent evidence from China (Zhang et al, 2021) indicates that the magnitude and trajectory of changes in blood pressure during pregnancy vary by quartile of exposure to ambient $PM_{2.5}$. Explorations of such changes in trajectory from HAP exposure may be valuable and would benefit from a repeat measurement strategy, as undertaken during the broader HAPIN trial.

Our study has several strengths. We performed high quality personal exposure and blood pressure measurement among pregnant women in four diverse low- and middle-income settings with a large sample size. As planned for the trial, baseline data was collected relatively early during pregnancy. We also acknowledge several limitations. First, this cross-sectional analysis assessed HAP exposure and

blood pressure at a single time point in early pregnancy. Findings from additional rounds of measurement during the HAPIN trial are being prepared. Second, single measurements of both blood pressure and HAP exposure are known to be variable, and thus some amount of measurement error is expected. Third, this analysis focuses only on the HAPIN baseline period, when all households were cooking with biomass; we do not benefit from potential heterogeneity in exposure due to the HAPIN stove, fuel, and behavioral intervention.

Forthcoming evaluation of the effect of the HAPIN intervention on blood pressure among both pregnant and older adult women will help elucidate the relationship between household air pollution exposure and blood pressure. Given the burden of ill-health associated with elevated blood pressure and related outcomes, further investigation of its relationship with HAP exposure is warranted.

Chapter 4

Effects of a cleaner energy intervention on gestational blood pressure: findings from the Household Air Pollution Intervention Network (HAPIN) randomized controlled trial

4.1 Background

Globally, about 2.6 billion people without access to clean cooking fuels and technologies and have to rely on solid fuels (wood, animal dung, coal, and agricultural residue) (IEA et al., 2021). These fuels are often burned in inefficient and poorly ventilated combustion devices (e.g., open fires, traditional stoves). The resulting household air pollution (HAP) accounts for an estimated 2.31 million premature deaths per year and 91.5 million disability-adjusted life years (GBD, 2020). Despite progress in recent years, this largely preventable exposure remains a leading risk factor for morbidity and mortality worldwide. Poor populations in low- and middle-income countries (LMICs) bear most of this burden (GBD 2017).

Elevated blood pressure, a risk factor for cardiovascular disease, has been shown to be associated with $PM_{2.5}$ in studies of ambient air (Yang et al. 2018). Studies of blood pressure in relation to HAP are sparse. HAP from solid fuel combustion has been studied in non-pregnant women in Guatemala (McCracken et al., 2007), Honduras (Young et al., 2019a), Nicaragua (Clark et al. 2013), Bolivia

(Alexander et al. 2015), and China (Baumgartner et al., 2011). These studies are reasonably consistent in finding an association between HAP and higher systolic blood pressure (SBP), particularly in older women. Most of these studies have provided data on the quantitative association of $PM_{2.5}$ and blood pressure (Baumgartner et al. 2011, Clark et al. 2103, Young et al. 2019, McCracken et al. 2007). A recent systematic review examining HAP and high blood pressure and hypertension also concluded that the use of solid fuel was associated with increased risk of hypertension (Li et al., 2020). The biological mechanisms by which air pollution exposure increases blood pressure have been well demonstrated, through an imbalance of lung autonomic nerve system, systematic oxidative stress and inflammatory, as well as endothelial, dysfunction (Giorgini et al. 2016).

Studies of blood pressure in older women may not be directly relevant to younger pregnant women. Blood pressure among pregnant women is known to vary during pregnancy, falling initially and rising in the third trimester (Hermida et al. 2000). Gestational blood pressure is important because elevated levels can lead to pre-eclampsia with serious results for mother and child (Mol et al. 2016).

There have been four studies of HAP effects on blood pressure for pregnant women, all of which have found some evidence that lower exposure to biomass smoke is associated with lower blood pressure. In a cross-sectional study of 817 pregnant women in Ghana, Quinn et al. (2016) reported a positive association between personal exposure to carbon monoxide (CO) and diastolic blood pressure (DBP) (increase 0.43 mmHg, 95% CI 0.01-0.86), and a positive non-significant association with SBP. Quinn et al. (2017) followed 44 pregnant women in Ghana and found peak CO exposure (>4.1 ppm) in the 2 hours before blood pressure measurement was associated positively and significantly with acute increases in both SBP (4.3 mmHg, 95% CI: 1.1, 7.2) and DBP (4.5 mmHg, 95% CI: 1.9, 7.2); these authors also found a greater post-intervention decrease in SBP among the intervention group compared to controls (-2.1 mmHg, 95% CI: -6.6, 2.4). Another study in Nigeria (n = 162 intervention,

n = 162 controls), using repeated measures, found an ethanol cookstove intervention can reduce DBP during pregnancy (Alexander et al., 2017b), compared to control subjects using kerosene (p-value = 0.04). No effect of the intervention was found for SBP. However, personal exposure monitoring for $PM_{2.5}$ found no significant exposure reduction in exposure due to the intervention in the Nigeria study (Alexander et al. 2018). A cross-sectional study in India of 1369 pregnant women reported that use of biomass cooking fuel was associated with both lower SBP (-2.0 mmHg, 95% CI: -3.77, -0.31) and DBP (-1.96 mmHg, 95% CI: -3.60, -0.30) compared to gas users, although no exposure data were reported (Wylie et al., 2017).

Here we present data to explore further the association between $PM_{2.5}$, BC and CO exposures and gestational blood pressure using data from the Household Air Pollution Intervention Network (HAPIN) trial (Clasen et al. 2020). HAPIN is a four country, individually randomized, unblinded randomized controlled trial (RCT) of liquid petroleum gas (LPG) stove, fuel distribution and behavioral messaging in 3,200 households in 4 resource-poor setting of low- and middle-income countries (LMICs) (India, Guatemala, Peru, and Rwanda). We enrolled and randomized 800 pregnant women at each of the 4 international research centers (IRCs) from households cooking on biomass fuels, and randomly assigned households to receive LPG stoves, free LPG supplies, and behavioral reinforcements.

4.2 Methods

4.2.1 Study Site and Population

This study was based on data from pregnant women participants enrolled in HAPIN trial, the detailed methods of which have been described (Clasen et al. 2020, Johnson et al. 2020, Barr et al. 2020). To be eligible to participate in the study, women were required to be between 19 and 35 years of age,

non-smokers, between 9 and 20 weeks in gestation (confirmed by ultrasound and last menstrual period) and cooking with on biomass. Potentially eligible women were first identified at local prenatal clinics, and then visited within two weeks after the ultrasound visit, to collected baseline clinical and demographic baseline information and schedule a follow-up visit to collect data on exposure, stove use, and other household characteristics. During that visit, we measured blood pressure and $PM_{2.5}$, BC, and CO air pollution personal exposures over past 24-hour. Participants were then randomized to either receive a gas stove and gas supplies, or to continue use of biomass stoves. Control households received no intervention on enrollment but were eligible to receive the same stove and fuel or alternative compensation after the completion of the trial (Quinn et al. 2020). The trial is registered with ClinicalTrials.gov (NCT02944682).

4.2.2 Measurement of blood pressure

Gestational blood pressure is a secondary outcome in this trial. Following informed consent to participate in the study, gestational blood pressure was assessed on enrollment (baseline, <20 weeks' gestation), and two follow up visits at approximately 24-28 weeks of gestation (follow-up 1) and 32-36 weeks of gestation (follow-up 2). At each measurement period, resting blood pressure was measured in triplicate on the right arm, using an automatic digital blood pressure machine, and the average of the three readings were used in the data analysis. SBP values less than 70 and DBP values less than 35 were excluded as implausible. There were no implausible high values. Trained field workers confirmed that the pregnant women participants had not smoked, nor had alcohol/caffeinated drinks or cooked using biomass in the 30-minute period prior to the blood pressure measurement. If the participant had done any of these activities in the 30 minutes prior to the test, she would be asked to refrain from doing these activities for 30 minutes before proceeding

with the measurements. If a participant was found to have a SBP >= 140 mmHg and/or a DBP >= 90 mmHg, she was referred to the nearest health center or hospital.

4.2.3 Measurement of household air pollution exposure

Exposure measurement procedures have been described previously (Johnson et al., 2020) (Johnson et al., under review). Briefly, personal exposure monitoring was conducted twenty-four hours prior to the blood pressure measurements. We measured personal exposures to $PM_{2.5}$, BC, and CO at baseline and at the subsequent two follow-up visits.

24-hour personal $PM_{2.5}$ exposures were monitored at baseline and at the subsequent two follow-up visits, using Enhanced Children's MicroPEM™ (ECM, RTI International, Research Triangle Park, USA) worn on clothing. ECM measures continuous $PM_{2.5}$ concentrations using a nephelometer and collects integrated gravimetric samples on 15 mm polytetrafluoroethylene filters (Measurement Technology Laboratories, USA). All filters were pre- and post-weighed using 1-μg resolution microbalances in a temperature- and humidity-controlled laboratory. Four field blanks were collected per 100 sample filters and the limit of detection (LoD) was calculated separately for each IRC as three times the standard deviation of the blank mass depositions. Samples deposition below the LoD were replaced with $LoD/(2^{0.5})$. If a gravimetric sample was considered invalid, due to missing or damaged filter or flow faults, the nephelometric concentrations were used to estimate personal exposure. Regression models were applied to the adjusted 24-h average nephelometer values for missing or invalid gravimetric samples, resulting in instrument-specific nephelometric $PM_{2.5}$ concentrations normalized to field-based filter samples (Johnson et al, under review). Personal exposure to BC was estimated for $PM_{2.5}$ filter samples with SootScan Model OT21 Optical Transmissometers (Magee Scientific, USA). CO concentrations were measured using the Lascar EL-USB-300 (Lascar Electronics, USA) at 1-minute interval. The Lascar CO device has a sensing range between 0 and 300 ppm.

Invalid $PM_{2.5}$/BC/CO samples were due to being missing, equipment failure (i.e., not run for a minimum of 20 hours, often due to batteries being exhausted and clogged filters which at times became overloaded with $PM_{2.5}$), damaged or misplaced filters and failure to meet quality assurance criteria.

4.2.4 Statistical analysis

a. Intention-to-Treat (ITT) Analysis We conducted an ITT analysis using a linear model in which the average post randomization blood pressure (both SPB and DBP) were regressed on treatment, adjusting for centered baseline blood pressure, and with indicator variables for the geographical strata where randomization took place (two in India, six in Peru, one in Rwanda and one in Guatemala). The average of the first and second follow-up SBP or DBP measurements were used as outcomes. if one of two measurements is missing, the other will be used. Women on blood pressure medication during any time of the pregnancy were excluded (n = 14, <0.3%). The model for this analysis is:

$$\bar{y}_i^{Post} = \beta_0 + \beta_1 X_{1i} + \beta_2 (y_i^{Base} - \bar{y}^{Base}) + \beta_3 X_{2i} \ + \ ... + \ \beta_{11} X_{10i} \ + \ \varepsilon_i \qquad \textbf{Eq. 1}$$

where for individual i, $\bar{y}_i^{Post}$ is the average post-randomization blood pressure measurements, X_{1i} is an indicator variable (0 for control and 1 for intervention), $(y_i^{Base} - \bar{y}^{Base})$ is the centered baseline measurement of blood pressure, X_{2i} through X_{10i} are indicator variables for randomization strata, and $\varepsilon_i \sim N(0, \tau_i^2)$ represents independent normal error. The parameter of interest β_1 captures differences in average blood pressure due to the intervention, accounting for baseline blood pressure. We checked to ensure baseline variables that might affect blood pressure did not differ by arm (Table 1) and found imbalance between control and intervention groups for nulliparity, mother's highest level of education and household food insecurity score. As secondary analysis, we included these three variables in the models and covariate-adjusted effects were evaluated. We also assessed potential effect

modification by IRC, mother's age, baseline BMI and gestational age. The latter three variables were divided into two strata by their median.

b. Exposure-Response Analysis We also conducted exposure-response analysis. We applied a two-step approach by first conducting IRC-specific exposure-response analyses, then combining them with inverse variance method to estimate the trial-wide exposure-response associations. In the first step, we used a mixed effects model to assess the longitudinal exposure-response relationship between personal $PM_{2.5}$/BC/CO exposures and gestational SBP/DBP in each IRC. The mixed effects model included 24-hour personal exposures (either continuous or categorical) as the exposure variable and adjusted for time-varying and time-invariant covariates. Covariate selection was based on conceptual directed acyclic graph (DAG), a minimal set of known confounders (i.e., gestational age, nulliparity, BMI at baseline), and factors that have been previously assessed from the literature (i.e., maternal age, mother's highest education level, socioeconomic status, physical activity, time [morning/afternoon] and date [weekday/weekend] of the blood pressure measurement, household food insecurity, and mother's minimum diet diversity). The minimal set of known confounders were included in all models. Other variables described above were retained in the model if their inclusion altered the exposure-response coefficient by 10% of more. Gestational age at the blood pressure measurement was modeled in both linear and quadratic terms given the known U-shape blood pressure pattern during pregnancy.

The model for this analysis is:

$$Y_{ij} = \beta_0 + \beta_1 PM_{ij} + \sum \boldsymbol{\beta_2 Z_{ij}} + \sum \boldsymbol{\beta_3 Z_i} + \delta_i + \varepsilon_{ij} \qquad \textbf{Eq. 2}$$

where Y_{ij} is the blood pressure level for participant i at observation j, β_0 is the population intercept, β_1 is the exposure coefficient of interest, $Z_{ij}$are time-dependent covariates, Z_i are time independent covariates, δ_i is the individual random intercept, and ε_{ij} is the model residual, both of which are

assumed to be normally distributed. Due to the use of a mixed-effects model in which blood pressure measurements were repeated on the same women over time, a random effect was included in the model for each woman. In the second step, we calculated a pooled trial-wide association for each exposure-outcome pair as the inverse-variance weighted average of the four IRC-specific associations using **Eq 3**:

$$\theta_{IV} = \frac{\sum w_i \theta_i}{\sum w_i} \qquad \textbf{Eq. 3}$$

where θ_{IV} is the pooled trial-wide association estimate, w_i is weight from IRC i, and it is the reciprocal of the squared standard error of θ_i. θ_i is the association estimate of IRC i.

We conducted multiple sensitivity analyses. We reproduced above exposure-response analysis by including the participants with missing baseline or any post-randomization blood pressure measurements, but who had at least one blood pressure measurement, which added 5-6% of the sample size. We also evaluated the effect of the average of baseline, follow-up 1 and 2 $PM_{2.5}$/BC/CO exposures on changes in SBP or DBP from baseline to follow-up 2 visit, controlling for blood pressure levels at baseline. Finally, we assessed potential effect modification by IRC, mother's age, baseline BMI and gestational age. The latter three variables were divided into two strata by their median.

For missing outcome, a complete-case analysis was carried out by excluding participants without a baseline blood pressure measurement or without any post randomization blood pressure measurements (this criterion was relaxed in the first supplementary analysis noted above). Missing confounder information was addressed with the use of a missing categorical variable for each covariate (i.e., the missing by indication approach), if the number of missing > 10. All primary, secondary and sensitivity analyses were conducted based on pre-developed statistical analysis plan independently by two investigators using SAS (SAS, 2020) and R (version 4.0.3), respectively.

4.3 Results

4.3.1 Participant characteristics

Figure 4.1 illustrates the trial profile in a Consolidated Standards of Reporting Trials (CONSORT) diagram. Between April 2018, and February 2020, 6447 pregnant women were identified for screening and recruitment. Among those, 3200 pregnant women were eligible for participation and 3195 had complete baseline assessment and were randomized to intervention and control arms on a 1:1 ratio. 14 participants were excluded because they took blood pressure medication at some point during the pregnancy, another 14 participants who had no baseline BP measurement were also excluded. We further excluded 165 pregnant women who had no BP measurement at either of the two post-intervention visits (visits P1 and P2), and this left 3002 pregnant women (intervention: 1500 vs. control: 1502) and 8845 observations in total to our analysis.

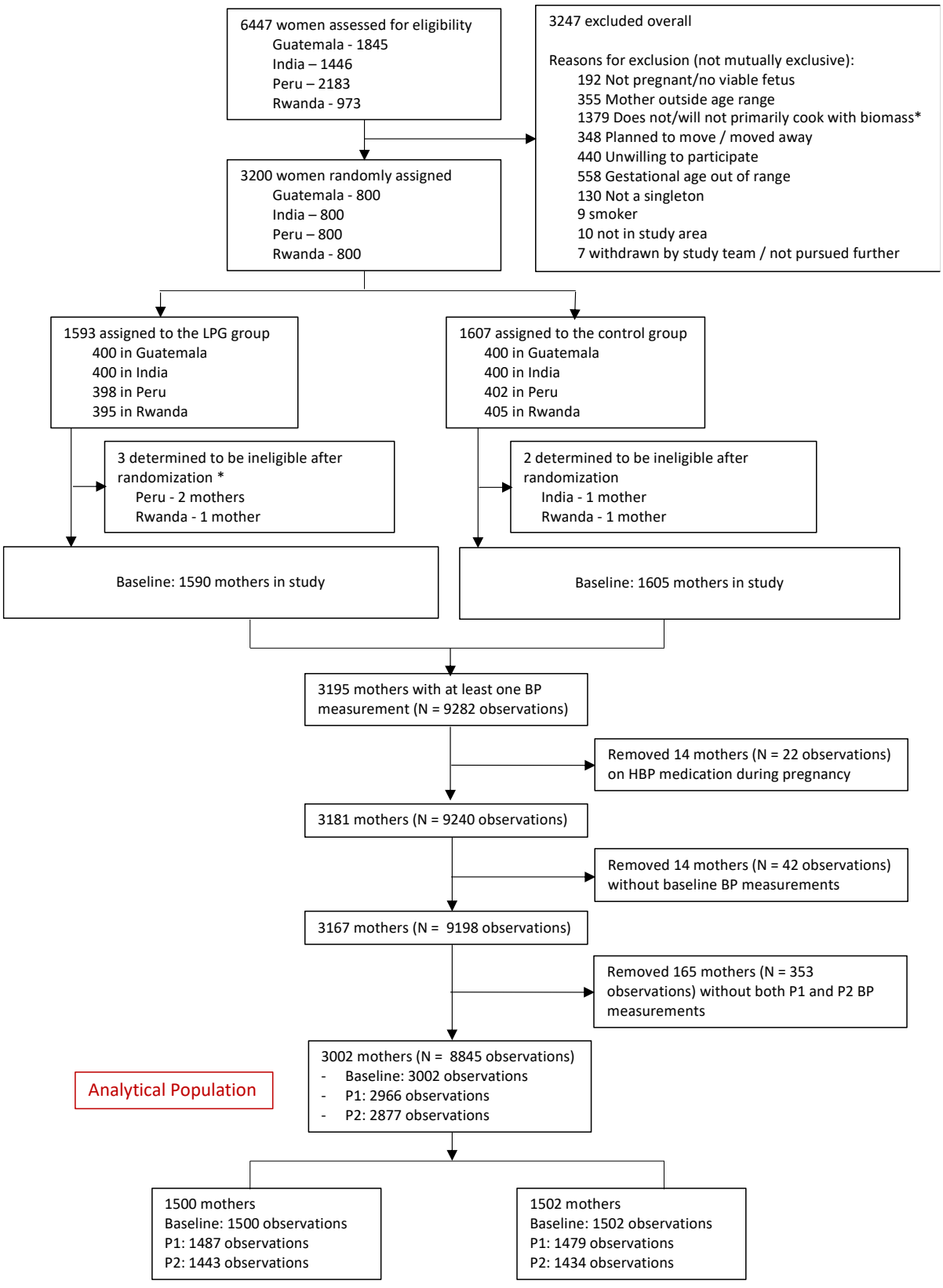


Figure 4.1 HAPIN trial profile and analytic population of current analysis

Baseline characteristics of the households and participants were largely similar by intervention arm except for nulliparity, mother's highest level of education and household food insecurity score (**Table 4.1**). More pregnant women were nulliparous, defined as zero pregnancies reaching 20 weeks and 0 days of gestation or beyond, in the intervention group compared to the control group (40% vs. 37%). The pregnant women in the intervention group also had relatively higher education level and less food insecurity. We did not observe consistent differences in baseline household and maternal characteristics between the excluded participants and the overall sample, nor between the excluded in the intervention and control groups.

