DISSERTATION

HOUSEHOLD AIR POLLUTION AMONG WOMEN USING BIOMASS STOVES IN HONDURAS: EXPOSURE CHARACTERIZATION AND ASSOCIATIONS WITH EXHALED NITRIC OXIDE AND MARKERS OF SYSTEMIC INFLAMMATION

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ABSTRACT

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Background

Nearly three billion people worldwide rely on solid fuels for cooking and heating (Bonjour et al. 2013). The incomplete combustion of solid fuels (i.e. within an open fire or traditional cookstove) often results in extremely high concentrations of air pollutants that have been linked to adverse health. These high pollutant exposures are estimated to cause over 2.5 million premature deaths and 77.2 million disability-adjusted life years in 2016; this largely preventable exposure is now estimated to be the 10th leading risk factor for morbidity and mortality worldwide (Gakidou et al. 2017). Despite these staggering estimates, robust, quantitative exposure assessment and epidemiologic evidence remains inadequate for understanding the association between household air pollution and disease risk.

Objectives

In this study, we sought to evaluate major gaps in the household air pollution literature: (i) a need to characterize the size distribution (fine and ultrafine particulate matter) and shorter-term concentrations and variability of household air pollution; most studies calculate a 24- or 48-hour average exposure (Northcross et al. 2015), (ii) a lack of direct exposure assessment in epidemiological household air pollution studies; many studies utilize a binary proxy for exposure

such as fuel type (Thomas et al. 2015; Bruce et al. 2015) (iii) an absence of direct measurements of personal exposure for epidemiological models, and (iv) a need to identify and utilize biomarkers of health that are indicative of chronic disease risk. Chapter 1 describes background information relevant to the dissertation; Chapter 2 reviews the literature and Chapter 3 outlines the study design. Aim 1 (Chapter 4) was an evaluation of real-time concentrations of fine particulate matter less than 2.5 μg ($PM_{2.5}$) and ultrafine particles among a sample of traditional biomass and cleaner-burning *Justa* stoves in rural Honduras. In Aims 2 and 3 (Chapters 5 and 6) we explored the cross-sectional association between household air pollution (direct kitchen and personal 24-hour measurements of particulate matter and black carbon) and biomarkers of airway (Chapter 5) and systemic inflammation (Chapter 6).

Methods

This dissertation utilized data from a cross-sectional field study of traditional biomass and cleaner-burning *Justa* biomass stove users in rural Honduras. The overall study population consisted of 150 female primary cooks, ages 25-56 years. For Aim 1, we utilized a subset of women from the study population to monitor exposure to real-time $PM_{2.5}$ mass and ultrafine particle number concentration in real time. Monitors were placed in the kitchens of 47 women for a 24-hour monitoring period. In Aims 2 and 3, we measured kitchen and personal levels of $PM_{2.5}$ (Triplex cyclone, SKC AirCheck pump, and 37-mm PFTE-coated glass fiber filters) and black carbon (Magee OT-21 transmissometer) for 24-hours. On the day following the household air pollution monitoring, we collected health measures from the participants; fractional exhaled nitric oxide was collected as a marker of airway inflammation (NIOX Mino; Aeorcine AB, Sweden), (Chapter 5) while finger-prick dried blood spots were collected for biomarkers of systemic inflammation

(Chapter 6). We explored effect modification of the adjusted associations between household air pollution and airway and systemic markers of inflammation, as well as effect modification of the associations by risk factors associated with cardiovascular chronic disease risk.

Results

Our study of real-time household air pollution concentrations (Aim 1, Chapter 4) demonstrated that on average, kitchen concentrations of $PM_{2.5}$ among women who owned traditional stoves (297 $\mu g/m^3$; SD: 417 $\mu g/m^3$) were higher compared to *Justa* stove owners (69 $\mu g/m^3$; SD: 50 $\mu g/m^3$) (Wilcox rank sum test, p = 0.07). Ultrafine particle number concentration was also lower in the kitchens with improved *Justa* cookstoves ($9.1x10^4$ pt/cm^3; SD: $6.9x10^4$ pt/cm^3) compared to kitchens with traditional cookstoves ($1.3x10^5$ pt/cm^3; SD: $1.1x10^5$ pt/cm^3) (Wilcox rank sum, p = 0.76). The Spearman correlation between the full sample of 24-hour average ultrafine concentration and 24-hour average $PM_{2.5}$ was 0.73 (N=24), however correlations by stove type were high among kitchens with traditional stoves (r=0.91), but only moderate among *Justa* stoves (r=0.55). The use of real-time monitors confirmed that the 24-hour average concentrations of $PM_{2.5}$ and ultrafine particle number concentration (PNC) were highly variable over the course of the monitoring period. The maximum values of various averaging windows (1-minute, 5-minute, 15-minute, and 60-minute) were highly correlated with the 24-hour averages for both $PM_{2.5}$ and PNC.

The associations between kitchen and personal $PM_{2.5}$ and black carbon and FeNO were consistent with null associations (Aim 2, Chapter 5). Results of the association of household air pollution on markers of systemic inflammation were largely inconsistent, however we observed associations between C - reactive protein (CRP) and serum amyloid-A (SAA). For example, a 25%

increase in personal $PM_{2.5}$ concentrations resulted in an 8.3% (95% CI: 2.3 – 14.6) increase in SAA concentrations after controlling for potential confounders (age, body mass index (BMI), number of assets (<2 or ≥2), electricity (yes/no), years of education (<6 or ≥6). Similar results were observed between higher kitchen concentrations of black carbon and higher CRP concentrations, while there was a suggestive positive association between kitchen $PM_{2.5}$ and personal black carbon with CRP. Associations between household air pollution concentrations and interleukin-1β (IL-1β), Intercellular Adhesion Molecule 1 (ICAM-1), and Vascular Cell Adhesion Molecule (VCAM-1), and Tumor Necrosis Factor-α (TNF-α) were consistent with the null. The results of effect modification analyses by risk factors associated with cardiovascular disease risk were also inconsistent.

Conclusion

Results from our study provide fundamental new knowledge regarding levels of household air pollution exposure from traditional and cleaner-burning biomass cookstoves and associations with markers of airway and systemic inflammation. Our data on 24-hour real-time $PM_{2.5}$ and ultrafine particulate matter concentrations is the first conducted, and offers pilot data that may inform future studies. Although we did not observe evidence to support a positive association between household air pollution and FeNO, our study has provoked several new questions about airway inflammation from different compartments of the airways. Regarding systemic inflammation, our results indicate that exposure to household air pollution is associated with several markers of systemic inflammation among women in rural Honduras. These findings support the hypothesis of a pathway from inhaled particles to systemic inflammation, however further investigation is needed to understand differences in inflammatory biomarker response and exposure to household air pollution. Our results demonstrating that higher concentrations of

household air pollution are associated with higher acute phase proteins, CRP and SAA, supports previous epidemiological ambient air pollution literature findings. CRP and SAA are both synthesized in the liver and we observed similar effect estimates for both inflammatory markers. These findings may provide more specific information regarding the mechanistic pathway from air pollution to cardiovascular disease.

This dissertation outlines the importance of improving the measurement of household air pollution concentrations. First, cookstove interventions studies may benefit from understanding additional components of household air pollution, such as the variability in concentrations over time, perhaps due to cooking behaviors. Second, epidemiological studies may benefit from measuring both personal and kitchen concentrations of household air pollution. Additionally, we learned that ultrafine particle number concentration may vary across different stove types and given the potentially large health implications, could be evaluated in future health models. Finally, we demonstrate the relative ease of collecting biomarkers of airway and systemic inflammation in field studies. Our cross-sectional health results demonstrate associations with several biomarkers of systemic inflammation and warrant further investigation.

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DEDICATION

I would like to dedicate this dissertation to all who have supported me on my journey in academia. To my family, thank you always believing in me. This dissertation would not be possible without the enduring love and support of my husband, Wande. You challenge me to become a better scientist. Your endless support and confidence in my abilities inspires me in both my professional and personal endeavors. I am thankful we have taken this journey together and I cannot wait to see what the next steps hold. Finally, to my daughter, Demilade, I dedicate this dissertation to you. You have brought such immense joy to our lives. I never knew that I could love someone the way I love you. Each day brings so many smiles and adventures. I hope that you grow up to pursue your own passions; we will be here to support you every step of the way. “Laughter is timeless. Imagination has no age. And dreams are forever.” –Walt Disney

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Chapter 1: Introduction

Approximately 3 billion people worldwide rely on solid biomass fuels, such as wood, coal or animal dung, for cooking and heating their homes (Bonjour et al. 2013). The incomplete combustion of such fuels in open fires or poorly constructed stoves results in harmful exposure to household air pollution (HAP) (Bruce et al. 2015). In 2016, it was estimated that HAP resulted in about 2.5 million deaths and 77.5 million disability-adjusted life years (DALYs) (Gakidou et al. 2017). Pollutants emitted in the smoke of biomass fuels include volatile organic compounds (VOCs), carbon monoxide, and particulate matter (Kim, Jahan, and Kabir 2011). Exposure to the incomplete combustion of solid fuels and resulting household air pollution (HAP) is associated with a variety of diseases. Respiratory diseases associated with HAP include upper and lower respiratory diseases, chronic obstructive pulmonary disease (COPD), tuberculosis, lung cancer, and asthma (Gordon et al. 2014; Smith et al. 2014a). Non-respiratory diseases include cardiovascular diseases (ischemic heart disease and stroke), cataracts and cancer (Kim, Jahan, and Kabir 2011; Smith et al. 2014a).

Improved Cookstove Technologies

Household air pollution is a modifiable exposure and improved cookstove technologies have the potential to increase cooking efficiency and reduce human exposure to harmful pollution. There is no one definition for “improved cookstoves”, however they are designed to improve combustion and heat transfer to improve efficiency and reduce emissions (Kshirsagar and Kalamkar 2014). Data from cleaner-burning stoves in the laboratory and controlled field tests have demonstrated reductions in PM emissions factors by almost 50% compared to traditional cookstoves (Roden et al. 2009). Despite laboratory and field testing, there remains little

understanding of real-world exposure to household air pollution from different stove types. Improved cookstove implementation programs face many challenges to achieving the levels of emissions observed in the laboratory due to variations in cooking styles and household characteristics which may alter stove performance and efficiency. For example, Roden et al. found that field measured particulate emissions in Honduras averaged three times as high as emissions measured in the laboratory (Roden et al. 2006). In addition to stove performance, the benefits of improved cookstove interventions may only be achieved with complete adoption and proper use and maintenance of stoves (Thomas et al. 2015; Urmee and Gyamfi 2014). Barriers to adoption and sustained use include issues of financing, user training and support, and perceptions of the improved technology (Rehfuess et al. 2014). Additionally, improved cookstove interventions must address specific cultural norms and cooking needs in order to be sustainable (Smith et al. 2007). Although improved cookstove programs often strive to provide fuels that emit the fewest emissions, such as alcohol-based fuels including liquid petroleum gas (LPG) or ethanol, there is often a transition period that requires use of an improved biomass cookstove until the opportunity to utilize alcohol-based cookstoves is available and appropriate (Bruce et al. 2015). In Central America, improved biomass cookstoves often include a rocket-elbow combustion chamber and a chimney (Kumar, Kumar, and Tyagi 2013; Kshirsagar and Kalamkar 2014).

Study Objectives

The overall objective of the study was to quantify personal and kitchen levels of exposure to household air pollution and to evaluate the association between exposure and specific markers of airway and systemic inflammation. We addressed the study objective through three specific aims:

Aim 1: Characterize fine and ultrafine kitchen particulate matter concentrations from traditional stove and cleaner-burning *Justa* cookstoves utilized in Honduran households. Our objectives were to:

1. Assess ultrafine particle number concentration (PNC)
2. Compare $PM_{2.5}$ mass and ultrafine PNC
3. Compare shorter-term averaging windows to 24-hour concentrations

Aim 2: Evaluate the cross-sectional association of exposure to household air pollution (stove type and measured personal and area concentrations of air pollution) and levels of fractional exhaled nitric oxide (FeNO), a marker of pulmonary inflammation, among primary female cooks in Honduras using traditional and Justa stoves.

Aim 3: Evaluate the cross-sectional association between exposure to household air pollution (cookstove type and measured personal and area concentrations of air pollution) and systemic inflammation among the same participants in Aim 2. We utilized markers of systemic inflammation in dried blood spots to assess inflammation: Cytokines: Interleukin-Iβ, Interleukin-6, Interleukin-8, and tumor necrosis factor-α; Acute phase proteins: C-reactive protein and Serum Amyloid A; Cellular Adhesion Molecules: Intercellular Adhesion Molecule 1 and Vascular Cell Adhesion Molecule 1.

Background

Exposure Assessment

Particulate Matter

Air pollution is comprised of particulates in solid or liquid phases in the atmosphere. Particulate air pollutants range in size from as small as 1 nm to as large as 100 µm. Particulate

matter has diverse chemical composition, which is highly dependent on the source of origin (World Health Organization 2006a). Suspended particle pollutants are classified into distinct size categories; coarse PM (aerodynamic diameter less than 10 µm [PM10]), fine PM (aerodynamic diameter less than 2.5 µm [$PM_{2.5}$]), and ultrafine PM (aerodynamic diameter of <0.1 µm). PM_{10} and $PM_{2.5}$ are the two size fractions of particulate matter monitored by the U.S. Environmental Protection Agency (EPA) and World Health Organization (WHO) (World Health Organization 2006a; WHO 2014). The EPA regulatory standards and the WHO air quality guidelines (AQGs) reflect public health concerns regarding the impact of exposure to PM_{10} and $PM_{2.5}$ (Bernstein et al. 2004). Additionally, the WHO guidelines for indoor pollutants include benzene, carbon monoxide, formaldehyde, naphthalene, nitrogen dioxide, polycyclic aromatic hydrocarbons, radon, trichloroethylene, and tetrachloroethylene (World Health Organization 2010).

Fine particulate matter ($PM_{2.5}$)

Our study focused on exposure to $PM_{2.5}$ from cookstoves. The WHO guideline for the mean concentration of $PM_{2.5}$ over a 24-hour period is 25 ug/m^3 (World Health Organization 2006a). Additional interim targets (IT) have been set for 24-hour mean PM. Interim target 1 (IT-1) is set to 75 ug/m^3, IT-2 is 50 ug/m^3 and IT-3 is 37.5 ug/m^3 (World Health Organization 2006b). These interim targets have been set in order to provide guidelines for incremental steps in air quality improvement where baseline levels of pollution are high. Although improved cookstove interventions often reduce HAP, field evaluations demonstrate that solid biomass cookstoves are often ten times higher than the IT-1 (Bruce et al. 2015).

Gravimetric measurement of $PM_{2.5}$

Exposure to $PM_{2.5}$ can be measured using either gravimetric sampling or optical direct-reading instruments. Gravimetric sampling is the "standard" of measuring $PM_{2.5}$ as it directly measures PM mass concentration using a filter that is weighed before and after sampling. The filter in gravimetric sampling is placed in a size-selective cyclone designed to capture particles of a certain size and limit loss of mass (Northcross et al. 2015). However, the standard, gravimetric sampling can be expensive (approximately $15 a sample) and appropriate laboratory space and equipment are needed for analysis (Northcross et al. 2015; Carter et al. 2017).

Real-time measurement of $PM_{2.5}$

The measurement of $PM_{2.5}$ can be also be done with optical direct-reading instruments. These instruments often utilize light scattering techniques to measure particle concentrations. Particles can be sampled either in passive or active modes (Northcross et al. 2015). Direct-reading light scattering techniques are only suitable for particles with a diameter from 300 nm to 10 µm where the light scattered is proportional to the mass concentration (Koehler and Peters 2015). Direct-reading instruments allow for sampling of particulate matter on a continuous basis and can have resolution up to one second. Although gravimetric measurements are considered the gold standard due to improved accuracy of emissions measurements, temporal variability cannot be captured using the a daily average. Temporal variability and peaks in emissions can be measured and described using real-time measurements and may provide improved insight into personal exposure and the impact of short-term impacts of exposure (Ezzati and Kammen 2002; Koehler and Peters 2015).

Ultrafine particulate matter

Ultrafine particulate matter is defined as particles with a diameter less than 0.1 μm (100 nm). Due to their relative low size and cubic diameter, ultrafine particles do not contribute much to overall mass concentrations, but dominate the particle number concentration (PNC) (Koehler and Peters 2015). Therefore, monitoring of ultrafine particles requires direct reading instruments rather than gravimetric methods. Several direct reading instruments are available for measuring ultrafine particles. Traditionally, the "gold standard" for sizing aerosol nanoparticles is the Scanning Mobility Particle Sizer (SMPS), while the particle number concentration is often assessed with condensation particle counters (CPCs) (Koehler and Peters 2015; Asbach et al. 2012). While the SMPS has excellent size resolution, the instrument is expensive and bulky and not well suited for field measurements (Mills, Hong Park, and Peters 2013). Similarly, handheld CPCs, such as the P-trak, are often used for field monitoring (although not personal monitoring), but are again limited by cost and size (Koehler and Peters 2015). Direct reading instruments, such as the DiSCmini, are a relatively new technology for field and personal monitoring of ultrafine particles. In both laboratory and field tests, the DiSCMini demonstrates high correlation and ±30% accuracy with CPCs tested in the same settings (Asbach et al. 2012; Mills, Hong Park, and Peters 2013; Bau et al. 2017; Meier, Clark, and Riediker 2013; Viana et al. 2015; Martin Fierz, Keller, and Burtscher 2009), making it an potentially appropriate field monitor for ultrafine particles.

Black Carbon

Particulates produced from biomass burning are known to have three main components; particulate organic carbon, black carbon (soot), and a small proportion of inorganic species. Organic carbon (OC) is defined by the carbon in the organic compounds. Black carbon (BC) has no

standard definition, but is typically defined as a high light-absorbing carbon-based material produced from incomplete combustion (Reid et al. 2004; Long, Nascarella, and Valberg 2013). Black carbon is a concern in air pollution research because it is the primary sunlight absorbing aerosol species and contributes to climate change radiative forcing in the Earth's atmosphere through the absorption of solar rays and global warming radiation (Kirchstetter and Novakov 2007). Black carbon is routinely measured using quartz filter samples using thermal or thermal-optical analysis (TOA) where samples are heated and carbon is oxidized to measurable CO_2 (Reid et al. 2004; Kirchstetter and Novakov 2007) . Another frequently used technique to measure black carbon uses optical absorption techniques, estimating the concentration of BC based on the transmission of light on a filter sample using an optical transmissometer (Reid et al. 2004). Additional absorption photometers for real-time measurements of light absorption from PM are also available, such as aethalometer (Janssen et al. 2012). In addition to the environmental impacts on climate change, studies of the black carbon component of PM have demonstrated harmful health impacts different to PM mass (Janssen et al. 2011). Although the mechanistic differences are unknown, research provides some evidence that the health effect estimates from several cohort studies of exposure to black carbon and $PM_{2.5}$ were higher for black carbon than $PM_{2.5}$ (Janssen et al. 2011).

Personal vs. Kitchen Exposure Measurements

Exposure to household air pollution can be measured at the level of the microenvironment (kitchen or household) or personal level. Concentration levels within a microenvironment can vary greatly depending on where the exposure monitors are placed, due to substantial spatial and temporal variability within a house (Ezzati and Kammen 2002; Northcross et al. 2015). Exposure

measurements often vary in monitoring time, but typically aim to capture a 24 or 48-hour time interval. Until recently, most exposure assessment in the field of household air pollution relied on microenvironment or kitchen-level measurements. Measurements of personal exposure may reduce exposure-response uncertainty, but requires participants to wear monitors or samplers that must be small in size, low weight and have the potential to be battery operated (Asbach et al. 2017). The personal sample integrates exposure measurements across space and time but requires compliance of the wearer. Personal sampling can utilize gravimetric or real-time monitoring techniques. Exposure assessment at the personal level is vital in improving the quantification of exposure to HAP in order to evaluate health endpoints and reduce uncertainty in exposure-response assessments (Clark et al. 2013). Although personal measurements provide some improvement in exposure classification, there remain difficulties in capturing health-relevant time periods of exposure, especially when evaluating chronic disease outcomes such as cardiovascular disease.

Cookstove Technology and Exposure

Improved cookstoves are those designed using scientific principles to improve combustion efficiency and heat transfer in order to improve cooking efficiency and reduce emissions (Kshirsagar and Kalamkar 2014). Improved cookstove designs can be categorized based on five different characteristics: combustion chamber type, air flow, fuel loading system, fuel type and heat transfer system (Still, Bentson, and Li 2014). One common improved biomass cookstove, such as the *Justa,* in Central America consists of an elbow-shaped "rocket" combustion chamber. (Still, Bentson, and Li 2014). Firewood is loaded from the front of the stove into the combustion

chamber and air flows through the chamber through a chimney. Heat is transferred for cooking through a metal griddle "*plancha*" (Scott, n.d.).

