DISSERTATION

ASSOCIATIONS BETWEEN AIR POLLUTION EMITTED FROM COOKSTOVES AND CENTRAL HEMODYNAMICS, ARTERIAL STIFFNESS, AND BLOOD LIPIDS IN LABORATORY AND FIELD SETTINGS

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ABSTRACT

ASSOCIATIONS BETWEEN AIR POLLUTION EMITTED FROM COOKSTOVES AND CENTRAL HEMODYNAMICS, ARTERIAL STIFFNESS, AND BLOOD LIPIDS IN LABORATORY AND FIELD SETTINGS

Household air pollution emitted from cookstoves that burn solid fuels is a leading environmental risk factor for morbidity and mortality worldwide. Fine particulate matter ($PM_{2.5}$; airborne particles less than 2.5 micrometers in aerodynamic diameter) exposures from the use of solid cooking fuels resulted in an estimated 60 million disability adjusted life-years in 2017, including 1.6 million premature deaths. It was estimated that 40% of the 1.6 million premature deaths that resulted from household air pollution exposures in 2017 occurred due to cardiovascular outcomes such as ischemic heart disease and stroke. “Improved” cookstoves (i.e., cookstoves designed to reduce air pollution exposures by using engineered combustion chambers or cleaner-burning fuels) have been distributed to reduce exposures to household air pollution, but whether such stoves meaningfully improve health remains unclear. The work in this dissertation assessed the effect of air pollution emitted from traditional and improved cookstoves on cardiovascular health measures in two settings: acute differences in carotid-femoral pulse wave velocity (PWV), central augmentation index (AIx), central pulse pressure (CPP), and blood lipids were assessed in a controlled exposure study in a laboratory setting, and AIx and CPP were assessed in a randomized field trial with a biomass cookstove intervention in a field setting.

In Aim 1, we assessed PWV, AIx, and CPP in 48 young, healthy adults in a controlled exposure study with a crossover design. Participants were assigned to six 2-hour controlled treatments of pollution from five different cookstoves and a filtered air control. Each treatment had a target concentration for $PM_{2.5}$: filtered air control = 0 $\mu g/m^3$, liquefied petroleum gas [LPG]

= 10 $\mu g/m^3$, gasifier = 35 $\mu g/m^3$, forced-draft fan rocket elbow = 100 $\mu g/m^3$, natural-draft rocket elbow = 250 $\mu g/m^3$, and three stone fire = 500 $\mu g/m^3$. We measured health endpoints immediately before and 0, 3, and 24 hours after each treatment. For Aim 1a, PWV, AIx, and CPP were measured using the SphygmoCor XCEL. For Aim 1b, non-fasting blood lipids (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides) were measured from venous blood samples obtained via venipuncture. We used linear mixed models to assess differences in the outcomes for each cookstove treatment compared to control.

In Aim 1a, PWV and CPP were higher 24 hours after all cookstove treatments compared to control. The magnitude of the effects for PWV and CPP did not vary by treatment type, even though the treatments spanned a broad range of $PM_{2.5}$ concentrations. For example, PWV was 0.15 m/s higher (95% confidence interval [CI]: -0.02, 0.31) 24 hours after the three stone fire treatment compared to control and 0.15 m/s higher (95% CI: -0.02, 0.32) 24 hours after the LPG treatment compared to control. CPP was 0.6 mmHg higher (95% CI: -0.8, 2.1) 24 hours after the three stone fire treatment compared to control and 1.3 mmHg higher (95% CI: -0.2, 2.7) 24 hours after the LPG treatment compared to control. We observed no consistent trends in PWV and CPP at the other post-treatment time points (0 and 3 hours), or at any post-treatment time point for AIx.

Results from Aim 1b suggest that triglycerides were higher 24 hours after treatments compared to control, with the exception of the rocket elbow treatment, which indicated no difference compared to control. For example, 24 hours after the three stone fire treatment versus control, the difference for triglycerides was 12.1% (95% CI: -0.5, 26.2). As with PWV and CPP, results for triglycerides had similar magnitude across cookstove treatment levels versus control. There were no meaningful differences for triglycerides at the 0- or 3-hour post-treatment time points. LDL was lower for each treatment compared to control at the 24-hour post-treatment time point, although the differences were only marginally suggestive based on the small magnitude of the effect estimates and the wide confidence intervals. Results from other

time points (0 and 3 hours) and outcomes (total cholesterol and HDL) were consistent with no difference compared to control for any treatment.

Results from Aims 1a and 1b suggest that short-term exposures to cookstove air pollution emitted from both traditional and improved cookstove technologies can result in acute changes (within 24 hours after exposure) in PWV, CPP, and triglycerides in healthy adults. The similar magnitude in the differences we observed between each cookstove treatment and control indicate that acute exposures from even the cleanest cookstove technologies can lead to adverse health outcomes. While the differences we observed were small and may not be clinically meaningful in young, healthy adults, we have reported results that suggest even short-term, transient exposures to cookstove air pollution can lead to changes in central hemodynamics and triglycerides. When individuals are exposed to cookstove air pollution daily over the course of many years, progressive cardiovascular disease could result from chronic elevation of central hemodynamic indices and blood lipids. Our findings could also be important to susceptible subpopulations of individuals with pre-existing cardiovascular disease, where small hemodynamic changes could lead to acute adverse health outcomes.

In Aim 2 we assessed AIx and CPP following the intervention of a *Justa* biomass cookstove (with chimney and combustion chamber designed to reduce air pollution emissions) among 230 women in rural Honduras who were primary household cooks and traditional biomass cookstove users (no improved combustion chamber). Data collection occurred during six household visits approximately every 6 months over 3 years. Women were randomly assigned to one of two study arms (n=115 per arm) to receive a *Justa* cookstove after visit 2 or after visit 4. Daily (24-hour) concentrations of personal and kitchen (area) $PM_{2.5}$ were measured during each study visit. AIx and CPP were measured at the end of the 24-hour exposure assessment during each visit using the SphygmoCor XCEL. We used linear mixed models in three analysis frameworks: an intent-to-treat (ITT) analysis framework, an exposure-response analysis framework, and a cookstove-use analysis framework. The ITT analysis used assigned

cookstove (traditional vs *Justa*) based on study arm assignment to assess the impact of the intervention on AIx and CPP. The exposure-response analysis assessed associations between personal and kitchen concentrations of $PM_{2.5}$ with AIx and CPP. To assess actual cookstove use, as compared to the assigned cookstove based on study arm, we used cookstove-use variables based on self-reported cookstove use and visual inspection of each participant's home during study visits. Additionally, we assessed age and several indicators of cardiometabolic health as potential effect modifiers.

Median personal $PM_{2.5}$ concentration for participants assigned to *Justa* cookstoves was 43 $\mu g/m^3$ (interquartile range [IQR]=46, n=586); median personal $PM_{2.5}$ concentrations for participants who used traditional cookstoves was 81 $\mu g/m^3$ (IQR=91, n=624). Median kitchen $PM_{2.5}$ concentrations for participants assigned to *Justa* cookstoves was 53 $\mu g/m^3$ (IQR=74, n=578); median kitchen $PM_{2.5}$ concentrations for participants who used traditional cookstoves was 178 $\mu g/m^3$ (IQR=371, n=631). Results for AIx and CPP in the ITT analysis indicated that the *Justa* cookstove intervention did not impact the outcomes: AIx was 0.3 percentage points higher in participants assigned to *Justa* vs traditional cookstoves (95% CI: -1.8, 2.5) and CPP was 0.3 mmHg lower in participants assigned to *Justa* vs traditional cookstoves (95% CI: -1.4, 0.9). We also observed results consistent with null associations in the exposure-response analysis. The cookstove-use analysis indicated that *Justa* cookstove users had higher AIx and similar CPP compared to traditional cookstove users (AIx = 2.8%, 95%CI: 0.4, 5.1; CPP = 0.2 mmHg, 95%CI: -1.1, 1.4); however, as explained in detail in Chapter 5, these results were likely impacted by missing data. We did not observe evidence that age (<40 years vs ≥40 years), waist circumference (<80cm vs ≥80cm), blood pressure (normal vs high), hemoglobin A1c (<5.7% vs ≥5.7%), or metabolic syndrome status modified the relationships in any of the analysis frameworks.

Results from Aim 2 suggest that although the improved *Justa* cookstove intervention was successful in reducing exposures to $PM_{2.5}$, the intervention did not meaningfully impact AIx

or CPP. The null associations may indicate that cookstove interventions that lead to larger reductions in household air pollution are necessary to see improvements in the health outcomes we assessed. While AIx and CPP were not impacted within the timeframe of our study, evaluation of a wider spectrum of health outcomes (i.e., peripheral blood pressure, C-reactive protein, and glycated hemoglobin) in future analyses will help provide clarity on how the *Justa* intervention impacted cardiometabolic health in our study population.

These aims indicate that air pollution emitted from a spectrum of cookstove technologies, compared to a filtered air control, can acutely impact PWV, CPP, and triglycerides among healthy adults following short-term, controlled exposures. However, in a real-world setting, we observed no benefit of a biomass *Justa* cookstove intervention on AIx or CPP among women in rural Honduras. Although the *Justa* cookstove intervention did result in lower 24-hour concentrations of $PM_{2.5}$ compared to traditional cookstoves, our results give us no clear indication of what alternative cookstove technology might improve central hemodynamic health outcomes in cookstove users. Further randomized controlled trials in field settings using different cookstove technologies will help us understand what types of interventions will lead to improved health outcomes among cookstove users.

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CHAPTER 1: INTRODUCTION

Summary and significance

An extensive area of research and global health concern is that of household air pollution from combustion of solid fuels for cooking purposes. Household air pollution is one of the leading causes of premature death and morbidity worldwide. Estimates from 2017 indicate that nearly 60 million disability adjusted life-years, including 1.6 million premature deaths, occurred due to fine particulate matter ($PM_{2.5}$; airborne particles less than 2.5 micrometers in aerodynamic diameter) exposures from the use of solid cooking fuels (Stanaway et al. 2018). Of the 1.6 million deaths attributable to household air pollution in 2017, 40% were estimated to be a result of cardiovascular disease (CVD), with chronic respiratory disease, lower respiratory and other infections, and neoplasms making up the other 60% (Stanaway et al. 2018).

Cookstove use has such a large global impact on health in part because around 40% of the global population, or nearly three billion people, still use biomass cookstoves as their primary method of cooking (Bonjour et al. 2013). With less access to cleaner cooking technologies and less income to spend on them, families in lower- and middle-income countries (LMICs) account for a high proportion of global cookstove users: in Sub-Saharan Africa and South Asia as much as 95% of the total population in some countries relies on solid fuels as their primary cooking fuel (Smith et al. 2014). In Honduras, where research for Aim 2 of this dissertation took place, nearly 90% of the rural population cooks with solid fuels (Global Alliance for Clean Cookstoves 2018). Women typically encounter high levels of exposure to household air pollution due to time spent indoors as primary household cooks, and as a consequence, infants and children in their care may also be more susceptible to higher levels of air pollution and adverse health outcomes (Bruce et al. 2000; Smith et al. 2000). As these examples illustrate, the burden of household air pollution often falls on the most vulnerable populations, and in this lens can be viewed as an issue of social injustice.

Considering the global health burden resulting from cookstove use, more widespread use of cookstoves designed to reduce air pollution exposures could have a large impact on global health outcomes. There have been attempts to distribute “improved” cookstoves (i.e., cookstoves designed to reduce air pollution exposures by using engineered combustion chambers or cleaner-burning fuels) throughout some populations, and systematic reviews have assessed the effectiveness of cookstove interventions (Bruce et al. 2015; Pope et al. 2017; Quansah et al. 2017). While there were reductions in $PM_{2.5}$ following many cookstove interventions, concentrations of $PM_{2.5}$ in these cases were still higher than World Health Organization (WHO) guidelines (World Health Organization 2006), and evidence of improved health outcomes following interventions was less certain (Bruce et al. 2015; Quansah et al. 2017).

The lack of clarity about health outcomes is in part a result of the numerous challenges that come with assessing health and exposure in the field. Many of the estimated three billion cookstove users around the world live in LMICs where longitudinal field studies are logistically difficult to conduct and expensive to manage (Balakrishnan et al. 2014; Bonjour et al. 2013). The high cost and time commitments required to collect quality exposure measurements mean that many studies rely on proxies of exposure with questionable reliability (Clark et al. 2013b). In addition, the difficult nature of measuring health outcomes in field settings means that a limited number of health outcomes have been assessed. Conclusive epidemiologic evidence is still lacking due to limitations in study designs and methods. Limited internal validity in observational studies and a lack of quantitative exposure assessment in many field studies could mean that some of the reported associations are potentially biased by residual confounding or exposure misclassification.

The aims of this dissertation contribute information to these knowledge gaps by improving on previous study designs and by assessing indicators of cardiovascular health that currently have a limited focus in household air pollution research. We have assessed the impact

of various improved cookstove technologies on outcomes of aortic arterial stiffness, central aortic hemodynamics, and blood lipids using two complementary study designs and settings: controlled exposures to air pollution emitted from multiple cookstove technologies in a laboratory setting and a longitudinal assessment of an improved biomass cookstove intervention in rural Honduras. Through this work we hope to further understand two objectives: 1) how short-term increases in exposure generated from a range of cookstove technologies impact indicators of CVD risk, and 2) if lower air pollution exposures from using the wood-burning *Justa* cookstove over the course of a 3-year randomized trial leads to lower CVD risk compared to using traditional cookstoves.

Aims

Aim 1: Assess the impact of exposure to air pollution emitted from multiple cookstove technologies on markers of aortic arterial stiffness, central aortic hemodynamics, and blood lipids in a controlled human exposure study with a crossover design. Aim 1 assessed acute changes in carotid-femoral pulse wave velocity (PWV), central augmentation index (AIx), central pulse pressure (CPP), and blood lipids following short-term exposures to household air pollution by using a crossover design in a controlled exposure setting. From 2016 to 2018, 48 young, healthy human volunteers were exposed to treatments of air pollution from five cookstove technologies (liquefied petroleum gas [LPG], gasifier, forced-draft fan rocket elbow, natural-draft rocket elbow, three stone fire) and a filtered air control. Each treatment had a target level of $PM_{2.5}$ ranging from 0 $\mu g/m^3$ (control) to 500 $\mu g/m^3$ (three stone fire). Outcomes were assessed at baseline (i.e., pre-treatment) and at 0, 3, and 24 hours after each treatment. We used linear mixed models for each post-treatment time point to assess acute differences in the health outcomes following each treatment compared to control.

Aim 1a: PWV, CPP, and AIx are measures of central aortic hemodynamics and aortic arterial stiffness (Vlachopoulos et al. 2010a; Vlachopoulos et al. 2010b). Studying acute

changes in these markers will help us understand how different levels of household air pollution exposures can impact the risk of CVD and future adverse cardiovascular events.

Aim 1b: An acute-phase inflammatory response can have downstream impacts on lipid metabolism (Khovidhunkit et al. 2004). A non-fasting lipid panel (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides) obtained via venipuncture was assessed to help us understand the potential impacts on atherosclerotic risk resulting from acute exposures to household air pollution.

Aim 2: Assess the impact of an improved biomass cookstove intervention on concentrations of household air pollution and outcomes of central aortic hemodynamics during a randomized field trial using three analysis frameworks: intent-to-treat analysis using a cookstove intervention, exposure-response analysis using personal and kitchen fine particulate matter concentrations, and cookstove-use analysis using self-reported stove use throughout the study. Aim 2 assessed a wood-burning *Justa* cookstove intervention among 230 women who were primary household cooks and traditional wood-burning cookstove users in rural Honduras. AIx, CPP, and 24-hour concentrations of personal and kitchen $PM_{2.5}$ were measured every six months over the course of a 3-year longitudinal study (up to six total measurements per participant). Studying AIx and CPP in this setting can help us understand the impact of an improved cookstove intervention on CVD risk.

Summary

The overall goal from this dissertation is to assess central aortic hemodynamics, aortic arterial stiffness, and blood lipids following exposure to air pollution emitted from both traditional and improved cookstove technologies. The complementary study designs and settings in the two aims will help us evaluate consistency in the associations of interest. This work will help us fill in knowledge gaps of how household air pollution emitted from a spectrum of cookstove technologies impacts cardiovascular health and will contribute valuable information in determining the direction of future household air pollution research and cookstove interventions.

CHAPTER 2: LITERATURE REVIEW

Introduction to household air pollution

Approximately 40% of the world's population, or nearly 3 billion people, rely on solid-fuel cookstoves for domestic cooking needs (Bonjour et al. 2013). $PM_{2.5}$ exposures from residential combustion of solid fuels resulted in an estimated 60 million disability-adjusted life years in 2017, including 1.6 million premature deaths (Stanaway et al. 2018). In addition to adverse health consequences, cookstove use and the resulting household air pollution affect many facets of life on a global scale, such as factors related to income, education, and climate change (Bonjour et al. 2013). While household air pollution touches the lives of billions of people around the world, individuals from LMICs are disproportionally impacted because they lack access to and income to spend on clean fuel and energy sources (Smith et al. 2014). In many LMICs around the world more than half of the population relies on solid fuels for cooking, and in some countries in Sub-Saharan Africa solid-fuel users make up more than 95% of the population (Smith et al. 2014). Research for Aim 2 of this dissertation focused on women who use biomass cookstoves in Honduras, where half of the population, including nearly 90% of the rural population, cooks with solid fuels (Global Alliance for Clean Cookstoves 2018). Approximately 1 million households in Honduras are impacted by the use of solid cooking fuels, which results in an estimated 3,600 deaths per year that are attributable to household air pollution (Global Alliance for Clean Cookstoves 2018).

Although reducing household air pollution has been a focus of global health for decades, an increasing global population has meant that the number of solid-fuel users around the world has not decreased, and in some LMICs the number of users continues to rise (Bonjour et al. 2013). Cookstoves designed to reduce air pollution exposures by using engineered combustion chambers or cleaner-burning fuels (referred to as "improved" cookstoves) have been distributed in an attempt to reduce household air pollution; however, the health benefits of these improved

cookstoves remain unclear (Bruce et al. 2015; Pope et al. 2017; Quansah et al. 2017). Further research is needed to understand how to improve the health and quality of life of the three billion individuals who continue to rely on solid fuels for cooking.

The following literature review will give an overview of household air pollution exposure assessment as well as explain our current understanding of the health impacts of household air pollution as assessed through various epidemiological study designs.

Exposure to household air pollution

Overview

Household air pollution emitted from wood-burning cookstoves is a complex mixture of thousands of gaseous and particulate compounds, many of which are known to be hazardous to human health (Naeher et al. 2007). Some pollutants emitted from cookstoves, including hydrocarbons such as benzene and benzo[a]pyrene, are known carcinogens and have been studied extensively; other pollutants found in wood smoke include numerous polycyclic aromatic hydrocarbons, nitrogen oxides, carbon monoxide, and particulate matter of various sizes (Naeher et al. 2007). The health impacts of these pollutants are extensive and range from respiratory symptoms and airway inflammation to cancer and neurotoxicity (Naeher et al. 2007).

In addition to adverse health effects, household air pollution also impacts other aspects of life on a global scale, including factors related to climate change, income, and quality of life (Bonjour et al. 2013). Individuals who rely on cookstoves for cooking and heating must spend time gathering fuel, which decreases the amount of time they have for other work or attending school (Bonjour et al. 2013). Incomplete combustion of biomass fuels from cookstoves releases a number of climate-impacting compounds such as black carbon, carbon dioxide, methane, nitrous oxide, and carbon monoxide (Goldemberg et al. 2018). Additionally, harvesting of wood fuel for use in cookstoves is often non-renewable and can lead to deforestation (Goldemberg et al. 2018).

$PM_{2.5}$ is commonly used as a proxy for exposure to household air pollution due to its association with adverse health outcomes (Naeher et al. 2007). While personal $PM_{2.5}$ measurement is considered the gold standard in household air pollution exposure assessment, it is a time consuming and expensive measurement to capture reliably (Clark et al. 2013b). In addition, household air pollution is a complex combination of hundreds of pollutants that vary in quantity depending on cookstove and fuel type, as well as other factors such as how the cookstove is used (Bruce et al. 2000). Due to the complexity of household air pollution and the challenges of obtaining accurate pollutant measurements, the effectiveness of improved cookstove interventions is difficult to assess. If $PM_{2.5}$ is reduced following an improved cookstove intervention, but other harmful pollutants are not, there may be little or no benefit in the associations between the improved cookstove and health outcomes. In contrast, if exposure is misclassified due to inaccurate measurement, biased associations between $PM_{2.5}$ and health outcomes could result. These examples highlight the importance of quality exposure measurement in assessing the effectiveness of different cookstove technologies at improving health outcomes.

Exposure assessment

Various methods of household air pollution exposure assessment have been previously outlined with strengths and weaknesses of each method highlighted (Clark et al. 2013b). The simplest method is to assess stove or fuel type used in a household; however, this method has limitations due to the large variation of pollutants from household to household within each stove or fuel type, which can lead to misclassification of exposure (Clark et al. 2013b). Quantitative measures of pollution concentrations (typically $PM_{2.5}$) in the area where the cookstove is used can give a better representation of exposure based on how the cookstove is used within each household; however, this method fails to capture personal variations in exposure that will differ depending on time spent near the stove versus time spent outdoors or performing other activities besides cooking (Clark et al. 2013b). Personal exposure levels can be assessed by

wearing portable monitors, although this method is expensive to implement and accuracy is highly dependent on the compliance of each participant (Clark et al. 2013b). Biomarkers of exposure could help assess internal dose of inhaled household air pollution, but reliable biomarkers of exposure have yet to be validated, and due to the metabolism of biomarkers they may only accurately represent recent exposures (Clark et al. 2013b).

As each exposure assessment method has strengths and weaknesses, using multiple methods in a single study can help quantify exposure more accurately. For example, collecting both area and personal measurements of $PM_{2.5}$ provides more information than each measurement individually; while area measurements give an indication of how the cookstove is used in a household and how efficient a particular cookstove may or may not be, personal measurements provide information on individual habits and daily cookstove use for specific cookstove users (Clark et al. 2013b). Quantitative methods are important, yet they also have substantial weaknesses. Due to the financial and logistical burden of performing these complex measurements in a field setting, measurements of $PM_{2.5}$ typically only last around 24 hours and may not accurately represent exposure concentrations from a typical day in each household (Clark et al. 2013b). In addition, due to the complex mixtures of pollutants found in cookstove air pollution, assessment of single pollutants such as $PM_{2.5}$ may not accurately quantify exposures and subsequent associations with health outcomes (Clark et al. 2013b; Naeher et al. 2007). Qualitative exposure assessment such as self-reported stove use may fill in some of the gaps where quantitative $PM_{2.5}$ assessment is lacking; however, self-report can be subject to bias and misclassification (Clark et al. 2013b). Due to the extreme difficulty in quality exposure assessment, new methods of accurately quantifying exposure could help assess the effectiveness of improved cookstoves at reducing exposures to air pollution and to assess associations between cookstoves and health outcomes.

Cookstove interventions and impact on exposure

The World Health Organization (WHO) recommends that mean concentrations of $PM_{2.5}$ remain below 25 $\mu g/m^3$ for a 24-hour period and below 10 $\mu g/m^3$ for an annual period (World Health Organization 2006). These air quality guidelines are based on extensive evidence surrounding the health effects of ambient air pollution exposure, but are not meant to represent a threshold below which no health effects are observed (World Health Organization 2006). Instead, the WHO air quality guidelines have been established to guide individual countries in setting standards for air quality given their own unique set of circumstances and priorities (World Health Organization 2006). Most cookstove users around the world experience $PM_{2.5}$ concentrations many times higher than these recommendations (Pope et al. 2017). A number of improved cookstoves have been designed and distributed into populations of traditional cookstove users around the world in an attempt to reduce their exposures to $PM_{2.5}$; the impact of these interventions on household air pollution levels has been assessed and summarized in recent reviews (Bruce et al. 2015; Pope et al. 2017; Quansah et al. 2017). Results indicated that improved cookstove interventions (including improved biomass cookstoves and stoves that use clean fuels such as ethanol, gas, or electricity) reduced personal and area concentrations of particulate matter; however, pollution concentrations following the interventions remained far above WHO recommended levels (Bruce et al. 2015; Pope et al. 2017; Quansah et al. 2017).

There are a number of reasons why improved cookstove interventions fail to reduce household concentrations of $PM_{2.5}$ below WHO recommendations. Many of the cookstove interventions thus far have been improved biomass cookstoves that implement a chimney and a combustion chamber designed to improve the efficiency of the stove (Pope et al. 2017). While these stoves do produce lower levels of pollution, measured concentrations emitted by improved biomass cookstoves vary substantially depending on factors such as type and quantity of fuel, as well as frequency of cookstove use (Clark et al. 2013b). In addition, other cultural and lifestyle factors such as burning incense, using candles for lighting, and using

multiple cookstoves in the household (referred to as cookstove "stacking") all have an impact on measured pollution concentrations during field research (Pope et al. 2017). In many communities, ambient "neighborhood" air pollution from other households and outdoor cooking and trash burning also contribute to high pollution concentrations; these may all be reasons that interventions of cookstoves that use even the cleanest fuels (e.g., gas or electricity) fail to reduce household air pollution to WHO recommended levels (Pope et al. 2017).

Additionally, it is difficult to ensure successful adoption and proper maintenance of improved cookstove interventions in complex field settings (Rehfuess et al. 2014). The factors impacting adoption and sustained use of improved cookstoves are numerous and span multiple domains: fuel and technology characteristics, household characteristics, knowledge and perceptions of the cookstove users, financial aspects, market development, and programmatic and policy mechanisms (Rehfuess et al. 2014). A cookstove that does not meet the needs of the target population may not be used exclusively, or at all (Naeher 2009; Ruiz-Mercado et al. 2011). Considerable forethought must be applied to choose an improved cookstove that meets the needs of the intended population, and continued reinforcement and education should also accompany a cookstove intervention to ensure sustained use and proper maintenance (Naeher 2009; Ruiz-Mercado et al. 2011). For these reasons, a framework of cookstove adoption that uses community-wide interventions and community engagement is encouraged (Bruce et al. 2015; Ruiz-Mercado et al. 2011).

Household air pollution and health outcomes

Overview

Exposure to air pollution from cookstoves is a leading risk factor for morbidity and mortality globally. Systematic reviews indicate strong evidence for an association between exposure to household air pollution and a number of adverse health outcomes including acute lower respiratory infections in children, and chronic obstructive pulmonary disease, lung cancer, and cataracts in adults (Bruce et al. 2015; Gordon et al. 2014; Sood et al. 2018). There is also

growing evidence of associations between household air pollution and low birth weight, stillbirth, stunted growth, and all-cause mortality in children, as well as various other cancers, acute lower respiratory infection mortality, and tuberculosis in adults (Bruce et al. 2015). Less research has been conducted to assess the association between exposure to household air pollution and cardiovascular disease. However, evidence suggests that household air pollution from cookstove use can adversely impact blood pressure, endothelial function, heart rate variability, and circulating biomarkers related to inflammation, coagulation, and oxidative stress (Fatmi and Coggon 2016; McCracken et al. 2012). More individuals in LMICs are expected to develop CVD as life-expectancy increases in these countries, and household air pollution is recognized as a contributor to this issue (McCracken et al. 2012). In Honduras, ischemic heart disease is the number one cause of death overall, and estimates suggest that nearly 12% of ischemic heart disease deaths in the country occur as a result of exposure to household air pollution from solid cooking fuels (IHME 2017).

In 2017 the Global Burden of Disease (GBD) study estimated that 1.6 million premature deaths occurred as a result of $PM_{2.5}$ exposures from solid cooking fuels (Stanaway et al. 2018). The deaths reported in the GBD study are attributed to a number of health outcomes: lower respiratory infections, cancer of the lungs and respiratory tract, ischemic heart disease, ischemic stroke, intracerebral and subarachnoid hemorrhage, chronic obstructive pulmonary disease, and type 2 diabetes mellitus (Stanaway et al. 2018). These outcomes were included in the study and subsequent report based on meeting World Cancer Research Fund grades of convincing or probable evidence (Stanaway et al. 2018). Of the estimated 1.6 million premature deaths attributable to $PM_{2.5}$ exposures from solid cooking fuels, approximately 40% occurred as a result of cardiovascular diseases (Stanaway et al. 2018).

The GBD estimates for household air pollution are calculated based on exposure-response curves developed primarily from research on ambient particulate matter and tobacco smoke exposures (Stanaway et al. 2018). Studies specifically exploring the CVD mortality

relationship with household air pollution are limited. A prospective cohort study conducted in Iran reported increased risk for all-cause and CVD mortality associated with kerosene/diesel burning (Mitter et al. 2016), and additional studies in China reported increased risk for all-cause mortality and ischemic heart disease associated with burning coal for cooking (Kim et al. 2016) and increased risk of all-cause and cardiovascular mortality associated with self-reported solid fuel use (Yu et al. 2018). These cohort studies help inform the integrated exposure-response curves for air pollution and CVD mortality used in global estimates of disease burden (Burnett et al. 2014; Pope et al. 2018), but they are limited by their lack of quantitative exposure assessment. Models that utilize field measurements of $PM_{2.5}$ and sociodemographic characteristics of cookstove users are implemented to estimate exposure to $PM_{2.5}$ so that exposure-response curves can be used to estimate the CVD mortality of household air pollution (Stanaway et al. 2018).

Due to the challenges of evaluating exposures and health outcomes in field settings, most of the associations between household air pollution and cardiovascular health outcomes come from observational field studies with limited internal validity and a narrow scope of the outcomes assessed (McCracken et al. 2012). Observational studies are typically the easiest to design and implement in a field setting, although they are also subject to bias (e.g., confounding) that can occur when comparison group assignment is not randomized. A number of studies have assessed the impact of improved cookstove interventions on cardiovascular health outcomes; however, conclusions from these studies remain unclear due to limitations in study design and health and exposure assessment (Bruce et al. 2015; McCracken et al. 2012; Quansah et al. 2017).

The two study designs utilized in this dissertation were implemented to improve upon the designs used in many of the previous studies on household air pollution. While specific details of the study designs will be discussed in subsequent chapters, the rationale for using the designs will be introduced here to give perspective alongside the discussion of previous

literature. For the Aim 2 study in Honduras, a stepped-wedge design was chosen to implement the *Justa* cookstove intervention into two separate arms of participants at different time points throughout the study. Using this design meant that study arm assignment could be randomized, which helped control for confounding biases that are major weaknesses in typical observational field studies (Hemming et al. 2015). Additionally, the study included six visits to measure exposure and outcome data over the course of three years, which meant that both study arms had multiple visits when using both the non-intervention and the intervention cookstoves.

The Aim 1 study took place in a laboratory setting and utilized a crossover design called a Latin square (R. Lyman Ott and Longnecker 2010). The Latin square crossover design controlled for confounding and potential selection bias from missed study sessions because participants were blinded to their sequence of assigned treatments; potential extraneous confounding variables and missed study sessions were unlikely to be related to individual assigned treatments and were therefore unlikely to bias associations between exposures and outcomes in the study. Time invariant confounders such as participant sex were also controlled for in the study design since each participant served as their own control and comparisons were made within-person. While previous controlled exposure studies have been conducted in household air pollution research, ours is the first to use a robust Latin square crossover design to produce high internal validity while also assessing a wider spectrum of cookstove and fuel combinations than any previous study.

Review of literature assessing household air pollution and cardiovascular outcomes

The Randomized Exposure Study of Pollution Indoors and Respiratory Effects (RESPIRE) Study was the first randomized cookstove intervention study to assess the health impacts of an improved cookstove (McCracken et al. 2007). While RESPIRE was mainly focused on respiratory health outcomes, investigators reported that the improved *Plancha* biomass cookstove intervention was associated with lower systolic and diastolic blood pressure (3.7 mmHg lower systolic blood pressure, 95% confidence interval [CI] -8.1 to 0.6; 3.0 mmHg

lower diastolic blood pressure, 95% CI -5.7 to -0.4) in the intent-to-treat analysis using between-group comparisons based on the randomized cookstove assignment; similar associations were observed in within-group comparisons (McCracken et al. 2007). The RESPIRE Study also reported reduced occurrence of ST-segment depression following the *Plancha* cookstove intervention, which could mean that cookstove-emitted air pollution can impact cardiac repolarization (McCracken et al. 2011). An improved cookstove intervention (no control arm) in Nicaragua resulted in 5.9 mmHg lower systolic blood pressure in women over 40 years old (95% CI: -11.3, -0.4) and 4.6 mmHg lower systolic blood pressure (95% CI: -10.0, 0.8) in obese women (Clark et al. 2013a). More recent intervention studies have reported lower diastolic blood pressure (-2.8 mmHg, 95% CI: -4.4, 1.8) in pregnant women using an ethanol cookstove intervention compared to controls using kerosene or wood in Nigeria (Alexander et al. 2017), and lower systolic blood pressure (-2.1 mmHg, 95% CI: -6.6, 2.4) in pregnant women using either an LPG or improved biomass cookstove intervention compared to controls using a traditional biomass stove in Ghana (Quinn et al. 2017). A rocket cookstove intervention in India found no change in blood pressure in the intent-to-treat analysis, but further analysis in exclusive users of the intervention cookstove did show slight decreases in systolic (-2.0 mmHg, 95%CI: -4.5, 0.5) and diastolic blood pressure (-1.1 mmHg, 95%CI: -2.9, 0.6) compared to baseline values (Aung et al. 2018). More recent results that assessed a government sponsored semi-gasifier cookstove intervention in China conflict with previous studies on cookstove interventions that lowered blood pressure; authors reported that the intervention did not improve blood pressure, CPP, or pulse wave velocity compared to participants who did not receive the intervention (Clark et al. 2019). Women who did not receive the intervention had higher decreases in systolic blood pressure (adjusted difference-in-difference effect estimate [DD]=1.3 mmHg; 95% credible interval [CrI]: -2.5, 5.2), diastolic blood pressure (DD=1.7 mmHg; 95% CrI: -0.3, 3.6), and pulse wave velocity (DD=3.7% m/s; 95% CrI: -2.2, 10.2), as well as similar decreases in CPP (DD=0.1 mmHg; 95% CrI: -1.9, 2.2) compared to those who received the

cookstove intervention (Clark et al. 2019). The authors speculate that the ineffectiveness of the cookstove intervention was due to increased use of gas and electric cookstoves among the non-intervention group during the study (Clark et al. 2019).

Other field studies assessing cookstoves and cardiovascular health have been observational in nature. Multiple cross-sectional studies have found associations between higher levels of cookstove air pollution and higher blood pressure (Baumgartner et al. 2011; Baumgartner et al. 2018; Burroughs Pena et al. 2015; Clark et al. 2011; Dutta et al. 2011; Lee et al. 2012; Ofori et al. 2018; Young et al. 2018). Cross-sectional associations have also been observed between cookstove smoke exposure and outcomes such as endothelial function (Buturak et al. 2011), carotid intima media thickness (Ofori et al. 2018), platelet activation (Dutta et al. 2011; Ray et al. 2006), and inflammation and oxidative stress (Dutta et al. 2012).

In addition to evidence from field studies, controlled exposure studies in laboratory settings have been used to assess the relationship between household air pollution and measures of cardiovascular health. A controlled exposure study with 13 healthy adult volunteers indicated increases in inflammatory and coagulation factors in study participants exposed to woodsmoke compared to filtered air (Barregard et al. 2006). Another controlled exposure study with 10 healthy adult participants reported associations between exposure to woodsmoke and markers of systemic and pulmonary inflammation compared to filtered air; however, the authors reported no associations between woodsmoke exposures and pulmonary function or indices of heart rate variability (Ghio et al. 2012). Further controlled exposure studies have not found evidence of an association between woodsmoke and markers of inflammation, coagulation, oxidative stress (Bonlokke et al. 2014; Forchhammer et al. 2012; Stockfelt et al. 2013), and microvascular function (Forchhammer et al. 2012). Results from the same study that was used in Aim 1 of this dissertation suggested that 2-hour exposures to cookstove air pollution can lead to acute (within 24 hours) increases in systolic blood pressure compared to a filtered air control (Fedak et al. 2019).

There is evidence to support an association between household air pollution and CVD, although further research on a wider scope of cardiovascular health outcomes in both field and laboratory settings is needed to draw definitive conclusions on this relationship (McCracken et al. 2012). Experimental field studies that implement randomized exposure assignment (e.g., randomized assignment to a study arm, as in Aim 2) to improve internal validity are few in number, and the scope of cardiovascular health outcomes assessed in these types of studies has been limited. Similarly, controlled exposure studies allow researchers to assess complex health outcomes in a controlled environment with robust study designs that help control for confounding factors, yet few measures of cardiovascular health have been assessed in such studies to date. Further experimental studies in both field and controlled exposure settings can complement the existing literature while improving on previous research by using enhanced study designs and assessing a wider scope of outcomes.

Air pollution, cardiovascular disease, and potential pathways

Particulate matter air pollution is thought to impact the cardiovascular system via three major pathways: 1) oxidative stress and inflammation, 2) autonomic nervous system (ANS) imbalance, and 3) through a direct process of transmitting pollutants into the blood (Brook et al. 2010). Acute changes (within minutes to hours) in cardiovascular endpoints are believed to be caused primarily by pathways 2 and 3, although there is less evidence of the latter pathway in general (Brook et al. 2010). Pathways of oxidative stress and inflammation take longer to initiate, and likely cause cardiovascular changes in a slightly longer timeframe of hours to days (Brook et al. 2010). The literature on pathways between air pollution and cardiovascular disease has typically been generalized to all types of air pollution exposure. The following summary will utilize this template and should not be considered specific to household air pollution.

Systemic inflammation and oxidative stress are closely related, and in human studies it is difficult to assess specific differences between the two processes and their respective associations with PM air pollution (Brook et al. 2010). In general, inflammatory and oxidative

stress pathways both begin in pulmonary tissues as PM is deposited in the lungs (Franklin et al. 2015). As reactive oxygen species and pro-inflammatory cytokines increase in the lungs, they can spill over into the systemic circulation and lead to a variety of adverse cardiovascular effects throughout the body (Brook et al. 2010; Franklin et al. 2015). Many epidemiologic studies have found increased circulating inflammatory markers after short- and long-term exposure to PM (Brook et al. 2010), and other studies show increasing evidence that PM exposure can lead to impaired vascular function and vasoconstriction (Franklin et al. 2015). While markers specific to systemic oxidative stress are more difficult to identify and study in humans, there is evidence of increased gene expression related to oxidative stress, as well as increased oxidized lipids following PM air pollution exposure (Rao et al. 2017).

Although specific pathways are not yet clear, an immediate response to PM exposure could take place through the ANS. ANS imbalance is likely initiated through particle interactions with airway receptors (i.e., C-nerve fibers and rapidly adapting pulmonary receptors, or RARs) that activate ANS reflex arcs (Brook et al. 2010; Perez et al. 2015). C-nerve fiber and RAR stimulation by PM can lead to changes in cardiovascular function such as heart rate and blood pressure, which vary in magnitude and direction depending on the level of inhalation and location of the receptor activation (Kodavanti 2016; Perez et al. 2015; Widdicombe and Lee 2001). Stimulation of the receptors in the upper airway has been shown to cause hypertension and tachycardia in animal models (Widdicombe and Lee 2001), while lower airway stimulation can cause the opposite effects (Perez et al. 2015; Widdicombe and Lee 2001).

Multiple studies of air pollution exposure have shown associations with a reduction in heart rate variability (HRV), which is consistent with sympathetic stimulation and ANS pathways described above (Middlekauff et al. 2014; Perez et al. 2015). While little is known about the ANS pathways induced by PM exposure specifically, more is known about these pathways after cigarette smoke exposure, and the similarities between the two exposures may give us important insight into the immediate cardiovascular effects of PM exposure (Middlekauff et al.

2014). There are differences in the specific makeup of cigarette smoke as compared to ambient and household air pollution; however, there is increasing evidence that air pollution can lead to adverse cardiovascular health effects through stimulation of the ANS (Middlekauff et al. 2014).

Air pollution in general, and possibly PM, may also be an environmental stressor capable of activating the hypothalamus-pituitary-adrenal (HPA) axis (Kodavanti 2016). Activation of the HPA axis can begin with airway receptor stimulation by PM similar to the ANS pathways described above (Kodavanti 2016). After a stressor has been sensed and neural pathways have been stimulated, corticotropin-releasing hormone is secreted by the hypothalamus, which then stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH) into circulation (Kodavanti 2016; Smith and Vale 2006). ACTH then targets the adrenal glands, which synthesize and release glucocorticoid stress hormones such as cortisol (Smith and Vale 2006). While few studies have assessed stress hormones and their relationship with PM exposure and health effects, there is increasing evidence that this is an important pathway to consider (Kodavanti 2016; Li et al. 2017). Elevated cortisol levels have well-established cardiovascular health effects, including increased blood pressure through higher cardiac output and vasoconstriction (Li et al. 2017; Whitworth et al. 2005). Hyperlipidemia can also occur with elevated cortisol levels, although evidence suggests that these changes may occur in chronic rather than acute timeframes (Whitworth et al. 2005).

Less is known in general about the third pathway of air pollution particles being directly transmitted into the blood stream. Some studies have suggested that components of air pollution such as ultrafine particles or metals may be transmitted directly into circulation (Brook et al. 2010; Franklin et al. 2015). This subject and the impact on human health remains controversial; however, evidence suggests that a high percentage of inhaled ultrafine particles are deposited deeply into the lungs and can cross directly into the blood stream (Chen et al. 2016). The pathways described above are not mutually exclusive; they likely occur in

overlapping timeframes and elicit similar responses to PM air pollution that are difficult to distinguish in humans (Brook et al. 2010; Franklin et al. 2015).

Central hemodynamics and arterial stiffness

Although peripheral (brachial) blood pressure is a well-established indicator of CVD risk, measuring indices of central hemodynamics and arterial stiffness can complement and provide additional information compared to measuring only peripheral blood pressure (Vlachopoulos et al. 2010a; Vlachopoulos et al. 2010b). Central hemodynamic indices and aortic arterial stiffness are pathophysiologically important because they represent the workload on the heart that impacts coronary perfusion and degenerative changes in the central elastic vessels; downstream muscular arteries, where peripheral blood pressure is measured, are impacted by other physiological factors and may not represent the progression of cardiovascular disease as accurately (Vlachopoulos et al. 2010a).

PWV is the gold standard for assessing aortic arterial stiffness and is a strong predictor of CVD events and all-cause mortality (Townsend et al. 2015; Vlachopoulos et al. 2010b). In a 2015 statement in *Hypertension*, the American Heart Association recommended using carotid-femoral pulse wave velocity (PWV as measured between defined points on the carotid and femoral arteries) to measure central aortic arterial stiffness (Townsend et al. 2015). For Aim 1a, we measured PWV using the SphygmoCor XCEL system (AtCor Medical, Australia). This method shows strong reproducibility in published works (Townsend et al. 2015). Arterial stiffness can vary depending on numerous pathways within the vessels; structural or passive changes are largely determined by the makeup of vessel wall components such as proteins elastin and collagen (Townsend et al. 2015; Zieman et al. 2005). Functional or active changes in arterial stiffness are more likely to occur after acute exposures, and general pathways that could lead to an increase in PWV and arterial stiffness include endothelial dysfunction and increased vascular smooth muscle cell tone (Townsend et al. 2015; Zanoli et al. 2017).

AIx is a measure of pulse wave reflection and an indirect measure of systemic vascular stiffening (Tomiyama and Yamashina 2010). AIx is calculated as the difference of the forward pressure wave leaving the heart and the reflected pressure wave coming back to the heart, divided by pulse pressure, and expressed as a percentage (Tomiyama et al. 2014). An outgoing pulse wave will reflect back to the heart when it reaches a point of resistance such as arterial branching; under normal conditions, elastic arteries have a cushioning effect to minimize arterial stiffness and central blood pressure, but pathophysiological changes can increase AIx through two major pathways of central arterial stiffness and peripheral artery resistance (Tomiyama and Yamashina 2010; Tomiyama et al. 2014). Due to the former pathway, increased PWV can lead to an increase in AIx: as the central elastic artery stiffens and PWV increases, the pulse wave will reach a point of resistance faster than under normal conditions, and subsequently be reflected back toward the heart sooner and at a faster rate (Tomiyama and Yamashina 2010). The reflected pulse wave traveling back up the aorta could then meet and augment a subsequent pulse wave leaving the heart, and lead to an increase in central blood pressure and AIx (Tomiyama and Yamashina 2010). Similarly, peripheral artery resistance from constriction of peripheral resistance arteries influences AIx by leading to earlier reflection of pulse waves back toward the heart (Tomiyama et al. 2014). We measured AIx and CPP for Aim 1a and Aim 2 using the SphygmoCor XCEL system, which produces highly reliable results (Hwang et al. 2014). AIx and CPP are both measures of central aortic hemodynamics and overall cardiovascular performance; both AIx and CPP have strong associations with adverse cardiovascular events and mortality and predict clinical events independently of peripheral blood pressure measures (Vlachopoulos et al. 2010a).

Potential changes in PWV, AIx, and CPP can be induced through impaired vasodilation from reduced nitric oxide bioavailability, which can be caused by systemic inflammation and oxidative stress that is initiated by $PM_{2.5}$ exposure (Brook et al. 2010; Huang and Vita 2006). Experimental studies specifically assessing particulate matter exposures and vascular function

have shown evidence of this pathway in humans (Franklin et al. 2015), and other experimental studies have examined the pathway between generalized systemic inflammation and endothelial dysfunction in depth (Huang and Vita 2006). Specifically, inflammatory cytokines such as tumor necrosis factor alpha can reduce expression of endothelial nitric oxide synthase and increase production of reactive oxygen species (Huang and Vita 2006; Sprague and Khalil 2009). Both of these pathways can lead to reduced nitric oxide bioavailability and subsequent endothelial dysfunction and impaired vasodilation (Huang and Vita 2006; Sprague and Khalil 2009), which can then result in hemodynamic changes.

Currently only one study has assessed measures of central hemodynamics and arterial stiffness and exposure to household air pollution. A field study in China found that a 1-unit increase in natural log-transformed $PM_{2.5}$ was associated with 1.1 percentage points higher AIx (95% CI: -0.2, 2.4) in a population of 205 women; among 102 women aged 50 years or more, increased $PM_{2.5}$ exposures were associated with 2.9 mmHg higher CPP (95% CI: 0.8, 5.1) (Baumgartner et al. 2018). The same study found no association between $PM_{2.5}$ and PWV (Baumgartner et al. 2018). After 1.5 years of follow-up, authors reported that a government sponsored semi-gasifier cookstove intervention did not improve hemodynamic outcomes of blood pressure, CPP, or pulse wave velocity compared to participants who did not receive the intervention (Clark et al. 2019).

Despite the lack of studies between household air pollution and hemodynamic outcomes, there is evidence that particulate and gaseous air pollution from ambient sources can impact measures of arterial stiffness and central hemodynamics (Zanoli et al. 2017). A systematic review assessing particulate and gaseous air pollution and outcomes of PWV, AIx, and augmentation pressure found eight relevant studies through January of 2017 (Zanoli et al. 2017). The study populations ranged in size and composition from a small group of 26 welders, to urban populations of healthy adults and elderly men, to participants with comorbidities such as hypertension or individuals undergoing hemodialysis (Zanoli et al. 2017). While the

heterogeneity of the study populations and exposures prevented the authors from conducting a meta-analysis, six out of the eight studies in the review reported higher arterial stiffness or wave reflection following air pollution exposures (Zanoli et al. 2017). These studies indicate that there may be an association between air pollution and central hemodynamic indices and warrant further investigation on this association within the scope of household air pollution.

Blood lipids

Similar to indices of central hemodynamics and arterial stiffness, very little research has been conducted on the association between blood lipids and household air pollution. Blood lipids such as total cholesterol, HDL, LDL, and triglycerides are important markers to assess because of their role in the development of atherosclerosis and advanced CVD (Bai and Sun 2016). LDL contributes directly to the atherosclerotic process by accumulating to form foam cells and fibrous plaques (Bai and Sun 2016). High levels of triglycerides can lead to triglyceride-rich lipoproteins accumulating in the plasma and initiating a pro-atherogenic inflammatory cascade (Talayero and Sacks 2011). In contrast, HDL is strongly protective against atherosclerosis by binding to and removing excess cholesterol from cells and extracellular tissues (Bai and Sun 2016).

There is increasing evidence to suggest that particulate matter air pollution can impact atherosclerotic development, potentially through pathways of inflammation and oxidative stress (Bai and Sun 2016; Brook et al. 2010). There is also evidence that generalized inflammation can acutely impact blood lipids (Khovidhunkit et al. 2004). Although these pathways have not been assessed following air pollution exposure, evidence indicates that cholesterol levels (total cholesterol, HDL, and LDL) can decrease after an acute inflammatory response in humans (Khovidhunkit et al. 2004). Inflammatory and oxidative stress pathways initiated by air pollution exposures could adversely impact blood lipids (i.e., increase total cholesterol, LDL and triglycerides; decrease HDL) in humans (Bai and Sun 2016; Franklin et al. 2015). Mechanisms are not well understood, but inflammatory markers such interleukins and tumor necrosis factor

are believed to inhibit cholesterol synthesis and secretion (Khovidhunkit et al. 2004). In contrast, an acute-phase inflammatory response increases triglycerides (Khovidhunkit et al. 2004). Inflammatory cytokines can cause an increase in production and secretion of triglycerides within two hours that is sustained for up to 24 hours (Khovidhunkit et al. 2004). There is also evidence that air pollution can oxidize LDL (Dutta et al. 2011; Jacobs et al. 2011). Oxidized LDL is pro-inflammatory and pro-atherogenic; it is scavenged by macrophages that can then lead to foam cell formation and development of atherosclerosis (Bai and Sun 2016).

A number of studies have assessed blood lipids and their association with ambient air pollution. Higher concentrations of ambient particulate matter air pollution have been associated with lower HDL in several studies (Bell et al. 2017; Chuang et al. 2010; Yang et al. 2018; Yitshak Sade et al. 2016), higher triglycerides (Chuang et al. 2010; Shanley et al. 2016; Yang et al. 2018; Yitshak Sade et al. 2016), higher total cholesterol (Shanley et al. 2016; Yang et al. 2018), and higher LDL (Yang et al. 2018; Yitshak Sade et al. 2016). Another study evaluated associations between ambient particulate matter air pollution and blood lipids in 12 adults with asthma and reported 4.8% higher triglycerides (95% CI: 0.81, 8.74) per 1 $\mu g/m^3$ increase in coarse particulate matter (Yeatts et al. 2007). Although less common, controlled exposure studies with designs more similar to ours in Aim 1b have been conducted. Ramanathan et al. reported lower HDL antioxidant/anti-inflammatory capacity 1 hour after concentrated ambient $PM_{2.5}$ exposures in a group of 30 healthy adults; the authors emphasized that acute changes in HDL antioxidant/anti-inflammatory functionality can take place in the absence of changes in serum HDL levels (Ramanathan et al. 2016). A study on 19 healthy adults reported lower levels of triglycerides (-14.5%, 95% CI: -30.1, -3.02) and very low-density lipoprotein (-17.3%, 95% CI: -31.0, -3.09) immediately after a 2-hour exposure to ultrafine ambient air pollution particles compared to filtered air, as well as a small decrease in HDL 18 hours after the controlled exposures compared to filtered air (Samet et al. 2009). In contrast, higher triglycerides (7.40%, standard error = 2.52) and very low-density lipoprotein (7.68%, standard error = 2.55) were

reported immediately after controlled exposures to concentrated ambient air pollution particles compared to filtered air in a group of 13 healthy middle-aged adults, with slightly attenuated levels reported 20 hours later (Tong et al. 2012). Others have reported higher levels of total cholesterol and HDL 18 hours after controlled exposures to nitrogen dioxide compared to filtered air (Huang et al. 2012).

While these studies demonstrate an association between ambient air pollution and blood lipids, there may be compositional differences between ambient and cookstove-emitted air pollution (Naeher et al. 2007) that lead to differential impacts on blood lipids. Only one study to date has assessed household air pollution and blood lipids. In this cross-sectional field study, no indication of adverse associations was observed between household air pollution exposures and outcomes of total cholesterol, HDL, LDL, and triglycerides in primary household cooks in rural Honduras (Rajkumar et al. 2019). Further studies using stronger designs will help us better understand the relationship between household air pollution and blood lipids.

CHAPTER 3: ACUTE DIFFERENCES IN PULSE WAVE VELOCITY, AUGMENTATION INDEX, AND CENTRAL PULSE PRESSURE FOLLOWING CONTROLLED EXPOSURES TO COOKSTOVE AIR POLLUTION IN THE SUBCLINICAL TESTS OF VOLUNTEERS EXPOSED TO SMOKE (STOVES) STUDY

Summary

Household air pollution emitted from solid-fuel cookstoves used for domestic cooking is a leading risk factor for morbidity and premature mortality globally. There have been attempts to design and distribute lower emission cookstoves, yet it is unclear if they meaningfully improve health. Using a crossover design, we assessed differences in central aortic hemodynamics and arterial stiffness following controlled exposures to air pollution emitted from five different cookstove technologies compared to a filtered air control.

Forty-eight young, healthy participants were assigned to six 2-hour controlled treatments of pollution from five different cookstoves and a filtered air control. Each treatment had a target concentration for fine particulate matter: filtered air control = 0 $\mu g/m^3$, liquefied petroleum gas = 10 $\mu g/m^3$, gasifier = 35 $\mu g/m^3$, fan rocket = 100 $\mu g/m^3$, rocket elbow = 250 $\mu g/m^3$, three stone fire = 500 $\mu g/m^3$. Pulse wave velocity (PWV), central augmentation index (AIx), and central pulse pressure (CPP) were measured before and at three time points after each treatment (0, 3, and 24 hours). Linear mixed models were used to assess differences in the outcomes for each cookstove treatment compared to control.

PWV and CPP were marginally higher 24 hours after all cookstove treatments compared to control. For example, PWV was 0.15 m/s higher (95% confidence interval: -0.02, 0.31) and CPP was 0.6 mmHg higher (95% confidence interval: -0.8, 2.1) 24 hours after the three stone fire treatment compared to control. The magnitude of the differences compared to control was similar across all cookstove treatments. PWV and CPP had no consistent trends at the other

post-treatment time points (0 and 3 hours). No consistent trends were observed for AIx at any post-treatment time point.

Our findings suggest higher levels of PWV and CPP within 24 hours after 2-hour controlled treatments of pollution from five different cookstove technologies. The similar magnitude of the differences following each cookstove treatment compared to control may indicate that acute exposures from even the cleanest cookstove technologies can adversely impact these subclinical markers of cardiovascular health, although differences were small and may not be clinically meaningful.

Introduction

Household air pollution resulting from combustion of solid fuels for domestic cooking is a leading environmental risk factor for global morbidity and mortality. Fine particulate matter ($PM_{2.5}$; particles less than 2.5 μm in aerodynamic diameter) exposures from solid cooking fuels resulted in an estimated 60 million disability adjusted life-years in 2017, including 1.6 million premature deaths (Stanaway et al. 2018). Improved, cleaner-burning cookstove technologies have been developed and distributed in an attempt to lower exposures to household air pollution, but it is still unclear if these new cookstoves are resulting in improved health outcomes (Bruce et al. 2015; Quansah et al. 2017). Further research is necessary to understand if currently available improved cookstove technologies are capable of reducing exposures enough to result in improved health outcomes compared to traditional cookstoves.

It is estimated that 40% of the 1.6 million premature deaths that resulted from household air pollution exposure in 2017 occurred due to cardiovascular outcomes such as ischemic heart disease and stroke (Stanaway et al. 2018). Current research suggests that household air pollution from cookstove use can adversely impact blood pressure, endothelial function, and heart rate variability, as well as alter circulating biomarkers related to inflammation, coagulation, and oxidative stress (Fatmi and Coggon 2016; McCracken et al. 2012). However, conclusive epidemiologic evidence is still lacking due to limitations in study designs (e.g., limited internal

validity in observational studies and lack of quantitative exposure assessment in many field studies) and a narrow scope of the outcomes assessed; further research is needed to understand how household air pollution impacts cardiovascular health (McCracken et al. 2012).

Measures of arterial stiffness and central hemodynamics provide information on cardiovascular disease risk beyond that of traditional measures such as peripheral blood pressure (Vlachopoulos et al. 2010a; Vlachopoulos et al. 2010b). Carotid-femoral pulse wave velocity (PWV) is the gold standard for assessing aortic arterial stiffness and is strongly associated with cardiovascular disease risk and mortality (Townsend et al. 2015; Vlachopoulos et al. 2010b). Central augmentation index (AIx) is a measure of pulse wave reflection and an indirect measure of peripheral vascular stiffening (Tomiyama and Yamashina 2010). AIx and central pulse pressure (CPP) are measures of central hemodynamics and overall cardiovascular performance, and similar to PWV, both are strongly associated with risk of adverse cardiovascular events and mortality (Vlachopoulos et al. 2010a). For PWV, AIx, and CPP, higher values are associated with increased risk of adverse cardiovascular outcomes (Vlachopoulos et al. 2010a; Vlachopoulos et al. 2010b). Studying the associations between household air pollution and these outcomes will give us a better understanding of the cardiovascular health impacts of cookstove use.

There is evidence that particulate and gaseous air pollution from ambient sources can impact measures of arterial stiffness and central hemodynamics (Zanoli et al. 2017). Currently only one study has evaluated the association between these outcomes and household air pollution; this field study reported associations between increased levels of household air pollution and higher central blood pressure, CPP, and AIx in a population of 205 women in rural China (Baumgartner et al. 2018). However, the authors reported that a semi-gasifier cookstove intervention did not improve hemodynamic outcomes compared to participants who did not receive the intervention (Clark et al. 2019). In a controlled human exposure study with a crossover design called the SToVES Study (Subclinical Tests on Volunteers Exposed to

Smoke), we assessed PWV, AIx, and CPP following 2-hour exposures to air pollution emitted from five cookstove technologies compared to filtered air. Our aim was to investigate the impact of exposure to different levels of cookstove air pollution on acute cardiovascular and respiratory health outcomes (other outcomes reported separately).

Methods

Study design

A description of the study design and methods has been published previously (Fedak et al. 2019). The crossover study design consisted of a Latin square with six 2-hour controlled treatments of pollution emitted from five cookstove technologies (referred to as "cookstove treatments") and a filtered air control (Figure 3.1). Each treatment had a target level of $PM_{2.5}$. The study was divided into three rounds that lasted 3 to 4 months in duration depending on holidays and academic schedules. The 16 participants in each round were divided into two groups of eight, primarily based on participant schedules and availability. Each group of eight participants was assigned to a unique sequence of the treatments with at least 2 weeks between treatments to minimize a carryover effect of the previous treatment. The 2-week washout period between treatments was chosen to be consistent with previous studies that had washout periods of 1 to 3 weeks (Barregard et al. 2008; Bonlokke et al. 2014; Riddervold et al. 2012; Sehlstedt et al. 2010; Stockfelt et al. 2013). Each group of eight participants who shared a unique treatment sequence received their assigned treatments during the same calendar week, with four participating on Monday and four on Wednesday. Participants were expected to follow their assigned sequence unless an illness or personal circumstance kept them from participating. After each of the assigned sequences in a round was completed, participants were allowed to return for out-of-sequence makeup visits in order to complete each of their six total treatments.

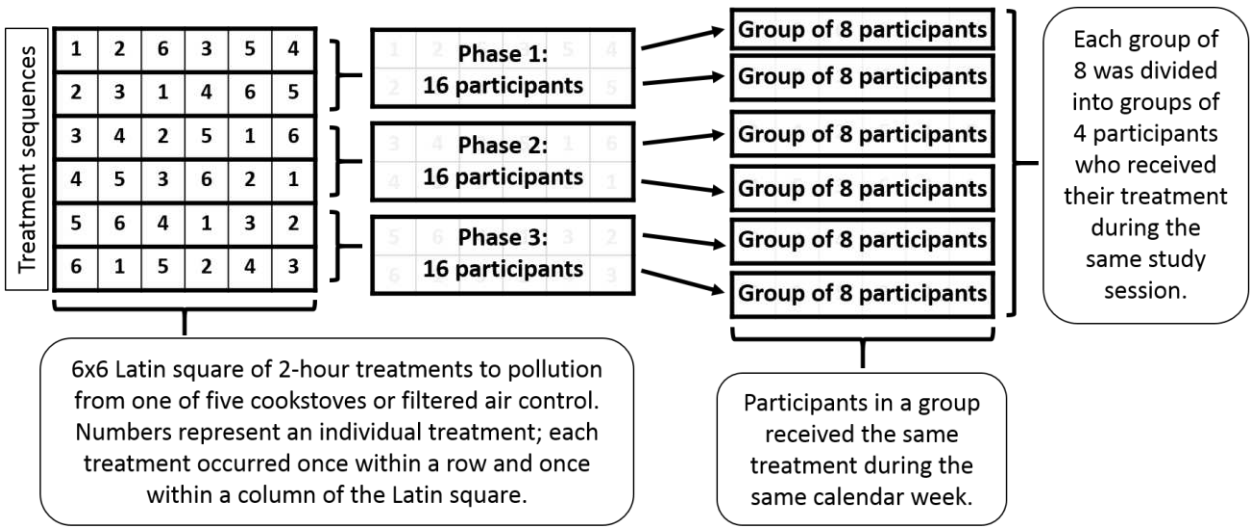

Figure 3.1: SToVES Study design

The crossover study design produced high internal validity. Each participant acted as their own control, which eliminated individual time-invariant factors (e.g., sex, race/ethnicity) as potential confounders. In addition, participants were divided into six groups with unique sequences of the treatments, which limited the potential effect that sequence of the treatments may have had on the outcomes. Some potential confounding factors may have varied across study days (e.g., ambient temperature and air pollution); however, these factors were unlikely to be associated with the individual treatments and were therefore unlikely to confound the associations in our analyses. Further details on statistical analyses and strengths of the study design are described below.