Overall, the average maternal age in our analytical population at baseline was 25.4 (range: 18 – 35) years and average gestational age at baseline was 15.4 (range: 8.4 – 24.9) weeks. The mean BMI was 23.1 (range: 13.3 – 44.2) kg/m^2. 94 (3%) women had had prior stillborn, and 398 (13%) women had had more than one miscarriage. 5 (0.2%) and 14 (0.5%) participants reported history of diabetes and high blood pressure. None of these differ by intervention arm.

Table 4.1 Baseline household and maternal characteristics, by intervention arm

Variable	Control (N = 1502)	Intervention (N = 1500)
Household characterisrics		
Household size, Mean (SD) [Range]	4.3 (2.0) [1, 18]	4.3 (2.1) [1, 17]
Someone in the household smokes, N (%)		
Yes	176 (12%)	143 (10%)
No	1325 (88%)	1356 (90%)
Missing	1 (<1%)	1 (<1%)
Maternal characteristics		
Age at baseline (yr), Mean (SD) [Range]	25.4 (4.5) [18, 35]	25.3 (4.4) [18, 35]
BMI, (kg/m^2), Mean (SD) [Range]	23.0 (3.9) [13.7, 44.2]	23.3 (4.1) [13.3, 42.3]
Mother's highest level of education completed, N (%)*		
No formal education or Primary school incomplete	542 (36%)	465 (31%)
Primary school complete or Secondary school incomplete	501 (33%)	529 (35%)
Secondary school complete or Vocational or Some college or university	459 (31%)	505 (34%)
Missing	0	1 (<1%)
Gestational age at baseline (wk), Mean (SD) [Range]	15.4 (3.2) [8.4, 24.9]	15.6 (3.1) [9, 23.7]

Previous history of high blood pressure, N (%)		
Yes	7 (1%)	7 (1%)
No	1494 (99%)	1492 (99%)
Missing	1 (<1%)	1 (<1%)
Physical Activity (MET-minutes/day), Mean (SD) [Range]		
Quartile 1	74.7 (54.3) [0, 200]	72.1 (55.1) [0, 200]
Quartile 2	470 (180) [206, 754]	464 (184) [206, 756]
Quartile 3	1080 (168) [771, 1434]	1074 (174) [760, 1423]
Quartile 4	2361 (782) [1440, 5829]	2378 (734) [1440, 6000]
Nulliparous, N (%)		
Yes	549 (37%)	602 (40%)
No	952 (63%)	895 (60%)
Missing	1 (<1%)	3 (<1%)
Household food insecurity score, n (%)*		
Severe/Moderate	257 (17%)	208 (14%)
Mild	423 (28%)	393 (26%)
None	801 (53%)	877 (58%)
Missing	21 (1%)	22 (1%)
Mother's minimum diet diversity, n (%)		
High	149 (10%)	181 (12%)
Medium	478 (32%)	460 (31%)
Low	874 (58%)	858 (57%)
Missing	1 (<1%)	1 (<1%)

Note:

Summary based on the 3002 women comprised the analytic population.

** Indicates the variable is significantly different ($\alpha = 0.05$) between arms using t-test (for continuous variables) or chi-square test (for categorical variables)*

4.3.2 Effects of the intervention on household air pollution exposures

Table 4.2 shows the descriptive statistics on $PM_{2.5}$, BC, and CO exposures at baseline (BL), first follow-up (P1), and second follow-up (P2) by intervention arm. **Table C1** provided a summary of missing and invalid exposure samples by visit. While the intervention and control groups had similar $PM_{2.5}$, BC and CO exposure at baseline, the LPG stove and fuel intervention consistently reduced the post-randomization personal exposures to all three pollutants in the intervention group, compared with the control group. The average post randomization $PM_{2.5}$, BC and CO exposures were 34.8 $\mu g/m^3$, 4.1 $\mu g/m^3$, 0.7 ppm in the intervention group, and 103.2 $\mu g/m^3$, 11.0 $\mu g/m^3$, 2.2 ppm in the control

group. Approximately 70% and 99% of the exposure measurements in the intervention group were below the 2021 WHO interim-target-1 (IT-1) of 35 ug/m^3 and 7 mg/m^3 (6.006 ppm) for $PM_{2.5}$ and CO, respectively. Detailed personal exposure results of pregnant women through their pregnancy are described elsewhere (Johnson et al., under review). We observed high correlations between the $PM_{2.5}$ and BC (Spearman's ρ = 0.86) and moderate correlation between $PM_{2.5}$ and CO (Spearman's ρ = 0.50), and BC and CO (Spearman's ρ = 0.48). The exposure correlations were similar in the intervention group and control group.

Table 4.2 Personal 24-hour $PM_{2.5}$ exposure (μg/m^3), BC exposure (μg/m^3) and CO (ppm) for mothers by treatment arm and visit (valid measurements only)

Visit	Arm	N	$PM_{2.5}$ Mean (SD), Median (IQR)	N	BC Mean (SD), Median (IQR)	N	CO Mean (SD), Median (IQR)
BL	Control	1328	112.0 (107.8) 84.9 (96.0)	1186	12.6 (9.4) 11.0 (8.7)	1354	2.3 (4.0) 1.2 (2.0)
	Intervention	1323	120.4 (134.0) 82.7 (105.8)	1192	12.6 (10.9) 10.6 (9.0)	1355	2.7 (4.5) 1.3 (2.5)
P1	Control	1236	104.0 (112.3) 71.7 (87.0)	1174	11.0 (9.3) 9.7 (9.1)	1298	2.3 (4.1) 1.1 (2.1)
	Intervention	1278	33.9 (33.2) 24.1 (24.5)	1219	4.0 (5.5) 2.7 (3.1)	1307	0.7 (1.5) 0.2 (0.7)
P2	Control	1127	102.3 (107.9) 69.2 (94.3)	1069	11.0 (10.2) 9.5 (8.4)	1201	2.2 (4.0) 1.1 (1.9)
	Intervention	1170	35.8 (54.8) 23.7 (24.6)	1128	4.3 (5.4) 2.8 (3.1)	1220	0.7 (1.3) 0.2 (0.7)

Note: *Summary based on the 3002 women comprised the analytic population.*

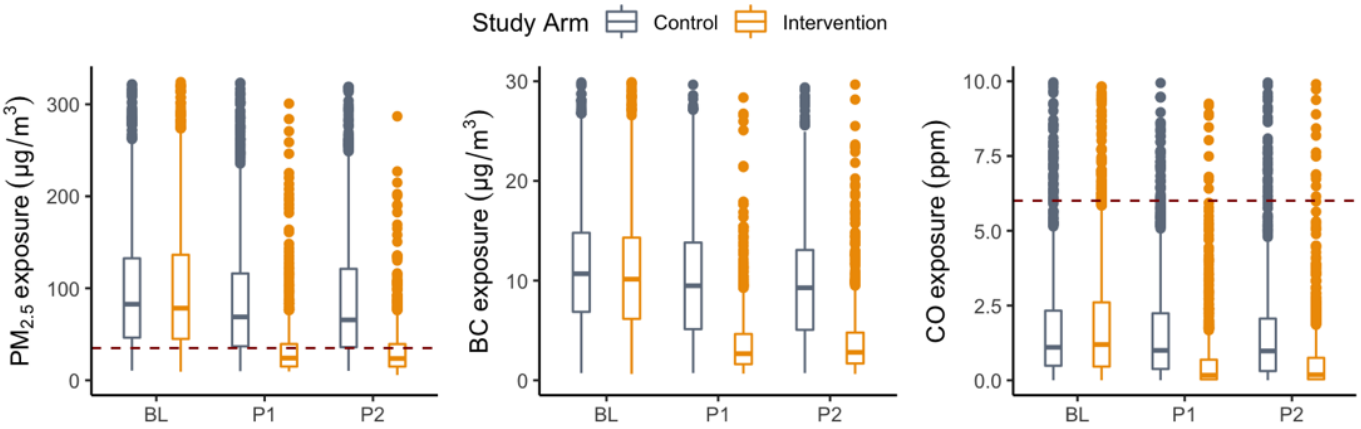


Figure 4.2 Boxplots of personal exposure to $PM_{2.5}$, BC and CO by intervention groups and visit (BL: baseline, P1: follow-up 1, and P2: follow-up 2). Dark red dashed lines in the $PM_{2.5}$ and CO panels indicate the 2021 WHO recommended interim target 1 (IT-1) for annual $PM_{2.5}$ (35 µg/m³), and 24-hour CO (6.006 ppm = 7 mg/m³, at 20 °C and 1013 hPa, 1 mg/m³ = 0.858 ppm). All plots represent 97% of the valid exposure data (the highest 3% of exposure observations are not shown in plots).

4.3.3 Blood pressure measurements

Figure 4.3 shows the mean (±SD) SBP/DBP by each visit (9 - < 20 weeks, 24 – 28 weeks, and 32 – 36 weeks) in the two groups. The line plots indicate the overall trends of blood pressure over the time in the two treatment groups. The curves confirm the known pattern of blood pressure during the pregnancy: steadily decreases up to the middle of gestation and increases up to the day of delivery (Hermida et al., 2000). **Table 4.3** presents the mean (SD) of SBP, DBP and gestational age by treatment arm at each visit. Note that blood pressure goes down slightly from baseline to follow-up 1, and then rises slightly at follow-up 2, as expected.

Table 4.3 Summary of SBP and DPB (mmHg), and gestational age (day) by visit and treatment arm

Visit	Arm	N	Gestational age (day), Mean (SD)	SBP, Mean (SD)	DBP, Mean (SD)
BL	Control	1502	111.7 (21.9)	105.3 (9.6)	60.8 (7.8)
	Intervention	1500	113.1 (21.3)	104.5 (9.7)	60.6 (7.7)
	NA	0	-	-	-
	Total	3002	112.4 (21.6)	104.9 (9.6)	60.7 (7.7)
P1	Control	1464/3*	179.1 (9.9)	104.4 (8.7)	59.7 (7.2)

	Intervention	1468	178.7 (9.6)	104.1 (8.8)	60.4 (7.6)
	NA	34/5*	173.5 (6.4)	-	-
	Total	2966	178.9 (9.7)	104.3 (8.8)	60.0 (7.4)
P2	Control	1335	234.3 (8.5)	105.8 (8.8)	62.5 (7.5)
	Intervention	1355	234.0 (8.5)	105.8 (8.7)	62.9 (8.0)
	NA	187	239.3 (8.3)	-	-
	Total	2877	234.2 (8.5)	105.8 (8.7)	62.7 (7.8)

Note:

Summary based on the 3002 women comprised the analytic population.

**One household only had SBP measurement at follow-up 1 visit (# of measurement for DBP is 1463 and missing for DBP is 35 at P1)*

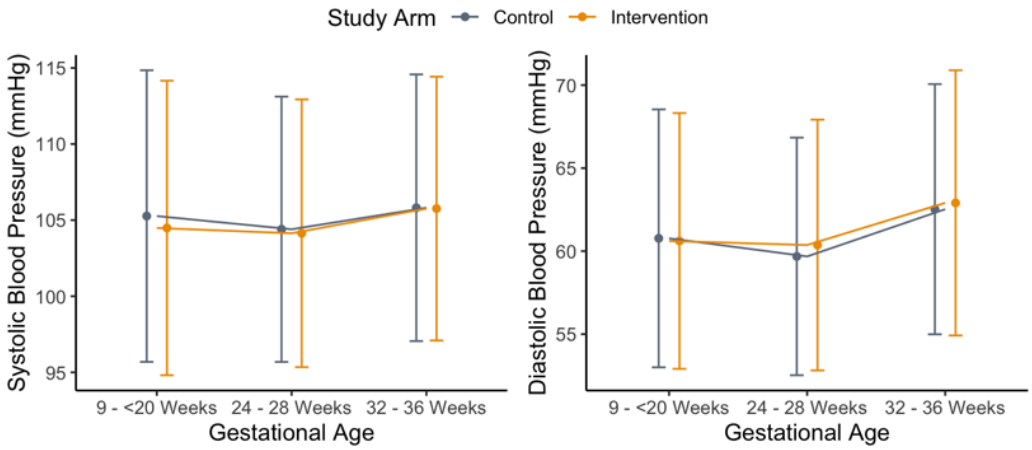


Figure 4.3 Line plot of systolic and diastolic blood pressure by visit. Dots indicate mean and error bars indicate one standard deviation.

4.3.4 Intention-to-Treat analysis

Table 4.4 describes the results of the primary and covariate-adjusted ITT analysis, where the estimate represents the difference in blood pressure between the intervention group and the control group, the latter being the reference. In **Table 4.4** we see that the post-randomization SBP between the intervention and control groups did not differ when controlled for the baseline (pre-intervention) blood pressure and randomization strata (0.23 mmHg, 95% CI: -0.22, 0.67). However, the post randomization DBP in the intervention group was statistically significantly higher than that in the control group (0.59 mmHg, 95% CI: 0.21, 0.98). Adjusting for baseline imbalance in nulliparity,

mother's highest education level and household food insecurity score between the two treatment groups resulted in slightly smaller estimates, but that did not appreciably change the results.

Table 4.4 Results of ITT analysis testing for difference in post-baseline average gestational blood pressure (2 measures)

	Primary ITT[a]		**Covariate-adjusted ITT[b]**	
	Estimate (mmHg)	95% CI	Estimate (mmHg)	95% CI
SBP	0.23	(-0.22, 0.67)	0.21	(-0.24, 0.65)
DBP	0.59	(0.20, 0.98)	0.56	(0.17, 0.96)

Note: *Based on 3002 pregnant women who enter the ITT analysis.*

[a] *Controlled for randomization sites (10 categorical variables (Peru [N = 6], India [N = 2], Rwanda [N = 1]and Guatemala [N = 1]), and centered baseline blood pressure.*

[b] *Additionally controlled for imbalanced baseline covariates related to HAP-GBP relationship: nulliparity, mother's highest education level and household food insecurity score.*

4.3.4 Exposure-Response analysis

In exposure-response analyses (**Table 4.5**), we find that for SBP, there were no marked trends with both $PM_{2.5}$ or the log of $PM_{2.5}$. Quartile analyses showed all quartiles above the referent had slightly higher BP, but the trend was not statistically significant for DBP, exposure-response analyses showed a significant inverse association with log transformed $PM_{2.5}$, which was generally supported by the quartile analysis. Results for BC paralleled those of $PM_{2.5}$. CO shows no consistent trends for SBP, although the log CO and the quartile analysis indicated positive trends (higher SBP) with higher CO. There were no significant trends between CO and DBP.

Table 4.5 Results of exposure-response analysis across 3 visits

Model Type	**$PM_{2.5}$**		**BC**		**CO**	
	Estimate	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Systolic Blood Pressure						
Log Linear	0.1222	(-0.0750, 0.3194)	0.1536	(-0.0678, 0.3750)	0.0304	(-0.0505, 0.1113)
Categorical [Ref. Quartile 1]						
Quartile 2	0.3400	(-0.1093, 0.7897)	0.2896	(-0.1815, 0.7607)	0.0771	(-0.3564, 0.5106)
Quartile 3	0.186	(-0.2919, 0.6631)	0.0508	(-0.4542, 0.5559)	0.2380	(-0.2115, 0.6875)
Quartile 4	0.326	(-0.1809, 0.8333)	0.3473	(-0.1792, 0.8739)	0.0818	(-0.3830, 0.5466)
Diastolic Blood Pressure						

Log Linear	-0.1988	(-0.3703, -0272)	-0.1728	(-0.3638, 0.0181)	-0.0291	(-0.0996, 0.0414)
Categorical [Ref. Quartile 1]						
Quartile 2	-0.194	(-0.5826, 0.1940)	-0.2666	(-0.6746, 0.1414)	-0.0870	(-0.4668, 0.2927)
Quartile 3	-0.466	(-0.8778, -0.0539)	-0.3527	(-0.7899, 0.0844)	-0.2333	(-0.6268, 0.1603)
Quartile 4	-0.473	(-0.9096, -0.0369)	-0.6161	(-1.0716, -0.1607)	-0.0800	(-0.4859, 0.3260)

Note:

1. All models controlled for nulliparity, mother's highest education level, BMI, maternal age, gestational age, gestational age squared and time (morning/ afternoon) of the blood pressure measurement.

2. Log linear and categorical exposure models are presented as main results given their lower AICs compared to linear models.

4.4 Discussion

We assessed the impact of an LPG stove and fuel intervention on blood pressure of pregnant women in four LMICs using the data collected from the HAPIN RCT. In the ITT analyses, we did not observe any protective effect of the intervention on the blood pressure in all enrolled pregnant women combined or in each IRC. We found that LPG stove and fuel intervention led to a small but significant increase in DBP among pregnant women in the intervention group. However, the observed increase was very small (< 1 mmHg) and would not consider as minimal clinically important difference (MCID) at the individual level. The exposure-response analysis results were largely consistent with the ITT analysis. We observed higher SBP with increased $PM_{2.5}$, BC, and CO exposures, though none of these associations reached conventional statistical significance. For DBP, again, we saw lower DBP levels with increased $PM_{2.5}$, BC, and CO exposures. The associations between $PM_{2.5}$/BC exposure and DBP were statistically significant, although the latter association was only observed among pregnant women with BC exposures in the highest quartile.