Laboratory Measures of Cookstove Emissions

Several laboratory tests have compared emissions from a variety of improved cookstoves. These laboratory tests demonstrate that improved cookstoves have the potential to reduce harmful emissions of particulate matter, carbon monoxide and black carbon (Just, Rogak, and Kandlikar 2013; Garland et al. 2017; Jetter et al. 2012; Shen et al. 2012; Still, Bentson, and Li 2014). A laboratory test by MacCarty, Still and Ogle found that rocket stoves can reduce PM emissions by about 46% on average compared to traditional three-stone fires (MacCarty, Still, and Ogle 2010). Only a few studies have tested the emissions of ultrafine particles from traditional and improved cookstoves. Results suggest a shift to smaller particle sizes with improved combustion as well as increased number of smaller particles (Just, Rogak, and Kandlikar 2013; L'Orange, Volckens, and DeFoort 2012; Shen et al. 2012).

Field Measures of Cookstove Emissions

Typical 24-hour kitchen concentrations of $PM_{2.5}$ among households using biomass traditional stoves vary significantly across stove types and locations, but are consistently 2 to 10 times higher than the WHO IT-1 annual level of 35 $\mu g/m^3$. A World Health Organization literature review of studies of indoor particulate matter concentrations from 46 studies in developing countries from 1997-2011 provides "pooled" PM concentrations. The pooled mean was calculated by summing the average concentration and sample sizes from individual studies and dividing by the total sample size. The pooled mean for $PM_{2.5}$ indoor concentrations (N=19) from household air pollution was 972 $\mu g/m^3$ (standard deviation: 876 $\mu g/m^3$) (Balakrishnan et al. 2014). The pooled

24-hour average personal $PM_{2.5}$ concentration from traditional cookstoves was estimated to be 267 $\mu g/m^3$ with a standard deviation of 297 $\mu g/m^3$ (Balakrishnan et al. 2014).

Improved cookstove interventions often fail to reach the same emissions reductions as observed in the laboratory setting. This is due to a variety of reasons including household ventilation, fuel type and moisture content, cooking practices, continued use of other stoves, and poor stove maintenance. Many improved cookstove interventions fail to see significant exposure reductions a year after implementation. Exposure measurements for improved cookstove implementations have occurred across the globe, but comparison across studies is complex due to variability in exposure methods. For example, there are differences in exposure measurement locations (kitchen vs. personal), averaging period for exposure assessment (8 hour vs. 24 or 48 hour), time of monitoring after the intervention (1 week vs. 4 years), and pollutants measured ($PM_{2.5}$ or carbon monoxide) (Thomas et al. 2015). Overall, improved cookstoves implementations have resulted in an estimated 25-85% reduction in average exposure as compared to measurements of traditional stoves (Balakrishnan et al. 2014), but additional studies are needed to understand the success of interventions.

Health Outcomes of Interest: Fractional Exhaled Nitric Oxide

Nitric Oxide

Nitric oxide (NO), an essential signaling molecule in mammals and humans, is involved in a multitude of physiological functions. Under normal physiological conditions, nitric oxide has effects on non-adrenergic and non-cholinergic neurotransmission. NO acts as a mediator of both vascular and non-vascular smooth muscle relaxation and protects against airway hyperresponsiveness (Taylor et al. 2006; Dweik et al. 2011). Nitric oxide has a short half-life of 1-5

seconds (Ricciardolo 2003). NO is synthesized by the amino acid L-arginine and catalyzed by three different nitric oxide synthases (NOS); 1. Constitutive NOS, 2. Inducible NOS, 3. Neuronal NOS (Dinh-Xuan 1992; Bowler and Crapo 2002; Ricciardolo 2003). Constitutive endothelial NOS (eNOS) is primarily found in the respiratory endothelium, nerve endings, and blood vessels and works to dilate blood vessels (Bowler and Crapo 2002). Neuronal NOS (nNOS), located in the nerve terminals, produces nitric oxide to dilate airway smooth muscle (Bowler and Crapo 2002). Under pathological conditions, nitric oxide acts a pro-inflammatory mediator which may induce airway hyper responsiveness (Taylor et al. 2006). The third nitric oxide synthase, inducible NOS (iNOS), is not present in resting cells (Aktan 2004), but is induced by pro-inflammatory cytokines, such as interleukin-1β and tumor necrosis factor alpha (TNF-α), in the respiratory epithelium (Bowler and Crapo 2002; Ricciardolo 2003; Jiang and George 2011; Lane et al. 2004).

Exhaled Nitric Oxide

Of the three different nitric oxide synthases that synthesize NO, it is evident that inducible NOS (iNOS) is the predominant actor in NO production under pathological conditions. The iNOS found in respiratory epithelium is activated by cytokines and macrophages (Bowler and Crapo 2002) and allows for the release of large quantities of pro-inflammatory NO from airway epithelial cells (Ricciardolo 2003; Shin et al. 2012). Exhaled nitric oxide in human breath has been identified as a possible biomarker for pathophysiological lung diseases including asthma and a general marker of airway inflammation (Dweik et al. 2011; Jones et al. 2001; S. A. Kharitonov et al. 2003; S. A. Kharitonov, Yates, and Barnes 1995). Research shows that iNOS is the main source of NO in exhaled breath and originates in the airway epithelia (Lane et al. 2004; Ricciardolo 2003; Jiang et al. 2009; Dweik et al. 2011; Guo and Erzurum 1998).

Measuring FeNO

Fractional exhaled nitric oxide (FeNO) has been identified as a simple, reproducible, noninvasive biomarker of eosinophilic airway inflammation (Munakata 2012; S. P. Eckel and Salam 2013; Ricciardolo 2003; Dweik et al. 2011). Several measurement techniques have been developed to quantify the amount of nitric oxide in exhaled breath (Munakata 2012). "Online" measurement devices display real-time NO breath profiles while "offline" testing involves collecting exhaled breath in a bag for delayed analysis (Silkoff 2005).

FeNO levels are flow dependent and an inverse of function of exhaled flow rate (Tsoukias and George 1998). Varying the flow rate at which FeNO measurements are collected may allow researchers to partition the source of nitric oxide into two distinct anatomical regions; the proximal and distal airways (Tsoukias and George 1998; S. P. Eckel and Salam 2013; Dweik et al. 2011; Puckett et al. 2010; Tsoukias et al. 1998; Olivieri et al. 2006). The current American Thoracic Society (ATS) standard is for a flow rate of 50 ml/sec, providing information from the proximal airways (Hogman et al. 1997; Dweik et al. 2011; Silkoff et al. 1997). FeNO measured or calculated for a higher flow rate, such as 270 ml/sec ($FeNO_{270}$), may be associated with airway inflammation from the distal compartment (S. P. Eckel and Salam 2013; George et al. 2004).

Several different instruments are available to measure FeNO. Chemiluminescence instruments measure NO indirectly via light generation due to a chemical reaction with ozone and can measure NO at different flow rates. Varying the flow rate at which FeNO measurements are collected may allow researchers to partition the source of nitric oxide into two distinct anatomical regions; the proximal and distal airways (Eckel & Salam, 2013; Tsoukias & George, 1998). These instruments are large and expensive, and generally used in clinical applications. Electrochemical

sensor instruments are handheld devices that measure NO concentrations with a chemical signal. Electrochemical analyzers are cost effective, but only measure FeNO at 50 ml/sec, giving an approximation of exhaled nitric oxide from the proximal airways (Horváth et al. 2017). Although research has explored exhaled nitric oxide for a variety of health endpoints and environmental exposures, the main clinical application for fractional exhaled nitric oxide is for monitoring eosinophilic asthma (Bucca et al. 2012). Using FeNO to measure nitric oxide in the human body has many advantages compared to lung function tests, including ease of use of the instrumentation, the ability to collect repeated measures, and the noninvasive nature of the test (Dweik et al. 2011). Several factors are associated with differing FeNO levels among individuals including a person's age, gender, height, smoking status, use of anti-inflammatory medications, nasal NO contamination, and the type of NO analyzer used (Dweik et al. 2011; Dressel et al. 2008; A.-C. Olin 2006; Olivieri et al. 2006).

The clinical use of FeNO as a marker of airway inflammation has typically been reserved for the monitoring of eosinophilic asthma. The American Thoracic Society (ATS) states that FeNO measurements in patient care can assist in detecting eosinophilic airway inflammation, determine the need for corticosteroids and the likelihood of corticosteroid responsiveness (Dweik et al. 2011). Patients with asthma demonstrate high levels of iNOS enzyme expression in epithelial cells in their airways and have high levels of exhaled NO in their breath (Dweik et al. 2011; S. Kharitonov et al. 1996). Although FeNO is mainly utilized for monitoring asthma, several studies have demonstrated elevated FeNO levels among groups with self-reported respiratory tract infections (Dressel et al. 2008; S. Kharitonov et al. 1996; S. A. Kharitonov, Yates, and Barnes 1995), among those who have allergies, rhinoviruses (Proud 2005; De Gouw et al. 1998), decreased airway

responsiveness (Salome et al. 1999) and atopy (A.-C. Olin 2006; A. C. Olin, Alving, and Torén 2004). Although less commonly used in healthy adult populations, studies utilizing FeNO measurements have explored the associations of air pollutants among healthy adults, especially the elderly who may have increased susceptibility to air pollution (Adamkiewicz et al. 2004; Dubowsky Adar et al. 2007; Vossoughi et al. 2014).

Mathematical Two-compartment models

With recent evidence that exhaled nitric oxide is flow dependent, several two compartment models have been developed to assess nitric oxide in conducting airways (proximal compartment) and the alveolar region of the lungs (distal compartment) (Tsoukias and George 1998; S. P. Eckel and Salam 2013; George et al. 2004; Jorres 2000). Measuring FeNO at various flow rates allows for the partitioning of exhaled nitric oxide into proximal and distal sources with a low flow rate providing information on proximal airway sources and a high flow rate providing information on a the distal alveolar sources (S. P. Eckel and Salam 2013). The mathematical models, either linear or non-linear, account for the increasing cross-sectional area of airways, and calculate tissue concentration of NO of the airway wall and diffusion capacity of NO from the airway wall (Horváth et al. 2017). The mathematical models require FeNO values from at least 3 different flow rates. Non-linear models utilize 3 flows (low: <20 ml/sec, medium: 100 ml/sec, and high: 350 or 400 ml/sec). Linear models utilize FeNO at 50 ml/sec and then three increasing exhalations at least 100 ml/sec and up to 400 ml/sec. A minimum of two measurements is required at each flow rate (Horváth et al. 2017). Using mathematical modeling to assess FeNO can increase understanding of physiological processes associate with NO in conducting airways and small airways.

Measurement of FeNO using the NIOX Mino

The NIOX Mino (Aeorcine AB, Sweden) is a portable electrochemical instrument that measures online fractional exhaled nitric oxide in human breath following the guidelines for NO measurement established by the American Thoracic Society. The NIOX Mino is suitable for children aged 7-17 and adults aged 18 and older. In order to conduct a FeNO measurement, each participant empties their lungs, inhales deeply to total lung capacity through the filter, and then exhales slowly through the filter into the device. The exhalation must last ten seconds, with the last three seconds of the exhalation analyzed by a calibrated electrochemical sensor to provide a measurement in parts per billion (ppb). The NIOX Mino is set to measure FeNO at 50ml/sec (Harnan et al. 2015). The NIOX Mino uses an external quality control to ensure the system is operating within its specifications. One daily quality control test is performed by a qualified staff member (Aerorine 2014).

Health Outcomes of Interest: Inflammatory Markers

Inflammation and Cardiovascular Disease

Inflammation, characterized as either acute or chronic, is a series of coordinated immune responses to tissue damage caused by physical trauma or external pathogens (Zhou et al. 2010). The cascade of events in inflammatory response provides a number of potentially useful measurable markers of cardiovascular disease (Pearson et al. 2003).

Biomarkers of Cardiovascular Disease

Cytokines and chemokines

Cytokines are a group of small soluble proteins that play key roles in mediating acute inflammatory reactions (Zhou et al. 2010). Monocytes are one type of cell that produce cytokines,

including Interluekin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), and chemokines, interluekin-8 (IL-8), through the innate immune system that works to recognize pathogens that do not occur in mammalian cells (Borish and Steinke 2003). Most cytokines have multiple sources, multiple targets, and multiple functions (Gabay and Kushner 1999). IL-1 cytokines, including IL-1β, have an important role in activating T lymphocytes to enhance the production of IL-2, without which there would be a diminished immune response. IL-1β also stimulates the synthesis of acute phase proteins such as C - reactive protein (CRP). TNF-α is a pro-inflammatory cytokine activated by macrophages, monocytes, fibroblasts, mast cells and T cells (Feghali and Wright 1997). IL-6 is also a pro-inflammatory cytokine involved in driving chronic inflammation. IL-8 is a low molecular weight chemokine and is responsible for the migration, activation, and recruitment of neutrophils at the site of inflammation. TNF- α, IL-8, and IL-1 β interact with endothelial cells to induce cellular adhesion molecules (Borish and Steinke 2003).

Cellular Adhesion Molecules

Endothelial activation is a fundamental event in cardiovascular disease and is initiated by the attachment of monocytes and lymphocytes to endothelial cells. This attachment is initiated by cellular adhesion molecules, induced by cytokines such as TNF-α, IL-1β, and CRP (Szmitko 2003). This endothelial cell activation and adhesion molecule expression is the first step in a pathway of atherosclerosis (Calderón-Garcidueñas et al. 2008). Intercellular adhesion molecule-1 (ICAM-1) and vascular cellular adhesion molecule (VCAM-1) are adhesion proteins from the immunoglobulin family and are upregulated by cytokines and may be used as markers indicative of damage of the endothelium (Blann and Lip 2000).

Acute Phase Proteins

Acute-phase proteins are defined as proteins whose plasma concentration increases or decreases by at least 25% during inflammatory disorders and includes C-reactive protein (CRP) and serum amyloid A (SAA) (Gabay and Kushner 1999). C-reactive protein is synthesized in the liver hepatocytes in response to IL-6. Under acute inflammation, CRP increases during the first 6-8 hours and is considered a biomarker of the process of endothelial dysfunction (Teixeira et al. 2014). In addition, C-Reactive protein increases IL-8 protein to promote monocyte-endothelial cell adhesion (Paffen and deMaat 2006). CRP levels that are only slightly elevated for a prolonged period of time are indicative of low-level chronic inflammation (Paffen and deMaat 2006). Although research is still determining if CRP has a "causal role" in cardiovascular disease, CRP is well-established as a marker of cardiovascular disease "risk". A number of prospective cohort studies have demonstrated that increased levels of CRP are associated with increased risk of coronary heart disease among both genders, in a variety of age ranges and ethnic groups (Madjid and Willerson 2011).

Serum amyloid A is similar to CRP in that it is released in the liver in response to pro-inflammatory cytokines such as IL-6, IL-1 and TNF. The concentration of SAA increases rapidly during acute inflammation and may increase as much as 1000 times within 5-6 hours (Figure 1.3) (Targońska-Stępniak et al. 2014). Unlike CRP however, the actions of SAA are largely unknown but may also include the induction of adhesion molecules. The concentrations of SAA usually coincide with those of CRP, however some studies indicate SAA to be a more sensitive marker to inflammatory disease than CRP (Gabay and Kushner 1999).

Measuring Biomarkers of CVD

Biological markers, biomarkers, are the "cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells, or fluids" (Mayeux 2004). Two major classifications of biomarkers exist: biomarkers of exposure, used in risk prediction and biomarkers of disease, which are used in screening and diagnosis (Mayeux 2004). Cytokines, cellular adhesion molecules, and acute phase proteins are all possible biomarkers of systemic inflammation (Keustermans et al. 2013). CRP has emerged as one of the most potentially useful biomarkers associated with cardiovascular disease risk. The use of CRP as a biomarker of CVD is not necessarily because it plays a more causal role than other biomarkers, but may be due to the analytic properties of the biomarker. For example, CRP has low within-person variability, lack of diurnal variability, is not impacted by food intake, and has a wide measurement range (Jenny and Cushman 2014; Ridker 2003).

Inflammatory Markers in Dried Blood Spots

Inflammatory markers of inflammation are most commonly assessed in plasma or serum blood samples (Keustermans et al. 2013). Dried blood spots (DBS) are drops of whole blood collected on filter paper via a finger prick from a patient (McDade, Williams, and Snodgrass 2007). The use of DBS in research and clinical applications began as early as the 1960s with the use of heel-prick samples in newborns (McDade, Williams, and Snodgrass 2007). Inflammatory markers measured in DBS samples have grown in utility over the past few decades in both clinical and research applications due to the increased convenience, low-cost, and reliability of the methods (E. M. Miller and McDade 2012).

DBS samples are relatively easy to collect. First a participant's finger is cleaned with alcohol and then pricked with a sterile, disposable lancet. The first drop of blood is wiped away and then the following blood drops are applied to filter paper. Each drop should be placed in the proper position on the sample card and be approximately the same size. The drops are dried on the filter paper overnight and then stored in plastic bags with desiccant and a humidity indicator card (McDade, Williams, and Snodgrass 2007). Long-term storage of the samples must be done in a laboratory-grade freezer. The analysis of DBS is similar to those for plasma or serum samples, however the sample must be hole-punched from the filter paper and be brought into a solution.

Using DBS samples for field-based research has several advantages including the relatively painless and noninvasive method for collection, no need for centrifuging, and the ability for the samples to remain stable while frozen. While it has advantages in the field setting, the analysis and interpretation of DBS has some challenges. First, most laboratory protocols for inflammatory markers are designed for plasma or serum samples and many laboratories are unfamiliar with protocols to analyze DBS. Additionally, inflammatory markers in DBS may not be directly comparable to concentrations of markers in plasma or serum. Research has shown that there are high correlations between serum and DBS samples (Skogstrand et al. 2008; Qian 2015; E. M. Miller and McDade 2012; Schmid et al. 2004), and correction factors could be developed and applied to DBS to derive plasma equivalents if needed (McDade, Williams, and Snodgrass 2007). The use of clinical cut points (such as 3 mg/L for CRP) may not be valid in DBS samples (McDade, Williams, and Snodgrass 2007).

Hypothesized Mechanisms for Air Pollution and CVD

Toxicological and animal studies demonstrate that particulate matter promotes the recruitment of monocytes into atherosclerotic plaques resulting in atherosclerosis (Yatera et al. 2008; Polichetti et al. 2009). Epidemiologic studies provide evidence that short term exposure to particulate matter is associated with an increased risk of hospitalization for myocardial infarction and premature mortality (Polichetti et al. 2009; Pope 2000; Franklin, Brook, and Arden Pope 2015; Gold and Mittleman 2013; Newby et al. 2015). Air pollution particulate matter has been hypothesized to impact cardiovascular disease through several potential mechanistic pathways. One proposed mechanism of the impact of particulate matter air pollution on cardiovascular disease stems from inhaled particles that are deposited into the lungs, resulting in the release of pro-inflammatory mediators, such as cytokines, contributing to overall systemic inflammation (R. D. Brook et al. 2010). This potential mechanistic pathway is often considered the "spillover" pathway in which oxidative stress mediators produced in the lungs "spillover" into systemic circulation (Franklin, Brook, and Arden Pope 2015). More specifically, particulate matter deposition in pulmonary tissue initiates oxidative stress and redox-pathways are activated leading to the production of pro-inflammatory cytokines. It is hypothesized that this response may not be confined to the lungs, but may "spillover" from the lungs into systemic circulation (Franklin, Brook, and Arden Pope 2015).

The second hypothesized pathway includes particulate matter impacting the lung receptors and resulting in autonomic nervous system imbalance. The third pathway results in particulate matter, such as ultrafine PM, penetrating directly into the blood stream and cardiovascular tissue (Franklin, Brook, and Arden Pope 2015). In the hypothesized pathways 2 and

3, lung receptors “sense” particulate matter and autonomic afferent reflexes may become activated and elicit systemic autonomic nervous system responses. The autonomic imbalance has been associated with alterations in heart rate, blood pressure, and chronic disease states such as hypertension (Franklin, Brook, and Arden Pope 2015).This dissertation will focus primarily on pathway number 1, the “spillover” mechanism, however the chapters on ultrafine particles may have relevance to health outcomes through the third, direct pathway.

A meta-analysis compiled estimates of exposure to $PM_{2.5}$ and all-cause cardiovascular mortality (Atkinson et al. 2014). The results of 23 single-city studies were pooled together and provide evidence that short-term exposure to 10 $\mu g/m^3$ of $PM_{2.5}$ was associated with increases in a 0.84% increase cardiovascular disease (95% CI: 0.41 – 1.28%) (Atkinson et al. 2014). In 2013 a meta-analysis was conducted of cohort studies of long-term air pollution exposure and cardiovascular disease mortality. The review provides a pooled effect of an 11% increase in cardiovascular mortality (95% CI: 5-16%) for every 10 $\mu g/m^3$ increase in $PM_{2.5}$ (Hoek et al. 2013).

Chapter 2: Literature review

Exposure to Household Air Pollution

Real-Time Exposure Monitoring

Exposure to household air pollution is typically quantified using gravimetric sampling, a standard method in which a time-integrated sample of PM is collected onto a filter over a fixed-sampling period (often 24-hour or 48-hours) (Northcross et al. 2015). Although gravimetric sampling is most often used in assessing the health outcomes associated with household air pollution, continuous real-time, or time-resolved, measurements may provide additional insight into PM concentrations with respect to temporal variability or intensity of exposure with cooking events (Northcross et al. 2015). The real-time concentrations can be collected in resolutions of seconds or minutes and may provide important clues into changes in cooking habits or stove use with the introduction of an improved cookstove. Additionally, researchers can assess elevated levels of PM concentrations at various time intervals using real-time data.