Participants and recruitment process

Participants (n=48) were recruited from the Fort Collins, Colorado area beginning in September of 2016. Specific eligibility criteria at the time of recruitment included age less than 36 years, body mass index (BMI) between 18 and 29 kg/m^2, never-smoker, no regular exposure to air pollution above ambient levels (including secondhand tobacco smoke and recreational drugs), no self-reported history of chronic diseases (e.g., cardiopulmonary disease or diabetes), no recent surgery, no claustrophobia or fear of needles, not pregnant/breastfeeding or planning on becoming pregnant, ability and willingness to refrain from prescription and over-the-counter

medication use during study sessions unless approved by the study physician, and willingness to comply with a strict study schedule. If participants passed eligibility screening they were asked to complete an individual health assessment conducted by a cardiologist to rule out any current or family history of cardiopulmonary disease. Further information on eligibility criteria and the individual health assessment is included in Appendix A.

All study procedures were approved by the Institutional Review Board at Colorado State University. Participants provided written consent for all study procedures.

Study sessions

Study sessions consisted of four health assessments and the assigned treatment (Figure 3.2). Start times for the four participants in a session were staggered by 30 minutes beginning at 7:30am. Participants kept the same study day (i.e., Monday vs Wednesday) and start time throughout each of their sessions. In addition, participants kept the same daily schedule for each session they completed (i.e., the treatment and health assessments were completed at the same time during the day for each study session a participant completed). After arriving for a study session, participants were assessed by a cardiologist to ensure they were not currently or recently sick or suffering an inflammatory or allergic reaction. Once the cardiologist authorized participation, the study session began with a baseline health assessment and was followed immediately by the assigned 2-hour treatment. Another health assessment took place immediately after the treatment. Participants then had a lunch break during which they remained in the testing facility building. A third health assessment took place 3 hours after each participant finished their treatment. Participants then left the testing facility overnight before returning the next day for the fourth health assessment 24 hours after each participant finished their treatment.

Participants were asked to eat a consistent, low-fat diet and to refrain from alcohol and smoke exposure starting 24 hours prior to each study session and ending after the 24-hour follow-up health assessment. Unless approved by the study physician, participants were also

asked to refrain from medication use starting 72 hours prior to each study session and ending after the 24-hour follow-up.

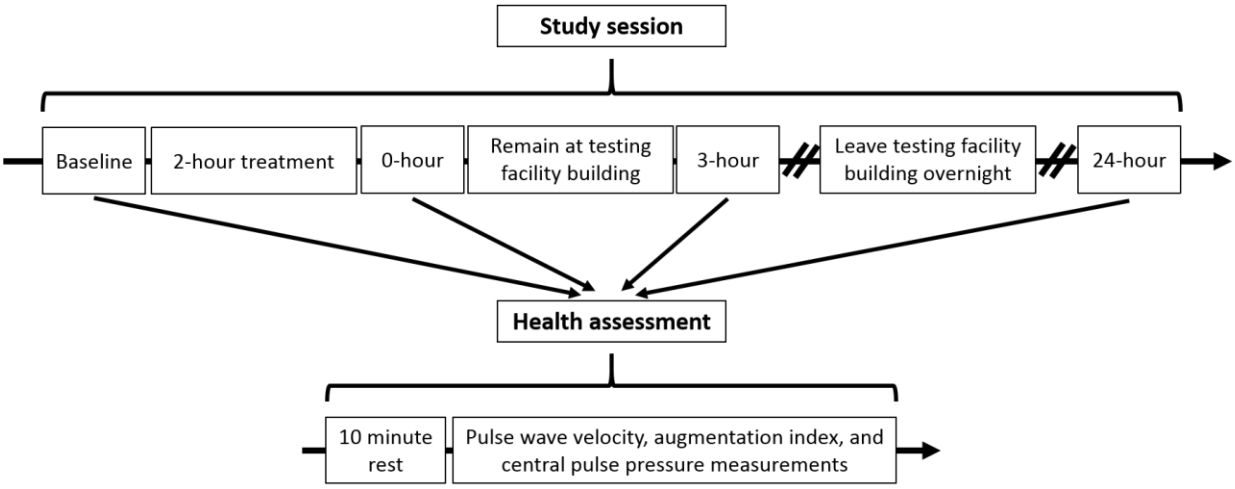

Figure 3.2: SToVES Study session sequence of events

Health assessments and study outcomes

Each health assessment lasted approximately 1 hour and consisted of a 10-minute rest period (supine position) followed by a series of health measurements (full list of health measurements in Appendix A). PWV, AIx, and CPP were measured using a non-invasive pressure waveform device (SphygmoCor XCEL, Atcor Medical, Australia) immediately following the 10-minute rest period. Study personnel were trained by a SphygmoCor representative and adhered to the manufacturer's protocols (see Appendix A). Quality control measures are integrated into the SphygmoCor software; only measurements that passed the instrument quality control guidelines were used for analysis. Heart rate was also measured during the AIx assessment and used as a covariate in some supplementary analyses. Height and weight were measured once at enrollment and used to calculate BMI (kg/m^2).

Controlled treatments

Controlled treatments were administered in a specially designed facility on the Colorado State University campus called the Simulated Environmental Testing (SET) facility. The SET facility was large enough to house four participants simultaneously; participants remained

seated throughout the 2-hour treatments. Participants were monitored for the entire duration of the controlled treatments by a registered nurse; the nurse also remotely (i.e., without entering the SET) measured blood pressure, heart rate, and oxygen saturation every 15 minutes while participants were in the SET facility. Participants were able to communicate with study staff if necessary via text message or intercom while inside the SET facility.

The six treatments included filtered air control ($PM_{2.5}$ target level of 0 $\mu g/m^3$), liquefied petroleum gas (LPG; 10 $\mu g/m^3$), gasifier (35 $\mu g/m^3$; fuel of pine wood chips), forced-draft fan rocket elbow (100 $\mu g/m^3$; fuel of pine wood sticks), natural-draft rocket elbow (250 $\mu g/m^3$; fuel of pine wood sticks), and three stone fire (500 $\mu g/m^3$; fuel of pine wood sticks). Emissions for each of the treatments were extracted from a total-capture fume hood where the cookstove was operated by study personnel, and mixed with HEPA (high efficiency particulate air) filtered air to reach the target concentration for each respective treatment. A nephelometer (DustTrak DRX 8533, TSI Incorporated, USA) with a $PM_{2.5}$ size-selective cyclone inlet and a gas analyzer (Siemens Ultramat 6E, Siemens AG, Germany) were used to monitor $PM_{2.5}$, carbon monoxide (CO), and oxygen levels in the SET facility in real time. The DustTrak was calibrated to the wood and LPG stoves separately, based on gravimetric analysis of $PM_{2.5}$ filter data collected within the SET facility prior to the study. Gravimetric filters were also collected on each sample day to ensure DustTrak accuracy and to detect any potential calibration drift. Humidity and temperature in the SET facility were also monitored (Omega HX94BC transmitter and Type K thermocouple, OMEGA Engineering, USA). A real-time control system (LabVIEW™, v15.0 32-bit, National Instruments, USA) was used to automate the flows of both dilution and pollution air based on real-time $PM_{2.5}$ data received from the DustTrak to maintain target concentrations.

We conducted further testing to characterize additional pollutant levels inside the SET facility for each of the treatments, including the filtered air treatment. For each treatment, at least two 2-hour tests were conducted under the same conditions as a typical study session. No human participants were present in the SET facility during this additional testing. The pollutants

characterized included $PM_{2.5}$ mass, particle number size distributions (10 nm to 500 nm), $PM_{2.5}$ elemental and organic carbon, nitrogen oxide, nitrogen dioxide, volatile organic compounds (VOCs), and carbonyls. Additional methods for the SET characterization have been previously published (Fedak et al. 2019).

Questionnaires and potential confounders

A questionnaire was administered during the initial study session to collect information on participant demographic characteristics such as race/ethnicity. Additional questionnaires were administered prior to the baseline and 24-hour follow-up health assessments during each study session to collect information on potential confounding variables. Participants self-reported frequency of alcohol and caffeine consumption, exposures to smoke and ambient air pollution, medication use, physical activity, and sleep quality during the 24 hours leading up to the study session and for the period between the 3-hour post and 24-hour post health assessments when participants were away from the testing facility. Participants also self-reported mode of travel to the study facility. Hourly ambient temperature and $PM_{2.5}$ concentrations were assessed as potential confounding factors in the analyses. $PM_{2.5}$ data were downloaded from the U.S. EPA's Air Quality Data API monitor in Fort Collins, Colorado (U.S. Environmental Protection Agency 2018), and ambient temperature data were downloaded from Colorado State University Atmospheric Science Department's Christman Field Weather Station (Colorado State University 2018).

Statistical analysis

Data cleaning, descriptive statistics, and data visualization were performed in R version 3.5.0 (The R Project for Statistical Computing). We used the R package lme4 (Bates et al. 2015) to run linear mixed models.

Summary statistics (mean, standard deviation [sd], median, minimum, maximum) of participant baseline characteristics were calculated for the total population and by sex. For each treatment level, we estimated mean $PM_{2.5}$ and CO exposures for each participant by averaging

the $PM_{2.5}$ and CO levels over the 2-hour periods they were inside the SET facility. We then averaged across all participants for each treatment level to produce the summary statistics. Paired t-tests were run to compare mean pre-treatment values of PWV, AIx, and CPP prior to control with mean pre-treatment values prior to the cookstove treatments.

We used linear mixed models to assess differences in outcomes for each cookstove treatment compared to control at the three post-treatment time points (0, 3, and 24 hours). Models included a fixed categorical term for treatment level, a fixed continuous term for baseline outcome measurement, a random term for participant, and a random term for date of the treatment. We included the baseline term to account for variations in the outcomes between treatments levels at the beginning of each study session (i.e., variations unrelated to the treatments), the term for participant to account for repeated measures within each participant, and the term for date to account for correlation that may occur between participants who were part of the same study session. Terms for sequence and visit were not used in the statistical models for the primary analyses because we included out-of-sequence makeup visits in the primary dataset. Sensitivity analyses were performed on a subset of the data which participants completed in sequence; models in these analyses included terms for sequence and visit number. In addition, we conducted sensitivity analyses to assess for potential confounding by including questionnaire variables and ambient temperature and $PM_{2.5}$ concentrations during the 24 hours prior to each health assessment as covariates in the statistical models (see Appendix A for further details).

Diagnostic plots (i.e., QQ plots and residuals vs fitted values plots) were evaluated and met assumptions for linear models.

Results

Participants

Baseline characteristics for the study population are presented in Table 3.1. The 48 participants (26 males and 22 females) had a mean age at baseline of 28 years (sd = 4) and a

mean BMI at baseline of 23 kg/m^2 (sd = 2). The study population largely identified as non-Hispanic white (42/48 participants).

Table 3.1: Participant characteristics

Variable	All participants (n = 48)	Females (n = 22)	Males (n = 26)
	mean (sd), min, max		
Age at study start, years	27 (4), 21, 36	28 (3), 23, 34	27 (4), 21, 36
Body mass index at study start, kg/m^2	23 (2), 19, 29	23 (3), 20, 29	23 (2), 19, 26
Baseline* pulse wave velocity, m/s	6.0 (0.6), 4.8, 7.2	5.9 (0.6), 4.8, 7.1	6.1 (0.6), 4.8, 7.2
Baseline* augmentation index, %	8 (12), -31, 34	11 (14), -31, 34	5 (10), -12, 24
Baseline* central pulse pressure, mmHg	31 (5), 19, 46	30 (5), 19, 39	32 (6), 22, 46
	n (%)		
Non-Hispanic white ethnicity/race	42 (88)	18 (82)	24 (92)
Participants present for all 6 treatments+	39 (81)	19 (86)	20 (77)
Participants present for 5 or 6 treatments+	45 (94)	22 (100)	23 (88)

*Baseline means are the average values across all participants for the pre-treatment measurement of each participant's first study visit.
+Participant included if present for baseline health assessment, treatment, and at least one follow-up health assessment.
sd = standard deviation

Twenty-two of 48 participants completed all six treatments in their assigned sequence; missed sessions were typically due to illness or unforeseen scheduling conflicts. Including out-of-sequence makeup sessions, 45 of 48 participants completed at least five of the treatments and 39 of 48 participants completed all six treatments. Three participants dropped out of the study for personal reasons after two sessions (one participant) and three sessions (two participants); the sessions they completed were included in primary analyses. Including additional missing observations due to technical reasons or scheduling conflicts, total missing data was 6.3% for PWV and 6.9% for AIx and CPP.

Controlled treatments

$PM_{2.5}$ exposure concentrations experienced by the participants were generally close to the targets (Table 3.2). The mean percent differences from the target $PM_{2.5}$ level for the fan rocket,

rocket elbow, and three stone fire cookstove treatments were all less than 9%. The mean percent differences from the target $PM_{2.5}$ level for the gasifier and LPG cookstove treatments were 31% and 18%, respectively, which equate to concentrations that were 11 $\mu g/m^3$ higher than the target value of 35 $\mu g/m^3$ for the gasifier treatment and 2 $\mu g/m^3$ lower than the target value of 10 $\mu g/m^3$ for the LPG treatment (Table 3.2). The mean $PM_{2.5}$ concentration for the control treatment was less than 1 $\mu g/m^3$ (target concentration of 0 $\mu g/m^3$). Mean CO mixing ratios within the SET facility were less than 10 ppm for all treatments and generally increased as target $PM_{2.5}$ concentrations increased (Table 3.2).

Concentrations of additional pollutants measured in the SET characterization analysis generally increased as treatment $PM_{2.5}$ target concentrations increased. Further results from the SET characterization have been previously published (Fedak et al. 2019).

Health outcomes

Mean baseline (i.e., pre-treatment) values for the health outcomes are presented in Table 3.1: mean PWV was 6.0 m/s (sd = 0.6), mean AIx was 7% (sd = 13), and mean CPP was 31 mmHg (sd = 5). There were small differences in baseline PWV and CPP between the treatments (Table A1). AIx also varied at baseline across the six treatments and had standard deviations as large as or larger in magnitude than the mean values. Based on paired t-tests between each cookstove treatment and control, only the baseline value of CPP for female participants prior to the rocket elbow cookstove treatment was significantly different (p-value < 0.05) from the baseline value prior to control (Table A1).

Linear mixed model estimates and 95% confidence intervals (CI) for the difference between each cookstove treatment compared to control at three post-treatment time points are presented in Table 3.3. At the immediate post-treatment and 3-hour post-treatment time points, differences for all cookstove treatments compared to control were generally consistent with a null association for all outcomes (Table 3.3; Figures 3.3-3.5). There were some exceptions to this trend, including higher PWV following the gasifier cookstove treatment at the 3-hour post-

Table 3.2: SET facility pollution concentrations compared to target levels of fine particulate matter

	Treatment					
	Control	**LPG**	**Gasifier**	**Fan rocket**	**Rocket elbow**	**Three stone fire**
	Fine particulate matter target concentration					
	0 µg/m^3	**10 µg/m^3**	**35 µg/m^3**	**100 µg/m^3**	**250 µg/m^3**	**500 µg/m^3**
Participants with completed treatment, n	47	45	44	44	45	47
Mean (sd) $PM_{2.5}$ concentration, µg/m^3	1 (2)	8 (3)	46 (9)	95 (9)	254 (9)	462 (41)
Mean difference from target level, µg/m^3	1	-2	11	-5	4	-38
Maximum difference from target level, µg/m^3	9	7	42	23	26	133
Mean percent difference from target level, %		-18	31	-5	2	-8
Mean (sd) CO mixing ratio*, ppm	2 (2)	3 (1)	5 (3)	8 (2)	6 (2)	9 (4)

SET = Simulated Environmental Testing; LPG = liquefied petroleum gas; sd = standard deviation; CO = carbon monoxide
*CO did not have a target level. This row is showing the measured mean CO mixing ratio for each treatment.

Table 3.3: Differences in health outcomes following cookstove treatments compared to control at three post-treatment time points using linear mixed models

Health measurement time point	Treatment					
	Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone fire
	Pulse wave velocity (m/s)					
	Mean (sd)	Difference compared to control (95% confidence interval)				
0-hour post-treatment	6.16 (0.69)	0.02 (-0.16, 0.21)	0.08 (-0.11, 0.26)	-0.06 (-0.25, 0.12)	-0.07 (-0.25, 0.11)	-0.11 (-0.29, 0.07)
3-hour post-treatment	6.05 (0.81)	-0.04 (-0.22, 0.14)	0.18 (0.01, 0.36)	-0.04 (-0.21, 0.14)	0.06 (-0.12, 0.24)	0.00 (-0.17, 0.18)
24-hour post-treatment	5.90 (0.64)	0.15 (-0.02, 0.32)	0.16 (-0.01, 0.33)	0.09 (-0.08, 0.26)	0.08 (-0.08, 0.25)	0.15 (-0.02, 0.31)
	Augmentation index (%)					
	Mean (sd)	Difference compared to control (95% confidence interval)				
0-hour post-treatment	10.5 (10.8)	-0.6 (-3.7, 2.4)	-2.5 (-5.5, 0.6)	0.0 (-3.1, 3.1)	-0.4 (-3.4, 2.6)	0.7 (-2.3, 3.7)
3-hour post-treatment	4.9 (8.5)	0.0 (-3.3, 3.2)	0.6 (-2.7, 3.8)	1.6 (-1.7, 4.9)	0.8 (-2.5, 4.0)	2.9 (-0.4, 6.1)
24-hour post-treatment	10.8 (9.3)	-1.1 (-4.3, 2.2)	0.6 (-2.7, 3.9)	0.3 (-3.0, 3.6)	-0.6 (-3.8, 2.6)	-1.5 (-4.7, 1.8)
	Central pulse pressure (mmHg)					
	Mean (sd)	Difference compared to control (95% Confidence Interval)				
0-hour post-treatment	32.6 (5.1)	0.0 (-1.4, 1.5)	-1.1 (-2.6, 0.4)	-0.1 (-1.6, 1.4)	-0.6 (-2.0, 0.9)	-0.9 (-2.4, 0.6)
3-hour post-treatment	31.5 (4.8)	0.5 (-1.0, 1.9)	0.3 (-1.2, 1.8)	-0.5 (-2.0, 1.0)	-0.3 (-1.8, 1.2)	-0.6 (-2.0, 0.9)
24-hour post-treatment	31.1 (5.5)	1.3 (-0.2, 2.7)	1.5 (0.0, 3.0)	1.6 (0.1, 3.0)	1.0 (-0.5, 2.4)	0.6 (-0.8, 2.1)

LPG = liquefied petroleum gas; sd = standard deviation

Model terms include cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

treatment time point (0.18 m/s; 95% CI: 0.01, 0.36). AIx was higher at the 3-hour post-treatment time point following the three stone fire cookstove treatment (2.9%; 95% CI: -0.4, 6.1), and lower at the immediate post-treatment time point following the gasifier cookstove treatment (-2.5%; 95% CI: -5.5, 0.6). CPP was between 0.1 and 1.1 mmHg lower at the immediate-post treatment time point for the four highest cookstove treatments compared to control (Table 3.3; Figure 3.5).

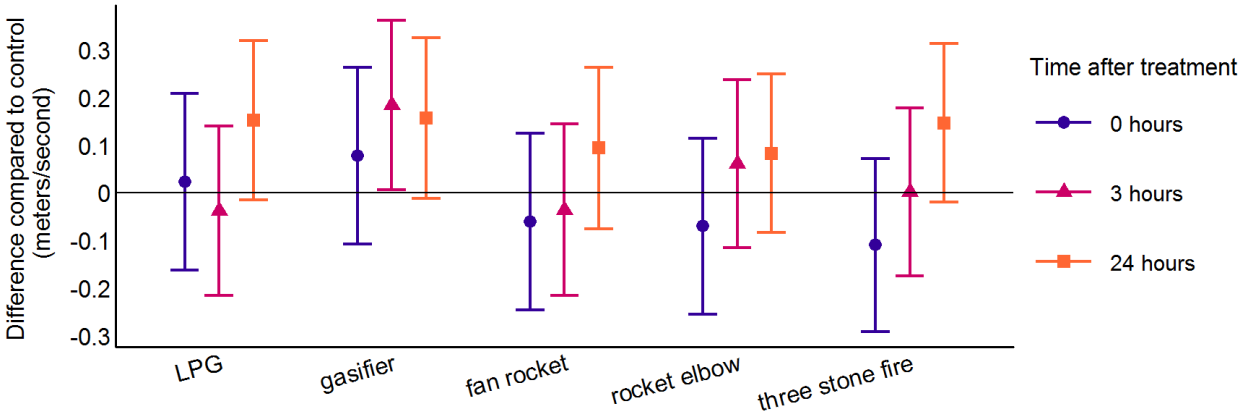

Figure 3.3: Differences in pulse wave velocity for each cookstove treatment compared to control at the three post-treatment time points using linear mixed models
LPG = liquefied petroleum gas
Model terms include cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

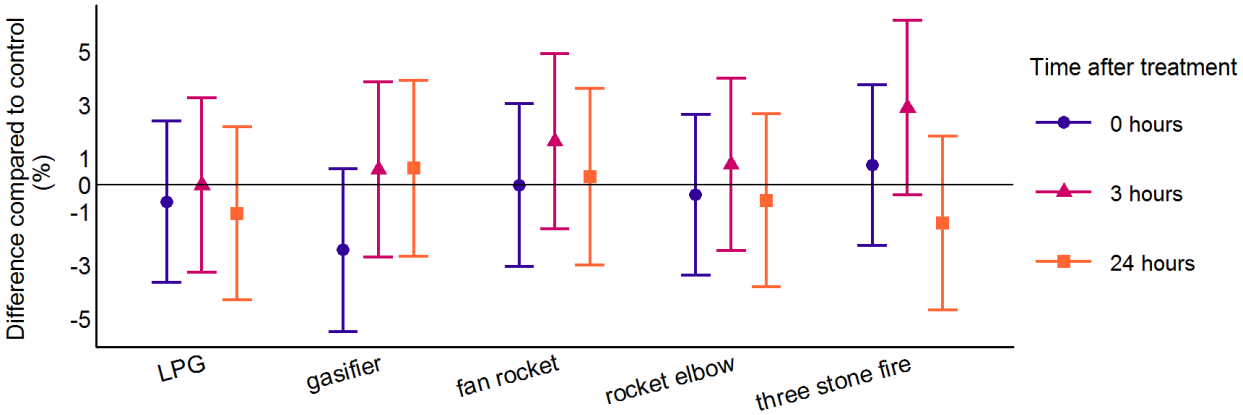

Figure 3.4: Differences in augmentation index for each cookstove treatment compared to control at the three post-treatment time points using linear mixed models
LPG = liquefied petroleum gas
Model terms include cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

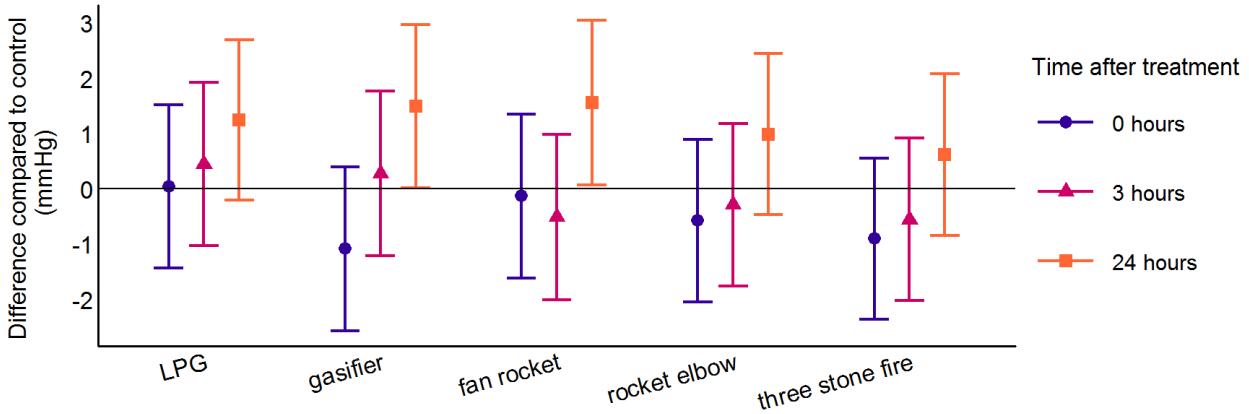

Figure 3.5: Differences in central pulse pressure for each cookstove treatment compared to control at the three post-treatment time points using linear mixed models
LPG = liquefied petroleum gas
Model terms include cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

PWV and CPP were higher 24 hours after all cookstove treatments compared to control (Table 3.3, Figures 3.3 and 3.5). The magnitude of the differences compared to control was similar across all cookstove treatments. Differences compared to control for PWV were between 0.08 and 0.16 m/s and differences compared to control for CPP were between 0.6 and 1.6 mmHg. Highlighting results following the treatments with the lowest and highest target $PM_{2.5}$ concentrations (LPG and three stone fire), PWV was 0.15 m/s higher (95% CI: -0.02, 0.31) 24 hours after the three stone fire cookstove treatment and 0.15 m/s higher (95% CI: -0.02, 0.32)

24 hours after the LPG cookstove treatment compared to control. CPP was 0.6 mmHg higher (95% CI: -0.8, 2.1) 24 hours after the three stone fire cookstove treatment and 1.3 mmHg higher (95% CI: -0.2, 2.7) 24 hours after the LPG cookstove treatment compared to control. Differences compared to control for AIx at the 24-hour post-treatment time point were consistent with a null association for all cookstove treatment levels (Table 3.3; Figure 3.4).

Results from sensitivity analyses are presented in Appendix A. None of the sensitivity analyses or inclusion of potential confounders resulted in meaningfully different model estimates compared to the primary model estimates presented in Table 3.3 and Figures 3.3-3.5.

Discussion

In the first study to assess the health impacts of air pollution emitted from multiple cookstove technologies using a crossover design, our results suggest that PWV and CPP were marginally higher 24 hours after the cookstove treatments compared to a filtered air control. PWV was between 0.08 and 0.16 m/s higher for each cookstove treatment compared to control at the 24-hour post-treatment time point; CPP was between 0.6 and 1.6 mmHg higher for each cookstove treatment compared to control at the same time point. There were no trends of higher or lower values across the cookstove treatment levels for AIx at any post-treatment time point. Our study design had strong internal validity that limited the impact of potential confounders, as confirmed by multiple sensitivity analyses.

Our results add to the small body of evidence that household air pollution can adversely impact central hemodynamics and arterial stiffness. Our study is the first to assess outcomes of central hemodynamics and arterial stiffness following controlled exposures to cookstove-generated air pollution; a study in China is the only study to date to evaluate this association in a field setting (Baumgartner et al. 2018). Among 205 women in the study in China, increased $PM_{2.5}$ exposures (1-ln $\mu g/m^3$) were associated with 1.1 percentage points higher AIx (95% CI: -0.2, 2.4) (Baumgartner et al. 2018). Among 102 women aged 50 years or more, increased $PM_{2.5}$ exposures were associated with 2.9 mmHg higher CPP (95% CI: 0.8, 5.1) (Baumgartner et al. 2018). After 1.5 years of follow-up, however, the authors reported that a government sponsored semi-gasifier cookstove intervention did not improve hemodynamic outcomes compared to control participants, likely due to other improved cookstove adoption in the control group (Clark et al. 2019). Other studies have found associations between PWV and AIx and particulate and gaseous air pollution from ambient sources (Zanoli et al. 2017). Our results add further consistency that air pollution in general, and specifically household air pollution, can adversely impact markers of central hemodynamics and arterial stiffness.

Central hemodynamic indices and measures of arterial stiffness are strongly associated with future cardiovascular events and all-cause mortality (Vlachopoulos et al. 2010a; Vlachopoulos et al. 2010b). Measures of central hemodynamics are pathophysiologically more relevant than peripheral indices because central pressures are a better indicator of cardiac workload and overall cardiovascular health (Vlachopoulos et al. 2010a). In a meta-analysis of longitudinal studies, Vlachopoulos et al. found that AIx predicts clinical events independently of peripheral blood pressure, and that CPP predicts clinical events better than peripheral pulse pressure (Vlachopoulos et al. 2010a). Numerous studies have shown the importance of PWV as an indicator of arterial stiffness and a predictor of future cardiovascular events and all-cause mortality (Townsend et al. 2015; Vlachopoulos et al. 2010b).

Potential biological pathways initiated by $PM_{2.5}$ exposure could help explain the higher values of PWV and CPP we observed 24 hours after each cookstove treatment. Inflammatory and oxidative stress pathways can be initiated within 24 hours after exposure to $PM_{2.5}$ (Brook et al. 2010). Inflammatory cytokines and reactive oxygen species can cause an increase in vascular smooth muscle tone through endothelial dysfunction and reduced nitric oxide bioavailability (Huang and Vita 2006; Sprague and Khalil 2009). Higher vascular smooth muscle tone can lead to increased arterial stiffness and higher PWV and CPP (Avolio et al. 2011; Townsend et al. 2015). These same pathways could also influence AIx; however, changes in PWV and AIx can occur independently depending on which region of the arterial tree is most impacted by the exposure or stimulus of interest (Kelly et al. 2001). It is possible that the cookstove air pollution in our study impacted the vascular smooth muscle tone of the larger arteries more than the smaller, distal arterioles. It is also possible that AIx was impacted on a different timeframe than PWV and CPP so that changes in AIx were not captured at any of the three post-treatment time points in our study. In addition, AIx is a more complex measurement than PWV and can be influenced by a variety of factors within the arterial tree (Tomiyama and Yamashina 2010). This complexity may be expressed in our results in the large standard

deviations that indicate high variability in the AIx measurements (Table 3.1 and Table A1). Since our study was powered based on other outcomes not reported here, it is possible that the high variability of AIx resulted in limited ability to detect changes in our statistical models.

Assessing short-term exposures and acute health outcomes in a group of young, healthy, and largely non-Hispanic white participants means that our results are not directly applicable to real-world cookstove users who are exposed repeatedly over the course of a lifetime. While generalizability is a weakness, the study setting allowed us to assess complex health outcomes resulting from exposures to pollution from multiple cookstove technologies in a controlled environment. This gives us a better understanding of the underlying acute differences in health resulting from household air pollution exposure. The strength of the crossover design also gave our study results high internal validity. For example, some potential confounding factors may have varied across study days (e.g., ambient air pollution); however, these factors were unlikely to be associated with the individual treatments and were, therefore, unlikely to confound the observed associations. Regardless, we performed numerous sensitivity analyses that included potential confounders as covariates, yet no meaningful differences from the primary analyses were observed (see Appendix A). In addition, inclusion of the baseline health outcome values and the date of the study sessions in the analyses helped account for potential confounders that may have varied at random between study days. Further, assessing differences within person in the mixed models helped control for potential time-invariant confounding variables such as participant sex.

Logistically, all 48 study participants could not experience each treatment simultaneously and exposures could not be held perfectly at target levels; this means that groups of participants experienced different levels of exposure to air pollution for the same cookstove treatment. However, our data indicate that each participant was exposed to $PM_{2.5}$ levels that were near target levels (Table 3.2), and that there was very little overlap in $PM_{2.5}$ levels when assessing each individual's personal mean exposure for each treatment level (see Figure A1). Our close

control over pollution levels inside the SET facility should have minimized an impact on our reported results from overlapping treatment levels.

Our results indicate that each cookstove treatment (compared to control) had a similar effect on PWV and CPP even though the $PM_{2.5}$ target concentrations for the cookstove treatments ranged from 10 to 500 $\mu g/m^3$. In an attempt to explain these unexpected findings, we characterized additional pollutants for each treatment (i.e., $PM_{2.5}$ mass, particle number size distributions (10 nm to 500 nm), $PM_{2.5}$ elemental and organic carbon, nitrogen oxide, nitrogen dioxide, VOCs, and carbonyls); results from the additional pollutant characterization have been published previously (Fedak et al. 2019). We found that none of the pollutants we measured explained the similar effect each treatment had on PWV and CPP. For example, $PM_{2.5}$ mass, particle numbers, concentrations of carbonyls, VOC levels, and concentrations of elemental and organic carbon generally increased as $PM_{2.5}$ target levels for each treatment increased. An exception to these trends was the LPG treatment, which had higher concentrations of carbonyls than both the gasifier and fan rocket treatments and the highest number of particles in the 10 to 30nm range out of any treatment. Additionally, while each cookstove treatment had higher levels of nitrogen oxide than control, levels for the fan rocket and rocket elbow treatments were several times higher than the other cookstove treatments. Finally, each treatment emitted similar levels of nitrogen dioxide. These results provide no clear evidence that any single pollutant was associated with the changes in PWV and CPP we observed in our results. It is possible that the complex nature of pollutants emitted from the cookstoves resulted in mixtures of pollution that impacted the health outcomes in a similar magnitude, or that the range of exposures experienced during the 2-hour treatments was not large enough to lead to detectable differences in the magnitude of the changes in PWV and CPP. Multipollutant characterization of a wider range of exposures in future studies may help provide clarity to these lingering uncertainties.

An alternative explanation for our findings is that the filtered air control treatment was beneficial for the health outcomes we measured as opposed to the cookstove treatments being detrimental. Since the control treatment was the reference level in our analysis, it may have given the appearance that the cookstove treatments each had a similar adverse impact on PWV and CPP, when in fact, it was the control treatment that had a beneficial impact. Air filter intervention studies have been conducted and found associations between air filtration and improved endothelial function and inflammatory markers (Allen et al. 2011), as well as improved blood pressure and stress hormones (Li et al. 2017). While these previous studies were designed to assess the impact of air filtration in real-world settings, as compared to our study in a laboratory setting, they do provide evidence of the potential health benefits of breathing filtered air. Future studies that incorporate an additional treatment of ambient air into a design similar to ours could help clarify whether the cookstove treatments or the filtered air treatments were driving the differences in PWV and CPP we observed in our study.

In analyses published separately, we also observed higher brachial systolic blood pressure following the cookstove treatments compared to control (Fedak et al. 2019), giving a broader context and adding consistency to the results presented here. While these results may not be relevant for people exposed to air pollution emitted from indoor cookstoves over a lifetime, our findings are still informative for a number of reasons. Repeated exposures to air pollution experienced in real-world settings may result in a chronic, underlying environment in which cardiovascular disease can manifest (Brook et al. 2010). In addition, individuals with existing cardiovascular disease may be more susceptible to clinically meaningful adverse cardiovascular events as a result of acute exposures to air pollution (Brook et al. 2010). Our results may be indicative of such subclinical, underlying changes in health. Although the differences we observed were small and may not be clinically meaningful, the similar magnitude of the differences following each cookstove treatment compared to control may indicate that acute exposures from even the cleanest cookstove technologies can adversely impact these

subclinical markers of cardiovascular health. Further research is necessary to help us understand if cookstove technology is capable of reducing household air pollution exposures enough to improve long term health.

Conclusion

Our results from a controlled exposure study with a crossover design are an important contribution to understanding the cardiovascular health effects resulting from exposure to household air pollution. Our findings suggest higher levels of PWV and CPP within 24 hours after 2-hour treatments to pollution from five different cookstove technologies. The similar differences in PWV and CPP we observed following each cookstove treatment compared to control may indicate that acute exposures from even the cleanest cookstove technologies can elicit adverse responses in markers of central hemodynamics and arterial stiffness. We recommend that future analyses also consider biomarkers that may be indicative of potential biological mechanisms.

CHAPTER 4: ACUTE DIFFERENCES IN BLOOD LIPIDS FOLLOWING CONTROLLED EXPOSURES TO COOKSTOVE AIR POLLUTION IN THE SUBCLINICAL TESTS OF VOLUNTEERS EXPOSED TO SMOKE (STOVES) STUDY

Summary

Household air pollution, which occurs primarily from solid fuel combustion for cooking, is a leading environmental risk factor for morbidity and mortality. Numerous cookstoves have been developed to reduce household air pollution exposures, but whether such "improved" cookstoves meaningfully improve health remains unclear. In a controlled exposure study with a crossover design, we assessed the effect of pollution from multiple cookstoves on acute differences in blood lipids (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglycerides).

Participants (n=48) were assigned to sequences of six 2-hour controlled treatments of pollution from five cookstoves and a filtered air control. Treatments had unique fine particulate matter target concentrations ($\mu g/m^3$): control (0); liquefied petroleum gas (10); gasifier (35); fan rocket (100); rocket elbow (250); three stone fire (500). Non-fasting lipids were measured before and 0, 3, and 24 hours after treatments. Linear mixed models were used to assess differences in outcomes for treatments versus control.

Results suggest no meaningful differences between treatments and control for total cholesterol, HDL, and LDL across post-treatment time points. Triglycerides were elevated at 24 hours following all cookstove treatments versus control (albeit with wide confidence intervals), except for the rocket elbow, which was similar to control. For example, 24 hours after the three stone fire treatment, the difference compared to control for triglycerides was 12.1% (95% confidence interval: -0.5, 26.2). There were no apparent differences for triglycerides at other post-treatment time points.

Our results suggest that short-term controlled exposures to cookstove air pollution may increase triglycerides within 24 hours.

Introduction

Nearly 3 billion people burn solid fuels to meet their household cooking needs (Bonjour et al. 2013). Exposure to fine particulate matter air pollution ($PM_{2.5}$; particles less than 2.5 micrometers in aerodynamic diameter) from the use of solid cooking fuels resulted in an estimated 1.6 million premature deaths in 2017; approximately 40% of these premature deaths were a result of cardiovascular outcomes such as ischemic heart disease and stroke (Stanaway et al. 2018). Many interventions have been attempted to lower this disease burden using various types of improved cookstoves. While some interventions succeed in reducing levels of household air pollution, whether these reductions lead to improved health outcomes remains unclear (Bruce et al. 2015; Quansah et al. 2017).

Literature suggests that household air pollution exposure is adversely associated with a number of cardiovascular outcomes such as blood pressure, endothelial function, heart rate variability, and biomarkers of inflammation and oxidative stress (Fatmi and Coggon 2016; McCracken et al. 2012). However, assessing household air pollution and health in real-world settings is inherently challenging due to the logistical difficulties and overall cost of performing quality health and exposure measurements in the field (Balakrishnan et al. 2014; Clark et al. 2013b). As a result, many of the studies that have assessed household air pollution and cardiovascular health have been observational in nature, with designs that are subject to confounding and exposure misclassification (Fatmi and Coggon 2016; McCracken et al. 2012). Additional research that improves upon previous study designs while assessing relevant cardiovascular health outcomes is needed to enhance our understanding of the cardiovascular health impacts of household air pollution.

Blood lipids such as total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides are important markers to assess within the scope of

household air pollution because of their role in the development of atherosclerosis and advanced cardiovascular disease (Bai and Sun 2016). Only one study to date has assessed household air pollution and blood lipids; no associations were observed between household air pollution exposures and total cholesterol, HDL, LDL, and triglycerides in primary household cooks in rural Honduras (Rajkumar et al. 2019). However, this observational field study was cross-sectional, and factors such as residual confounding and exposure misclassification may have impacted the results (Rajkumar et al. 2019). Studies assessing ambient air pollution and blood lipids have been more common and have observed that higher concentrations of long term exposure to ambient particulate matter are associated with lower HDL (Bell et al. 2017; Chuang et al. 2010; Yang et al. 2018; Yitshak Sade et al. 2016), higher triglycerides (Chuang et al. 2010; Shanley et al. 2016; Yang et al. 2018; Yeatts et al. 2007; Yitshak Sade et al. 2016), higher total cholesterol (Shanley et al. 2016; Yang et al. 2018), and higher LDL (Yang et al. 2018; Yitshak Sade et al. 2016). Studies assessing the impact of controlled exposures to ambient air pollution on blood lipids have also been conducted, although results are conflicting. Both higher and lower levels of triglycerides and very low-density lipoprotein have been reported immediately following exposures to concentration air pollution particles compared to filtered air (Samet et al. 2009; Tong et al. 2012). Others have reported higher levels of total cholesterol and HDL 18 hours after controlled exposures to nitrogen dioxide compared to filtered air (Huang et al. 2012). While these studies demonstrate an association between ambient air pollution and blood lipids, there may be compositional differences between ambient and cookstove-emitted air pollution (Naeher et al. 2007) that lead to differential impacts on blood lipids. Further research is needed to understand how household air pollution impacts blood lipids.

In a controlled human exposure study referred to as the Subclinical Tests on Volunteers Exposed to Smoke (SToVES) Study, we assessed the impact of short-term exposures to multiple levels of cookstove air pollution on acute differences in total cholesterol, HDL, LDL, and triglycerides compared to a filtered air exposure. Our study adds to the limited body of research

assessing household air pollution and blood lipids by implementing a crossover study design with high internal validity to assess the impact of multiple types of cookstove technologies on cardiovascular and pulmonary health outcomes. Other outcomes from the SToVES Study are reported separately (Fedak et al. 2019).

Methods

Study design

A description of the study design and methods has been published previously (Fedak et al. 2019). The crossover design included six sequences of six treatments to air pollution emitted from cookstoves that made up a 6x6 Latin square (Figure 4.1). The 2-hour treatments consisted of air pollution emitted from any one of five cookstove technologies or a filtered air control; each treatment had a target level of $PM_{2.5}$. The 48 participants were divided into three phases (n=16 per phase). Participants within a phase were divided into two groups of eight participants, and each group was assigned to a unique sequence of the six treatments with a two-week washout period between treatments. Individuals within each group of eight participants received the treatments during the same calendar week; they were further divided into groups of four participants who received the treatments during the same study session. Participants were allowed to return for out-of-sequence makeup sessions if they missed a scheduled session.

Participants and recruitment process

Participants (n=48) were recruited from Fort Collins, Colorado beginning in September of 2016. Eligibility criteria at the time of recruitment included age less than 36 years, body mass index (BMI) between 18 and 29 kg/m^2, never-smoker, no regular air pollution exposure (above ambient levels), no history of chronic disease, no recent surgery or cancer diagnosis, no claustrophobia or fear of needles, not pregnant/breastfeeding or planning on becoming pregnant during the study, and the ability to refrain from medication use (prescription and over-the-counter). Participants who passed eligibility screening completed a health assessment

conducted by a cardiologist to rule out current or family history of cardiovascular or pulmonary disease.

All study procedures were approved by the Institutional Review Board at Colorado State University. Participants provided written consent for all study procedures.

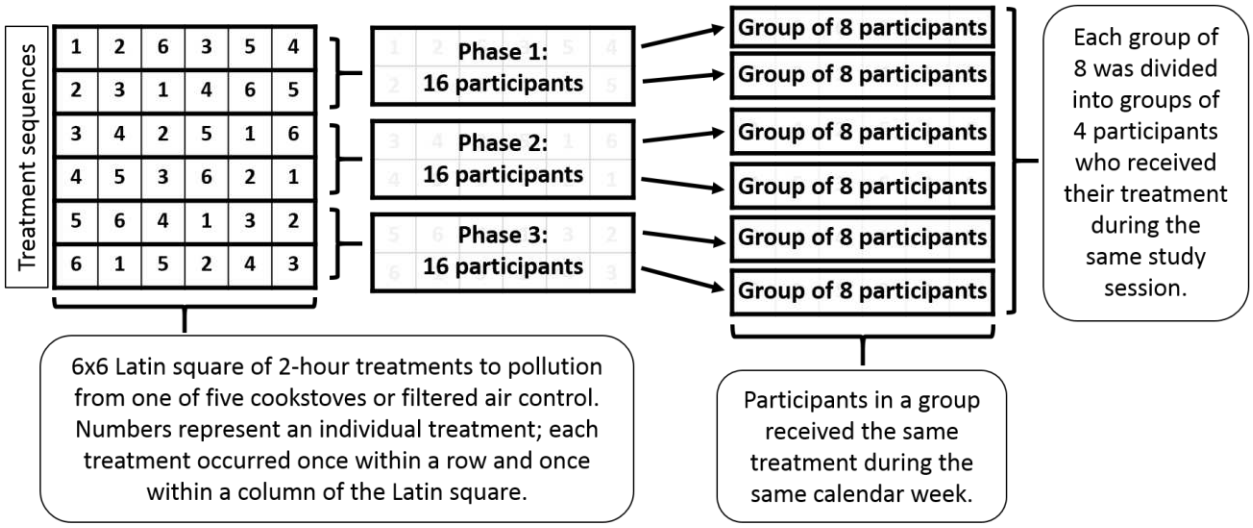

Figure 4.1: SToVES Study design

Study sessions

Each study session consisted of a 2-day period where four participants underwent a common assigned treatment and four separate health assessments (Figure 4.2). In relation to the treatment, the health assessments took place at baseline (pre-treatment), 0 hours post-, 3 hours post-, and 24 hours post-treatment. Participants arrived at the study facility staggered by 30 minutes, beginning at 7:30am. After arrival, participants were assessed by a cardiologist to ensure they were not sick or suffering an inflammatory or allergic reaction. Once approved to participate in the study session, the baseline health assessment was performed and followed immediately by the assigned 2-hour treatment. Following the treatment, the 0-hour post-treatment health assessment was performed. Participants remained in the testing facility building between the 0-hour and 3-hour post-treatment health assessments. Following the 3-

hour post-treatment health assessment, participants left the testing facility overnight before returning the next day for the 24-hour post-treatment health assessment.

Since diet can impact non-fasting blood lipids (Langsted and Nordestgaard 2019), we asked participants to eat a consistent, low-fat diet and refrain from alcohol and caffeine during the 24 hours leading up to each study session and lasting until after the 24-hour post-treatment health assessment. To encourage consistency in diet while participants were at the testing facility, we provided a healthy lunch after the 0-hour post-treatment health assessment that was consistent across all study sessions. Although abstaining from medication use was part of the study eligibility criteria, certain medications were approved by the study physician on a case-by-case basis (e.g., oral contraceptives); participants were asked to refrain from using unapproved medications starting 72 hours prior to each study session until after the 24-hour post-treatment health assessment.

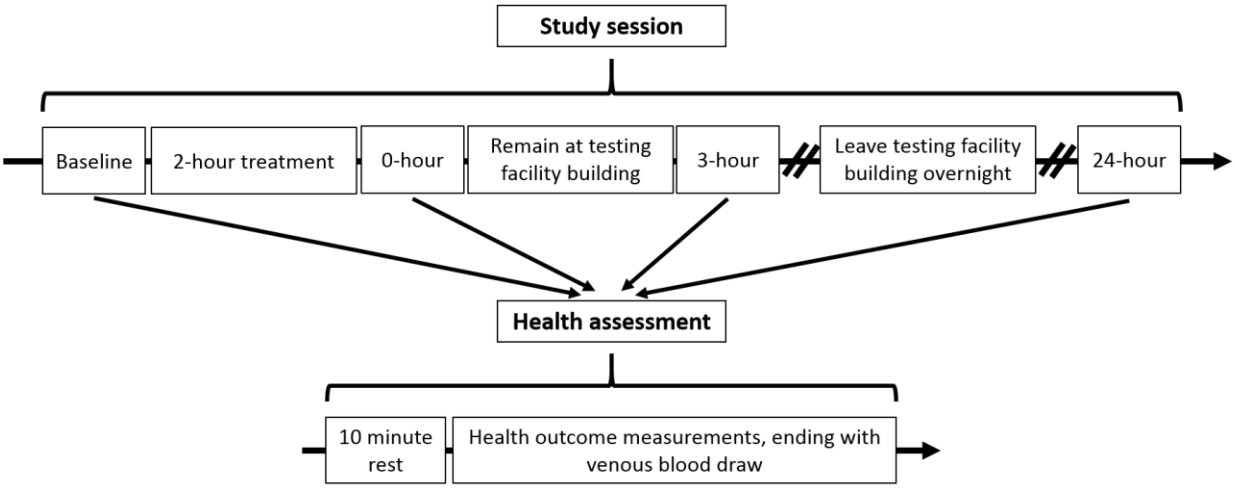

Figure 4.2: SToVES Study session sequence of events

Health assessments and study outcomes

Participants completed a series of health measurements following a 10 minute rest period in supine position (Figure 4.2). Blood samples were collected via venipuncture at the end of each health assessment by a trained phlebotomist. Samples were collected into SST tubes (BD Diagnostics, USA), inverted 5 times, allowed to clot for at least 30 minutes, and then

centrifuged for 10 minutes at 1300 relative centrifugal force (Model MP4R, International Equipment Company, USA) to separate the serum from the clot. Samples were then left at room temperature and collected at the end of the study day by a local laboratory for analysis (Cobas 8000, Roche Diagnostics, USA).

Height and weight were measured once at enrollment and used to calculate BMI (kg/m^2).

Controlled exposure treatments

Treatments were administered on campus at Colorado State University using a controlled exposure facility called the Simulated Environmental Testing (SET) facility. A registered nurse monitored participants continuously as the treatments were administered to ensure participant well-being; nursing staff also remotely (i.e., without entering the SET) measured and monitored participant blood pressure, heart rate, and oxygen saturation every 15 minutes throughout the treatments. Participants could communicate with the nursing staff via text message or intercom.

The six controlled treatments (with $PM_{2.5}$ target levels) included filtered air control (0 $\mu g/m^3$), liquefied petroleum gas (LPG; 10 $\mu g/m^3$), gasifier (35 $\mu g/m^3$; fuel of pine wood chips), forced-draft fan rocket elbow (100 $\mu g/m^3$; fuel of pine wood sticks), natural-draft rocket elbow (250 $\mu g/m^3$; fuel of pine wood sticks), and three stone fire (500 $\mu g/m^3$; fuel of pine wood sticks). Details on the SET facility operation have been published previously (Fedak et al. 2019). Briefly, study personnel operated the cookstoves in a total-capture fume hood (located adjacent to the SET) during the treatments. Emissions were drawn from the fume hood, mixed with high efficiency particulate air (HEPA) filtered air to reach the target concentration for each respective treatment, and then directed into the SET through a mixing plenum. Flow of dilution and pollution air were automated to keep $PM_{2.5}$ concentrations in the SET near target values using a dynamic control system (LabVIEW™, v15.0 32-bit, National Instruments, USA). $PM_{2.5}$ (DustTrak DRX 8533, TSI Incorporated, USA), carbon monoxide and oxygen (Siemens Ultramat 6E gas analyzer, Siemens AG, Germany), and humidity and temperature (Omega HX94BC transmitter

and Type K thermocouple, OMEGA Engineering, USA) were monitored in real time within the SET facility during the controlled treatments.

We characterized additional pollutant concentrations ($PM_{2.5}$ mass, particle number size distributions [10 nm to 500 nm], $PM_{2.5}$ elemental and organic carbon, nitrogen oxide, nitrogen dioxide, and carbonyls) inside the SET facility for each of the six treatments. Detailed methods and results for the additional pollutant characterization are published elsewhere (Fedak et al. 2019).

Questionnaires and potential confounders

We administered a questionnaire during each participant's first study session to collect demographic information. We administered additional questionnaires during each study session to collect information on potential confounders. Prior to the baseline health assessment, participants were asked to report their mode of transportation to the study facility, as well as frequency of alcohol and caffeine consumption, smoke exposures, medication use, physical activity, and sleep quality during the previous 24 hours. Participants answered the same questionnaire prior to the 24-hour post-treatment health assessment regarding the period between the 3-hour post- and 24-hour post-treatment health assessments. Additional questions prompted participants to record their dietary intake during the morning prior to the baseline and 24-hour post-treatment health assessments. In addition to the self-reported activities on the questionnaires, ambient temperature and $PM_{2.5}$ were considered as potential confounders (Colorado State University 2018; U.S. Environmental Protection Agency 2018).

Statistical analysis

We used R version 3.5.0 (The R Project for Statistical Computing) for data cleaning, visualization, and analysis. Individual mean $PM_{2.5}$ concentrations and carbon monoxide mixing ratios were calculated by averaging the concentrations/mixing ratios for each 2-hour treatment completed by each participant. We then used average concentrations/mixing ratios across all participants for each treatment to summarize pollutant levels over the duration of the study. We

ran paired t-tests comparing mean pre-treatment values of total cholesterol, LDL, HDL, and triglycerides prior to control with mean pre-treatment values prior to each cookstove treatment. Self-reported dietary consumption the morning of each study day for each participant was assessed for frequency of high-fat or high-cholesterol items (e.g., red meats, fried foods, eggs, and cheese). In addition, consistency of breakfast food items consumed prior to each study day across all study visits was evaluated for each participant; participants were considered to have eaten consistently across the study visits if they ate similar types and quantities of food groups (e.g., grains, dairy, fruits, meats, and eggs) prior to each visit.

We used the lme4 (Bates et al. 2015) and lmerTest (Kuznetsova et al. 2017) packages to fit linear mixed models to our data. Our analyses using linear mixed models included a fixed categorical term for treatment, a fixed continuous term for baseline outcome measurement, a random term for participant, and a random term for date of the treatment. We used separate models for each outcome and each post-treatment time point (0, 3, and 24 hours) to assess differences in the outcomes for each cookstove treatment compared to control. The fixed term for baseline (pre-treatment) measurement of the outcomes was included in the models to account for outcome variations at the beginning of each study day that were unrelated to the treatments. The random term for participant was included to account for correlation of the repeated measures within each participant. The term for date of the health measurement was included in the models to account for potential correlation between participants who were part of the same study session. To allow us to use out-of-sequence makeup visits in the primary dataset, additional terms from the Latin square for sequence and visit number were not used in the primary analyses.

We performed sensitivity analyses using a dataset that did not include out-of-sequence makeup visits. These analyses used the Latin square terms for sequence and visit as additional terms in the models. We also conducted additional sensitivity analyses that included potential confounders (questionnaire variables and ambient temperature and $PM_{2.5}$) as covariates.

Further details on sensitivity analyses are available in Appendix B. Diagnostic plots (i.e., QQ plots and residuals vs fitted values plots) were evaluated for all models to determine if linear model assumptions were met.

Results

Participants

Baseline characteristics for the study participants (n = 48; 26 males and 22 females) are presented in Table 4.1. Participants largely identified as non-Hispanic white (42/48 participants) and were generally students or young professionals from Colorado State University. Participants had mean age at baseline of 28 years (sd = 4) and mean BMI at baseline of 23 kg/m^2 (sd = 2). Participants self-reported eating higher fat and cholesterol food items (e.g., red meats, fried foods, eggs, and cheese) for breakfast prior to 30% of the study days; the distribution of these food items was generally consistent across the treatment levels (Table B2). The evaluation of consistency in diet across the study visits indicated that half of the participants (24/48) generally ate a consistent breakfast prior to each study day.

Twenty-two of the 48 participants completed all six treatments in their assigned sequence. Missed sessions were typically due to illness or unplanned scheduling conflicts. Including out-of-sequence makeup sessions, 45 of 48 participants completed at least five of the treatments and 39 of 48 participants completed all six treatments. For personal reasons, two participants dropped out of the study after three sessions and one participant dropped out after two sessions; the sessions they completed were included in analyses. Overall, the missing data rate was 6.8% for blood lipids after accounting for missing observations due to blood collection and lab processing errors or participant scheduling conflicts.

Controlled exposure treatments

Concentrations of $PM_{2.5}$ and carbon monoxide mixing ratios measured in the SET facility during treatments are presented in Table 4.2. Mean $PM_{2.5}$ exposure concentrations for each treatment were generally close to the target concentrations for the respective treatments. The

Table 4.1: Participant characteristics

Variable	All participants (n = 48)	Females (n = 22)	Males (n = 26)
	mean (sd), minimum, maximum		
Age at study start, years	28 (4), 21, 36	27 (3), 23, 33	28 (4), 21, 36
Body mass index at study start, kg/m^2	23 (2), 19, 29	23 (2), 20, 29	23 (2), 19, 26
Baseline* total cholesterol, mg/dL	170 (34), 91, 299	182 (37), 138, 299	159 (28), 91, 211
Baseline* high density lipoprotein, mg/dL	60 (14), 37, 93	66 (15), 46, 93	54 (11), 37, 80
Baseline* low density lipoprotein, mg/dL	87 (29), 30, 190	95 (32), 49, 190	79 (23), 30, 136
Baseline* triglycerides, mg/dL	120 (64), 43, 315	108 (61), 43, 275	130 (66), 54, 315
	n (%)		
Non-Hispanic white ethnicity/race	42 (88)	18 (82)	24 (92)
Participants with data for all 6 treatments+	39 (81)	19 (86)	20 (77)
Participants with data for 5 or 6 treatments+	45 (94)	22 (100)	23 (88)

*Baseline means represent averages across all participants for the pre-treatment measurement of each participant's first study visit.
+Participant included if present for baseline health assessment, treatment, and at least one follow-up health assessment. sd = standard deviation

three highest treatment levels of fan rocket, rocket elbow, and three stone fire had mean percent differences that were less than 9% from the target $PM_{2.5}$ concentrations. The two lowest cookstove treatment levels of gasifier and LPG had mean percent differences from the target $PM_{2.5}$ concentrations of 31% and 18%, respectively, which equated to concentrations that were 11 $\mu g/m^3$ higher than target values for the gasifier treatment and 2 $\mu g/m^3$ lower than target values for the LPG treatment (Table 4.2). The filtered air control treatment, which had a target concentration of 0 $\mu g/m^3$, had a mean $PM_{2.5}$ concentration of less than 1 $\mu g/m^3$. Carbon monoxide, which did not have a target level for each treatment, generally increased as target $PM_{2.5}$ concentrations increased and had mean mixing ratios of less than 10 ppm for each treatment (Table 4.2).

Concentrations of additional pollutants measured in the SET characterization analysis have been published previously (Fedak et al. 2019). In general, concentrations of the additional pollutants increased as $PM_{2.5}$ target concentrations for the treatments increased.

Blood lipids

Total cholesterol, LDL, and HDL met linear model assumptions evaluated by assessing QQ plots and residuals vs fitted-values plots. Triglycerides were natural log-transformed to meet model assumptions for linear regression. Thus, results for triglycerides are presented as percent changes for ease of interpretation.

Baseline values of total cholesterol, LDL, HDL, and triglycerides were within normal ranges for young, healthy adults (American College of Cardiology 2018). There were small baseline (i.e., pre-treatment) differences in the outcomes between the treatments (Table B1). Based on paired t-tests between each cookstove treatment and control, only the baseline value of HDL for female participants prior to the LPG and three stone fire treatments were significantly different (p-value < 0.05) from the baseline value prior to control (Table B1).

Model estimates and 95% confidence intervals (CI) for the difference between each treatment and control at the three post-treatment time points are presented in Table 4.3 and Figures 4.3-4.6. For total cholesterol and HDL, we observed no meaningful differences compared to control for all cookstove treatments at any post-treatment time point (Table 4.3; Figures 4.3 and 4.4), although some estimates were larger than others. For example, total cholesterol was lower (-3.1 mg/dL, 95% CI: -7.7, 1.4) and HDL was lower (-1.5 mg/dL, 95% CI: -3.5, 0.5) 24 hours after the gasifier treatment compared to control.

Results for LDL were also generally consistent with no meaningful differences compared to control at the 0-hour and 3-hour post-treatment time points (Table 4.3, Figure 4.5). LDL was marginally lower than control for all cookstove treatments at the 24-hour post-treatment time point, although differences were small and confidence intervals were wide. For example, at the

Table 4.2: SET facility 2-hour pollution concentrations compared to target levels of fine particulate matter

Treatment	Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone fire
$PM_{2.5}$ target concentration	**0 µg/m³**	**10 µg/m³**	**35 µg/m³**	**100 µg/m³**	**250 µg/m³**	**500 µg/m³**
Participants with completed treatment, n	47	45	44	44	45	47
Mean (sd) $PM_{2.5}$ concentration, µg/m³	1 (2)	8 (3)	46 (9)	95 (9)	254 (9)	462 (41)
Mean difference from target level, µg/m³	1	-2	11	-5	4	-38
Maximum difference from target level, µg/m³	9	7	42	23	26	133
Mean percent difference from target level, %		-18	31	-5	2	-8
Mean (sd) CO mixing ratio*, ppm	2 (2)	3 (1)	5 (3)	8 (2)	6 (2)	9 (4)

SET = Simulated Environmental Testing; LPG = liquefied petroleum gas; $PM_{2.5}$ = fine particulate matter; sd = standard deviation; CO = carbon monoxide

*CO did not have a target level; values represent the mean CO mixing ratio measured for each treatment.