Elevated blood pressure during pregnancy may lead to hypertensive disorders of pregnancy and these are comprising one of the greatest causes of maternal and perinatal morbidity and mortality in the world (Task Force on Hypertension in Pregnancy, 2013). Despite the epidemiological evidence supporting an exposure-response association between HAP exposure and blood pressure, evidence

for that association is mixed in pregnant women. One RCT of an ethanol cookstove intervention conducted in Nigeria (Alexander et al., 2017) and two cross-sectional studies in Ghana (Quinn et al., 2016) and India (Agrawal and Yamamoto, 2015) found some evidence of decreased blood pressure from using cleaner fuels/the ethanol cookstove intervention or lower exposure to CO. In the ethanol cookstove intervention RCT conducted in pregnant Nigerian women, Alexander et al., (2017) reported that at the last visit, mean DBP was 2.8 mmHg higher in control subjects than in ethanol users (3.6 mmHg higher in control subjects than in ethanol users among preintervention kerosene users). Similarly, in Ghana, a significant positive association was found between CO exposure and DBP: on average, each 1 ppm increase in CO exposure was associated with 0.43 mmHg higher DBP (95%CI: 0.01, 0.86) (Quinn et al., 2016). In another study conducted in India, Agrawal and Yamamoto, (2015) found women living in households using solid fuels had two times higher likelihood of reporting preeclampsia/eclampsia symptoms than do those living in households using cleaner fuels (OR = 2.21; 95% CI: 1.26–3.87; p = 0.006). Conversely, Wylie et al. (2015) showed that wood user was one-third less likely to have postpartum blood pressure in the hypertensive range compared with women in central east India cooking in primarily with gas, although this difference did not reach statistical significance.

The null result of the intervention on gestational blood pressure in this analysis did not appear to be driven by the noncompliance with the intervention. The assessment of intervention adherence showed that 96.1% of intervention households reported LPG stove use in the previous 24 hours at both follow-up visits during the pregnancy. 498 (31.3%) intervention households removed their traditional stoves after receiving their LPG stove. Among those retaining a traditional stove and with valid temperature-logging stove use monitors (SUMs) data (n = 992 households), traditional stove use was never detected among 620 (59.5%) and the median [Q1, Q3] percent of monitored days with traditional stove use was 0.0 [0.0, 1.6] (Quinn et al., 2021b).

Remarkably, the LPG stove and fuel intervention did lead to large reductions in the post-randomization personal exposures to $PM_{2.5}$, BC, and CO, and approximately 70% of the $PM_{2.5}$ exposure measurements in the intervention group were below the 2021 WHO interim-target-1 (IT-1) of 35 ug/m^3. Therefore, the question raised by the results of this analysis is why this intervention showed no protective effect on blood pressure in pregnant women from this cohort.

Several factors may explain our findings. First of all, our pregnant women cohort had a low-risk antenatal profile with very few cases of pre-existing medical conditions or previous pregnancy complications. The average maternal age of this singleton cohort is about 25 years, only 6% of the pregnant women were classified as obese (BMI $\geq$ 30.0) and none of the participant entered the final analysis smoked or consumed alcohol during pregnancy. For most of the participants, both their SBP and DBP remained in the normal range throughout the pregnancy, even among those in the control group with much higher HAP exposures. This could partially explain the observed small associations with blood pressure and null trial result on gestational blood pressure.

Although no statistically significant difference was observed in the last blood pressure measurements between the intervention and control groups, we found a significant DBP increase in the intervention group between the baseline and the first follow-up visit (during 2^{nd} trimester) and that yielded an effect of the intervention on elevated DBP, as well as negative association between $PM_{2.5}$ /BC and DBP in the exposure-response analyses. These findings suggest that future studies may further examine the trimester-specific association between HAP exposures and blood pressure in pregnant women. It is also possible that the observed DBP elevation in the intervention group was attributable to exposures to other unmeasured pollutants from using the LPG stove, such as NO_2 (Chan et al., 2015; N. Li et al., 2020), PAHs (Poursafa et al., 2017), and volatile organic compound (VOCs) (Singh et al., 2017).

More comprehensive personal HAP exposure characterization is needed to fully understand the effect of a specific HAP constituent on blood pressure.

Additionally, most of the blood pressure measurements in this study were conducted several hours from the morning cooking. A controlled human-exposure study investigating the acute responses in blood pressure following exposures to air pollution emissions from different cookstoves showed lower blood pressure levels in participants exposed to smoke from the three stone fire, fan rocket and LPG stoves, compared to the high-efficiency particulate air-filtered control groups in several hours post-exposure (Fedak et al., 2019). However, they found that at 24-hours post-exposure, SBP was significantly higher than the control by 2 to 3 mmHg for almost all treatment groups and indicated that short-term exposure to air pollution from cookstoves can elicit an increase in SBP within 24 hours. This could be another explanation of our findings given most of our blood pressure measurements were within several hours of stove use.

Nevertheless, this study has many strengths. The HAPIN trial is the first multi-center RCT to assess the efficacy of an LPG stove and fuel intervention on health. The study has a large sample size in four selected LMICs to represent a variety of factors expected to influence the intervention effects. The HAPIN trial is also the first RCT that measured repeated personal exposures to three major household air pollutants, $PM_{2.5}$, BC, and CO, simultaneously on all participants. Most importantly, the trial had the highest reported intervention adherence among the clean cooking studies so far: over 96% of pregnant women reported cooking exclusively with LPG at two follow-up visits during pregnancy. Complete abandonment of traditional stove cooking was observed in over 67% of intervention households, and among those who retained traditional stoves, the majority did not use them (Quinn et al., 2021b). Other important strengths of the study include ultrasound-determined gestational age and very low missing rates in outcome and key covariates measurements.

We also acknowledge the limitations of the study, and these should be taken into consideration when interpreting our findings. First, given the nature of the intervention, we were unable to blind the participants and field workers to the study arm. Second, it is also possible that the frequent interactions between the participants and study team might have improved the overall health of this cohort and added health benefit of the intervention became undetectable. Third, we were not able to include some of the key confounders such as salt consumption and ambient air pollution level in our exposure-response analyses. Fourth, we assumed the participants in the intervention group would continue conducting their normal cooking practices with the LPG stoves. However, we cannot rule out the possibility of altered lifestyle and behavior factors introduced by using LPG stove and fuel, such as changes in physical activity (no need to collect fuel) and in diet etc. Finally, our findings may not be generalizable to medium- or high-risk pregnant populations given the fact that majority of the pregnant women in our cohort did not have pre-existing medical conditions or common antenatal risk factors, such as smoking, drinking, and obese etc.

To conclude, we did not observe a protective effect of the LPG stove and fuel intervention on blood pressure in pregnant women in this low-risk antenatal profile cohort, despite the remarkable reduction of post-randomization exposures to $PM_{2.5}$, BC, and CO. The observed associations in this cohort were in small magnitude and might not lead to differential risk of elevating blood pressure and developing hypertensive disorders during pregnancy.

Chapter 5

Discussion

5.1 Key contributions

Applying the Translation Research Framework for Environmental Health Sciences, this dissertation tackled various research gaps of HAP exposure and associated health effects in low- and middle-income countries (LMICs), including: 1) characterized the personal exposures to $PM_{2.5}$, BC, PAHs, and elements from burning solid fuel among Tibetan women and children, an under researched population and location in China; 2) added new evidence to the association between HAP exposure and blood pressure among normotensive pregnant women using solid fuels exclusively in Guatemala, India, Peru, and Rwanda; and 3) assessed the efficacy of an LPG cookstove and fuel intervention on personal exposure reduction and its effect on gestational blood pressure with an RCT design in above countries. Findings arising from this dissertation highlight the alarming level of air pollution exposure from various sources in Tibet and the complexities in the relationship between HAP exposure and blood pressure among pregnant women that warrant further research.

Aim 1 (Chapter 2) of this dissertation focuses on assessing the sources, magnitudes, and chemical composition of personal HAP exposures in traditional Tibetan households. Using MicroPEM and microAeth, we measured 24-hour personal exposure to $PM_{2.5}$ and kitchen area BC concentration. We also quantified the exposures to particle-bound PAHs and inorganic elements via post-analyses of the

MicroPEM filters. To our knowledge, this is one of the most comprehensive characterization of personal HAP exposure conducted in the Tibetan region and the first exposure assessment performed on both Tibetan women and children. Two types of villages were identified in our study area, agricultural and nomadic villages, based on the housing, stove and fuel types. We found that the personal exposure level in residents of nomadic village were much higher than those of agricultural village, due to poorer ventilation of nomadic dwelling, worsen conditions of stoves and chimneys, and burning of yak dung and shrubs that contained a lot of moisture. Noteworthily, the average daily personal exposure to BaP, a Group 1 carcinogen listed by the International Agency for Research on Cancer (IARC), in this population was more than 50 times higher than the concentration limit for BaP in China's National Air Quality Standard for indoor air at 1.0 ng/m^3. More importantly, our findings in various high concentration elements challenged the commonly accepted assumption that biomass burning was the single most important source of air pollution exposure in rural Tibet as the ambient air is deemed to be the cleanest in the region. With the rapid infrastructure development and urbanization in China, pollution sources such as traffic, road/construction dust and garbage burning may contribute more to personal air pollution exposure. We would observe the issues of household and ambient air pollution co-exist in Tibet, like in many other developing/industrializing regions of the world.

Aim 2 and 3 (Chapter 3 and 4) leverage the large sample size and rich data points collected through the HAPIN trial in four different LMICs: Guatemala, India, Peru, and Rwanda. Chapter 3 describes the association between personal exposure to $PM_{2.5}$/BC/CO and blood pressure in 3190 pregnant women before they receive the LPG stove and fuel intervention. Exposure to $PM_{2.5}$/BC/CO has been linked to increased blood pressure. Elevated blood pressure complicates an estimate of 3 - 10% of pregnancies worldwide (Steegers et al., 2010) and contributes to 30,000 maternal deaths annually (von Dadelszen and Magee, 2016). However, few studies have evaluated the impact of HAP exposure on

blood pressure during pregnancy (Alexander et al., 2018; Quinn et al., 2017, 2016; Thompson et al., 2011). Pregnant women enrolled in the HAPIN trial were largely normotensive (<120/<80 mmHg) (93%), only 5% were classified as Elevated Blood Pressure (120-129/<80 mmHg), 2% were in the High Blood Pressure (Stage 1) (130-139/80-89 mmHg) category, and very few (9, <1%) were categorized as High Blood Pressure (Stage 2) (≥140/≥90 mmHg). In this pregnant women cohort exclusively using solid fuels, we found that 82% of the participants' exposures to $PM_{2.5}$ were higher than the World Health Organization's annual interim target 1 guideline value of 35 $\mu g/m^3$. In the association analysis, we found that exposures to BC were significantly associated with SBP in the positive direction among pregnant women with exposures in the highest quartile, compared to those with BC exposures in the lowest quartile (1.21 mmHg; 95% CI: 0.22, 2019). There were also borderline significant associations between exposures to $PM_{2.5}$ and SBP in pregnant women with exposures in the highest quartile compared to the lowest (0.93 mmHg; 95% CI: -0.04, 1.90; p-value: 0.059), as well as natural log transformed BC exposures and SBP (0.45 mmHg; 95% CI: -0.01, 0.89; p-value: 0.058). No significant association was observed between $PM_{2.5}$/BC/CO exposures and DBP and the associations were inconsistent in the direction.

Findings form this analysis added to the scarce evidence of the HAP-blood pressure association in pregnant women. It also provided a HAP exposure profile of women relying on biomass in four countries where the large-scale and objective personal exposure measurements were limited or not available. Furthermore, this study described the distribution and variability of blood pressure among young and healthy mothers in early- to mid-pregnancy. These direct assessments of personal exposure to three major household air pollutants simultaneously and their relationship to blood pressure among pregnant women in their 1st and 2nd trimester will contribute to a better understanding and estimation of the full disease burden of HAP in these countries and the broader developing world. The observed

association between $PM_{2.5}$/BC and SBP among pregnant women with exposures in the highest quartile also confirms that high HAP exposure raises SBP in normotensive adults.

Using data collected from the same cohort, Chapter 4 focuses on assessing the effects of the LPG stove and fuel intervention on serial blood pressure levels of women over their pregnancy. Results from the ITT analysis revealed statistically significant differences in gestational DBP between in the intervention and control groups. Surprisingly, we found a small but significant increase in DBP among the intervention group participants, even though the exposure reductions to all three pollutants were large and generally achieved WHO interim targets. Trial-wide exposure-response analyses were largely consistent with the ITT analysis results. Increased $PM_{2.5}$ and BC exposures were significantly associated with lower DBP, especially among women with $PM_{2.5}$ and BC exposures in the highest quartile, compared to the lowest. Although in this analysis, we did not observe any protective effect of the LPG stove and fuel intervention on gestational blood pressure, this study demonstrated the effectiveness of LPG stove and fuel use on HAP exposure reduction, given the observed large decreases in the post-randomization personal exposure to $PM_{2.5}$, BC, and CO. This longitudinal analysis also added to the limited evidence of the association between HAP exposure and blood pressure in pregnant women with repeated exposure and outcome measurements in four LMICs across Asia, African and Latin America. Additionally, the gestational blood pressure level and trajectory described in our analysis provide valuable information to inform the blood pressure management strategies over the pregnancy in these four LMICs, where such data are often scarce or not available.

5.2 Reflection and future work

Villages in our sampling area of the Chapter 2 analysis in Tibet are not "typical" traditional Tibetan villages where people reside in traditional black tents and herd yaks for a living. Residents in these villages are living a mixed "traditional" and "modern" lifestyle and we expect this trend to continue and expand in other Tibetan regions, as a result of the current poverty alleviation efforts, transportation/utility infrastructure development in the inner land, and the fast-growing lower-tier marker in China. These changes would have many implications in HAP and household energy research. The use of multiple energy sources, or fuel stacking, become increasingly popular in Tibet. A household may use electricity or gas for cooking and boiling of water, and solid fuels for space heating (Tao et al., 2021). Additionally, in Tibet, burning yak dung and sitting round the traditional stove have their cultural and spiritual significance. Clean household energy intervention implemented in this region should consider and incorporate these aspects into the design. Although cooking and heating with biomass remain the major sources of HAP exposure, other sources such as traffic and garbage burning cannot be ignored.

HAP exposure level and composition in these Tibetan household may have also been influenced, directly or indirectly, by local environmental governance practices. For example, in our study area, as part of the forest preservation efforts, local government only give 10 days each year for residents to collect firewood in the forest. The intention was to stop deforestation; however, this practice actually led to overcut. Before implementing this regulation, people collected firewood as they needed, and used to spend time in forest and search for dying trees or dried wood. The 10-day firewood collecting window now gives them no time to search but cut as many trees as possible, and many of these trees are easily accessed young and strong trees. Firewood made from these trees contains higher moisture and more likely to cause incomplete combustion and increased HAP. This regulation may also

introduce new inequality for families without cars and had only females and elderly members at home. These families would not be able to conduct this labor-intensive work and collect enough firewood for the whole year. They might then have to purchase firewood from others and that would add additional economic burden to these families. We have also observed frequent exposure to potentially toxic pollutants from garbage burning indoors and outdoors due to the lack of proper waste management facilities in these remote villages. Additionally, although we were able to take exposure measurement on children, the health implication in children may be limited by the fact that many of the children were away from home for about 2/3 of the year for boarding school or living with their migrant worker parents in nearby towns/cities. Future HAP and household energy research in Tibet may focus on longitudinal measurement of personal exposures across different seasons, epidemiological study with measurable health indicators, as well as intervention studies to reduce HAP and other environmental exposures.

For the analyses conducted in Chapter 2 and 3, we assumed that personal HAP exposure is well represented by the monitored personal exposures to $PM_{2.5}$, BC, and CO. However, these exposure measurements may not be enough to fully uncover the relationship between HAP exposure and gestational blood pressure. We observed negative association between exposure to $PM_{2.5}$/BC and DBP in pregnant women. In ITT analysis, the DBP levels were also significantly higher in the intervention arm. These unexpected findings may have been caused by exposures to pollutants other than what we measured, e.g., NO_2, PAHs, VOCs, in the intervention group. Additional analyses will be conducted by digging in the information collected from exposure questionnaires to better understand the exposure characteristics in each IRC. Furthermore, we report all personal exposure measurements as 24-hour average. This exposure metric does not provide details on the exposure pattern over a day. It is not clear whether the average was due to several very high exposure events or moderate exposure for a prolonged period. Future analysis on real-time data collected by ECMs would

allow us to understand the diurnal pattern of $PM_{2.5}$ exposures and the short-term effect of HAP exposure on blood pressure. The longitudinal measurements may also help establish the duration of air pollution effects on blood pressure.

Finding a variable to accurately represent a participant's socioeconomic status was another challenge in Chapter 2 and 3 analyses. The questionnaire was designed to apply the EquityTool, a simple way to measure relative wealth (in national quintiles) using short, country-specific questionnaire based on the ownership of a set of pre-identified assets (https://www.equitytool.org). This method is useful to capture the difference in household wealth within a country, however, it is less helpful in a multi-center study. If sampled households were concentrated in a relatively small area (compared to if spread around the whole country), we may find a large proportion of households fell into the same quintile, because the wealth difference in these household were small compared against the national household wealth distribution.

We also did not have accurate measurement on some of the key confounders in the association between air pollution exposure and blood pressure, such as salt intake and physical activity. The diet and nutrition questionnaire focused more on diet diversity and based on self-reported food consumption in the last 30 days. Physical activity was also assessed based on self-reported time spent on different types of activities within a week using the WHO Global Physical Activity Questionnaire. Recall bias is inevitable using these measurements. Objective measures are needed for these lifestyle indicators, e.g., measuring the household food seasoning consumption and introducing the pedometer to capture daily activity level.

Another lesson learned from the trial-wide exposure-response association analysis was the consideration of controlling for geographic location indicator in the model. Including the geographic location indicator in statistical models is the common practice for modeling the exposure-response

relationship involving multiple locations. However, in our models, we found the effect of covariates differ substantially by IRC (covariates were significantly interact with IRC). Therefore, simply controlling for IRC in our models resulted in biased estimates. In future study with multiple locations, it is important to check beforehand if the other covariates controlled in the model are important confounders and significantly interact with the geographic location indicator. We also need to check if the results without including location-covariate interaction terms differ meaningfully from those in which location-covariate interaction terms are included in the model.

Applying a translational research framework, this dissertation contributed to the first three phases of the research translation, moving from environmental exposure discovery (T1) to health (T2) and policy/practice (T3) implications. The next phase: policy/practice implementation (T4) is centered on the application of identified intervention or policies/practices within a community or societal setting. This process required evaluation of the available evidence for the efficacy of various interventions, understanding of the acceptability of each potential intervention, consideration of alternative solutions and competing risk and benefits, cost-benefit analysis, and ultimately, policy development (Kaufman and Curl, 2019). In the context of promoting and scaling up LPG in the developing world, it is critical to evaluate the magnitude and quality of the evidence in a holistic view. Therefore, the observed null effect of the LPG stove and fuel intervention on gestational blood pressure in our low antenatal risk pregnant women cohort should not be evaluated carefully and interpreted with caution. The last phase: evaluating population-level health impacts (T5) also has special relevance to public health interventions. In this phase, the intervention effects (both exposure and health outcomes) of interventions after their implementation will be measured to inform further policy changes. On this point, more work needs to be done to improving the translatability of scientific evidence into policies and practices.