Studies that have implemented real-time PM measurements in field settings have explored temporal variability of cookstove emissions and characterized intensity of exposure (Carter et al. 2016; Chen et al. 2016; Ezzati, Mbinda, and Kammen 2000; Van Vliet et al. 2013; Park and Lee 2003; S. L. Fischer and Koshland 2007).

Such studies have found that short-term concentrations of elevated $PM_{2.5}$ constitute a substantial portion of daily exposure (Van Vliet et al. 2013). For example, Van Vliet et al. observed that reducing the overall highest 1-5% of the $PM_{2.5}$ concentrations in Ghana field study reduced mean exposure by 49-75% (Van Vliet et al. 2013). For example, Park and Lee observed peak values

between 32-39 times higher than 24-hour averages among traditional and improved biomass stove users in Costa Rica (Park and Lee 2003).

Twenty-four hour average exposure to $PM_{2.5}$ in Central America varies by study location and stove type. For example, in Costa Rica average daily $PM_{2.5}$ concentrations among 23 houses was 44 $\mu g/m^3$ (SD: 31) (Park and Lee 2003). In Honduras, Clark et al. observed a mean 8-hour average personal $PM_{2.5}$ concentration of 133.5 $\mu g/m^3$ (SD: 114.9 $\mu g/m^3$) among 58 women (Clark et al. 2010). Eight-hour kitchen $PM_{2.5}$ concentrations among 57 households averaged 614.9 $\mu g/m^3$ (SD: 847.5 $\mu g/m^3$) (Clark et al. 2010).

Ultrafine Particulate Matter

Evidence suggests that particles with diameters less than 0.1 µm (ultrafine particles) are the most likely to penetrate deep into the lungs, resulting in oxidative stress and systemic inflammation. (Ken Donaldson and Stone 2003; K Donaldson et al. 2001; Brauer et al. 2001; R. D. Brook et al. 2010; Brauner et al. 2007). Little is known about in-home ultrafine particle concentrations from traditional or improved cookstoves due to the logistical and monetary barriers of monitoring ultrafine particles in field settings. Laboratory studies have been conducted with varying results. Some laboratory emissions studies have suggested that improved cookstoves may emit fewer ultrafine particles compared to traditional cookstoves (such as a three-stone fire) (Jetter et al. 2012), while other studies have suggested that improved force-draft gasifiers, may increase ultrafine particles due to improved combustion efficiency despite their ability to substantially reduce emissions of $PM_{2.5}$ mass compared to traditional stoves (Just, Rogak, and Kandlikar 2013). In addition to being driven by the cookstove design, ultrafine particle emissions may depend on cooking practices. For example, ultrafine concentrations emitted during cooking

events with modern stoves (e.g., gas range stoves) in developed countries depend on type of cooking (i.e. grilling or frying), cooking temperature, and cooking phase (Zhang et al. 2010; Lunden, Delp, and Singer 2015). Particle size distribution data from solid-fuel stoves in China provide additional evidence that particle number and particle size may depend on fuel feeding practices and the power output of the stove (X. Li et al. 2007).

Given the potential adverse health effects associated with ultrafine particles, we must measure ultrafine particle number concentrations from both traditional and cleaner-burning cookstoves. Health and risk assessments have been estimated based entirely on $PM_{2.5}$ mass exposure (Armendáriz-Arnez et al. 2010; Jetter et al. 2012; Smith et al. 2014b); therefore, if the correlations between emissions of ultrafine particles and $PM_{2.5}$ mass are dissimilar for various improved cookstoves, the health improvements thought to be associated with cleaner-burning cookstoves may be inaccurate. To our knowledge, only one study has used a portable monitor to measure ultrafine particle number concentration from traditional and improved biomass cookstoves in the field (de la Sota et al. 2018). Among 6 households in Senegal, de la Sota used the DiSCMini observed lower ultrafine particle number concentration (PNC) during cooking events among improved biomass stove users (Median PNC 1.5×10^6 pt/cm^3) compared to traditional biomass stove users (Median PNC 2.2×10^6 pt/cm^3) (de la Sota et al. 2018). The mean number concentration observed during a cooking period was 2.5×10^6 pt/cm^3 among traditional stoves and 1.71×10^6 pt/cm^3 for improved rocket stoves (de la Sota et al. 2018).

Association of FeNO and Air Pollution

Chamber Studies

The association between particulate matter and FeNO has been evaluated in several chamber studies in which participants were directly exposed to wood smoke. The results of the studies demonstrate mixed results regarding the impact of particle exposure on FeNO levels. A study by Pietropaoli et al. found no association between ultrafine particles and FeNO from the distal airways and Sehlstedt et al. found no association between exposure to wood smoke and FeNO measured at four different flow rates (Pietropaoli et al., 2004; Sehlstedt et al., 2010). Other chamber studies, have found mixed results between exposure to wood smoke and the association with FeNO at different flow rates. For example, Barrgard et al. conducted a chamber study in which 13 participants were exposed to clean air for 4 hours and then wood smoke for 4 hours, 1 week apart (L Barregard et al. 2008). The authors found a net increase in $FeNO_{270}$ (flow rate of 270 mls/sec) from distal airways among subjects 3 hours post exposure, after adjusting for clean air, but no change in $FeNO_{50}$ from the proximal airways (L Barregard et al. 2008). In another study of 13 participants, Stockfelt et al. exposed subjects to filtered air for 3 hours, wood smoke from stove start-up and burning cycle one week later, and wood smoke from a burn-out phase and wood burning cycle two weeks later (Stockfelt et al. 2012). Stockfelt et al. collected FeNO measurements at two exhalation flow rates, 50 and 270 mL/sec and found a high correlation between $FeNO_{50}$ and $FeNO_{270}$. After adjusting for clean air, FeNO measured at 50 mls/sec increased significantly after exposure to burn-out session; $FeNO_{50}$ increased 12% after 23-hours and 19% after 47 hours post-exposure. FeNO measured at 270 mls/sec also increased significantly following exposure to wood smoke start-up and burn-out sessions 23 and 47 hours post-exposure. $FeNO_{270}$ increased

significantly after exposure in start-up and burn-out sessions (compared to filtered air), while $FeNO_{50}$ only showed a significant increase after exposure in the burn-out session after adjusting for filtered air (Stockfelt et al. 2012). The authors caution the interpretation of the $FeNO_{270}$ association because it may be due to a relative increase due a high FeNO at baseline, and shed light into the inconsistency of the null finding compared to the significance in their previous study (L Barregard et al. 2008).

Outdoor Air Pollution

Most of the research investigating the potential link between air pollution and exhaled nitric oxide has focused on ambient outdoor air pollution or traffic-related air pollution. The results on the association between ambient air pollution and exhaled nitric oxide are mixed, which may in part be due to different experimental approaches and exposures (Holgate et al. 2003). Among healthy adults, FeNO concentrations have been shown to increase significantly due to ozone (Yoda et al. 2014) and ambient carbon monoxide (CO) (Van Amsterdam et al. 1999). In addition, among the healthy elderly population, an interquartile range increase in 24-hour average of $PM_{2.5}$ was associated with a 1.45 ppb increase in FeNO (95% confidence interval [CI]: 0.33-2.57) (Adamkiewicz et al. 2004). Another study conducted among the elderly following a bus trip, demonstrated a pre-trip change in $FeNO_{50}$ of 17.0% (95% CI: 6.7-28.2) per interquartile range increase in previous 6-hour average $PM_{2.5}$ exposure. (Dubowsky Adar et al. 2007). Among 12 healthy urban cyclists, Strak et al. found that 6-hours after cycling a 100$\mu g/m^3$ change in PM_{10} exposure was associated with a -0.97 change in FeNO (standard error: 9.09, p-value=0.92) (Strak et al. 2010).

Increased levels of acute ambient air pollution including $PM_{10,}$ black carbon, and ozone have also been associated with significantly increased levels of FeNO among healthy children (Graveland et al. 2011; De Prins et al. 2014; Nickmilder et al. 2007; P. H. Fischer et al. 2002). For example, for every 148.8 μg/m^3 increase in 24-hour ambient black carbon concentration Lin et al observed a 16.6% increase in exhaled NO among children (Lin et al. 2011). Long-term averages of $PM_{2.5}$ were also demonstrated to be significantly associated with increased changes in FeNO levels among children, independent of asthma or allergy (Berhane et al. 2014).

Other studies have explored the relationship between ambient air pollution and FeNO levels by children's asthma status. Brazza-Villarreal et al. found an increase in $FeNO_{50}$ levels with increasing ambient $PM_{2.5}$, but only among asthmatic children (Barraza-Villarreal et al. 2008). In a study on traffic-related air pollution, Eckel et al. found that among children with asthma, length of the roads in their neighborhood was positively associated with $FeNO_{50}$, while traffic density and distance to the road were not associated with $FeNO_{50}$ (Eckel et al. 2011). Among a group of nineteen asthmatic children, Koeing et al. observed increased levels of $PM_{2.5}$ associated with increases in exhaled nitric oxide (Koenig et al. 2003). Although some studies have demonstrated increased FeNO associated with increased ambient air pollution among asthmatic children, Liu et al. found that ambient concentrations of ozone and $PM_{2.5}$ were not associated with an increase in FeNO among asthmatic children (same day percent change in $FeNO_{50}$ per IQR increase in $PM_{2.5}$ was 5.3 (95% CI: -3.6-15) (Liu et al. 2009).

Two population-based studies have utilized the new development of the two compartment models to explore the association between air pollution and FeNO. In 2014, Modig et al. explored the relationship between short-term exposure to ozone and PM_{10} and FeNO at two different flow

rates ($FeNO_{50}$ and $FeNO_{270}$). The authors found no significant association between lags of 3 hours, 24 hours, or 120 hour average PM_{10} exposure and FeNO at either a flow rate of 50mls/sec or 270mls/sec., The authors did however, observe that an IQR change in 120-hour average ozone levels were associated with higher levels of $FeNO_{270}$ from the distal airways (4.0%: 95% CI: 1.0-7.1%) and $FeNO_{50}$ from the proximal airways (4.4% 95% CI: 1.0-7.9%) (Modig et al. 2014). In 2016, Eckel et al. explored FeNO at four different flow rates among 1635 children exposed to indoor NO in schools as a marker of traffic-related air pollution. After adjusting for confounders, the authors concluded a 10ppb higher indoor NO concentration was associated with higher $FeNO_{50}$ (2.8%; 95% CI: -3.3-9.3%), a 6.5% higher $FENO_{300}$ (95% CI: 0.3-13.1%). An additional metric calculated for distal airways demonstrated that a 10ppb higher NO concentrations was associated with a 0.10 ppb higher distal airway inflammation (95% CI: -.04-0.16ppb). This study provides evidence that there may be associations between indoor NO exposure and FeNO from the distal airways, but not from proximal airways (Eckel et al. 2016).

Household Air Pollution

To our knowledge, only one study has considered the association between household air pollution and adult $FeNO_{50}$ values. Pollard et al. monitored $PM_{2.5}$ and carbon monoxide among 75 households in Peru. FeNO values among the 75 women increased by 2 ppb (p=0.006) from before cooking to after cooking among all stove users. The post-cooking median FeNO levels were 10 ppb among rural households and 10.5 ppb among urban households (Pollard et al. 2014).

Association of Inflammatory Markers and Air Pollution

Biomarkers of systemic inflammation have been used to assess the association between ambient air pollution and particulate matter exposure and cardiovascular disease. Epidemiologic

studies in a variety of populations have reported inconsistent results between particulate matter and biomarkers such as cytokines and acute phase proteins. For example, the Framingham Heart Study evaluated short-term exposure to ambient air pollution among 3996 nonsmoking adults who lived near Boston, MA. The authors found that a 5 $\mu g/m^3$ increase in the 5-day moving average of $PM_{2.5}$ was associated with a 4.2% (95% CI: 0.6 – 7.6) higher level of CRP, but no association was observed between PM and TNF-α (W. Li et al. 2017). Another large cohort study, the CoLaus Study, enrolled 6183 in Switzerland and observed significant increases in IL-1β, and TNF-α for every 10 $\mu g/m^3$ change in 24-hour increase in PM_{10} (IL-1β: 0.034, 95% CI: 0.007 – 0.060; TNF-α: 0.024; 95% CI: 0.013, 0.035), but observed no significant association with CRP (estimate: -0.002, 95% CI: -0.017, 0.013) (Tsai et al. 2012). In a study on long-term air pollution in the SALIA cohort in Germany, researchers observed that one IQR increase in land-use regression modeled $PM_{2.5}$ (five year means from 2003-2007) resulted in a 15.8% change in TNF-α (95% CI: 2.5-30.8%), but no associations with IL-8 or IL-1β (Vossoughi et al. 2014).

C-reactive protein is perhaps the most studied biomarker in the association of air pollution and systemic inflammation. A literature review of the studies on air pollution and CRP provides inconclusive evidence between levels of air pollution and the biomarker (Y. Li et al. 2012). The inconclusive research may be in part due to the vast array of study designs utilized in the research and study populations.

The association of black carbon from ambient or traffic-related air pollution with markers of systemic inflammation has also been studied. A study among 624 elderly men evaluated the association between cumulative traffic-related air pollution and inflammation using 4, 8, and 12 week averaging periods (Alexeeff et al. 2011). Alexeeff et al. found that an IQR increase in 8-week

black carbon exposure was associated with a 1.58% increase in ICAM-1 concentrations (95% CI: 0.18-3.00%) and a 1.20% (95% CI: -0.58-3.02) increase in VCAM-1 concentrations (Alexeeff et al. 2011). Alexeff also found that the 4 and 12 week averages for black carbon were associated with significant increases in ICAM-1, and similar but non-significant increases in VCAM-1 (Alexeeff et al. 2011). Additional evidence supports the long-term association between black carbon concentrations and increased inflammation. A longitudinal study of 809 male veterans explored the association of 24-hour, 2 day, and 30-day moving averages of black carbon on ICAM-1 and VCAM-1 (Madrigano et al. 2010). A 1 $\mu g/m^3$ 2-day average black carbon was associated with a 4.26% change in VCAM-1 (95% CI: 1.02-7.49) (Madrigano et al. 2010). Similar, positive associations were observed for VCAM-1, however none reached significance (Madrigano et al. 2010).

Association of Inflammatory Markers and Woodsmoke

Short-term exposure to woodsmoke and systemic inflammation was evaluated among thirteen subjects in a chamber study by Barregard et al (Lars Barregard et al. 2006). Each subject was exposed to woodsmoke exposures ranging from 240-280 $\mu g/m^3$ during two, four-hour sessions, one week apart. Exposure to woodsmoke increased levels of serum amyloid A (SAA) and factor VIII in plasma post exposure (Lars Barregard et al. 2006).

Association of Inflammatory Markers and Household Air Pollution

A few studies have explored the association between household air pollution and markers of system inflammation. Caravedo et al. compared serum concentrations of SAA, CRP, ICAM-1 and VCAM-1 among 228 biomass-exposed and 228 non-exposed men and women in Peru. Adjusted analyses demonstrated that chronic exposure to biomass fuels was positively associated with increased levels of ICAM-1 and VCAM-1, but was unexpectedly negatively associated with CRP

(Caravedo et al. 2016). No association was observed for SAA (Caravedo et al. 2016).

A study by Dutta et al. in India evaluated sputum cytology for markers of airway inflammation associated with cookstove exposure and PM_{10}. Women who cooked with biomass fuels had 6.9 times increased levels of TNF-α in the sputum samples compared to women cooking with LPG (86.9 ± 28.1 vs. 12.6 ± 6.2 pg/ml, p <0.001). Similar results were observed for sputum concentrations of IL-8 (26.7 ± 7.4 for biomass users vs. 10.1 ± 3.3 pg/ml for LPG users, p <0.001) (Dutta et al. 2013).

Another study by Dutta et al. measured serum inflammatory markers, IL-8, CRP, and TNF-α among an age-matched group of 452 women who cooked with either biomass fuels or LPG. Biomass stove type was associated with increased levels of all three inflammatory markers; biomass users had 2.4 times more serum IL-8, 3.3 times more serum CRP and 1.6 times more serum TNF-α. Additionally, measured concentrations of PM_{10} and $PM_{2.5}$ were associated with increased levels of the inflammatory markers after adjusting for age, BMI, education, family income and kitchen location (Dutta, Ray, and Banerjee 2012).

A new study by Misra et al. explored the association of biomass wood fuel use (vs. electricity) and markers of systemic inflammation (CRP, SAA, IL-8, IL-1β, TNF-α, ICAM-1 and VCAM-1) among 415 women in Southern Africa (Misra et al. 2018). After adjusting for confounders, age, gravidity, caffeine consumption, passive smoking and water source, the authors found only an association among women who used wood mostly indoors compared to electricity users (estimate: -.38, 95% CI: -.68,-0.08). In all other analyses the authors found no associations with levels of inflammatory markers comparing biomass users vs. non-biomass users (Misra et al. 2018).

Olopade et al. randomized a group of women cooking with firewood in Nigeria to either cook with ethanol or continue cooking with firewood. Measured levels of serum TNF-α decreased by an average of 6.20 pg/ml (SE: 5.24) among pregnant women switching from firewood to ethanol and increased by 14.03 pg/ml (SE: 5.89) among women continuing to cook with firewood. No explanation however was provided for why women continuing to cook with firewood had increasing levels of TNF-α (Olopade et al. 2017). Women randomized to continue cooking with firewood (control) had 68% higher levels of post-randomized TNF-α compared to women randomized to cook with ethanol. Statistically significant increase in IL-8 and TNF-α were also observed in associations with measured concentrations of $PM_{2.5}$ (both log-transformed); IL-8: 0.24 (95% CI: 0.02, 0.44); TNF-α: 0.18 (95% CI: 0.03, 0.34) (Olopade et al. 2017).

Although the studies above have observed associations with household air pollution, mostly stove-type categorizations, and inflammatory markers, several studies of woodsmoke and biomarkers provide inconclusive evidence on the association with systemic inflammation. For example, several studies have observed no associations between increased woodsmoke exposure and levels of CRP among healthy adults (Allen 2009; Clark et al. 2009; Shan et al. 2014).

Air Pollution and Inflammatory Markers: Effect Modification

Several risk factors, such as diabetes, hypertension, obesity, and age (elderly) are thought to increase susceptibility for air pollution-related cardiovascular events (Dubowsky et al. 2006; R. D. Brook et al. 2010). There is extensive scientific and mechanistic evidence that obesity, diabetes, age, and hypertension as all associated with cardiovascular disease (R. H. Eckel 1997; Ortega, Lavie, and Blair 2016; Leon 2015). Proposed mechanistic pathways also support the association between air pollution and increased levels of obesity, diabetes, and hypertension (Sanidas et al. 2017).

Additionally, epidemiologic evidence supports stronger associations of air pollution on cardiovascular disease among those with susceptible conditions. For example, diabetes was observed to modify the effect of PM_{10} on stroke mortality in a study by Zeka, Zanobetti, and Schwartz (Zeka, Zanobetti, and Schwartz 2006). Among women, a stronger association between $PM_{2.5}$ and PM_{10} exposure and cardiovascular disease has been observed among women who are obese (Puett et al. 2008; K. A. Miller et al. 2007). Results for effect modification for obesity and diabetes between particulate matter and markers of systemic inflammation, such as CRP, are mixed (Y. Li et al. 2012). Dubowsky et al. observed that associations between $PM_{2.5}$ and CRP were elevated among people classified as diabetic, obese, and hypertensive. For example, a 6.1 $\mu g/m^3$ increase in the 5-day average $PM_{2.5}$ was associated with a 48% increase in CRP for people with obesity and a 74% increase in people with diabetes, compared to 12% increase among people without the conditions (Dubowsky et al. 2006).

Effect Modification and Household Air Pollution

As described above, Caravedo et al. found differences in ICAM-1 and VCAM-1 between users of biomass fuels compared to clean-fuel stove users. Carvedo et al. also explored effect modification by age categories (35-44 years, 45-54, 55-64, and 65 and over) and sex, however found no interaction (Caravedo et al. 2016). Additionally, Dutta et al. evaluated the association of inflammatory markers and hypertension and found that after controlling for confounders CRP concentrations among women with hypertension (systolic blood pressure: > 140 mmHg and diastolic blood pressure ≥ 90 mm Hg) were significantly elevated compared to those without hypertensions (OR = 1.14, 95% CI: 1.04-2.29) (Dutta, Ray, and Banerjee 2012).

Chapter 3: Overview of Study Design

Study Setting

We used a cross-sectional study design to evaluate the three aims of this dissertation. The study was conducted in nine communities surrounding the town of La Esperanza, Honduras. La Esperanza, located in the mountainous region of Western Honduras (elevation 1800 meters), is home to approximately 15,000 people. The rural communities are primarily agricultural; families typically grow corn, beans, potatoes for personal consumption and local market sale. The rural populations are primarily indigenous Lenca descent. Our target population included all female primary cooks who used a traditional cookstove or a cleaner-burning *Justa* cookstove (See Figure 3.1). Traditional cookstoves in our population were typically self-built wood-burning stoves, with a metal griddle, large combustion chamber, and possibly a chimney. The cleaner-burning *Justa* stove is a common wood-burning improved stove in Latin America with a rocket-elbow combustion chamber, chimney, and metal griddle suited to making tortillas.