Table 4.3: Differences in health outcomes following 2-hour cookstove treatments compared to control at three post-treatment time points using linear mixed models

Health measurement time point	Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone fire
	Total cholesterol (mg/dL)					
	Mean (sd)	**Difference compared to control (95% confidence interval)**				
0-hour post-treatment	171 (32)	0.9 (-2.1, 3.9)	0.0 (-3.0, 3.0)	1.5 (-1.5, 4.5)	-0.1 (-3.1, 2.9)	-0.7 (-3.7, 2.3)
3-hour post-treatment	172 (33)	2.0 (-0.7, 4.8)	-0.6 (-3.4, 2.2)	1.6 (-1.3, 4.4)	0.8 (-1.9, 3.6)	-1.2 (-3.9, 1.6)
24-hour post-treatment	170 (34)	0.8 (-3.7, 5.3)	-3.1 (-7.7, 1.4)	0.3 (-4.3, 4.8)	-0.5 (-5.0, 4.0)	-0.5 (-5.0, 4.0)
	High density lipoprotein (mg/dL)					
	Mean (sd)	**Difference compared to control (95% confidence interval)**				
0-hour post-treatment	60 (16)	0.5 (-0.8, 1.7)	-0.2 (-1.4, 1.0)	0.0 (-1.2, 1.3)	0.3 (-1.0, 1.5)	-0.9 (-2.1, 0.3)
3-hour post-treatment	59 (15)	0.9 (-0.5, 2.3)	-0.5 (-2.0, 0.9)	-0.1 (-1.6, 1.3)	-0.2 (-1.6, 1.2)	-0.3 (-1.7, 1.2)
24-hour post-treatment	59 (14)	0.1 (-1.9, 2.0)	-1.5 (-3.5, 0.5)	-0.5 (-2.4, 1.5)	-0.3 (-2.3, 1.6)	-0.9 (-2.8, 1.1)
	Low density lipoprotein (mg/dL)					
	Mean (sd)	**Difference compared to control (95% confidence interval)**				
0-hour post-treatment	90 (29)	-0.8 (-3.2, 1.6)	-1.0 (-3.4, 1.4)	0.5 (-2.0, 2.9)	-0.1 (-2.5, 2.4)	-0.3 (-2.7, 2.0)
3-hour post-treatment	88 (30)	0.6 (-2.5, 3.6)	-1.5 (-4.5, 1.6)	1.1 (-2.0, 4.2)	-0.8 (-3.8, 2.3)	-0.8 (-3.9, 2.2)
24-hour post-treatment	91 (32)	-2.1 (-7.0, 2.7)	-4.4 (-9.2, 0.5)	-1.5 (-6.3, 3.4)	-1.6 (-6.4, 3.3)	-2.7 (-7.5, 2.2)
	Triglycerides (percent difference)[+]					
	Mean (sd)	**Difference compared to control (95% confidence interval)**				
0-hour post-treatment	104[+] (59)	3.4 (-3.7, 11.0)	4.8 (-2.5, 12.6)	1.3 (-5.8, 8.9)	-2.2 (-9.0, 5.1)	2.7 (-4.2, 10.2)
3-hour post-treatment	123[+] (64)	2.2 (-6.7, 11.9)	6.0 (-3.2, 16.0)	2.1 (-7.0, 12.1)	6.7 (-2.6, 16.8)	0.9 (-7.7, 10.4)
24-hour post-treatment	102[+] (50)	8.6 (-3.6, 22.4)	9.7 (-2.8, 23.7)	7.6 (-4.7, 21.4)	-0.2 (-11.5, 12.6)	12.1 (-0.5, 26.2)

LPG = liquefied petroleum gas; sd = standard deviation

Model terms include cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

[+]Units for mean values during the control treatment are in mg/dL

24-hour post-treatment time point, the difference between the LPG treatment and control was -2.1 mg/dL (95% CI: -7.0, 2.7) and the difference between the three stone fire treatment and control was -2.7 mg/dL (95% CI: -7.5, 2.2) for LDL. The largest difference compared to control for LDL was -4.4 mg/dL (95% CI: -9.2, 0.5) at 24 hours after the gasifier treatment.

Triglycerides were generally higher than control for all cookstove treatments at the 24-hour post-treatment time point, with the exception of the rocket elbow treatment (Table 4.3;

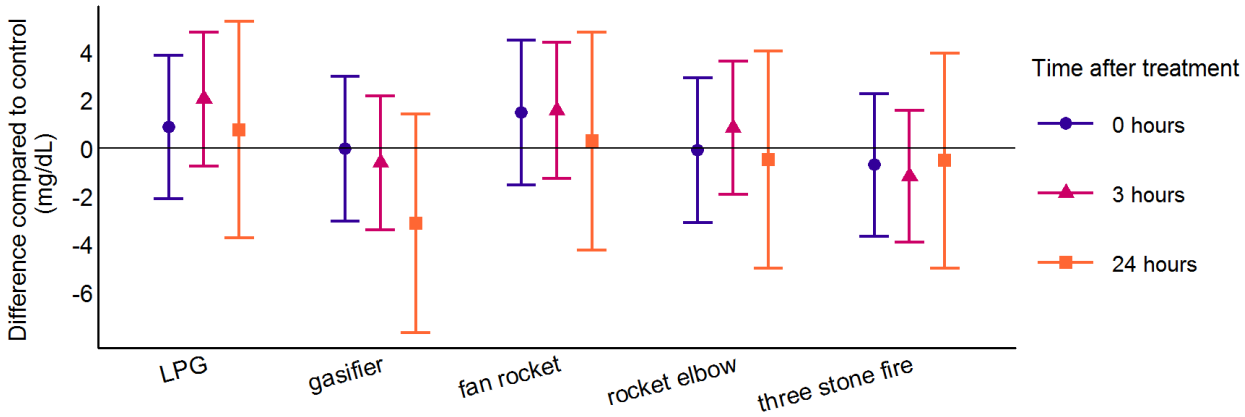

Figure 4.3: Differences in total cholesterol for each cookstove treatment compared to control at three post-treatment time points using linear mixed models
LPG = liquefied petroleum gas
Model terms include cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

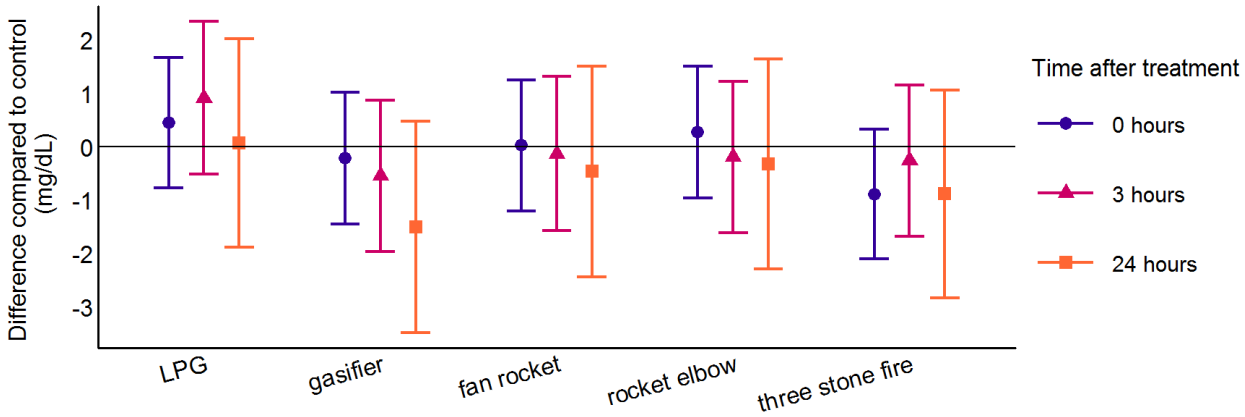

Figure 4.4: Differences in high density lipoprotein for each cookstove treatment compared to control at three post-treatment time points using linear mixed models
LPG = liquefied petroleum gas
Model terms include cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

Figure 4.6). For example, triglycerides were 8.6% higher 24 hours after the LPG treatment compared to control (95% CI: -3.6, 22.4) and 12.1% higher 24 hours after the three stone fire treatment compared to control (95% CI: -0.5, 26.2). The magnitude of the differences compared to control for each cookstove treatment was similar for triglycerides (except for the rocket elbow treatment, which was similar to control); however, none of the differences were statistically significant (p-value < 0.05). Triglycerides were marginally higher 0 hours after the gasifier

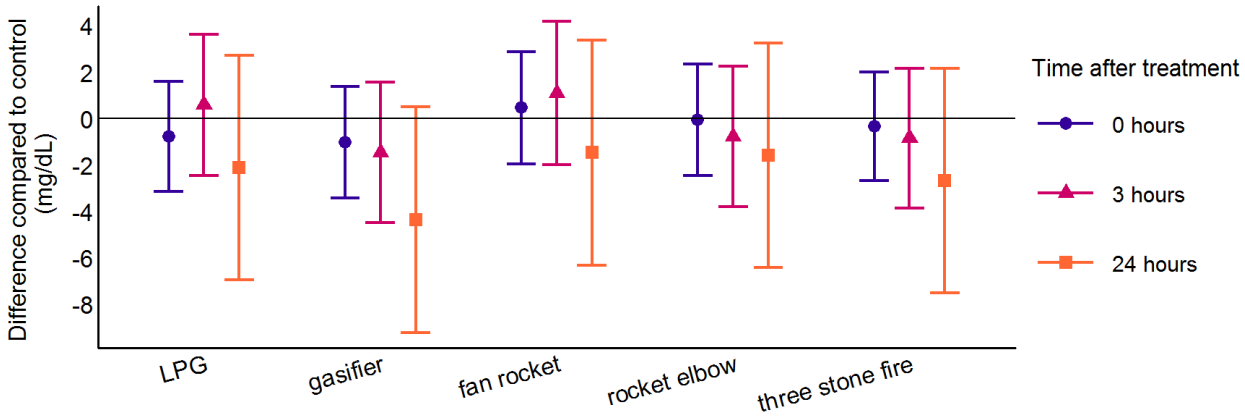

Figure 4.5: Differences in low density lipoprotein for each cookstove treatment compared to control at three post-treatment time points using linear mixed models
LPG = liquefied petroleum gas
Model terms include cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

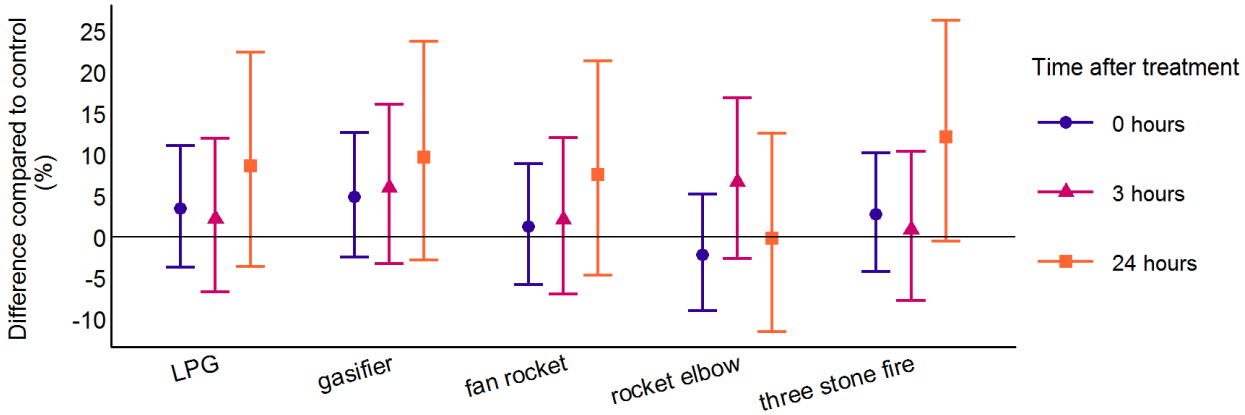

Figure 4.6: Percent differences in triglycerides for each cookstove treatment compared to control at three post-treatment time points using linear mixed models
LPG = liquefied petroleum gas
Model terms include cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

treatment (4.8%; 95% CI: -2.5, 12.6) and 3 hours after the gasifier (6.0%; 95% CI: -3.2, 16.0) and rocket elbow (6.7%; 95% CI: -2.6, 16.8) treatments compared to control; however, there were no meaningful differences for any other treatment compared to control at the 0-hour and 3-hour post-treatment time points.

Results from sensitivity analyses are presented in Appendix B. None of the sensitivity analyses or inclusion of potential confounders resulted in meaningfully different model estimates compared to the primary model estimates presented in Table 4.3 and Figures 4.3-4.6.

Discussion

Our study is unique in that it was the first to assess the impact of air pollution emitted from multiple cookstove technologies on blood lipids in a controlled exposure setting. Compared to control, our results suggest that triglycerides were higher 24 hours after all of the treatments except for the rocket elbow treatment; the magnitude of the differences (compared to control) was similar for each treatment and ranged from 7.6% to 12.1%. LDL was lower for each treatment compared to control at the 24-hour post-treatment time point, although the differences were only marginally suggestive based on the small magnitude of the effect estimates and the wide confidence intervals. There were no patterns of higher or lower values across the cookstove treatments for total cholesterol or HDL at any post-treatment time point, or for LDL and triglycerides at the 0- and 3-hour post-treatment time points. Sensitivity analyses using potential confounders and subsets of the data had similar results to the primary analyses.

Our results are the first to suggest that cookstove-emitted air pollution can acutely impact blood lipids in humans, and our results add to the body of evidence that particulate matter air pollution in general may have an impact on blood lipids. Multiple population-based studies have reported associations between higher levels of ambient particulate matter air pollution and higher triglycerides (Chuang et al. 2010; Shanley et al. 2016; Yang et al. 2018; Yitshak Sade et al. 2016). Another study evaluated associations between ambient particulate matter air pollution and blood lipids in 12 adults with asthma and reported 4.8% higher

triglycerides (95% CI: 0.81, 8.74) per 1 $\mu g/m^3$ increase in coarse particulate matter (Yeatts et al. 2007). Associations between ambient particulate matter air pollution and LDL have also been reported (Yang et al. 2018; Yitshak Sade et al. 2016); however, contrary to our results of marginally lower LDL levels following cookstove air pollution exposures, these studies reported that ambient air pollution was associated with higher levels of LDL. Ambient air pollution studies have also reported lower HDL (Bell et al. 2017; Chuang et al. 2010; Yang et al. 2018; Yitshak Sade et al. 2016) and higher total cholesterol (Shanley et al. 2016; Yang et al. 2018), whereas we saw no differences in these outcomes.

While our results are not entirely consistent with previous literature, most previous studies have been observational in design and have assessed long-term exposures to ambient air pollution. Results from these studies may differ from what we reported for a number of reasons including differences in study designs (i.e., observational vs experimental), length of exposure to air pollution, as well as differences in the composition between ambient and cookstove-emitted air pollution (Naeher et al. 2007). Although less common, controlled exposure studies with designs more similar to ours have been conducted. Ramanathan et al. reported lower HDL antioxidant/anti-inflammatory capacity 1 hour after concentrated ambient $PM_{2.5}$ exposures in a group of 30 healthy adults; these authors emphasized that acute changes in HDL antioxidant/anti-inflammatory functionality can take place in the absence of changes in serum HDL levels (Ramanathan et al. 2016). A study on 19 healthy adults reported lower levels of triglycerides (-14.5%, 95% CI: -30.1, -3.02) and very low-density lipoprotein (-17.3%, 95% CI: -31.0, -3.09) immediately after a 2-hour exposure to ultrafine ambient air pollution particles compared to filtered air, as well as a small decrease in HDL 18 hours after the controlled exposures compared to filtered air (Samet et al. 2009). In contrast, higher triglycerides (7.40%, standard error = 2.52) and very low-density lipoprotein (7.68%, standard error = 2.55) were reported immediately after controlled exposures to concentrated ambient air pollution particles compared to filtered air in a group of 13 healthy middle-aged adults, with slightly attenuated

levels reported 20 hours later (Tong et al. 2012). Our results add further evidence that short-term exposures to particulate matter air pollution can acutely impact blood lipids.

Physiologically, blood lipids are important outcomes to assess because of their role in the development of atherosclerosis, a major cause of cardiovascular disease (Bai and Sun 2016). LDL contributes directly to the atherosclerotic process by accumulating to form foam cells and fibrous plaques (Bai and Sun 2016). There is also evidence that air pollution can oxidize LDL (Dutta et al. 2011; Jacobs et al. 2011). Oxidized LDL is pro-inflammatory and pro-atherogenic; it is scavenged by macrophages that can then lead to foam cell formation and development of atherosclerosis (Bai and Sun 2016). Triglyceride-rich lipoproteins contribute to this process by accumulating in the plasma and initiating a pro-atherogenic inflammatory cascade (Talayero and Sacks 2011). In contrast, HDL is strongly protective against atherosclerosis by binding to and removing excess cholesterol from cells and extracellular tissues (Bai and Sun 2016).

The pathophysiology of atherosclerosis and the contribution of blood lipids to this process are generally well-understood, yet specific mechanisms through which air pollution may impact blood lipids remains unclear (Bai and Sun 2016). Current evidence suggests that inflammatory and oxidative stress pathways initiated by air pollution exposures could adversely impact blood lipids (i.e., increase total cholesterol, LDL and triglycerides; decrease HDL) in humans (Bai and Sun 2016; Franklin et al. 2015). In contrast to long-term exposures, a generalized acute phase inflammatory response can lead to an acute decrease in cholesterol levels by inhibiting cholesterol synthesis and secretion (Khovidhunkit et al. 2004). While these mechanisms are not entirely understood in humans, they may provide an explanation for the lower LDL we observed following the short-term treatments in our study. Also consistent with our results, inflammatory cytokines can cause an acute (within 2 to 24 hours) increase in production and secretion of triglycerides (Khovidhunkit et al. 2004).

There may be a number of reasons why we did not observe differences in total cholesterol and HDL. The short-term treatments in our study may not have been long enough or at high enough pollution concentrations to initiate an acute response in these outcomes. Furthermore, our study was designed and powered based on other outcomes not reported here (Fedak et al. 2019); there may have been differences in total cholesterol and HDL that were smaller in magnitude than we were able to detect in our analyses. Additionally, small decreases in HDL have been observed 18 hours after exposure to welding fumes (Rice et al. 2011); it is possible that there were differences in total cholesterol and HDL at earlier or later time points after the treatments when we did not measure blood lipids.

Logistically, to measure blood lipids at multiple time points within a 24-hour period they had to be non-fasting measurements. We do not believe this was a weakness in our assessment of blood lipids as indicators of cardiovascular risk. While blood lipid levels, particularly triglycerides, can vary acutely depending on dietary fat intake, there is strong evidence that non-fasting lipids predict cardiovascular disease as well as lipids assessed in a fasting state (Langsted and Nordestgaard 2019). It is possible that the non-fasting nature of the blood lipids we assessed could have impacted the results by increasing the variability in the blood lipids and consequently giving us less power to detect differences. However, we asked participants to eat low-fat meals during the 24 hours leading up to each study session until after the 24-hour post-treatment follow-up, and to eat a consistent diet across study sessions. Our analysis of the participants' self-reported diet showed that they were not entirely consistent in adhering to these restrictions; however, sensitivity analyses that included variables for self-reported consumption of high-fat food items did not impact the results.

The differences in blood lipids we observed in young, healthy adults may not accurately depict the impact of household air pollution exposures in populations which are exposed repeatedly over many years. Although the external validity of our study is limited, the internal validity of the crossover design is much stronger than the observational studies typically used in

household air pollution research. Potential confounders were unlikely to be associated with the individual treatments in our study, so the impact of confounding on our results was limited; results from sensitivity analyses had minimal differences from the primary model results and helped confirm this. The statistical models we used in our analyses additionally helped control for confounding: by including a term for the baseline health outcome prior to each treatment, we were able to account for potential time-variant confounders that may have varied at random between study days. Additionally, the mixed-model approach that used a random intercept for each individual participant helped control for potential time-invariant confounders that did not change within person throughout our study (e.g., sex).

The differences in triglycerides across the treatments compared to control were similar in magnitude at the 24-hour post-treatment time point. These results are consistent with the impact of the treatments on blood pressure in our study, which also had differences of similar magnitude between all treatments (except for the rocket elbow treatment) and control at the 24-hour post-treatment time point (Fedak et al. 2019). Our characterization of additional pollutants for each treatment did not provide an explanation for these trends: based on the pollutants we were able to measure, no single pollutant had a concentration (different from control) of similar magnitude across all of the treatments (Fedak et al. 2019). Other studies have reported that gaseous air pollutants such as nitrogen dioxide and sulfur dioxide can adversely impact blood lipids (Sorensen et al. 2015; Yang et al. 2018). Instead of a single pollutant causing the observed results, it is possible that each cookstove in our study emitted a unique, complex mixture of pollutants that had a similar impact on triglycerides. Alternatively, our results may be indicating that the health impact of short-term exposures to any level of particulate matter air pollution may have a threshold and elicit similar responses across exposure levels. Future studies which assess a wider range of pollutants and measure outcomes at more post-treatment time points may help answer these remaining questions.

Our results add to the evidence from previous studies which suggest that exposure to air pollution can impact blood lipids. While the acute differences we observed in triglycerides following short-term treatments of cookstove air pollution may not be relevant to populations that use cookstoves in their homes daily, our findings help us understand the underlying acute health impacts of household air pollution exposures. Repeated particulate matter air pollution exposures may result in an underlying increase in cardiovascular disease risk (Brook et al. 2010), and in the case of higher triglycerides, may lead to an increased risk of the progression of atherosclerosis (Talayero and Sacks 2011). Future analyses that assess inflammatory markers may help us understand the potential pathophysiologic mechanisms initiated by the treatments in our study.

Conclusions

We used a crossover study design to assess the impact of controlled treatments to pollution emitted from five cookstove technologies on acute differences in blood lipids. Although our results largely indicate that the cookstove treatments did not impact blood lipids, there is evidence of higher triglycerides 24 hours after the treatments compared to control (except for the rocket elbow treatment) and suggestive evidence of marginally lower LDL 24 hours after all treatments compared to control. We recommend that future field studies assess the impact of cookstove interventions on blood lipids to complement our findings.

CHAPTER 5: EFFECTS OF A BIOMASS COOKSTOVE INTERVENTION ON AUGMENTATION INDEX AND CENTRAL PULSE PRESSURE FROM A RANDOMIZED CONTROLLED TRIAL IN RURAL HONDURAS

Summary

Household air pollution from combustion of solid fuels for cooking and heating is a leading environmental risk factor for global morbidity and mortality. Biomass cookstoves that use an engineered combustion chamber and chimney have been developed to reduce exposure to air pollution, but the health benefits of these improved cookstoves are unclear. We assessed a *Justa* biomass cookstove intervention on measures of central hemodynamics (augmentation index [AIx], central pulse pressure [CPP]) in a randomized controlled trial among women in rural Honduras.

Participants (n=230 women) used only traditional biomass cookstoves at baseline. Data collection occurred during six household visits approximately every six months over three years. In a stepped-wedge design, women were randomly assigned to one of two study arms (n=115 per arm) to receive a wood-burning *Justa* cookstove (with a chimney and engineered combustion chamber) after the second visit or after the fourth visit. At each visit, 24-hour concentrations of personal and kitchen fine particulate matter ($PM_{2.5}$) concentrations were measured for each participant. AIx and CPP were measured during each visit using the SphygmoCor XCEL. Linear mixed models were used in an intent-to-treat (ITT) analysis to assess the intervention. Separate models evaluated the exposure-response relationship between the outcomes and $PM_{2.5}$ and the impact of self-reported cookstove use on the outcomes. Several sociodemographic indicators were evaluated as potential effect modifiers.

Median personal $PM_{2.5}$ concentrations for *Justa* users was 43 $\mu g/m^3$ (interquartile range [IQR]=46, n=586) and for traditional users was 81 $\mu g/m^3$ (IQR=91, n=624). Median kitchen $PM_{2.5}$ concentrations for *Justa* users was 53 $\mu g/m^3$ (IQR=74, n=578) and for traditional users was 178

μg/m^3 (IQR=371, n=631). Results from the ITT analysis suggest the intervention had little impact on AIx and CPP: AIx was 0.1 percentage points lower for *Justa* vs traditional cookstove users (95% confidence interval: -2.2, 2.1) and CPP was 0.2 mmHg lower for *Justa* vs traditional cookstove users (95% confidence interval: -1.3, 0.9). Other model variations were generally consistent with a null association.

Although personal and kitchen concentrations of $PM_{2.5}$ were lower following the cookstove intervention, we did not observe meaningful changes in AIx or CPP. The *Justa* biomass cookstove may not reduce household air pollution enough to improve measures of central hemodynamic health.

Introduction

Nearly 3 billion people around the world burn solid fuels in open fires or traditional cookstoves for cooking purposes (Bonjour et al. 2013). The resulting household air pollution is a leading environmental risk factor for global morbidity and mortality, resulting an estimated 60 million disability adjusted life-years in 2017, including 1.6 million premature deaths (Stanaway et al. 2018). Solid-fuel cookstoves that use chimneys and combustion chambers designed to reduce air pollution emissions have been introduced into some communities in an attempt to reduce cookstove-emitted exposures. While these “improved” cookstoves often succeed in lowering concentrations of household air pollution compared to traditional cookstoves, household air pollution concentrations typically remain far above World Health Organization (WHO) guidelines for mean $PM_{2.5}$ concentrations of 25 μg/m^3 for a 24-hour period and 10 μg/m^3 for an annual period (Bruce et al. 2015; Quansah et al. 2017; World Health Organization 2006). In addition, there is no clear evidence that improved cookstove interventions are resulting in improved health outcomes (Quansah et al. 2017).

Evidence suggests that particulate matter (PM) air pollution is causally associated with adverse cardiovascular outcomes (Brook et al. 2010), although less is known about the association between cardiovascular disease (CVD) and exposures to household air pollution

(McCracken et al. 2012). Current evidence indicates that household air pollution can adversely impact blood pressure, endothelial function, and heart rate variability, and increase markers of inflammation and oxidative stress, but conclusive evidence on the association between household air pollution and clinical CVD outcomes is limited due to the difficult nature of conducting research in field settings (Fatmi and Coggon 2016; McCracken et al. 2012). Central hemodynamic measures are important cardiovascular outcomes to assess because of their pathophysiological relevance (Vlachopoulos et al. 2010a). Central augmentation index (AIx; a measure of pulse wave reflection) and central pulse pressure (CPP) both predict future adverse cardiovascular events independent of traditional cardiovascular measures such as peripheral blood pressure (Vlachopoulos et al. 2010a).

There is evidence that ambient air pollution can adversely impact measures of central hemodynamics (Zanoli et al. 2017), although only one study to date in rural China has assessed household air pollution and central hemodynamic outcomes (Baumgartner et al. 2018; Clark et al. 2019). Following analysis of the baseline data from the study in China, authors reported that a natural log unit increase in fine particulate matter ($PM_{2.5}$; particles with aerodynamic diameter < 2.5µm) was associated with higher AIx and CPP among 205 women, with larger associations for CPP (2.9 mmHg, 95% confidence interval [CI]: 0.8, 5.1) in women over 50 years old (Baumgartner et al. 2018). However, after 1.5 years of follow-up, the authors reported that a government sponsored semi-gasifier cookstove intervention did not improve hemodynamic outcomes of blood pressure, CPP, or pulse wave velocity compared to participants who did not receive the intervention (Clark et al. 2019). Our work adds to the limited research on household air pollution and central hemodynamic health outcomes. We assessed the effects of a culturally appropriate improved biomass cookstove intervention on central hemodynamic outcomes of AIx and CPP among 230 women in rural Honduras. Other health outcomes were assessed and are reported elsewhere.

Methods

Study design

A detailed description of the study design and methods has been published previously (Young et al. 2019). The study was made up of six visits that occurred approximately every six months over the course of the 3-year study period. Participants were visited up to six times to collect data on health outcomes and exposure measurements. A total of 230 female participants were enrolled in the study and randomly assigned to one of two study arms (n=115 per arm). Using a stepped-wedge design (Figure 5.1), participants from arm 1 received an intervention of an improved biomass *Justa* cookstove after visit 2; arm 2 received the intervention cookstove after visit 4. The use of a stepped-wedge design allowed us to utilize the benefits of randomization to limit confounding in the intent-to-treat (ITT) analysis, while also allowing all participants to receive the improved *Justa* cookstove (Hemming et al. 2015).

Years:	Visit:	Arm 1 (n=115) cookstove:	Arm 2 (n=115) cookstove:
0	1	Traditional	Traditional
0.5	2	Traditional	Traditional
		Arm 1 Intervention	
1	3	*Justa*	Traditional
1.5	4	*Justa*	Traditional
			Arm 2 Intervention
2	5	*Justa*	*Justa*
2.5	6	*Justa*	*Justa*

Figure 5.1: Study design
Stepped-wedge study design: years since study start, cookstove assignment, and timing of intervention for study arms during each study visit.

Participants and recruitment process

Participants were recruited from 10 communities around La Esperanza, Department of Intibucá, Honduras. The rural communities in the mountainous region were primarily

agriculturally-based and relied heavily on biomass fuels for cooking. Across the country of Honduras, nearly 90% of the rural population cooks with solid fuels (Global Alliance for Clean Cookstoves 2018).

Formative research for the study began in 2014 by implementing in-person surveys to assess intervention readiness and potential obstacles of intervention cookstove adoption. Feedback from the communities helped support the selection of the improved biomass *Justa* cookstove as the intervention cookstove. The *Justa* cookstove (Figure 5.2) was culturally appropriate and included a combustion chamber designed to reduce emissions, a chimney, a metal griddle, and a compartment to remove soot (Kshirsagar and Kalamkar 2014).The *Justa* cookstove also performed well in laboratory tests, emitting less than half the amount of carbon monoxide and particulate matter as a traditional three stone fire cookstove (Kshirsagar and Kalamkar 2014). A cross-sectional feasibility study was conducted in 2015 in the same study area to assess field equipment and methods prior to the randomized controlled trial. Results from the cross-sectional study have been published previously (Benka-Coker et al. 2018; Rajkumar et al. 2018; Rajkumar et al. 2019; Walker et al. 2019; Young et al. 2018). *Justa* cookstove users in the cross-sectional study had lower 24-hour average concentrations of personal (48% lower) and kitchen (62% lower) $PM_{2.5}$ compared to traditional cookstove users (Young et al. 2018).

Recruitment for the randomized controlled trial took place at community meetings where residents were introduced to the research team and the study objectives. Eligibility criteria included: female aged 24-59 years, primary household cook, non-smoking (including second-hand smoke exposure), not pregnant, and use of only biomass traditional cookstoves at the time of recruitment. A total of 230 participants met eligibility criteria and were enrolled in the study. Randomization into arm 1 or arm 2 was chosen by having participants blindly draw their study arm assignment from a bag.

The study was approved by the Institutional Review Board at Colorado State University. Participants provided verbal consent for all study procedures prior to enrollment and at each visit.

Study visits

We visited each participant at their household up to six times over the course of the study to collect exposure and health measurements. Study visits took place Monday through Saturday; Sundays were excluded to avoid abnormal cooking practices and cookstove use. Exposure monitoring equipment was set up during the morning of the first day of the study visit after receiving verbal informed consent. We returned to the home at least 24 hours later to collect the exposure equipment and perform a health assessment.

An incentive bag of food items worth $5 USD was given to each woman at each study visit to encourage continued participation. When arm 1 participants received the *Justa* cookstove, arm 2 participants received a one-time gift of similar value to the *Justa* (radio, kitchen utensils, or a basket of specialty food items). Options for the one-time gifts were chosen in order to not influence exposure. The same gift was given to arm 1 participants when arm 2 received the intervention cookstove to encourage continued participation.

Exposure measurements

The exposure of interest for the ITT analysis that utilized the stepped-wedge design was assigned cookstove type (traditional vs *Justa*). Cookstoves were defined as traditional if they lacked an improved combustion chamber designed to reduce air pollution emissions. The design of traditional cookstoves in the study population ranged from primitive open fires to built-in cookstoves with griddles and chimneys. The *Justa* cookstoves, which used an improved rocket elbow combustion chamber, were built in each participant's home after their primary traditional cookstove was destroyed. In-person training for the *Justa* cookstove was conducted at the time of construction (Young et al. 2019). Some participants utilized secondary cookstoves throughout the study in addition to their primary assigned cookstove, a practice referred to as

cookstove stacking. To quantify the impact of cookstove stacking, a stove-use analysis was performed using a 3-level cookstove use variable as the exposure of interest. The 3-level cookstove-use variable included a reference level of participants with a primary traditional cookstove with or without cookstove stacking; the second level included participants with a primary improved cookstove with traditional cookstove stacking; the third level included participants with a primary improved cookstove with or without improved cookstove stacking. Cookstove stacking was assessed using a combination of self-report and visual inspection of a participant's home during each study visit. Other cookstove use variables were assessed that 1) split *Justa* and other improved cookstove users into separate levels, 2) incorporated self-reported days per month of traditional cookstove stacking by participants who used the *Justa* as their primary cookstove, and 3) incorporated self-reported hours per day of primary cookstove use.

Figure 5.2: Examples of traditional (left) and *Justa* stoves (right) in rural Honduras. Photo credit: Bonnie Young.

We measured 24-hour concentrations of personal and kitchen $PM_{2.5}$ during each study visit. Personal $PM_{2.5}$ was collected using personal air pollution monitors worn near the participant's breathing zone for 24 hours. Women were asked to place the monitor nearby when sleeping and bathing, and to wear the monitor at all other times. Kitchen $PM_{2.5}$ was collected by hanging air pollution monitors near the front of the cookstove in an area that represented the

participant's typical breathing zone during cooking, while also avoiding drafts from windows and doors and interfering with her daily cooking activities. Kitchen temperature and relative humidity were measured in the same location as the kitchen $PM_{2.5}$ measurements (Lascar electronics data logger, Erie, PA, USA).

We collected 24-hour personal and kitchen $PM_{2.5}$ samples on 37 mm filters (Fiberfilm, Pall Corporation, NY, USA [visits 1 through 4] and Teflo filters, VWR, Radnor, PA, USA [visits 5 and 6]). Air sampling pumps (AirChek XR5000, SKC Inc., PA, USA) calibrated to 1.5 liters per minute (DryCal Lite, Mesa Labs, NJ, USA) pulled air through $PM_{2.5}$ size-selective cyclones (Triplex, BGI, Inc., NJ, USA) and deposited the particles onto the sample filters. For visits 5 and 6 we used a personal exposure monitor called the Ultrasonic Personal Aerosol Sampler (UPAS, Access Sensor Technologies, Fort Collins, CO, USA). The UPAS, which was smaller and more quiet than the personal sampler used for visits 1 through 4, sampled air at 1.0 liter per minute and used a customized cyclone to collect $PM_{2.5}$ on an enclosed filter (Volckens et al. 2017). Comparability between the two personal sampling systems was evaluated in the field; samples from the two systems were strongly correlated (Spearman coefficient = 0.91 between 43 paired measures) (Pillarisetti et al. 2018).

Sample filters were stored at -20 °C in Honduras prior to being transported to Colorado State University, where they were stored at -80 °C prior to analysis. Filters were equilibrated for at least 24 hours prior to gravimetric analysis (Mettler Toledo MX5 Microbalance, Mettler Toledo, Columbus, OH, USA). The average of two filter weights was used to calculate $PM_{2.5}$ mass; if the weights differed by more than 5 µg the filter was weighed a third time and the average of all three weights was used. $PM_{2.5}$ sample mass was calculated as the difference in average pre- and post-sample filter weights. The limit of detection (LOD) for $PM_{2.5}$ mass was calculated (separately for each visit) by adding the average mass of the field blanks (collected once per week) to three times the standard deviation of field blank masses (MacDougall et al. 1980). If filter weights were below the LOD for a given visit they were substituted with the

LOD/$\sqrt{2}$ (Hewett and Ganser 2007; Hornung and Reed 1990; Nieuwenhuijsen 2015). Time-weighted-average $PM_{2.5}$ concentrations were calculated by subtracting the average field blank mass from the final filter weights and dividing the resulting blank-corrected mass by the volume of air from which the $PM_{2.5}$ sample was collected.

Health measurements

We measured AIx and CPP using a non-invasive pressure waveform device (SphygmoCor XCEL, Atcor Medical, Australia). Health measurements were taken during the morning and after the participant's morning meal. Following a 10-minute seated rest period, three blood pressure measurements were recorded using a brachial cuff on the woman's right arm while in a seated position with feet flat on the floor. After the blood pressure measurements, the cuff partially inflated and recorded a 10-second pulse wave analysis measurement to estimate AIx and CPP. Participants were asked to avoid speaking and moving during the measurements as to not impact the measured health outcomes.

Potential confounders were also measured during study visits. Height and weight were measured and used to calculate body mass index (BMI; kg/m^2). Waist circumference (measured at the smallest circumference of the natural waist) and hip circumference (measured at the widest point of the hips) were measured and used to calculate waist-to-hip ratio. Systolic and diastolic blood pressure (measured using the Sphygmocor XCEL), hemoglobin A1c, and metabolic syndrome were assessed as potential effect modifiers. Metabolic syndrome was defined as waist circumference ≥80 cm plus any two of the following: triglycerides > 200 mg/dL, high-density lipoprotein <50 mg/dL, systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥ 85 mmHg, and hemoglobin A1c >5.6% (Driver et al. 2016; International Diabetes Federation 2006). Triglycerides, high-density lipoprotein (PTS Diagnostics, Indianapolis, IN, USA) and hemoglobin A1c (A1CNow+ kit, Bayer Diabetes Care, Sunnyvale, CA, USA) were measured by finger-stick blood draw.

A full list of the health measurements assessed in the study is described elsewhere (Young et al. 2019).

Questionnaires

Questionnaires were administered in Spanish by a trained interviewer during each study visit to assess sociodemographic characteristics and potential confounders for use in the study analyses. Responses were entered into Open Data Kit (ODK Collect 1.4.5, UK).

We reviewed each participant's national identification card to confirm her age. Participants self-reported the age they started cooking with biomass cookstoves, which was subtracted from their current age to calculate total years of cooking with a biomass cookstove. Participants also self-reported multiple indicators of socioeconomic status: number of beds per person in their household, years of formal education, household assets, and dietary diversity score. Household assets was calculated as a sum of owning nine household items: bicycle, car, motorcycle, television, radio, refrigerator, cell phone, computer, and sewing machine. A weighted household assets variable (range 0 to 45) was created using the ranked value of each of the nine household items, ordered by their prevalence in the study population; weighted assets were summed for each participant to calculate their final weighted household asset score (Howe et al. 2008). Dietary diversity score was calculated as a sum of 11 food categories found in a 24-hour dietary recall: grains (corn, cereals, rice, chips), pulses and nuts, roots (potatoes), other vegetables, fruits, sweets, eggs, dairy (cheese, milk), meat (beef, chicken, pork, fish), oils, and beverages (coffee, soda, juice). Salt, sugar, and Manteca (butter or lard) daily intake was assessed by asking how many days it took to consume one bag or packet of each item, then dividing that amount by total number of household members. In addition, participants self-reported blood pressure medication use (confirmed by reviewing prescription bottles), exposure to second-hand smoke, and hours per week of lifestyle activities used to calculate metabolic equivalent (MET) values (Ainsworth et al. 2011): cut wood, grind corn, wash clothes, milk the

cow, work in the field, walk moderately outside the house, cook, clean the house, sit relaxed, and sleep.

Statistical analysis

We used R version 3.5.0 (The R Project for Statistical Computing) and SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA) to conduct data cleaning and descriptive statistics. Linear mixed model analyses were run in R using the lme4 (Bates et al. 2015) and lmerTest (Kuznetsova et al. 2017) packages.

Baseline (visit 1) summary statistics (mean, standard deviation [sd], minimum, median, maximum) of participant characteristics and health outcomes were calculated for all households in the study and by study arm. Summary statistics for personal and kitchen $PM_{2.5}$ concentrations (mean, sd, 25^{th} and 75^{th} percentiles, median) were calculated for all households, by study arm, by assigned cookstove type (traditional vs *Justa*), and by the 3-level cookstove use variable (improved with or without improved stacking, improved with traditional stacking, traditional with or without stacking). Simple linear regression analyses at baseline (visit 1) were run between the health outcomes of interest (AIx and CPP) and potential confounders identified *a priori* (various sociodemographic measures). Within-person sd using pre-intervention study data for AIx and CPP was calculated by taking the square root of the residual mean square from a one-way analysis of variance model between each outcome (dependent variable) and participant id (independent variable) (Bland and Altman 1996). The intraclass correlation coefficient (ICC) was calculated using the sjstats package in R (Lüdecke 2019).

In the ITT analysis, we used linear mixed models to assess the impact of the intervention on AIx and CPP. The exposure of interest in this analysis was a fixed effect for assigned cookstove type (traditional vs *Justa*). The model also included a random effect for participant to account for repeated measures within person, and a fixed natural cubic spline trend function (degrees of freedom=6) for visit date to account for potential temporal changes (unrelated to the intervention) in AIx and CPP over the 3-year study period.

We conducted exposure-response and cookstove-use analyses in addition to the ITT analysis. The exposure-response analysis included personal and kitchen $PM_{2.5}$ concentrations as the exposures of interest, in separate models. The cookstove-use analysis used a 3-level variable designed to capture actual cookstove use (traditional cookstove; improved cookstove with traditional cookstove stacking; improved cookstove with or without improved cookstove stacking) as the exposure of interest. These analyses used models similar to the ITT analysis (random effect for participant and spline trend function for date); however, they also included potential confounders identified *a priori* as fixed terms since confounding was not accounted for by the study's randomization in these models. Potential cofounders were included in the models if they were theoretically associated with both the exposure and outcome of interest and if they were independently associated with the outcomes (assessed using the simple linear regression models between potential confounders and AIx/CPP at baseline). Based on these criteria, the exposure-response and cookstove-use analyses were adjusted for age (years, continuous), waist circumference (cm, continuous) and self-reported years of education (dichotomous, <6 vs 6+).

Sensitivity analyses were conducted that added additional confounders to the exposure-response and cookstove-use analyses. Further sensitivity analyses assessed the use of the spline trend function with varying degrees of freedom; others assessed categorical indicators of season or visit number instead of the spline trend function to account for time in the models. We conducted additional analyses using subsets of the data that 1) removed participants who used blood pressure medications and 2) removed participants who did not complete all six visits of the study (complete-case analysis). To further evaluate the exposure-response relationship between $PM_{2.5}$ and the outcomes, we assessed additional exposure-response models that included personal and kitchen $PM_{2.5}$ in cubic spline trend functions.

Effect modification was assessed in the ITT, exposure-response, and cookstove-use analyses by including interaction terms in the statistical models. Effect modification was

assessed for the following variables with the exposure of interest in each model: age (<40 years vs ≥40 years), waist circumference (<80 cm vs ≥80 cm), blood pressure (systolic <120 and diastolic <80 vs systolic ≥120 or diastolic ≥80), hemoglobin A1c (<5.7% vs ≥5.7%), and metabolic syndrome (presence vs absence).

Lastly, as a simpler sensitivity analysis we conducted two-sample t-tests to assess the differences in the mean values of AIx and CPP between study arms during visits 3 and 4 (i.e., the visits when study arms 1 and 2 were assigned to different cookstove types).

We evaluated diagnostic plots (i.e., QQ plots and residuals vs fitted values plots) for each of the linear model analyses.

Results

Participants

Population characteristics measured at visit 1 for the 230 participants are presented in Table 5.1. The women had mean age at baseline of 38 years (sd=9), mean BMI of 26 kg/m^2 (sd=4), and self-reported that they cooked with a biomass cookstove for an average of 27 years (sd=10). In general, participants in arm 1 and arm 2 were similar for characteristics of age, BMI, and physical activity, although there were small differences between the study arms in the characteristics measured to represent socioeconomic status (Table 5.1). Arm 1 had a larger proportion of women with 0.5 or more beds per person in their household (arm 1=69%, arm 2=63%), and arm 2 had more women who reported a dietary diversity score of 6 or more (arm 1=62%, arm 2=72%) and household assets of 3 or more (arm 1=43%, arm 2=50%) (Table 5.1). Self-reported years of education, which was more highly associated with AIx and CPP than the other socioeconomic indicators (Table C2), was similar across the study arms (Table 5.1).

Table C1 and Chart C1 present the number of women (with data for AIx and CPP) who participated in each visit of the study. Overall, there was 16% missing data across all six visits (1162 of 1380 potential observations). Of the 230 participants, 181 (79%) completed AIx and CPP measurements for at least five visits of the study. Participants from Arm 2 (19%) had a

higher proportion of missing data than those from Arm 1 (13%). Visit 2 had a higher number of missing observations than other visits due to a malfunction of the SphygmoCor XCEL device that impacted 46 participants. Other reasons for missing data were participant refusal, participants not being home for a planned visit, participants moving to a new home, or participants being pregnant during a visit (n=22).

Table 5.1: Participant characteristics at baseline (visit 1), total and by study arm[a]

	All households n=230	**Arm 1 n=115**	**Arm 2 n=115**
Participant characteristic	**mean (sd) min; median; max or n (%)**	**mean (sd) min; median; max or n (%)**	**mean (sd) min; median; max or n (%)**
Age, years	38.2 (8.6) 24.0; 37.0; 59.0	38.5 (8.0) 24.0; 38.0; 56.0	37.8 (9.2) 25.0; 36.0; 59.0
Age, years Less than 40 40 or more	 137 (60) 93 (40)	 65 (57) 50 (43)	 72 (63) 43 (37)
Total years cooking with a biomass cookstove	26.5 (9.5) 9.0; 25.0; 49.0	27.0 (8.7) 12.0; 27.0; 45.0	25.9 (10.3) 9.0; 23.0; 49.0
Beds per person in the household Fewer than 0.5 0.5 or more	 78 (34) 152 (66)	 36 (31) 79 (69)	 42 (37) 73 (63)
Education Less than six years Six or more years	 121 (53) 109 (47)	 60 (52) 55 (48)	 61 (53) 54 (47)
Dietary diversity score[b] Less than 6 6 or more	 76 (33) 154 (67)	 44 (38) 71 (62)	 32 (28) 83 (72)
Household assets[c] Two or fewer household assets More than two household assets	 122 (53) 108 (47)	 65 (57) 50 (43)	 57 (50) 58 (50)
Body mass index, kg/m^2	26.1 (4.1) 18.4; 25.9; 39.2	26.2 (3.9) 18.7; 26.3; 36.9	26.0 (4.4) 18.3; 25.6; 39.2
Waist circumference, cm	84.2 (9.4) 61.0; 83.8; 114.3	84.3 (9.3) 66.0; 83.8; 111.8	84.1 (9.6) 61.0; 83.8; 114.3
Waist-to-hip ratio[d] Normal Abdominal obesity	 77 (33) 153 (67)	 37 (32) 78 (68)	 40 (35) 75 (65)
Blood pressure medication use	12 (5)	8 (7)	4 (3)
Physical activity, METS	301 (99) 114; 288; 699	307 (95) 148; 306; 596	297 (103) 114; 280; 699

Augmentation index[e], %	21.4 (14.2) -17.5; 22.1; 58.9	22.1 (13.4) -9.3; 23.0; 58.9	20.6 (15.1) -17.5; 21.6; 57.2
Central pulse pressure[f], mmHg	33.4 (7.3) 21.4; 31.9; 58.4	33.5 (7.2) 21.4; 31.9; 55.9	33.2 (7.5) 21.7; 31.8; 58.4

sd = standard deviation, METS = metabolic equivalent (kcal/kg/hour)
[a] Study Arm 1 received intervention *Justa* cookstove after visit 2; study Arm 2 received intervention *Justa* cookstove after visit 4. See Figure 5.1 for further detail.
[b] Sum of 11 food categories found in a 24-hour dietary recall: grains (corn, cereals, rice, chips), pulses and nuts (nuts, beans), roots (potatoes), other vegetables, fruits, sweets, eggs, dairy (cheese, milk), meat (beef, chicken, pork, fish), oils, and beverages (coffee, soda, juice).
[c] Sum of 9 household assets: bicycle, car, motorcycle, television, radio, refrigerator, cell phone, computer, and sewing machine
[d] Abdominal obesity defined as waist-to-hip ratio ≥ 0.85
[e] Including missing outcome data, total n=222, n=113 for Arm 1, and n=109 for Arm 2. Includes removal of one augmentation index value over 75% (95% from Arm 2) and one augmentation index value less than -25% (-35% from Arm 1).
[f] Including missing outcome data, total n=223, n=114 for Arm 1, and n=109 for Arm 2. Includes removal of one central pulse pressure value over 75 mmHg (86 mmHg from Arm 2).

Exposure measurements

Twenty-four hour time-weighted-average personal and kitchen concentrations of $PM_{2.5}$ are presented in Table 2. Across all study visits, the median concentration for personal $PM_{2.5}$ was 60 $\mu g/m^3$ (interquartile range [IQR]=75, mean=113, standard deviation [sd]=253, n=1210) and the median concentration for kitchen $PM_{2.5}$ was 90 $\mu g/m^3$ (IQR=202, mean=274, sd=566, n=1209). Participants assigned to *Justa* stoves had lower concentrations of personal and kitchen $PM_{2.5}$ than traditional cookstove users: median personal $PM_{2.5}$ concentration for *Justa* = 43 $\mu g/m^3$ (IQR=46, mean=83, sd=216, n=586) vs traditional = 81 $\mu g/m^3$ (IQR=91, mean=142, sd=281, n=624); median kitchen $PM_{2.5}$ concentration for *Justa* = 53 $\mu g/m^3$ (IQR=74, mean=107, sd=211, n=578) vs traditional = 178 $\mu g/m^3$ (IQR=371, mean=427, sd=724, n=631). Participants in arm 1 had slightly higher median personal $PM_{2.5}$ concentrations at baseline (visit 1) than those in arm 2 (80 $\mu g/m^3$ vs 75 $\mu g/m^3$), and participants in arm 2 had slightly higher median kitchen $PM_{2.5}$ concentrations at visit 1 than those in arm 2 (197 $\mu g/m^3$ vs 167 $\mu g/m^3$). Decreasing levels of the 3-level cookstove-use variable generally corresponded with lower personal and kitchen $PM_{2.5}$ concentrations (Table 2). The Spearman correlation coefficient between personal and kitchen $PM_{2.5}$ concentrations was 0.68.

Table 5.2: Personal and kitchen 24-hour time-weighted-average fine particulate matter concentrations

	24-hour average personal $PM_{2.5}$ (μg/m³)		**24-hour average kitchen $PM_{2.5}$ (μg/m³)**	
	mean (sd) n	25th-75th percentile median	mean (sd) n	25th-75th percentile median
	Total – all visits			
All households	113 (253) 1210	35 – 110 60	274 (566) 1209	41 – 243 90
	Assigned cookstove type – all visits			
Traditional stove users	142 (281) 624	50 – 141 81	427 (724) 631	69 – 440 178
***Justa* stove users**	83 (216) 586	27 – 73 43	107 (211) 578	29 – 103 53
	Study arm[a] – baseline[b]			
Study arm[a] 1	159 (518) 114	51 – 128 80	431 (762) 115	74 – 438 167
Study arm[a] 2	125 (135) 115	46 – 141 75	469 (737) 115	76 – 559 197
	Actual cookstove use[c]			
Traditional primary stove, with or without secondary stove[d]	141 (280) 627	50 – 141 81	427 (722) 634	70 – 440 178
***Justa* primary stove, plus traditional secondary stove**	91 (261) 367	27 – 74 45	106 (218) 362	28 – 100 52
***Justa* primary stove, with or without improved secondary stove[e]**	69 (105) 216	25 – 69 40	105 (199) 213	30 – 103 51

$PM_{2.5}$ = fine particulate matter, sd = standard deviation

[a] Study Arm 1 received intervention *Justa* cookstove after visit 2; study Arm 2 received intervention *Justa* cookstove after visit 4. See Figure 5.1 for further detail.

[b] Baseline measurements were taken during Visit 1 of the 6 field data collection visits (Aug-Dec 2015).

[c] Actual cookstove use was a 3-level variable defined by a combination of self-reported cookstove use and observed cookstove use during visits to participant households for each of the six study visits.

[d] Secondary stove could be improved or traditional.

[e] Secondary stove could be improved biomass stove or clean-fuel stove (e.g., electric or gas).

Health outcomes

Baseline health outcomes, total and by study arm, are presented in Table 5.1. Mean AIx for the study population at baseline was 21.4% (sd=14.2), and mean CPP at baseline was 33.4 mmHg (sd=7.3). Mean AIx and CPP were similar at baseline across the study arms (Table 5.1). Within-person sd prior to the intervention was 9.5 for AIx and 4.8 for CPP. The ICC was 0.58 for AIx and 0.62 for CPP. Age was strongly associated with AIx and CPP at baseline (Table C2),

providing confidence in our use of these outcomes in a field setting: compared to those aged less than 40 years, participants aged 40 years or more had higher AIx (9.8%, p<0.00), and higher CPP (5.1 mmHg, p<0.00).

Results from the ITT analysis indicate that the *Justa* cookstove intervention did not impact AIx or CPP (Table 5.3). AIx was 0.3 percentage points higher for participants assigned to a *Justa* cookstove vs participants assigned to a traditional cookstove (95% confidence interval [CI]: -1.8, 2.5). CPP was 0.3 mmHg lower for participants assigned to a *Justa* cookstove vs participants assigned to a traditional cookstove (95% CI: -1.4, 0.9). Personal and kitchen $PM_{2.5}$ concentrations were natural log transformed for the exposure-response analysis; results were consistent with a null association (Table 5.3). For a 25% increase in kitchen $PM_{2.5}$, AIx was unchanged (0.00 percentage points, 95% CI: -0.12, 0.14) and CPP was 0.01 mmHg higher (95% CI: -0.06, 0.08). For a 25% increase in personal $PM_{2.5}$, AIx was 0.03 percentage points lower (95% CI: -0.19, 0.14) and CPP was 0.03 mmHg higher (95% CI: -0.06, 0.11). We did not observe evidence that age or cardiometabolic indicators modified the relationships in the ITT, exposure-response, or cookstove-use analyses (Table C4).

Results from the cookstove-use analysis with the 3-level cookstove use variable indicate that participants who used the *Justa* cookstove without traditional cookstove stacking had higher AIx (2.8 percentage points; 95% CI: -0.4, 5.1) and similar CPP (0.2 mmHg; 95% CI: -1.1, 1.4) compared to participants who used traditional cookstoves (Table 5.3). Participants who used the *Justa* cookstove with traditional cookstove stacking had slightly lower AIx (-0.2 percentage points; 95% CI: -2.3, 1.9) and CPP (-0.5 mmHg; 95% CI: -1.6, 0.7) compared to participants who used traditional cookstoves. Results from other cookstove use variables are presented in Appendix C, and are generally consistent with the results from the 3-level cookstove use variable.

Results from the two-sample t-tests assessing the differences in the mean values of AIx and CPP between study arms indicate that means were not significantly different across study arms for AIx or CPP during visit 3 or 4 (Table C3).

Results from sensitivity analyses are presented in Appendix C. Models including other potential confounders and covariates did not change the model estimates compared to the primary model estimates presented in Table 5.3. Exclusion of participants who used blood pressure medications did not meaningfully impact the model results. Analyses that used the complete-case dataset (only participants who completed all six visits of the study) did result in different model estimates compared to the primary analyses that used the full dataset, although model estimates were only marginally different in the ITT and exposure-response analysis frameworks (Figures C1-C6). However, in the cookstove-use analysis framework,

Table 5.3: Estimates and 95% confidence intervals for the association between exposure to household air pollution and augmentation index and central pulse pressure

Exposure to household air pollution	**Augmentation index (%)**		**Central pulse pressure (mmHg)**	
Assigned cookstove[a]	N[c]	Estimate (95% CI)	N[c]	Estimate (95% CI)
Justa cookstove	581	0.33 (-1.80, 2.46)	582	-0.25 (-1.36, 0.87)
Traditional cookstove		Ref		Ref
Measured particulate matter[b]				
24-hour average personal $PM_{2.5}$, $\mu g/m^3$, per 25% increase	1121	-0.03 (-0.19, 0.14)	1123	0.03 (-0.06, 0.11)
24-hour average kitchen $PM_{2.5}$, $\mu g/m^3$, per 25% increase	1122	0.00 (-0.12, 0.14)	1124	0.01 (-0.06, 0.08)
Actual cooktove use[b]				
Justa primary with or without improved secondary cookstove	213	2.75 (0.36, 5.13)	213	0.15 (-1.11, 1.41)
Justa plus traditional	366	-0.22 (-2.34, 1.89)	367	-0.45 (-1.57, 0.67)
Traditional primary with or without secondary cookstove	583	Ref	584	Ref

$PM_{2.5}$, fine particulate matter; CI, confidence interval
[a] Intent-to-treat analysis: model includes a fixed term for assigned stove, a fixed spline term for date, and a random term for participant.
[b] In addition to terms from intent-to-treat analysis, results are adjusted for age (years, continuous), waist circumference (cm, continuous) and self-reported years of education (dichotomous, < 6 vs 6+).
[c] N = number of total observations in each model across all study visits.

analyses that used the complete-case data had substantially attenuated results compared to analyses that used the full dataset (Figures C7-C14). For example, using complete-case data, participants who used the *Justa* cookstove without traditional cookstove stacking had similar AIx (0.0%; 95% CI: -3.3, 3.3) and lower CPP (-0.9 mmHg; 95% CI: -2.7, 0.8) compared to participants who used traditional cookstoves as their primary cookstove. These results, and the possible impact of missing data, are discussed further below.

Discussion

We used a randomized field trial to assess the impact of an improved biomass *Justa* cookstove among traditional cookstove users in rural Honduras. The mean percent difference in personal (42%) and kitchen (75%) $PM_{2.5}$ concentrations in participants assigned to the *Justa* cookstove compared to participants who used a traditional cookstove is similar to previous solid fuel cookstove interventions that have used chimneys (Pope et al. 2017). Yet, as with previous studies, personal and kitchen concentrations of $PM_{2.5}$ following the *Justa* intervention were highly variable and remained above WHO recommendations (Pope et al. 2017). Our results indicate that the intervention cookstove did not meaningfully impact AIx or CPP in the ITT analysis, and the exposure-response analysis was generally consistent with a null association for both outcomes (Table 5.3). The results from the cookstove-use analysis show that *Justa* cookstove users had higher levels of AIx compared to traditional cookstove users, although a selection bias from missing data may have played a role in these counterintuitive results.

The results from our study are comparable to those from the only other study that has assessed the impact of household air pollution on central hemodynamic outcomes in a field setting. Baumgartner and coauthors reported small associations between measured household air pollution and central hemodynamic outcomes at baseline among 205 Chinese women in their study (Baumgartner et al. 2018). A natural log unit increase in personal $PM_{2.5}$ exposure was associated with 1.1 percentage points higher AIx (95% CI: -0.2, 2.4); associations between increased $PM_{2.5}$ exposures and CPP were higher among 102 women aged 50 years or more

(2.9 mmHg; 95% CI: 0.8, 5.1) than 96 women aged 28-49 years (-0.1 mmHg; 95% CI: -2.0, 1.8) (Baumgartner et al. 2018). However, the authors reported that a semi-gasifier cookstove intervention did not improve blood pressure, CPP, or pulse wave velocity compared to participants who did not receive the intervention (Clark et al. 2019). Women who did not receive the intervention had higher decreases in systolic blood pressure (adjusted difference-in-difference effect estimate [DD]=1.3 mmHg; 95% credible interval [CrI]: -2.5, 5.2), diastolic blood pressure (DD=1.7 mmHg; 95% CrI: -0.3, 3.6), and pulse wave velocity (DD=3.7% m/s; 95% CrI: -2.2, 10.2), as well as similar decreases in CPP (DD=0.1 mmHg; 95% CrI: -1.9, 2.2) compared to those who received the cookstove intervention (Clark et al. 2019). The authors speculate that the ineffectiveness of the cookstove intervention was due to increased use of gas and electric cookstoves among the non-intervention group during the study (Clark et al. 2019). Other studies have assessed AIx and particulate and gaseous air pollution from ambient sources (Zanoli et al. 2017). Multiple studies in a systematic review reported adverse associations between AIx and ambient air pollution; however, results across studies were inconsistent and the heterogeneity of the studies did not allow for a meta-analysis to be conducted (Zanoli et al. 2017).

Central hemodynamic indices are important to study in household air pollution research because they are pathophysiologically more relevant and predict clinical events independently of traditional indicators of cardiovascular risk such as peripheral (brachial) blood pressure (Vlachopoulos et al. 2010a). AIx and CPP are indicators of central aortic and overall cardiac workload, and both have strong associations with future adverse cardiovascular events and all-cause mortality (Vlachopoulos et al. 2010a). Although we did not observe changes in our study, $PM_{2.5}$ exposure can initiate biological pathways that induce changes in hemodynamic outcomes like AIx and CPP (Brook et al. 2010). Numerous studies have reported increased levels of circulating inflammatory markers following exposure to particulate matter air pollution (Brook et al. 2010), and a number of studies have reported adverse associations between inflammatory markers and household air pollution (Fatmi and Coggon 2016; McCracken et al. 2012). Potential

changes in central hemodynamic health outcomes such as AIx and CPP could occur through inflammatory and oxidative stress pathways that are initiated by $PM_{2.5}$ exposures and lead to impaired vascular function and vasoconstriction (Franklin et al. 2015). Such acute changes in vascular function could occur repeatedly due to chronic air pollution exposures, and over time, could result in structural changes in vasculature that impact hemodynamics (Brook et al. 2010).

Although there is limited evidence on how household air pollution impacts measures of central hemodynamics and arterial stiffness, there is strong evidence that acute and chronic exposures to cigarette smoke can adversely impact hemodynamic indices (Doonan et al. 2010). Further research also suggests that hemodynamic outcomes can improve within months following smoking cessation (Oren et al. 2006; Xue et al. 2019). In contrast to these studies which observed improved hemodynamic function following smoking cessation, our participants were still exposed to high levels of air pollution even after the *Justa* cookstove intervention. It is possible that the *Justa* cookstove did not lower concentrations of household air pollution in our study enough to improve AIx or CPP in the participants.

Other possible reasons for the null associations we observed may be related to the inherent weaknesses in conducting field research: exposure misclassification and secondary cookstove use may have had an impact on our results. Measurement error on a numerical scale can attenuate associations (Armstrong 1998); our measurements of $PM_{2.5}$ occurred once every six months during the study and may not represent typical levels of household air pollution in our study population. However, we made up to six 24-hour measurements of personal and kitchen $PM_{2.5}$ in each household during both rainy and dry seasons. These efforts to classify exposure are much more thorough than typical field studies assessing health outcomes in household air pollution research (Clark et al. 2013b). The categorical stove-type exposure variables in our analyses may also have been subject to misclassification. For the ITT analysis, women were expected to use the assigned cookstove (traditional vs *Justa*) based on their randomized study arm assignment. While the primary traditional cookstove was destroyed when

participants received the intervention *Justa* cookstove, women still used secondary traditional cookstoves along with the primary assigned cookstove, which may have attenuated the impact of the *Justa* cookstove and biased the results toward the null.