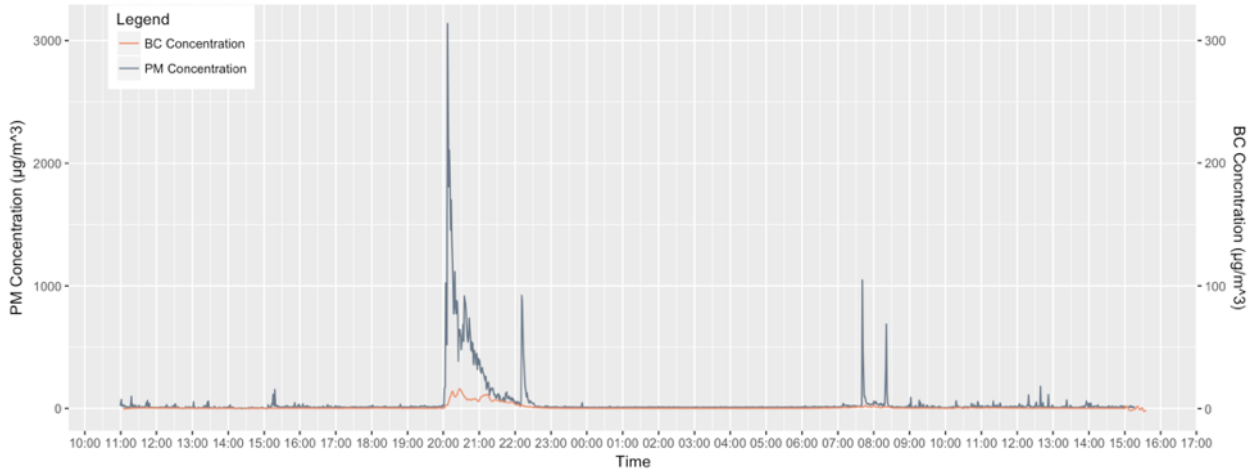
5.3 Investigator Role and Responsibility

For the research described in Chapter 2, my responsibilities include: assisting with field sampling, data cleaning and analysis, results summary and visualization, preparing manuscript (all sections). For the research presented in Chapter 3, my responsibilities include: conceptualization and methodology, data cleaning and analysis, results summary and visualization, writing manuscript (methods and results sections), reviewing and editing manuscript (introduction and discussion sections). For the research described in Chapter 4, my responsibilities include: conceptualization and methodology, data cleaning and analysis, results summary and visualization, writing manuscript (methods, results and discussion sections), reviewing and editing manuscript (introduction section).

APPENDICES

Appendix A Supplementary Information for Chapter 2

Figure A1. Traditional Tibetan style cast-iron stoves with chimneys from surveyed households. a) stove in a traditional Tibetan house from the agricultural village, b) stove in a tent from the nomadic village.



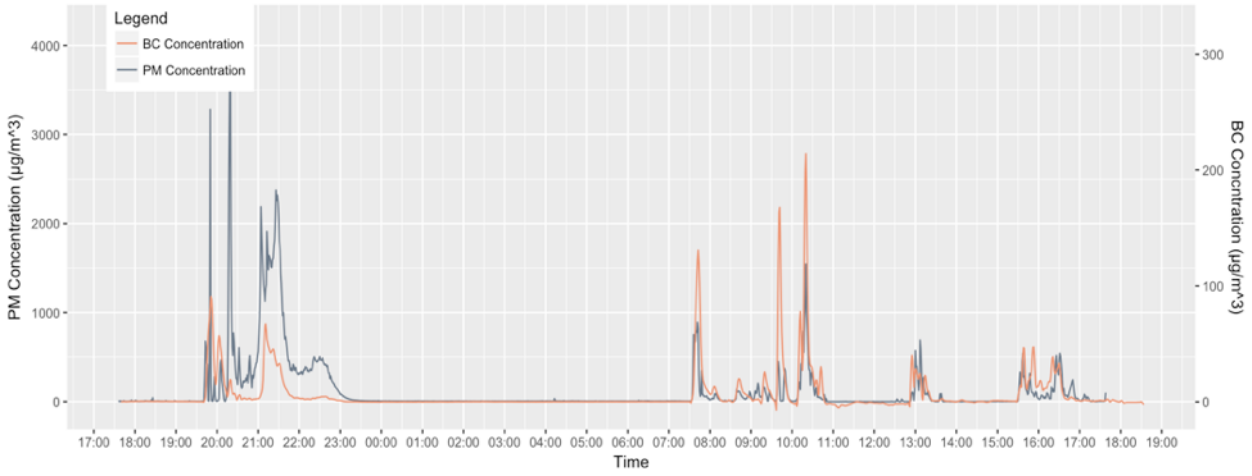


Figure A2. 24-hour real-time personal $PM_{2.5}$ and kitchen BC concentrations from selected agricultural (top) and nomadic (bottom) village households

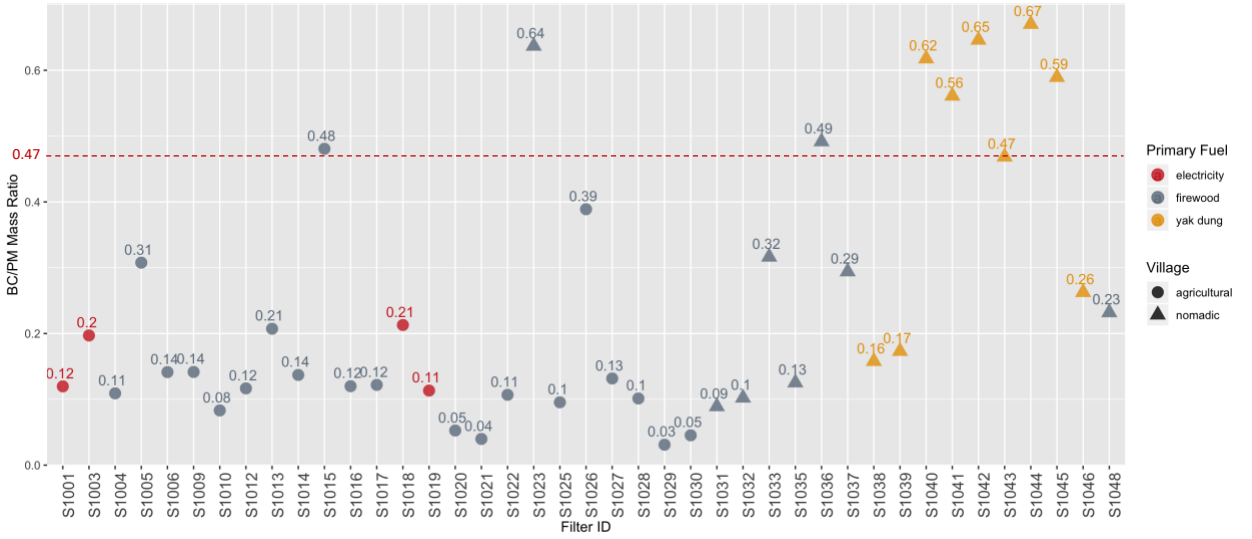


Figure A3. Scatter plot of BC/PM mass ratio of 41 effective filters for personal exposure measurements. Red dotted line indicated the higher end of previously-reported mean BC/PM mass ratio (Li et al., 2009). Numbers to the upper left of the points are the ratios for each of the observed values.

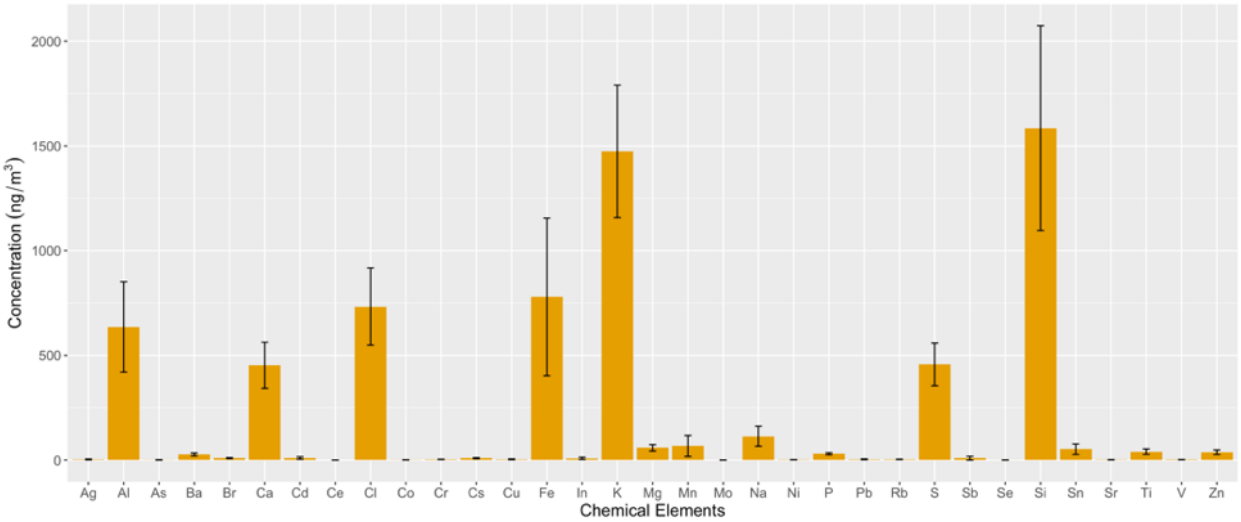


Figure A4. Bar plot of mass concentrations of elements in $PM_{2.5}$ from all samples (ng/m^3). Error bars indicate one standard deviation.

Table A1. Characteristics of households and individuals interviewed in this study

	Agricultural Village	**Nomadic Village**	**Total**
Household demographics	(n = 14)	(n = 10)	(n = 24)
Household members, mean (SD)	6.07 (2.20)	3.90 (1.37)	5.17 (2.16)
Survey covered population, n	85	39	124
Gender, n (%)			
Female	42 (49%)	22 (56%)	64 (52%)
Male	43 (51%)	17 (44%)	60 (48%)
Population group, n (%)			
Child	29 (34%)	14 (36%)	43 (35%)
Adult	56 (66%)	25 (64%)	81 (65%)
Range of Age, [minimum, maximum]			
Child	[5, 16]	[5, 14]	[5, 16]
Adult	[27, 65]	[22, 63]	[22, 65]
Active smoking, n (%)	6 (43%)	3 (10%)	9 (37.5%)
Annual income ($), mean (SD)	5,155 (2,754)	3,102 (1,532)	4,300 (2,505)
Time spent at home (hours), mean (SD)	18.3 (2.6)	N/A	N/A
Summer	16.1 (3.8)	15.7 (1.6)	15.9 (3.1)
Winter	20.4 (2.7)	N/A	N/A
Stove, fuel, and cooking behavior			
Households with more than one stove, n (%)	14 (100%)	1 (10%)	15 (62.5%)
Households with type of stove, n (%)			
Traditional chimney stove (in-house)	14 (100%)	10 (100%)	24 (100%)
Electric stove (heating wire, in-house)	9 (64.3%)	0 (0%)	9 (37.5%)
Traditional stove for livestock (outdoor)	5 (35.7%)	0 (0%)	5 (20.8%)

Open fire for livestock (outdoor)	4 (28.6%)	0 (0%)	3 (12.5%)
Gas stove	0 (0%)	1 (10%)	1 (4%)
Age of main stove (years), mean (SD)	7 (4.16)	4 (1.93)	5 (3.66)
Daily operation time (hours), mean (SD)	7.5 (3.7)	N/A	N/A
Summer	5.3 (2.6)	7.1 (1.3)	6 (2.3)
Winter	9.6 (5.2)	N/A	N/A
Primary cooking fuel, n (%)			
Electricity	2 (14%)	0 (0%)	2 (8%)
Firewood	12 (86%)	5 (50%)	17 (71%)
Yak dung	0 (0%)	5 (50%)	5 (21%)
Secondary cooking fuel, n (%)			
Firewood	2 (14%)	5 (50%)	7 (29%)
Yak dung	12 (86%)	2 (20%)	14 (58%)
Solar/Gas/None	0 (0%)	3 (30%)	3 (13%)
Health awareness and concern			
Feel uncomfortable while burning, n (%)			
Never	6 (43%)	5 (50%)	11 (46%)
Sometimes	8 (57%)	5 (50%)	13 (54%)
Aware that smoke may affect health, n (%)			
Yes	2 (14%)	0 (0%)	2 (8%)
No	10 (71%)	10 (100%)	20 (84%)
Not sure	2 (14%)	0 (0%)	2 (8%)
Self-reported health concerns, n (%)			
None	4 (29%)	0 (0%)	4 (17%)
Respiratory	4 (29%)	0 (0%)	4 (17%)
Gastrointestinal	2 (14%)	3 (30%)	5 (21%)
Cardiovascular	2 (14%)	2 (20%)	4 (17%)
Rheumatism & Joint pain	1 (7%)	9 (90%)	10 (42%)

Table A2. Summary of mean, SD of the hourly $PM_{2.5}$ concentrations and total sampling time of 45 real-time personal $PM_{2.5}$ exposure measurements.

Time of the Day	**$PM_{2.5}$ Concentration ($\mu g/m^3$), Mean (SD)**	**Total Sampling Time (minute)**
1:00 – 2:00	16.7 (23.7)	2543
2:00 – 3:00	14.7 (13.5)	2580
3:00 – 4:00	61.5 (168)	2580
4:00 – 5:00	46.8 (115)	2627
5:00 – 6:00	20.4 (41.9)	2586
6:00 – 7:00	41.5 (102)	2601
7:00 – 8:00	356 (791)	2580
8:00 – 9:00	366 (863)	2560
9:00 – 10:00	325 (634)	2532
10:00 – 11:00	154 (266)	2641

11:00 – 12:00	231 (641)	2703
12:00 – 13:00	189 (560)	2769
13:00 – 14:00	83.1 (165)	2785
14:00 – 15:00	97.0 (288)	2847
15:00 – 16:00	36.9 (68.2)	2546
16:00 – 17:00	71.7 (97.0)	2388
17:00 – 18:00	161 (617)	2457
18:00 – 19:00	178 (558)	2515
19:00 – 20:00	178 (455)	2529
20:00 – 21:00	153 (246)	2460
21:00 – 22:00	113 (303)	2460
22:00 – 23:00	42.0 (79.7)	2514
23:00 – 24:00	17.0 (14.8)	2541
24:00 – 1:00	14.8 (15.1)	2520

Table A3. Short-term (minute-level) exposure to $PM_{2.5}$ and kitchen area concentration of BC in eight households form agricultural (Household 1-5) and nomadic village (Household 6-8).

Household	HAP Type	Population/Fuel*	Minimum ($\mu g/m^3$)	Maximum ($\mu g/m^3$)
1	PM	Adult	5.11	2.26×10^3
		Child	0.02	531
	BC	Electricity	-1.33	18.3
2	PM	Adult	0.10	497
		Child	6.41	1.76×10^3
	BC	Firewood	-1.98	64.1
3	PM	Adult	1.61	1.97×10^3
		Adult	0.00	1.07×10^3
	BC	Firewood	-0.55	10.1
4	PM	Child	0.09	2.50×10^3
		Adult	0.01	3.14×10^3
	BC	Firewood	-2.47	15.9
5	PM	Adult	0.12	723
		Child	0.00	533
	BC	Firewood	-1.49	30.9
6	PM	Adult	0.01	3.51×10^3
		Adult	0.00	4.24×10^3
	BC	Firewood	-7.36	214
7	PM	Adult	0.36	7.49×10^3
		Child	1.49	8.10×10^3
	BC	Yak dung	-9.07	559
8	PM	Adult	0.31	6.77×10^3
		Child	0.00	4.70×10^3
	BC	Yak dung	-7.34	341

**Indicate the participant type (adult/child) for personal $PM_{2.5}$ exposure measurement and primary fuel type used in the kitchen where BC concentrations were measured.*

Table A4. Mass concentration of assessed inorganic elements in $PM_{2.5}$ in agricultural and nomadic villages (mean ± SD ng/m^3)

	Agricultural Village (ng/m^3)	**Nomadic Village** (ng/m^3)		**Agricultural Village** (ng/m^3)	**Nomadic Village** (ng/m^3)
Ag	5.37 x 10^{-1} ± 1.20	4.27 ± 6.92	Mn	1.11 x 10^2 ± 2.02 x 10^2	10.6 ± 7.51
Al*	9.81 x 10^2 ± 6.40 x 10^2	1.52 x 10^2 ± 60.3	Mo	3.75 x 10^{-1} ± 8.38 x 10^{-1}	0.00 ± 0.00
As	1.89 ± 3.06	2.45 x 10^{-1} ± 6.01 x 10^{-1}	Na	1.63 x 10^2 ± 1.81 x 10^2	38.1 ± 15.2
Ba	34.8 ± 23.7	12.8 ± 6.60	Ni	1.68 ± 1.36	1.11 ± 8.30 x 10^{-1}
Br	4.50 ± 3.20	10.6 ± 6.59	P	28.1 ± 16.6	23.0 ± 14.0
Ca	5.31 x 10^2 ± 4.07 x 10^2	2.49 x 10^2 ± 92.6	Pb	4.68 ± 7.64	1.71 ± 2.00
Cd	16.0 ± 22.2	1.81 ± 4.44	Rb	3.67 ± 2.50	1.98 ± 1.76
Ce	Not Detected	Not Detected	S*	1.62 x 10^2 ± 97.1	5.63 x 10^2 ± 2.50 x 10^2
Cl*	2.56 x 10^2 ± 3.52 x 10^2	9.08 x 10^2 ± 4.36 x 10^2	Sb	Not Detected	13.6 ± 33.3
Co	9.89 x 10^{-1} ± 1.19	5.66 x 10^{-1} ± 6.59 x 10^{-1}	Se	2.33 x 10^{-1} ± 5.22 x 10^{-1}	3.51 x 10^{-1} ± 6.54 x 10^{-1}
Cr	2.98 ± 2.30	2.46 ± 1.41	Si	2.30 x 10^3 ± 1.52 x 10^3	5.02 x 10^2 ± 1.63 x 10^2
Cs	8.67 ± 9.05	6.42 ± 4.70	Sn	33.4 ± 74.7	51.7 ± 68.6
Cu	4.35 ± 7.54	2.08 ± 1.33	Sr	1.14 ± 1.65	1.45 ± 2.00
Fe	1.20 x 10^3 ± 1.41 x 10^3	1.87 x 10^2 ± 92.0	Ti	57.6 ± 42.3	13.8 ± 5.54
In	7.30 ± 14.9	6.43 ± 15.8	V*	2.84 ± 1.54	9.05 x 10^{-1} ± 8.19 x 10^{-1}
K	6.91 x 10^2 ± 5.10 x 10^2	1.68 x 10^3 ± 8.94 x 10^2	Zn	14.2 ± 14.9	45.8 ± 32.4
Mg	72.5 ± 47.0	28.8 ± 24.3			

**Element concentrations significantly different by village type (p<0.05). Chemical elements in shade were below the MDL.*

Table A5. Univariate associations of household characteristics and exposure determinants with personal $PM_{2.5}$ exposure [a.]