Figure 3.1: Typical traditional (left) and Justa (right) cookstoves in the homes of Honduran women

Study Population

The study team held local community meetings in villages surrounding La Esperanza and presented detailed information regarding the study to the community members. From 500 households, we selected a convenience sample and visited 170 households from February 9th-April 30th 2015. We recruited one female cook per household that met the following eligibility criteria; age 25-56, non-smoker, not pregnant, and owned a traditional cookstove or *Justa* cookstove at least 4 months prior to the interview. Upon visitation, eighteen of the 170 households were excluded as they did not have a female who met the eligibility criteria. Two women chose not to participate in the study. We enrolled a total of 150 women into the study.

Each study participant committed to a 24-hour exposure-monitoring session. This included both kitchen and personal concentrations of $PM_{2.5}$ and black carbon. All exposure instruments were placed in the homes of participants and in a bag worn by the participant in the early morning and collected the following morning. Detailed information on exposure assessment is provided in the individual chapters. Health measurements were collected immediately following the completion of the 24-hour exposure measurements. All participants were provided a USD $5 incentive for their participation in the study. This incentive included rice, vegetable oil, sugar and beans.

Overall Study Methods

This dissertation used data from two NIH funded grants (Figure 3.2). The first was an NIH R21 cross-sectional pilot grant was entitled "Woodsmoke exposure and novel health indicators: a feasibility field study" (1 R21 ES022810). The second study was an NIH R00 grant "Community-based Participatory Research: A Tool to Advance Cookstove Interventions" (ES022269). The Colorado State University Institutional Review Board approved both study protocols.

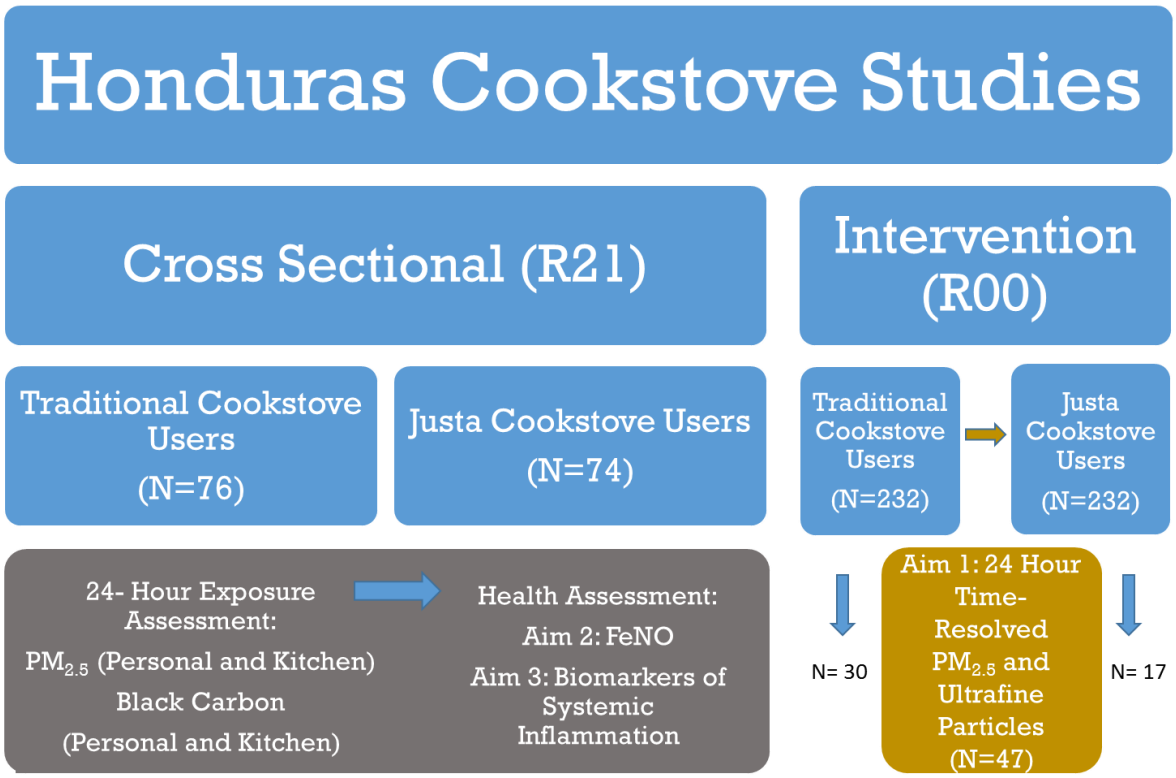

Figure 3.2: Overview of aims and data for the dissertation (n=150)

Aim 1 Methods

For Aim 1, fine particulate matter ($PM_{2.5}$) was measured by pump using an aerosol nephelometer; (personal DataRam [(pDR]) 1200, (Thermo Fisher Scientific Inc., Waltham, MA). The pDR was set up in an active-flow mode, with a pump (SKC AirChek XR5000 pump) and cyclone attached. The active mode setup provides both real-time mass concentrations and gravimetric mass. The pDR recorded the average $PM_{2.5}$ concentration for each minute sampled. A Triplex cyclone inlet with a cut point of 2.5 microns was placed on one end of the pDR, while a 37mm Filberilm^{TM} filter (T60A20 Pall Corporation) was placed downstream of the pDR photometric sensing chamber. The pump pulled air samples through the pDR at a rate of 1 L/min. An external data logger (EasyLog, Lascar Electronics Ltd.) was placed in the pDR port to record an analog

output in volts that is proportional to the measured concentration. The upper limit of detection was set to 4,000 μg/m^3. Prior to field setup, all filters were equilibrated and weighed at Colorado State University. In addition, at the field site, the team zeroed the pDR in clean air in the field laboratory and the pump was calibrated with a flow meter (Bios International DryCal DC-lite). The pDR has been used as a portable device to assess ambient air pollution exposure and has demonstrated good agreement with other continuous $PM_{2.5}$ monitors at low humidity (Chakrabarti et al. 2004). Gravimetric $PM_{2.5}$ in μg/m^3 was calculated using pre- and post-exposure weights from the Mettler Toledo Microbalance (model MX5) as described above.

In Aim 1, ultrafine particle number concentration (PNC) was measured with the DiSCMini (Testo AG, Germany; Fierz et al., 2011). In brief, the instrument utilizes a positive corona wire to produce a high concentration of positive ions that attach to particles entering the DiSCMini. The charge assigned to the particle is approximately proportional to the particle diameter (Fierz, Houle, Steigmeier, & Burtscher, 2011). Excess ions are removed by a particle trap and the remaining charged particles pass through a diffusion stage where some are captured. The remaining particles then flow to a second stage equipped with a high-efficiency particulate air (HEPA) filter (Fierz et al., 2011). Smaller particles have a large diffusion coefficient and are more likely to be collected in the diffusion stage, while larger particles are more likely to end up in the filter stage (Koehler and Peters 2015). An electrometer measures the charge of the depositing particles at the diffusion stage and HEPA filter and the average particle size is calculated as the ratio of the currents at the two distinct electrometer stages (Koehler and Peters 2015; Asbach et al. 2017). A final PNC is estimated based on the total current and particle size information. These values are based on the

hypothesis that particles are spherical and lognormally distributed with a geometric standard deviation particle size distribution of 1.9.

The DiSCMini was operated at a flow rate of 1.0 L/min and was equipped with an external impactor to remove all particles larger than 700 nm from entering the instrument. In order to monitor household PNC for 24 hours, we equipped the instrument with an external rechargeable battery. All ultrafine data were recorded on a SD card that accompanied the DiSCMini. Data were downloaded immediately following the monitoring period.

The DiSCMini and pDR were collocated and placed between 40-70 inches from the edge of the stove at each household. Both instruments were manually turned on to begin measurements and the DiSCMini conducted a 5-minute warm-up. The pump for the active $PM_{2.5}$ measurement was programmed to turn off after 24 hours of measurement while the DiSCmini was manually switched off after returning to the house after at least 24 hours. After each household measurement, the impactor for the DiSCMini was thoroughly cleaned and tested to ensure the flow rate returned to 1 L/min. A temperature and relative humidity monitor (EasyLog Lascar Electronics Ltd) was also placed in the kitchen.

Aims 2 and 3 Methods

We assessed exposure to household air pollution using stove type (traditional or *Justa*) and by measuring 24-hour average kitchen and personal concentrations of $PM_{2.5}$ and black carbon. For kitchen exposure, monitors for $PM_{2.5}$ were placed in the kitchen between 76 and 127 centimetres above the stove, to represent the participant's breathing zone, and away from open windows and doors. For personal exposure measurements, we placed $PM_{2.5}$ monitors in a small bag that each

woman wore throughout the monitoring period, except for bathing or sleeping. The inlet was clipped to the shoulder strap at the front of the woman's chest.

$PM_{2.5}$ was collected on 37mm Teflon-coated glass fiber filters (Fiberfilm^{TM} T60A20, Pall Corporation, Port Washington KY, USA). The filters were equilibrated for at least 24 hours and then pre-weighed at Colorado State University (CSU) using the Mettler Toledo Microbalance (model MX5, resolution and repeatability of 1ug). In the field laboratory, filters were placed into Triplex cyclones with a particle cut size of 2.5µm (BGI by Mesa Labs, Butler NJ, USA). Cyclones were attached to SKC AirCheck XR5000 pumps (SCKInc, Eighty Four, PA, USA) with a flow rate of 1.5L/min. Pumps were pre-calibrated daily using a Bios International DryCal Dc-Lite primary flow meter. We collected one filter blank every two weeks. After collection of the sample, filters were stored at -20 degrees Celsius and then transported to CSU, equilibrated, and post-weighed. We calculated a $PM_{2.5}$ 24-hour time-weighted average by subtracting the average blank concentration for the field session and accounting for the sampled volume. We calculated the limit of detection (LOD) for $PM_{2.5}$ as follows: average weight of blanks + 3*standard deviation of the weights. All samples with a concentration less than the LOD (7 kitchen samples and 7 personal samples) were replaced with a value of LOD/√2. PM values were not available for 41 houses due to faulty equipment or missing data.

We estimated $PM_{2.5}$ black carbon concentrations based on the optical transmission of light through the air sampling filters. A transmissometer (model OT-21, Magee Scientific, USA) estimated the attenuation at 880 nm light intensity through the sample filter which is proportional to the amount of black carbon on the filter. To estimate the black carbon loading we first define a

measure of attenuation (ATN) as the natural log of the ratio of light transmittance of a reference filter (I_0) to a sample filter (I) multiplied by 100:

$$ATN = 100 \times ln\left(\frac{I_0}{I}\right) \quad (1)$$

We used a single value for reference transmittance (I_0 = 224571), taken as the average transmittance of 54 field blank filters. This reference method is similar to that reported previously with laboratory blank filters () and one that also allows us to account for contamination that may have occurred with filter handling during non-sampling periods.

The measured attenuation was then used to derive the attenuation coefficient (b_{atn}) in units of inverse megameters (Mm^{-1}), adjusting for field sampling factors such as the sampled area on the filter (m^2), and the volume of the air sampled (m^3, calculated using the sample flow rate and the sample duration). The attenuation coefficient was calculated as described by Presler-Jur et al (Presler-Jur et al. 2017):

$$b_{atn} = \frac{Filter\ Area}{Sample\ Volume} \times ATN \times 10^4 \quad (2)$$

Assumptions of black carbon concentration estimates have uncertainties given the properties of particles (e.g. differences in light scattering and combustion source). We used a mass attenuation cross-section), σ_{atn}, to convert from ATN to an equivalent BC concentration, which implies a linear relationship between the BC and the ATN of the sample filter. To account for the primarily wood-burning nature of the exposure, we defined σ_{atn} = 12.5 m^2/g as derived previously for carbonaceous smoke by Chylek et al., 1981. Additionally, previous studies have demonstrated a measurement artifact wherein an underestimation of the ATN becomes more pronounced at

higher black carbon concentration. We therefore used a loading correction r, calculated according Kirchstetter and Novakov 2007 (Kirchstetter and Novakov 2007):

$$r = \left(exp^{-ATN/100}\right) \times 0.88 + 0.12 \qquad (3)$$

The final estimated BC concentration (BC, μg/m^3) was calculated as follows:

$$BC = \frac{b_{atn}}{\sigma_{atn} \times r} \qquad (4)$$

We used a single value for reference transmittance (I_0 = 224571), taken as the average transmittance of 54 field blank filters. This reference method is similar to that reported previously with laboratory blank filters (Presler-Jur et al. 2017) and one that also allows us to account for contamination that may have occurred with filter handling during non-sampling periods. Although these field blanks were not collected during the same sampling period; samples were collected within a year and with similar field methods.

Chapter 4: Kitchen concentrations of $PM_{2.5}$ and ultrafine particulate matter in rural Honduras

Summary

Background: Household air pollution from cooking with solid biomass fuels results in exposure to high levels of particulate matter (PM); however, limited data exist for size fractions other than $PM_{2.5}$ (diameter less than 2.5 μm). We compared levels of $PM_{2.5}$ and ultrafine PM (diameter less than 0.1 μm) from traditional and cleaner-burning Justa wood-burning cookstoves in rural Honduras using real-time measurements.

Methods: $PM_{2.5}$ concentrations were actively sampled using a personal DataRam (pDR) 1200. Ultrafine particle number concentrations (PNC) were measured using the Testo DiSCMini. Monitors were collocated inside the kitchens for a 24-hour period. Our final sample size was 44 houses for PNC (traditional: 27, Justa: 17), and 27 houses for $PM_{2.5}$ (traditional: 15, Justa: 12).

Results: Twenty four hour kitchen concentrations of $PM_{2.5}$ and PNC were highly variable during the course of the monitoring period. The median 24-hour PNC was 8.5×10^4; IQR (interquartile range): $3.8 \times 10^4 – 1.8 \times 10^5$ (traditional cookstoves: 1.3×10^5, IQR: $3.3 \times 10^4 – 2.0 \times 10^5$; Justa cookstoves: 6.3×10^4, IQR: $4.0 \times 10^4 – 1.2 \times 10^5$). The median 24-hour $PM_{2.5}$ concentration was 91 $\mu g/m^3$; IQR: 40 – 195 $\mu g/m^3$ (traditional cookstoves: 176 $\mu g/m^3$, IQR: 47 - 262 $\mu g/m^3$; Justa cookstoves: 52 $\mu g/m^3$, IQR: 30 - 104 $\mu g/m^3$). The 24-hour average ultrafine PNC and $PM_{2.5}$ levels were highly correlated (Spearman rho: 0.73), and more highly correlated for traditional stoves (rho: 0.91) than for Justa stoves (rho: 0.55). In addition, 24-hour average values

were highly correlated with 1, 5, 15, and 60-minute maximum values for both $PM_{2.5}$ and PNC (Spearman rho ranging from 0.68-0.86 for both stove types).

Conclusion: Measuring $PM_{2.5}$ may capture most of the variability in PNC for wood-burning cookstoves in similar types of settings (i.e., rural areas with few PM sources other than the cookstove); however, the correlation between size fractions may be impacted by the combustion efficiency of the stove. Given the potentially large implications on health, further investigation into the concentrations of ultrafine PNC and $PM_{2.5}$ from cleaner-burning stoves is warranted. High correlations in daily and shorter-term averaging times suggest that time-integrated gravimetric 24-hour $PM_{2.5}$ exposure measurements may provide a sufficient, cost-effective exposure assessment approach in similar settings with wood-burning stoves.

Introduction

Approximately 3 billion people, primarily in low- and middle-income countries, rely on solid biomass fuel as their primary energy source (Bonjour et al. 2013). The combustion of solid-fuels in traditional cooking stoves results in levels of air pollution that are often substantially higher than the World Health Organization's (WHO air quality guidelines of a 24-hour mean concentration of 25 $\mu g/m^3$ (World Health Organization 2006a; Thomas et al. 2015).

Fine particulate matter ($PM_{2.5}$) concentration is the most commonly used metric for assessing exposure to household air pollution. Although gravimetric sampling is most often used in assessing the health outcomes associated with household air pollution, continuous real-time, or time-resolved, measurements may provide additional insight into PM concentrations with respect to temporal variability or intensity of exposure with cooking events (Northcross et al. 2015). Studies that have implemented real-time PM measurements in field settings have explored

temporal variability of cookstove emissions and characterized intensity of exposure (Carter et al. 2016; Chen et al. 2016; Ezzati, Mbinda, and Kammen 2000; Van Vliet et al. 2013; Park and Lee 2003; S. L. Fischer and Koshland 2007). Such studies have found that short-term concentrations of elevated $PM_{2.5}$ constitute a substantial portion of daily exposure (Van Vliet et al. 2013). It is unclear, however, whether shorter-term metrics, such as 1-hour maximum concentrations, may be relevant for health models evaluating effects of household air pollution.

Evidence suggests that particles with diameters less than 0.1 μm (ultrafine particles) are the most likely to penetrate deep into the lungs resulting in oxidative stress and systemic inflammation. (Ken Donaldson and Stone 2003; K Donaldson et al. 2001; Brauer et al. 2001; R. D. Brook et al. 2010; Brauner et al. 2007). Little is known about in-home ultrafine particle concentrations from traditional or improved cookstoves due to the logistical and monetary barriers of monitoring ultrafine particles in field settings. Laboratory studies have been conducted with varying results. Some laboratory emissions studies have suggested that improved cookstoves may emit fewer ultrafine particles compared to traditional cookstoves (such as a three-stone fire) (Jetter et al. 2012), while other studies have suggested that improved force-draft gasifiers, may increase ultrafine particles due to improved combustion efficiency despite their ability to substantially reduce emissions of $PM_{2.5}$ mass compared to traditional stoves (Just, Rogak, and Kandlikar 2013).

Given the potential adverse health effects associated with ultrafine particles, we must measure ultrafine particle number concentrations from both traditional and cleaner-burning cookstoves. Health and risk assessments have been estimated based entirely on $PM_{2.5}$ mass exposure (Armendáriz-Arnez et al. 2010; Jetter et al. 2012; Smith et al. 2014b); therefore, if the

correlations between emissions of ultrafine particles and $PM_{2.5}$ mass are dissimilar for various improved cookstoves, the health improvements thought to be associated with cleaner-burning cookstoves may be inaccurate. To our knowledge only one study has used a portable monitor to measure ultrafine particle number concentration from traditional and improved biomass cookstoves in the field (de la Sota et al. 2018). Among 6 households in Senegal, de la Sota observed lower ultrafine particle number concentration during cooking events among improved biomass stove users (Median PNC $1.5x10^6$ pt/cm^3) compared to traditional biomass stove users (Median PNC $2.2x10^6$ pt/cm^3) (de la Sota et al. 2018). Given the small sample size and the short monitoring period in the previous study, there is a need for additional comprehensive measurement of ultrafine particle concentrations among different cookstoves.

In this study we used real-time instrumentation to quantify kitchen concentrations of $PM_{2.5}$ and ultrafine PM in La Esperanza, Honduras where solid-fuel cookstoves were the primary cooking apparatus. We evaluated both traditional and cleaner-burning *Justa* cookstoves. Our primary goals were to (1) assess ultrafine particle number concentration, (2) compare $PM_{2.5}$ mass and ultrafine PNC, and (3) compare shorter-term averaging windows to 24-hour average concentrations for both pollutants. To our knowledge our study is the first to measure 24-hour time-resolved concentrations of $PM_{2.5}$ and ultrafine particles among solid biomass traditional and cleaner-burning stove users.

Methods

Study Site and Population

This study was conducted in rural communities surrounding La Esperanza, Honduras as part of a lager study monitoring the effects of exposure to household air pollution. In brief, the

larger study included 150 women aged 25-56, who were non-smokers and not pregnant. We measured real-time $PM_{2.5}$ and ultrafine particle number concentrations in a subsample of these homes. With only one set of monitoring equipment, we were limited to collecting data from one household per day. The study team generally chose the first house visited in the morning (Monday, Wednesday, and Friday) to include in the subsample. We collected data from 47 households in October 2015 and from February to December 2016. Of the 47 houses, we visited 11 households twice, approximately 6 months apart.

Traditional and Improved Cookstoves

Our study population included households that used either a traditional open fire or a cleaner-burning *Justa* cookstove. The traditional cookstoves were typically self-built adobe stoves, with a *plancha* (griddle), large combustion chamber, and chimney. The *Justa* stoves feature an insulated, rock-elbow combustion chamber, chimney, and plancha. Wood was the primary fuel used in both cookstoves. All *Justa* stoves were built in homes by our study team approximately 6 months prior to the measurement. Seventeen *Justa* stove users and 30 traditional stove users were enrolled. Of the 44 households with complete 24-hour ultrafine data, 27 of the households had a traditional cookstove, while the remaining 17 used an improved cleaner-burning *Justa* cookstove.