Knowing that actual cookstove use may have been different than the assigned cookstove from the ITT analysis, in a separate analysis we assessed the impact of self-reported cookstove use. Contrary to our expectations, when we used all study observations the cookstove-use analysis indicated that participants who used the *Justa* as their primary cookstove had higher AIx compared to those who used traditional cookstoves (Table 5.3; Figure C7). We observed similar, although less extreme associations when CPP was the outcome of interest (Table 5.3; Figure C12). These findings were unexpected; however, we believe the results may have been impacted by missing data. The associations disappeared when we completed the cookstove-use analysis using complete-case data (only participants who completed all six visits). We cannot make the assumption that the complete-case data is unbiased (i.e., data were missing completely at random), as there could have been a selection bias that resulted from using only participants who did *not* miss a study visit (Lewin et al. 2018). However, we believe it is likely that at least some of the effect seen in the cookstove-use analysis using the full dataset was at least partially caused by missing data. For example, during visit 2, 46 participants had missing outcome data due to a malfunction in the Sphygmocor XCEL used to measure AIx and CPP; these 46 participants had a missing observation when they were using traditional cookstoves. The same 46 participants also happened to have higher indicators of socioeconomic status at baseline (Table C6), were slightly older than the general study population (40 years vs 38 years), and had higher AIx throughout the study (22.8 % vs 21.1%) compared to the overall study population. Therefore, these 46 missing datapoints from visit 2 were not completely at random, but were related to both the exposure and the outcomes of interest and may have caused a selection bias that impacted the results. In a sensitivity analysis that excluded these 46 participants (all observations), the cookstove-use analysis results are

attenuated (Figure C7 for AIx; Figure C12 for CPP). There may have been other instances of selection bias in the cookstove-use analysis, as participants who missed a study visit had different age and socioeconomic characteristics (Table C5 vs Table C7), and produced distinctly different model estimates compared to those who did not miss a study visit (Figures C7-C16).

There are statistical approaches to account for missing data in some scenarios, such as inverse probability weighting or multiple imputation; however, when outcome data follow a missing-at-random pattern, as is the assumption with our data, inverse probability weighting and multiple imputation do not perform better than a complete case analysis at producing an unbiased estimate (Lewin et al. 2018). In fact, these methods can even perform worse and add additional noise to the estimates compared to a complete case analysis (Lewin et al. 2018). Such missing data issues are common in randomized controlled trials, and we have followed recommendations by presenting an analysis using all data alongside sensitivity analyses such as a complete case analysis (Bell et al. 2014). In a separate sensitivity analysis, we also assessed cookstove-use compliance across the 6 study visits. Figures C11 and C16 indicate that participants who were compliant and used only the assigned cookstove throughout the study produced similar model results compared to participants who used secondary traditional cookstoves or were non-compliant and used various cookstoves throughout the study. After assessing the primary results and multiple sensitivity analyses, it appears that the overall conclusion from the analyses is that the *Justa* cookstove intervention likely did not meaningfully impact AIx or CPP in our study population.

We attempted to improve on previous household air pollution studies by implementing an experimental design with high internal validity to help minimize confounding, using an in-depth and multifaceted approach to capture exposure, and by using a community-engaged approach to encourage adoption of the intervention *Justa* cookstove. The reasons for our null results are unknown and likely complex; regardless of why we did not observe strong associations in our study, our results indicate that the *Justa* biomass cookstove intervention did

not impact central hemodynamic outcomes of AIx and CPP. Other studies have reported lower blood pressure values following biomass cookstove interventions (Clark et al. 2013a; McCracken et al. 2007), yet the only other field study to assess central hemodynamic outcomes following a cookstove intervention reported results similar to ours (Clark et al. 2019). Combined, these results indicate that biomass cookstove interventions can lead to reduced levels of household air pollution but may have limited impact on central hemodynamic health outcomes (Bruce et al. 2015; Quansah et al. 2017). We recommend that future studies evaluate the impact of community-wide interventions using cookstoves that burn cleaner fuels while also discouraging the use of secondary traditional cookstoves.

Conclusions

We conducted a randomized controlled trial with a community-engaged approach to introduce an improved biomass *Justa* cookstove into a study population of 230 traditional biomass cookstove users in rural Honduras. Personal and kitchen $PM_{2.5}$ concentrations were lower following the cookstove intervention; however, our results from the ITT and stove-use analyses indicate that the improved cookstove intervention did not meaningfully impact AIx or CPP, nor were these outcomes associated with personal or kitchen $PM_{2.5}$ in the exposure-response analysis. Future analyses will assess the impact of the cookstove intervention on outcomes of blood pressure and biomarkers of inflammation.

CHAPTER 6: CONCLUSIONS

Summary

This dissertation utilized two complementary study designs to assess the cardiovascular health effects of air pollution emitted from cookstoves. In a controlled exposure study with a crossover design and a randomized controlled trial with a cookstove intervention, we assessed the impacts of various cookstove technologies on blood lipids and markers of central hemodynamics and arterial stiffness. The findings and overall contribution of this work are presented below.

Cardiovascular health effects following cookstove air pollution exposures in a controlled exposure study

Previous research has assessed the health impacts of different levels of household air pollution emitted from various cookstove technologies in both field and laboratory settings. However, previous studies have been limited by assessing only one cookstove intervention or exposure level within a study population; the health impacts across a spectrum of cookstove technologies and exposure levels has never been assessed within one study design. Our controlled exposure study from Aim 1 used a crossover design with treatments from five different cookstove technologies – each with a unique target concentration of $PM_{2.5}$ – to assess the health impacts of $PM_{2.5}$ emitted from multiple cookstove technologies within a single study population.

While there were weaknesses in our study design and research question, including limited generalizability from our study population and questionable applicability of acute changes in health outcomes, the strengths of the study were numerous. By assessing controlled exposures in a laboratory setting, we were able to quantify the health impacts resulting from a wide range of $PM_{2.5}$ concentrations (10 $\mu g/m^3$ to 500 $\mu g/m^3$) emitted from multiple different cookstove technologies; this type of design is not feasible in a field setting. In addition, we were

able to include a filtered air control in our matrix of treatment levels so that each participant could serve as their own control; this design helped limit confounding factors and produce a study with high internal validity. Furthermore, the laboratory setting of the study gave us the ability to measure complex health outcomes in a controlled setting.

The results we have presented suggest that air pollution emitted from each of the cookstoves in our study can adversely impact central hemodynamics, arterial stiffness, and blood lipids within 24 hours after exposure. We observed marginally higher PWV, CPP, and triglycerides 24-hours after the 2-hour cookstove treatments compared to control. The magnitude of the differences in the health outcomes was similar across each of the cookstove treatments compared to control even though the target $PM_{2.5}$ concentrations had a range of nearly 500 $\mu g/m^3$. At 24 hours after the cookstove treatments compared to control, PWV was between 0.08 and 0.16 meters/second higher for all treatments, CPP was between 0.6 and 1.6 mmHg higher for all treatments, and triglycerides were between 7.6% and 12.1% higher for all treatments except for the rocket elbow treatment. Results at other time points after the treatments, and for AIx, total cholesterol, HDL, and LDL at all time points, indicated no meaningful differences between the treatments and control.

Few studies have previously assessed associations between household air pollution and central hemodynamic indices and blood lipids. We have done so in a study that is designed to have high internal validity across a wide spectrum of exposures, and our results provide evidence that short-term exposures to air pollution emitted from cookstoves can adversely impact PWV, CPP, and triglycerides within 24 hours. The similar magnitude of the differences we observed in PWV, CPP, and triglycerides across each cookstove treatment indicates that even exposures from the cleanest cookstove technologies can adversely impact health. These are important findings as we attempt to interpret what impact different levels of cookstove air pollution may have on health. It is possible that no amount of cookstove air pollution can be considered “safe”.

Central hemodynamic health effects following a biomass cookstove intervention in a randomized controlled trial in Honduras

The WHO recommends that 24-hour mean concentrations of ambient $PM_{2.5}$ remain below 25 µg/m^3 and that annual mean concentrations remain below 10 µg/m^3 (World Health Organization 2006), yet cookstove interventions are typically unable to achieve this (Quansah et al. 2017). The question remains of whether or not lowering $PM_{2.5}$ exposures in populations of cookstove users to levels below what they typically experience, but still higher than WHO recommendations, can result in improved health outcomes. The answer to this question will impact the lives of billions of individuals around the world and inform future decisions on the design and dissemination of cookstove technologies. The randomized trial in Aim 2 used an experimental design in a field setting in Honduras to contribute further information to this important question.

We assessed the impact of an improved biomass cookstove intervention in a group of 230 Honduran women. The results from Aim 2 were largely null, and analyses indicated that the improved *Justa* cookstove intervention did not meaningfully impact AIx or CPP. These indicators of central aortic hemodynamics were also not associated with $PM_{2.5}$ in the exposure-response analysis, although 24-hour concentrations of personal and kitchen $PM_{2.5}$ were reduced in the study population following the cookstove intervention.

The study design used in Aim 2 was complementary to the controlled exposure study in Aim 1. Whereas the controlled exposure study lacked generalizability and could only assess health impacts following short-term exposures on an acute timeframe, the randomized trial implemented in Aim 2 took place in a field setting in Honduras over the course of three years. Although this study only assessed one type of intervention cookstove technology, it did so within a randomized design that produced high internal validity. Additionally, the Aim 2 study in Honduras attempted to improve on past cookstove interventions by using a community-engaged approach to encourage adoption and continued use of the *Justa* cookstove.

The ineffectiveness of the intervention at improving AIx and CPP could be due to numerous reasons, including secondary traditional cookstove use, additional exposure to air pollution from neighboring households, or that the cookstove intervention did not lower air pollution exposures enough to result in observable improvements in AIx or CPP. Future analyses on other outcomes (i.e., peripheral blood pressure, C-reactive protein, and glycated hemoglobin) will help provide clarity on how the *Justa* cookstove intervention impacted cardiometabolic health in our study population. Regardless of the reason for the null results, our findings from this study will help inform future research and cookstove interventions.

Overall conclusions

The findings from this dissertation indicate that household air pollution can impact triglycerides and indices of central hemodynamics and arterial stiffness on an acute timeframe across a broad spectrum of $PM_{2.5}$ exposure levels. In addition, results from Aim 1 do not indicate that, compared to a filtered air control, lower levels of cookstove air pollution emitted from improved cookstove technologies are any less harmful (in the outcomes we assessed) than higher levels of cookstove air pollution emitted from a traditional open fire. Results from Aim 2 are complementary to Aim 1, and indicate that modest reductions in household air pollution from the use of a *Justa* biomass cookstove did not impact central hemodynamic health measures. Assessing further health measures in both studies will help paint a clearer picture of the overall impacts of the controlled exposures and the *Justa* cookstove intervention. The cookstove exposures in these studies may impact other outcomes in a different manner than the outcomes assessed here. Additionally, assessing other biomarkers such as inflammatory cytokines could help describe some of the underlying impact on physiological pathways that was not observed in the measurements we assessed.

Beyond this dissertation, it will be important to continue to assess the health impacts of various types of cookstove technologies. Given the body of research and what our results contribute, and particularly if further studies continue to produce similar findings, organizations

and governments may be hesitant to invest in cookstove interventions which produce minimal improvements in health. Assessing the impact of cookstoves that use alternative fuels and power sources (e.g., LPG or solar) in field studies with strong designs, such as the randomized trial used in Aim 2, will help provide clarity on the type of cookstove interventions that will ultimately lead to improved health outcomes. Future studies should also assess the health impacts of a wider range of participants, including children and younger adults. It is important to know how lower exposures from various cookstove technologies impact the health of those with varying levels of cumulative lifetime exposure.

While the results from this dissertation have not revealed an obvious solution that will change the lives of cookstove users around the world, the conclusions are important nonetheless: the current approach is not enough. This global issue will continue for years to come unless more drastic, widespread interventions are evaluated and implemented. Continued research and novel ideas are needed to understand what changes in the cookstove paradigm are necessary to improve the health of the nearly 3 billion individuals across the world who currently use biomass fuels for cooking purposes.

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APPENDIX A: SUPPLEMENTAL MATERIAL FOR CHAPTER 3

Methods

Participants and recruitment process

Participant recruitment took place separately for each of the three study sessions. Emails to Colorado State University students and staff and articles in local newspapers were the primary form of advertising for the study. Once an inquiry was made by a potential participant they were asked to fill out an initial checklist of eligibility criteria (described in main text). If participants met the eligibility criteria from the checklist, they were contacted to schedule an individual health assessment. As a part of the health assessment, participants completed a physical examination, health history, electrocardiogram, lung function assessment by spirometry, blood pressure assessment, and a blood draw to measure complete blood count, complete metabolic panel, and lipid panel. Written, informed consent was obtained for participation in the individual health assessment, separate from consent for the main study. The study physician reviewed all health assessment results and made a final decision regarding each individual's ability to participate in the study. Study staff also spoke with each potential participant regarding any concerns about study participation and any potential regular exposures to particulates or other pollutants.

Study sessions

The main text describes that study participants were asked to refrain from alcohol, smoke exposures, and medications during the study sessions. Beginning 24 hours prior to each treatment and continuing until after the 24 hour follow-up health assessment, participants were asked to eat a low fat, low cholesterol diet, and to eat a consistent diet during each of their six study sessions. In order to facilitate this consistency in diet, the study provided lunch for the participants during their six sessions. On their first session, participants chose from a selection of sandwiches or salads catered by a local business; they received the same item for lunch

each of the following sessions. Low fat snacks were also available to the participants throughout their time at the study facility.

Health assessments

Study personnel were trained by a Sphygmocor representative to perform health measurements using the Sphygmocor Xcel device; manufacturer protocols were adhered to. After a 10 minute rest period with the participant in supine position, study personnel placed a cuff on the participant's left arm over the brachial artery. Three consecutive blood pressure measurements were taken and recorded with the participant lying supine. After the blood pressure measurements, the cuff partially inflated again and captured a five-second reading of the brachial artery waveform to calculate central augmentation index (AIx) and central pulse pressure (CPP). Immediately following the AIx and CPP measurements, carotid-femoral pulse wave velocity (PWV) was assessed with the participant remaining in supine position. Study personnel were trained to use a hand-held tonometer to capture a carotid artery waveform and a leg cuff to capture a femoral artery waveform. Sphygmocor software calculated PWV (meters/second) using the measured distance and waveform travel time between the carotid and femoral artery measurement sites. Participants were advised to avoid movement and talking during all measurements. Quality control measures were integrated into the SphygmoCor software to assess magnitude and consistency of pulse waves. If a measurement did not pass quality control it was repeated; only measurements that passed quality control were used for analysis.

Some health outcomes assessed in the study may have been influenced by the participant's level of physical activity. In order to limit variability in health outcomes, participants inside the Simulated Environmental Testing (SET) facility were asked to remain seated, avoid watching suspenseful videos, and avoid talking during the 2-hour treatments. During the times before and after the treatments when the participants remained at the testing facility building, they were asked to work quietly and limit physical activity; participants were asked to take the

elevator when it was necessary to access different floors of the testing facility building. In addition, participants were given noise-canceling headphones to wear during the treatments, which reduced external noise from the SET facility and allowed participants to communicate with study personnel via an intercom system.

Other health outcomes performed during each health assessment, but not reported here, included the following: heart rate variability and cardiac repolarization using a 12-lead holter monitor; brachial blood pressure; lung function assessment via spirometry; complete blood count, lipid panel, and C-reactive protein via venous blood draw. Additional aliquots of blood plasma were processed and frozen for future analysis.

Controlled treatments

Make and model of cookstoves used to generate controlled treatments:

- Liquefied petroleum gas (LPG): Classic Single Burner 25000 BTU, WokSmith, China
    - Fine particulate matter ($PM_{2.5}$) target level: 10 $\mu g/m^3$
- Gasifier: Ace 1 Gasifier, African Clean Energy (Pty) Ltd, Lesotho
    - $PM_{2.5}$ target level: 35 $\mu g/m^3$
- Forced-draft fan rocket elbow: HomeStove, Biolite, USA
    - $PM_{2.5}$ target level: 100 $\mu g/m^3$
- Natural-draft rocket elbow: G3300, Envirofit International, USA
    - $PM_{2.5}$ target level: 250 $\mu g/m^3$
- Traditional three stone fire: open fire, bricks in U-shape used to contain fuel
    - $PM_{2.5}$ target level: 500 $\mu g/m^3$

Results

Table A1: Baseline values of health outcomes prior to each treatment level

Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone fire
Pulse wave velocity, m/s: mean (sd); n; p-value*					
Females					
6.0 (1.0); 22; *ref*	5.7 (0.6); 22; *p = 0.07*	5.7 (0.6); 20; *p = 0.13*	5.9 (0.8); 21; *p = 0.72*	5.8 (0.6); 22; *p = 0.22*	5.9 (1.0); 22; *p = 0.15*
Males					
6.1 (0.7); 25; *ref*	6.1 (0.6); 23; *p = 0.93*	6.1 (0.6); 24; *p = 0.62*	6.0 (0.4); 23; *p = 0.97*	6.1 (0.5); 23; *p = 0.56*	6.2 (0.6); 25; *p = 0.31*
Augmentation index, %: mean (sd); n; p-value*					
Females					
10.3 (14.3); 22; *ref*	12.4 (8.3); 22; *p = 0.40*	14.9 (10.6); 20; *p = 0.15*	13.4 (10.3); 21; *p = 0.40*	13.1 (8.6); 22; *p = 0.34*	12.8 (12.2); 22; *p = 0.40*
Males					
5.3 (8.5); 25; *ref*	5.4 (11.3); 23; *p = 0.83*	8.8 (10.4); 24; *p = 0.13*	7.0 (12.2); 23; *p = 0.24*	6.4 (9.6); 23; *p = 0.44*	6.1 (9.6); 24; *p = 0.59*
Central pulse pressure, mmHg: mean (sd); n; p-value*					
Females					
29.5 (4.9); 22; *ref*	30.9 (4.7); 22; *p = 0.07*	30.8 (4.7); 20; *p = 0.10*	31.5 (4.2); 21; *p = 0.08*	31.2 (4.4); 22; *p = 0.03*	30.4 (4.2); 22; *p = 0.40*
Males					
32.8 (5.4); 25; *ref*	32.5 (6.1); 23; *p = 0.50*	33.3 (5.9); 24; *p = 0.72*	31.8 (5.1); 23; *p = 0.16*	32.5 (4.8); 23; *p = 0.80*	32.8 (5.3); 24; *p = 0.97*

LPG = liquefied petroleum gas; sd = standard deviation

*Based on paired t-tests comparing mean values prior to each cookstove treatment level and filtered-air control.

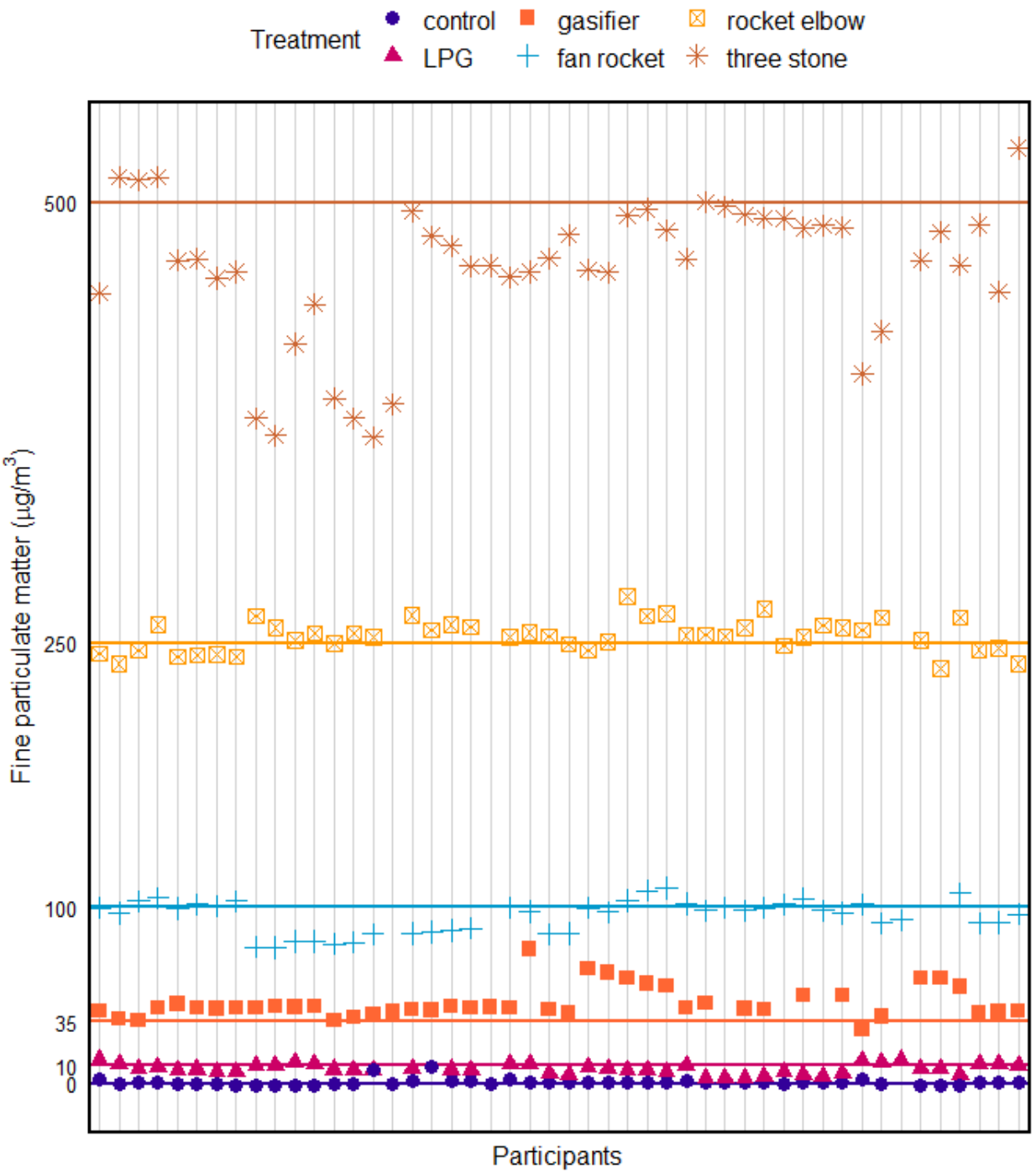

Figure A1: Mean fine particulate matter exposures experienced by study participants
Horizontal lines indicate target concentrations of fine particulate matter for each treatment level. Symbols are marking concentrations of personal mean fine particulate matter exposure for each participant during their 2-hour treatments.
LPG = liquefied petroleum gas

Sensitivity analyses

The primary model used in our analyses was a linear mixed model that included a fixed categorical term for treatment level, a fixed continuous term for baseline health measurement, a random term for participant, and a random term for date of treatment. Sensitivity analyses were performed to assess other model variations, subsets of the data, and to check for potential confounding. Further description of these analyses and subsequent results are described below.

Additional model variations

A secondary model included additional terms to explicitly model the Latin square design and was run on a subset of the data in which treatments were attended in the assigned sequence (excluding out-of-sequence makeup visits). This secondary model included a fixed interaction term for study day and assigned sequence, and a random nested term for study day, assigned sequence, and participant. This model was not considered the primary model because makeup visits could be used in the analysis if we did not include the additional terms. Table A2 shows the number of observations at each post-treatment time point in the full dataset vs the in-sequence dataset. The figures below show there were no meaningful differences between this model and the primary model presented in the main text.

Table A2: Number of observations in full dataset vs in-sequence dataset

	Full dataset (# observations)	In-sequence dataset (# observations)
0 hours post-treatment:		
Pulse wave velocity	272	244
Augmentation index	272	244
Central pulse pressure	272	244
3 hours post-treatment:		
Pulse wave velocity	272	241
Augmentation index	268	241
Central pulse pressure	268	241
24 hours post-treatment:		
Pulse wave velocity	274	241
Augmentation index	261	237
Central pulse pressure	261	237

Table A3: Mean concentrations of ambient fine particulate matter 24 hours before each health measurement time point

Health measurement timepoint	Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone fire
	Mean ambient $PM_{2.5}$ (sd), $\mu g/m^3$					
Baseline (pre-treatment)	5.1 (3.1)	8.4 (4.4)	5.6 (2.7)	8.7 (4.3)	7.1 (3.0)	6.3 (3.1)
0-hour post-treatment	5.0 (2.8)	8.2 (4.2)	5.4 (2.5)	8.7 (4.2)	7.0 (3.0)	6.1 (3.1)
3-hour post-treatment	5.0 (2.6)	7.8 (4.1)	5.3 (2.5)	8.9 (4.1)	7.0 (3.1)	6.0 (3.2)
24-hour post-treatment	5.3 (2.5)	6.2 (2.5)	5.9 (3.5)	9.6 (4.1)	7.3 (4.0)	6.4 (3.2)

LPG = liquefied petroleum gas; sd = standard deviation; $PM_{2.5}$ = fine particulate matter

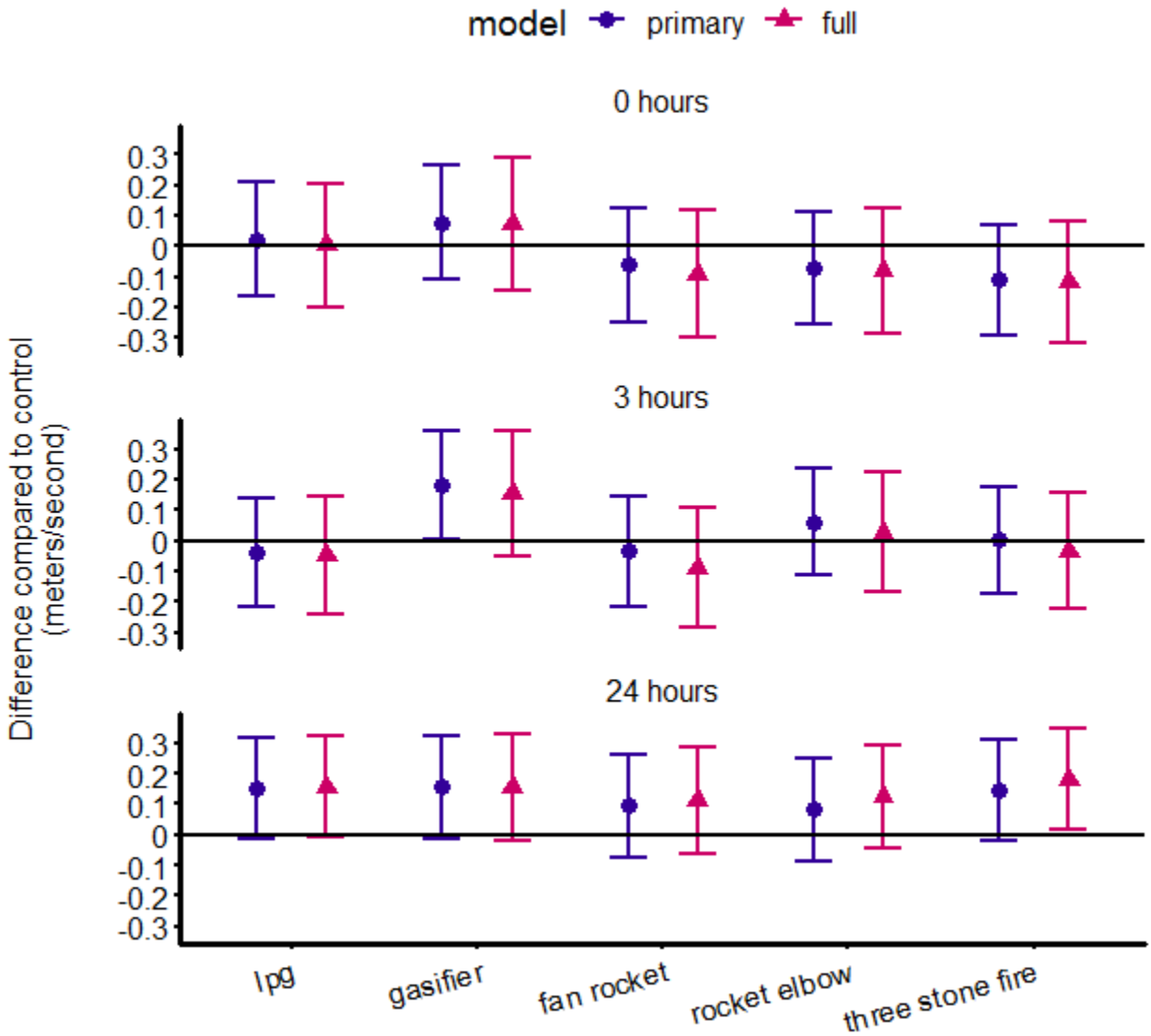

Figure A2: Pulse Wave Velocity primary versus full model results
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
full model terms: primary model + day*sequence (fixed) + nested day:sequence:participant (random)

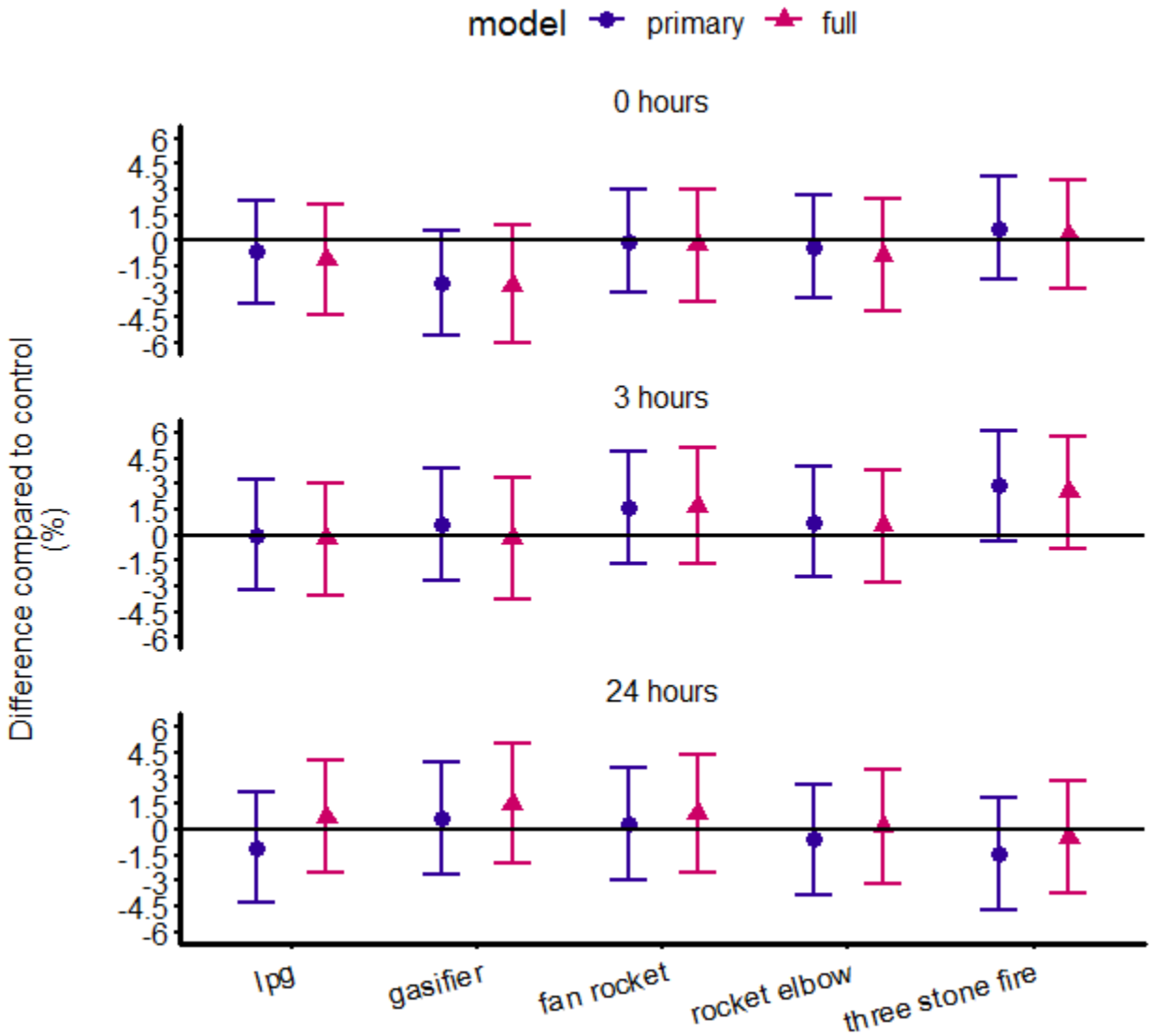

Figure A3: Augmentation Index primary versus full model results
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
full model terms: primary model + day*sequence (fixed) + nested day:sequence:participant (random)

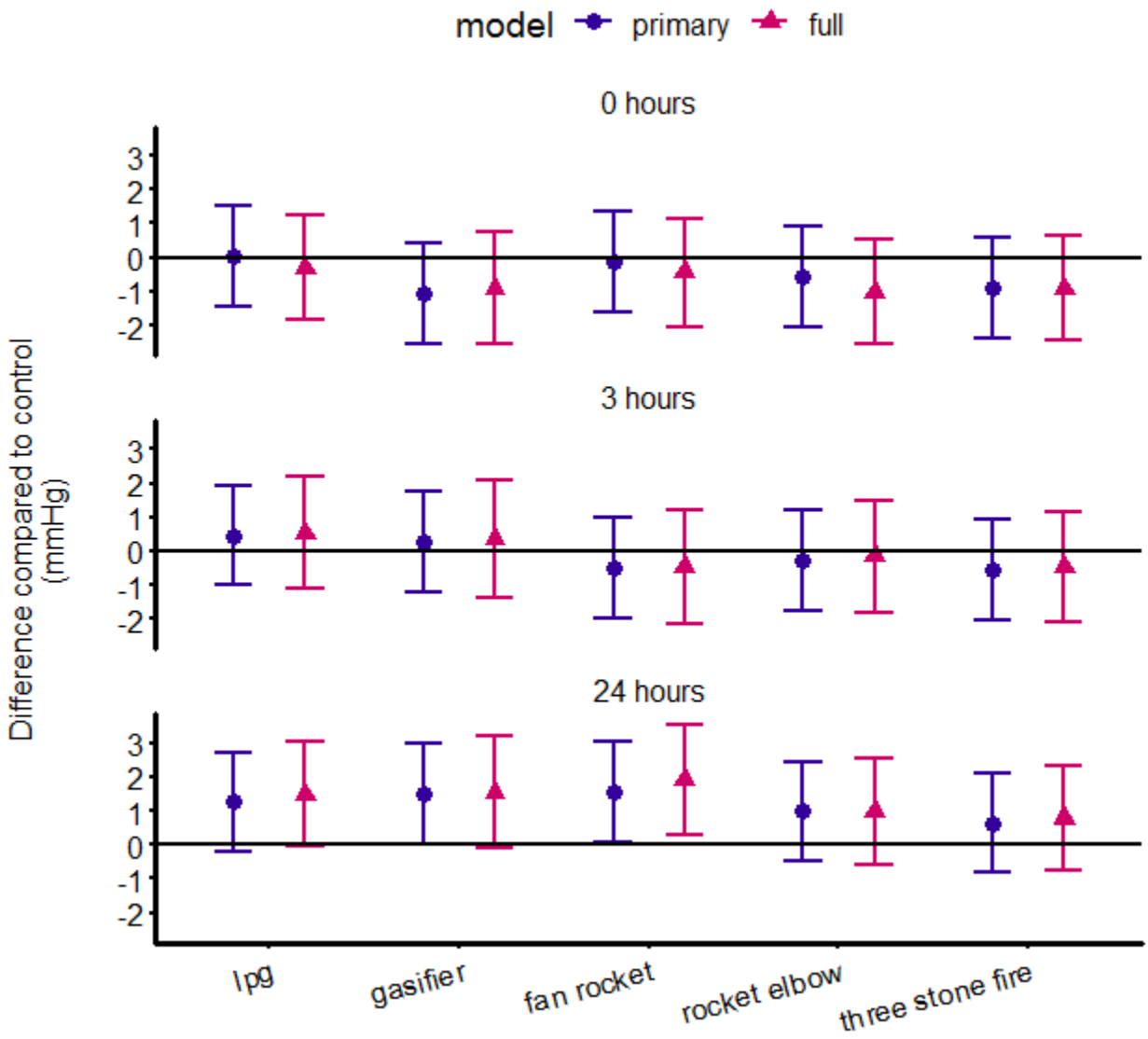

Figure A4: Central Pulse Pressure primary versus full model results
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
full model terms: primary model + day*sequence (fixed) + nested day:sequence:participant (random)

Results using subsets of the data

Additional analyses were performed using a subset of the data in which study sessions were only included if participants had data from all three follow-up time points (0, 3, and 24 hours after treatment). This sensitivity analysis was done to see if results were potentially biased by participants missing time points throughout the study. If missed time points were related to both the exposure of interest and the outcome, reported results could have been biased. The sensitivity analyses confirmed that results were similar when comparing the full dataset to those who did not miss a time point.

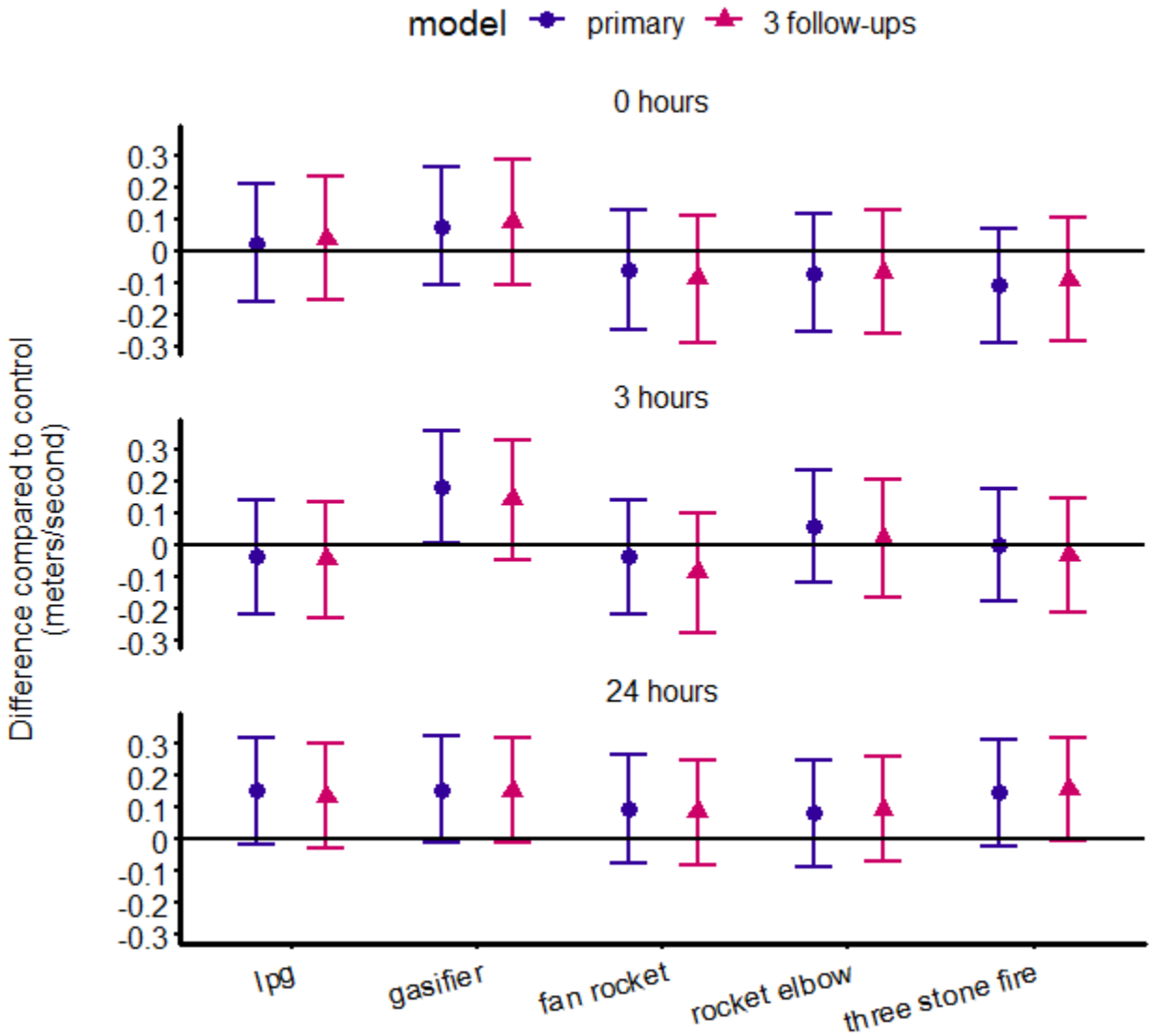

Figure A5: Pulse Wave Velocity primary versus 3 follow-ups model results
lpg: liquefied petroleum gas; primary model n=1079 observations; 3 follow-ups model n=1008 observations
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
3 follow-ups model: subset of the data in which study sessions were only included if participants had data from all three follow-up time points (0, 3, and 24 hours after cookstove treatment)

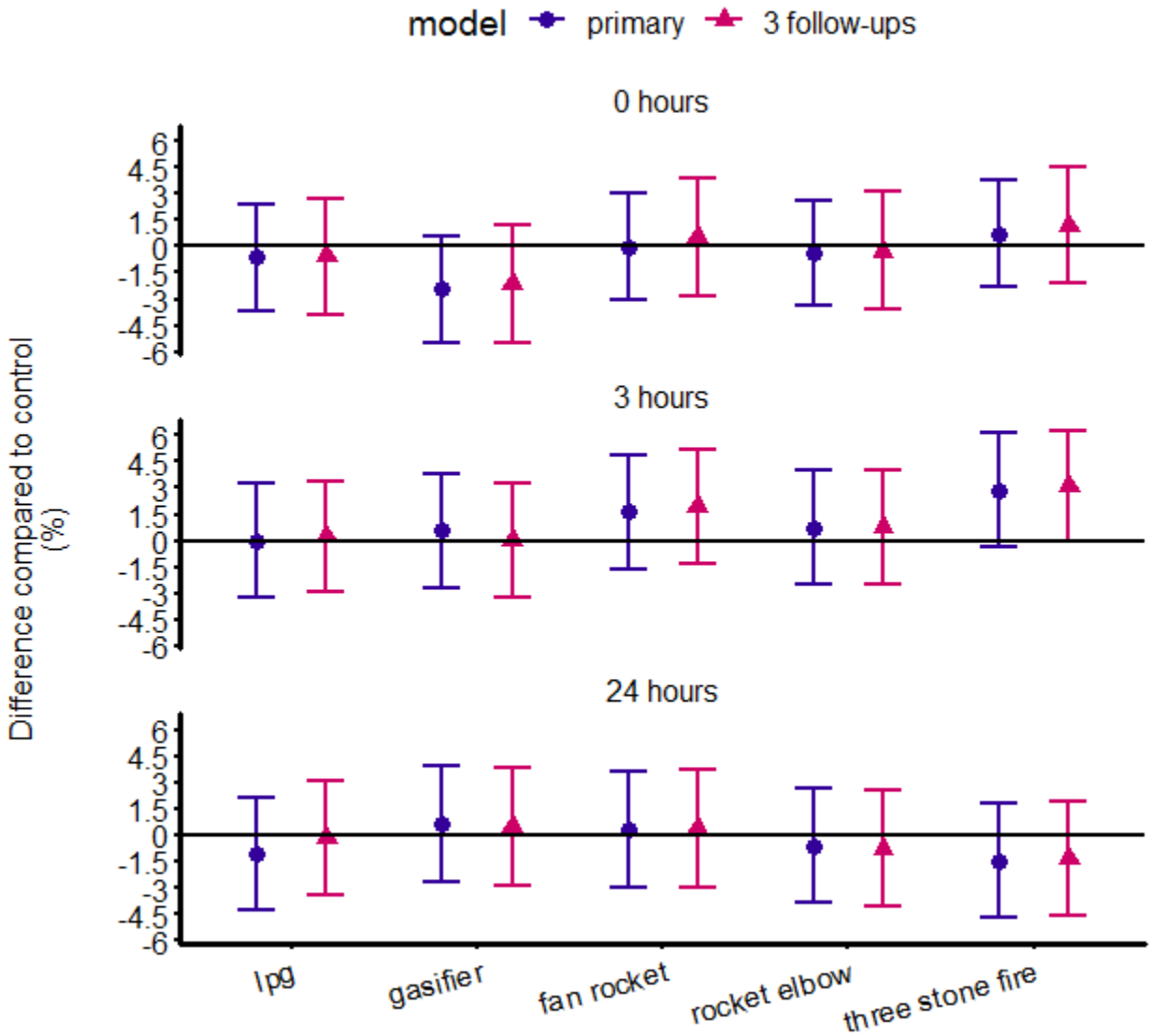

Figure A6: Augmentation Index primary versus 3 follow-ups model results
lpg: liquefied petroleum gas; primary model n=1072 observations; 3 follow-ups model n=988 observations
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
3 follow-ups model: subset of the data in which study sessions were only included if participants had data from all three follow-up time points (0, 3, and 24 hours after cookstove treatment)

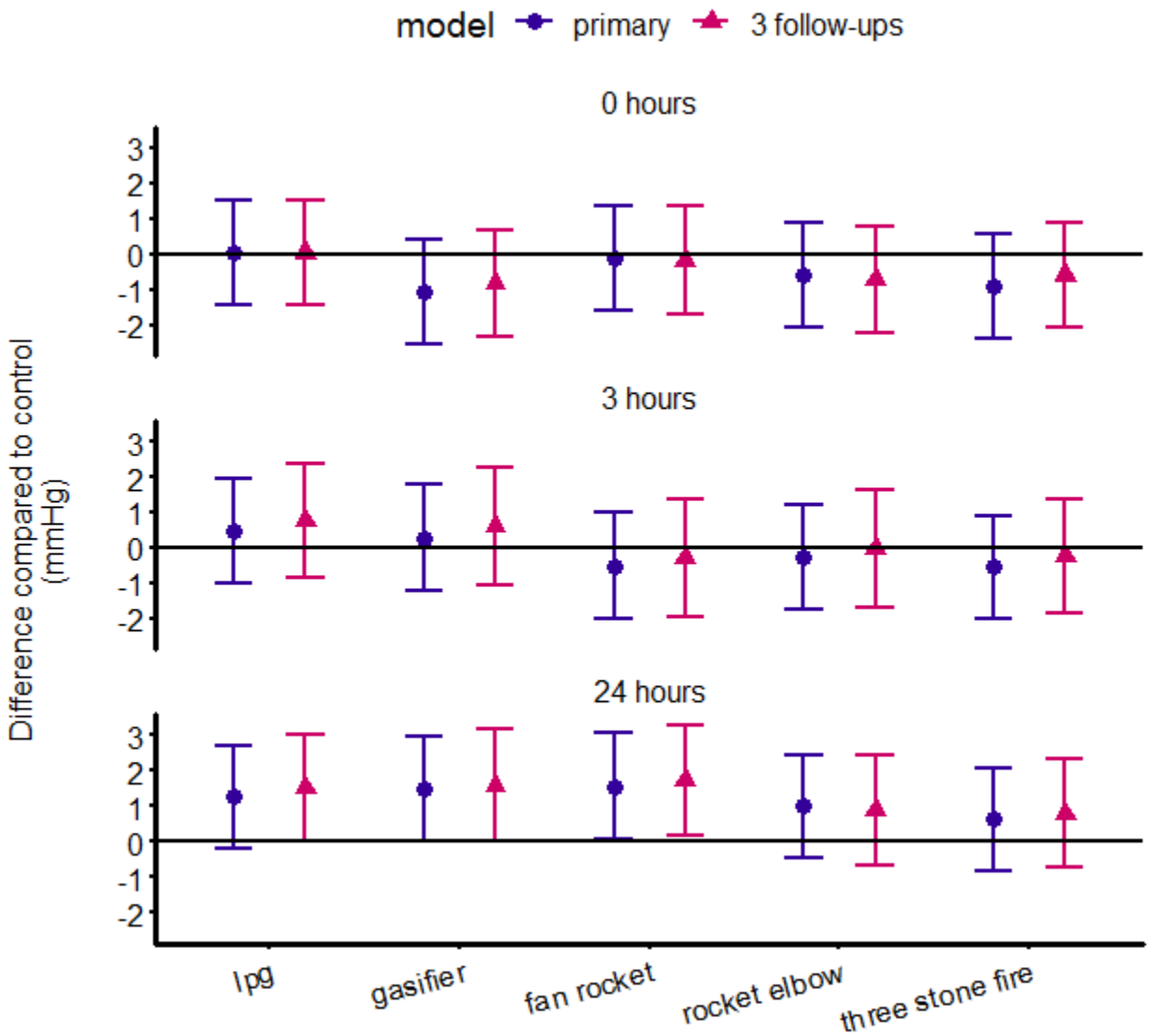

Figure A7: Central Pulse Pressure primary versus 3 follow-ups model results
lpg: liquefied petroleum gas; primary model n=1072 observations; 3 follow-ups model n=988 observations
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
3 follow-ups model: subset of the data in which study sessions were only included if participants had data from all three follow-up time points (0, 3, and 24 hours after cookstove treatment)

Potential confounders

The crossover study design helped limit the effect of potential confounding in our study (see main text for further description). However, sensitivity analyses were performed to assess for potential confounding that may have occurred by chance. Sensitivity analyses were conducted by including the following terms into the primary model and comparing results to those from the primary model:

- ambient temperature 24 hours prior to each health measurement
- ambient fine particulate matter 24 hours prior to each health measurement
- participant sex
- self-reported alcohol consumption (dichotomous) during the 24 hours prior to each study day
- self-reported caffeine consumption (dichotomous) during the 24 hours prior to each study day
- self-reported medication use (dichotomous) during the 24 hours prior to each study day
- self-reported smoke exposure (dichotomous) during the 24 hours prior to each study day
- self-reported strenuous physical activity (dichotomous) during the 24 hours prior to each study day
- self-reported sleep (less than typical, typical, more than typical) prior to each study day
- self-reported bike travel to study facility (dichotomous) prior to each study day

- self-reported walking travel to study facility (dichotomous) prior to each study day
- self-reported car travel to study facility (dichotomous) prior to each study day

Results from the sensitivity analyses are similar to those from the primary analyses, and indicate that the potential impact of confounding during our study was minimal.

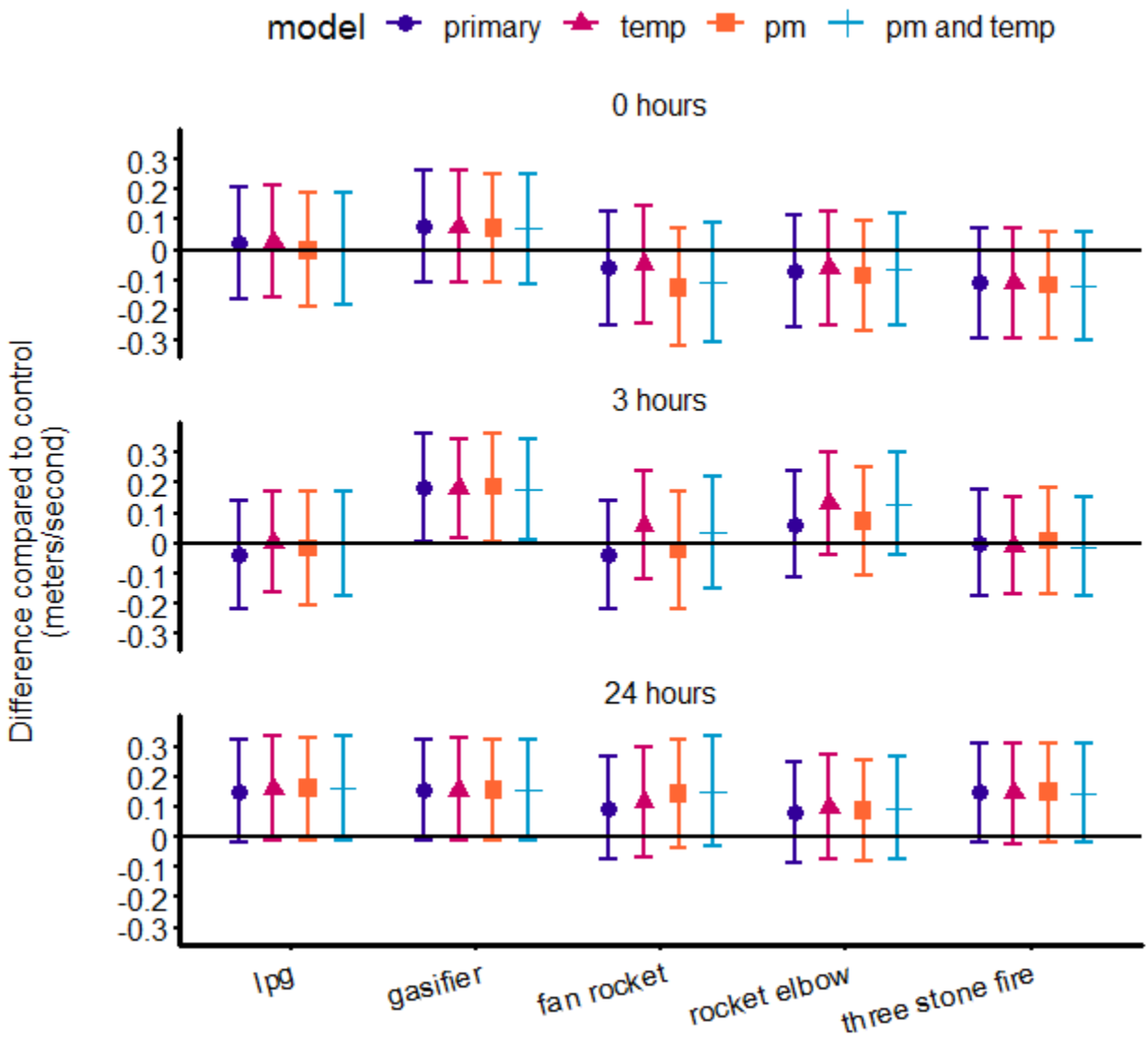

Figure A8: Pulse Wave Velocity sensitivity analyses with potential confounders
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
temp model terms: primary model + ambient temperature 24 hours prior to each health measurement
pm model terms: primary model + ambient fine particulate matter 24 hours prior to each health measurement
pm and temp model terms: temp and pm models combined

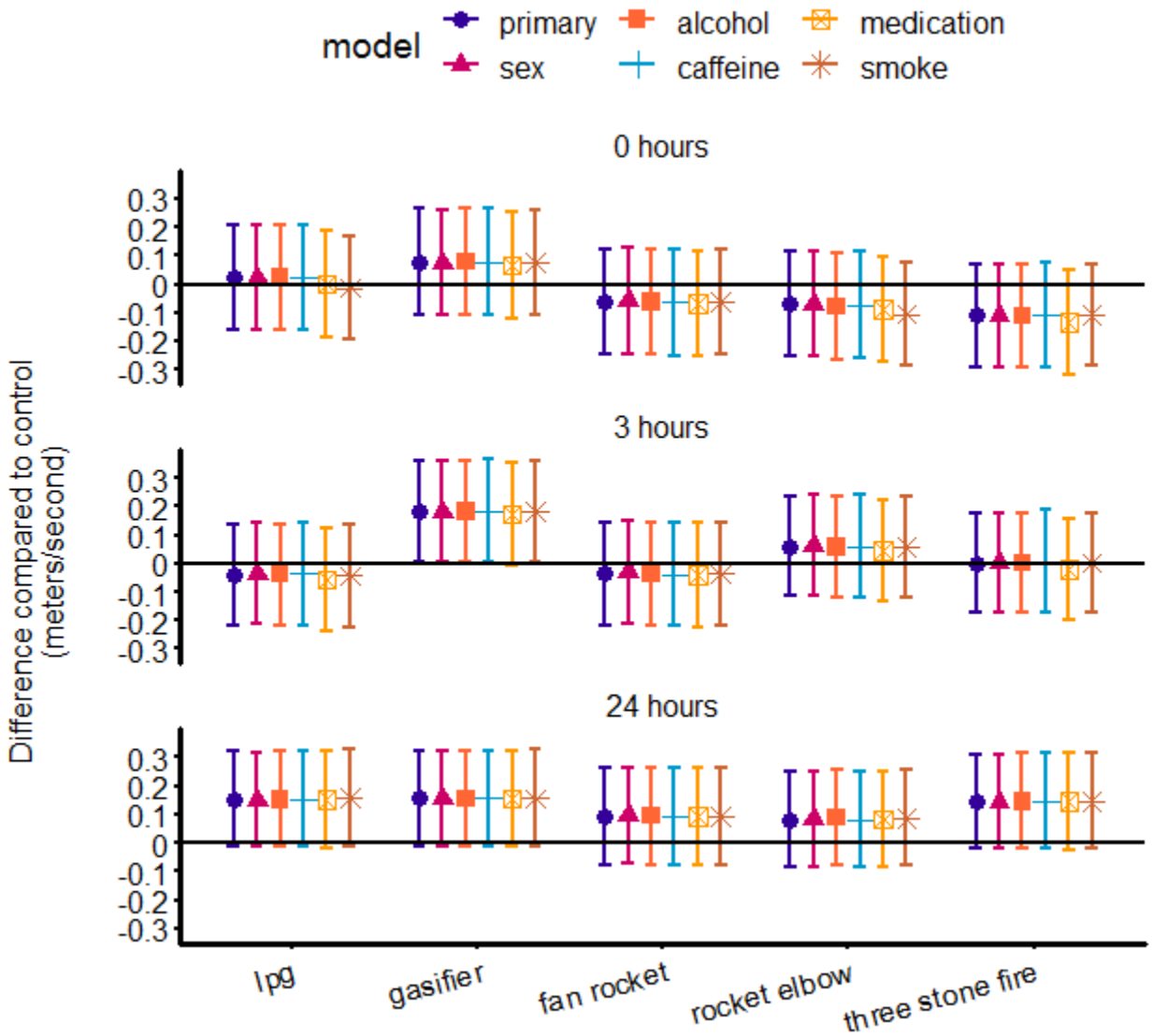

Figure A9: Pulse Wave Velocity sensitivity analyses with potential confounders, continued

lpg: liquefied petroleum gas

primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

sex model terms: primary model + participant sex

alcohol model terms: primary model + self-reported alcohol consumption (dichotomous) prior to each study day

caffeine model terms: primary model + self-reported caffeine consumption (dichotomous) prior to each study day

medication model terms: primary model + self-reported medication use (dichotomous) prior to each study day

smoke model terms: primary model + self-reported smoke exposure (dichotomous) prior to each study day

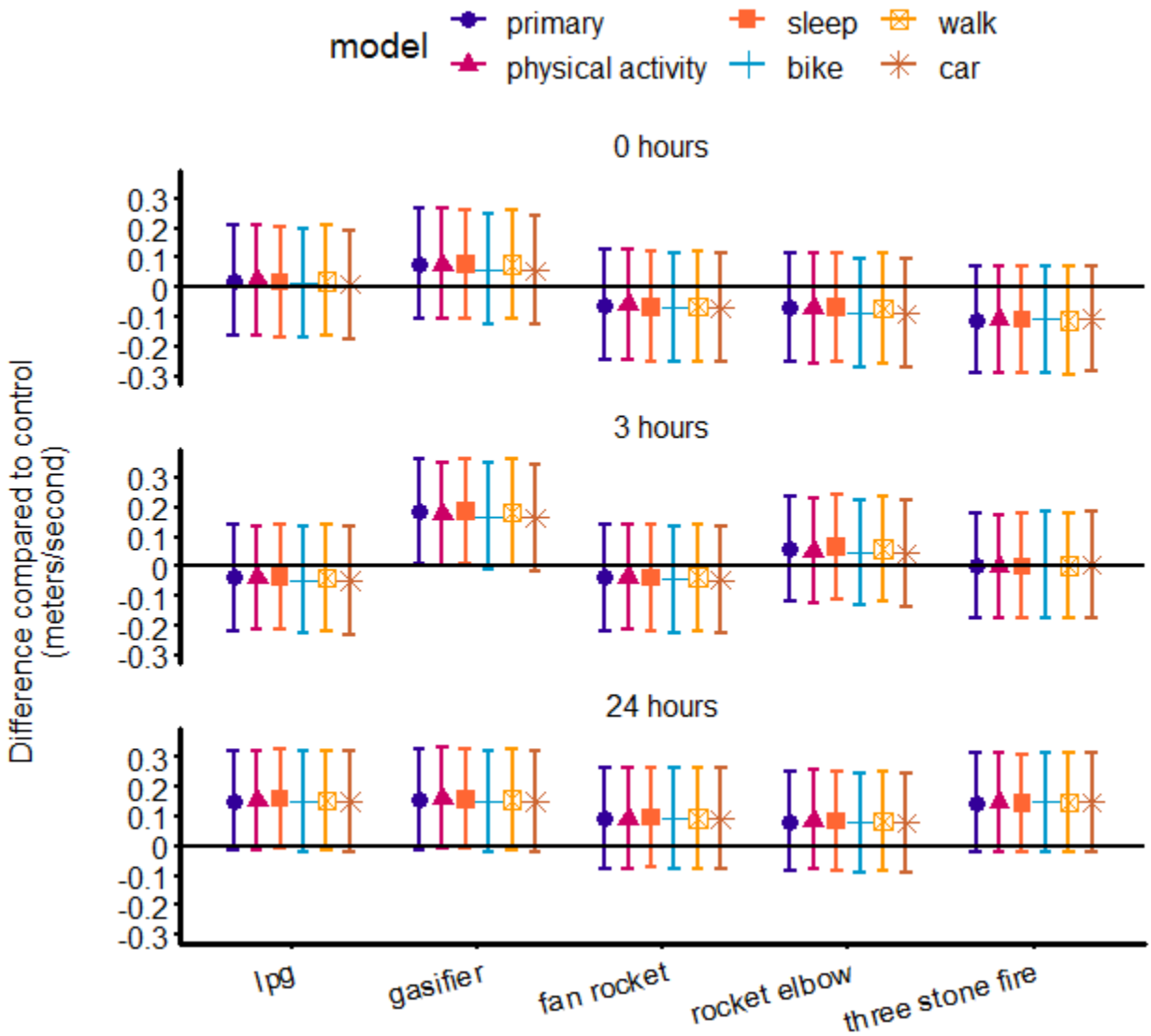

Figure A10: Pulse Wave Velocity sensitivity analyses with potential confounders, continued

lpg: liquefied petroleum gas

primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

physical activity model terms: primary model + self-reported strenuous physical activity (dichotomous) prior to each study day

sleep model terms: primary model + self-reported sleep (less than typical, typical, more than typical) prior to each study day

bike model terms: primary model + self-reported bike travel to study facility (dichotomous) prior to each study day

walk model terms: primary model + self-reported walking travel to study facility (dichotomous) prior to each study day

car model terms: primary model + self-reported car travel to study facility (dichotomous) prior to each study day