Variables	**β Coefficient (Standard Error)**	**P value**
Household Characteristics		
Village type (ref. Agricultural village)		
Nomadic village	1.74 (0.19)	< 0.001
Household size	-0.24 (0.07)	< 0.001
Age group (ref. Adult)		
Child	-0.61 (0.33)	0.08
Active Smoking (ref. No)		
Yes	0.21 (0.35)	0.55
Annual household income	-0.02 (0.01)	0.03
Daily time spend at home in summer	-0.05 (0.04)	0.22
Stove/Fuel/Cooking Characteristics		

Number of stoves used (ref. one stove)		
Two stoves	-1.76 (0.17)	< 0.001
Three stoves	-1.51 (0.27)	< 0.001
Four stoves	-2.04 (0.68)	0.01
Main stove age	-0.12 (0.05)	0.01
Daily stove operation time in summer	0.08 (0.07)	0.27
Chimney age	-0.14 (0.04)	< 0.001
Daily cooking time	0.11 (0.17)	0.50
Primary household fuel (ref. electricity)		
Firewood	0.63 (0.48)	0.20
Yak dung	1.80 (0.52)	0.001
Feel uncomfortable while burning (ref. No)		
Sometimes	-0.12 (0.33)	0.75

[a] *Modeled on natural log scale*

Survey Questions

1. How many family members do you have at home (including children)? What is their age and gender?

2. Are there any smokers in your family? If yes, where do they smoke and how many per day?

3. What's the average monthly income of your family and what's the main source of your family income?

4. What type of fuel do you use as primary source? Secondary fuel source? (If you use different types of fuel, let us know how often you use each type fuel.)

    a. What is the reason you use that fuel?

    b. Would you prefer to use an alternative fuel source?

    c. How do you get the fuel you use?

    d. Have you considered any other types of fuel like biogas or charcoal?

    e. Does the primary/secondary fuel source change at any time of year?

5. Does your family use renewable energy like solar power? If not, would you consider using it? Broken, freeze, last year; not consider for new one (repair) If not, what's the main reason?

6. How many stoves do you usually use? What are their types? How old are they?

7. Do you use the stove mainly for cooking? Do you use it for anything else (e.g., heating, lighting)?
    a. How many hours does the stove operate a day averagely? If the stove operation times vary with different seasons, please report the operating hours in different seasons.
    b. Does the stove require maintenance? If yes, please describe.
8. Do you have a chimney on your stove? Or in your kitchen? If so, how long have you used it?
    a. Would you consider building one if someone taught you how to correctly install it?
    b. Would you be willing to pay someone to install?
    c. If yes, what prevents you from doing so?
    d. If not, what is the reason you would not consider it?
    e. If it is cost-related, how much are you willing to spend?
9. Who is responsible for cooking in your family?
    a. Does he/she have any assistance? From whom?
    b. How many times does he/she cook per day?
    c. How much time in total is spent cooking each day?
10. Can you tell us your everyday routine in a household?
11. How many hours do you and your family members usually spend in a house per day?
    a. How many hours do you and your family members spend in tent when the stove is on?
12. While burning the fuel, do you smell the pungent, suffocating, uncomfortable odor?
    a. Do you have any coughing, wheezing, or other acute symptoms? Please describe it.
13. Do you know the smoke affects your health and/or your family's health? Why or why not?
    a. Do you consider it as air pollution, which will harm your health? Why or why not?
    b. Are you worried that the smoke will harm your health? Why or why not?
14. Do any of your family members have any health issues? If so, what kind of health issue is it? (Like burning of the nose, throat, and respiratory tract; coughing and nose/throat irritation while burning fuel wood) When did it happen and how long did it last?

a. Any history of pneumonia? Tuberculosis? Low-birthweight? Asthma?

Would you be willing to let us measure concentration of air pollutants in your tent/house for a day?

Methods of Exposure Assessment and Data Processing

Personal exposure and indoor air quality sampling strategy

During the field sampling period (July-August 2016), the average daily temperature was between 9 C° and 22 C° in Ganzi and average daily precipitation was 7.5 mm during the sampling period (https://www.ncdc.noaa.gov/data-access/land-based-station-data). 24-hour integrated personal $PM_{2.5}$ concentrations were measured in agricultural (n = 26) and nomadic (n = 20) villages. MicroPEM was distributed to voluntary participants, usually the primary adult cook and a child in each household. MicroPEM was carried by participants, using a wearable crossbody pouch to approximate subjects' breathing zone without disturbing their daily activities (i.e. farming, herding and housework). Participants were instructed to wear the instrument, while conducting their daily routines and place the instrument next to them (within 1 m) when sleeping or showering. Instruments were given and started, measuring right after the household interview and retrieved during the second household visit after at least 24 hours. 24-hour BC concentrations in the kitchen area were also measured in agricultural (n = 5) and nomadic (n = 3) households. The BC monitor microAeth was placed on the shelves, open closets or other safe locations in the kitchen with minimal interruption of household activities. The microAeth was usually placed at around 0.5 m above the ground to approximate the exposure environment of stove users. MicroAeth was set up and retrieved at about the same time as MicroPEM for each household visit.

Air quality data processing

Real-time $PM_{2.5}$ monitor MicroPEM data were processed with MicroPEM Docking Station beta edition software (RTI International, Research Triangle Park, NC) and R software (version 3.4.1) at ten-second intervals and were calibrated with corresponding gravimetric filter measurements. Real-time BC monitor microAeth data were sampled at one-minute intervals and processed with microAeth online data processing software (AethLabs, San Francisco, CA). Smoothing was conducted for BC real-time data with local polynomial regression by every seven points. R software was later used to analyze the peak, correlation and daily variation of $PM_{2.5}$ and BC concentrations for the entire measurement period. T-tests, univariate and multivariate linear regressions were performed to examine the relationship between $PM_{2.5}$/BC concentrations and demographic as well as lifestyle-related variables.

MicroPEM sample filters were pre- and post-weighed at RTI International (RTP, NC), using a microbalance (Mettler Toledo UMX2) housed in a temperature and humidity controlled environmental chamber (21°C, 35% RH). All filters were equilibrated in the environmental chamber for 24 hours prior to both pre- and post-weighing. Quality assurance samples were also analyzed

together that include standard weight and laboratory blank filters. The filters were subsequently analyzed for black carbon in RTI-proprietary integrating sphere via optical transmittance method. This technique measures optical transmittance through the filter and deposited sample at seven discrete wavelengths ranging from blue (430nm) to near-infrared (940nm) (Thygerson et al., 2019). The wavelength-dependent change in transmission thru the filter from pre- to post-sampling is used to estimate the species-specific mass loading collected during sampling, for example, BC absorbs strongly at all wavelengths including near-infrared (Thygerson et al., 2019; Yan et al., 2011). The mass fraction of BC is calculated using an empirically derived algorithm that iteratively adjusts the mass fraction to minimize the difference between the measured and modeled optical properties of the collected particulate matter (Thygerson et al., 2019). Following post-weighing and BC measurements, they were stored in a -20°C freezer until compositional analysis.

PAHs and metal analysis

Two different subsets of the filters in MicroPEM were used to assess the composition and mass of each PAHs (n = 12) and inorganic elements (n = 11). For PAHs, the sample filters were extracted in 2 mL of dichloromethane containing internal standards (mix of isotope-labeled compounds), and then subsequently in 2 mL of acetone in a sonication water bath for 30 minutes each. Method control and method blank samples were prepared with certified "EPA 16-PAHs" standards. The extracts were combined, filtered, and concentrated ten times under a stream of nitrogen using a solvent evaporator before analyzed by gas chromatography–mass spectrometry (GC-MS). The GC instrument (Agilent 6890/5975) operated with the mass spectrometer in selected ion monitoring mode. The instrument was calibrated using a nine-point curve for each analyte from 5 ng/mL to 2500 ng/mL. Solvent blanks were below instrument detection limits, and check standards were required to fall within 20% of expected values. For metals, a total of 33 elements, including Ag, Al, As, Ba, Br, Ca, Cd, Ce, Cl, Co, Cr, Cs, Cu, Fe, In, K, Mg, Mn, Mo, Na, Ni, P, Pb, Rb, S, Sb, Se, Si, Sn, Sr, Ti, V, and Zn were analyzed by energy-dispersive X-ray fluorescence spectroscopy (EDXRF) (ARL™ QUANT'X EDXRF Spectrometer, Thermo Scientific). RTI's EDXRF instrument uses an X-ray beam collimator to optimize performance for the small sample surface area (10mm diameter circle) of PM collected on MicroPEM filters. EDXRF analysis of MicroPEM filters followed U.S. EPA Method IO-3.3 (EPA 625/R-96/010a). The output of power ranges in six different excitation conditions within 4–50 kV to achieve maximum response for the 33 project-specific elements. A calibration curve was developed, using 25-mm single or dual element thin film standards. With each analytical run, a certified multi-element thin film standard was analyzed to verify the instrument functionality and stability across the six excitation conditions. The quality control (QC) acceptance for the multi-element standard is less than 5% coefficient of variation and a recovery of 90-110%. Additionally, replicate samples were analyzed at a rate of 10% of the total number of samples.

Appendix B Supplementary Information for Chapter 3

Table B1. Measured 24-hour personal exposures to $PM_{2.5}$, BC, and CO by IRC, after removing the highest 1% and 5% of exposure samples)

	N	Median	IQR	Mean	Min	Max
$PM_{2.5}$ < 559.7 µg/m³ (removed highest 1%)						
All IRCs	2789	81.9	97.8	107.8	9.4	555.5
Guatemala	726	112.7	122.9	139.9	9.9	555.5
India	703	75.1	80.9	101.4	9.4	518.9
Peru	653	49.5	85.8	79.5	10.7	520.0
Rwanda	707	88.8	83.9	107.1	14.2	523.3
$PM_{2.5}$ < 312.7 µg/m³(removed highest 5%)						
All IRCs	2677	78.4	88.8	96.0	9.4	312.6
Guatemala	670	105.4	108.2	119.0	9.9	312.6
India	683	72.7	75.1	92.8	9.4	311.8
Peru	635	47.0	81.0	71.0	10.7	310.7
Rwanda	689	86.7	77.3	99.9	14.2	308.3
BC < 54.2 µg/m³ (removed highest 1%)						
All IRCs	2510	10.6	8.8	11.9	0.6	54.2
Guatemala	669	11.9	5.8	12.5	2.5	41.6
India	693	9.4	10.5	12.4	0.6	54.0
Peru	588	8.1	12.2	10.6	1.5	48.7
Rwanda	560	10.9	7.5	11.7	2.7	54.2
BC < 29.4 µg/m³ (removed highest 5%)						
All IRCs	2409	10.3	8.3	10.8	0.6	29.3
Guatemala	659	11.9	5.7	12.2	2.5	26.8
India	644	8.8	9.0	10.4	0.6	29.1
Peru	556	7.5	11.0	9.1	1.5	29.3
Rwanda	550	10.8	7.3	11.2	2.7	27.4
CO < 20.9 ppm (removed highest 1%)						
All IRCs	2843	1.2	2.2	2.2	0.0	20.6
Guatemala	754	1.3	2.0	1.9	0.0	12.6
India	742	0.8	1.8	1.6	0.0	19.9
Peru	644	1.9	3.5	3.2	0.0	19.9
Rwanda	703	1.1	1.9	2.2	0.0	20.6
CO < 9.0 ppm (removed highest 5%)						
All IRCs	2728	1.1	2.0	1.7	0.0	9.0
Guatemala	744	1.3	1.9	1.8	0.0	8.8
India	728	0.8	1.6	1.4	0.0	8.7
Peru	587	1.6	2.8	2.3	0.0	8.7
Rwanda	669	1.0	1.6	1.6	0.0	9.0

Table B2. Association between HAP exposure and gestational blood pressure at baseline. Results from unadjusted models (all valid samples)

	Model Type	Estimate	p-value	95% CI	AIC
Systolic Blood Pressure					
PM2.5	Linear	0.0029	0.0570	(-0.0001, 0.0058)	20746
	Log linear	0.9817	0.0000	(0.5702, 1.3932)	20727
	Categorical [Ref. Quartile 1)				
	Quartile 2	2.1782	0.0000	(1.158, 3.1984)	20725
	Quartile 3	2.2047	0.0000	(1.1838, 3.2256)	
	Quartile 4	2.3786	0.0000	(1.3591, 3.3981)	
BC	Linear	0.0482	0.0097	(0.0117, 0.0848)	18580
	Log linear	0.9970	0.0001	(0.5154, 1.4786)	18570
	Categorical [Ref. Quartile 1)				
	Quartile 2	1.0557	0.0508	(-0.0039, 2.1154)	18574
	Quartile 3	1.9470	0.0003	(0.8857, 3.0083)	
	Quartile 4	1.8220	0.0008	(0.7619, 2.882)	
CO	Linear	-0.1015	0.0139	(-0.1824, -0.0206)	20851
	Log linear	-0.2429	0.0579	(-0.494, 0.0081)	20854
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.2168	0.6748	(-0.7963, 1.2299)	20848
	Quartile 3	-0.2279	0.6591	(-1.2411, 0.7852)	
	Quartile 4	-1.4960	0.0038	(-2.5091, -0.4829)	
Diastolic Blood Pressure					
PM2.5	Linear	-0.0007	0.5408	(-0.0031, 0.0016)	19506
	Log linear	0.1034	0.5404	(-0.2276, 0.4343)	19506
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.9440	0.0242	(0.1233, 1.7647)	19505
	Quartile 3	0.6862	0.1015	(-0.1351, 1.5075)	
	Quartile 4	0.2378	0.5697	(-0.5823, 1.0579)	
BC	Linear	-0.0093	0.5354	(-0.0389, 0.0202)	17511
	Log linear	0.0474	0.8119	(-0.3431, 0.4379)	17512
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.7345	0.0935	(-0.1239, 1.593)	17512
	Quartile 3	0.2723	0.5347	(-0.5876, 1.1321)	
	Quartile 4	-0.0755	0.8632	(-0.9343, 0.7834)	
CO	Linear	-0.0360	0.2792	(-0.1012, 0.0292)	19631
	Log linear	-0.2344	0.0230	(-0.4365, -0.0323)	19627
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.0247	0.9527	(-0.7916, 0.8411)	19627
	Quartile 3	-0.6270	0.1322	(-1.4434, 0.1893)	
	Quartile 4	-1.0531	0.0115	(-1.8695, -0.2368)	

Table B3. Association between HAP exposure and gestational blood pressure at baseline. Results from minimally adjusted models (all valid samples)

	Model Type	Estimate	p-value	95% CI	AIC
Systolic Blood Pressure					
PM2.5	Linear	0.0019	0.1638	(-0.0008, 0.0046)	20001
	Log linear	0.3611	0.0698	(-0.0292, 0.7513)	20000
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.5384	0.2609	(-0.4003, 1.477)	20000
	Quartile 3	0.2228	0.6446	(-0.7242, 1.1698)	
	Quartile 4	1.2163	0.0125	(0.2622, 2.1703)	
BC	Linear	0.0520	0.0021	(0.0189, 0.0851)	17953
	Log linear	0.5700	0.0130	(0.1205, 1.0196)	17957
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.1229	0.8064	(-0.8605, 1.1063)	17956
	Quartile 3	0.8216	0.1136	(-0.1963, 1.8395)	
	Quartile 4	1.4521	0.0035	(0.4779, 2.4262)	
CO	Linear	-0.0186	0.6208	(-0.0924, 0.0552)	20104
	Log linear	0.0454	0.6998	(-0.1855, 0.2763)	20104
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.1341	0.7735	(-1.0476, 0.7794)	20107
	Quartile 3	0.2456	0.6003	(-0.6736, 1.1649)	
	Quartile 4	-0.2773	0.5581	(-1.2056, 0.651)	
Diastolic Blood Pressure					
PM2.5	Linear	-0.0009	0.4011	(-0.0031, 0.0012)	18841
	Log linear	-0.2628	0.1041	(-0.5797, 0.0542)	18839
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.2196	0.5725	(-0.9825, 0.5433)	18843
	Quartile 3	-0.5938	0.1305	(-1.3635, 0.1759)	
	Quartile 4	-0.3765	0.3412	(-1.1519, 0.3989)	
BC	Linear	-0.0035	0.7977	(-0.0305, 0.0234)	16929
	Log linear	-0.1760	0.3460	(-0.5423, 0.1902)	16928
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.2863	0.4839	(-0.5156, 1.0881)	16931
	Quartile 3	-0.1384	0.7438	(-0.9683, 0.6916)	
	Quartile 4	-0.1609	0.6912	(-0.9552, 0.6334)	
CO	Linear	0.0288	0.3498	(-0.0316, 0.0891)	18972
	Log linear	0.0363	0.7059	(-0.1525, 0.2251)	18973
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.0878	0.8178	(-0.8349, 0.6593)	18977
	Quartile 3	-0.0901	0.8142	(-0.8419, 0.6616)	
	Quartile 4	0.0376	0.9227	(-0.7216, 0.7967)	

Note: *All models adjusted for IRC, gestational age at blood pressure measurement (weeks), nulliparity, BMI.*

Table B4. Association between HAP exposure and gestational blood pressure at baseline. Results from fully adjusted models (removed the highest 1% of exposure samples)