Exposure Concentration Measurements

Ultrafine particulate matter

Ultrafine particle number concentration (PNC) was measured with the DiSCMini (Testo AG, Germany; Fierz et al., 2011). The DiSCMini is a handheld diffusion size classifier that measures mean particle diameter (between 10-300nm) and airborne particle number concentration

between 10^3 and 10^6 cm^3 at 30% accuracy (Asbach et al. 2012). We equipped the instrument with an external rechargeable battery to ensure 24-hours of continuous household monitoring. The DiSCMini recorded and logged concentrations at one-second intervals. Data were downloaded immediately following the monitoring period.

$PM_{2.5}$

Fine particulate matter ($PM_{2.5}$) was sampled using an aerosol nephelometer, the personal DataRam (pDR) 1200 (Thermo Fisher Scientific Inc., Waltham, MA). The pDR was set up in an active-flow mode with a pump (SKC AirChek XR5000 pump) and cyclone attached. The active mode setup provides both real-time mass concentrations and gravimetric mass. The pDR recorded the average $PM_{2.5}$ concentration for each minute sampled. A Triplex cyclone inlet with a cut point of 2.5 microns was placed on one end of the pDR, while a 37mm Filberilm™ filter (T60A20 Pall Corporation) was placed downstream of the pDR photometric sensing chamber. The pump pulled air samples through the pDR at a rate of 1.5 L/min. An external data logger (EasyLog, Lascar Electronics Ltd.) was placed in the pDR port to record an analog output in volts that is proportional to the measured concentration. The upper limit of detection was set to 4,000 $\mu g/m^3$. Prior to field setup, all filters were equilibrated and weighed to the nearest microgram (Mettler Toledo Microbalance; model MX5) at Colorado State University. In addition, at the field site, the team zeroed the pDR in clean air in the field laboratory and the pump was calibrated with a flow meter (Bios International DryCal DC-lite). The pDR has been used as a portable device to assess ambient air pollution exposure and has demonstrated good agreement with other continuous $PM_{2.5}$ monitors at low humidity (Chakrabarti et al. 2004). Blank corrected gravimetric $PM_{2.5}$ in $\mu g/m^3$ was calculated using pre- and post-exposure weights.

Field Measurements

The DiSCMini and pDR were collocated and placed between 40-70 inches from the edge of the stove at each household. Both instruments were manually turned on to begin measurements and the DiSCMini conducted a 5-minute warm-up. The pump for the active $PM_{2.5}$ measurement was programmed to turn off after 24 hours of measurement while the DiSCmini was manually switched off after returning to the house after at least 24 hours. After each household measurement, the impactor for the DiSCMini was thoroughly cleaned and tested to ensure the flow rate returned to 1 L/min. A temperature and relative humidity monitor (EasyLog Lascar Electronics Ltd) was also placed in the kitchen (Figure 4.1).

Data Processing

PNC

The data from the DiSCmini SD card were uploaded using the DiSCmini data conversion tool (Matter Aerosol 2011, version 2.0) and all data were processed in R 3.4.1 (R Core Team, Vienna, Austria). The DiSCMini electrometer relies on low current measurements and conducts a "zero-offset" every hour in order to maintain accurate measurements. The instrument did not collect any data during the 1-minute offset. Each minute corresponding with a "zero-offset" was set to "missing" in the 24-hour sample. In addition, given that the DiSCMini monitor was subject to high levels of emission from the cookstoves, we checked each household measurement for various error codes for each second sampled. When concentrations reach the maximal levels above the limit of detection, the maximal electrometer current is reached, impacting both the filter and diffusion stages of the instrument (Martin Fierz, Weimer, and Burtscher 2009). Within our dataset we observed error codes for 5 different scenarios: the filter stage below 0 fA, diffusion

stage below 0 fA, filter stage over 4096 fA, diffusion stage over 4096 fA, and a negative lung-deposited surface area (LDSA) measurement. Of the 4,060,800 total seconds sampled, 2.1% of the sample had an error code for a filter stage below zero, 2.2% of the sample had an error code for diffusion stage below zero, 1.9% of the sample had a negative LDSA and <1% of the sample had filter stage or diffusion stage over 4096 fA (total current). All seconds flagged with an error code were excluded from the data analyses. Following the removal of seconds flagged with errors, we calculated the average PNC in each minute sampled. Data from three of the 47 households were excluded, because the DiSCMini turned off prior to completing the 24-hour sampling period (3 traditional stoves).

Fine particulate matter ($PM_{2.5}$)

Real-time pDR measurements were corrected for relative humidity using the formula described by Chakrabarti et al. (Chakrabarti et al. 2004) where the correction factor (CF) = 1 + 0.25(relative humidity^2)/(1-relative humidity). Concentrations were converted to μg/m^3 and values below the limit of detection (LOD) of 5.5 μg/m^3 were substituted with the LOD/(√2). In addition, we normalized real-time pDR concentrations for gravimetric measurements as described by Benton-Vitz and Volckens (Benton-Vitz and Volckens 2008). We calculated the average response factor (pDR real-time concentration/pDR gravimetric concentration) for the full sample. Minute level concentrations for individual households were then corrected for the average response factor. Of the 47 households monitored for $PM_{2.5}$ we excluded 20 household samples (16 households with external data logger failure; three with missing temperature and humidity data; one with unreliable (negative) gravimetric data). Our final sample size for $PM_{2.5}$ was 27 households.

Data Analysis

All data were analyzed in R version 3.4.1 (R Core Team, Vienna, Austria). Utilizing one-minute averages for both the $PM_{2.5}$ and ultrafine particle data sets, we calculated descriptive statistics including: the 24-hour minimum, maximum, mean, median, standard deviation, 25^{th} and 75^{th} percentiles, as well as maximum 5-minute, 15-minute, and 60-minute moving averages for each household. We utilized the real-time pDR data to calculate the total time in hours that each household's $PM_{2.5}$ concentration was above 100 $\mu g/m^3$ (the equivalent of four times the WHO 24-hour air quality guidelines standard) (World Health Organization 2006a), a metric previously observed to be associated with negative health endpoints among children (Gurley et al. 2013; Chen et al. 2016). We also calculated the 95^{th} percentile concentration for each household and removed minute-level values above this concentration to determine the impact of elevated exposure on the overall 24-hour average. Wilcoxon rank sum tests were used to test for differences in 24-hour average $PM_{2.5}$, 24-hour average PNC, and number of hours spent above 100 $\mu g/m^3$ by stove type.

We calculated Spearman rank-order correlation coefficients to assess: 1) the correlation of 24-hour ultrafine and $PM_{2.5}$ measurements and 2) the correlation for averaging windows (maximum 24-hour, 1-minute, 5-minute, and 60-minute) within both PNC and $PM_{2.5}$. We created descriptive plots of the 24-hour real-time concentrations of PNC and $PM_{2.5}$ for each household.

Results

Kitchen characteristics of the sample population are described in Table 4.1. We visited 11 households at two different times, 6 months apart. Of the 24 houses that had both $PM_{2.5}$ and PNC, two households had two measurements. Overall, kitchens were constructed of mud or stuccoed

adobe walls (60%), with dirt floors (70%) and sheet metal roofs (70%). About 30% of households reported the use of a secondary stove. In Honduras, secondary stoves are used outside the home for cooking large pots of beans or corn. During the monitoring period, women reported cooking an average of 3.1 meals (SD: 0.88 meals) and for an average of 5.5 people (SD: 2.5 people).

The average ratio of the uncorrected nephelometer pDR readings to the gravimetric net filter weights (response factor) was 0.58 (SD: 0.19). Three of these households had two measurements. The response factor indicates the real-time nephelometer readings were 58% lower than average time-integrated filter measurements. The response factors by stove type were 0.62 (SD: 0.20) for traditional stoves and 0.53 (SD: 0.18) for cleaner-burning *Justa* cookstoves (See supplement). Using data from the nephelometer, the gravimetric corrected 24-hour average $PM_{2.5}$ for all households was 196 $\mu g/m^3$ (SD: 329 $\mu g/m^3$) (Table 4.2). On average, women who owned traditional stoves (297 $\mu g/m^3$; SD: 417 $\mu g/m^3$) were exposed to higher concentrations of $PM_{2.5}$ compared to *Justa* stove owners (69 $\mu g/m^3$; SD: 50 $\mu g/m^3$) (Wilcox rank sum test, p = 0.07) (Table 2).

The 24-hour average mean particle number concentrations (PNC) for 44 households (35 distinct households, 9 with two measures) are shown in Figure 4.2; the mean concentration was $1.2x10^5$ pt/cm^3 (SD: $1.0x10^5$). PNC was lower among the improved *Justa* cookstoves ($9.1x10^4$ pt/cm^3; SD: $6.9x10^4$ pt/cm^3) compared to the traditional cookstoves ($1.3x10^5$ pt/cm^3; SD: $1.1x10^5$ pt/cm^3) (Wilcox rank sum, p = 0.76). The Spearman correlation between 24-hour average PNC and 24-hour average $PM_{2.5}$ was 0.73 (N=24). Correlations between 24-hour average PNC and $PM_{2.5}$ were high among traditional stoves (r=0.91), but only moderate among *Justa* stoves (r=0.55).

For the 1-hour averaging period, we observed 1-hour $PM_{2.5}$ maximum values ranging from 54 μg/m^3 to 4194 μg/m^3 (Figure 4.3). The highest concentration observed for traditional stove users was 4194 μg /m^3 and the highest concentration among *Justa* stove users was 1546 μg /m^3. The average of the 1-hour maximum concentrations among all households was also higher for traditional stoves (1395 μg/m^3; SD: 1219 μg/m^3), compared to *Justa* stove users (664 μg/m^3; SD: 505 μg/m^3; Figure 2). The $PM_{2.5}$ averaging times of 1-minute, 5-minute, 15-minute and 60-minute were highly correlated with the 24-hour average ranging from 0.73-0.97 (Figure 4.4). Concentrations for ultrafine PNC during the 1-minute, 5-minute, 15-minute, and 60-minute averaging windows and 24-hour average were also highly correlated (Figure 4.5). The Spearman correlation between 1-hour maximum $PM_{2.5}$ and 1-hour maximum ultrafine PNC was 0.55, while the 1-minute maximum correlation between these two pollutants was 0.35. Descriptive plots of the 24-hour concentrations for PNC and $PM_{2.5}$ mass for individual households demonstrate similar patterns in PNC and $PM_{2.5}$ emissions throughout the course of the day (Figure 4.6).

We observed that the average number of hours a household concentration was over a $PM_{2.5}$ concentration of 100 μg/m^3 was 4.1 hours (SD: 4.0) and ranged from less than 1 hour to over 15 hours. Traditional cookstove users spent an average of 5.7 hours (SD: 4.8) above 100 μg/m^3 in the 24-hour time period, while cleaner-burning *Justa* stove users spent an average of 2.2 (SD: 1.3) hours above 100 μg/m^3 (p=0.14). When household concentrations were stripped of minute values above the 95^{th} percentile the mean-exposure based on real-time data was 47 μg/m^3 (SD: 214 μg/m^3); (Traditional stoves: 66 μg/m^3; SD: 278 μg/m^3; *Justa* stoves: 26 μg/m^3 (100 μg/m^3).

Discussion

Gravimetric and Real-Time $PM_{2.5}$

This cross-sectional study presents $PM_{2.5}$ concentrations in kitchens of women cooking with traditional and cleaner-burning cookstoves. Kitchen concentrations of $PM_{2.5}$ among households with traditional stove were higher compared to kitchen concentrations where *Justa* stoves were used, however, the mean 24-hour average $PM_{2.5}$ concentrations exceeded the World Health Organization (WHO) air quality guidelines of 25 $\mu g/m^3$ for both cookstove types (World Health Organization 2006b). Only six of 47 (13%) houses had exposures below the WHO guideline in a 24-hour period (three traditional, three *Justa*).

Time-resolved $PM_{2.5}$ concentrations measured by the pDR were highly correlated with the gravimetric time-integrated measurements (r=0.93). The high correlation between nephelometer and gravimetric measurements has been observed in other field studies measuring household air pollution. For example, Van Vliet and colleagues observed a Spearman rho of 0.90 in a field study in Ghana (Van Vliet et al. 2013). Nephelometers are known to respond linearly across several orders of aerosol mass concentration but must be calibrated to the aerosol of interest. Thus, a strong correlation with gravimetric filter measurements can be expected when the exposures are dominated by a single emission source.

PNC

To our knowledge, this is only the second study to use the DiscMini handheld monitor to quantify exposure to ultrafine particles in the homes from biomass cooking. Traditionally, the "gold standard" for sizing aerosol ultrafine particles is the Scanning Mobility Particle Sizer (SMPS), while the particle number concentration is often assessed with condensation particle counters

(CPCs) (Koehler and Peters 2015; Asbach et al. 2012). However, the SMPS is expensive, bulky, and not well suited for field measurements (Mills, Hong Park, and Peters 2013). Handheld CPCs, such as the P-trak, are often used for field monitoring. However, CPCs are also limited by cost and the fact that the condensing fluid reservoir lasts about only eight hours (Koehler and Peters 2015). Direct reading instruments, such as the DiSCmini, are a relatively new technology for field and personal monitoring of ultrafine particles. In both laboratory and field tests, the DiSCMini demonstrates high correlation and ±30% accuracy with CPCs tested in the same settings (Asbach et al. 2012; Mills, Hong Park, and Peters 2013; Bau et al. 2017; Meier, Clark, and Riediker 2013; Viana et al. 2015; Martin Fierz, Keller, and Burtscher 2009), making it an ideal field monitor for ultrafine particles.

Our results show a reduction in ultrafine PNC among the cleaner-burning *Justa* cookstoves. De la Sota et al. used the DiSCmini to monitor ultrafine particles during cooking periods among three households using a traditional stove and three households using an improved rocket stove in Senegal (de la Sota et al. 2018). The mean number concentration observed during a cooking period was 2.5 x 10^6 pt/cm^3 among traditional stoves and 1.71 x 10^6 pt/cm^3 for improved rocket stoves (de la Sota et al. 2018). Our study did not calculate cooking event concentrations therefore limiting comparability to the de la Sota study, yet we observed similar results in reduced PNC among the cleaner-burning biomass cookstoves. Similarly, a field study of 15 households that used coal or wood for heating and cooking in China measured PNC with an AEROTRAK 9000 and observed that cookstoves with chimneys reduced ultrafine particle exposures by a factor of 4 during cooking periods (Hosgood et al. 2012).

PNC and $PM_{2.5}$

The correlation of the 1-hour and 1-minute maximum PNC and $PM_{2.5}$ mass values were low to moderate at 0.55 and 0.35, respectively. These results indicate possible differences in exposure to $PM_{2.5}$ and ultrafine particles during short time periods perhaps during the times of starting or fueling the fire. Evidence from both lab and field studies support the hypothesis that particle size and particle number concentration are related to certain cooking activities and phases of cooking. We observed differences in the 24-hour average correlation between PNC and $PM_{2.5}$ mass by stove type. The correlation was high among traditional stoves (0.91), but only moderate among improved stoves (0.55). The mechanism influencing the correlation of PNC and $PM_{2.5}$ mass for the cleaner-burning *Justa* stove is unclear and may be driven by only a small number of households or combustion efficiency. We observed that several of the *Justa* cookstoves had high concentrations of $PM_{2.5}$ with relatively low PNC (Appendix 4.2). This may also be due to measurement error with the DiSCMini or pDR.

Shorter-Term Concentrations

Our 1-hour maximum concentrations ranged from 54 $\mu g/m^3$ to 4194 $\mu g/m^3$ and were slightly lower than 1-hour concentrations reported by Fischer (159 $\mu g/m^3$ to 6200 $\mu g/m^3$) (S. L. Fischer and Koshland 2007). The 1-minute maximum average values among traditional and *Justa* stove users, 4194 $\mu g/m^3$ and 1546 $\mu g/m^3$ respectively, were 14 and 22 times higher than the 24-hour averages for each stove group. Park and Lee observed peak values between 32-39 times higher than 24-hour averages among traditional and improved biomass stove users in Costa Rica (Park and Lee 2003). Such results complement known increases in concentrations of particulate matter and gases from cooking activities and tending or adding fuel to the fire (Bartington et al.

2017; Just, Rogak, and Kandlikar 2013; Ezzati, Mbinda, and Kammen 2000). Additionally, Van Vliet et al. observed that reducing the overall highest 1-5% of the $PM_{2.5}$ concentrations in Ghana field study reduced mean exposure by 49-75% (Van Vliet et al. 2013). We observed that removing real-time concentrations above the 95^{th} percentile decreased the overall 24-hour average concentrations by 24%; 22% among traditional stoves and 38% among *Justa* stoves. The average number of hours spent at over 100 $\mu g/m^3$ (4.1 hours; add SD or IQR) among our study population was similar to the results observed by Gurley et al. in Bangladesh among biomass stove users where the mean number of hours was 5.3 (IQR: 4.0-6.9) (Gurley et al. 2013). The implications of short-term high concentrations of PM mass or ultrafine PNC is unclear in the field of household air pollution. Ambient air pollution studies have observed the association of 1-hour maximum ambient $PM_{2.5}$ on hospital admission and mortality, but this association has not been studied among cookstove exposures (Burgan et al. 2010). Although our measured short-term kitchen concentrations of $PM_{2.5}$ are highly correlated with 24-hour concentrations, we do not know if this relationship is similar for personal exposure. It may be useful to measure short-term intensity of exposure in studying the exposure-response relationships, especially for cardiovascular endpoints.

We observed temporal variation over each 24-hour sampling period. Indoor $PM_{2.5}$ and ultrafine particles peaked in the morning with the cookstove startup (generally between 4am-5am) and were lowest overnight when the stove was off. Similar studies using temporally-resolved emissions monitoring in Kenya and China have also observed elevated concentrations of $PM_{2.5}$ coinciding with diurnal patterns and phases of cooking (i.e. startup) (Kaur et al. 2017; Ezzati, Mbinda, and Kammen 2000; Carter et al. 2016; Park and Lee 2003). The substantial variation in household concentrations of $PM_{2.5}$ provides evidence that peaks of exposure occur during cooking

(especially in scenarios without other sources of pollution), and highlight the importance of using personal monitoring to capture a better estimate of true exposure (Clark et al. 2012).

Limitations

Our study is limited by a small sample size. The use of the DiSCmini in settings with very high exposures over a long period was also challenging. The DiSCmini impactor cut point of 0.7 µm was often clogged by large particles in the household setting, resulting in reduced flow to the instrumentation. The triplex cyclone was also subject to particle deposition and was cleaned after every use. Placement of the collocated instruments in the households also varied due to logistical challenges of placing the instrument away from the stove and windows or door, which could affect the measurements. There are currently no standards for measuring ultrafine particles in the household setting, and we are unsure how the distance from the stove may have affected individual household concentrations. Given the lack of standards, it is possible our 24-hour concentrations and correlations between $PM_{2.5}$ mass and PNC would not be generalizable to other populations with different environments, fuels, and stove types. Both the pDR and DiSCMini results were also impacted by the inability of the instruments to measure high exposure levels that could have led to exposure measurement error potentially impacting the correlation between the 1-minute maximum values for $PM_{2.5}$ and PNC. The pDR reports a maximum concentration of 4,000 $\mu g/m^3$ and the DiSCMini is designed to only count to 1,000,000 particles/cm^3. Our data may be impacted by an upper limit of detection and the true levels of exposure may be higher than reported. Finally, our measurements are for the kitchen concentrations of $PM_{2.5}$ and ultrafine particles and may not capture a person's true exposure that could be measured with personal monitoring.

Conclusions

This study is the first to characterize 24-hour concentrations of both time-resolved $PM_{2.5}$ and ultrafine particles from traditional and improved cookstoves. Our results of high correlations between 24-hour averages and sub-daily concentrations, indicate that monitoring 24-hour average concentrations in similar rural settings may be a reliable and cost-effective method to evaluating household-level concentrations of $PM_{2.5}$ and ultrafine particulate matter. We observed differences in correlations in $PM_{2.5}$ mass and PNC by stove type; additional research is needed to understand how the relationship between $PM_{2.5}$ mass and ultrafine particle concentrations may differ by cookstove types, especially given the potential differences in health impacts of these small particles. Handheld, portable, instrumentation for monitoring ultrafine particles are useful in the field setting and standardized protocols should be developed for use in additional field settings. Future studies would benefit from conducting personal monitoring of ultrafine particle exposures to include in health models.

Figure 4.1: Left: DiSCmini instrument used to collect ultrafine particle number concentration. Right: Example set-up of DiSCMini and pDR monitors.