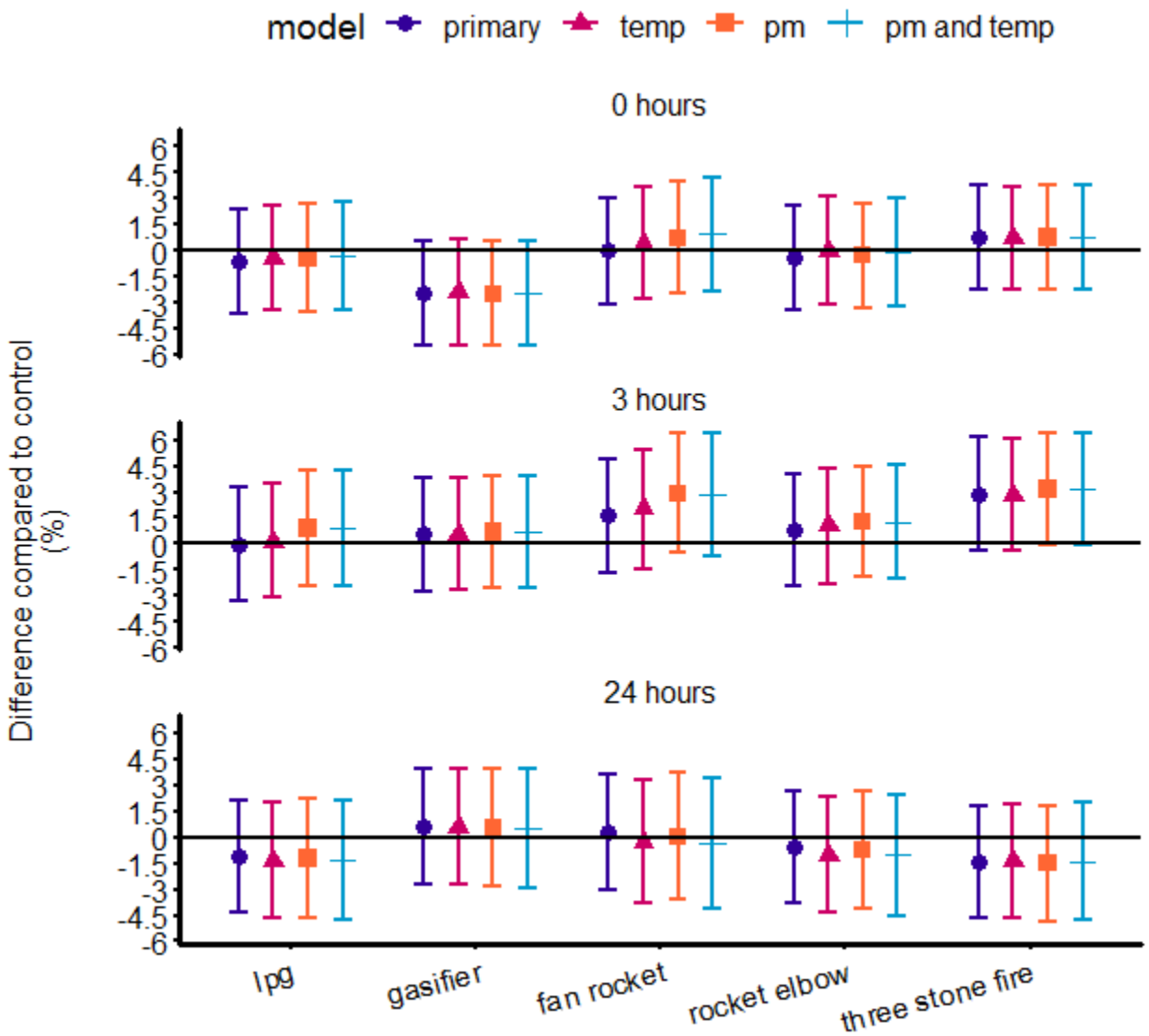

Figure A11: Augmentation Index sensitivity analyses with potential confounders
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
temp model terms: primary model + ambient temperature 24 hours prior to each health measurement
pm model terms: primary model + ambient fine particulate matter 24 hours prior to each health measurement
pm and temp model terms: temp and pm models combined

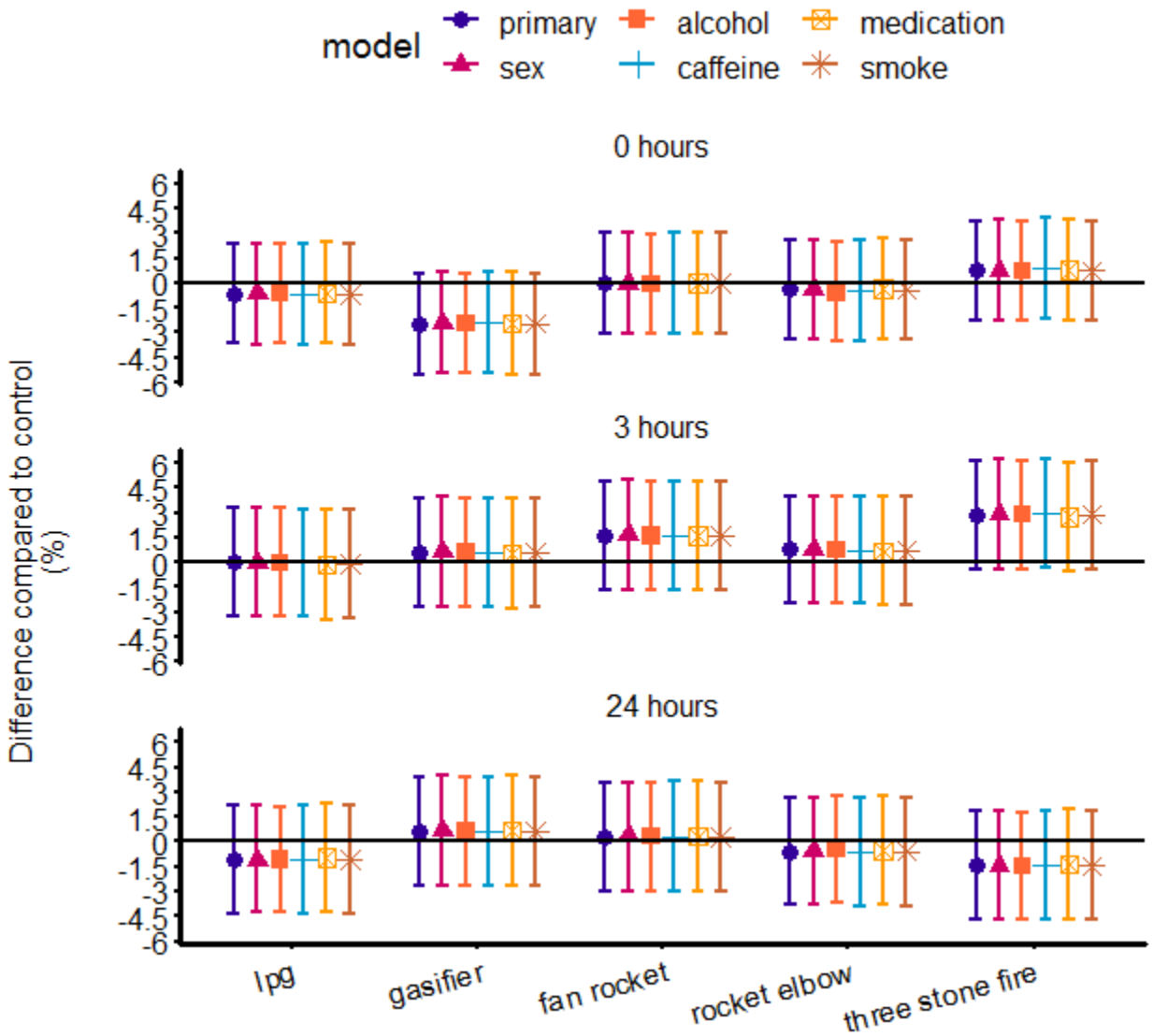

Figure A12: Augmentation Index sensitivity analyses with potential confounders, continued

lpg: liquefied petroleum gas

primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

sex model terms: primary model + participant sex

alcohol model terms: primary model + self-reported alcohol consumption (dichotomous) prior to each study day

caffeine model terms: primary model + self-reported caffeine consumption (dichotomous) prior to each study day

medication model terms: primary model + self-reported medication use (dichotomous) prior to each study day

smoke model terms: primary model + self-reported smoke exposure (dichotomous) prior to each study day

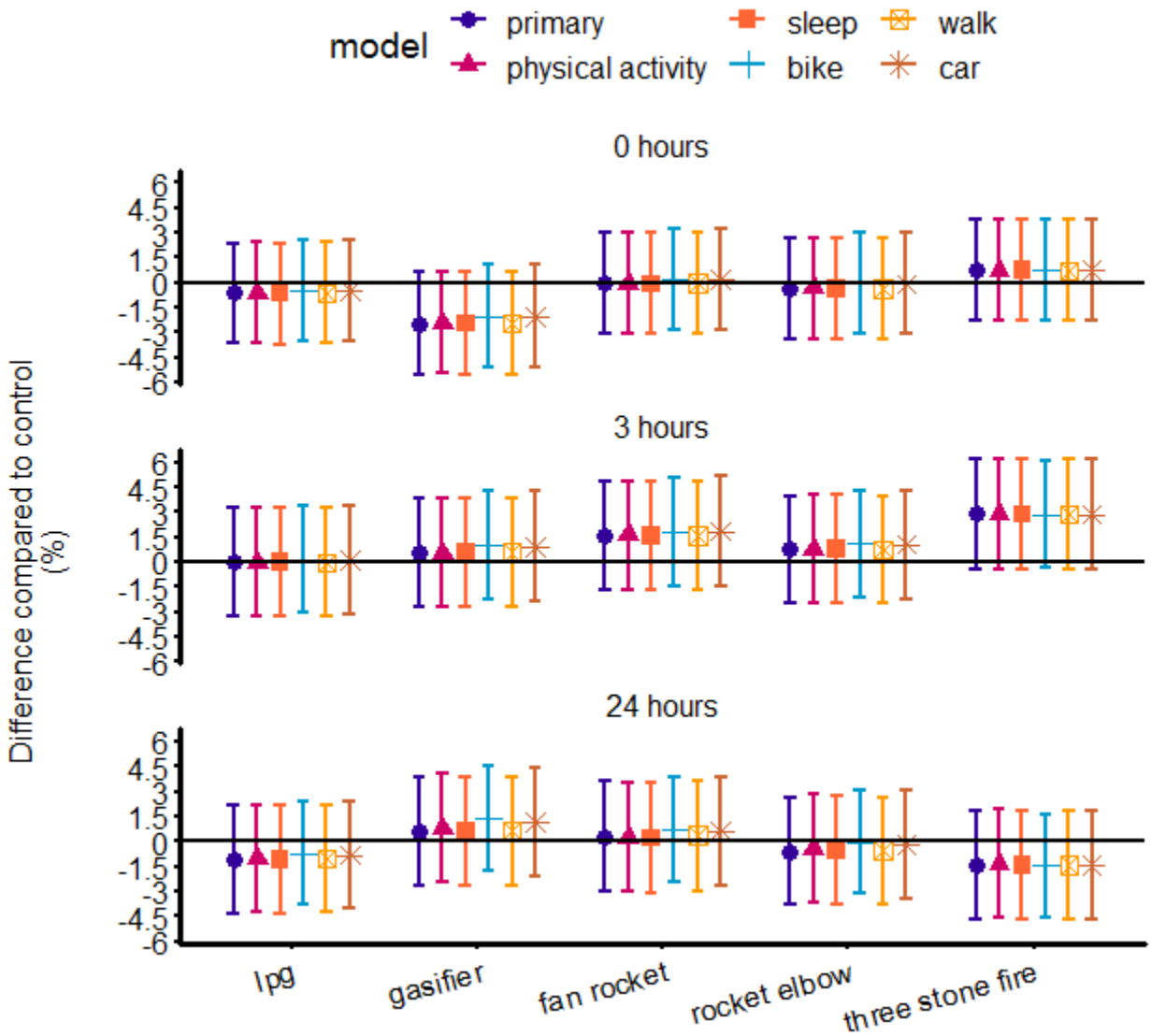

Figure A13: Augmentation Index sensitivity analyses with potential confounders, continued

lpg: liquefied petroleum gas

primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

physical activity model terms: primary model + self-reported strenuous physical activity (dichotomous) prior to each study day

sleep model terms: primary model + self-reported sleep (less than typical, typical, more than typical) prior to each study day

bike model terms: primary model + self-reported bike travel to study facility (dichotomous) prior to each study day

walk model terms: primary model + self-reported walking travel to study facility (dichotomous) prior to each study day

car model terms: primary model + self-reported car travel to study facility (dichotomous) prior to each study day

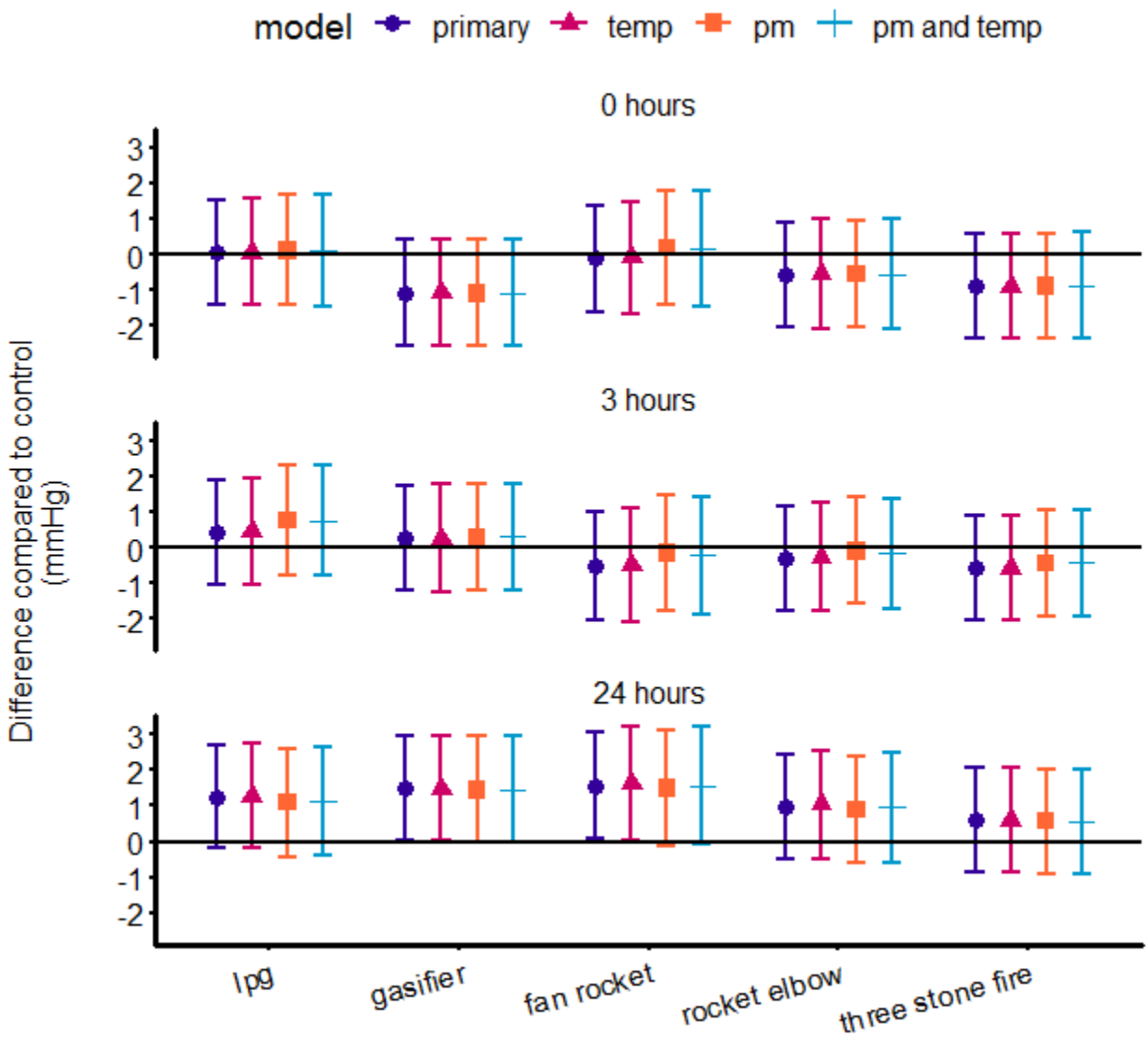

Figure A14: Central Pulse Pressure sensitivity analyses with potential confounders
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
temp model terms: primary model + ambient temperature 24 hours prior to each health measurement
pm model terms: primary model + ambient fine particulate matter 24 hours prior to each health measurement
pm and temp model terms: temp and pm models combined

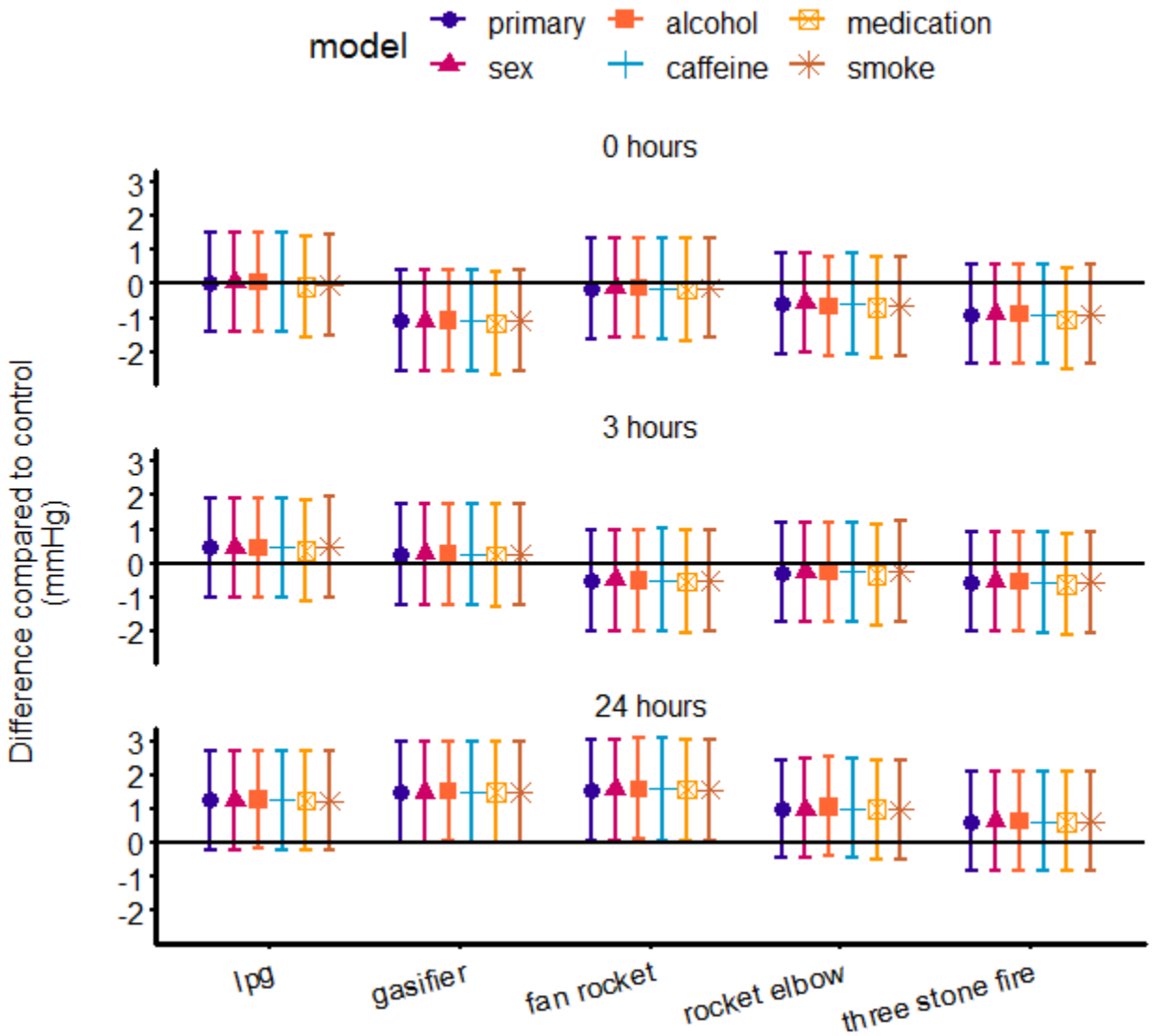

Figure A15: Central Pulse Pressure sensitivity analyses with potential confounders, continued

lpg: liquefied petroleum gas

primary model terms: cookstove treatment level (fixed) + treatment type (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

sex model terms: primary model + participant sex

alcohol model terms: primary model + self-reported alcohol consumption (dichotomous) prior to each study day

caffeine model terms: primary model + self-reported caffeine consumption (dichotomous) prior to each study day

medication model terms: primary model + self-reported medication use (dichotomous) prior to each study day

smoke model terms: primary model + self-reported smoke exposure (dichotomous) prior to each study day

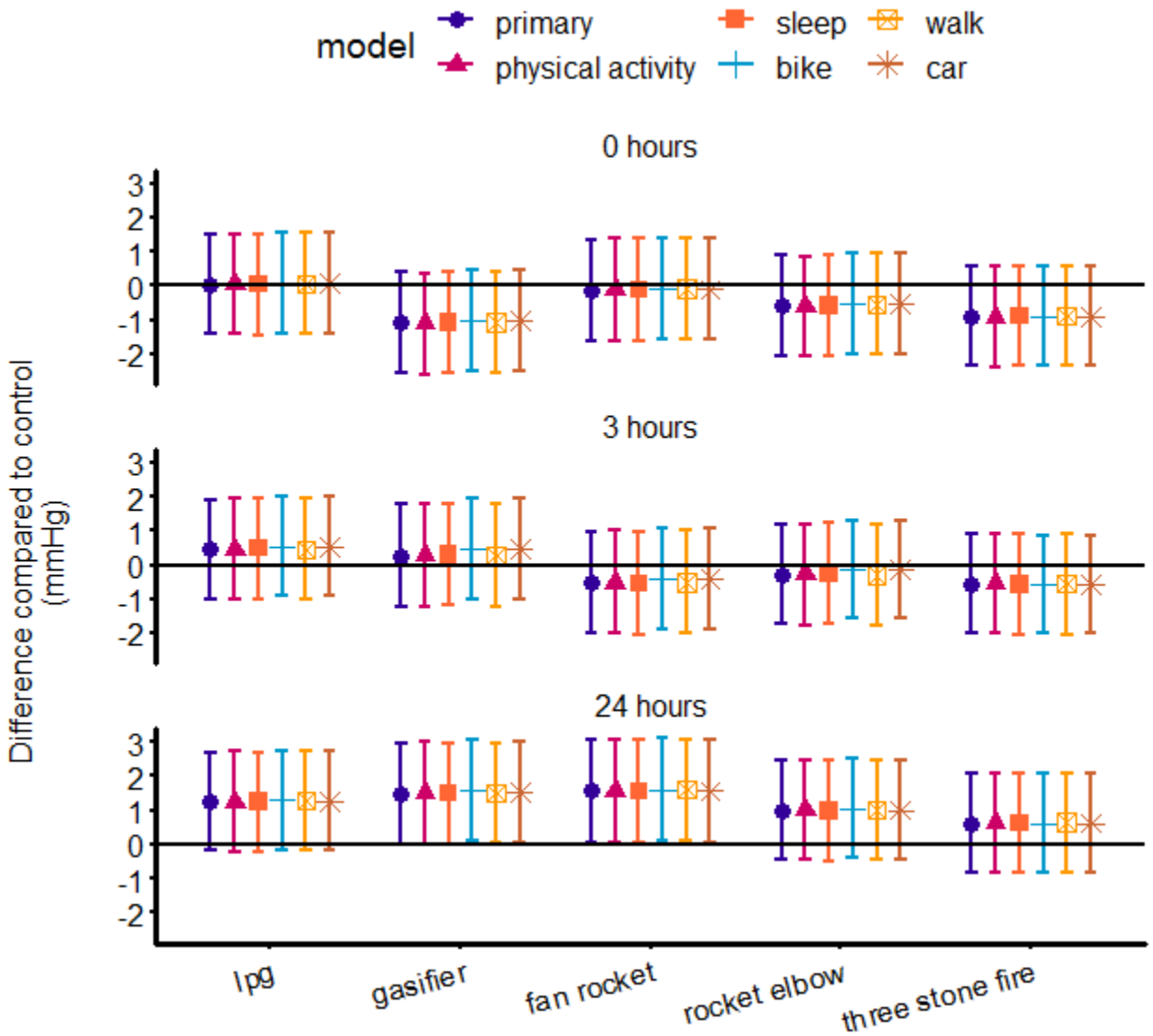

Figure A16: Central Pulse Pressure sensitivity analyses with potential confounders, continued

lpg: liquefied petroleum gas

primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

physical activity model terms: primary model + self-reported strenuous physical activity (dichotomous) prior to each study day

sleep model terms: primary model + self-reported sleep (less than typical, typical, more than typical) prior to each study day

bike model terms: primary model + self-reported bike travel to study facility (dichotomous) prior to each study day

walk model terms: primary model + self-reported walking travel to study facility (dichotomous) prior to each study day

car model terms: primary model + self-reported car travel to study facility (dichotomous) prior to each study day

Augmentation index standardized to heart rate of 75 beats per minute

Augmentation index (AIx) standardized to a heart rate of 75 beats per minute (AIx75) is commonly used in other research studies and in clinical settings. We used an unstandardized version of AIx in our analyses, as we believed heart rate to be a mediator between cookstove air pollution exposure and AIx. Rather than adjust out the effect of this potential mediator, our goal was to see the impact of the treatments on the outcome including any effect that may have occurred through changes in heart rate. As a sensitivity analysis, we assessed the impact of the treatments on AIx75 and compared the results to those from the primary analysis. Results were similar between AIx and AIx75, indicating that heart rate had minimal impact on AIx in our study.

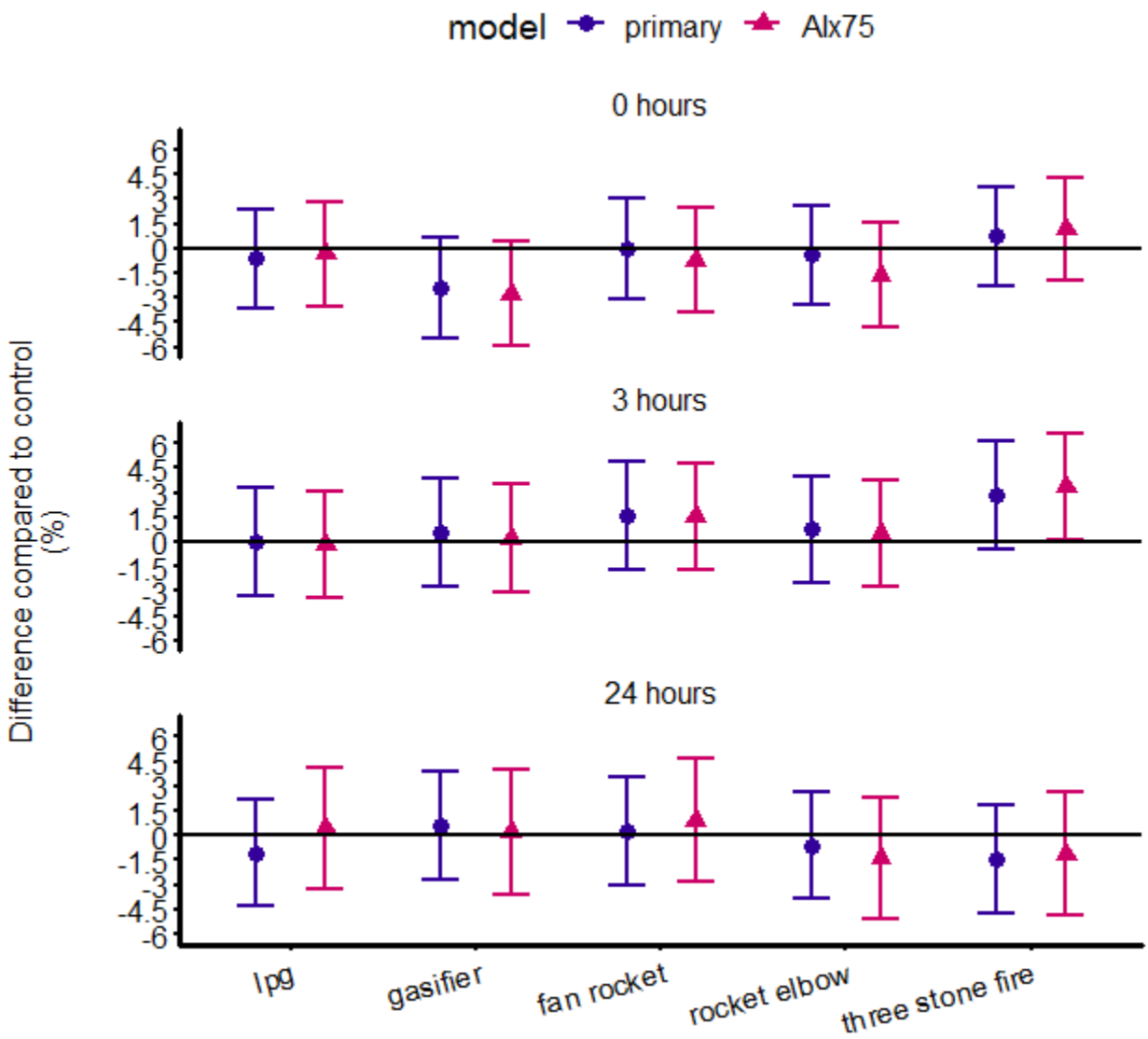

Figure A17: Augmentation Index standardized to heart rate of 75 beats per minute
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
AIx75 model: same terms as primary model; outcome is augmentation index standardized to heart rate of 75 beats/minute

APPENDIX B: SUPPLEMENTAL MATERIAL FOR CHAPTER 4

Results

Table B1: Baseline values of health outcomes prior to each treatment level

Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone fire
Total Cholesterol, mg/dL: mean (sd); n; p-value[1]					
Females					
184 (31); 22; *ref*	181 (30); 22; *p = 0.57*	191 (38); 20; *p = 0.40*	188 (33); 21; *p = 0.47*	182 (29); 21; *p = 0.61*	182 (37); 22; *p = 0.80*
Males					
159 (25); 25; *ref*	160 (26); 23; *p = 0.98*	156 (27); 24; *p = 0.55*	160 (25); 23; *p = 0.65*	160 (27); 23; *p = 0.89*	163 (32); 25; *p = 0.30*
High density lipoprotein, mg/dL: mean (sd); n; p-value[1]					
Females					
65 (16); 22; *ref*	61 (13); 22; *p = 0.01*	63 (16); 20; *p = 0.64*	66 (18); 21; *p = 0.94*	62 (15); 21; *p = 0.17*	61 (15); 22; *p = 0.02*
Males					
54 (11); 25; *ref*	55 (10); 23; *p = 0.97*	52 (10); 24; *p = 0.24*	54 (11); 23; *p = 0.74*	54 (12); 23; *p = 0.77*	54 (11); 25; *p = 0.59*
Low density lipoprotein, mg/dL : mean (sd); n; p-value[1]					
Females					
98 (31); 22; *ref*	100 (31); 22; *p = 0.64*	106 (31); 20; *p = 0.22*	101 (34); 21; *p = 0.38*	100 (30); 21; *p = 0.67*	100 (36); 22; *p = 0.72*
Males					
80 (23); 25; *ref*	81 (24); 23; *p = 0.82*	80 (24); 24; *p = 0.51*	79 (24); 23; *p = 0.49*	82 (24); 23; *p = 0.50*	83 (28); 25; *p = 0.16*
Triglycerides, mg/dL : mean (sd); n; p-value[2]					
Females					
108 (66); 22; *ref*	102 (42); 22; *p = 0.71*	108 (64); 20; *p = 0.71*	104 (53); 21; *p = 1.0*	93 (50); 21; *p = 0.07*	106 (56); 22; *p = 0.71*
Males					
125 (73); 25; *ref*	121 (51); 23; *p = 0.75*	119 (58); 24; *p = 0.63*	133 (75); 23; *p = 0.86*	122 (66); 23; *p = 0.73*	128 (56); 25; *p = 0.57*

LPG = liquefied petroleum gas; sd = standard deviation

[1] Based on paired t-tests comparing mean values prior to each cookstove treatment level and filtered-air control.

[2] Based on paired Wilcoxon tests comparing mean values prior to each cookstove treatment level and filtered-air control. Wilcoxon test used due to non-normal distribution of triglycerides.

Table B2: Frequency of self-reported consumption of higher fat or cholesterol food items

Health assessment time point*	Treatment					
	Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone fire
	n (%)					
Baseline (pre-treatment)	17 (36)	15 (33)	10 (23)	16 (36)	13 (29)	14 (30)
24-hour post-treatment	13 (29)	16 (36)	12 (29)	10 (23)	12 (27)	15 (32)

LPG = liquefied petroleum gas
Higher-fat or cholesterol food items were categorized by including the following terms: egg, cheese, bacon, sausage, ham, fried, burrito, pizza.
*Indicating the health assessment time point when the participant self-reported their dietary intake; food items were consumed in the morning prior to the respective health assessment time point.

Sensitivity analyses

Our primary model was a linear mixed model with a fixed categorical term for treatment level, a fixed continuous term for baseline health measurement, a random term for participant, and a random term for date of treatment. We performed a number of sensitivity analyses using other model variations, subsets of the data, and including potential confounders. Methods and results from the sensitivity analyses are presented below.

Additional model variations

We assessed a model with additional terms that explicitly modelled the Latin square design. In this model we included a fixed interaction term for study day and assigned sequence, and a random nested term for study day, assigned sequence, and participant. We ran the model on a subset of the data that excluding out-of-sequence makeup visits; visits were only included in the dataset if treatments were attended in the originally assigned sequence. Although only 22 of 48 participants completed all six of their treatments in the assigned sequence, most participants who were out of sequence only attended one study session out of the originally assigned order. Table B3 shows the number of observations at each post-treatment time point in the full dataset vs the in-sequence dataset. Results from the following figures show that there

were no meaningful differences between the full model using in-sequence data compared to the primary model that includes out-of-sequence data.

Table B3: Number of observations for blood lipids in full dataset vs in-sequence dataset

	Full dataset (# observations)	**In-sequence dataset (# observations)**
0 hours post-treatment	269	244
3 hours post-treatment	267	241
24 hours post-treatment	265	241

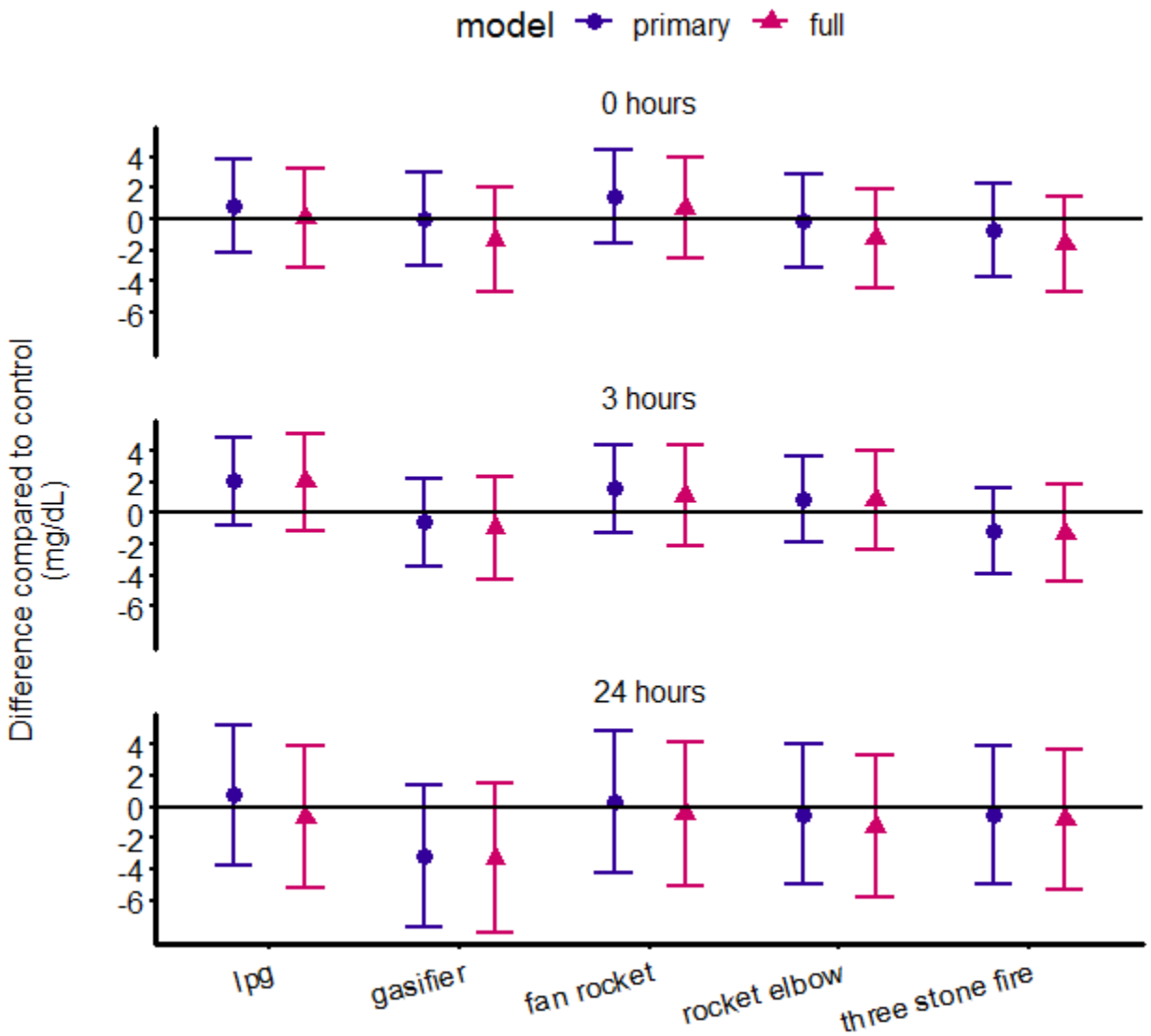

Figure B1: Total Cholesterol primary versus full model results
lpg: liquefied petroleum gas
Primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
Primary model used full dataset (# observations provided in Table B3)
Full model terms: primary model + day*sequence (fixed) + nested day:sequence:participant (random)
Full model used in-sequence dataset (# observations provided in Table B3)

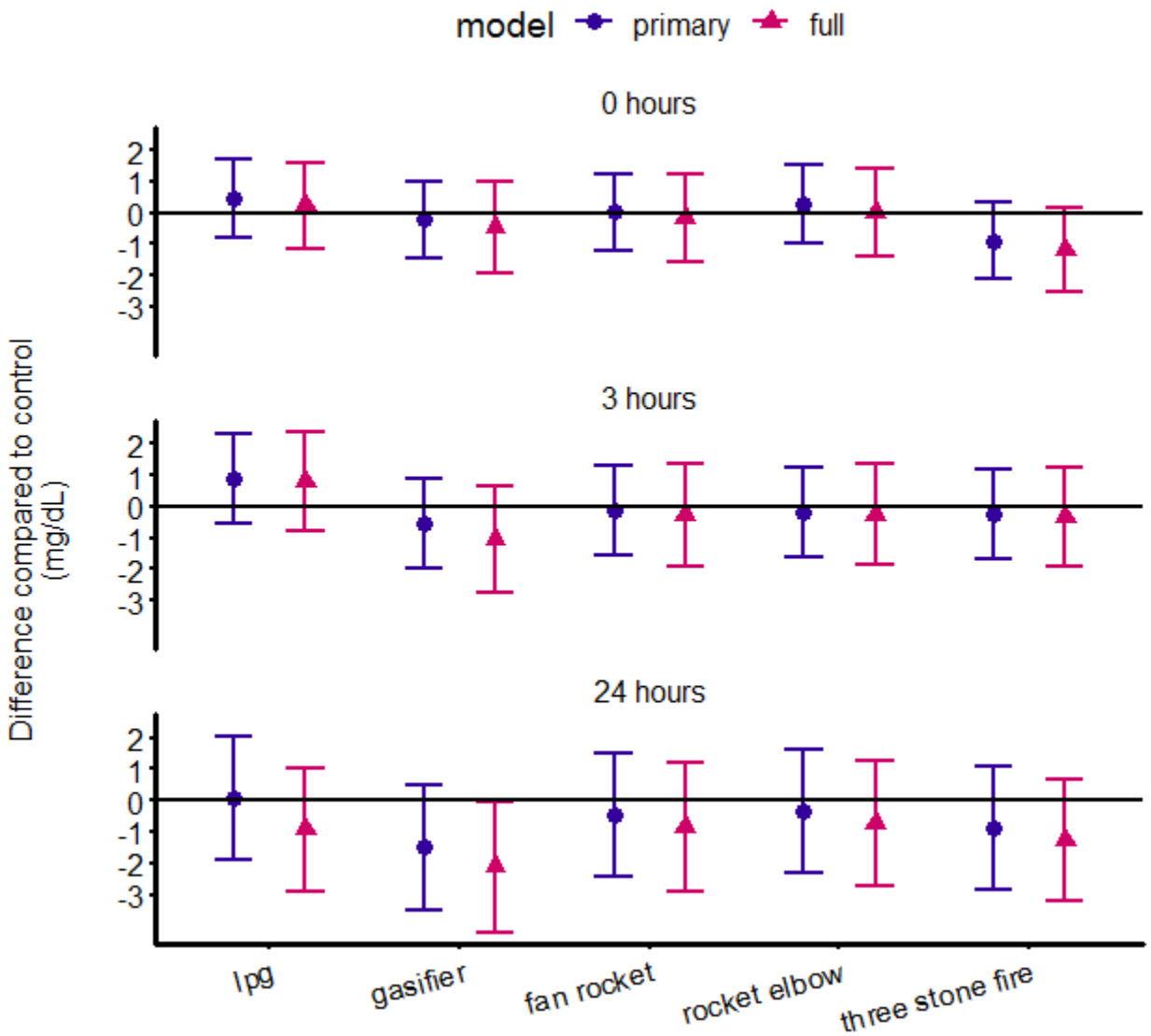

Figure B2: High Density Lipoprotein primary versus full model results
lpg: liquefied petroleum gas
Primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
Primary model used full dataset (# observations provided in Table B3)
Full model terms: primary model + day*sequence (fixed) + nested day:sequence:participant (random)
Full model used in-sequence dataset (# observations provided in Table B3)

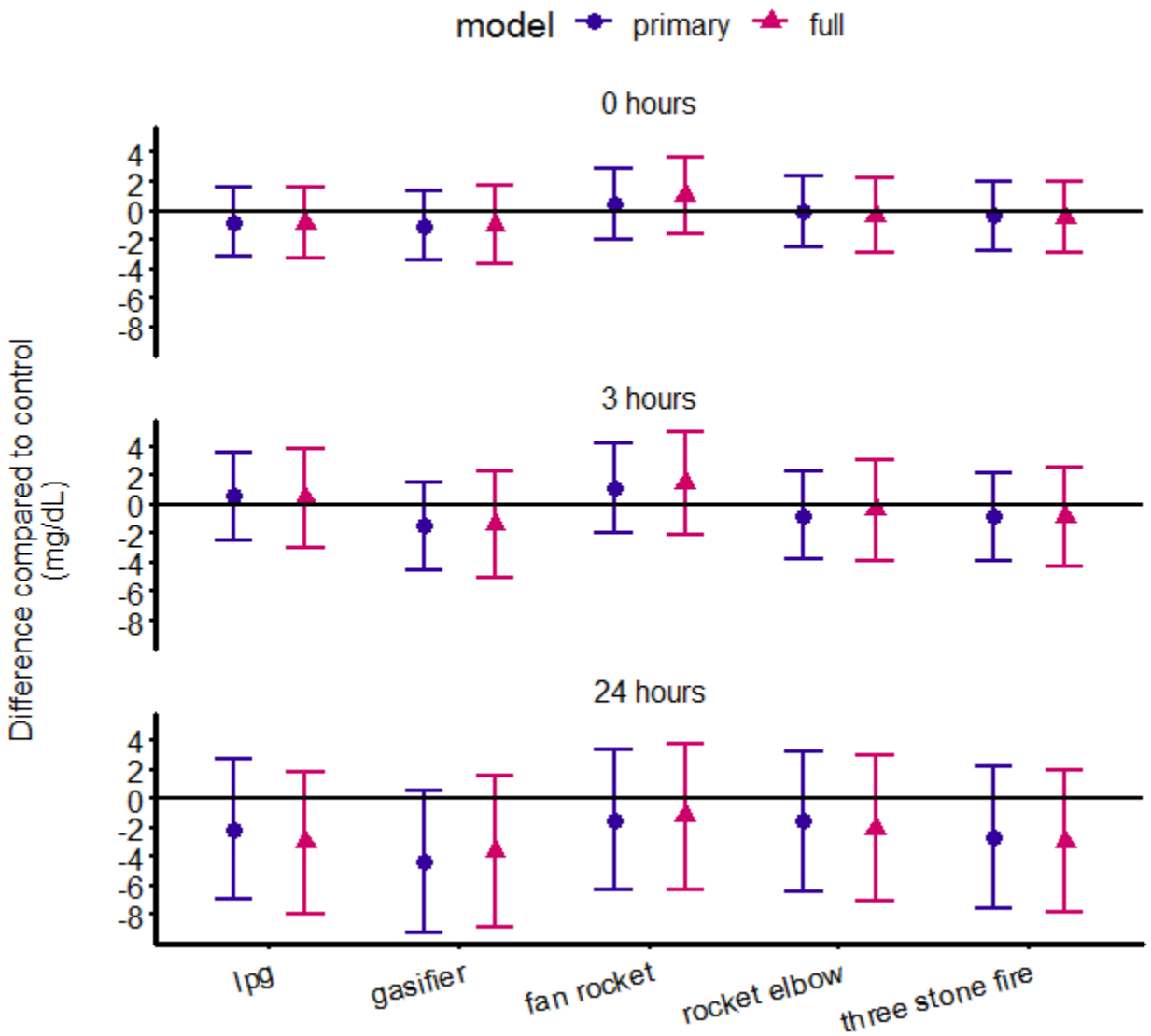

Figure B3: Low Density Lipoprotein primary versus full model results
lpg: liquefied petroleum gas
Primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
Primary model used full dataset (# observations provided in Table B3)
Full model terms: primary model + day*sequence (fixed) + nested day:sequence:participant (random)
Full model used in-sequence dataset (# observations provided in Table B3)

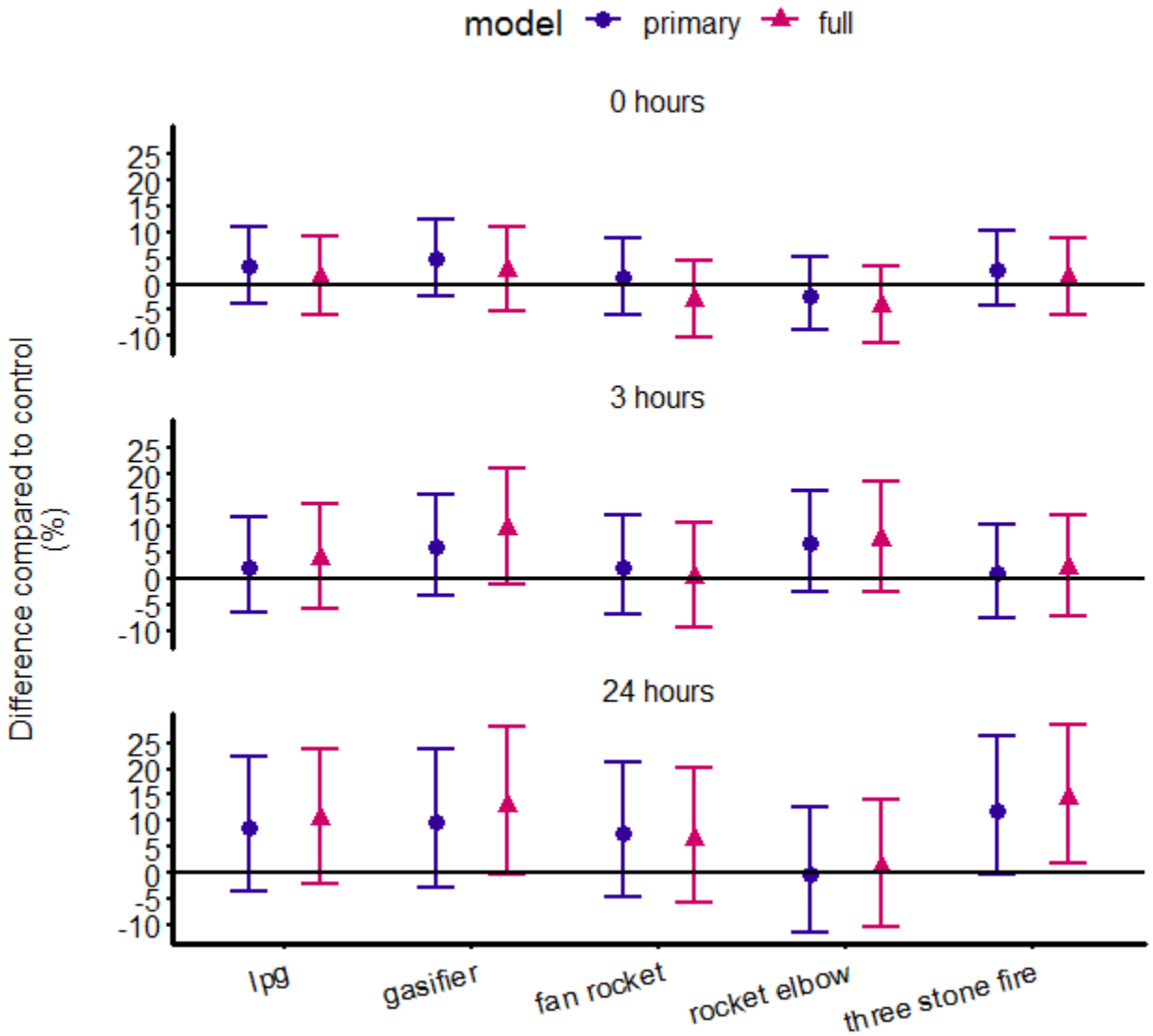

Figure B4: Triglycerides primary versus full model results
lpg: liquefied petroleum gas
Primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
Primary model used full dataset (# observations provided in Table B3)
Full model terms: primary model + day*sequence (fixed) + nested day:sequence:participant (random)
Full model used in-sequence dataset (# observations provided in Table B3)

Results using subsets of the data

To assess for potential bias from participants missing health assessments and not completing full study days, we performed an additional analysis using a subset of the data that only included sessions if participants attended all three follow-up health assessments (0, 3, and 24 hours after treatment). The following figures indicate that results were similar among those who missed a follow-up health assessment compared to those who did not.

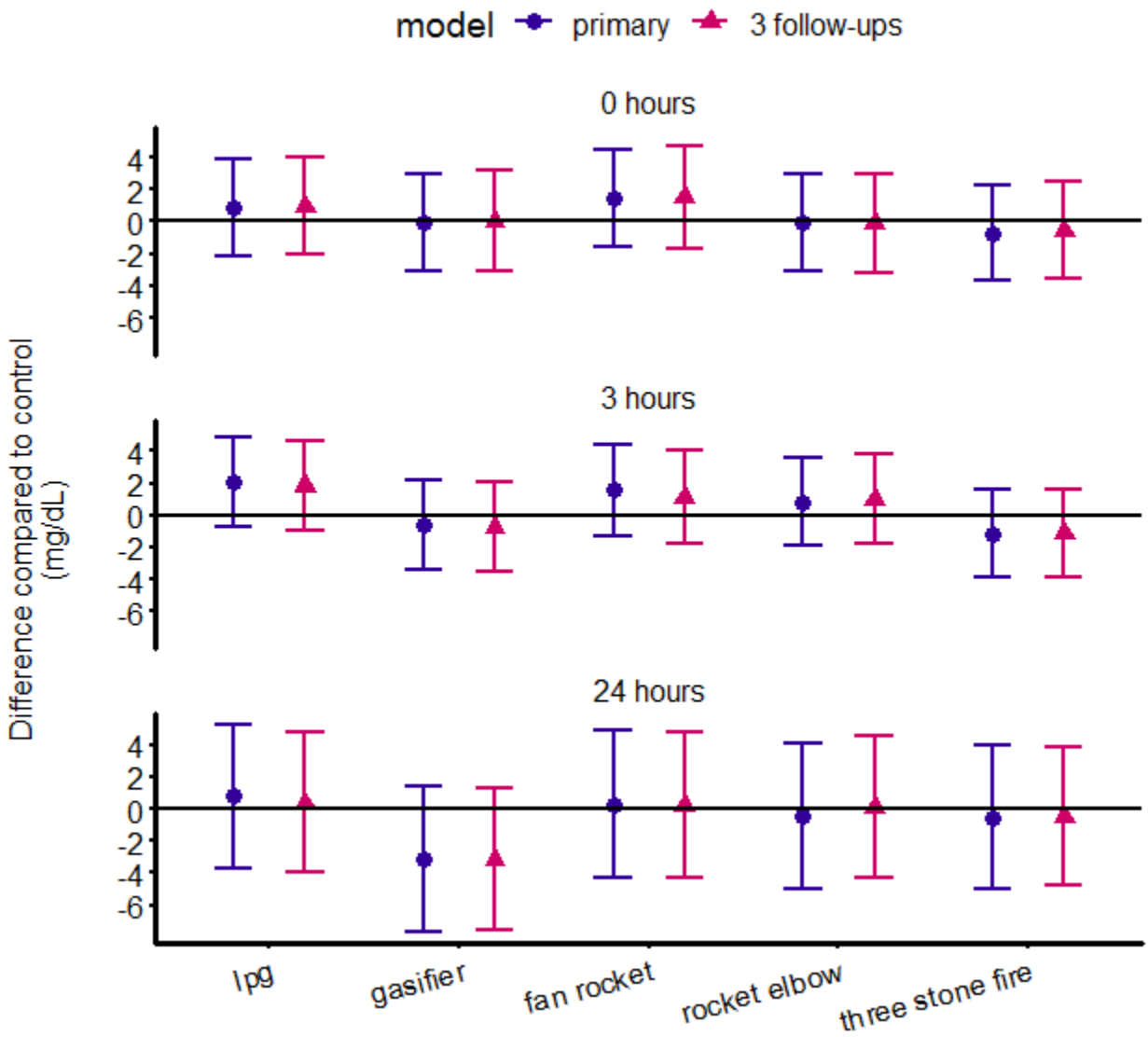

Figure B5: Total Cholesterol primary versus 3 follow-ups model results
lpg: liquefied petroleum gas; primary model n=1079 observations; 3 follow-ups model n=1008 observations
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
3 follow-ups model: subset of the data in which study sessions were only included if participants had data from all three follow-up time points (0, 3, and 24 hours after cookstove treatment)

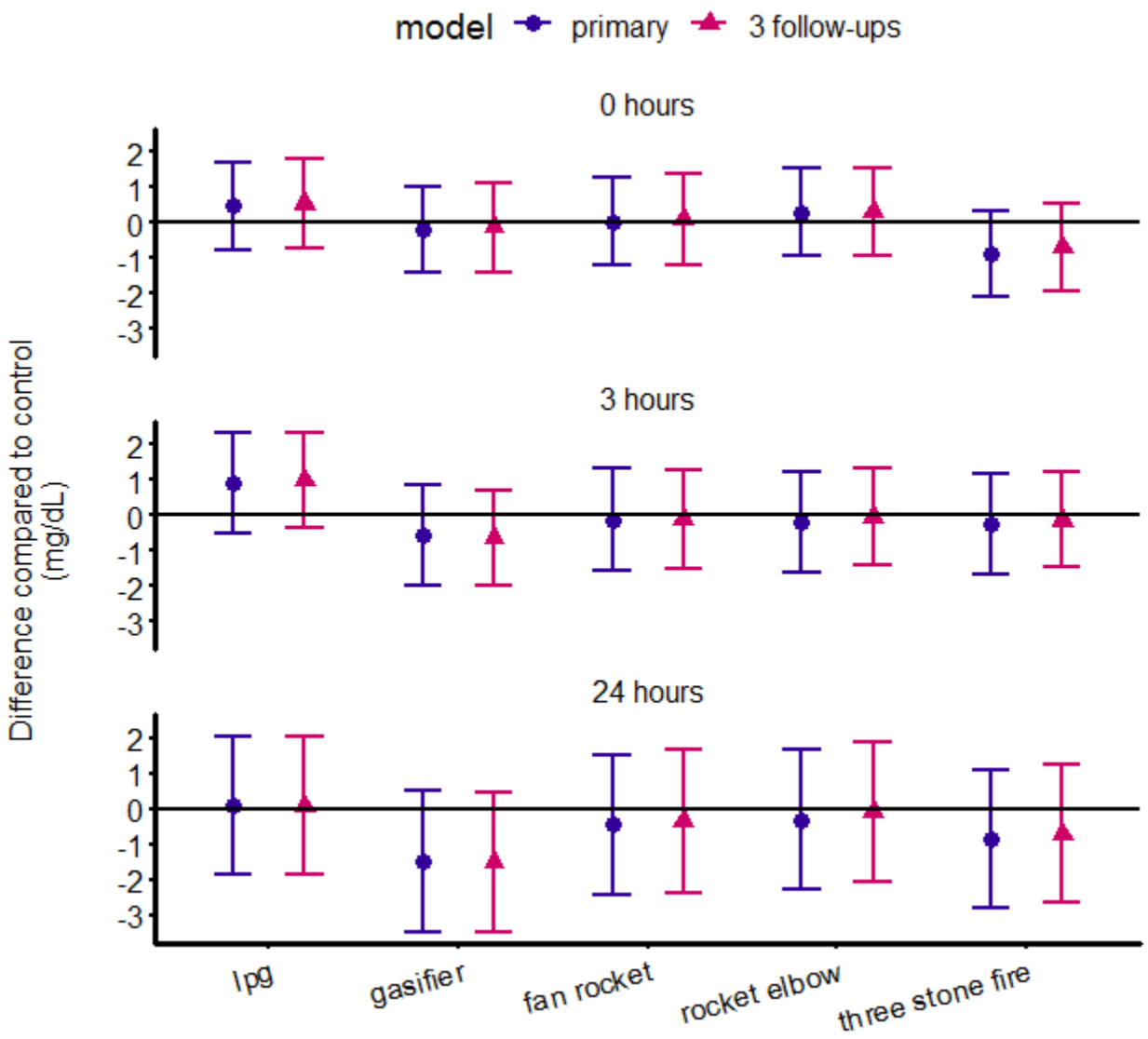

Figure B6: High Density Lipoprotein primary versus 3 follow-ups model results
lpg: liquefied petroleum gas; primary model n=1072 observations; 3 follow-ups model n=988 observations
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
3 follow-ups model: subset of the data in which study sessions were only included if participants had data from all three follow-up time points (0, 3, and 24 hours after cookstove treatment)

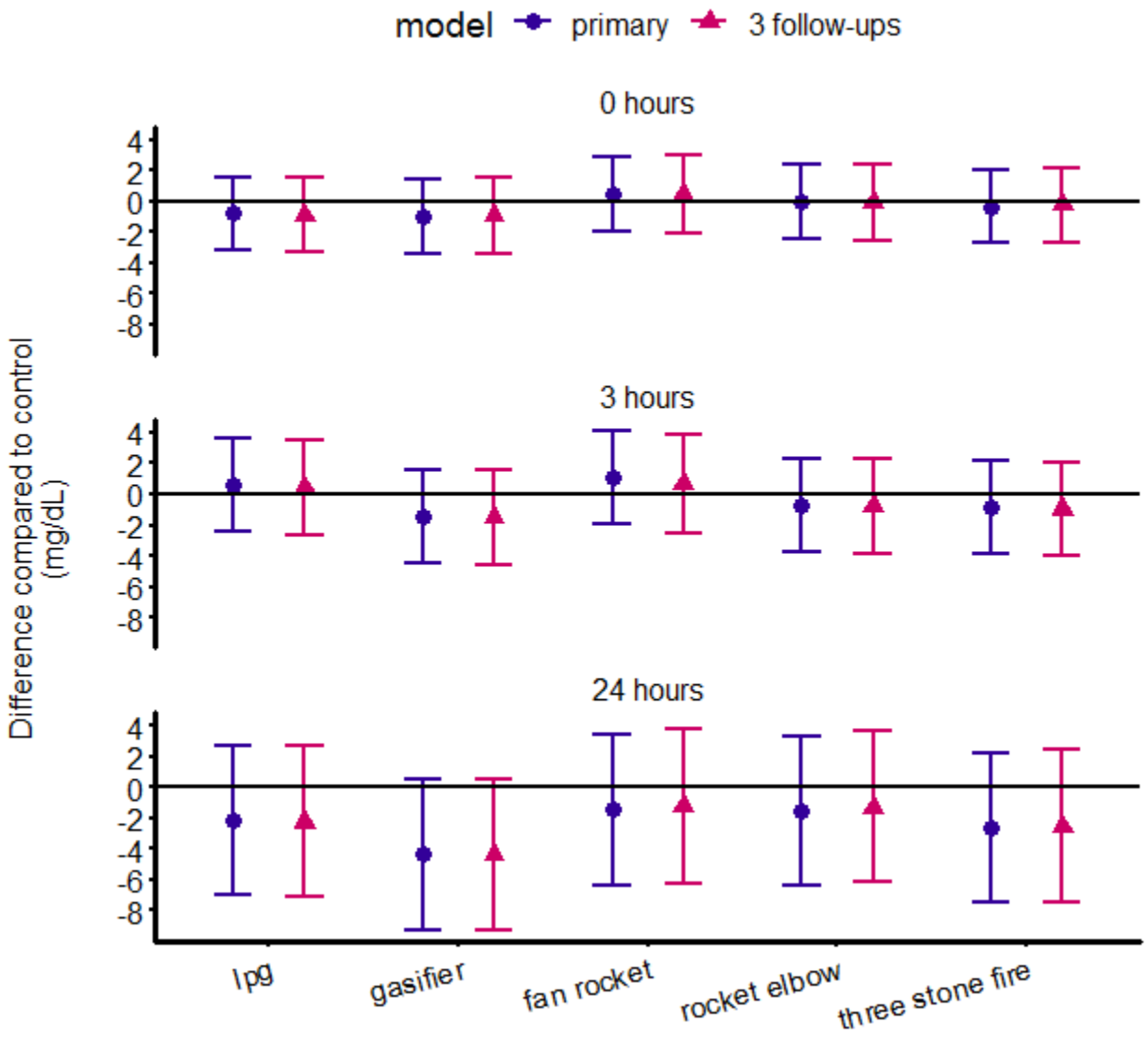

Figure B7: Low Density Lipoprotein primary versus 3 follow-ups model results
lpg: liquefied petroleum gas; primary model n=1072 observations; 3 follow-ups model n=988 observations
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
3 follow-ups model: subset of the data in which study sessions were only included if participants had data from all three follow-up time points (0, 3, and 24 hours after cookstove treatment)

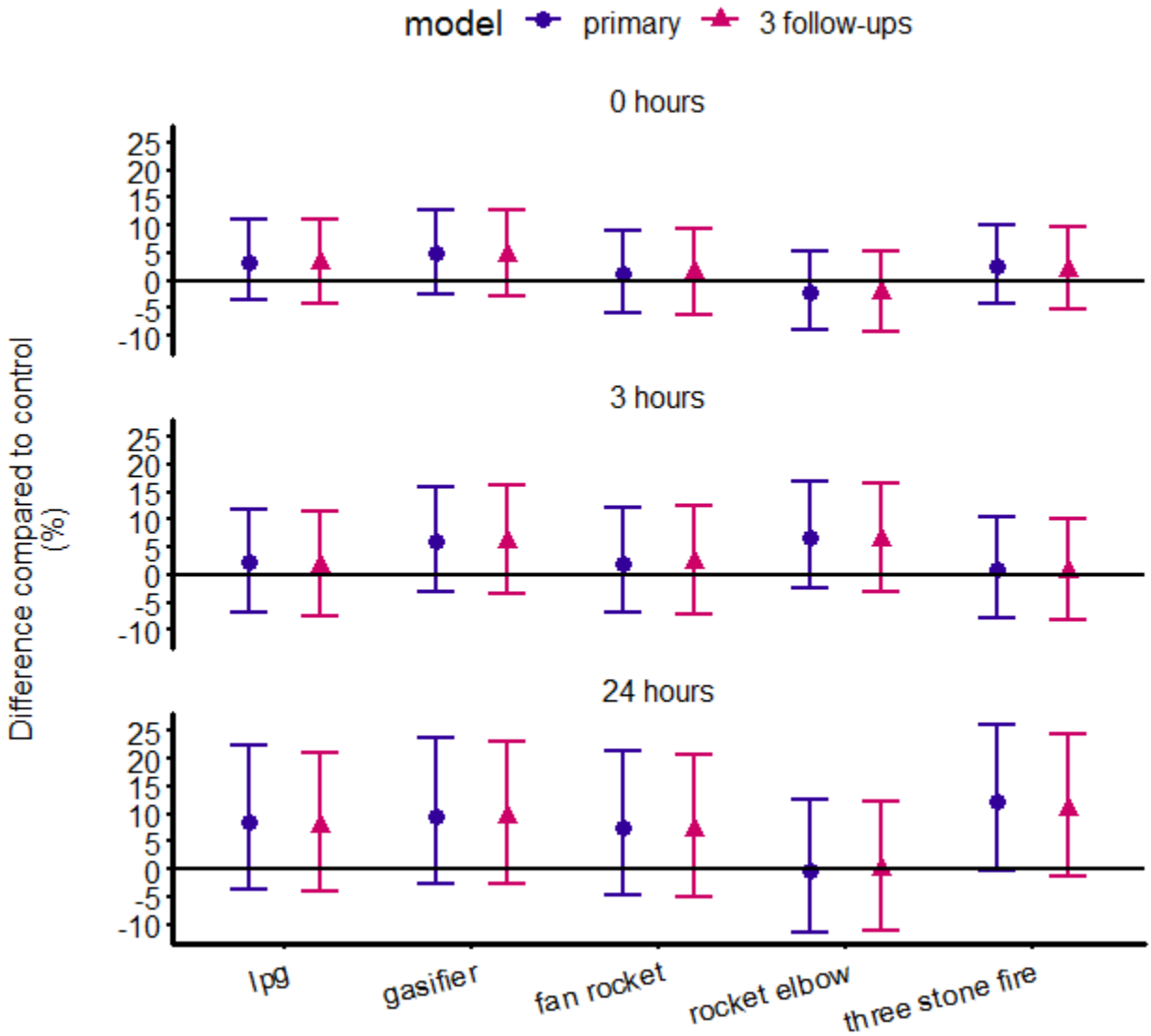

Figure B8: Triglycerides primary versus 3 follow-ups model results
lpg: liquefied petroleum gas; primary model n=1072 observations; 3 follow-ups model n=988 observations
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
3 follow-ups model: subset of the data in which study sessions were only included if participants had data from all three follow-up time points (0, 3, and 24 hours after cookstove treatment)

Potential confounders

The crossover design in our study was implemented to help limit the impact of potential confounders on the reported results. To ensure that the study design worked as intended, we performed multiple sensitivity analyses to assess for potential confounding. We assessed the impact of potential confounding by comparing model results with and without terms for the following potential confounders:

- self-reported consumption of higher-fat food items (dichotomous) prior to each study day
- self-reported consistent diet (dichotomous) prior to each study day across all treatments
- ambient temperature 24 hours prior to each health measurement
- ambient fine particulate matter 24 hours prior to each health measurement
- participant sex
- self-reported alcohol consumption (dichotomous) during the 24 hours prior to each study day
- self-reported caffeine consumption (dichotomous) during the 24 hours prior to each study day
- self-reported medication use (dichotomous) during the 24 hours prior to each study day
- self-reported smoke exposure (dichotomous) during the 24 hours prior to each study day
- self-reported strenuous physical activity (dichotomous) during the 24 hours prior to each study day
- self-reported sleep (less than typical, typical, more than typical) prior to each study day
- self-reported bike travel to study facility (dichotomous) prior to each study day

- self-reported walking travel to study facility (dichotomous) prior to each study day
- self-reported car travel to study facility (dichotomous) prior to each study day

The following figures show that results from the sensitivity analyses are similar to those from the primary analyses. The sensitivity analyses indicate that the crossover design worked as intended and minimized the impact of confounding during our study.