	Model Type	Estimate	p-value	95% CI	AIC
Systolic Blood Pressure					
PM2.5	Linear	0.0023	0.2297	(-0.0015, 0.0061)	19778
	Log linear	0.2372	0.2584	(-0.1743, 0.6487)	19779
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.3621	0.4501	(-0.5777, 1.3019)	19779
	Quartile 3	-0.0924	0.8492	(-1.045, 0.8602)	
	Quartile 4	0.8809	0.0763	(-0.0931, 1.855)	
BC	Linear	0.0465	0.0342	(0.0035, 0.0895)	17768
	Log linear	0.3605	0.1368	(-0.1144, 0.8354)	17770
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.0391	0.9381	(-0.9472, 1.0253)	17770
	Quartile 3	0.5721	0.2741	(-0.4536, 1.5978)	
	Quartile 4	1.1095	0.0292	(0.1124, 2.1066)	
CO	Linear	-0.0423	0.4667	(-0.1562, 0.0716)	19885
	Log linear	0.045	0.7098	(-0.1923, 0.2824)	19885
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.1526	0.7429	(-1.0649, 0.7596)	19888
	Quartile 3	0.184	0.6943	(-0.7341, 1.1022)	
	Quartile 4	-0.2343	0.6241	(-1.1718, 0.7031)	
Diastolic Blood Pressure					
PM2.5	Linear	-0.0022	0.1717	(-0.0052, 0.0009)	18644
	Log linear	-0.3012	0.0779	(-0.6362, 0.0337)	18642
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.3114	0.4253	(-1.077, 0.4543)	18647
	Quartile 3	-0.5973	0.1314	(-1.3734, 0.1788)	
	Quartile 4	-0.4107	0.3103	(-1.2042, 0.3828)	
BC	Linear	-0.0155	0.3852	(-0.0506, 0.0195)	16754
	Log linear	-0.2561	0.1944	(-0.6431, 0.1308)	16753
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.1881	0.6466	(-0.6162, 0.9923)	16757
	Quartile 3	-0.2266	0.5953	(-1.063, 0.6098)	
	Quartile 4	-0.2619	0.5277	(-1.075, 0.5512)	
CO	Linear	0.019	0.6907	(-0.0745, 0.1125)	18789
	Log linear	0.0226	0.8202	(-0.1723, 0.2175)	18789
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.1347	0.7243	(-0.8838, 0.6143)	18793
	Quartile 3	-0.0902	0.8145	(-0.8442, 0.6637)	
	Quartile 4	-0.0038	0.9922	(-0.7736, 0.766)	

Note: *All models adjusted for IRC, gestational age at blood pressure measurement (weeks), nulliparity, BMI, maternal age, mother's level of education, time of blood pressure measurement, mother's diet diversity.*

Table B5. Association between HAP exposure and gestational blood pressure at baseline. Results from fully models (removed the highest 5% of exposure samples)

	Model Type	Estimate	p-value	95% CI	AIC
Systolic Blood Pressure					
PM2.5	Linear	0.0039	0.1337	(-0.0012, 0.009)	18997
	Log linear	0.2374	0.3	(-0.2117, 0.6865)	18998
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.3408	0.4795	(-0.604, 1.2855)	18999
	Quartile 3	-0.1136	0.8162	(-1.0718, 0.8446)	
	Quartile 4	0.8875	0.0888	(-0.1347, 1.9097)	
BC	Linear	0.0435	0.1506	(-0.0158, 0.1027)	17041
	Log linear	0.2689	0.312	(-0.2525, 0.7903)	17042
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.0738	0.8833	(-0.9124, 1.06)	17042
	Quartile 3	0.6057	0.2475	(-0.4211, 1.6325)	
	Quartile 4	1.0048	0.0601	(-0.0429, 2.0526)	
CO	Linear	-0.0603	0.528	(-0.2475, 0.127)	19038
	Log linear	0.0813	0.5278	(-0.1713, 0.334)	19038
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.159	0.7311	(-1.0659, 0.748)	19042
	Quartile 3	0.1655	0.7223	(-0.7475, 1.0785)	
	Quartile 4	-0.1575	0.7513	(-1.1316, 0.8167)	
Diastolic Blood Pressure					
PM2.5	Linear	-0.0015	0.4724	(-0.0056, 0.0026)	17879
	Log linear	-0.2804	0.1304	(-0.6438, 0.083)	17877
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.3323	0.3943	(-1.0973, 0.4326)	17881
	Quartile 3	-0.6169	0.1191	(-1.3927, 0.159)	
	Quartile 4	-0.3293	0.4353	(-1.1569, 0.4983)	
BC	Linear	-0.0292	0.2344	(-0.0773, 0.0189)	16047
	Log linear	-0.305	0.1576	(-0.7281, 0.1181)	16046
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.2154	0.5979	(-0.5855, 1.0163)	16051
	Quartile 3	-0.1991	0.6397	(-1.0329, 0.6348)	
	Quartile 4	-0.3175	0.4644	(-1.1683, 0.5333)	
CO	Linear	-0.02	0.7978	(-0.1734, 0.1333)	17973
	Log linear	0.0123	0.907	(-0.1945, 0.2192)	17973
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.1346	0.7223	(-0.8773, 0.6081)	17976
	Quartile 3	-0.0981	0.7971	(-0.8457, 0.6496)	
	Quartile 4	-0.0126	0.9754	(-0.8103, 0.7852)	

Note: *All models adjusted for IRC, gestational age at blood pressure measurement (weeks), nulliparity, BMI, maternal age, mother's level of education, time of blood pressure measurement, mother's diet diversity.*

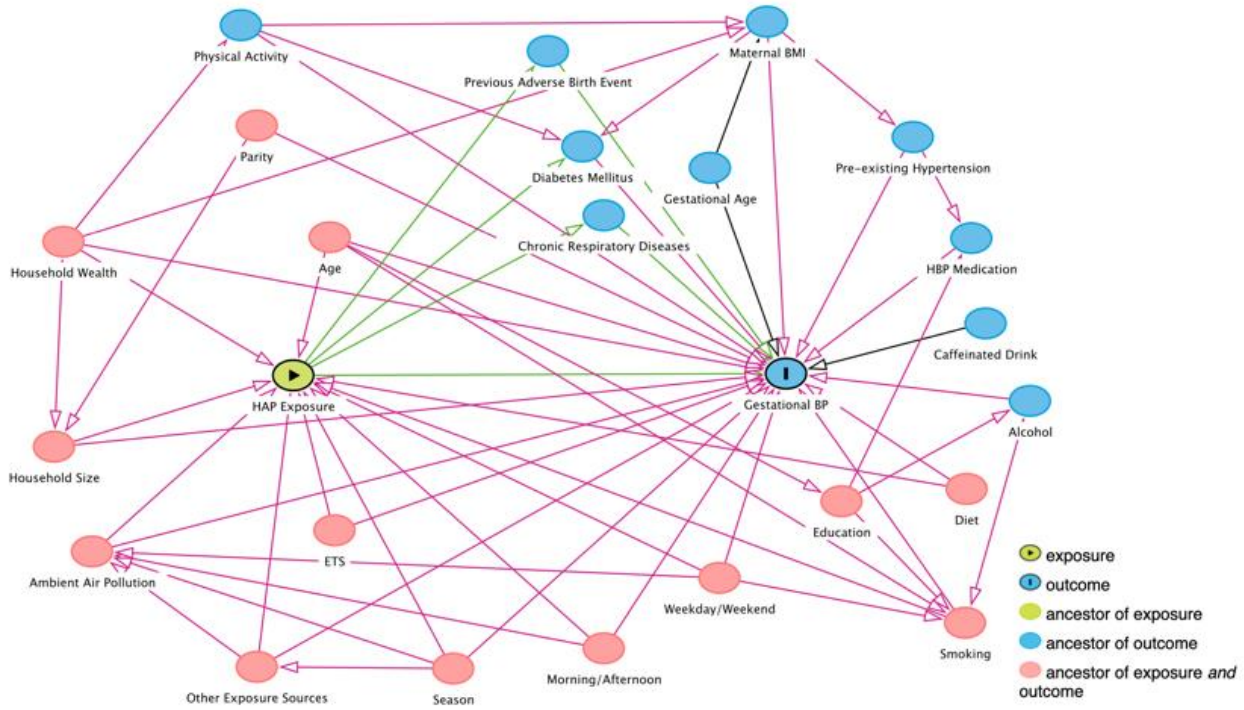


Figure B1. DAG to guide the selection of confounders for the association between household air pollution exposure and gestational blood pressure. Causal path (green line); Biasing path (red line)

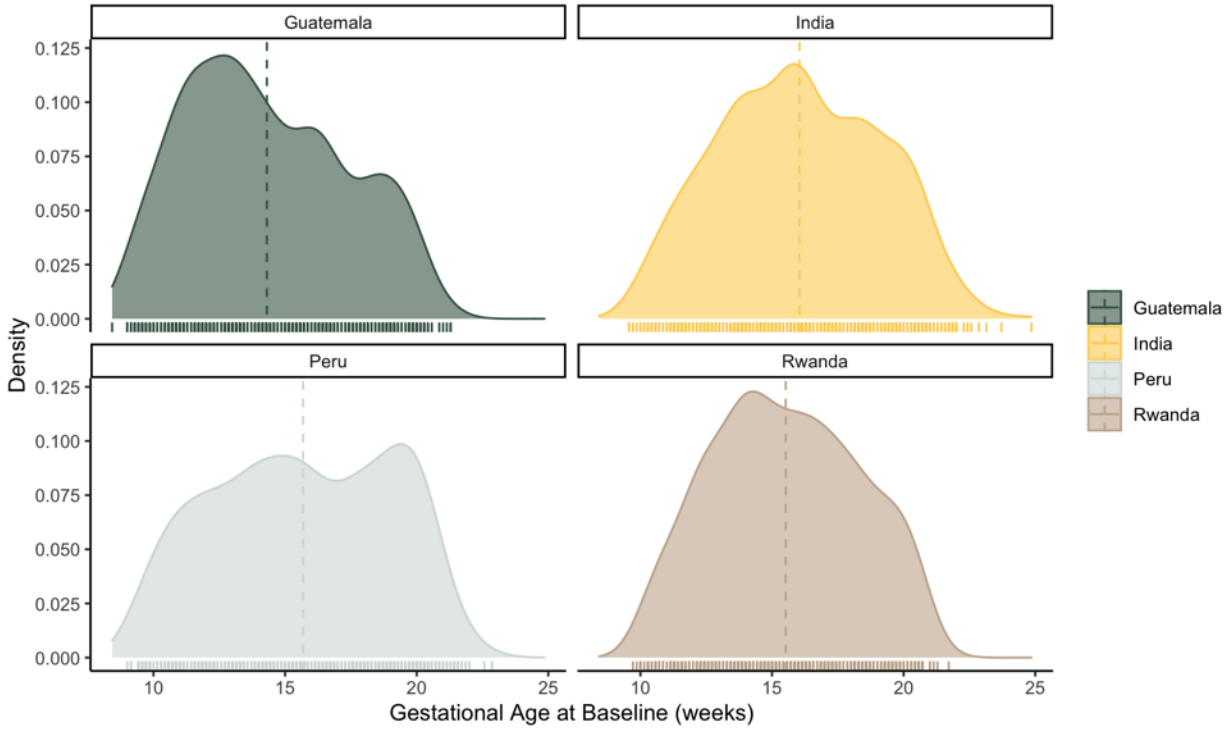
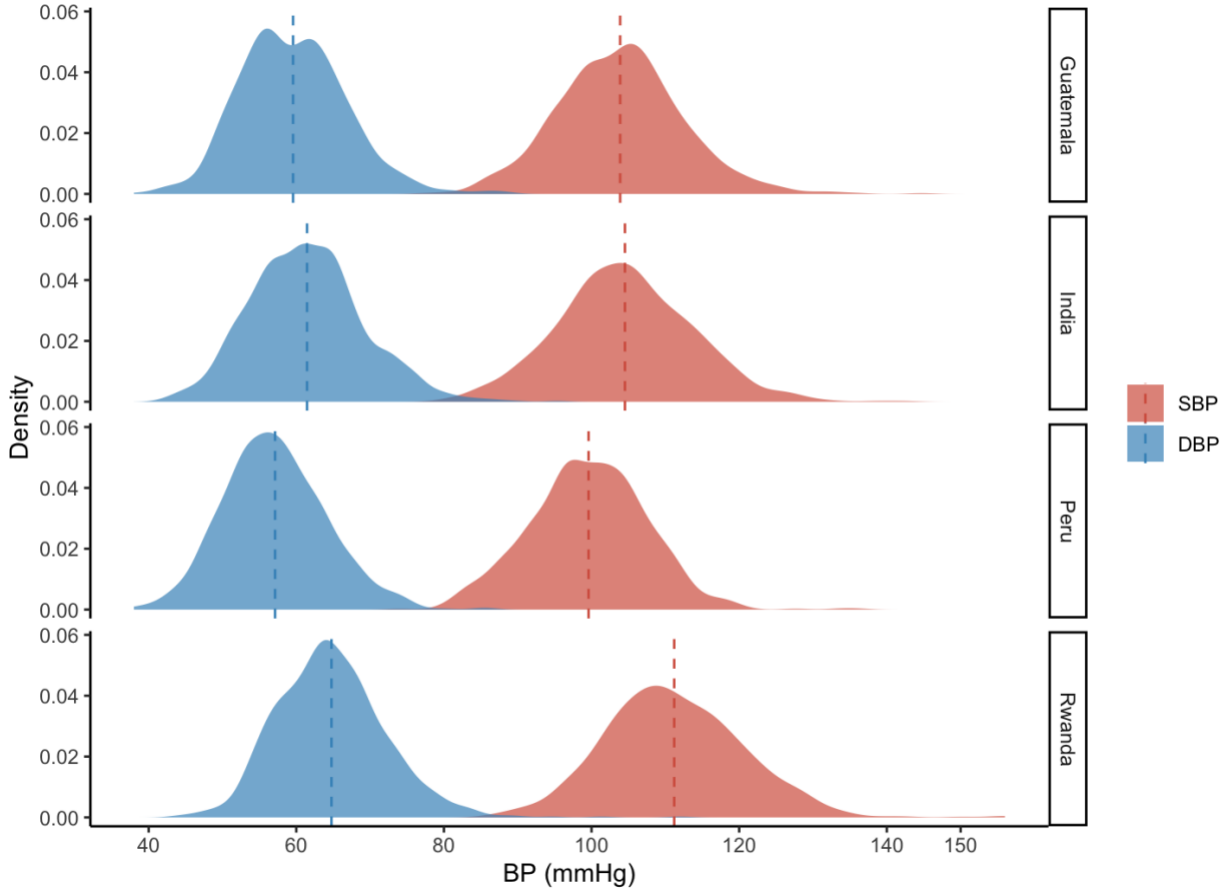


Figure B2. Distributions of gestational age at baseline. Solid lines along the x-axes are individual data points. Dashed lines are mean values.

Figure B3. Distributions of systolic and diastolic blood pressure at baseline. Filled density plots are individual IRC distributions.



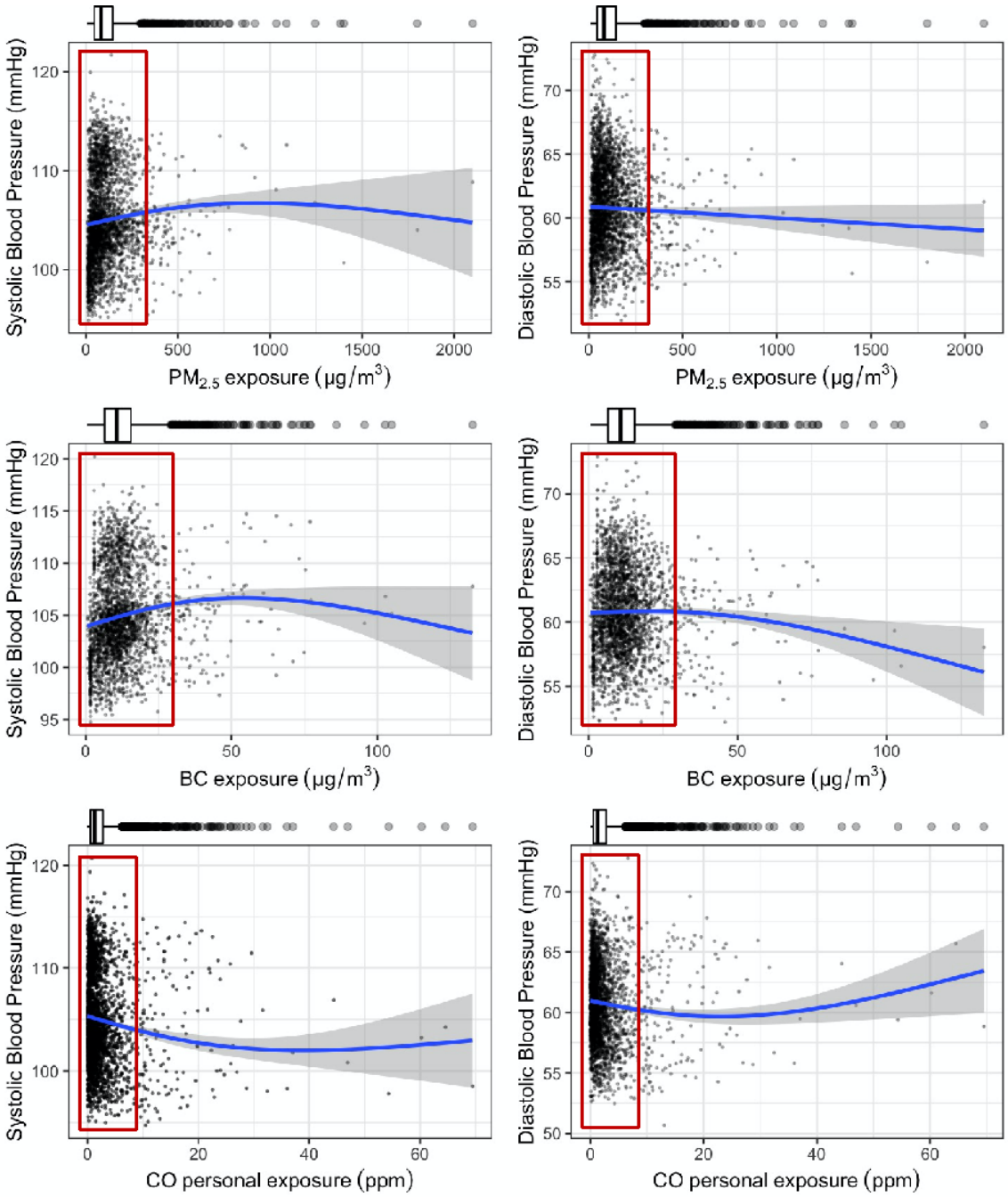


Figure B4. HAP-GBP association (blue line) and 95% confidence intervals (shade) generated from generalized additive models (GAMs) controlling for random strata, gestational age (weeks), nulliparity, BMI, maternal age, mother's level of education, household wealth index, time of blood pressure measurement, mother's diet diversity. Red outlined boxes indicate the exposure range of 95% of the data for each household air pollutant.