Table 4.1: Kitchen Characteristics of Study Homes in Rural Honduras			
	N*	Mean	SD
Stove Type			
Kitchen Volume (m^3)	36	35.4	15.4
Number of Walls	36	4.0	0.0
Number of Windows	36	1.1	0.7
Number of Doors	36	1.6	0.7
Number of People Cooked For	47	5.5	2.5
Number of Times Cooked	47	3.1	0.88
		N	%
Wall Material	36		
Mud (adobe)		13	0.3
Stuccoed adobe		16	0.3
Wood/sticks		4	0.1
Concrete		3	0.1
Floor Material			
Dirt	36	24	0.7
Concrete		10	0.3
Ceramic tile		3	0.1
Roof Material	36		
Sheet metal		25	0.7
Tiles		12	0.3
Use of Secondary Stove			
Yes	47	12	0.3

*Full sample size is 47; 11 houses had repeated measurements and household characteristics remained the same

Table 4.2: 24-hour Average Real-Time $PM_{2.5}$ and Particle Number Concentration (PNC)						
	$PM_{2.5}$ µg/m^{3*}			PNC (pt/cm^3)		
	All Stoves (27)	*Justa* (N=12)	Traditional (N= 15)	All Stoves (N=44)	*Justa* Cookstoves (N=17)	Traditional Cookstoves (N=27)
Mean	196	69	297	1.2E+05	9.1E+04	1.3E+05
Median	91	52	176	8.5E+04	6.3E+04	1.3E+05
Min	9	9	16	4.4E+02	2.5E+04	4.4E+02
25th Percentile	40	30	47	3.8E+04	4.0E+04	3.3E+04
75th Percentile	195	104	262	1.8E+05	1.2E+05	2.0E+05
Max	1438	158	1438	4.1E+05	2.4E+05	4.1E+05
Standard Deviation	329	50	417	1.0E+05	6.9E+04	1.1E+05

Reduced Sample Among Households that Have Both $PM_{2.5}$ and PNC						
	$PM_{2.5}$ µg/m^{3*}			PNC (pt/cm^3)		
	All Stoves (24)	*Justa* (N=12)	Traditional (N= 12)	All Stoves (N=24)	*Justa* Cookstoves (N=12)	Traditional Cookstoves (N=12)
Mean	142	69	215	9.5E+04	8.1E+04	1.1E+05
Median	66	52	94	6.2E+04	5.5E+04	8.0E+04
Min	9	9	16	1.9E+04	2.5E+04	1.9E+04
25th Percentile	30	30	41	3.8E+04	3.8E+04	3.8E+04
75th Percentile	147	104	237	1.4E+05	8.5E+04	1.6E+05
Max	1093	158	1093	2.6E+05	2.4E+05	2.6E+05
Standard Deviation	228	50	307	7.9E+04	7.1E+04	8.6E+04
*Corrected for gravimetric $PM_{2.5}$						

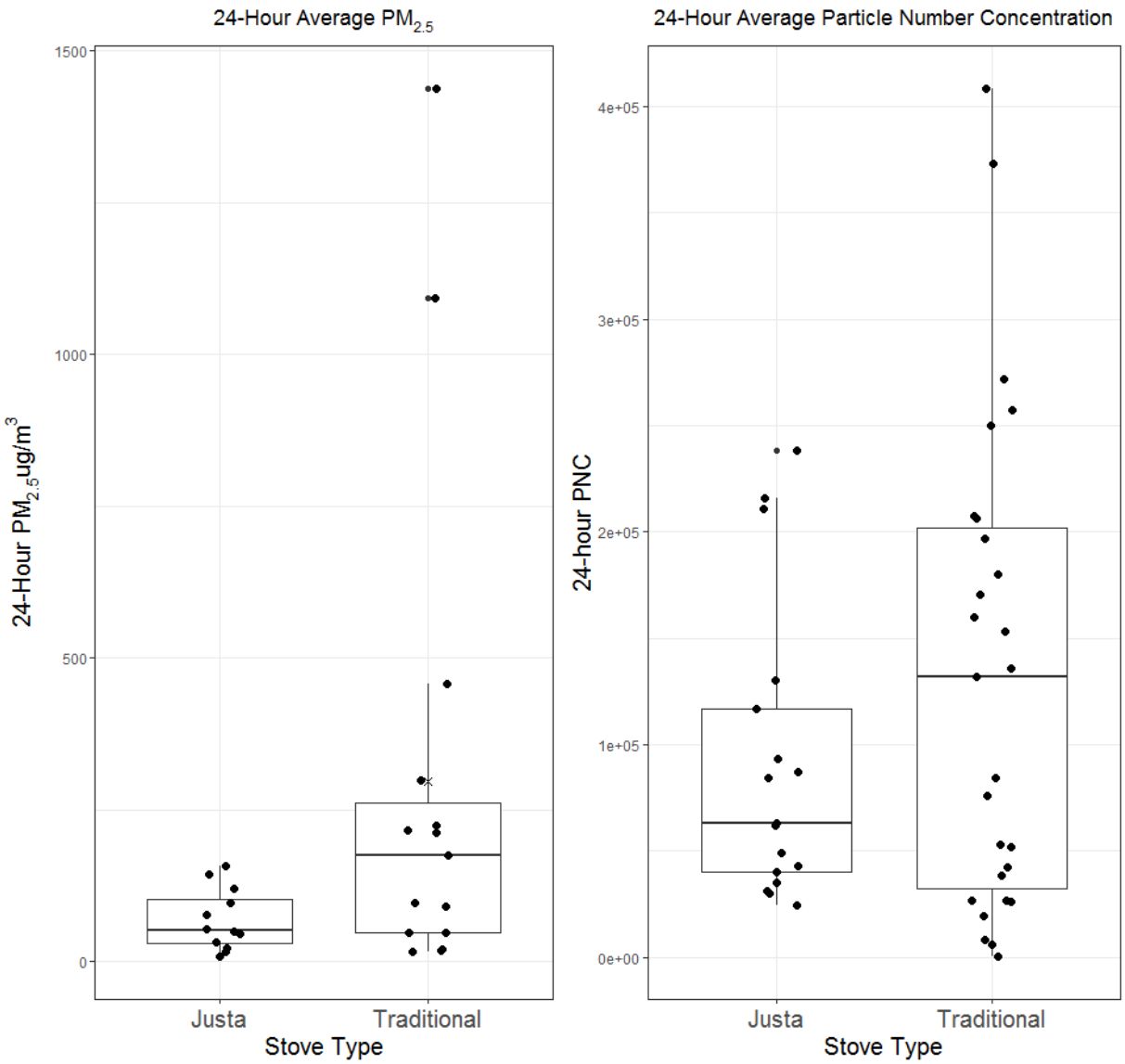

Figure 4.2: Distributions of 24-hour $PM_{2.5}$ concentrations (N=27) and 24-hour particle number concentration (N=44) for traditional and cleaner-burning Justa cookstoves in rural Honduras. Black dots represent the observed concentrations

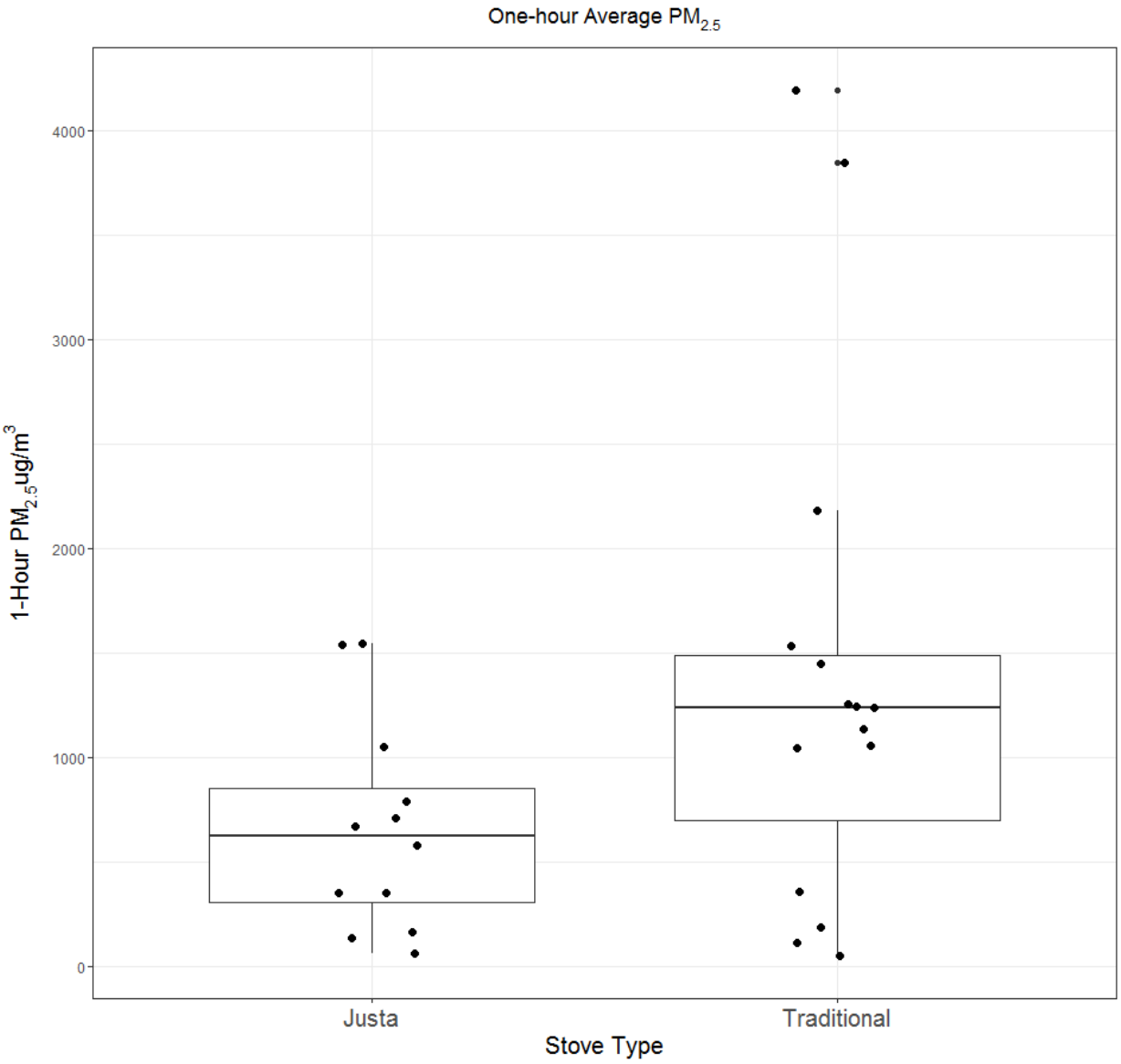

Figure 4.3: 1-Hour Maximum $PM_{2.5}$ for traditional and improved Justa stoves (N = 27) in rural Honduras

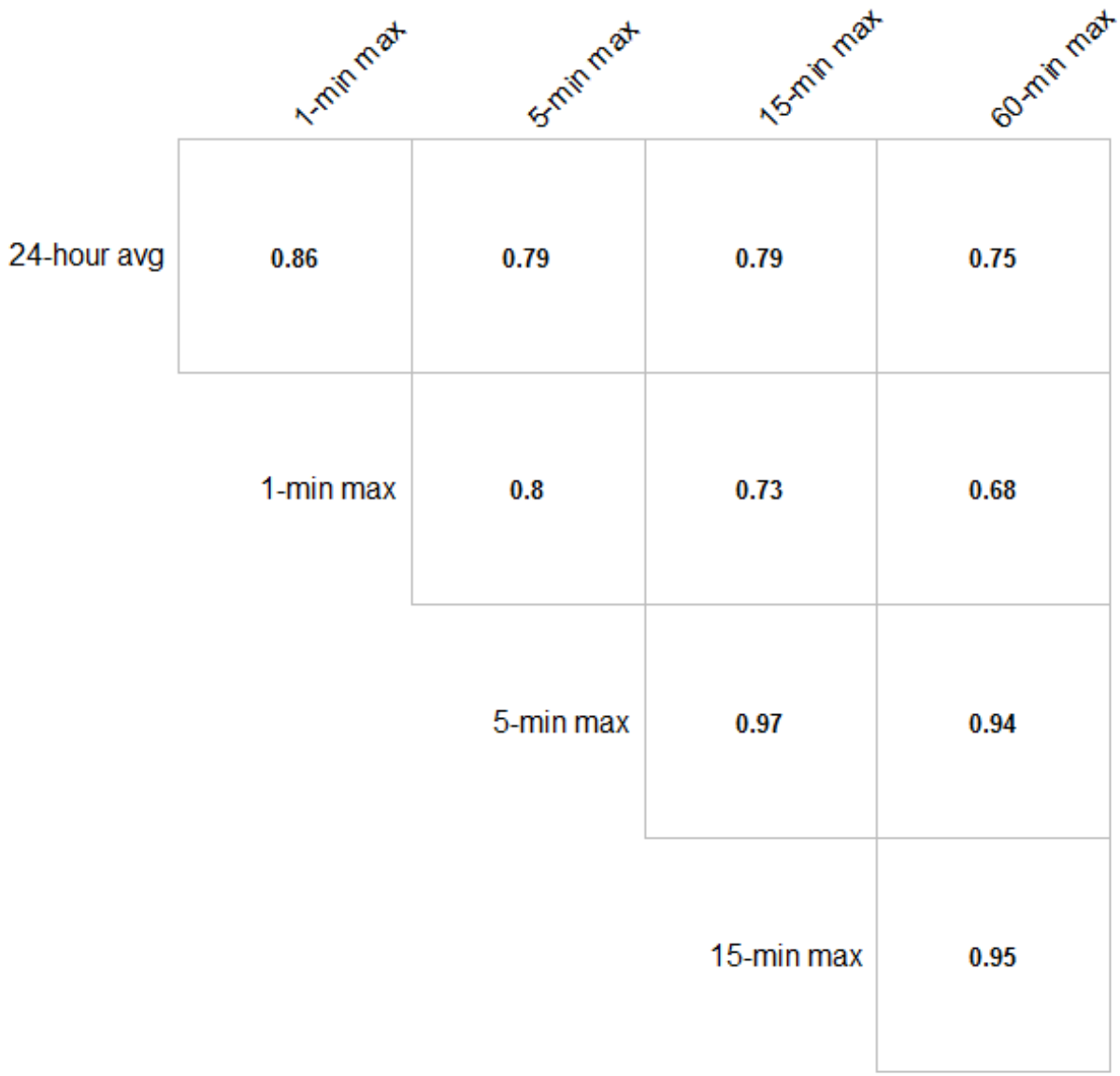

Figure 4.4: Spearman's rho correlation matrix of averaging windows for $PM_{2.5}$ (N=27)

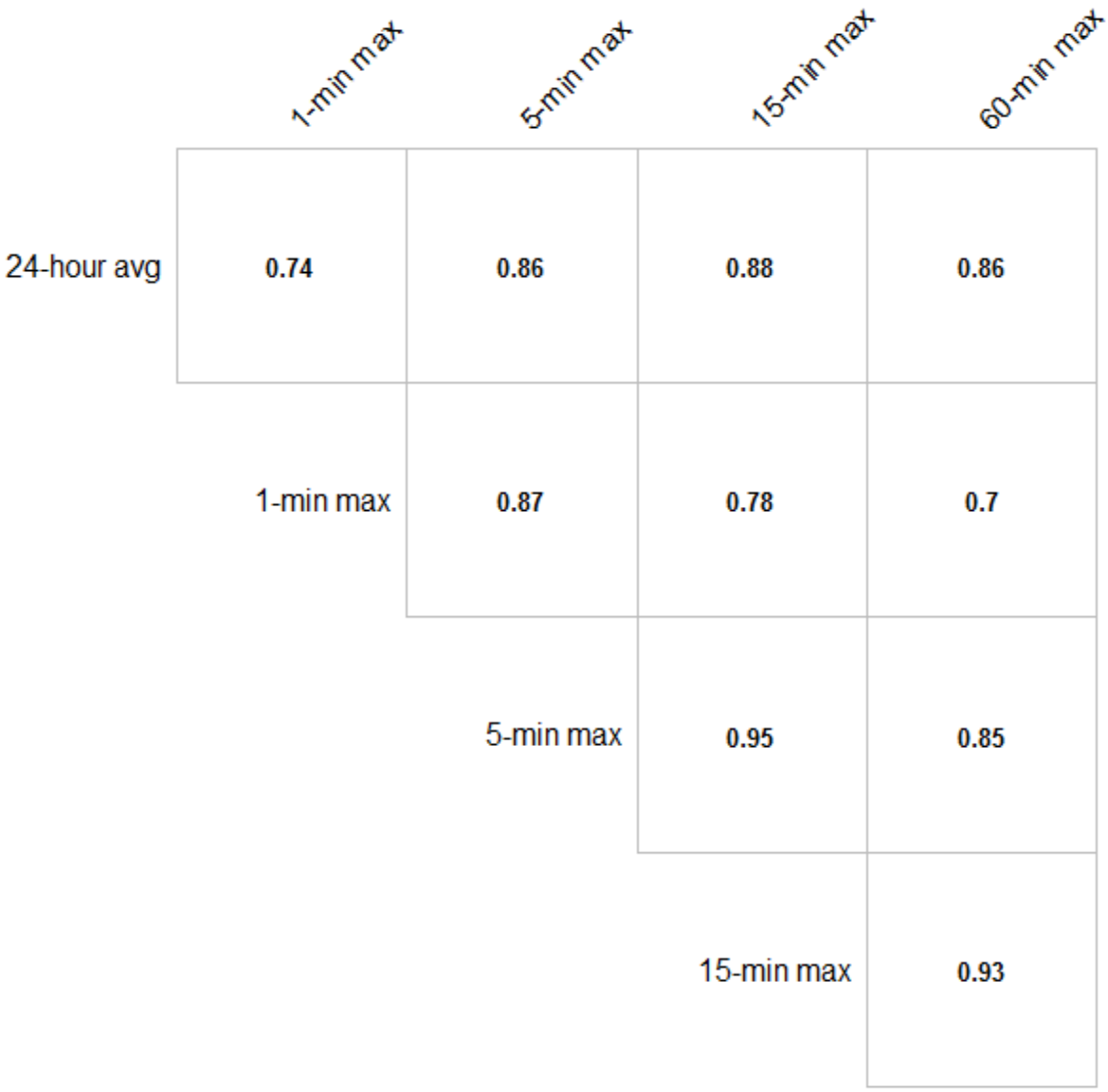

Figure 4.5: Spearman's rho correlation matrix of averaging windows for PNC (N=44)

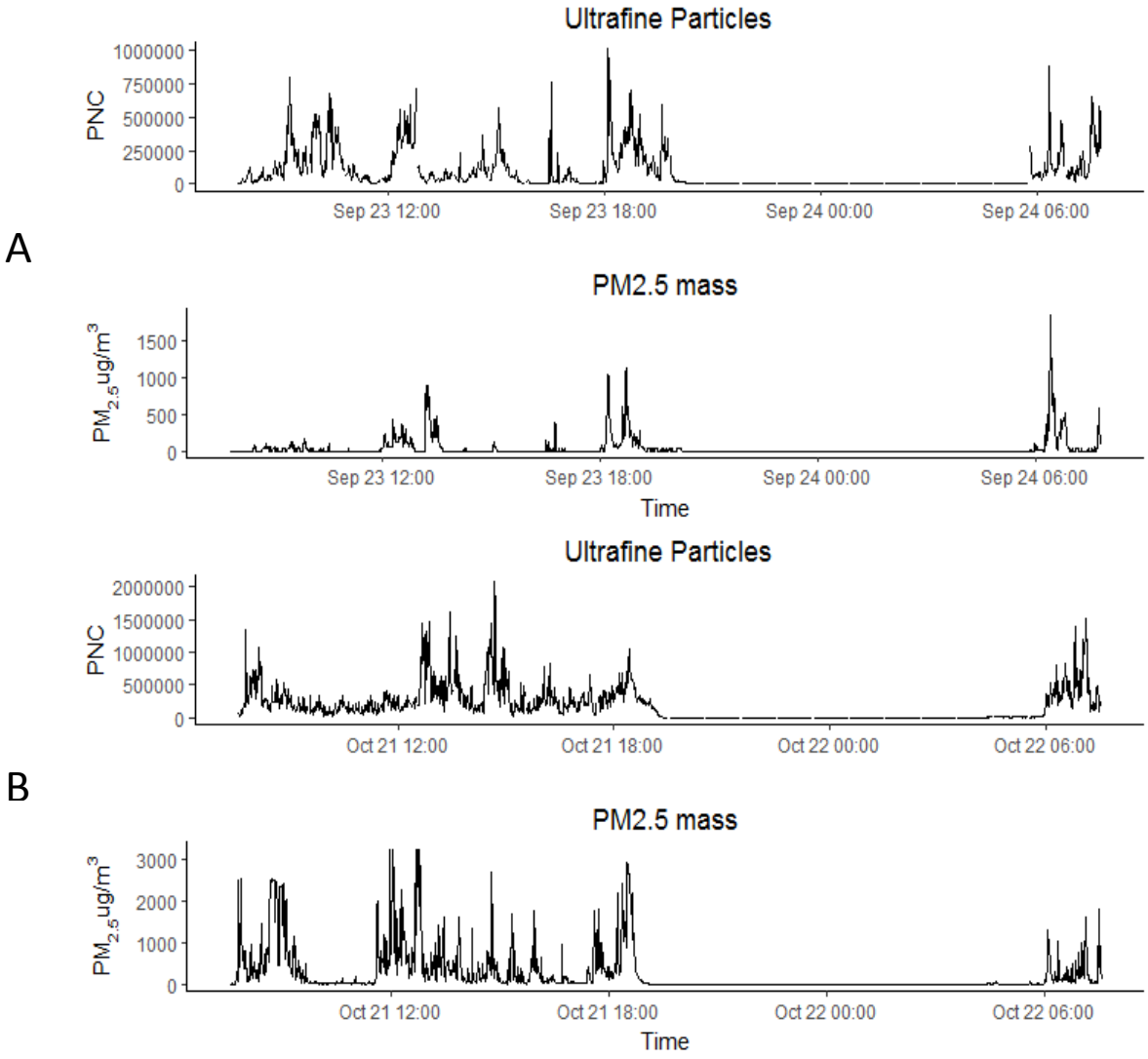

Figure 4.6: Example of real-time minute kitchen concentrations of PNC and $PM_{2.5}$ mass as 24-hour time series. (A: Improved Justa stove, B: Traditional stove

Chapter 5: Exposure to household air pollution from biomass cookstoves and levels of fractional exhaled nitric oxide (FeNO) among Honduran women

Summary

Background: Household air pollution is estimated to be responsible for nearly three million premature deaths annually. Fractional exhaled nitric oxide (FeNO) may improve the limited understanding of the association of household air pollution and airway inflammation.