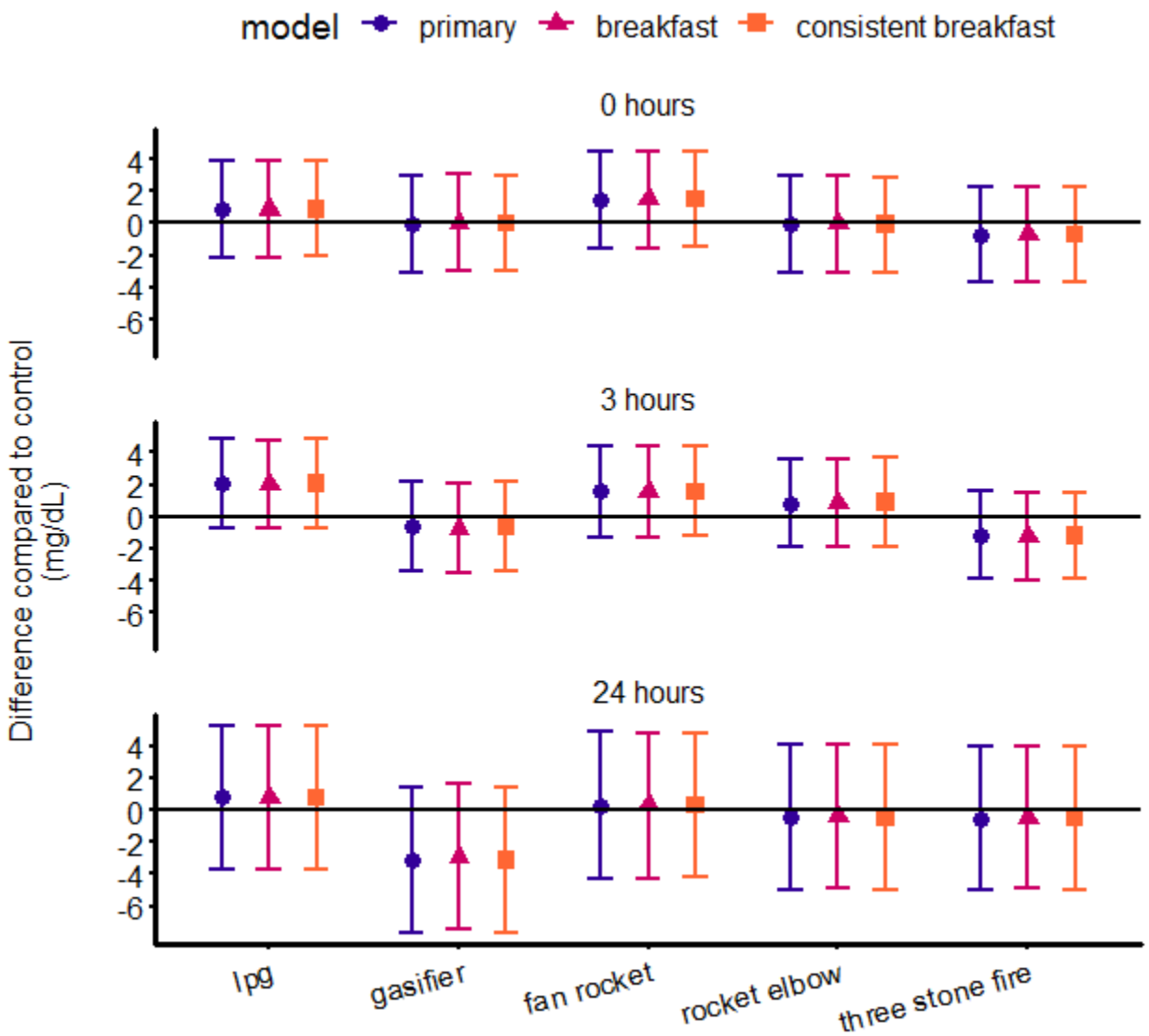

Figure B9: Total Cholesterol sensitivity analyses with potential confounders
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
breakfast model terms: primary model + self-reported consumption of higher-fat food items (dichotomous) prior to each study day
consistent breakfast model terms: primary model + self-reported consistent diet (dichotomous) prior to each study day across all treatments

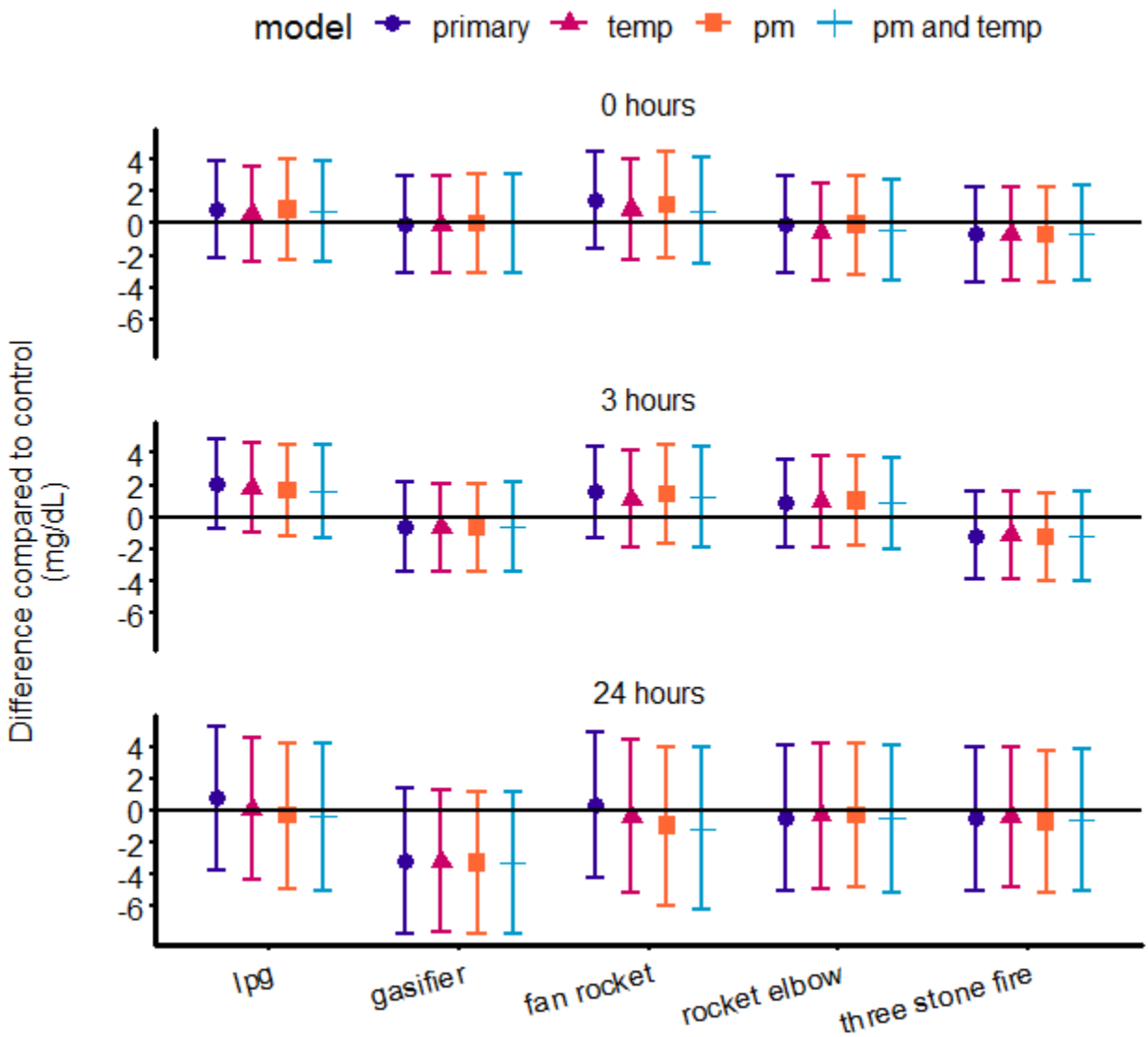

Figure B10: Total Cholesterol sensitivity analyses with potential confounders, continued
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
temp model terms: primary model + ambient temperature 24 hours prior to each health measurement
pm model terms: primary model + ambient fine particulate matter 24 hours prior to each health measurement
pm and temp model terms: temp and pm models combined

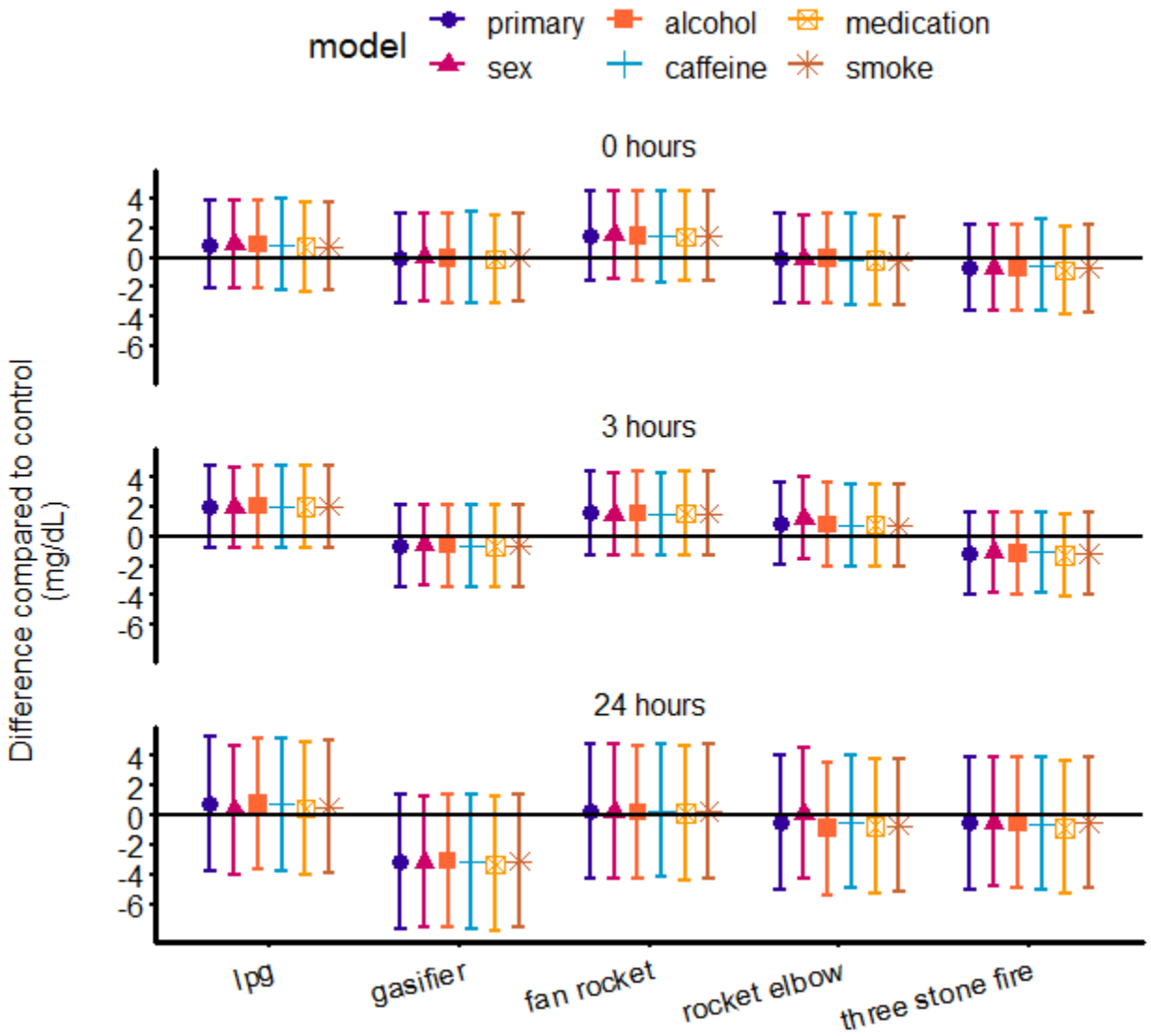

Figure B11: Total Cholesterol sensitivity analyses with potential confounders, continued
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
sex model terms: primary model + participant sex
alcohol model terms: primary model + self-reported alcohol consumption (dichotomous) prior to each study day
caffeine model terms: primary model + self-reported caffeine consumption (dichotomous) prior to each study day
medication model terms: primary model + self-reported medication use (dichotomous) prior to each study day
smoke model terms: primary model + self-reported smoke exposure (dichotomous) prior to each study day

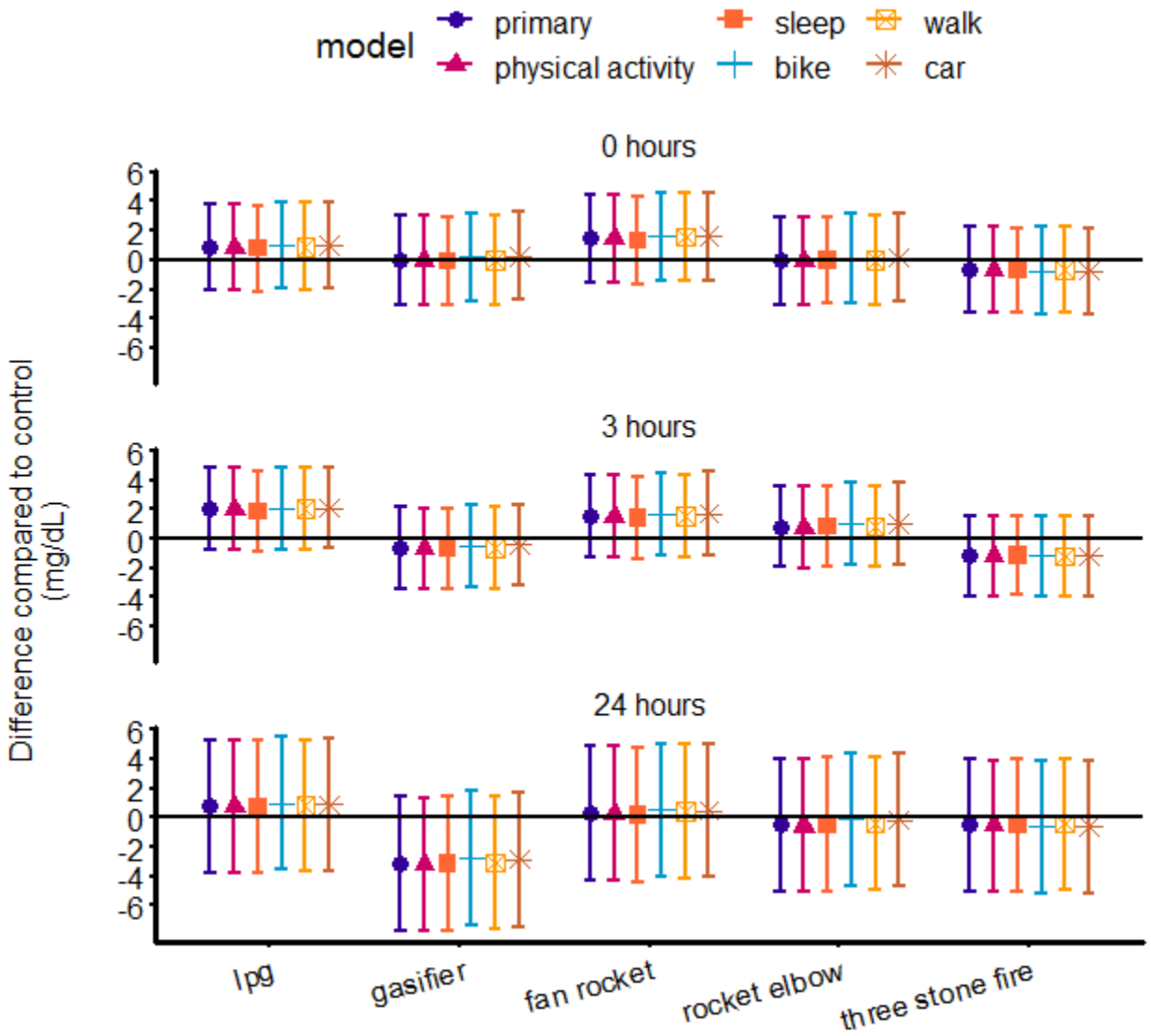

Figure B12: Total Cholesterol sensitivity analyses with potential confounders, continued
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
physical activity model terms: primary model + self-reported strenuous physical activity (dichotomous) prior to each study day
sleep model terms: primary model + self-reported sleep (less than typical, typical, more than typical) prior to each study day
bike model terms: primary model + self-reported bike travel to study facility (dichotomous) prior to each study day
walk model terms: primary model + self-reported walking travel to study facility (dichotomous) prior to each study day
car model terms: primary model + self-reported car travel to study facility (dichotomous) prior to each study day

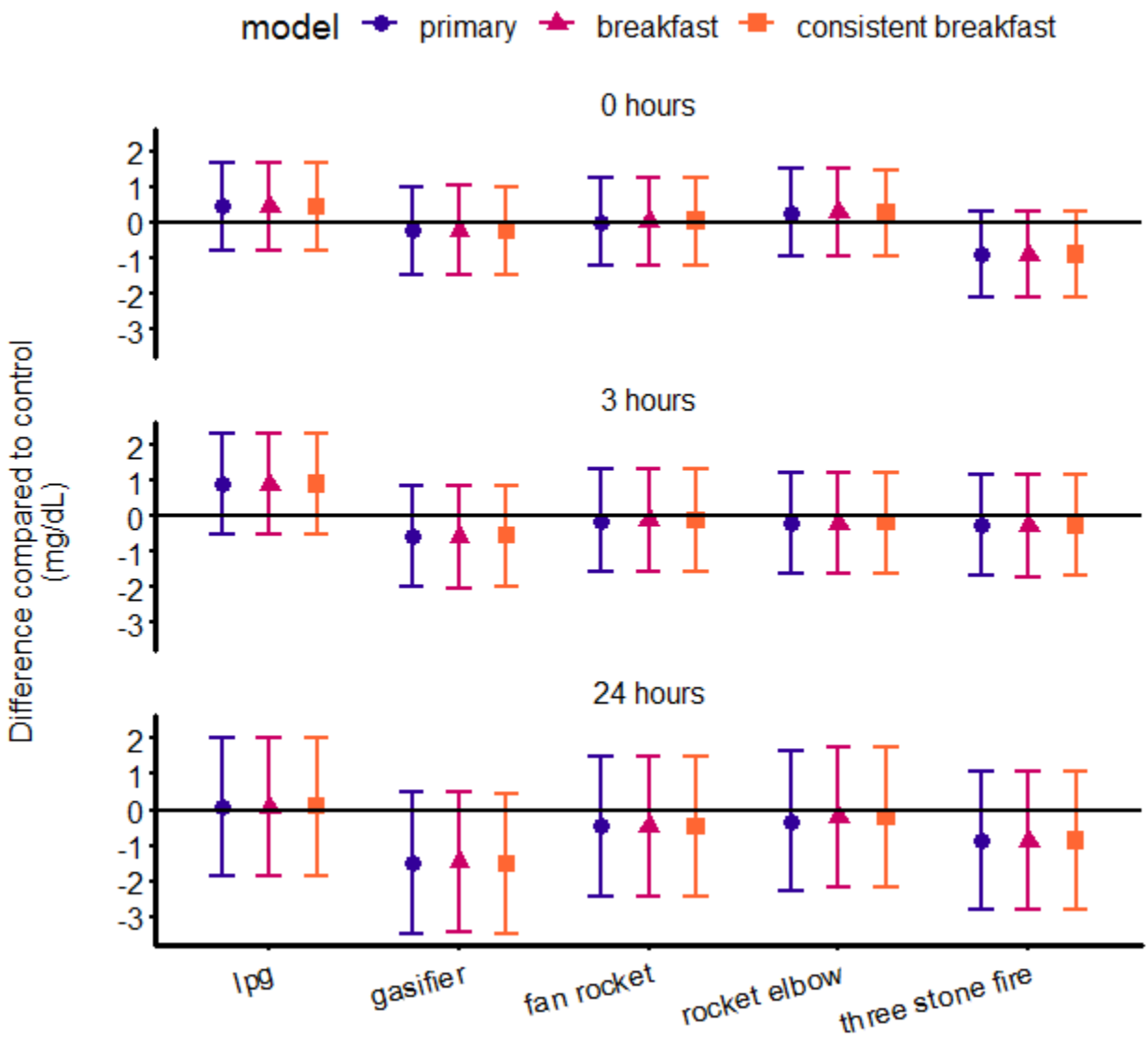

Figure B13: High Density Lipoprotein sensitivity analyses with potential confounders
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
breakfast model terms: primary model + self-reported consumption of higher-fat food items (dichotomous) prior to each study day
consistent breakfast model terms: primary model + self-reported consistent diet (dichotomous) prior to each study day across all treatments

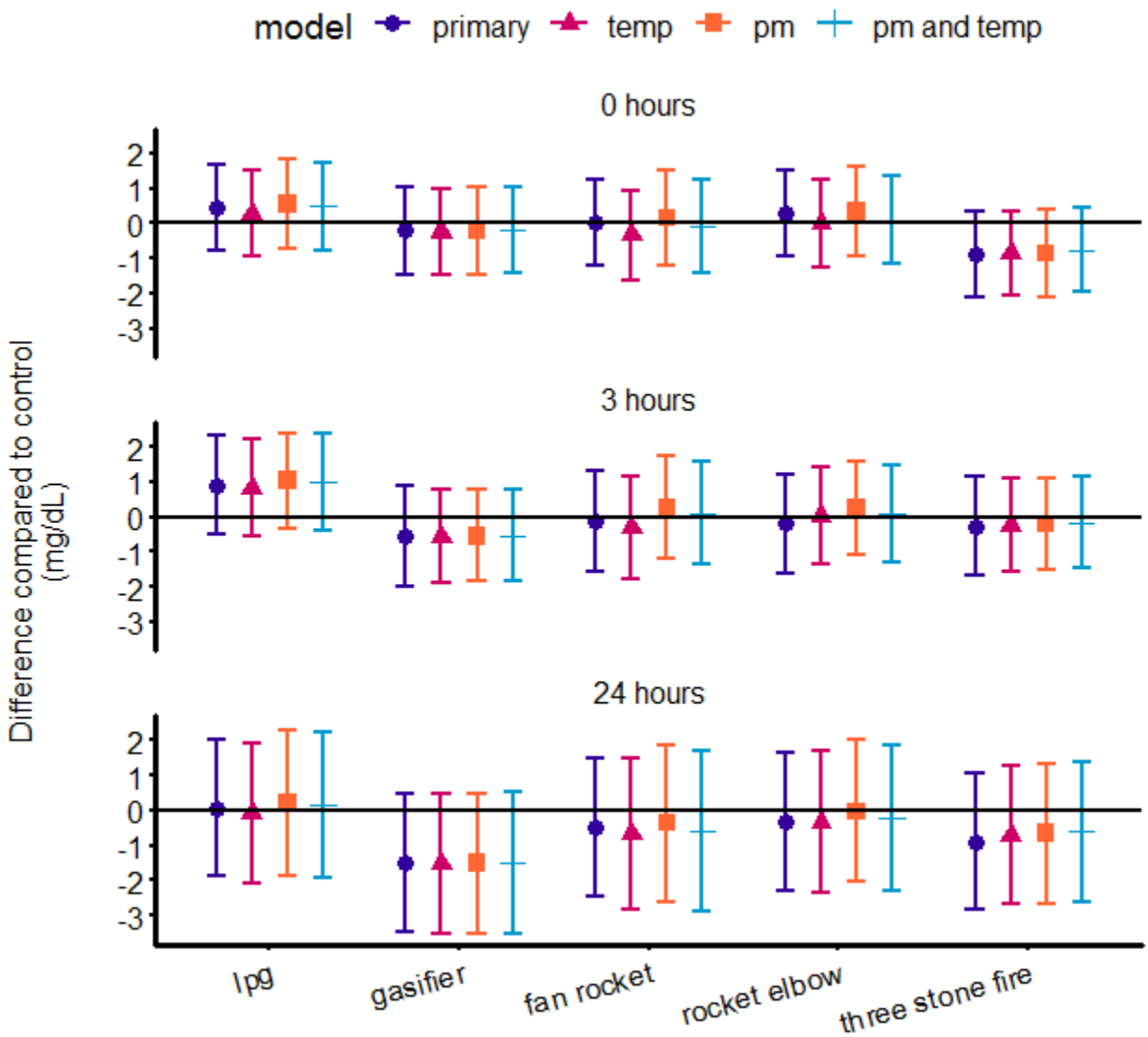

Figure B14: High Density Lipoprotein sensitivity analyses with potential confounders, continued

lpg: liquefied petroleum gas

primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

temp model terms: primary model + ambient temperature 24 hours prior to each health measurement

pm model terms: primary model + ambient fine particulate matter 24 hours prior to each health measurement

pm and temp model terms: temp and pm models combined

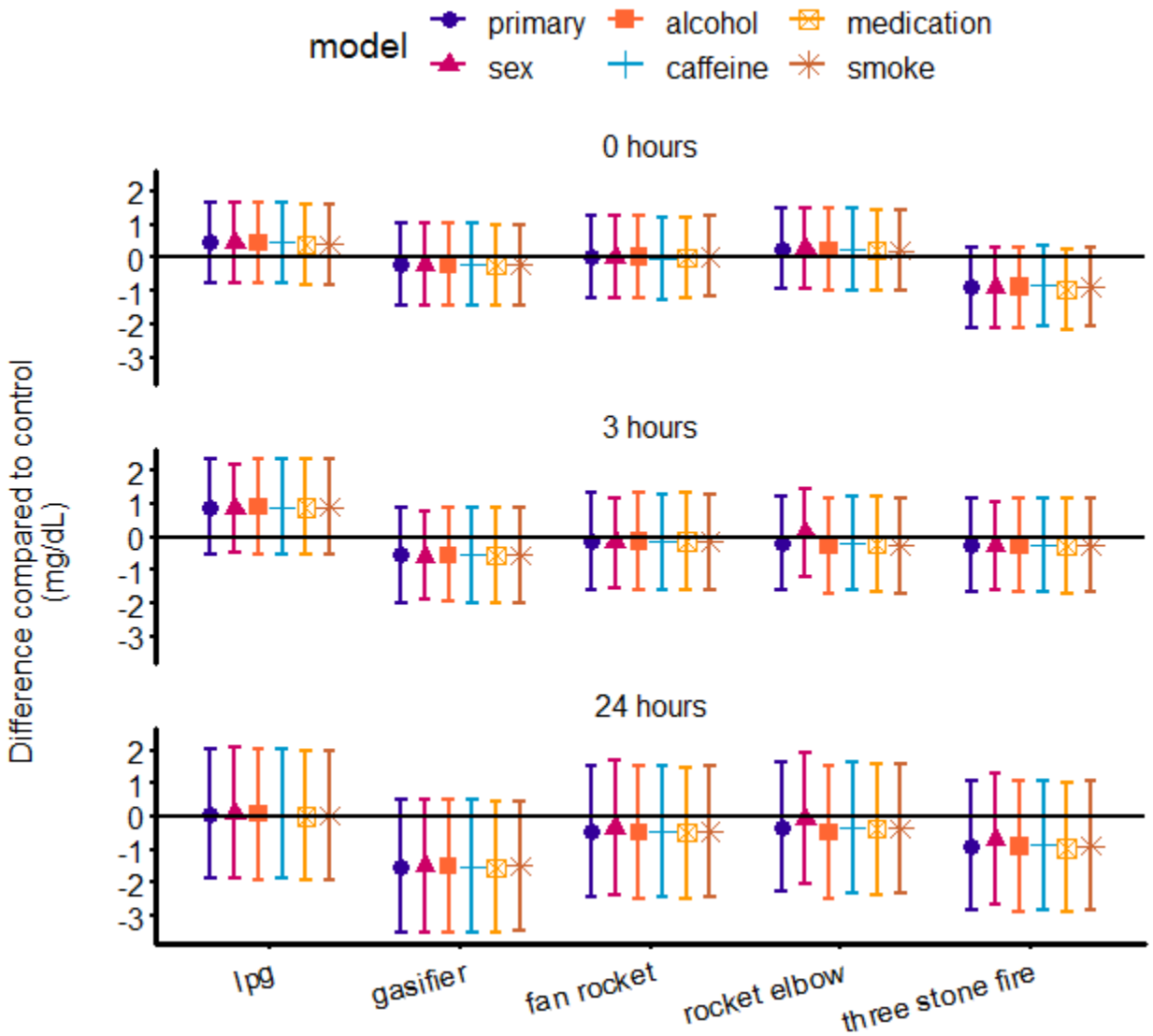

Figure B15: High Density Lipoprotein sensitivity analyses with potential confounders, continued

lpg: liquefied petroleum gas

primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

sex model terms: primary model + participant sex

alcohol model terms: primary model + self-reported alcohol consumption (dichotomous) prior to each study day

caffeine model terms: primary model + self-reported caffeine consumption (dichotomous) prior to each study day

medication model terms: primary model + self-reported medication use (dichotomous) prior to each study day

smoke model terms: primary model + self-reported smoke exposure (dichotomous) prior to each study day

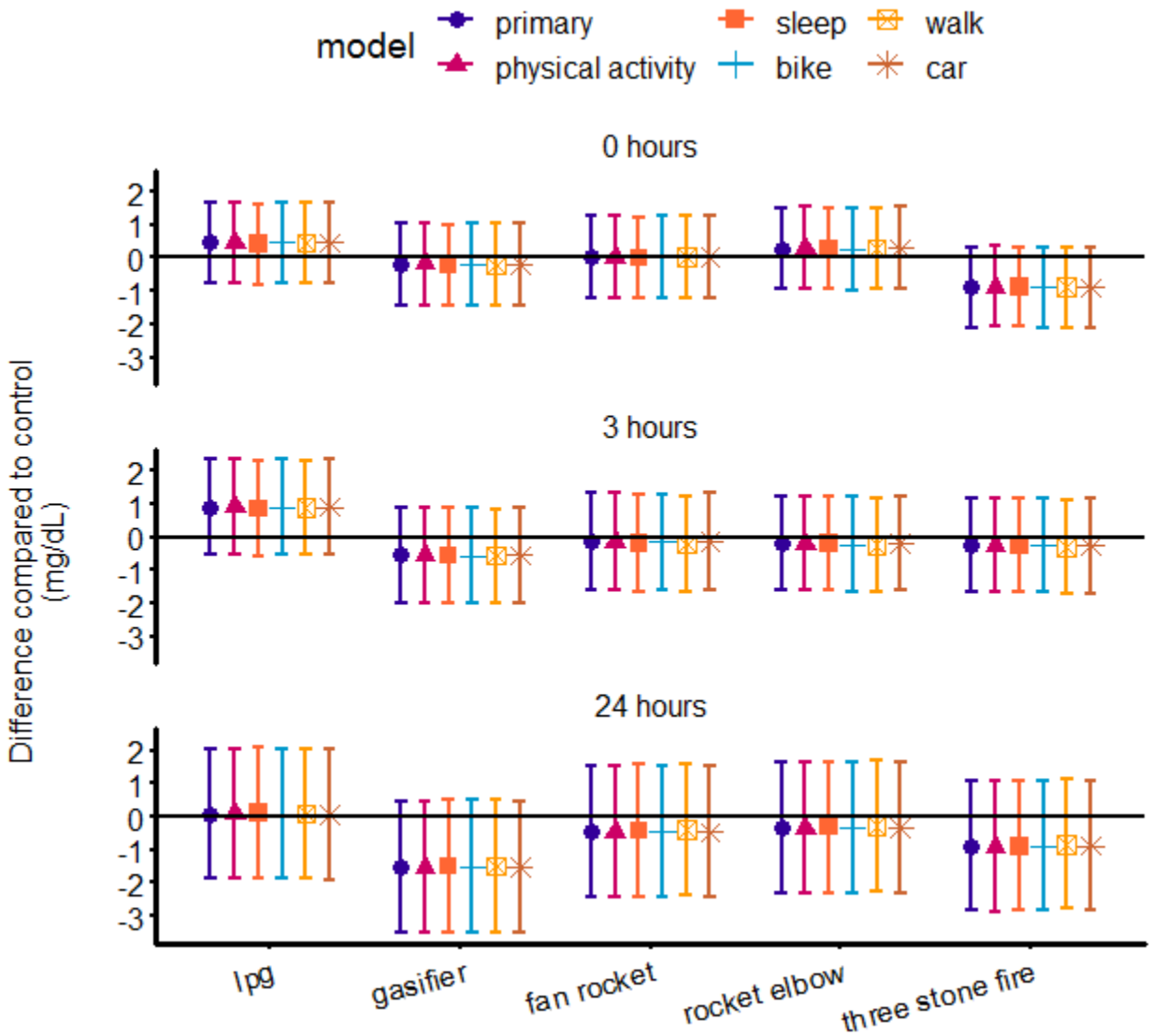

Figure B16: High Density Lipoprotein sensitivity analyses with potential confounders, continued

lpg: liquefied petroleum gas

primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

physical activity model terms: primary model + self-reported strenuous physical activity (dichotomous) prior to each study day

sleep model terms: primary model + self-reported sleep (less than typical, typical, more than typical) prior to each study day

bike model terms: primary model + self-reported bike travel to study facility (dichotomous) prior to each study day

walk model terms: primary model + self-reported walking travel to study facility (dichotomous) prior to each study day

car model terms: primary model + self-reported car travel to study facility (dichotomous) prior to each study day

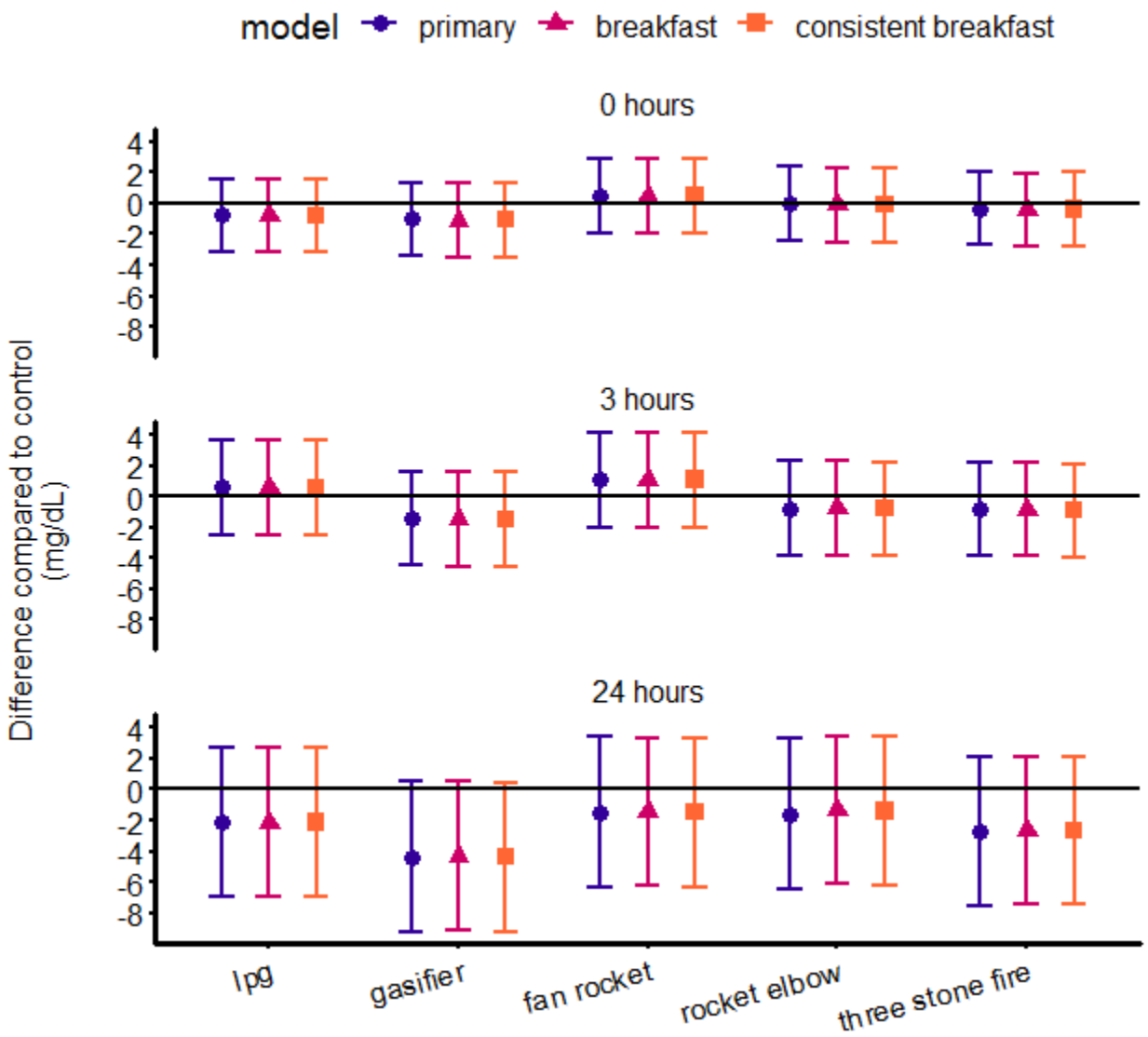

Figure B17: Low Density Lipoprotein sensitivity analyses with potential confounders
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
breakfast model terms: primary model + self-reported consumption of higher-fat food items (dichotomous) prior to each study day
consistent breakfast model terms: primary model + self-reported consistent diet (dichotomous) prior to each study day across all treatments

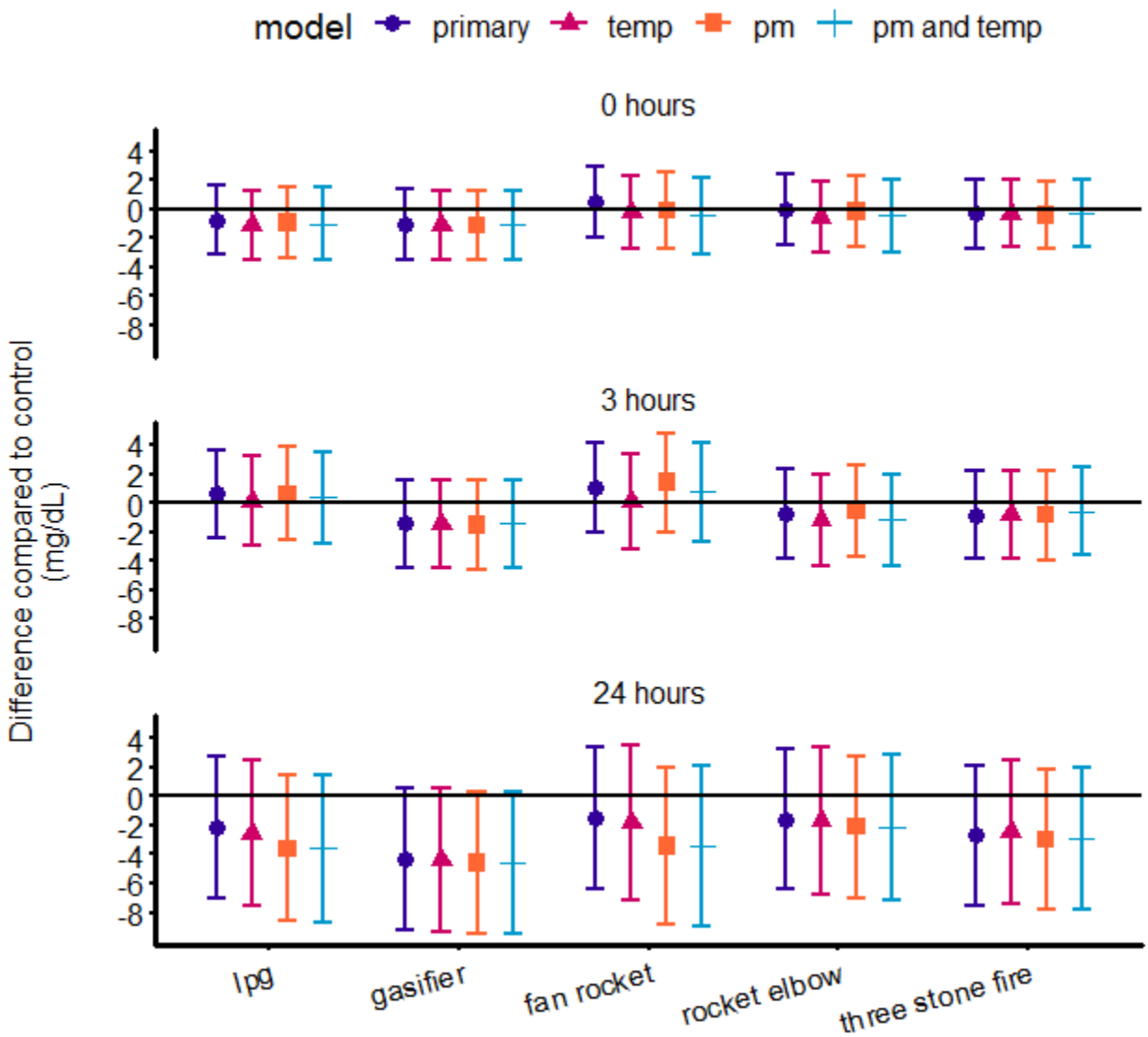

Figure B18: Low Density Lipoprotein sensitivity analyses with potential confounders, continued
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
temp model terms: primary model + ambient temperature 24 hours prior to each health measurement
pm model terms: primary model + ambient fine particulate matter 24 hours prior to each health measurement
pm and temp model terms: temp and pm models combined

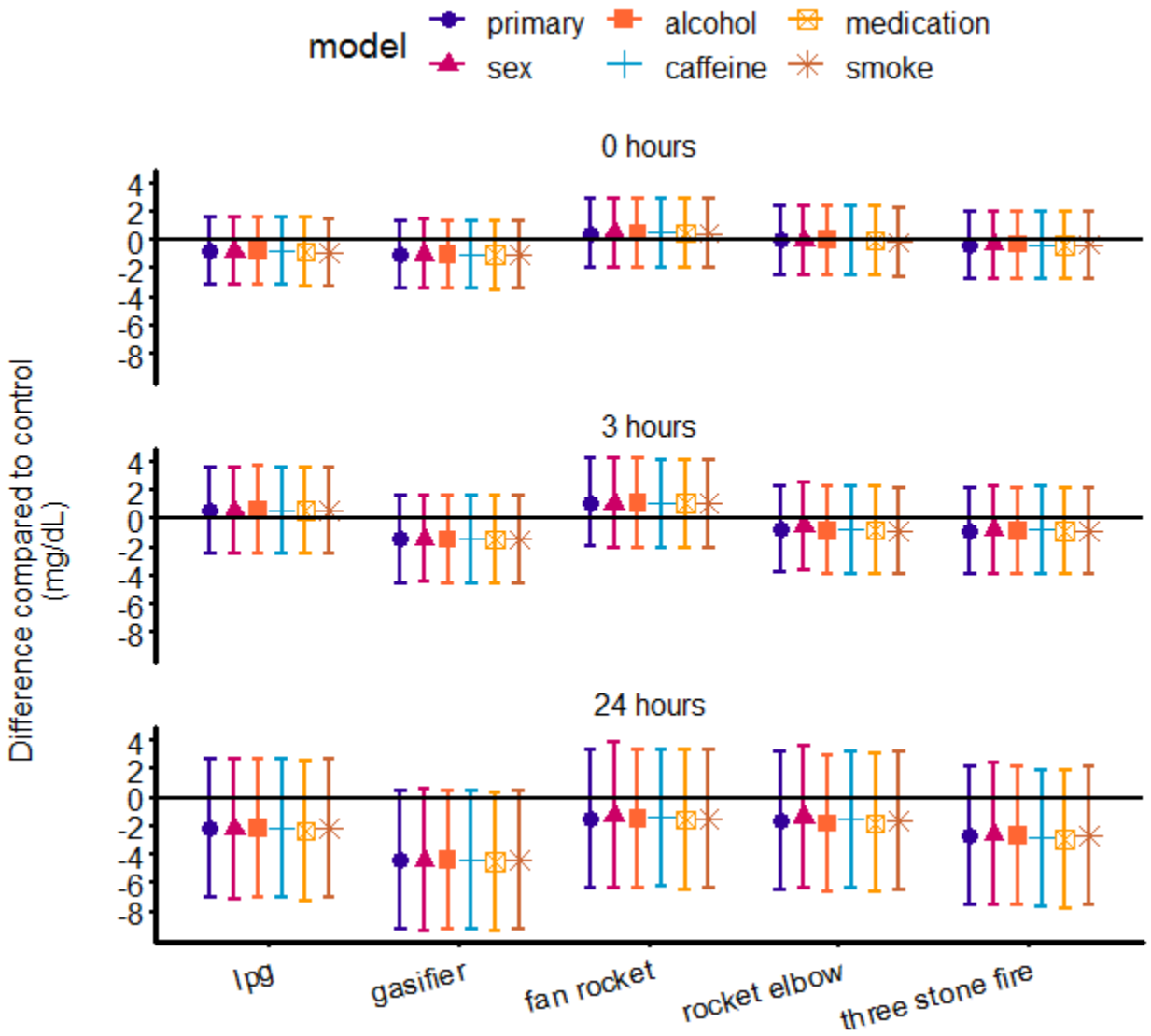

Figure B19: Low Density Lipoprotein sensitivity analyses with potential confounders, continued

lpg: liquefied petroleum gas

primary model terms: cookstove treatment level (fixed) + treatment type (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

sex model terms: primary model + participant sex

alcohol model terms: primary model + self-reported alcohol consumption (dichotomous) prior to each study day

caffeine model terms: primary model + self-reported caffeine consumption (dichotomous) prior to each study day

medication model terms: primary model + self-reported medication use (dichotomous) prior to each study day

smoke model terms: primary model + self-reported smoke exposure (dichotomous) prior to each study day

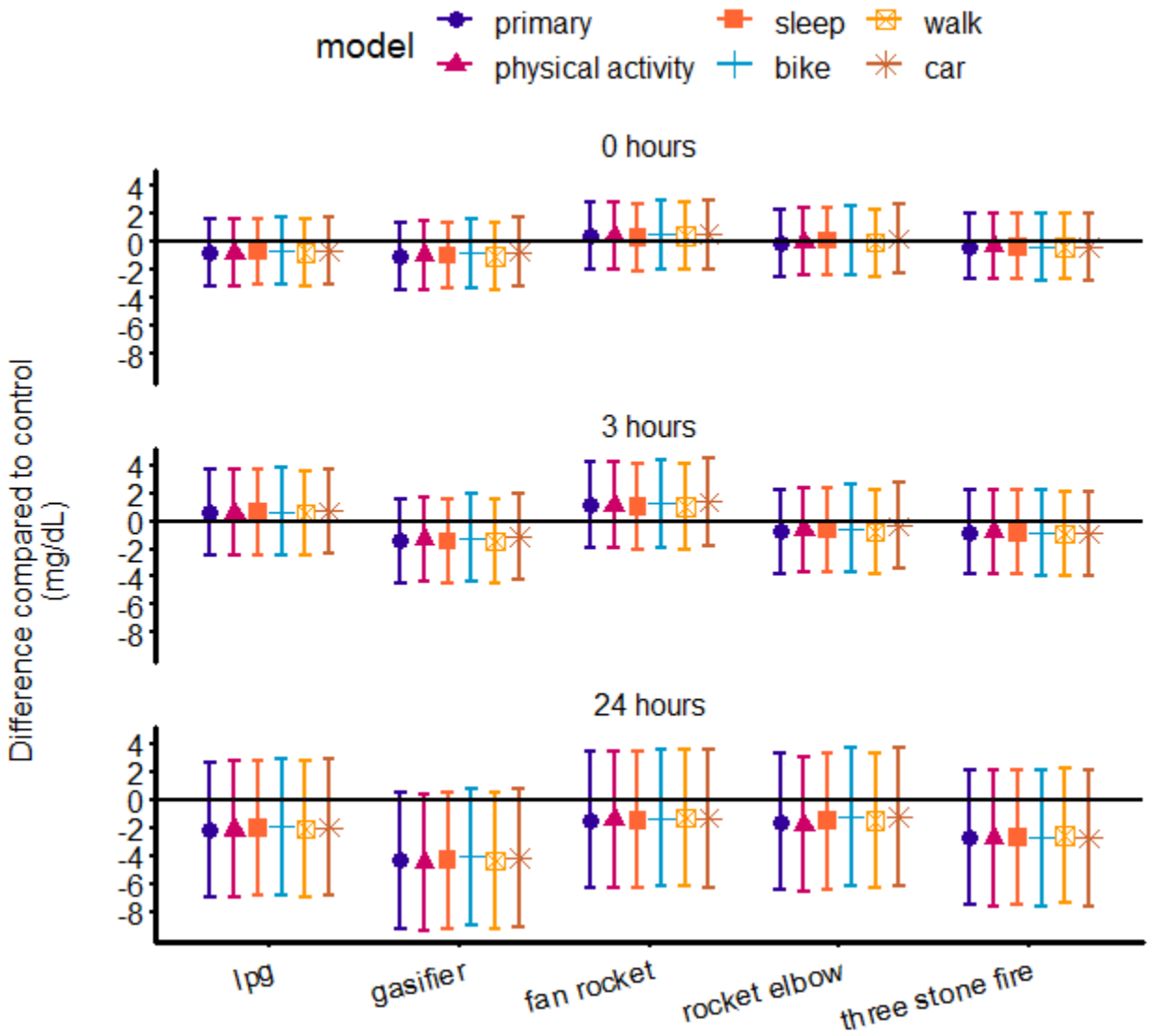

Figure B20: Low Density Lipoprotein sensitivity analyses with potential confounders, continued

lpg: liquefied petroleum gas

primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)

physical activity model terms: primary model + self-reported strenuous physical activity (dichotomous) prior to each study day

sleep model terms: primary model + self-reported sleep (less than typical, typical, more than typical) prior to each study day

bike model terms: primary model + self-reported bike travel to study facility (dichotomous) prior to each study day

walk model terms: primary model + self-reported walking travel to study facility (dichotomous) prior to each study day

car model terms: primary model + self-reported car travel to study facility (dichotomous) prior to each study day

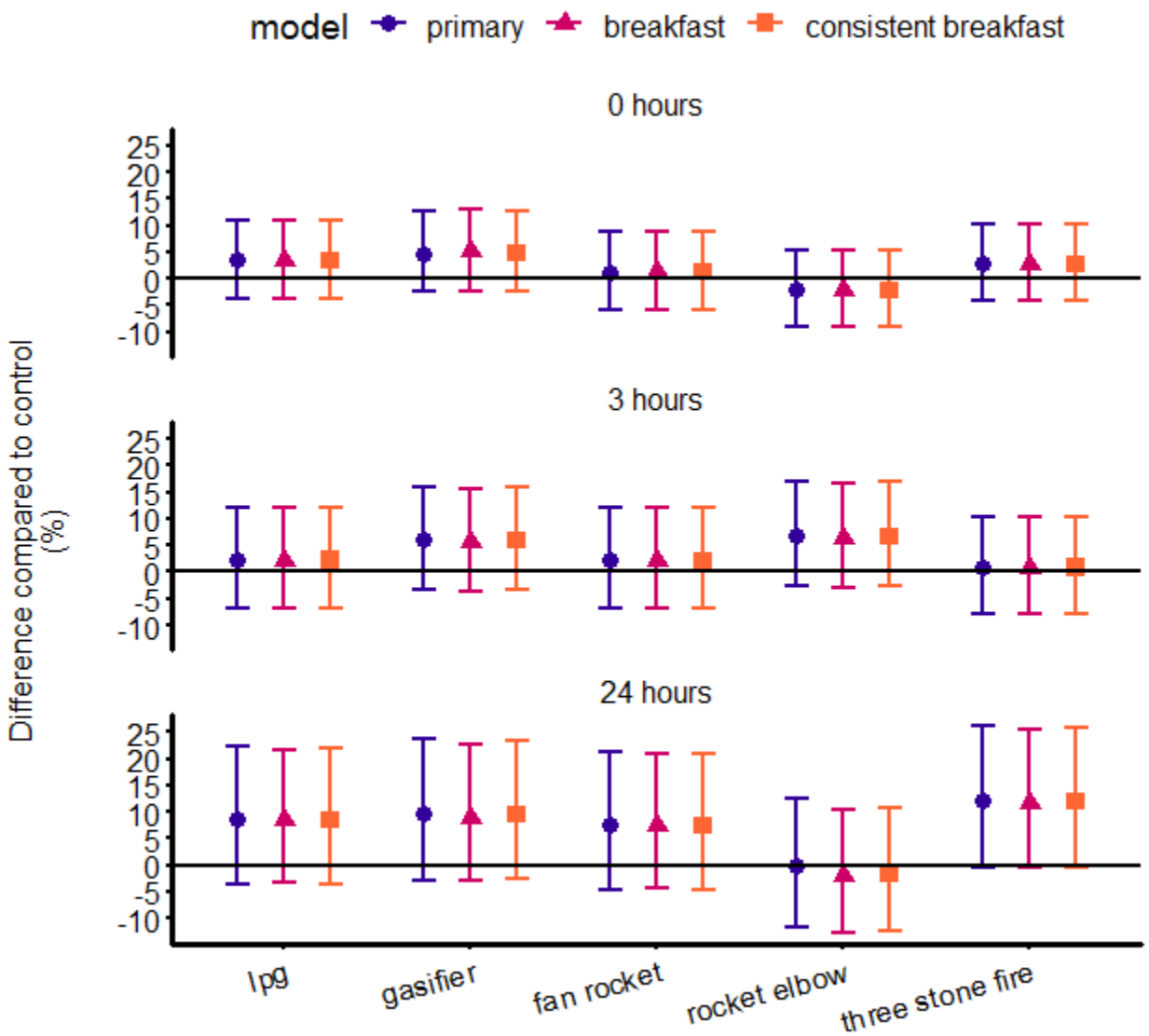

Figure B21: Triglycerides sensitivity analyses with potential confounders
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
breakfast model terms: primary model + self-reported consumption of higher-fat food items (dichotomous) prior to each study day
consistent breakfast model terms: primary model + self-reported consistent diet (dichotomous) prior to each study day across all treatments