Appendix C Supplementary Information for Chapter 4

Table C1. Summary of missing and invalid exposure measurements

		Missing, n (%)	Not Missing, n (%)		
			Total, n (%)	Invalid, n (%)	Valid, n (%)
Baseline (N = 3002)	$PM_{2.5}$	80 (3%)	2922 (97%)	271 (9%)	2651 (88%)
	BC	292 (10%)	2710 (90%)	332 (11%)	2378 (79%)
	CO	132 (4%)	2870 (96%)	161 (5%)	2709 (91%)
P1 (N = 2966)	$PM_{2.5}$	134 (5%)	2832 (95%)	318 (10%)	2514 (85%)
	BC	202 (7%)	2764 (93%)	371 (12%)	2393 (81%)
	CO	196 (7%)	2770 (93%)	165 (5%)	2605 (88%)
P2 (N = 2877)	$PM_{2.5}$	289 (10%)	2588 (90%)	291 (10%)	2297 (80%)
	BC	329 (11%)	2548 (89%)	351 (12%)	2197 (77%)
	CO	308 (11%)	2569 (89%)	148 (5%)	2421 (84%)

Table C2. Exposure-response analyses results in Guatemala IRC

	Model Type	**Estimate**	**p-value**	**95% CI**	**AIC**
Systolic Blood Pressure					
PM2.5	Linear	0.0008	0.5421	(-0.0018, 0.0035)	13665
	Log linear	0.2294	0.1621	(-0.0921, 0.5509)	13653
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.5436	0.1655	(-0.2243, 1.3115)	13654
	Quartile 3	0.2583	0.546	(-0.5799, 1.0964)	
	Quartile 4	0.7521	0.0987	(-0.1402, 1.6445)	
BC	Linear	0.0124	0.4972	(-0.0234, 0.0481)	13130
	Log linear	0.2076	0.3707	(-0.2469, 0.6621)	13124
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.5821	0.1506	(-0.2112, 1.3754)	13126
	Quartile 3	0.2973	0.4986	(-0.5637, 1.1583)	
	Quartile 4	0.3509	0.4388	(-0.5373, 1.2391)	
CO	Linear	0.0830	0.1589	(-0.0324, 0.1984)	14091
	Log linear	0.0466	0.5297	(-0.0986, 0.1917)	14092
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.2675	0.4702	(-0.4584, 0.9935)	14090
	Quartile 3	-0.1413	0.7154	(-0.9006, 0.6181)	
	Quartile 4	0.5017	0.2162	(-0.2931, 1.2965)	
Diastolic Blood Pressure					
PM2.5	Linear	-0.0015	0.2444	(-0.004, 0.001)	13309
	Log linear	-0.1297	0.3927	(-0.4272, 0.1677)	13300
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.0847	0.8168	(-0.8007, 0.6314)	13302
	Quartile 3	-0.4796	0.2276	(-1.2584, 0.2992)	

	Quartile 4	-0.2793	0.5078	(-1.1059, 0.5473)	
BC	Linear	-0.0236	0.164	(-0.0567, 0.0096)	12790
	Log linear	-0.3656	0.0889	(-0.7865, 0.0554)	12784
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.0139	0.9707	(-0.7525, 0.7248)	12783
	Quartile 3	-0.4559	0.2636	(-1.2548, 0.3431)	
	Quartile 4	-0.9553	0.0231	(-1.7787, -0.1319)	
CO	Linear	-0.0585	0.292	(-0.1674, 0.0503)	13774
	Log linear	-0.0778	0.2645	(-0.2143, 0.0588)	13773
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.0529	0.8798	(-0.6323, 0.738)	13772
	Quartile 3	-0.6388	0.0804	(-1.3546, 0.0769)	
	Quartile 4	-0.3967	0.2983	(-1.1439, 0.3506)	

Note:

** All models controlled for nulliparity, mother's highest education level, BMI, maternal age, gestational age, gestational squared and time (morning/ afternoon) of the blood pressure measurement.*

Table C3. Exposure-response analyses results in India IRC

	Model Type	Estimate	p-value	95% CI	AIC
Systolic Blood Pressure					
PM2.5	Linear	0.0022	0.1714	(-0.001, 0.0054)	13327
	Log linear	0.2359	0.2873	(-0.1985, 0.6704)	13318
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.7142	0.1665	(-0.297, 1.7253)	13318
	Quartile 3	0.0504	0.9269	(-1.0252, 1.1259)	
	Quartile 4	0.5446	0.3329	(-0.5574, 1.6465)	
BC	Linear	0.0021	0.9117	(-0.0345, 0.0387)	13041
	Log linear	0.1527	0.4482	(-0.2419, 0.5474)	13036
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.1138	0.8323	(-0.9398, 1.1674)	13037
	Quartile 3	0.3978	0.4882	(-0.7268, 1.5223)	
	Quartile 4	0.0595	0.9192	(-1.0899, 1.2089)	
CO	Linear	0.0654	0.2851	(-0.0545, 0.1854)	14384
	Log linear	0.0322	0.6534	(-0.1084, 0.1729)	14385
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.2920	0.5514	(-1.2527, 0.6686)	14381
	Quartile 3	0.6616	0.1978	(-0.3449, 1.6681)	
	Quartile 4	0.1114	0.8283	(-0.8957, 1.1186)	
Diastolic Blood Pressure					
PM2.5	Linear	0.0011	0.3887	(-0.0014, 0.0037)	12632
	Log linear	0.1642	0.3672	(-0.1926, 0.521)	12622
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.8740	0.0375	(0.0513, 1.6967)	12618

	Quartile 3	0.1220	0.7854	(-0.7563, 1.0004)	
	Quartile 4	0.8073	0.0797	(-0.0952, 1.7097)	
BC	Linear	-0.0078	0.61	(-0.0377, 0.0221)	12352
	Log linear	0.0656	0.6912	(-0.258, 0.3891)	12348
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.1376	0.7533	(-0.9954, 0.7202)	12350
	Quartile 3	0.1253	0.7895	(-0.7944, 1.045)	
	Quartile 4	-0.0327	0.9457	(-0.9741, 0.9087)	
CO	Linear	0.0567	0.2679	(-0.0436, 0.1571)	13701
	Log linear	-0.0379	0.5285	(-0.1555, 0.0798)	13702
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.6606	0.1065	(-1.4624, 0.1412)	13700
	Quartile 3	-0.3718	0.387	(-1.2138, 0.4703)	
	Quartile 4	-0.0953	0.8246	(-0.9379, 0.7473)	

Note:

** All models controlled for nulliparity, mother's highest education level, BMI, maternal age, gestational age, gestational squared and time (morning/ afternoon) of the blood pressure measurement.*

Table C4. Exposure-response analyses results in Peru IRC

	Model Type	Estimate	p-value	95% CI	AIC
Systolic Blood Pressure					
PM2.5	Linear	-0.0024	0.1909	(-0.0061, 0.0012)	10700
	Log linear	-0.2124	0.2921	(-0.6075, 0.1826)	10691
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.5386	0.2691	(-1.4935, 0.4162)	10691
	Quartile 3	-0.2657	0.595	(-1.2449, 0.7135)	
	Quartile 4	-0.8926	0.1015	(-1.9602, 0.1751)	
BC	Linear	-0.0143	0.475	(-0.0535, 0.0249)	9786
	Log linear	-0.2792	0.1692	(-0.6771, 0.1187)	9780
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.4671	0.3616	(-1.4701, 0.536)	9778
	Quartile 3	-0.9591	0.0745	(-2.0121, 0.0938)	
	Quartile 4	-1.1553	0.0445	(-2.2812, -0.0295)	
CO	Linear	0.0055	0.8722	(-0.0614, 0.0724)	10444
	Log linear	0.0640	0.5062	(-0.1246, 0.2526)	10442
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.3786	0.4517	(-1.3643, 0.6071)	10440
	Quartile 3	0.1243	0.8086	(-0.8813, 1.1299)	
	Quartile 4	-0.6457	0.2264	(-1.6916, 0.4001)	
Diastolic Blood Pressure					
PM2.5	Linear	-0.0042	0.0127	(-0.0075, -0.0009)	10342
	Log linear	-0.3376	0.0623	(-0.6922, 0.0171)	10336
	Categorical [Ref. Quartile 1)				

	Quartile 2	-0.8933	0.0423	(-1.7546, -0.032)	10332
	Quartile 3	-0.2458	0.5852	(-1.128, 0.6364)	
	Quartile 4	-1.2742	0.0093	(-2.2328, -0.3155)	
BC	Linear	-0.0293	0.1044	(-0.0646, 0.006)	9481
	Log linear	-0.2233	0.2228	(-0.5821, 0.1355)	9478
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.3867	0.405	(-1.2964, 0.5231)	9478
	Quartile 3	-0.3945	0.4178	(-1.3483, 0.5594)	
	Quartile 4	-0.9671	0.0628	(-1.9849, 0.0507)	
CO	Linear	0.0202	0.5117	(-0.0402, 0.0806)	10107
	Log linear	-0.0031	0.972	(-0.1736, 0.1675)	10105
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.3477	0.4462	(-1.242, 0.5466)	10105
	Quartile 3	-0.1773	0.7031	(-1.089, 0.7343)	
	Quartile 4	-0.4165	0.3886	(-1.363, 0.53)	

Note:

** All models controlled for nulliparity, mother's highest education level, BMI, maternal age, gestational age, gestational squared and time (morning/ afternoon) of the blood pressure measurement.*

Table C5. Exposure-response analyses results in Rwanda IRC

	Model Type	Estimate	p-value	95% CI	AIC
Systolic Blood Pressure					
PM2.5	Linear	-0.0002	0.9302	(-0.0043, 0.004)	13421
	Log linear	0.2385	0.3302	(-0.2415, 0.7186)	13410
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.5549	0.2378	(-0.3661, 1.4758)	13411
	Quartile 3	0.6447	0.1946	(-0.329, 1.6184)	
	Quartile 4	0.7068	0.1814	(-0.3292, 1.7429)	
BC	Linear	0.0763	0.0014	(0.0297, 0.1229)	11840
	Log linear	1.0335	7.00E-04	(0.4376, 1.6293)	11834
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.7253	0.1507	(-0.2634, 1.714)	11831
	Quartile 3	0.3969	0.466	(-0.6699, 1.4638)	
	Quartile 4	2.1117	2.00E-04	(0.9887, 3.2348)	
CO	Linear	-0.0673	0.1814	(-0.166, 0.0314)	13866
	Log linear	-0.0368	0.7089	(-0.2299, 0.1563)	13866
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.4645	0.2974	(-0.409, 1.338)	13865
	Quartile 3	0.5221	0.2547	(-0.3761, 1.4203)	
	Quartile 4	0.0567	0.9054	(-0.8773, 0.9906)	
Diastolic Blood Pressure					
PM2.5	Linear	-0.0047	0.0048	(-0.008, -0.0015)	12522
	Log linear	-0.5670	0.0036	(-0.9487, -0.1853)	12512

	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.6524	0.0817	(-1.3866, 0.0818)	12514
	Quartile 3	-1.0806	0.0064	(-1.8562, -0.305)	
	Quartile 4	-1.1423	0.0067	(-1.9666, -0.318)	
BC	Linear	-0.0192	0.3105	(-0.0562, 0.0179)	11054
	Log linear	-0.3515	0.1458	(-0.8249, 0.1219)	11048
	Categorical [Ref. Quartile 1)				
	Quartile 2	-0.5735	0.1543	(-1.3621, 0.2152)	11051
	Quartile 3	-0.6111	0.1589	(-1.4608, 0.2387)	
	Quartile 4	-0.4716	0.3012	(-1.3654, 0.4221)	
CO	Linear	0.0165	0.6856	(-0.0633, 0.0963)	12994
	Log linear	0.0282	0.7238	(-0.1281, 0.1844)	12993
	Categorical [Ref. Quartile 1)				
	Quartile 2	0.3737	0.3008	(-0.3339, 1.0814)	12993
	Quartile 3	0.2529	0.4955	(-0.4742, 0.98)	
	Quartile 4	0.4701	0.2226	(-0.2851, 1.2253)	

Note:

** All models controlled for nulliparity, mother's highest education level, BMI, maternal age, gestational age, gestational squared and time (morning/afternoon) of the blood pressure measurement.*

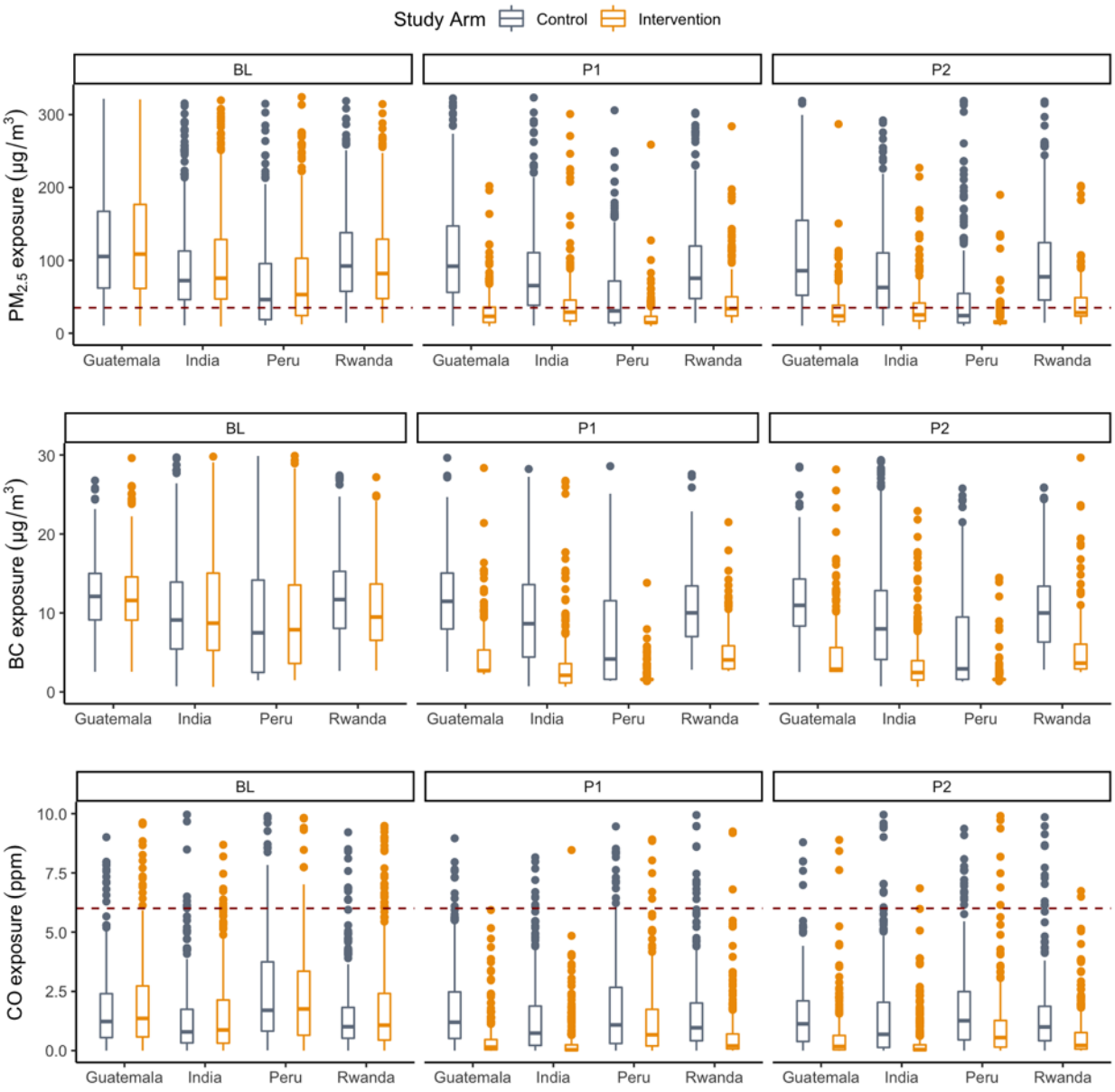


Figure C1. Boxplots of personal exposure to $PM_{2.5}$, BC and CO by intervention groups and visit (BL: baseline, P1: follow-up 1, and P2: follow-up 2) in each IRC. Dark red dashed lines in the $PM_{2.5}$ and CO panels indicate the 2021 WHO recommended interim target 1 (IT-1) for annual $PM_{2.5}$ (35 µg/m^3), and 24-hour CO (6.006 ppm = 7 mg/m^3, at 20 °C and 1013 hPa, 1 mg/m^3 = 0.858 ppm). All plots represent 97% of the exposure data.

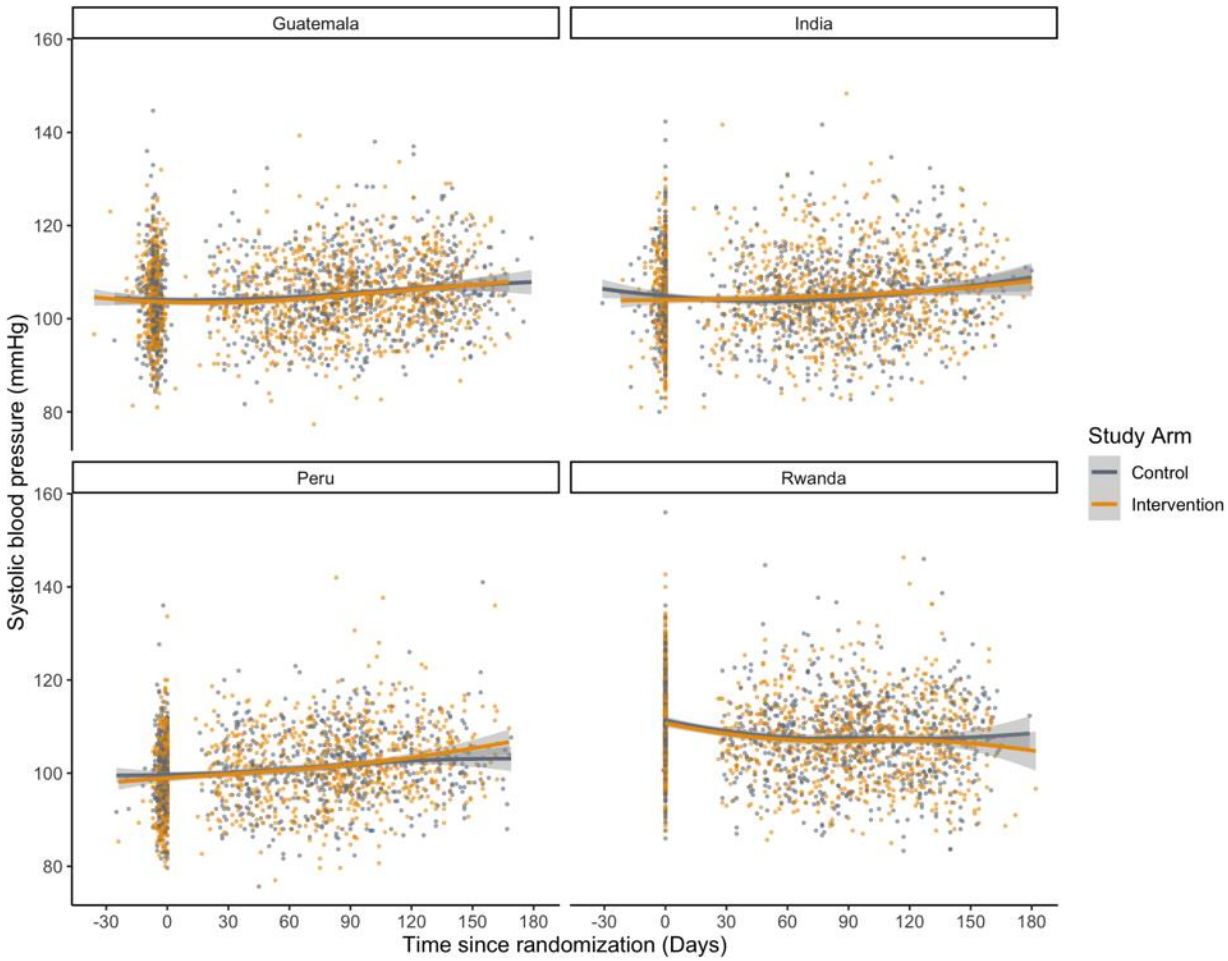


Figure C2. Systolic blood pressure by time since randomization (in days) and locally weighted scatterplot smoothing (LOWESS) curves in each IRC.