Methods: We evaluated the cross-sectional association of FeNO with exposure to household air pollution (24-hour average kitchen and personal fine particulate matter and black carbon; stove type) among 139 women in rural Honduras using traditional stoves or cleaner-burning *Justa* stoves. We additionally evaluated the effect modifying role of age on the observed relationship.

Results: Results were generally consistent with a null association; we did not observe a consistent pattern for interaction by age.

Conclusion: Evidence from ambient and household air pollution regarding FeNO is inconsistent, and may be attributable to differing study populations, exposures, and FeNO measurement procedures (e.g., the flow rate used to measure FeNO).

Introduction

Exposure to household air pollution from the combustion of solid fuels was estimated to be responsible for 2.5 million deaths and 77.2 million DALYS (disability-adjusted life years) in 2016 (Gakidou et al. 2017). The incomplete combustion of solid fuels used for cooking and heating, such

as wood or crop residue, emits extremely high levels of particulate matter (PM) and black carbon (Roden et al. 2009; Jetter et al. 2012), among other pollutants (Naeher et al. 2007). The resulting household air pollution is associated with adverse health outcomes including chronic obstructive pulmonary disease (COPD), lung cancer, adult lower respiratory infections, and cardiovascular disease (Smith et al. 2014a; Forouzanfar et al. 2016). Household air pollution is a modifiable exposure, and cleaner-burning cookstove technologies have demonstrated the potential to increase cooking efficiency and reduce human exposure to $PM_{2.5}$ (fine particulate matter) by 50% or more (Bruce et al. 2015).

The underlying mechanisms of pulmonary diseases associated with air pollution are not well understood; however, evidence suggests that exposure may result in increased reactive oxygen species and production of proinflammatory cytokines, leading to airway inflammation (Bernstein et al. 2004; Holgate et al. 2003; van Eeden et al. 2001). Previous household air pollution studies have focused on COPD, acute lower respiratory diseases, and forced expiratory volume; however, other pulmonary impacts, such as asthma and airway inflammation, have not been well studied.

Fractional exhaled nitric oxide (FeNO) measured in human breath is a non-invasive method to assess subclinical airway inflammation (Dweik et al. 2011). A measure of FeNO quantifies nitric oxide (NO) as an indication of eosinophilic inflammation initialized by cytokines and Type 2 helper cells (Th2) (Fahy 2009; Zamora, Vodovotz, and Billiar 2000; Possa et al. 2013). A measure of FeNO provides unique information on airway inflammation that may complement spirometry, which quantifies degree of airflow obstruction (Harnan et al. 2015). Acute and chronic exposure to air pollution may result in airway inflammation, which can be quantified by measuring FeNO. Evidence

for an association between exposure to ambient air pollution and measured FeNO remains mixed (Adamkiewicz et al. 2004; Dubowsky et al. 2006; Dubowsky Adar et al. 2007; Van Amsterdam et al. 1999; Modig et al. 2014; Huang et al. 2012; Lars Barregard et al. 2006; Sehlstedt et al. 2010; Strak et al. 2010; Riddervold et al. 2012; Muala et al. 2013; Yoda et al. 2014). Strong evidence exists for association between exposure to household air pollution and respiratory disease such as COPD and lung cancer, while evidence for an association with asthma is inconclusive (Torres-Duque et al. 2008; Po, FitzGerald, and Carlsten 2011; Schei et al. 2004; Kraai et al. 2013; Wong et al. 2013; Oluwole et al. 2017). To our knowledge, only one study has assessed the association between household air pollution and FeNO, reporting a small increase in FeNO (2 ppb) immediately after cooking (Pollard et al. 2014).

Measures of FeNO have the potential to provide insight into airway inflammation and respiratory disease in household air pollution studies when clinical disease outcomes are unavailable. Our objective was to evaluate the cross-sectional association of exposure to household air pollution (measured personal concentrations and kitchen concentrations of air pollutants and stove type) with exhaled nitric oxide in adult women in rural Honduras using traditional and cleaner-burning *Justa* stoves; we additionally evaluated the effect modifying role of age on the observed relationship.

Methods

All study protocols were approved by the Colorado State University Institutional Review Board. All study participants provided informed consent and received food items worth $5 U.S dollars.

Study Setting

The study was conducted in nine communities surrounding the town of La Esperanza, Honduras. La Esperanza, located in the mountainous region of Western Honduras, is home to approximately 15,000 people. Our target population included all female primary cooks who used a traditional cookstove or a cleaner-burning *Justa* cookstove (See Figure 1). Traditional cookstoves in our population are typically self-built wood-burning stoves, with a metal griddle, large combustion chamber, and possibly a chimney. The cleaner-burning *Justa* stove is a common wood-burning cleaner-burning stove in Latin America with a rocket-elbow combustion chamber, chimney, and metal griddle suited to making tortillas.

Participants

The study team held local community meetings in villages surrounding La Esperanza and presented detailed information regarding the study to the community members. From 500 households, we selected a convenience sample and visited 170 households from February 9th-April 30th 2015. We recruited one female cook per household that met the following eligibility criteria; age 25-56, non-smoker, not pregnant, and ownership a traditional cookstove or *Justa* cookstove at least 4 months prior to the interview. Upon visitation, eighteen of the 170 households were excluded as they did not have a female who meet the eligibility criteria. Two women chose not to participate in the study. We enrolled a total of 150 women into the study.

Exposure to Household Air Pollution

We assessed exposure to household air pollution using stove type (traditional or *Justa*) and by measuring 24-hour average personal concentrations and kitchen concentrations of $PM_{2.5}$ and black carbon. For kitchen concentrations, monitors for $PM_{2.5}$ were placed in the kitchen between

76 and 127 centimetres above the stove, in the area where a woman cooks, and away from open windows and doors. For personal concentration measurements, we placed $PM_{2.5}$ monitors in a small bag that each woman wore throughout the monitoring period except when bathing or sleeping. Women were asked to place the bag next to them (on a table or hanging on the wall) when not wearing it. The inlet was clipped to the shoulder strap at the front of the woman's chest near her breathing zone.

$PM_{2.5}$ was collected on 37-mm PTFE-coated glass fiber filters (Fiberfilm^{TM} T60A20, Pall Corporation, Port Washington KY, USA). The filters were equilibrated at controlled temperature and relative humidity for at least 24-hours and then pre-weighed at Colorado State University (CSU) using the microbalance (Mettler Toledo Microbalance, model MX5, resolution and repeatability of 1-ug). In the field laboratory, filters were placed into Triplex cyclones with a particle cut size of 2.5µm (BGI by Mesa Labs, Butler NJ, USA). Cyclones were attached to pumps (SKC AirCheck XR5000, SCKInc, Eighty Four, PA, USA) with a flow rate of 1.5 L/min. Pumps were pre-calibrated daily using a flow meter (DryCal Dc-Lite, Bios International, Mesa Labs, NJ, USA). We collected one filter blank every two weeks. After collection of the sample filters were stored at -22°C and then transported to CSU, equilibrated for temperature and relative humidity, and post-weighed. The 24-hour average $PM_{2.5}$ concentration was calculated from the change in filter mass adjusted for the average blank mass. We calculated the limit of detection (LOD) for $PM_{2.5}$ as follows: average mass of blanks + 3 times the standard deviation of the sample masses. All samples with a concentration less than the LOD (7 kitchen samples and 7 personal samples) were replaced with a value of LOD/√2. Due to a broken DryCal pump needed to calibrate the equipment used for $PM_{2.5}$, we were unable to gather PM exposure measures from 41 houses. In addition, other

samples were excluded from analysis due to; AirCheck pumps ran for less than 75% of the intended time (<18 hours) (three personal and two kitchen samples); faulty post-weight (one personal sample); missing post-calibration data in the field (one kitchen sample).

Black carbon concentrations were estimated based on the optical transmission of light through the air sampling filters (Hansen et al, 1984) using a transmissometer (model OT-21, Magee Scientific, USA). Transmission data were converted to mass concentrations based on published mass-absorption values for combustion aerosol (Chylek et al, 1981) and corrected for a filter loading artefact that leads to an underestimation of the estimation at high sample loading (Kirchstetter and Novakov, 2007). The limit of detection was estimated to be 0.86 $\mu g/m^3$, which corresponds to three times the standard deviation of 54 blank samples (additional blank filters were used from field sampling campaigns conducted within the same year to estimate the reference values for the transmissometer since pre-sampling transmission data were not collected on sample filters). Values below the LOD (kitchen: n=3; personal: n=10) were substituted by LOD/√2. Detailed information on black carbon is available as supplementary materials.

Fractional Exhaled Nitric Oxide

FeNO was measured at a flow rate of 50 ml/s within a range of 5 to 300 ppb using a NIOX MINO (Version 9, Aerocrine AB, Solna, Sweden). Each participant completed the FeNO measurement on the morning after the 24-hour exposure assessment. Participants stood upright, emptied their lungs, inhaled steadily through the NIOX MINO, and then exhaled at a slow and steady rate for 10 seconds.

Two participants had a value for the FeNO below the limit of detection (LOD) of 5 ppb; we replaced these values with the limit of detection divided by the √2. There were no values above 300 ppb.

Covariate Assessment

Questionnaires in Spanish were administered to obtain demographic data and anthropometric information in the homes of participants. Responses were entered into the electronic data collection system, Open Data Kit (Brunette et al. 2013). As indicators of socioeconomic status, we measured the number of beds per person in the household, years of formal education, electricity availability, number of assets (cars, bikes, motorbikes, televisions, radios, refrigerators, sewing machines, electricity) and a dietary diversity score for each participant. To determine an individual's dietary diversity score women were asked to report all food they had eaten in the previous 24-hour period including the number of portions (Arps 2011). The final dietary diversity score was a sum of the number of food groups a woman had eaten at least one portion of in the past 24 hours, ranging from 1 to 10. Elevation of the household was measured using Maps.me, a cell-phone GPS application (My.com B.V., Version 6.5.3).

The body mass index (BMI) (kg/m^2) and waist-to-hip ratio was measured for each woman as measures of obesity. Women self-reported symptoms of nose irritation, cough, mucus, and difficulty breathing at the time of our visit. Women were noted to have exposure to second-hand smoke if there were any smokers in the household. Physical activity was assessed by obtaining information on the number of hours per day and number of days per week women performed particular tasks (cut and carried wood, ground corn, washed clothes, milked cows, worked in the field, carried heavy items or children, walked normally, walked uphill, and sat relaxing). The

number of hours dedicated to each activity was multiplied by a corresponding metabolic equivalent (MET) and summed over a week to evaluate overall physical effort (Ainsworth et al. 2011).

Statistical analysis

Data were analysed using SAS® software version 9.4 (SAS Institute, Inc., Cary, NC, USA). We used descriptive statistics, such as frequencies and relative frequencies, to summarize the exposure measures, health measures, and covariates for all participants who had a FeNO value.

We calculated Spearman correlation coefficients for the kitchen and personal $PM_{2.5}$ and kitchen and personal black carbon. We used linear regression to assess the association between age and FeNO and height and FeNO. In addition, we evaluated the association between self-reported health symptoms and FeNO using linear regression, adjusting for a-priori confounders age, height, waist-to-hip ratio and dietary-diversity score.

We used separate linear regression models to evaluate the association between stove type and FeNO and between each of the four measured pollutants (kitchen $PM_{2.5}$, personal $PM_{2.5}$, kitchen black carbon, and personal black carbon) and FeNO. FeNO and pollutant measurements were log transformed to meet model assumptions. We chose potential confounders based on a-priori knowledge (A.-C. Olin 2006; Dressel et al. 2008). These included age, height, a measure of obesity (BMI or waist-to-hip ratio), and a measure of socio-economic status (years of education, beds per person, electricity status, number of assets, and dietary diversity score). We evaluated the crude association between FeNO and the various options for confounding by obesity and socio-economic status (SES). Among the obesity and socio-economic status options, the variable with the strongest crude association with FeNO was chosen for inclusion in the model. All final

models were adjusted for age, height, waist-to-hip ratio, and dietary diversity score as a measure of SES (Savy et al. 2006).

We also assessed additive interaction between air pollution concentrations and age using a dichotomous age variable (less than 40 years and older or equal 40 years old) by including a multiplication term in both crude and adjusted models (Clark and Peel 2014). In additional sensitivity analyses, we evaluated for confounding using additional alternative measures of obesity (weight and BMI) and socioeconomic status mentioned above. We also conducted the analysis after removing five participants who reported exposure to second-hand smoke and after removing persons who reported having a respiratory symptom at the time of measurement (difficulty breathing, sore throat, mucus, tight chest, or cough). Finally, we removed the upper and lower 5% of FeNO values to assess the sensitivity of the model results to extreme values. In addition, we conducted a sensitivity analysis removing all persons who reported having a respiratory symptom at the time of measurement (difficulty breathing, sore throat, mucus, tight chest, or cough).

Results

A total of 150 women completed the study; 139 had FeNO measurements, 98 had measurements of FeNO, $PM_{2.5}$, and black carbon. Baseline population characteristics are presented in Table 1. The average age of women in the study was 37.1 years (SD: 9.1), average BMI was 25.8 kg/m^2 (SD: 4.2), and about half the population (n=66) had less than 6 years of education. Age, height, waist-to-hip ratio, and diet diversity score were similar between the two stove type groups. Years of school varied somewhat between the two stove groups, with more traditional stove users having less than 6 years of education (53.5%) compared to *Justa* stove users (42.4%).

Fractional exhaled nitric oxide values ranged from 3.5 ppb to 95 ppb, with a mean of 17.9 ppb and median of 15.0 ppb (standard deviation [SD]:12.1). Among traditional stove users, mean FeNO was 17.4 ppb and the median was 14.5 ppb (SD: 10.8), while *Justa* stove users had a mean FeNO of 18.5 ppb and median 16.0 ppb (SD: 13.4). Of the 11 women who did not complete the FeNO measurement, eight women attempted the measurement but were not successful in maintaining their exhaled breath after more than eight attempts. In addition, three women did not attempt the FeNO measurement due to recent surgery or stroke. The 11 women excluded from the analysis had similar exposures to the rest of the sample population.

The four 24-hour continuous pollutant measures were strongly correlated. Within pollutants, there was a positive correlation between kitchen concentrations and personal concentrations to $PM_{2.5}$ (0.80) and kitchen and personal black carbon (0.77). $PM_{2.5}$ and black carbon exposures were correlated among kitchen measurements (0.89) and personal measurements (0.78). Twenty-four hour average concentrations of each pollutant are shown in Table 2. As expected, kitchen $PM_{2.5}$ was higher than personal $PM_{2.5}$ with means of 254 $\mu g/m^3$ (SD: 329) and 100 $\mu g/m^3$ (SD: 70) respectively. The same pattern holds for kitchen and personal black carbon. In addition, women who owned traditional stoves were exposed to higher concentrations of each of the two pollutants than women who owned *Justa* stoves.

We did not observe associations between age or height and FeNO (Table 3). Several self-reported respiratory symptoms were associated with increasing FeNO (Table 3). For example, after adjusting for age, height, waist-to-hip ratio and dietary diversity score, women who reported having a cough at the time of the assessment had a 78% higher FeNO level than those who did not

report a cough (95% CI: 37.9%, 129.9%). Similarly, women who reported having current mucus had a 46% higher FeNO level (95% CI: 9.6%, 93.7%) than those who did not report current mucus.

Crude and adjusted linear regression results for household air pollution are presented in Table 4. Given the log-transformed dependent variables (FeNO) and the log-transformed independent continuous pollution exposure variables, we present the results for continuous exposures as the percent increase or decrease in FeNO for a 25% increase in pollutant exposure. Overall results for the continuous pollution measurements were consistent with a null association. For example, a 25% higher personal $PM_{2.5}$ concentration was associated with a 0.6% higher FeNO level (95% CI: -3.39-4.82). The estimates for categorical stove type are presented as a percent increase in FeNO as compared to the reference group (*Justa* stove). Again, the results were consistent with a null association. In Table 5.4, we also present a sensitivity analysis removing the top and bottom 5% of FeNO values. The results demonstrate that the adjusted models were somewhat sensitive to the highest and lowest FeNO values, but overall it is difficult to determine the impact, given the wide confidence intervals. In our interaction analysis, presented in Table 5, participants who were 40 years or older tended to have a larger percent increase in FeNO in relation to exposure to household air pollution compared to the younger participants, although the evidence for interaction was not strong. The additional sensitivity analyses had similar results (results not presented).

Discussion

Our study provided a unique opportunity to examine associations between measures of exposure to household air pollution and FeNO, a measure of airway inflammation. We add to the limited body of evidence investigating these associations among adults; particularly, our study is

the first (to our knowledge) to examine the association of FeNO and household air pollution among healthy adult women using direct exposure measurements of $PM_{2.5}$ and black carbon.

We observed that although traditional stove users were exposed to an average of 40% higher levels of fine particulate matter compared to *Justa* stove users, the 24-hour measures of pollutant exposure for both stove users surpassed the concentration guideline for $PM_{2.5}$ of 25 $\mu g/m^3$ 24-hour average set by the World Health Organization (WHO) (World Health Organization 2006a) (Figure 3). It is critical that cleaner-burning cookstove exposure levels are reduced as close as possible to the WHO guidelines in order observe population-level improvements on health outcomes. The median FeNO levels observed in our population are slightly higher (14.5 ppb among traditional stove users and 16.0 ppb among *Justa* stove users) than the levels seen in a similar study among a sample of women in Peru using biomass burning cookstoves (10 ppb among traditional stove users and 10.5 ppb among cleaner-burning stove users) (Pollard et al. 2014). Pollard et al. reported a non-meaningful 2 ppb increase in exhaled nitric oxide among all participants in rural households immediately after a cooking event; however, they did not directly measure pollutant concentrations.

Overall, we did not observe evidence supporting the hypothesis that increased exposure to household air pollution was linked to airway inflammation as measured by FeNO, after adjusting for potential confounders. Evidence from studies on associations of ambient air pollution with FeNO have been inconsistent (Dubowsky Adar et al. 2007; Adamkiewicz et al. 2004; Huang et al. 2012; Strak et al. 2010; Yoda et al. 2014; Sehlstedt et al. 2010; Riddervold et al. 2012; Muala et al. 2013). For example, although positive associations have been demonstrated between increased levels of ambient $PM_{2.5}$ and black carbon and FeNO among healthy adults (Adamkiewicz et al.

2004; Dubowsky Adar et al. 2007; Huang et al. 2012), several studies reported null results similar to ours (Yoda et al. 2014; Strak et al. 2010). Additionally, several chamber and panel studies of direct exposure to wood smoke and FeNO have also reported results that do not support an association. (Riddervold et al. 2012; Sehlstedt et al. 2010; Muala et al. 2013; Stockfelt et al. 2012).

FeNO measured at a constant flow rate has been highlighted as a simple, reproducible, non-invasive biomarker of eosinophilic airway inflammation for use in air pollution studies. The inconsistent results observed in the literature may be due in part to the technology available to assess FeNO. Varying the flow rate at which FeNO measurements are collected may allow researchers to partition the source of nitric oxide into two distinct anatomical regions; the proximal and distal airways (Tsoukias & George 1998; Eckel & Salam 2013). The current ATS standard is for a flow rate of 50 ml/sec, providing information from the proximal airways (Hogman et al. 1997; Dweik et al. 2011; Silkoff et al. 1997). FeNO measured or calculated for a higher flow rate, such as 270 ml/sec ($FeNO_{270}$), may be associated with airway inflammation from the distal compartment (S. P. Eckel and Salam 2013; George et al. 2004).

Previous studies examining the association between air pollution and FeNO at different flow rates have reported inconsistent results for the proximal and distal airways, indicating potential mechanistic differences of exposure (L Barregard et al. 2008; Stockfelt et al. 2012). For example, a cohort study among 5,841 Swedish adults explored the association between ozone and PM_{10} on FeNO measured at 50 ml/sec and 270 ml/sec, respectively (Modig et al. 2014). The authors observed no clear effect of PM_{10} on either measure of FeNO, however after adjusting for other pollutants, they observed an interquartile range increase in 120-hour ozone was associated with a 5.1% (95% CI: 1.7%-8.5%) higher $FeNO_{270}$ measurement and associated (although not

significantly) with a 3.6% (-0.4% to 3.4%) higher $FeNO_{50}$ (Modig et al. 2014). In addition, a wood smoke chamber study by Barregard et al. 2008 reported a net increase in $FeNO_{270}$ from distal airways three hours post exposure, but no increase in $FeNO_{50}$ from proximal airways (L Barregard et al. 2008).