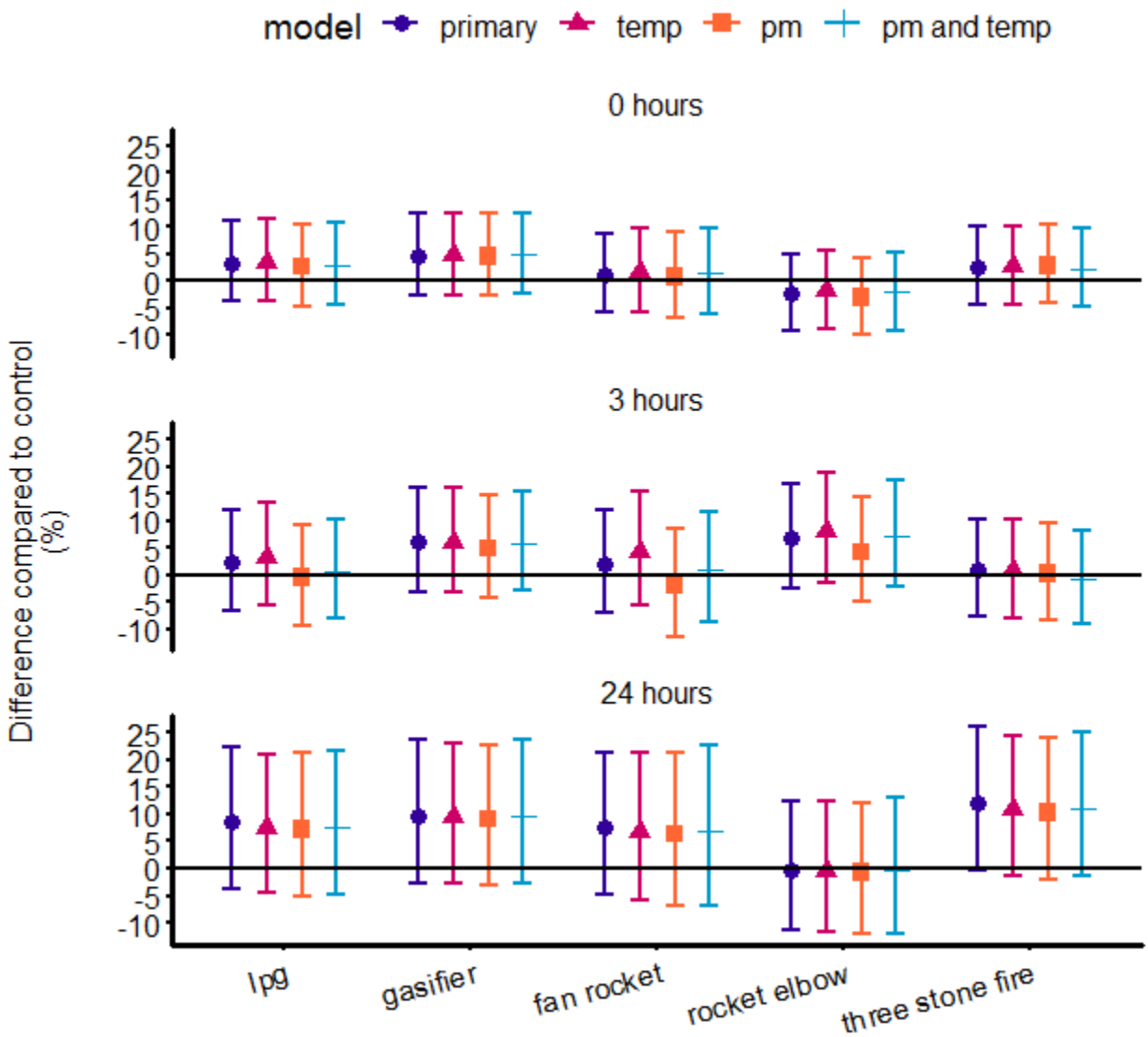

Figure B22: Triglycerides sensitivity analyses with potential confounders, continued
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
temp model terms: primary model + ambient temperature 24 hours prior to each health measurement
pm model terms: primary model + ambient fine particulate matter 24 hours prior to each health measurement
pm and temp model terms: temp and pm models combined

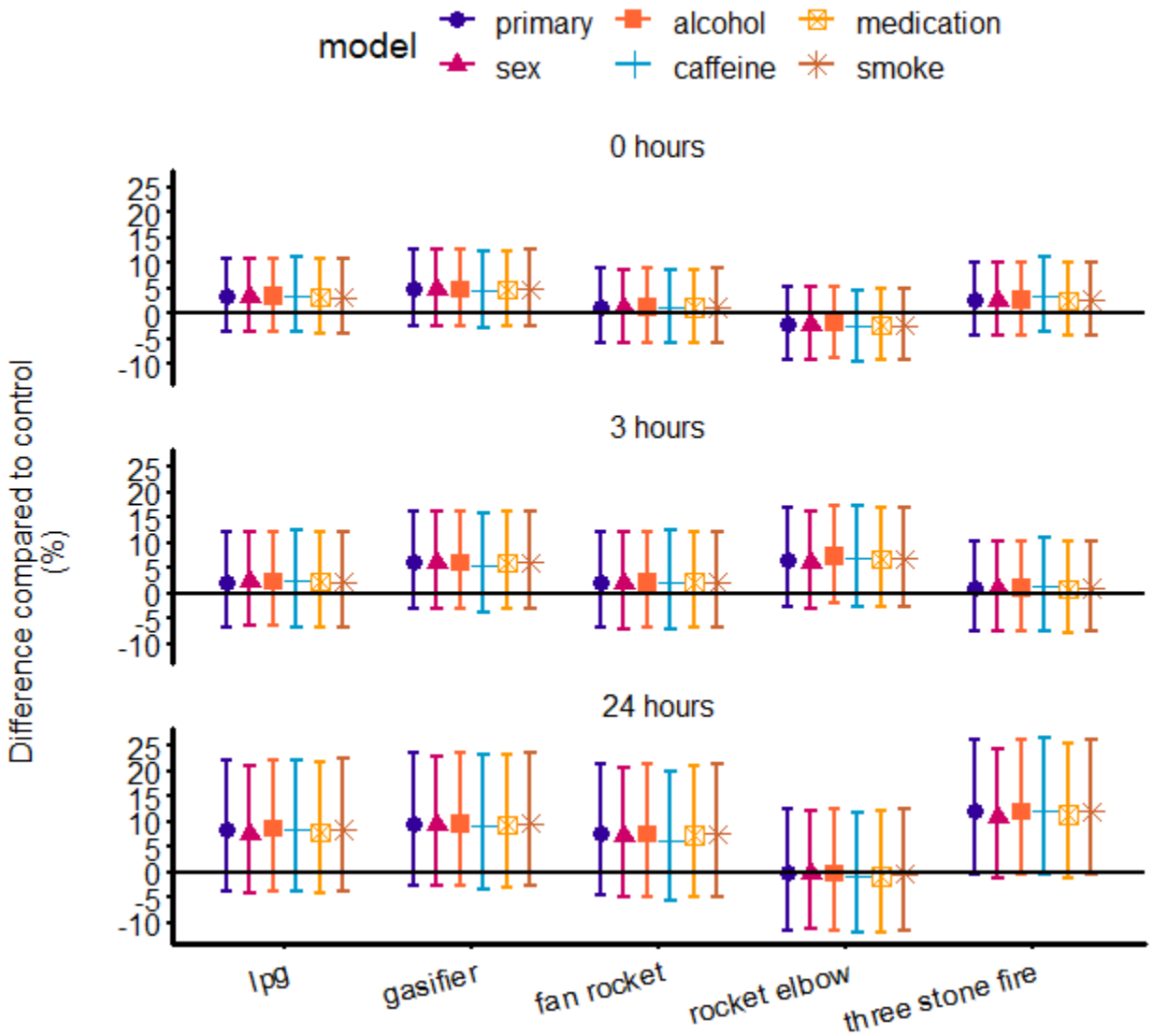

Figure B23: Triglycerides sensitivity analyses with potential confounders, continued
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + treatment type (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
sex model terms: primary model + participant sex
alcohol model terms: primary model + self-reported alcohol consumption (dichotomous) prior to each study day
caffeine model terms: primary model + self-reported caffeine consumption (dichotomous) prior to each study day
medication model terms: primary model + self-reported medication use (dichotomous) prior to each study day
smoke model terms: primary model + self-reported smoke exposure (dichotomous) prior to each study day

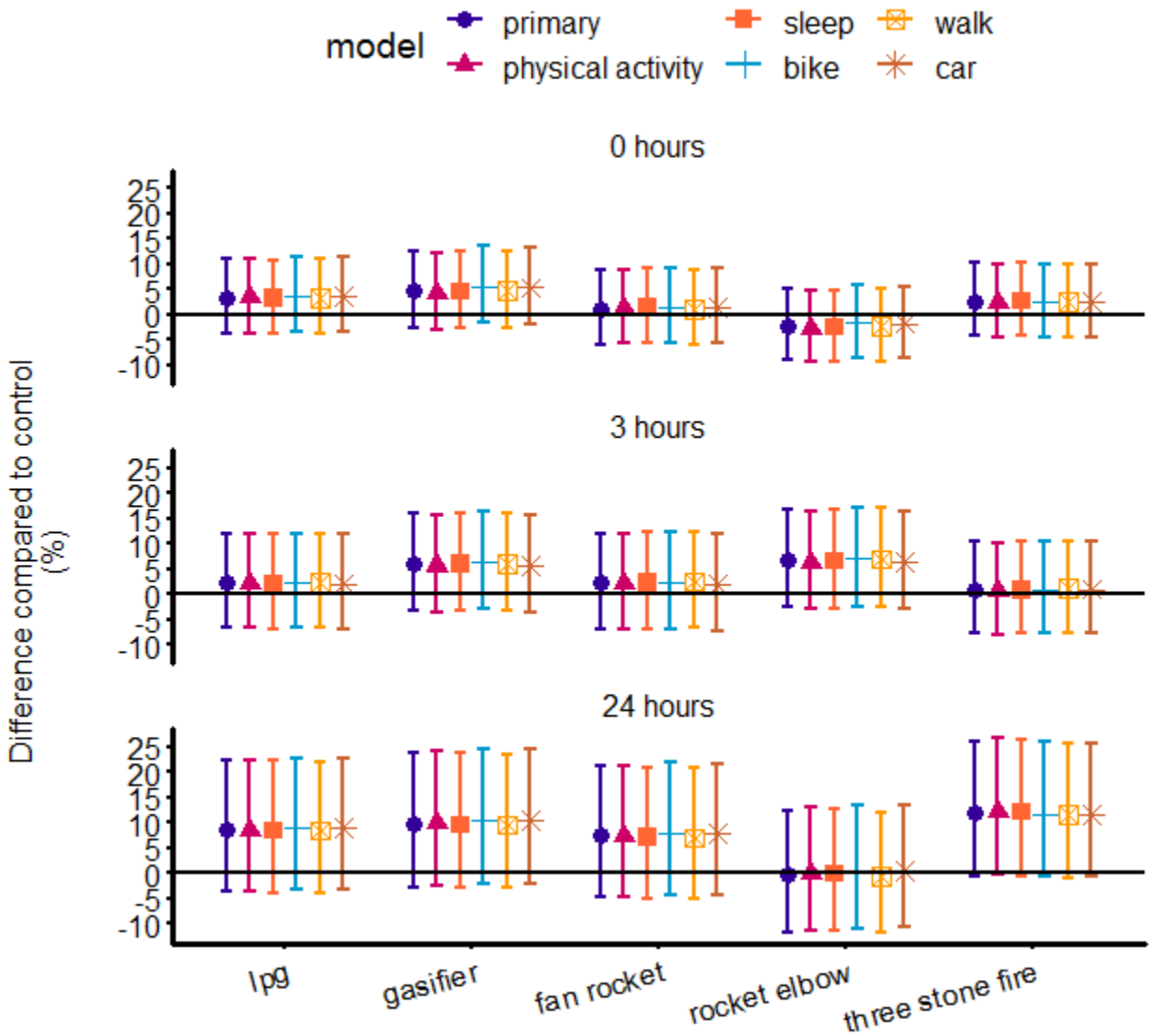

Figure B24: Triglycerides sensitivity analyses with potential confounders, continued
lpg: liquefied petroleum gas
primary model terms: cookstove treatment level (fixed) + baseline health measurement (fixed) + date (random) + participant (random)
physical activity model terms: primary model + self-reported strenuous physical activity (dichotomous) prior to each study day
sleep model terms: primary model + self-reported sleep (less than typical, typical, more than typical) prior to each study day
bike model terms: primary model + self-reported bike travel to study facility (dichotomous) prior to each study day
walk model terms: primary model + self-reported walking travel to study facility (dichotomous) prior to each study day
car model terms: primary model + self-reported car travel to study facility (dichotomous) prior to each study day

APPENDIX C: SUPPLEMENTAL MATERIAL FOR CHAPTER 5

Table C1. Number of participants with outcome data[a] by visit, total and by study arm

	All households n (%)	Arm 1 n (%)	Arm 2 n (%)
Visit 1			
Augmentation index	222 (97)	113 (98)	109 (95)
Central pulse pressure	223 (97)	114 (99)	109 (95)
Visit 2			
Augmentation index	162 (70)	83 (72)	79 (69)
Central pulse pressure	162 (70)	84 (73)	78 (68)
Visit 3			
Augmentation index	203 (88)	105 (91)	98 (85)
Central pulse pressure	203 (88)	105 (91)	98 (85)
Visit 4			
Augmentation index	203 (88)	104 (90)	99 (86)
Central pulse pressure	204 (89)	105 (91)	99 (86)
Visit 5			
Augmentation index	190 (83)	99 (86)	91 (79)
Central pulse pressure	190 (83)	99 (86)	91 (79)
Visit 6			
Augmentation index	182 (79)	95 (83)	87 (76)
Central pulse pressure	182 (79)	95 (83)	87 (76)
Participants with data from 6 visits			
Augmentation index	108 (47)	59 (51)	49 (43)
Central pulse pressure	112 (49)	62 (54)	50 (43)
Participants with data from 5 visits			
Augmentation index	75 (33)	37 (32)	38 (33)
Central pulse pressure	70 (30)	34 (30)	36 (31)
Participants with data from 4 visits			
Augmentation index	26 (11)	12 (10)	14 (12)
Central pulse pressure	26 (11)	12 (10)	14 (12)
Participants with data from 3 visits			
Augmentation index	5 (2)	1 (1)	4 (3)
Central pulse pressure	6 (3)	1 (1)	5 (4)
Participants with data from 2 visits			
Augmentation index	6 (3)	3 (3)	3 (3)
Central pulse pressure	6 (3)	3 (3)	3 (3)
Participants with data from 1 visits			
Augmentation index	10 (4)	3 (3)	7 (6)
Central pulse pressure	10 (4)	3 (3)	7 (6)

[a] Includes removal of four augmentation index values over 75% (143% and 150% from Arm 1; 95% and 150% from Arm 2; from visits 1, 2, 4, and 5; all from different participants), two augmentation index values less than -25% (-35% from Arm 1; -28% from Arm 2; from visits 1 and 6; different participants), and four central pulse pressure values over 75 mmHg (76, 86, 98, and 108 mmHg from Arm 2 – the three highest values were from the same participant; from visits 1, 2, 5, and 6).

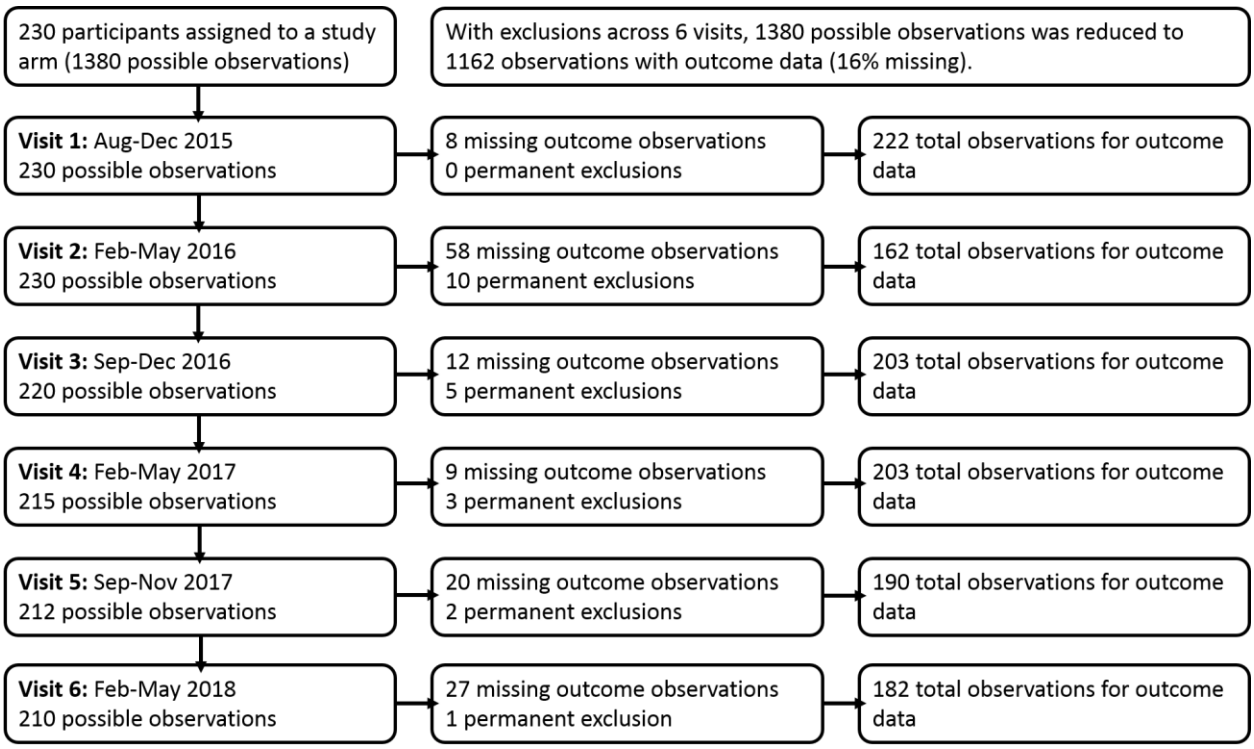

Chart C1. Flow chart of missing outcome data and total observations by study visit

Table C2. Association (simple linear regression) between augmentation index and central pulse pressure and potential confounders at baseline (visit 1)

	All households		
	Estimate	p-value	ICC[a]
Age (years) at baseline			
Augmentation Index	0.78	<0.00	
Central Pulse Pressure	0.35	<0.00	
Age 40+ (years) at baseline			
Augmentation Index	9.81	<0.00	
Central Pulse Pressure	5.08	<0.00	
Beds per person, 0.5+ vs < 0.5			
Augmentation Index	0.64	0.75	
Central Pulse Pressure	1.61	0.13	
Education (years), 6 + vs < 6			
Augmentation Index	-6.96	<0.00	
Central Pulse Pressure	-3.65	<0.00	
Household assets[b], 3+ vs < 3			
Augmentation Index	0.61	0.75	
Central Pulse Pressure	1.38	0.16	
Household assets (weighted)[c]			
Augmentation Index	0.13	0.29	
Central Pulse Pressure	0.10	0.12	
Household assets (weighted; 5+ vs <5)[c]			
Augmentation Index	1.57	0.41	
Central Pulse Pressure	1.52	0.12	
Dietary diversity score[d] 6+ vs < 6			0.46
Augmentation Index	-0.97	0.64	
Central Pulse Pressure	-0.79	0.46	
Body mass index (kg/m^2)			0.94
Augmentation Index	0.44	0.05	
Central Pulse Pressure	0.31	0.01	
Body mass index (kg/m^2), 25+ vs < 25			
Augmentation Index	2.60	0.18	
Central Pulse Pressure	2.76	0.01	
Waist circumference (cm)			0.62
Augmentation Index	0.28	0.01	
Central Pulse Pressure	0.16	<0.00	
Waist circumference (cm), 80+ vs < 80			
Augmentation Index	2.51	0.21	
Central Pulse Pressure	3.59	<0.00	
Waist-to-hip ratio – abdominal obesity[e]			0.27
Augmentation Index	3.66	0.07	
Central Pulse Pressure	1.91	0.07	
Physical activity (METS), 300+ vs < 300			
Augmentation Index	-0.75	0.70	

Central Pulse Pressure	-0.87	0.38	
Physical activity (METS), Per 50 METS			0.47
Augmentation Index	-0.54	0.26	
Central Pulse Pressure	-0.29	0.25	
Salt (days to use 1 bag), 8+ vs < 8			0.51
Augmentation Index	2.62	0.32	
Central Pulse Pressure	0.34	0.81	
Sugar (days to use 1 bag), 4+ vs < 4			0.82
Augmentation Index	3.40	0.07	
Central Pulse Pressure	-1.16	0.24	
Manteca (days to use 1 packet) 7+ vs < 7			0.53
Augmentation Index	-0.02	0.85	
Central Pulse Pressure	-1.71	0.09	
Kitchen temperature, mean degrees Celsius			0.29
Augmentation Index	-1.48	0.45	
Central Pulse Pressure	-0.15	0.48	

METS = metabolic equivalent (kcal/kg/hour); ICC = intraclass correlation coefficient

[a] ICC reported for numeric variables that were evaluated at each of the 6 study visits

[b] Sum of 9 household assets: bicycle, car, motorcycle, television, radio, refrigerator, cell phone, computer, and sewing machine

[c] Household assets were weighted based on their ranked prevalence in the study population at visit 1: 1) radio (82%), 2) cell phone (74%), 3) bicycle (38%), 4) television (23%), 5) sewing machine (13%), 6) refrigerator (10%), 7) car (7%), 8) motorcycle (6%), 9) computer (3%)

[d] Sum of 11 food categories found in a 24-hour dietary recall: grains (corn, cereals, rice, chips), pulses and nuts (nuts, beans), roots (potatoes), other vegetables, fruits, sweets, eggs, dairy (cheese, milk), meat (beef, chicken, pork, fish), oils, and beverages (coffee, soda, juice).

[e] Abdominal obesity defined as waist-to-hip ratio ≥ 0.85

Table C3. Sample means from two-sample t-tests between study arms during visit 3 and visit 4

Assigned cookstove	**Augmentation index (%)**		**Central pulse pressure (mmHg)**	
Visit 3	Sample means	t-value (p-value)	Sample means	t-value (p-value)
Arm 1 (*Justa*) (n=105) Arm 2 (traditional) (n=99)	20.7 19.9	0.41 (0.68)	33.5 33.1	0.35 (0.73)
Visit 4	Sample means	t-value (p-value)	Sample means	t-value (p-value)
Arm 1 (*Justa*) (n=104) Arm 2 (traditional) (n=100)	22.1 21.0	0.60 (0.50)	33.3 34.0	-0.58 (0.56)

Table C4. Results from analyses assessing effect modification

Exposure to household air pollution	Augmentation index (%)	Central pulse pressure (mmHg)
Assigned cookstove: traditional vs *Justa*[a]	Estimate (95% CI) *P-value for interaction*	Estimate (95% CI) *P-value for interaction*
Age < 40 years (n = 683): Age ≥ 40 years (n = 478):	-0.16 (-2.48, 2.16) -0.40 (-2.93, 2.12) *0.84*	0.44 (-0.77, 1.66) 0.07 (-1.25, 1.39) *0.54*
Waist circumference < 80cm (n = 374): Waist circumference ≥ 80cm (n = 787):	-0.77 (-3.53, 2.00) -0.19 (-2.45, 2.06) *0.65*	0.48 (-0.96, 1.92) 0.10 (-1.07, 1.27) *0.56*
Blood pressure normal[c](n = 715): Blood pressure high[c] (n = 446):	0.05 (-2.29, 2.38) -0.87 (-3.44, 1.71) *0.45*	0.17 (-0.98, 1.33) 0.50 (-0.78, 1.78) *0.58*
Hemoglobin A1c < 5.7% (n = 851): Hemoglobin A1c ≥ 5.7% (n = 289):	-0.33 (-2.71, 2.04) -0.20 (-2.98, 2.58) *0.92*	0.17 (-1.08, 1.41) 0.57 (-0.89, 2.03) *0.57*
No metabolic syndrome[d] (n = 637): Metabolic syndrome[d] (n = 511):	-0.49 (-2.92, 1.94) -0.17 (-2.65, 2.31) *0.79*	0.47 (-0.79, 1.73) 0.34 (-0.94, 1.61) *0.83*
Personal $PM_{2.5}$, µg/m^3: per natural log unit increase[b]	Estimate (95% CI) *P-value for interaction*	Estimate (95% CI) *P-value for interaction*
Age < 40 years (n = 655): Age ≥ 40 years (n = 465):	-0.30 (-1.20, 0.59) 0.16 (-0.98, 1.30) *0.51*	0.05 (-0.43, 0.52) 0.25 (-0.35, 0.85) *0.58*
Waist circumference < 80cm (n = 367): Waist circumference ≥ 80cm (n = 753):	-0.18 (-1.37, 1.00) -0.10 (-0.94, 0.75) *0.90*	0.30 (-0.33, 0.92) 0.03 (-0.42, 0.48) *0.47*
Blood pressure normal[c] (n = 690): Blood pressure high[c] (n = 430):	0.09 (-0.77, 0.96) -0.54 (-1.69, 0.62) *0.36*	0.05 (-0.38, 0.48) 0.15 (-0.43, 0.73) *0.77*
Hemoglobin A1c < 5.7% (n = 824): Hemoglobin A1c ≥ 5.7% (n = 276):	-0.07 (-0.89, 0.76) -0.07 (-1.41, 1.27) *0.99*	0.25 (-0.19, 0.69) -0.18 (-0.89, 0.53) *0.29*
No metabolic syndrome[d] (n = 616): Metabolic syndrome[d] (n = 493):	0.07 (-0.89, 1.03) -0.32 (-1.34, 0.70) *0.56*	0.21 (-0.30, 0.71) 0.05 (-0.49, 0.58) *0.65*
Kitchen $PM_{2.5}$, µg/m^3: per natural log unit increase[b]	Estimate (95% CI) *P-value for interaction*	Estimate (95% CI) *P-value for interaction*
Age < 40 years (n = 656): Age ≥ 40 years (n = 464):	0.13 (-0.61, 0.87) -0.11 (-0.92, 0.69) *0.64*	0.06 (-0.33, 0.45) -0.01 (-0.44, 0.42) *0.79*
Waist circumference < 80cm (n = 359): Waist circumference ≥ 80cm (n = 761):	0.05 (-0.80, 0.90) 0.01 (-0.69, 0.70) *0.93*	0.28 (-0.17, 0.73) -0.12 (-0.49, 0.25) *0.14*
Blood pressure normal[c] (n = 691):	0.26 (-0.43, 0.95)	0.04 (-0.31, 0.38)

Blood pressure high[c] (n = 429):	-0.38 (-1.22, 0.46) *0.21*	-0.09 (-0.51, 0.34) *0.62*
Hemoglobin A1c < 5.7% (n = 821): Hemoglobin A1c ≥ 5.7% (n = 278):	0.18 (-0.46, 0.82) -0.46 (-1.53, 0.61) *0.27*	0.06 (-0.28, 0.40) -0.14 (-0.71, 0.43) *0.51*
No metabolic syndrome[d] (n = 612): Metabolic syndrome[d] (n = 495):	0.19 (-0.51, 0.88) -0.34 (-1.17, 0.49) *0.28*	0.08 (-0.28, 0.45) -0.10 (-0.54, 0.33) *0.48*
Cookstove-use: traditional vs *Justa* + traditional stacking[b]	Estimate (95% CI) *P-value for interaction*	Estimate (95% CI) *P-value for interaction*
Age < 40 years (n = 531): Age ≥ 40 years (n = 418):	0.62 (-2.33, 3.58) -0.43 (-3.47, 2.62) *0.44*	0.48 (-1.08, 2.04) 0.28 (-1.32, 1.89) *0.78*
Waist circumference < 80cm (n = 317): Waist circumference ≥ 80cm (n = 632):	0.31 (-3.18, 3.80) 0.13 (-2.60, 2.86) *0.90*	0.81 (-1.03, 2.65) 0.22 (-1.22, 1.66) *0.44*
Blood pressure normal[c] (n = 574): Blood pressure high[c] (n = 375):	0.16 (-2.68, 2.99) 0.39 (-2.80, 3.57) *0.87*	0.13 (-1.29, 1.55) 0.98 (-0.61, 2.58) *0.21*
Hemoglobin A1c < 5.7% (n = 686): Hemoglobin A1c ≥ 5.7% (n = 250):	-0.04 (-2.88, 2.80) 0.09 (-3.41, 3.59) *0.93*	0.28 (-1.23, 1.79) 0.74 (-1.12, 2.59) *0.57*
No metabolic syndrome[d] (n = 518): Metabolic syndrome[d] (n = 422):	0.37 (-2.60, 3.34) -0.18 (-3.23, 2.88) *0.69*	0.65 (-0.90, 2.21) 0.42 (-1.18, 2.01) *0.74*
Cookstove-use: traditional vs *Justa* with or without improved stacking[b]	Estimate (95% CI) *P-value for interaction*	Estimate (95% CI) *P-value for interaction*
Age < 40 years (n = 502): Age ≥ 40 years (n = 294):	-2.25 (-5.37, 0.88) -4.01 (-8.13, 0.11) *0.33*	0.40 (-1.25, 2.05) -1.50 (-3.70, 0.70) *0.05*
Waist circumference < 80cm (n = 259): Waist circumference ≥ 80cm (n = 537):	-3.57 (-7.78, 0.65) -2.45 (-5.52, 0.61) *0.53*	0.02 (-2.21, 2.25) -0.22 (-1.85, 1.40) *0.79*
Blood pressure normal[c](n = 490): Blood pressure high[c] (n = 306):	-1.78 (-5.05, 1.48) -4.14 (-7.92, -0.36) *0.17*	0.20 (-1.43, 1.84) -0.24 (-2.15, 1.67) *0.61*
Hemoglobin A1c < 5.7% (n = 577): Hemoglobin A1c ≥ 5.7% (n = 200):	-2.55 (-5.71, 0.61) -4.16 (-8.69, 0.37) *0.42*	-0.19 (-1.87, 1.48) -0.37 (-2.81, 2.08) *0.87*
No metabolic syndrome[d] (n = 440): Metabolic syndrome[d] (n = 343):	-3.73 (-7.13, -0.33) -1.68 (-5.26, 1.89) *0.22*	-0.18 (-1.97, 1.60) 0.09 (-1.78, 1.96) *0.76*

$PM_{2.5}$ = fine particulate matter; CI = confidence interval;

[a] Intent-to-treat analysis: model includes a fixed term for assigned stove, a fixed spline term for date, and a random term for participant.

[b] In addition to terms from intent-to-treat analysis, results are adjusted for age (years, continuous), waist circumference (cm, continuous) and self-reported years of education (dichotomous, < 6 vs 6+).
[c] Blood pressure normal: systolic blood pressure ≤ 120 mmHg and diastolic blood pressure ≤ 80 mmHg; Blood pressure high: systolic blood pressure > 120 mmHg or diastolic blood pressure > 80 mmHg
[d] Metabolic syndrome defined as waist circumference ≥ 80cm and at least two of the following: hemoglobin A1c > 5.6%, triglycerides > 200 mg/dL, high-density lipoprotein < 50 mg/dL, systolic blood pressure ≥ 130 mmHg, or diastolic blood pressure ≥ 85 mmHg.

Table C5. Participant characteristics at baseline (visit 1) for participants who completed all 6 visits (complete-case), total and by study arm

	All households n=106	Arm 1 n=59	Arm 2 n=47
Participant characteristic	**mean (sd) min; median; max or n (%)**	**mean (sd) min; median; max or n (%)**	**mean (sd) min; median; max or n (%)**
Age, years	39.2 (9.3) 24.0; 38.5; 59.0	39.0 (8.7) 24.0; 39.0; 56.0	39.3 (10.0) 25.0; 37.0; 59.0
Total years cooking with a biomass cookstove	26.9 (10.0) 9.0; 26.5; 49.0	27.1 (9.3) 12.0; 27.0; 45.0	26.7 (11.0) 9.0; 23.0; 49.0
Beds per person in the household			
Fewer than 0.5	39 (37)	18 (31)	21 (45)
0.5 or more	67 (63)	41 (69)	26 (55)
Education			
Less than six years	64 (60)	36 (61)	28 (60)
Six or more years	42 (40)	23 (39)	19 (40)
Dietary diversity score[a]			
Less than 6	44 (42)	28 (47)	16 (34)
6 or more	62 (58)	31 (53)	31 (66)
Household assets[b]			
Two or fewer household assets	71 (63)	39 (66)	28 (60)
More than two household assets	42 (37)	20 (34)	19 (40)
Body mass index, kg/m^2	25.8 (4.2) 18.4; 25.6; 39.2	26.4 (3.9) 19.8; 26.9; 34.1	25.0 (4.6) 18.4; 24.4; 39.2
Waist circumference, cm	83.4 (9.6) 61.0; 82.2; 114.3	84.9 (8.9) 68.6; 84.5; 99.1	81.6 (10.2) 61.0; 81.3; 114.3
Physical activity, METS	314 (99) 148; 309; 699	313 (90) 148; 315; 559	316 (111) 164; 308; 699

sd = standard deviation, METS = metabolic equivalent (kcal/kg/hour)

[a] Sum of 11 food categories found in a 24-hour dietary recall: grains (corn, cereals, rice, chips), pulses and nuts (nuts, beans), roots (potatoes), other vegetables, fruits, sweets, eggs, dairy (cheese, milk), meat (beef, chicken, pork, fish), oils, and beverages (coffee, soda, juice).

[b] Sum of 9 household assets: bicycle, car, motorcycle, television, radio, refrigerator, cell phone, computer, and sewing machine

Table C6. Participant characteristics at baseline (visit 1) for participants who missed visit 2 due to Sphygmocor XCEL malfunction, total and by study arm

	All households n=45	Arm 1 n=19	Arm 2 n=26
Participant characteristic	**mean (sd) min; median; max or n (%)**	**mean (sd) min; median; max or n (%)**	**mean (sd) min; median; max or n (%)**
Age, years	39.6 (7.9) 26.0; 39.0; 56.0	39.4 (7.3) 26.0; 39.0; 52.0	39.7 (8.4) 26.0; 39.5; 56.0
Total years cooking with a biomass cookstove	28.3 (8.6) 14.0; 28.0; 43.0	28.5 (8.4) 15.0; 29.0; 43.0	28.2 (9.0) 14.0; 27.5; 43.0
Beds per person in the household			
Fewer than 0.5	6 (13)	4 (21)	2 (8)
0.5 or more	39 (87)	15 (79)	24 (92)
Education			
Less than six years	17 (38)	5 (26)	12 (46)
Six or more years	28 (62)	14 (74)	14 (54)
Dietary diversity score[a]			
Less than 6	9 (20)	5 (26)	4 (15)
6 or more	36 (80)	14 (74)	22 (85)
Household assets[b]			
Two or fewer household assets	9 (20)	4 (21)	5 (19)
More than two household assets	36 (80)	15 (79)	21 (81)
Body mass index, kg/m^2	26.9 (4.2) 20.0; 26.1; 37.2	26.2 (3.7) 20.5; 25.7; 33.7	27.5 (4.6) 20.0; 27.0; 37.2
Waist circumference, cm	85.6 (8.7) 68.6; 86.4; 101.6	84.2 (7.6) 69.9; 81.3; 96.5	86.7 (9.4) 68.6; 88.9; 101.6
Physical activity, METS	248 (67) 126; 245; 456	270 (78) 168; 251; 456	231 (53) 126; 227; 342

sd = standard deviation, METS = metabolic equivalent (kcal/kg/hour)

[a] Sum of 11 food categories found in a 24-hour dietary recall: grains (corn, cereals, rice, chips), pulses and nuts (nuts, beans), roots (potatoes), other vegetables, fruits, sweets, eggs, dairy (cheese, milk), meat (beef, chicken, pork, fish), oils, and beverages (coffee, soda, juice).

[b] Sum of 9 household assets: bicycle, car, motorcycle, television, radio, refrigerator, cell phone, computer, and sewing machine

Table C7. Participant characteristics at baseline (visit 1) for participants who missed a visit for any reason besides the Sphygmocor XCEL malfunction, total and by study arm

	All households n=71	Arm 1 n=35	Arm 2 n=36
Participant characteristic	**mean (sd) min; median; max or n (%)**	**mean (sd) min; median; max or n (%)**	**mean (sd) min; median; max or n (%)**
Age, years	36.2 (7.5) 25.0; 35.0; 55.0	36.9 (7.3) 25.0; 36.0; 55.0	35.5 (7.7) 25.0; 34.0; 54.0
Total years cooking with a biomass cookstove	24.3 (8.2) 12.0; 23.0; 47.0	25.2 (7.5) 13.0; 26.0; 42.0	23.1 (9.1) 12.0; 22.0; 47.0
Beds per person in the household			
Fewer than 0.5	29 (41)	14 (40)	15 (42)
0.5 or more	42 (59)	21 (60)	21 (58)
Education			
Less than six years	37 (52)	19 (54)	18 (50)
Six or more years	34 (48)	16 (46)	18 (50)
Dietary diversity score[a]			
Less than 6	21 (30)	11 (31)	10 (28)
6 or more	50 (70)	24 (69)	26 (72)
Household assets[b]			
Two or fewer household assets	42 (59)	22 (63)	20 (56)
More than two household assets	29 (41)	13 (37)	16 (44)
Body mass index, kg/m^2	26.0 (4.1) 18.6; 25.9; 36.9	26.0 (4.2) 18.7; 25.7; 36.9	26.1 (4.0) 18.6; 26.0; 35.8
Waist circumference, cm	84.4 (10.1) 66.0; 83.8; 111.8	82.9 (11.1) 66.0; 80.0; 111.8	85.8 (9.0) 71.1; 86.4; 105.4
Physical activity, METS	316 (107) 114; 302; 676	316 (110) 155; 300; 596	315 (106) 114; 306; 676

sd = standard deviation, METS = metabolic equivalent (kcal/kg/hour)

[a] Sum of 11 food categories found in a 24-hour dietary recall: grains (corn, cereals, rice, chips), pulses and nuts (nuts, beans), roots (potatoes), other vegetables, fruits, sweets, eggs, dairy (cheese, milk), meat (beef, chicken, pork, fish), oils, and beverages (coffee, soda, juice).

[b] Sum of 9 household assets: bicycle, car, motorcycle, television, radio, refrigerator, cell phone, computer, and sewing machine

Table C8. Frequency of stove-use combinations across 6 study visits

Study arm[a]	Stove-use label[b]	Stove-use combination[c]	Frequency
1	stacker	trad, trad, justa+trad, justa+trad, justa+trad, justa+trad	41
1	complier	trad, trad, justa/imprvd, justa/imprvd, justa/imprvd, justa/imprvd	13
1	inconsistent	trad, trad, justa+trad, justa+trad, justa+trad, justa/imprvd	7
1	inconsistent	trad, trad, justa+trad, justa/imprvd, justa/imprvd, justa/imprvd	6
1	inconsistent	trad, trad, NA, NA, NA, NA	5
1	inconsistent	trad, trad, justa/imprvd, justa+trad, justa/imprvd, justa/imprvd	4
1	inconsistent	trad, trad, justa+trad, justa/imprvd, justa+trad, justa+trad	4
1	inconsistent	trad, trad, justa+trad, justa+trad, justa/imprvd, justa+trad	3
1	inconsistent	trad, trad, justa/imprvd, justa/imprvd, justa/imprvd, justa+trad	2
1	inconsistent	trad, trad, justa/imprvd, justa/imprvd, NA, NA	2
1	inconsistent	trad, trad, justa/imprvd, justa+trad, justa/imprvd, justa+trad	2
1	inconsistent	trad, trad, justa/imprvd, justa+trad, justa+trad, justa+trad	2
1	inconsistent	trad, trad, justa+trad, justa+trad, justa/imprvd, justa/imprvd	2
1	stacker	trad, trad, justa+trad, justa+trad, justa+trad, NA	2
1	stacker	trad, trad, justa+trad, justa+trad, NA, justa+trad	2
1	complier	trad, NA, justa/imprvd, justa/imprvd, justa/imprvd, justa/imprvd	1
1	inconsistent	trad, NA, justa/imprvd, justa+trad, justa/imprvd, justa/imprvd	1
1	inconsistent	trad, NA, justa/imprvd, justa+trad, justa/imprvd, justa+trad	1
1	inconsistent	trad, NA, justa+trad, justa/imprvd, justa/imprvd, justa/imprvd	1
1	inconsistent	trad, trad, justa/imprvd, justa/imprvd, justa/imprvd, trad	1
1	complier	trad, trad, justa/imprvd, justa/imprvd, NA, justa/imprvd	1
1	inconsistent	trad, trad, justa/imprvd, justa/imprvd, trad, justa/imprvd	1
1	inconsistent	trad, trad, justa/imprvd, justa+trad, justa/imprvd, NA	1
1	inconsistent	trad, trad, justa/imprvd, justa+trad, justa+trad, justa/imprvd	1
1	inconsistent	trad, trad, justa/imprvd, justa+trad, NA, NA	1
1	inconsistent	trad, trad, justa+trad, justa+trad, justa/imprvd, NA	1
1	inconsistent	trad, trad, justa+trad, NA, justa/imprvd, justa/imprvd	1
1	inconsistent	trad, trad, justa+trad, NA, justa/imprvd, justa+trad	1
1	inconsistent	trad, trad, justa+trad, NA, NA, justa/imprvd	1
1	inconsistent	trad, trad, justa+trad, NA, NA, justa+trad	1
1	inconsistent	trad, trad, justa+trad, NA, NA, NA	1
1	complier	trad, trad, NA, justa/imprvd, justa/imprvd, justa/imprvd	1

1	inconsistent	trad, trad, NA, justa/imprvd, justa/imprvd, justa+trad	1
2	stacker	trad, trad, trad, trad, justa+trad, justa+trad	45
2	complier	trad, trad, trad, trad, justa/imprvd, justa/imprvd	15
2	inconsistent	trad, trad, NA, NA, NA, NA	10
2	inconsistent	trad, trad, trad, trad, justa+trad, justa/imprvd	9
2	inconsistent	trad, trad, trad, trad, justa/imprvd, justa+trad	7
2	complier	trad, trad, NA, trad, justa/imprvd, justa/imprvd	3
2	inconsistent	trad, trad, trad, NA, NA, NA	3
2	stacker	trad, trad, trad, trad, justa+trad, NA	3
2	inconsistent	trad, trad, trad, trad, NA, NA	3
2	inconsistent	trad, trad, trad, trad, trad, NA	2
2	inconsistent	trad, trad, trad, trad, trad, trad	2
2	inconsistent	trad, NA, justa/imprvd, justa/imprvd, justa/imprvd, justa/imprvd	1
2	inconsistent	trad, NA, trad, trad, NA, justa+trad	1
2	inconsistent	trad, trad, justa/imprvd, justa/imprvd, justa/imprvd, justa+trad	1
2	inconsistent	trad, trad, justa/imprvd, trad, justa/imprvd, justa/imprvd	1
2	inconsistent	trad, trad, NA, NA, justa/imprvd, justa+trad	1
2	stacker	trad, trad, NA, trad, justa+trad, justa+trad	1
2	inconsistent	trad, trad, trad, justa/imprvd, justa/imprvd, justa/imprvd	1
2	complier	trad, trad, trad, NA, justa/imprvd, justa/imprvd	1
2	inconsistent	trad, trad, trad, NA, justa/imprvd, justa+trad	1
2	complier	trad, trad, trad, trad, justa/imprvd, NA	1
2	inconsistent	trad, trad, trad, trad, justa+trad, trad	1
2	complier	trad, trad, trad, trad, NA, justa/imprvd	1
2	stacker	trad, trad, trad, trad, NA, justa+trad	1

[a] Study Arm 1 received intervention *Justa* cookstove after visit 2; study Arm 2 received intervention *Justa* cookstove after visit 4.

[b] Compliant participants used assigned cookstove at all visits and did not use a secondary traditional cookstove with the *Justa* cookstove; inconsistent participants did not use the assigned cookstove at all visits or used a secondary traditional cookstove with the *Justa* cookstove during at least one visit; stackers used the assigned cookstove at all visits but also used a secondary traditional cookstove with the *Justa* cookstove. Stackers/compliers were allowed to miss 1 pre-intervention visit or 1 post-intervention visit and still meet the above definitions.

[c] Combinations are in order from visit 1 to visit 6. Based on 3-level cookstove-use variable: traditional primary with or without traditional secondary cookstove (reference), *Justa* plus traditional secondary cookstove, *Justa* primary with or without improved secondary cookstove.

Sensitivity analyses

We performed a number of sensitivity analyses within each model framework to help confirm the primary analysis results. In the intent-to-treat (ITT) model framework, potential confounders were accounted for through the study arm assignment randomization. However, we performed sensitivity analyses using subsets of the data and using different variables to account for time within the models. In general, these different model variations had little impact on the results compared to the primary model. An exception to this generalization is when we assessed the complete case data versus a dataset with participants who missed one or more visits throughout the study. Missing data did seem to impact the model results in the ITT analysis framework. The impact of missing data is discussed in detail in the main text.

In the exposure-response and cookstove-use analysis frameworks, study arm assignment randomization did not account for potential confounding variables. In these analysis frameworks, we conducted additional sensitivity analyses to assess the potential impact of confounding. As with the ITT model results, models that used various potential confounders and subsets of the data produced results with very few differences compared to the primary models. However, missing data also appears to have impacted the cookstove-use model framework, and to a lesser extent, the exposure-response model framework. An explanation and interpretation of these results is presented in the main text.

The final sensitivity analyses in figures C17-C20 present graphical results for quantitative personal and kitchen $PM_{2.5}$ concentrations modelled as spline trend functions. These visualizations confirm the null associations seen in the exposure-response analyses; where the bulk of the observations lie, there appears to be very little association between quantitative $PM_{2.5}$ concentrations and the outcomes of AIx and CPP.

A further description of specific model terms for each sensitivity analysis within each model framework is presented in the subtext below each figure. Overall, the sensitivity analyses help confirm that the primary models produced results that were very similar to models that use

subsets of the data and various potential confounders. These analyses help give confidence in our primary results which indicate that the *Justa* intervention did not meaningfully impact AIx or CPP, and that neither of these outcomes are strongly associated with personal or kitchen $PM_{2.5}$.

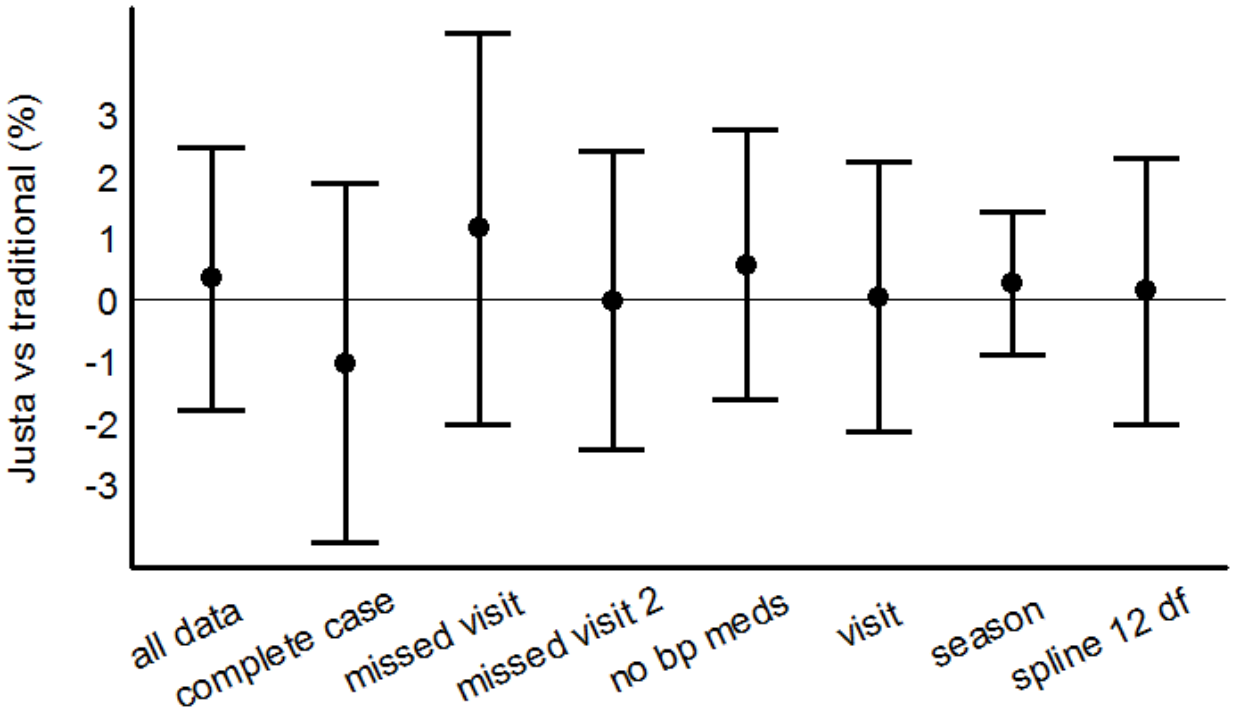

Figure C1. Sensitivity analyses for augmentation index intent-to-treat analysis
Intent-to-treat analysis: "all data" model included a fixed term for assigned stove, a fixed spline term for date (df=6), and a random term for participant; using full dataset (n=1161).
"complete case" model used the primary model on a subset of the data in which participants were only included if they completed all six study visits (n=636).
"missed visit" model used the primary model on a subset of the data in which participants were only included if they missed a visit at any time throughout the study (n=526).
"missed visit 2" model used the primary model on a subset of the data in which filtered out 46 participants (all observations) who missed visit 2 due to a Sphygmocor malfunction (n=949).
"no bp meds" model used the primary model on a subset of the data in which participants who used blood pressure medications were excluded from analysis (n=1107).
"visit" model used the same terms as the primary model, with the spline term for date replaced with a six-level term for study visit (n=1161).
"season" model used the same terms as the primary model, with the spline term for date replaced with a two-level term for season (rainy vs dry) (n=1161).
"spline 12 df" model used the same terms as the primary model, with the spline term for date (df=6) replaced with a spline term for date (df=12) (n=1161).

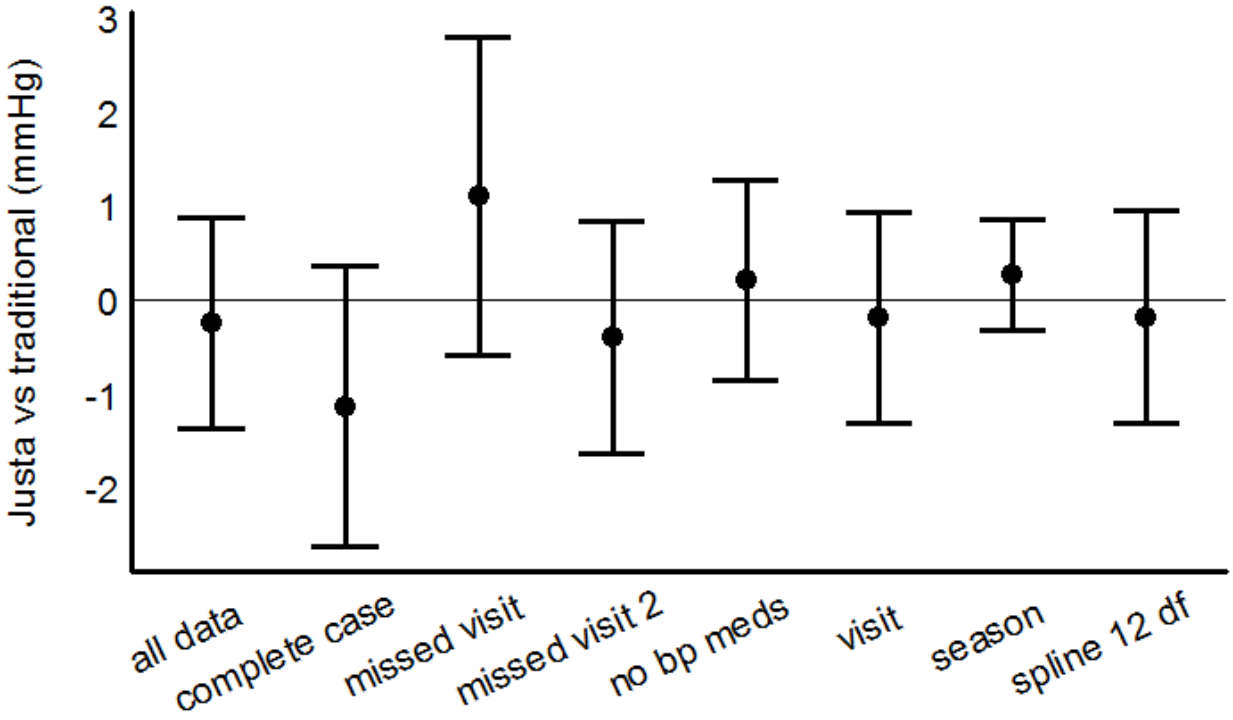

Figure C2. Sensitivity analyses for central pulse pressure intent-to-treat analysis
Intent-to-treat analysis: "all data" model included a fixed term for assigned stove, a fixed spline term for date (df=6), and a random term for participant; using full dataset (n=1161).
"complete case" model used the primary model on a subset of the data in which participants were only included if they completed all six study visits (n=636).
"missed visit" model used the primary model on a subset of the data in which participants were only included if they missed a visit at any time throughout the study (n=526).
"missed visit 2" model used the primary model on a subset of the data in which filtered out 46 participants (all observations) who missed visit 2 due to a Sphygmocor malfunction (n=949).
"no bp meds" model used the primary model on a subset of the data in which participants who used blood pressure medications were excluded from analysis (n=1107).
"visit" model used the same terms as the primary model, with the spline term for date replaced with a six-level term for study visit (n=1161).
"season" model used the same terms as the primary model, with the spline term for date replaced with a two-level term for season (rainy vs dry) (n=1161).
"spline 12 df" model used the same terms as the primary model, with the spline term for date (df=6) replaced with a spline term for date (df=12) (n=1161).

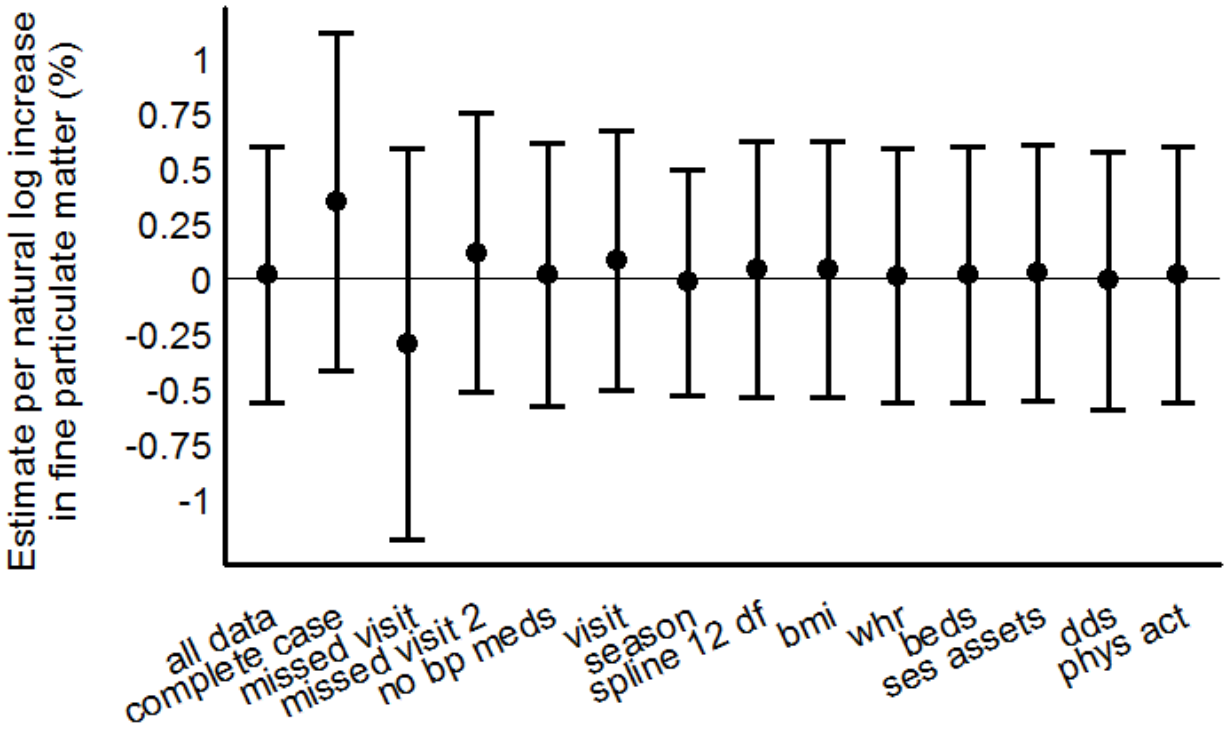

Figure C3. Sensitivity analyses for augmentation index exposure-response analysis with kitchen fine particulate matter

Exposure-response analysis: "all data" model included a continuous term for kitchen fine particulate matter, a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); using full dataset (n=1120).
"complete case" model used the primary model on a subset of the data in which participants were only included if they completed all six study visits (n=636).
"missed visit" model used the primary model on a subset of the data in which participants were only included if they missed a visit at any time throughout the study (n=526).
"missed visit 2" model used the primary model on a subset of the data in which filtered out 46 participants (all observations) who missed visit 2 due to a Sphygmocor malfunction (n=949).
"no bp meds" model used the primary model on a subset of the data in which participants who used blood pressure medications were excluded from analysis (n=1069).
"visit" model used the same terms as the primary model, with the spline term for date replaced with a six-level term for study visit (n=1120).
"season" model used the same terms as the primary model, with the spline term for date replaced with a two-level term for season (rainy vs dry) (n=1120).
"spline 12 df" model used the same terms as the primary model, with the spline term for date (df=6) replaced with a spline term for date (df=12) (n=1120).
"bmi" model used the same terms as the primary model, with the waist circumference term replaced with a continuous term for body mass index (n=1120).
"whr" model used the same terms as the primary model, with the waist circumference term replaced with a continuous term for waist-to-hip ratio (n=1120).
"beds" model used the same terms as the primary model, with the education term replaced with a dichotomous term for beds per person (<5 vs 5+) (n=1120).

“ses assets” model used the same terms as the primary model, with the education term replaced with a dichotomous term for socioeconomic assets (<3 vs 3+) (n=1120).
“dds” model used the same terms as the primary model, including a dichotomous term for dietary diversity score (<6 vs 6+) (n=1120).
“phys act” model used the same terms as the primary model, including a continuous term for physical activity (measured in metabolic equivalents [kcal/kg/hour]) (n=1120).

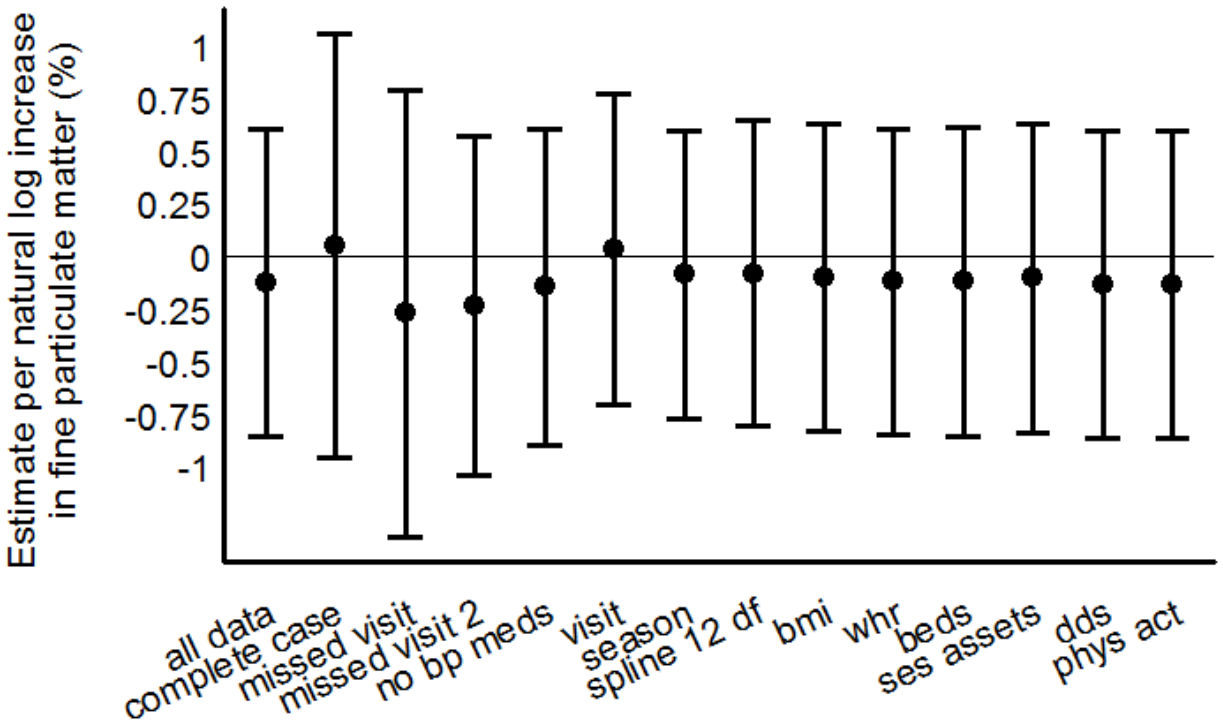

Figure C4. Sensitivity analyses for augmentation index exposure-response analysis with personal fine particulate matter

Exposure-response analysis: "all data" model included a continuous term for personal fine particulate matter, a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); using full dataset (n=1120).
"complete case" model used the primary model on a subset of the data in which participants were only included if they completed all six study visits (n=636).
"missed visit" model used the primary model on a subset of the data in which participants were only included if they missed a visit at any time throughout the study (n=526).
"missed visit 2" model used the primary model on a subset of the data in which filtered out 46 participants (all observations) who missed visit 2 due to a Sphygmocor malfunction (n=949).
"no bp meds" model used the primary model on a subset of the data in which participants who used blood pressure medications were excluded from analysis (n=1069).
"visit" model used the same terms as the primary model, with the spline term for date replaced with a six-level term for study visit (n=1120).
"season" model used the same terms as the primary model, with the spline term for date replaced with a two-level term for season (rainy vs dry) (n=1120).
"spline 12 df" model used the same terms as the primary model, with the spline term for date (df=6) replaced with a spline term for date (df=12) (n=1120).
"bmi" model used the same terms as the primary model, with the waist circumference term replaced with a continuous term for body mass index (n=1120).
"whr" model used the same terms as the primary model, with the waist circumference term replaced with a continuous term for waist-to-hip ratio (n=1120).
"beds" model used the same terms as the primary model, with the education term replaced with a dichotomous term for beds per person (<5 vs 5+) (n=1120).