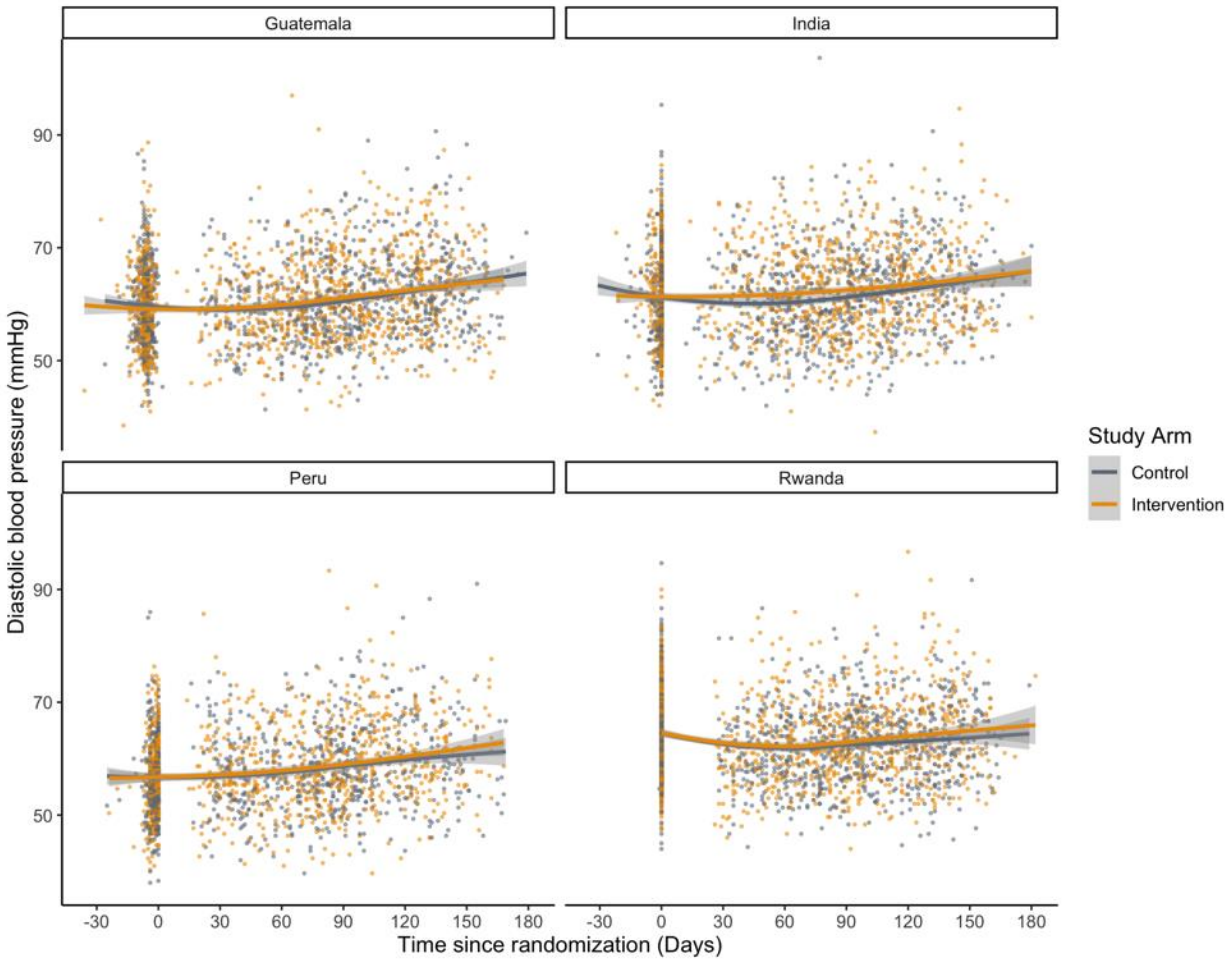


Figure C3. Diastolic blood pressure by time since randomization (in days) and locally weighted scatterplot smoothing (LOWESS) curves in each IRC.

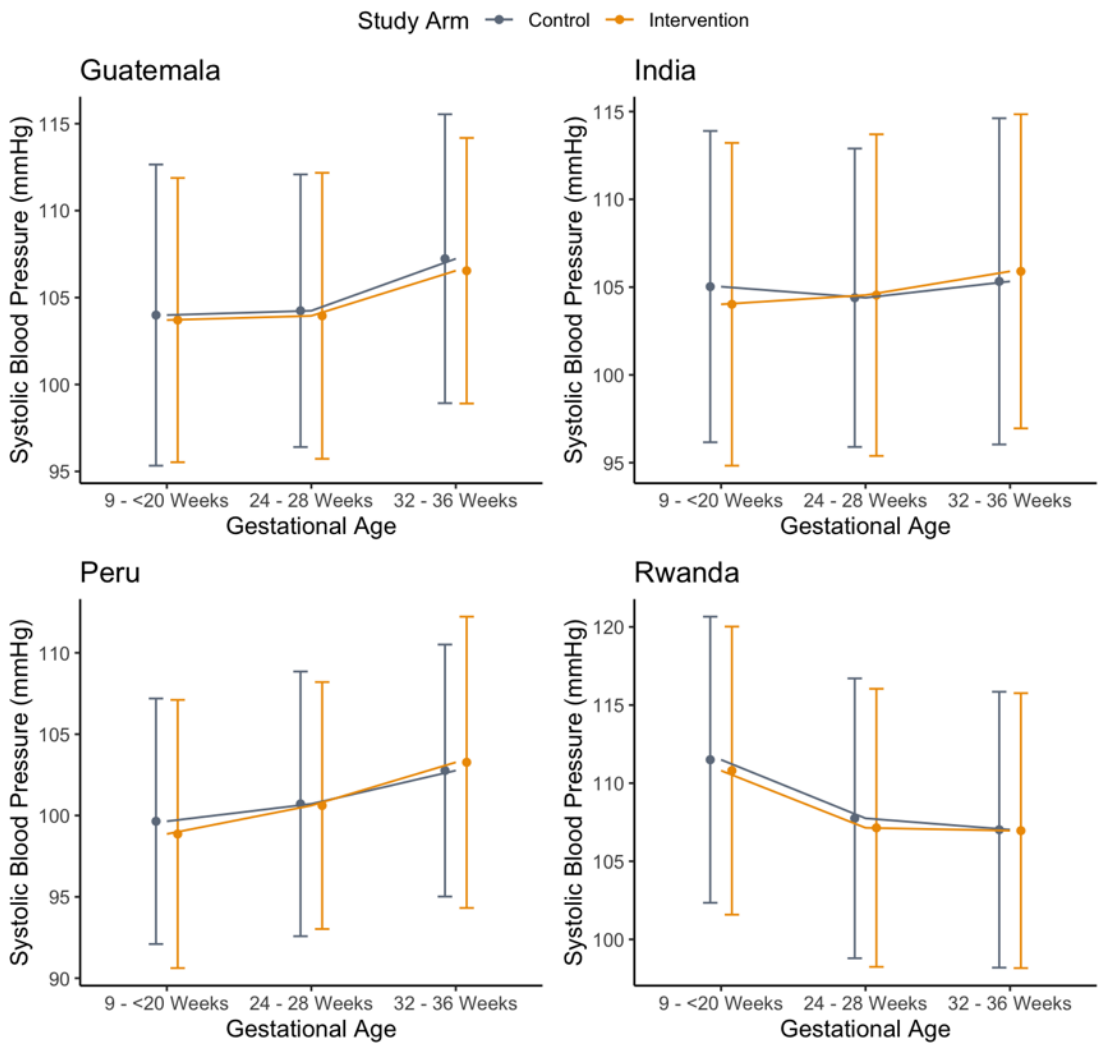


Figure C4. Line plot of systolic blood pressure by visit in each IRC. Dots indicate mean and error bars indicate one standard deviation.

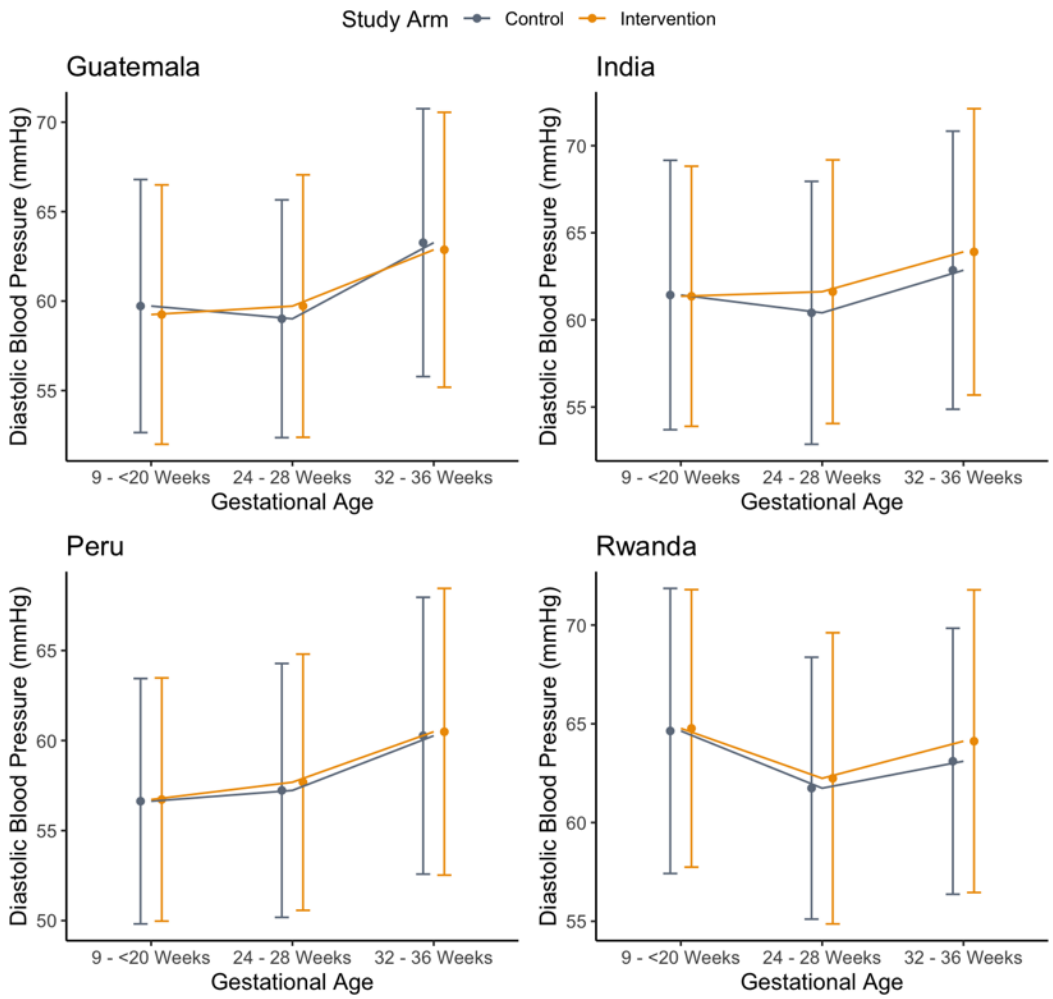


Figure C5. Line plot of diastolic blood pressure by visit in each IRC. Dots indicate mean and error bars indicate one standard deviation.

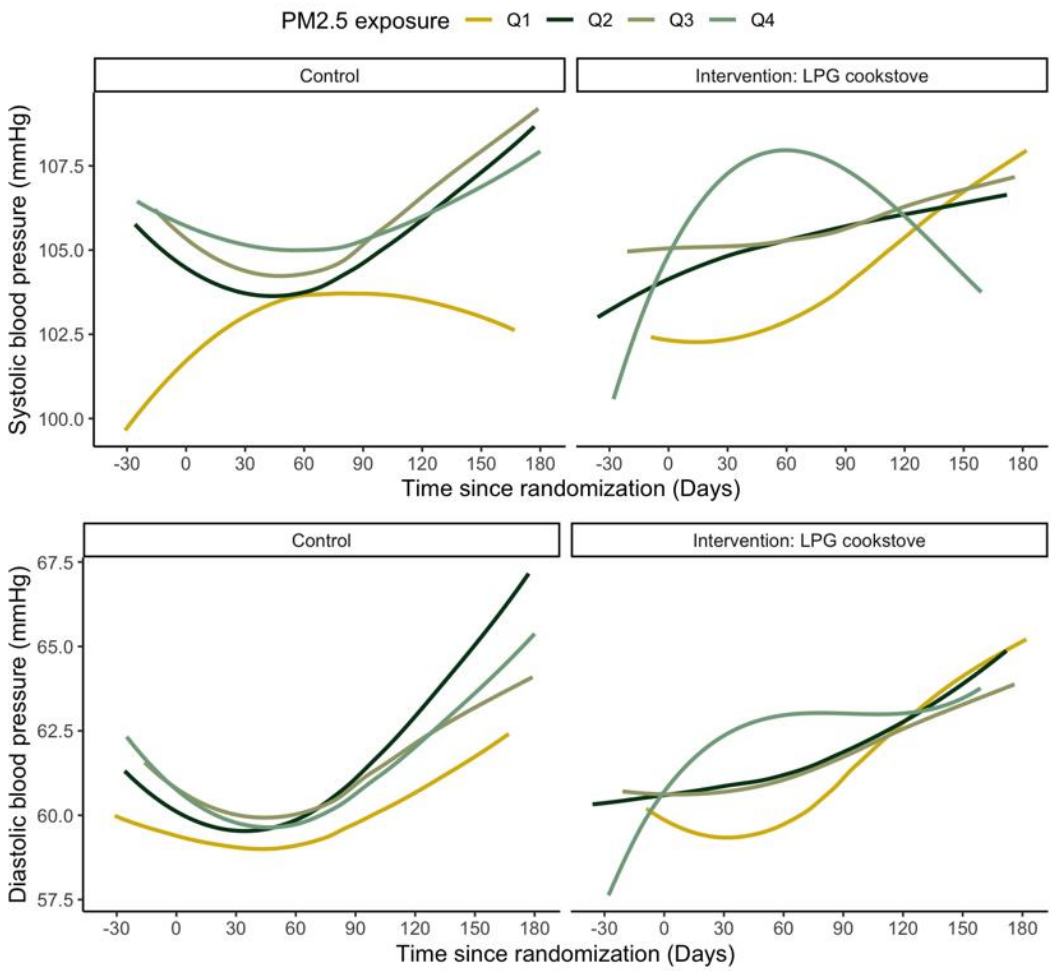


Figure C6. Gestational blood pressure patterns of women in different $PM_{2.5}$ exposure quartiles during pregnancy (shown as time since randomization).

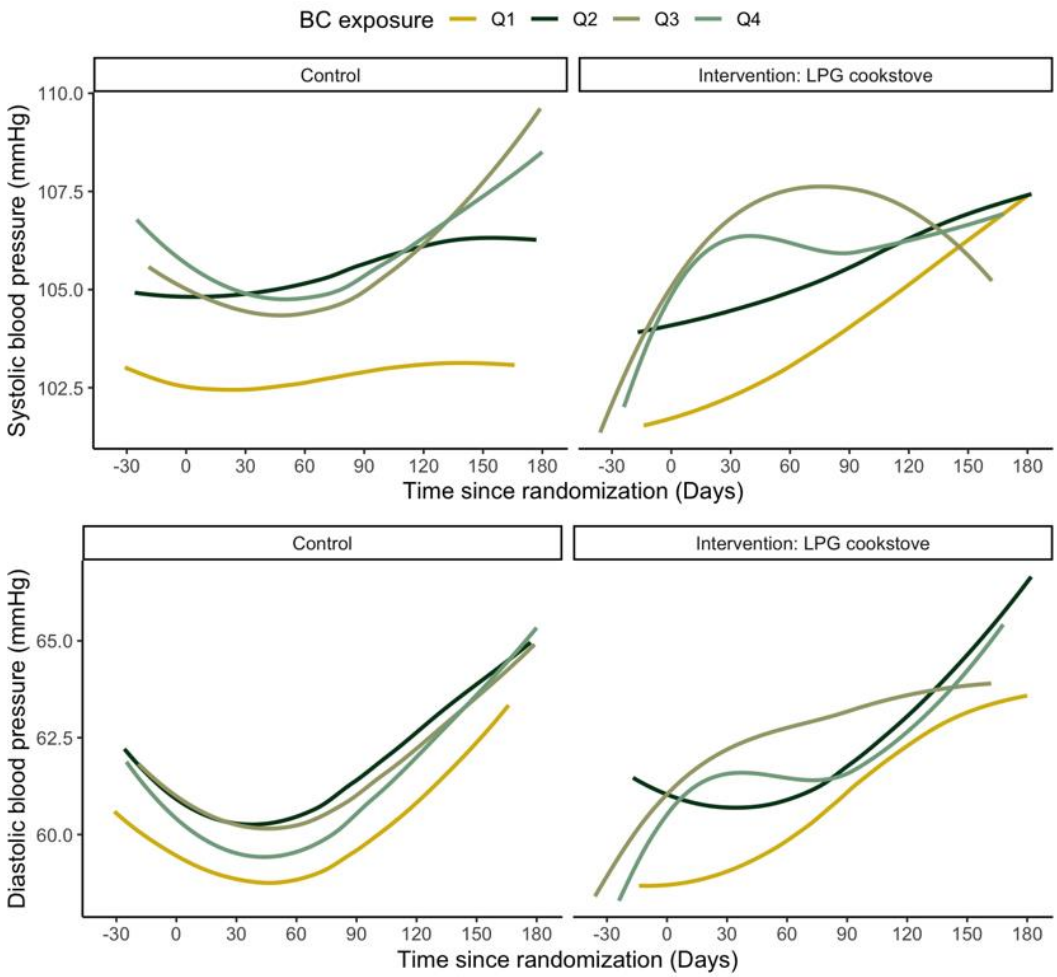


Figure C7. Gestational blood pressure patterns of women in different BC exposure quartiles during pregnancy (shown as time since randomization).

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