“ses assets” model used the same terms as the primary model, with the education term replaced with a dichotomous term for socioeconomic assets (<3 vs 3+) (n=1120).
“dds” model used the same terms as the primary model, including a dichotomous term for dietary diversity score (<6 vs 6+) (n=1120).
“phys act” model used the same terms as the primary model, including a continuous term for physical activity (measured in metabolic equivalents [kcal/kg/hour]) (n=1120).

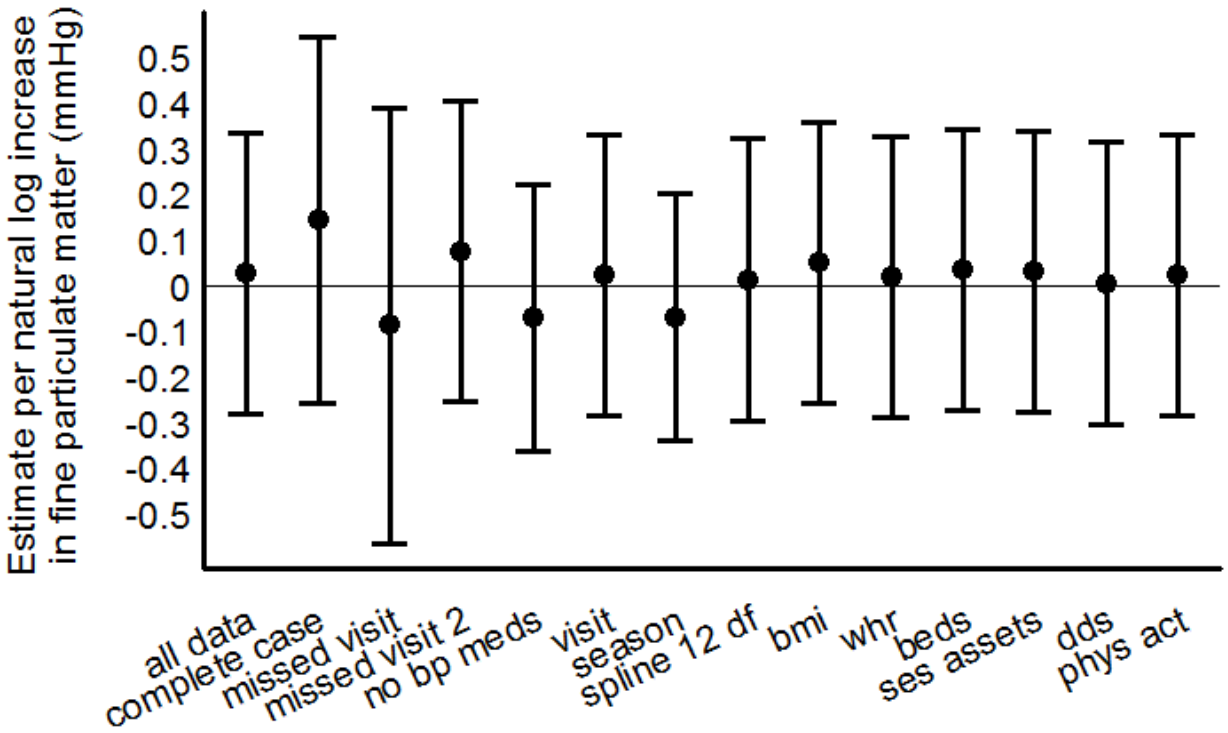

Figure C5. Sensitivity analyses for central pulse pressure exposure-response analysis with kitchen fine particulate matter

Exposure-response analysis: "all data" model included a continuous term for kitchen fine particulate matter, a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); using full dataset (n=1120).
"complete case" model used the primary model on a subset of the data in which participants were only included if they completed all six study visits (n=636).
"missed visit" model used the primary model on a subset of the data in which participants were only included if they missed a visit at any time throughout the study (n=526).
"missed visit 2" model used the primary model on a subset of the data in which filtered out 46 participants (all observations) who missed visit 2 due to a Sphygmocor malfunction (n=949).
"no bp meds" model used the primary model on a subset of the data in which participants who used blood pressure medications were excluded from analysis (n=1069).
"visit" model used the same terms as the primary model, with the spline term for date replaced with a six-level term for study visit (n=1120).
"season" model used the same terms as the primary model, with the spline term for date replaced with a two-level term for season (rainy vs dry) (n=1120).
"spline 12 df" model used the same terms as the primary model, with the spline term for date (df=6) replaced with a spline term for date (df=12) (n=1120).
"bmi" model used the same terms as the primary model, with the waist circumference term replaced with a continuous term for body mass index (n=1120).
"whr" model used the same terms as the primary model, with the waist circumference term replaced with a continuous term for waist-to-hip ratio (n=1120).
"beds" model used the same terms as the primary model, with the education term replaced with a dichotomous term for beds per person (<5 vs 5+) (n=1120).

“ses assets” model used the same terms as the primary model, with the education term replaced with a dichotomous term for socioeconomic assets (<3 vs 3+) (n=1120).
“dds” model used the same terms as the primary model, including a dichotomous term for dietary diversity score (<6 vs 6+) (n=1120).
“phys act” model used the same terms as the primary model, including a continuous term for physical activity (measured in metabolic equivalents [kcal/kg/hour]) (n=1120).

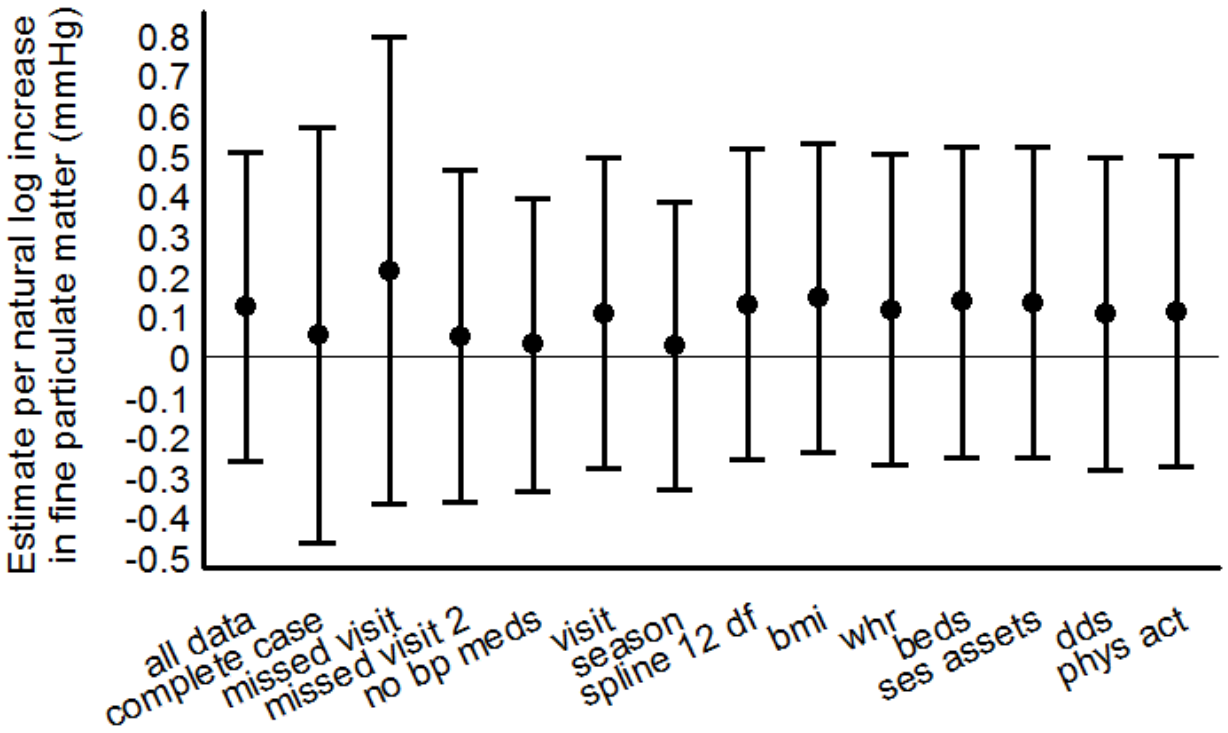

Figure C6. Sensitivity analyses for central pulse pressure exposure-response analysis with personal fine particulate matter

Exposure-response analysis: "all data" model included a continuous term for personal fine particulate matter, a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); using full dataset (n=1120).
"complete case" model used the primary model on a subset of the data in which participants were only included if they completed all six study visits (n=636).
"missed visit" model used the primary model on a subset of the data in which participants were only included if they missed a visit at any time throughout the study (n=526).
"missed visit 2" model used the primary model on a subset of the data in which filtered out 46 participants (all observations) who missed visit 2 due to a Sphygmocor malfunction (n=949).
"no bp meds" model used the primary model on a subset of the data in which participants who used blood pressure medications were excluded from analysis (n=1069).
"visit" model used the same terms as the primary model, with the spline term for date replaced with a six-level term for study visit (n=1120).
"season" model used the same terms as the primary model, with the spline term for date replaced with a two-level term for season (rainy vs dry) (n=1120).
"spline 12 df" model used the same terms as the primary model, with the spline term for date (df=6) replaced with a spline term for date (df=12) (n=1120).
"bmi" model used the same terms as the primary model, with the waist circumference term replaced with a continuous term for body mass index (n=1120).
"whr" model used the same terms as the primary model, with the waist circumference term replaced with a continuous term for waist-to-hip ratio (n=1120).
"beds" model used the same terms as the primary model, with the education term replaced with a dichotomous term for beds per person (<5 vs 5+) (n=1120).

“ses assets” model used the same terms as the primary model, with the education term replaced with a dichotomous term for socioeconomic assets (<3 vs 3+) (n=1120).
“dds” model used the same terms as the primary model, including a dichotomous term for dietary diversity score (<6 vs 6+) (n=1120).
“phys act” model used the same terms as the primary model, including a continuous term for physical activity (measured in metabolic equivalents [kcal/kg/hour]) (n=1120).

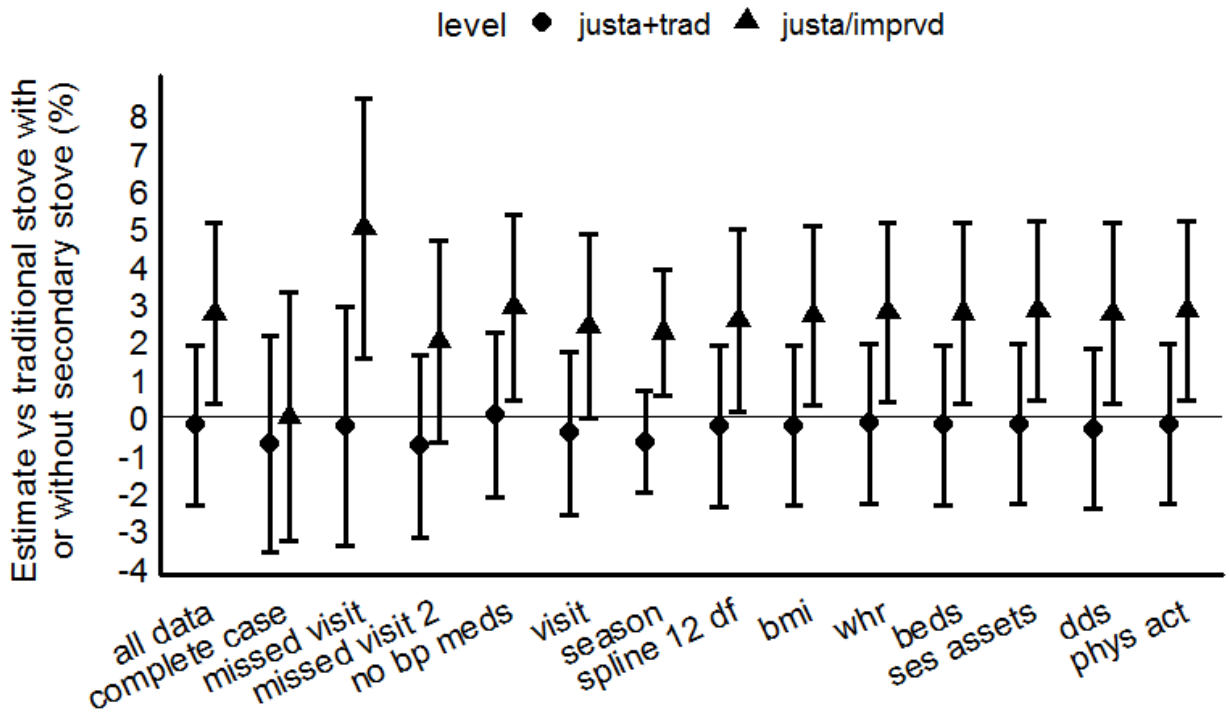

Figure C7. Stove-use (3-level) analysis for augmentation index
"all data" model included a 3-level term for cookstove use (traditional primary with or without traditional secondary cookstove (reference), *Justa* plus traditional secondary cookstove, *Justa* primary with or without improved secondary cookstove), a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); all study observations included (n=1162).
"complete case" model used the primary model on a subset of the data in which participants were only included if they completed all six study visits (n=636).
"missed visit" model used the primary model on a subset of the data in which participants were only included if they missed a visit at any time throughout the study (n=526).
"missed visit 2" model used the primary model on a subset of the data in which filtered out 46 participants (all observations) who missed visit 2 due to a Sphygmocor malfunction (n=949).
"no bp meds" model used the primary model on a subset of the data in which participants who used blood pressure medications were excluded from analysis (n=1106).
"visit" model used the same terms as the primary model, with the spline term for date replaced with a six-level term for study visit (n=1162).
"season" model used the same terms as the primary model, with the spline term for date replaced with a two-level term for season (rainy vs dry) (n=1162).
"spline 12 df" model used the same terms as the primary model, with the spline term for date (df=6) replaced with a spline term for date (df=12) (n=1162).
"bmi" model used the same terms as the primary model, with the waist circumference term replaced with a continuous term for body mass index (n=1162).
"whr" model used the same terms as the primary model, with the waist circumference term replaced with a continuous term for waist-to-hip ratio (n=1162).
"beds" model used the same terms as the primary model, with the education term replaced with a dichotomous term for beds per person (<5 vs 5+) (n=1162).

“ses assets” model used the same terms as the primary model, with the education term replaced with a dichotomous term for socioeconomic assets (<3 vs 3+) (n=1162).
“dds” model used the same terms as the primary model, including a dichotomous term for dietary diversity score (<6 vs 6+) (n=1162).
“phys act” model used the same terms as the primary model, including a continuous term for physical activity (measured in metabolic equivalents [kcal/kg/hour]) (n=1162).

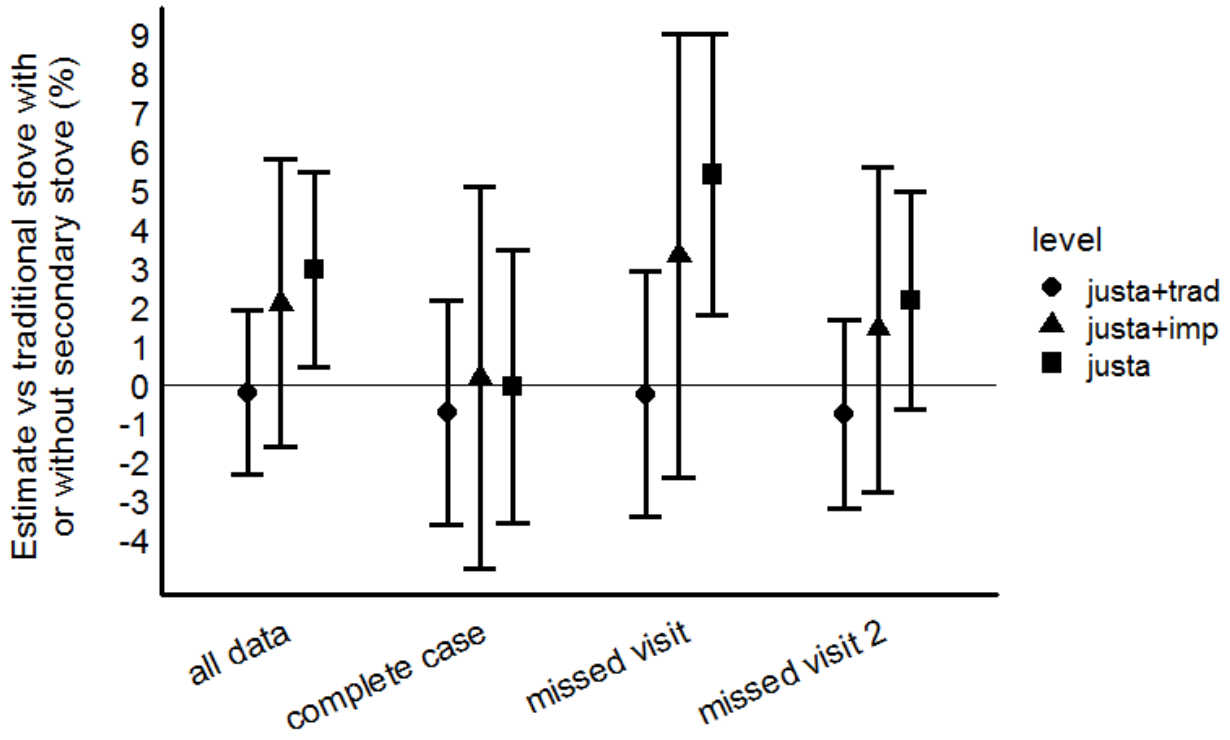

Figure C8. Stove-use (4-level) analysis for augmentation index
"all data" model included a 4-level term for cookstove use (traditional primary with or without traditional secondary cookstove (reference), *Justa* plus traditional secondary cookstove, *Justa* plus improved secondary cookstove, *Justa* without secondary cookstove), a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); all study observations included (n=1162).
"complete case" model used the primary model on a subset of the data in which participants were only included if they completed all six study visits (n=636).
"missed visit" model used the primary model on a subset of the data in which participants were only included if they missed a visit at any time throughout the study (n=526).
"missed visit 2" model used the primary model on a subset of the data in which filtered out 46 participants (all observations) who missed visit 2 due to a Sphygmocor malfunction (n=949).

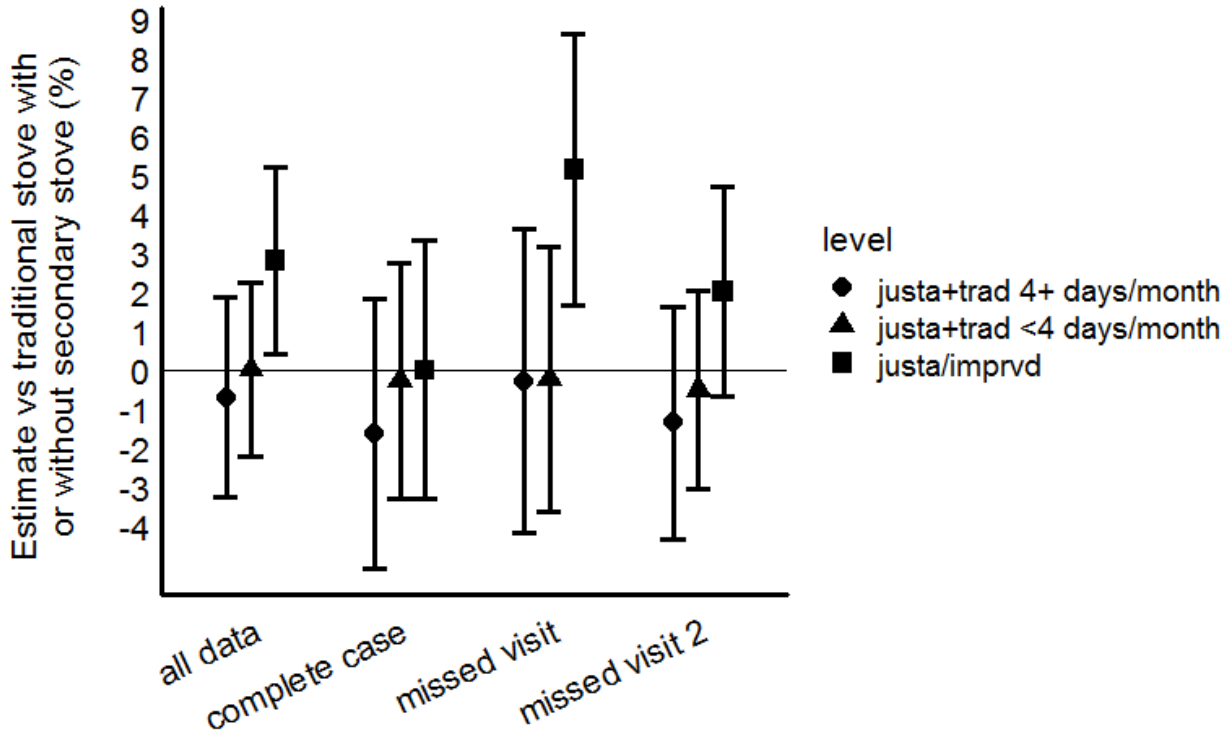

Figure C9. Stove-use analysis for augmentation index: days/month stove stacking
"all data" model included a 4-level term for cookstove use (traditional primary with or without traditional secondary cookstove (reference), *Justa* plus traditional secondary cookstove used 4+ days per month (self-report), *Justa* plus traditional secondary cookstove used <4 days per month (self-report), *Justa* primary with or without improved secondary cookstove), a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); all study observations included (n=1162).
"complete case" model used the primary model on a subset of the data in which participants were only included if they completed all six study visits (n=636).
"missed visit" model used the primary model on a subset of the data in which participants were only included if they missed a visit at any time throughout the study (n=526).
"missed visit 2" model used the primary model on a subset of the data in which filtered out 46 participants (all observations) who missed visit 2 due to a Sphygmocor malfunction (n=949).

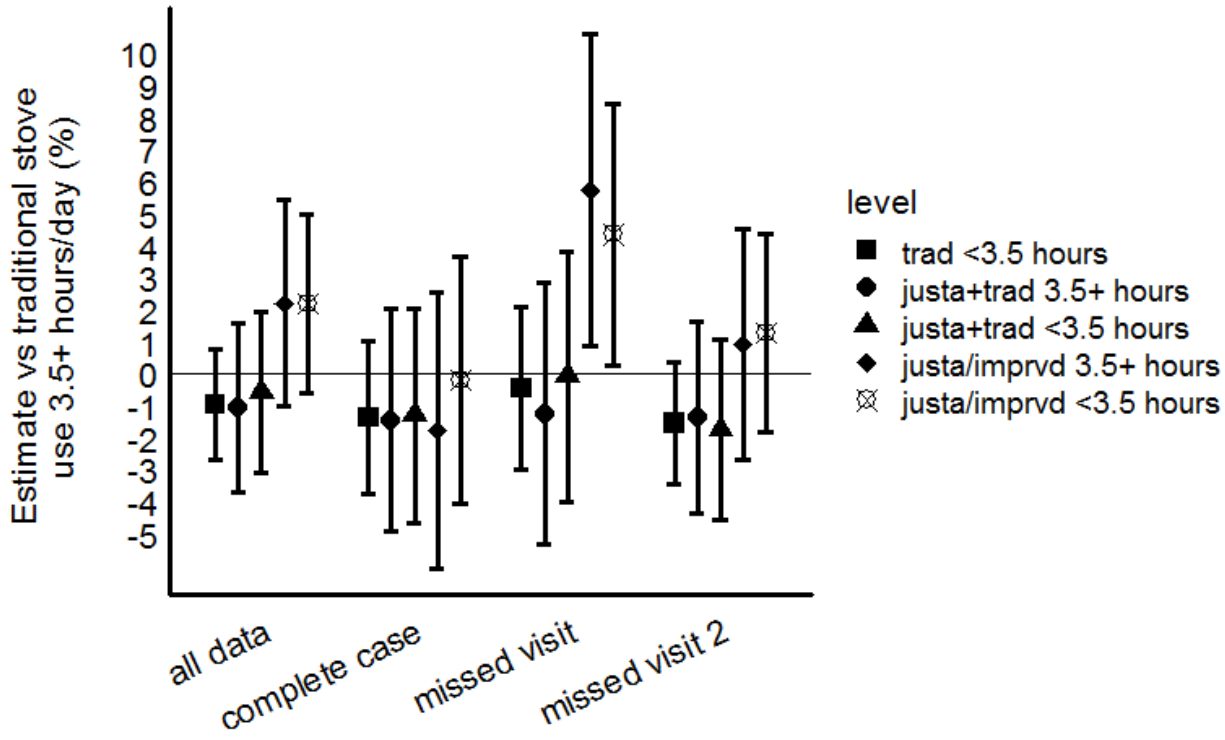

Figure C10. Stove-use analysis for augmentation index: hours/day primary cookstove use

"all data" model included a 6-level term for cookstove use (traditional primary used 3.5+ hours/day with or without traditional secondary cookstove (reference), traditional primary used <3.5 hours/day with or without traditional secondary cookstove, *Justa* used 3.5+ hours/day plus traditional secondary cookstove, *Justa* used <3.5 hours/day plus traditional secondary cookstove, *Justa* primary used 3.5+ hours/day with or without improved secondary cookstove, *Justa* primary used <3.5 hours/day with or without improved secondary cookstove), a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); all study observations included (n=1162).
"complete case" model used the primary model on a subset of the data in which participants were only included if they completed all six study visits (n=636).
"missed visit" model used the primary model on a subset of the data in which participants were only included if they missed a visit at any time throughout the study (n=526).
"missed visit 2" model used the primary model on a subset of the data in which filtered out 46 participants (all observations) who missed visit 2 due to a Sphygmocor malfunction (n=949).

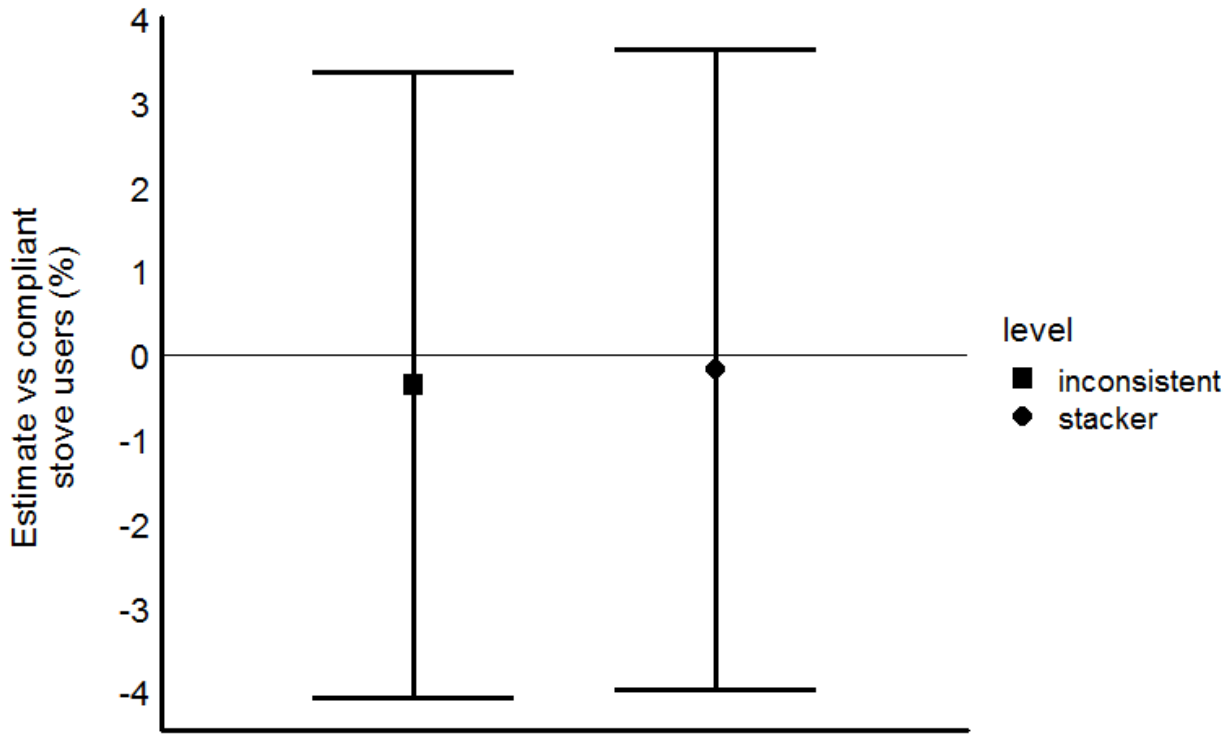

Figure C11. Stove-use analysis for augmentation index: stove assignment compliance
Model included a 3-level term for cookstove assignment compliance (compliant participants who used assigned cookstove at all visits and did not use a secondary traditional cookstove with the *Justa* cookstove (reference); inconsistent participants who did not use the assigned cookstove at all visits or used a secondary traditional cookstove with the *Justa* cookstove during at least one visit; stackers who used the assigned cookstove at all visits but also used a secondary traditional cookstove with the *Justa* cookstove [stackers/compliers were allowed to miss 1 pre-intervention visit or 1 post-intervention visit and still meet the above definitions]), a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); all study observations included (n=1162).

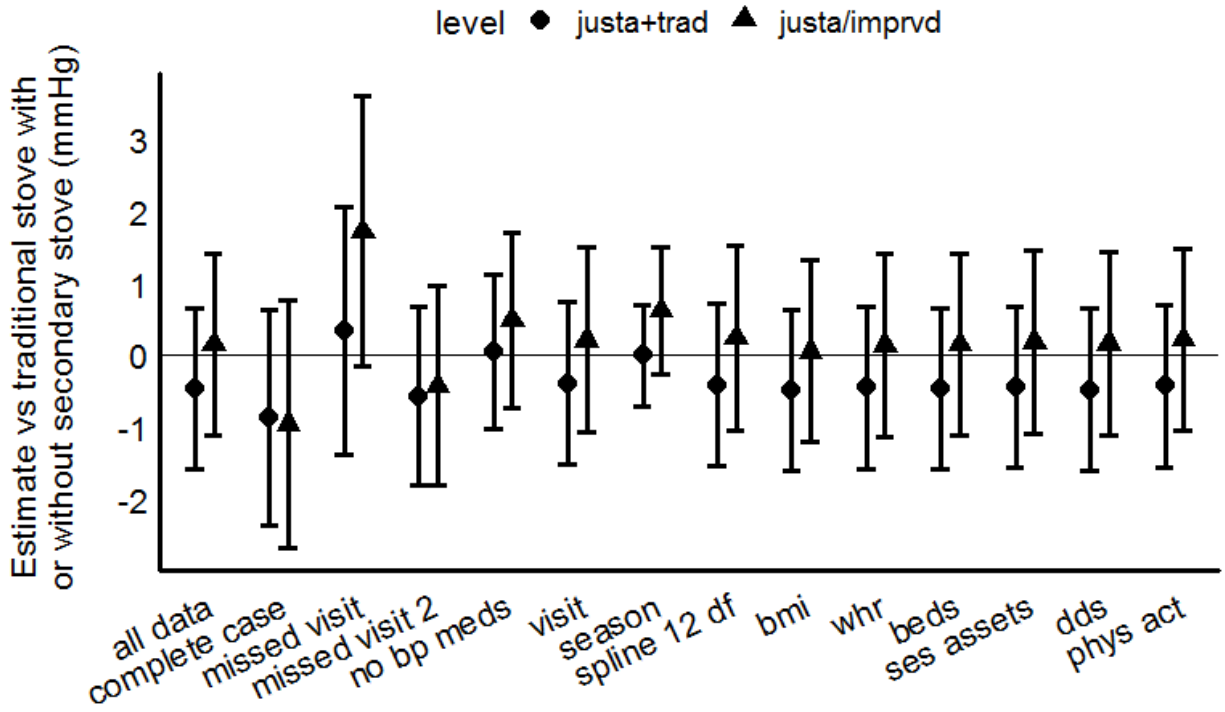

Figure C12. Stove-use (3-level) analysis for central pulse pressure
"all data" model included a 3-level term for cookstove use (traditional primary with or without traditional secondary cookstove (reference), *Justa* plus traditional secondary cookstove, *Justa* primary with or without improved secondary cookstove), a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); all study observations included (n=1162).
"complete case" model used the primary model on a subset of the data in which participants were only included if they completed all six study visits (n=636).
"missed visit" model used the primary model on a subset of the data in which participants were only included if they missed a visit at any time throughout the study (n=526).
"missed visit 2" model used the primary model on a subset of the data in which filtered out 46 participants (all observations) who missed visit 2 due to a Sphygmocor malfunction (n=949).
"no bp meds" model used the primary model on a subset of the data in which participants who used blood pressure medications were excluded from analysis (n=1106).
"visit" model used the same terms as the primary model, with the spline term for date replaced with a six-level term for study visit (n=1162).
"season" model used the same terms as the primary model, with the spline term for date replaced with a two-level term for season (rainy vs dry) (n=1162).
"spline 12 df" model used the same terms as the primary model, with the spline term for date (df=6) replaced with a spline term for date (df=12) (n=1162).
"bmi" model used the same terms as the primary model, with the waist circumference term replaced with a continuous term for body mass index (n=1162).
"whr" model used the same terms as the primary model, with the waist circumference term replaced with a continuous term for waist-to-hip ratio (n=1162).
"beds" model used the same terms as the primary model, with the education term replaced with a dichotomous term for beds per person (<5 vs 5+) (n=1162).

“ses assets” model used the same terms as the primary model, with the education term replaced with a dichotomous term for socioeconomic assets (<3 vs 3+) (n=1162).
“dds” model used the same terms as the primary model, including a dichotomous term for dietary diversity score (<6 vs 6+) (n=1162).
“phys act” model used the same terms as the primary model, including a continuous term for physical activity (measured in metabolic equivalents [kcal/kg/hour]) (n=1162).

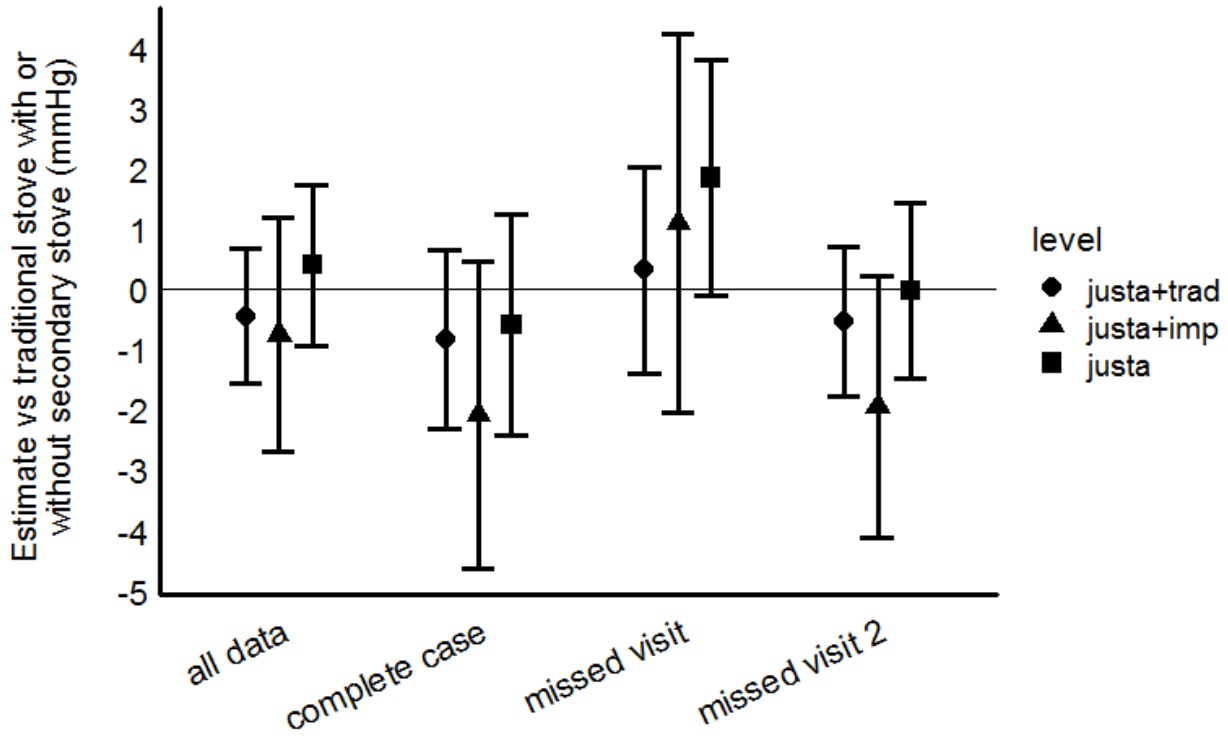

Figure C13. Stove-use (4-level) analysis for central pulse pressure
"all data" model included a 4-level term for cookstove use (traditional primary with or without traditional secondary cookstove (reference), *Justa* plus traditional secondary cookstove, *Justa* plus improved secondary cookstove, *Justa* without secondary cookstove), a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); all study observations included (n=1162).
"complete case" model used the primary model on a subset of the data in which participants were only included if they completed all six study visits (n=636).
"missed visit" model used the primary model on a subset of the data in which participants were only included if they missed a visit at any time throughout the study (n=526).
"missed visit 2" model used the primary model on a subset of the data in which filtered out 46 participants (all observations) who missed visit 2 due to a Sphygmocor malfunction (n=949).

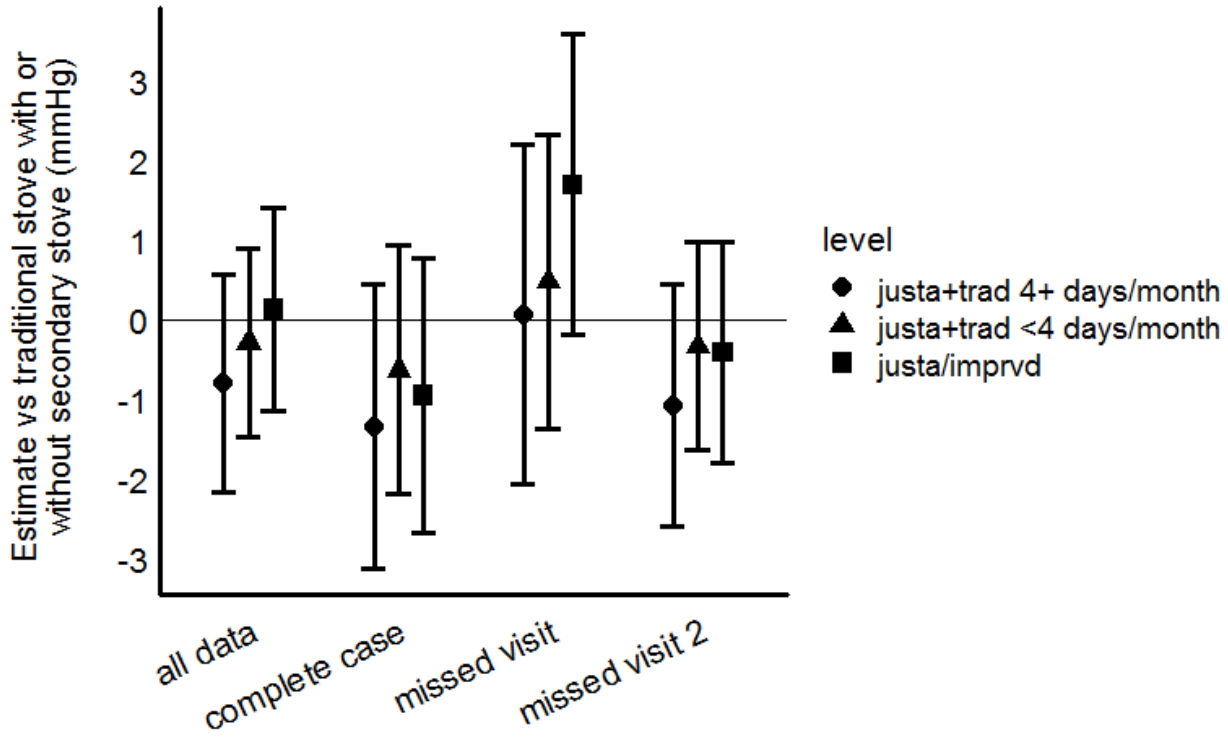

Figure C14. Stove-use analysis for central pulse pressure: days/month stove stacking
"all data" model included a 4-level term for cookstove use (traditional primary with or without traditional secondary cookstove (reference), *Justa* plus traditional secondary cookstove used 4+ days per month (self-report), *Justa* plus traditional secondary cookstove used <4 days per month (self-report), *Justa* primary with or without improved secondary cookstove), a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); all study observations included (n=1162).
"complete case" model used the primary model on a subset of the data in which participants were only included if they completed all six study visits (n=636).
"missed visit" model used the primary model on a subset of the data in which participants were only included if they missed a visit at any time throughout the study (n=526).
"missed visit 2" model used the primary model on a subset of the data in which filtered out 46 participants (all observations) who missed visit 2 due to a Sphygmocor malfunction (n=949).

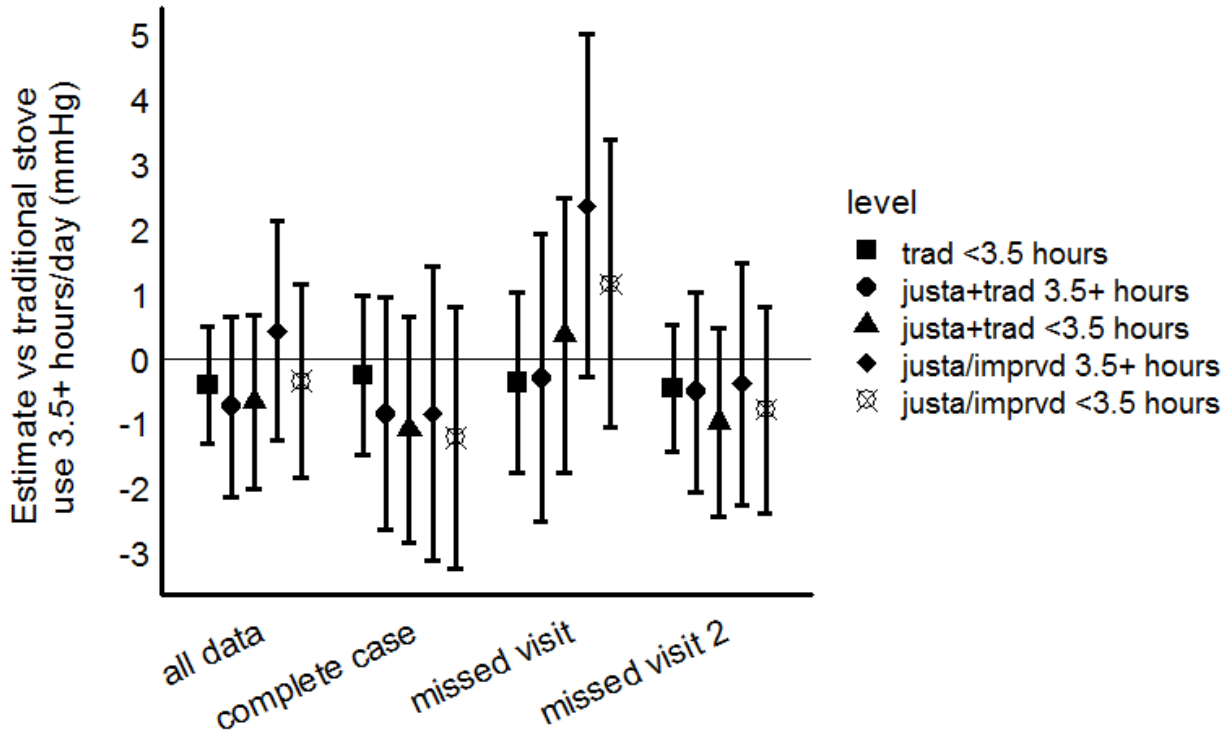

Figure C15. Stove-use analysis for central pulse pressure: hours/day primary cookstove use

"all data" model included a 6-level term for cookstove use (traditional primary used 3.5+ hours/day with or without traditional secondary cookstove (reference), traditional primary used <3.5 hours/day with or without traditional secondary cookstove, *Justa* used 3.5+ hours/day plus traditional secondary cookstove, *Justa* used <3.5 hours/day plus traditional secondary cookstove, *Justa* primary used 3.5+ hours/day with or without improved secondary cookstove, *Justa* primary used <3.5 hours/day with or without improved secondary cookstove), a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); all study observations included (n=1162).
"complete case" model used the primary model on a subset of the data in which participants were only included if they completed all six study visits (n=636).
"missed visit" model used the primary model on a subset of the data in which participants were only included if they missed a visit at any time throughout the study (n=526).
"missed visit 2" model used the primary model on a subset of the data in which filtered out 46 participants (all observations) who missed visit 2 due to a Sphygmocor malfunction (n=949).

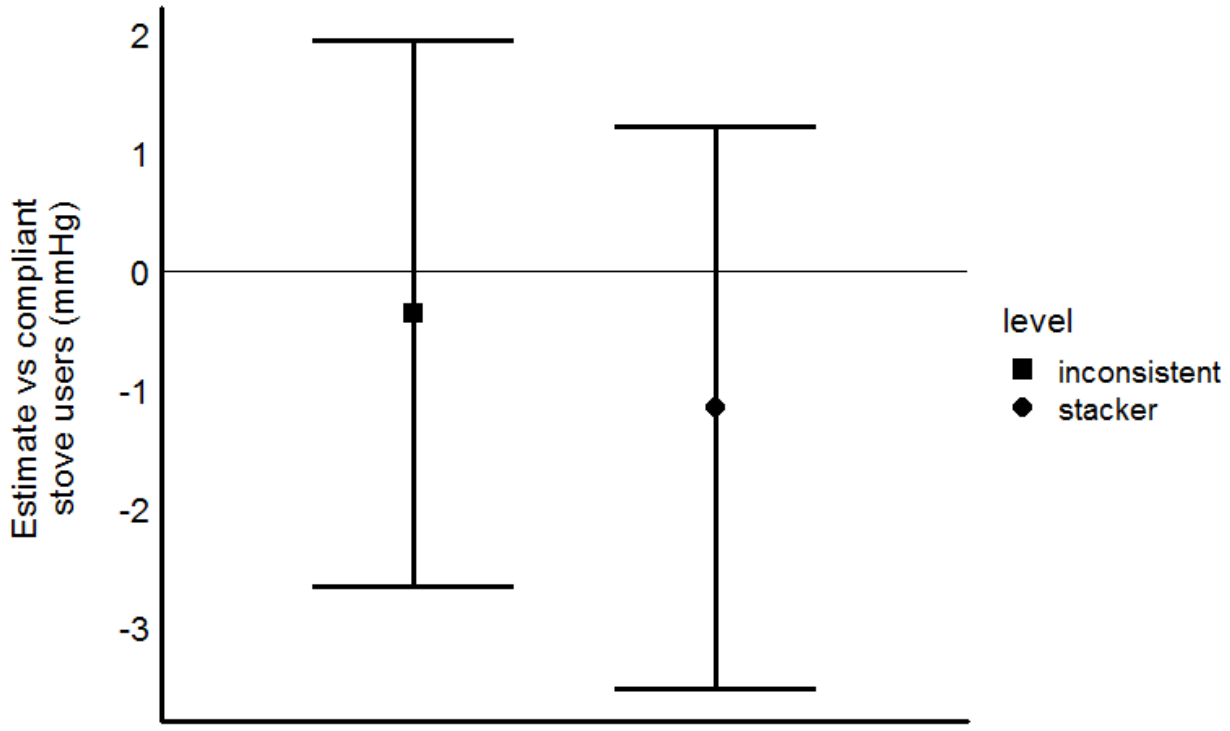

Figure C16. Stove-use analysis for central pulse pressure: stove assignment compliance
Model included a 3-level term for cookstove assignment compliance (compliant participants who used assigned cookstove at all visits and did not use a secondary traditional cookstove with the *Justa* cookstove (reference); inconsistent participants who did not use the assigned cookstove at all visits or used a secondary traditional cookstove with the *Justa* cookstove during at least one visit; stackers who used the assigned cookstove at all visits but also used a secondary traditional cookstove with the *Justa* cookstove [stackers/compliers were allowed to miss 1 pre-intervention visit or 1 post-intervention visit and still meet the above definitions]), a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); all study observations included (n=1162).

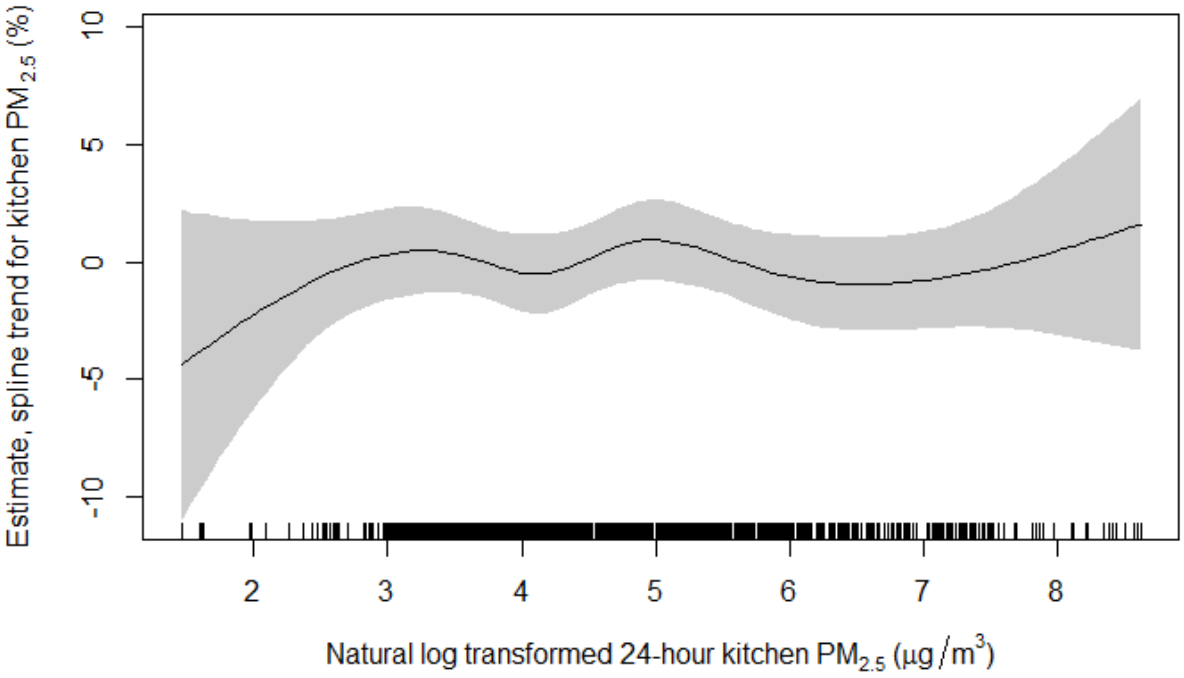

Figure C17. Exposure-response analysis for augmentation index using a spline trend function for kitchen fine particulate matter

$PM_{2.5}$ = fine particulate matter

Exposure-response analysis: "primary" model included a spline trend function for kitchen fine particulate matter with 5 degrees of freedom, a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); using full dataset (n=1120).

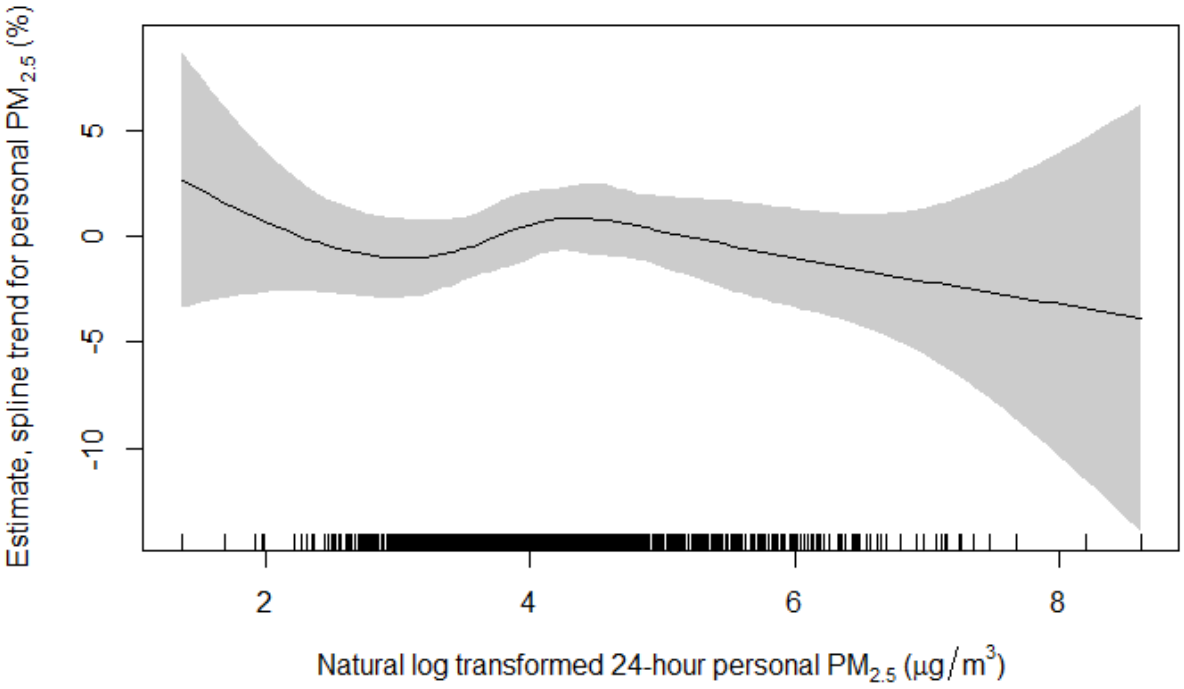

Figure C18. Exposure-response analysis for augmentation index using a spline trend function for personal fine particulate matter

$PM_{2.5}$ = fine particulate matter

Exposure-response analysis: "primary" model included a spline trend function for personal fine particulate matter with 5 degrees of freedom, a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); using full dataset (n=1120).

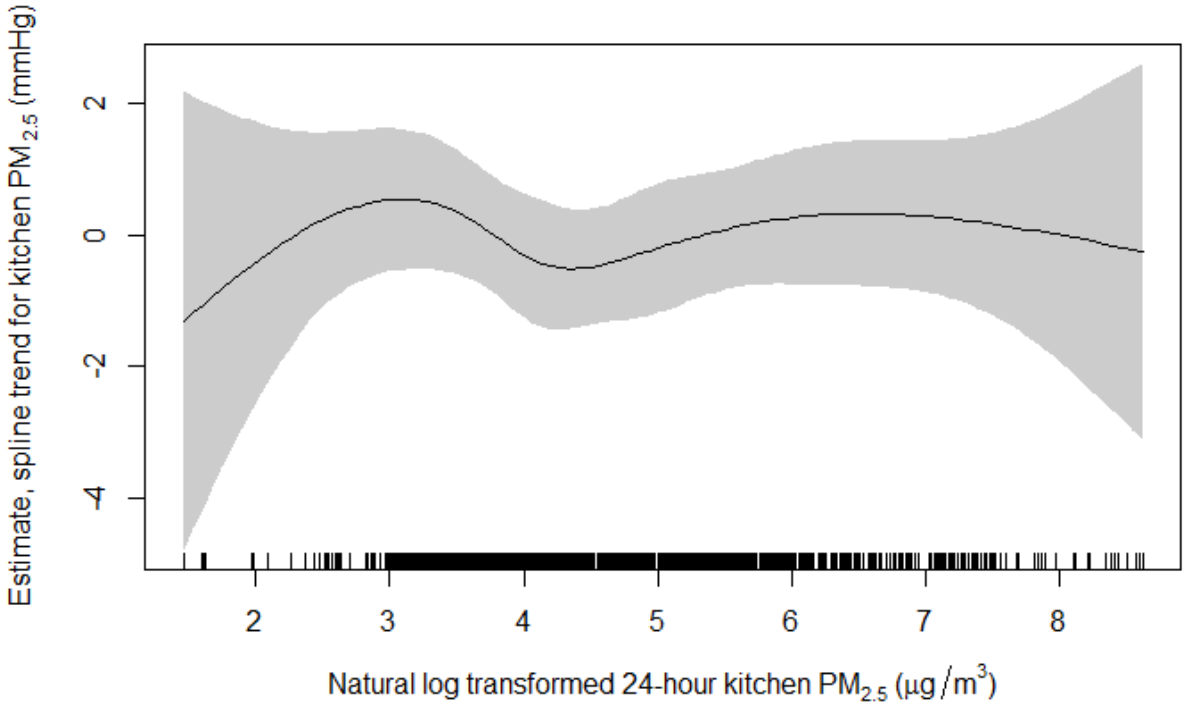

Figure C19. Exposure-response analysis for central pulse pressure using a spline trend function for kitchen fine particulate matter

$PM_{2.5}$ = fine particulate matter

Exposure-response analysis: "primary" model included a spline trend function for kitchen fine particulate matter with 5 degrees of freedom, a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); using full dataset (n=1120).

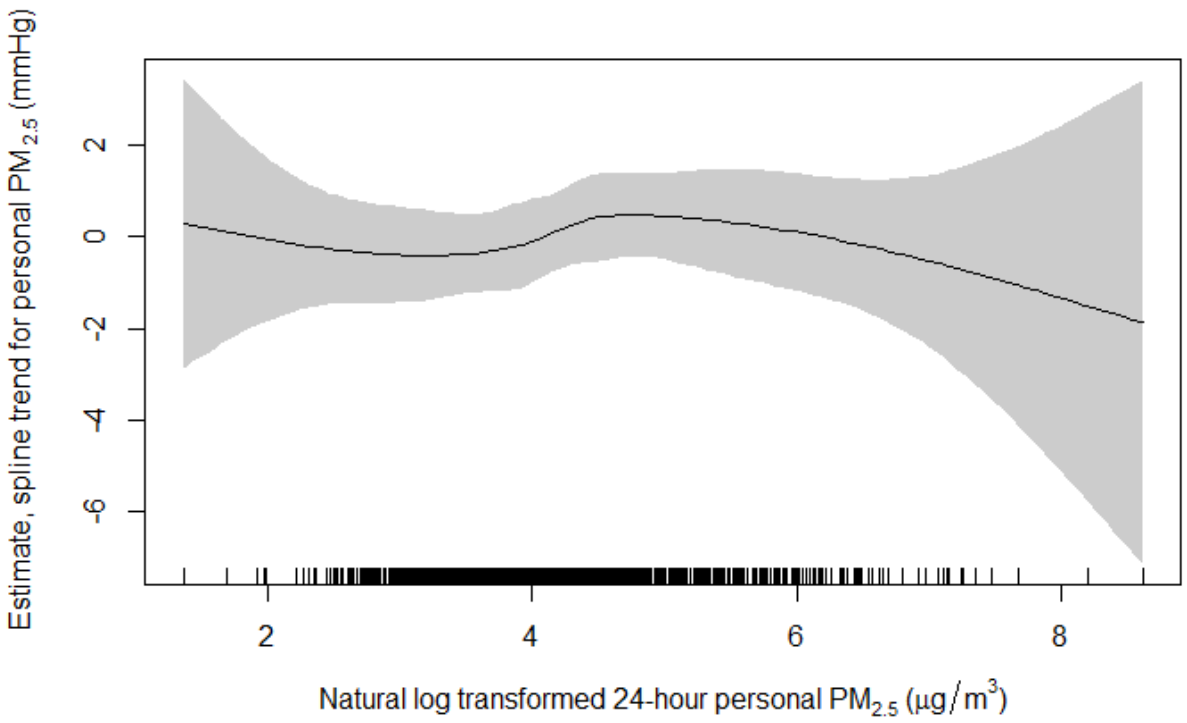

Figure C20. Exposure-response analysis for central pulse pressure using a spline trend function for personal fine particulate matter

$PM_{2.5}$ = fine particulate matter

Exposure-response analysis: "primary" model included a spline trend function for personal fine particulate matter with 5 degrees of freedom, a fixed spline term for date (df=6), a random term for participant, a fixed term for age (years, continuous), a fixed term for waist circumference (cm, continuous) and a fixed term for self-reported years of education (dichotomous, < 6 vs 6+); using full dataset (n=1120).