Our study is limited to the approximation of eosinophilic inflammation in the proximal airways measured by a flow rate of 50 ml/sec ($FeNO_{50}$). It may be useful for future studies to assess FeNO associated with the distal airways because $PM_{2.5}$ is small enough to deposit in the distal airways and alveoli (Muhammad T Salam et al. 2012; Brauer et al. 2001). Assessing inflammation that may have a stronger expected association to the distal airways would require measurements of exhaled NO at a different flow rate. For example, the semi-portable electrochemical analyser Hypair FeNO mediansoft Exp'air (50, 100, 150 ml/sec), could be used in the field setting.

The cross-sectional nature of the study design may limit our ability to establish that exposure preceded airway inflammation. We attempted to address this potential limitation by including only women who had been using a cleaner-burning cookstove for more than four months (average length of *Justa* stove ownership was just under two years). Selection bias is not expected given that selection into the study was not likely related to both exposure and FeNO levels. In addition, we believe any exposure measurement error would not be responsible for our null findings. Although we had a relatively small sample size, the association between FeNO and self-reported respiratory symptoms indicates we may have accurately captured airway inflammation as it relates to the presence of symptoms (Dressel et al. 2008; S. A. Kharitonov, Yates, and Barnes 1995; Anna Carin Olin et al. 2010). While we did not see an association between FeNO and age or FeNO and height, as we would have expected based on previous literature, (A. C. Olin, Alving, and

Torén 2004; A.-C. Olin 2006; Anna Carin Olin et al. 2010; Dressel et al. 2008; Pignatti and Spanevello 2016), this may be due to the relatively small range of age and height in our study. For example, our study population only covered adults age 25-56 (mean 37.1 years, SD: 9.1 years). In addition, we observed very little variability in height (mean: 57 inches, SD: 1.8 inches) which may have influenced our inability to capture an association between FeNO and height. Our crude and adjusted linear regression models were not substantially different, indicating that measured confounding was likely not a concern in our study; however measurement error or residual confounding, for example by SES, may still exist. Finally, we did not include questions in our demographic and health survey that would provide insight into the asthma, atopy, or genetic variations the participants. Asthma or atopy status and genetic variations are thought to modify the effect of air pollution on FeNO (M T Salam et al. 2011; Muhammad T Salam et al. 2012; Muhammad T. Salam et al. 2015); similar effect modification could be expected in household air pollution.

In conclusion, we did not observe evidence of increased eosinophilic airway inflammation from exposure to household air pollution. It may be important to consider measurements of this biomarker at differing airflow rates, in well-designed longitudinal studies.

Table 5.1: Population characteristics among nonsmoking primary female cooks using traditional or cleaner-burning *Justa* stoves, rural Honduras (N=139)

	Total (N=139)	Traditional (N=72)	*Justa* (N=67)
	N (%) or Mean (SD) ; range	N (%) or Mean (SD) ; range	N (%) or Mean (SD) ; range
Age (years)	37.1 (9.1); 25-56	38.3 (9.9); 25-56	35.9 (7.9); 25-56
Height (inches)	57.0 (1.8); 53.75-62.5	56.9 (1.9); 53.5-62.5	57.2 (1.7); 54.0-61.3
Waist-to-hip ratio	0.87 (0.06); 0.7-1.1	0.88 (0.06); 0.74-1.09	0.86 (0.05); 0.8-0.1
Body mass index (kg/m^2)	25.8 (4.2); 17.6-37.5	25.5 (4.4); 17.5-37.5	26.2 (3.8); 18.2-33.6
Physical activity (MET)[1]	212 (103); 31-542	216 (110); 31-542	209 (95); 46-444
Elevation (meters)	1916 (107); 1729-2157	1896 (98); 1736-2152	1938 (112); 1729-2157
Beds per person[2]	0.52 (0.18); 0.2-1.0	0.50 (0.17); 0.2-1.0	0.55 (0.19); 0.25-1.0
Diet diversity score[3]	6.1 (1.7); 2-10	6.1 (1.7); 3-10	5.9 (1.6); 2-10
Years of education			
Less than six years	66 (48.1%)	38 (53.5%)	28 (42.4%)
Six or more years	71 (51.8%)	33 (46.5%)	38 (57.6%)
Years spent cooking with biomass	25.6 (9.9); 7-50	26.6 (10.8); 7-49	24.5 (8.8); 9-50
Self-reported exposure to secondhand smoke	5 (3.6%)	5 (3.6%)	0 (0%)
Fractional exhale nitric oxide (ppb)	17.9 (12.1); 3.5-95	17.4 (10.8); 3.5-62	18.5 (13.4); 5-95

PPB, parts per billion; SD, Standard Deviation

[1]*Physical Activity: The sum of metabolic equivalents including the following self-reported activities: cut wood, grind corn, wash clothes, milk the cow, work in the field, carry a heavy weight and walk normally outside the house. For each activity the number of hours per week was calculated and multiplied with the corresponding metabolic equivalent (MET) from the Compendium of Physical Activities (Ainsworth et al. 2015).*

[2] *Total N=138; Traditional = 72; Justa = 67*

[3] *Dietary Diversity Score: The sum of the number of food categories consumed in the past 24-hours (10 categories); used as an indicator of socioeconomic status* (Savy et al. 2006)

Table 5.2: 24-hour average kitchen and personal fine particulate matter and black carbon concentrations, traditional and Justa stove users, rural Honduras

	All Participants						Traditional Stove Users						*Justa* Stove Users					
	N	Min	25th	Median	75th	Max	N	Min	25th	Median	75th	Max	N	Min	25th	Median	75th	Max
24–hour average kitchen $PM_{2.5}$ *(µg/m³)*	*98*	18	61	116	369	1654	*58*	18	90	172	448	1654	*40*	18	37	68	150	1134
24–hour average personal $PM_{2.5}$ *(µg/m3)*	*98*	18	48	80	138	346	*59*	18	62	112	154	346	*39*	18	39	52	81	174
24–hour average kitchen Black Carbon *(µg/m3)*	*98*	1	8	18	78	1172	*58*	1	14	44	113	1172	*40*	1	4	11	15	469
24–hour average personal Black Carbon *(µg/m3)*	*98*	1	4	7	17	123	*58*	1	6	14	32	123	*40*	1	1	4	8	47

Table 5.3: Estimated crude and adjusted percentage difference in fractional exhaled nitric oxide in relation to measures of current, self-reported symptoms among traditional and *Justa* stove users, rural Honduras

	N	Crude Percent Difference in FeNO	95% CI	Adjusted Percent Difference in FeNO[1]	95% CI
Age (years)[1]	139	<0.1	(-0.2, 0.3)	<0.1	(-0.2, 0.3)
Height (inches)[2]	139	-0.1	(-1.3, 1.1)	-0.01	(-1.2, 1.2)
Cough[3]					
No	118	ref			
Yes	21	78.8	(38.8, 130.2)	78.1	(37.9, 129.9)
Chest Tightness[3]					
No	128	ref			
Yes	11	17.6	(-17.9, 68.3)	19.0	(-17.4, 71.4)
Mucus[3]					
No	121	ref			
Yes	18	47.4	(11.2, 95.3)	45.7	(9.6, 93.7)
Difficulty Breathing[3]					
No	129	ref			
Yes	10	42.1	(-2.0, 105.9)	39.6	(-4.34, 103.7)

Cl: Confidence interval; $PM_{2.5}$: fine particulate matter

[1] Model was adjusted for height, waist-to-hip ratio, and dietary diversity score

[2] Model was adjusted for age, waist-to-hip ratio, and dietary diversity score

*[3] Exhaled nitric oxide was log-transformed. Categorical variable beta coefficients were entered into the formula (e^β-1)*100). The estimates for the categorical measures of exposure can be interpreted as the percent difference in FeNO when comparing those who had the health system to those who did not.*

Table 5.4: Estimated crude and adjusted[1] percentage difference in fractional exhaled nitric oxide in relation to measures of exposure to household air pollution (per 25% increase in 24-hour average measured pollution, or by stove type) among traditional and *Justa* stove users, rural Honduras

	N	Crude Percent Difference in FeNO	95% CI	Adjusted Percent Difference in FeNO[1]	95% CI
24–hour average kitchen $PM_{2.5}$ (µg/m3)[2]	98	0.3	(-2.0, 2.7)	0.4	(-2.0, 2.9)
24–hour average personal $PM_{2.5}$ (µg/m3)[2]	98	0.8	(-3.1, 4.9)	0.6	(-3.4, 4.8)
24–hour average kitchen Black Carbon (µg/m3)[2]	98	-0.1	(-1.8, 1.6)	-0.1	(-1.9, 1.7)
24–hour average personal Black Carbon (µg/m3)[2]	98	<0.0	(-2.1, 1.9)	-0.1	(-2.1, 2.0)
Stove Type[3]	139				
Justa	67	ref		ref	
Traditional	72	-6.5	(-22.9, 13.6)	-6.2	(-23.3, 14.6)
Top and Bottom 5% Removed	N	Crude Estimate	95% CI	Adjusted Estimate	95% CI
24–hour average kitchen $PM_{2.5}$ (µg/m3)[2]	86	0.4	(-1.6, 2.5)	-0.1	(-2.2, 2.1)
24–hour average personal $PM_{2.5}$ (µg/m3)[2]	86	0.8	(-2.5, 4.2)	-0.2	(-3.5, 3.3)
24–hour average kitchen Black Carbon (µg/m3)[2]	86	0.4	(-1.0, 1.9)	<0.0	(-1.7, 1.7)
24–hour average personal Black Carbon (µg/m3)[2]	86	0.2	(-1.5, 1.9)	-0.3	(-2.0, 1.5)
Stove Type[3]	122				
Justa	59	ref			
Traditional	63	5.3	(-10.6, 24.0)	2.4	(-13.2, 20.9)

Cl: Confidence interval; $PM_{2.5}$: fine particulate matter

[1]Models were adjusted for age, height, waist-to-hip ratio, and dietary diversity score

[2]Exhaled nitric oxide and measured pollution were both log transformed. Beta coefficients were entered into the formula ((1.25^ß)-1) and multiplied by 100. We can interpret the estimate of the continuous pollution exposures as a percent increase in exhaled nitric oxide for each 25% increase in exposure. Example: There is a 0.4% higher FeNO level with a 25% higher kitchen $PM_{2.5}$ concentration.

*[3]Exhaled nitric oxide was log-transformed. Categorical variable beta coefficients were entered into the formula (e^ß-1)*100). The estimates for the categorical measures of exposure can be interpreted as the percent difference in FeNO when comparing traditional stove to the reference (Justa stove)*

Table 5.5: Estimates for effect modification by age (dichotomized at the median value of 40 years) for the percentage difference in fractional exhaled nitric oxide in relation to measures of exposure to household air pollution (per 25% increase in 24-hour average measured pollution, or by stove type) among traditional and *Justa* stove users, rural Honduras.[1]

	N	Adjusted Percent Difference[1]	95% CI	P-value for interaction
24–hour average kitchen $PM_{2.5}$ ($\mu g/m^3$)[2]				0.8
Age < 40	66	0.2	(-3.1, 3.5)	
Age ≥ 40	32	0.7	(-3.1, 4.6)	
24–hour average personal $PM_{2.5}$ ($\mu g/m^3$)[2]				0.4
Age < 40	66	-0.6	(-5.4, 4.5)	
Age ≥ 40	32	3.6	(-3.9, 11.6)	
24–hour average kitchen Black Carbon ($\mu g/m^3$)[2]				0.9
Age < 40	66	-0.2	(-2.5, 2.1)	
Age ≥ 40	32	0.05	(-2.7, 2.8)	
24–hour average personal Black Carbon ($\mu g/m^3$)[2]				0.8
Age < 40	66	-0.2	(-2.7, 2.4)	
Age ≥ 40	32	0.4	(-3.1, 3.9)	
Stove Type[3] (traditional compared to *Justa* [ref])				
Traditional				
Age < 40	72	-12.9	(-31.9, 11.3)	0.3
Age ≥ 40	67	10.3	(-21.8, 55.7)	

CI: Confidence interval; $PM_{2.5}$: fine particulate matter

[1]All models adjusted for height, waist-to-hip ratio, and dietary diversity score

[2]Exhaled nitric oxide and measured pollution are both log transformed. Beta coefficients were entered into the formula ((1.25^ß)-1) and multiplied by 100. We can interpret the estimate of the continuous pollution exposures as a percent increase in exhaled nitric oxide for each 25% increase in exposure. Example: There is a 0.2% higher FeNO level with a 25% higher kitchen $PM_{2.5}$ concentration among women less than 40 years old.

*[3]Exhaled nitric oxide was log-transformed. Categorical variable beta coefficients were entered into the formula (e^ß-1)*100). The estimates for the categorical measures of exposure can be interpreted as the percent difference in FeNO when comparing a specific stove type to the reference (traditional stove).*

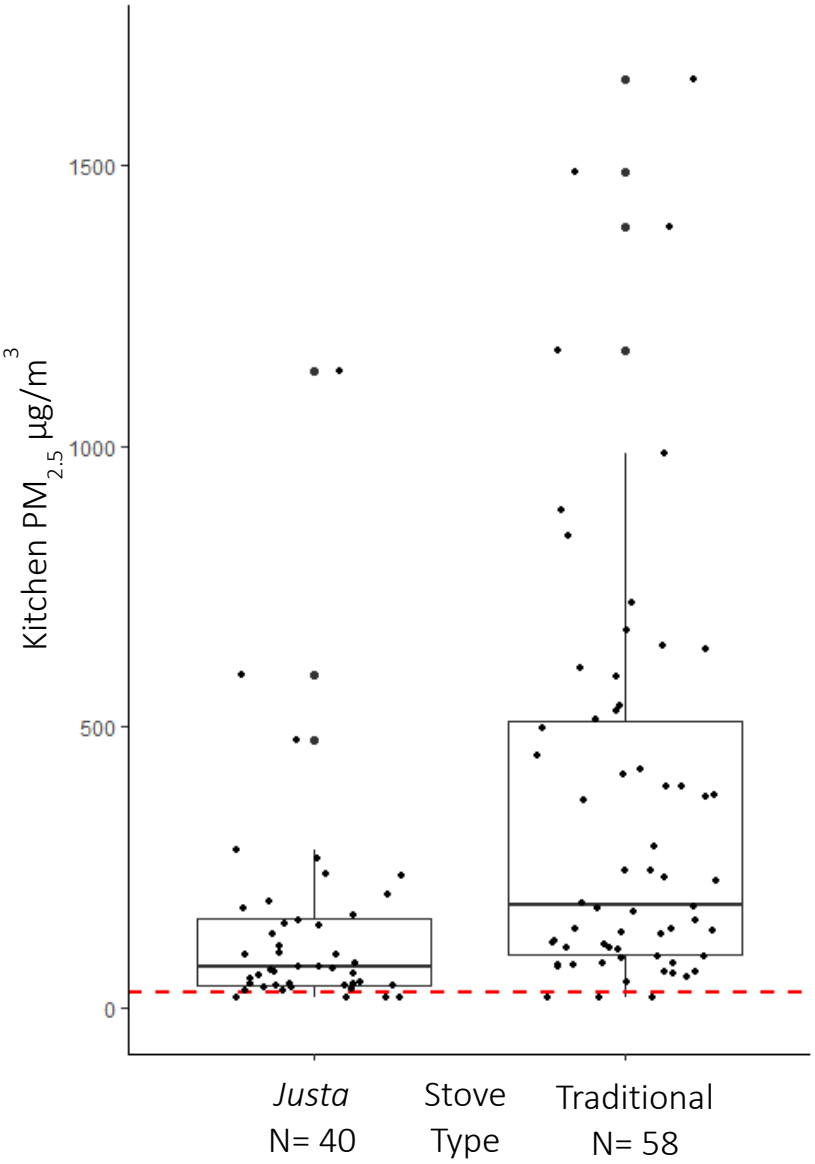

Figure 5.1: 24-hour average kitchen PM2.5 concentrations, Traditional and Justa Stove Users, Rural Honduras (n=98)

$PM_{2.5}$: fine particulate matter. Top and bottom lines of rectangle represent the75th and 25th percentiles. The middle line represents the median. The top whisker denotes the value of the 3rd quartile plus 1.5 times the IQR. The bottom whisker denotes the value of the 1st quartile minus 1.5 times the IQR. The red line indicates the World Health Organization (WHO) 24-hour guideline of 25 µg/m^3

Chapter 6: Household air pollution from wood-burning cookstoves and markers of systemic of inflammation among women in rural Honduras

Summary

Household air pollution from the burning of solid fuels is estimated to cause 2.5 million deaths worldwide each year. Cardiovascular and related disease is suspected to contribute substantially to the burden, although evidence is limited. We evaluated the cross-sectional association of household air pollution with inflammatory markers, as indicators of cardiovascular disease risk, among women in rural Honduras using traditional or cleaner-burning *Justa* stoves.

In a cross-sectional study, we measured 24-hour gravimetric kitchen and personal fine particulate matter ($PM_{2.5}$) and black carbon concentrations for 106 female primary cooks. Markers of systemic inflammation (C-reactive protein [CRP], Serum Amyloid A [SAA], Interleukin 1-β [IL-1 β], IL-8, Tumor Necrosis Factor-α [TNF- α], Intercellular Adhesion Molecule 1 [ICAM-1], and Vascular Cell Adhesion Molecule [VCAM]) were measured from dried blood spots. We used linear regression, adjusting for age, body mass index, education, and number of household assets. We also assessed effect modification by risk factors, including age, obesity, diabetes and hypertension, associated with cardiovascular disease.

The median 24-hour-average kitchen $PM_{2.5}$ concentration was 132 μg/m^3, 25^{th}-75^{th}: 62-374 μg/m^3 (Traditional stoves: 181μg/m^3, 25^{th}-75^{th}: 91-511 μg/m^3; *Justa* stoves: 71 μg/m^3; 25^{th}-75^{th}: 38-159 μg/m^3). Increased concentrations of average 24-hour kitchen and personal $PM_{2.5}$ and black carbon were associated with increased levels of SAA (e.g. a 25% higher personal $PM_{2.5}$ concentration was associated with an 8.3% increase in SAA levels [95% CI (confidence interval):

2.3-14.7]). Similar results were observed for CRP (e.g., a 25% increase in personal $PM_{2.5}$ exposure was associated with a 10.5 % increase in CRP levels [95% CI: 1.2-20.6]). Results for IL-8, IL-1 β, TNF-α, ICAM-1, and VCAM were generally consistent with a null association. We observed inconsistent results for effect modification by several risk factors in the association of exposure and various markers of inflammation.

The results are consistent with air pollution literature and support the hypothesis that exposure to household air pollution is associated with some markers of systemic inflammation, such as CRP and SAA.

Introduction

Short-term and long-term exposure to particulate matter is associated with increased risk for cardiovascular morbidity and mortality (Polichetti et al. 2009; Pope 2000; Franklin, Brook, and Arden Pope 2015; Gold and Mittleman 2013; Newby et al. 2015; Hoek et al. 2013; Atkinson et al. 2014; Robert D Brook et al. 2010). The use of solid biomass fuels, such as wood, dung or crop residue, for cooking results in chronically high levels of exposure to particulate matter and black carbon. The majority of the household air pollution burden of disease is among those living in low and middle income countries (LMIC), where approximately 80% of all cardiovascular deaths also occur (Bowry et al. 2015). Exposure to household air pollution was estimated to be responsible for 77.2 million DALYS (disability-adjusted life years) and 2.5 million deaths in 2016 (Gakidou et al. 2017), with cardiovascular-related illness making up about 16.8% of the disease total burden (Gakidou et al. 2017).

Although there is suggestive evidence that exposure to household air pollution is associated with cardiovascular disease (CVD), much of our understanding relies on the extrapolation of evidence from the fields of ambient air pollution and second-hand smoke (Smith et al. 2014a).

The mechanisms of the association between particulate matter and cardiovascular disease remain unclear, but include potential pathways through systemic inflammation, endothelial dysfunction, and oxidative stress (R. D. Brook et al. 2010; Pearson et al. 2003; Caravedo et al. 2016). One proposed mechanistic pathway of inhaled particles linking particulate matter exposure to CVD begins when inhaled particles are deposited into the lungs. The deposition of particles in pulmonary tissue initiates oxidative stress and the redox-pathways that activate the production of pro-inflammatory cytokines (Franklin, Brook, and Arden Pope 2015). This potential mechanistic pathway is often considered the "spillover" pathway in which oxidative stress mediators produced in the lungs "spillover" into systemic circulation (Franklin, Brook, and Arden Pope 2015).

Clinical biomarkers of cardiovascular disease risk, such as inflammatory markers like cytokines, acute phase proteins, and cellular-adhesion molecules, may provide critical information into disease pathways (Pearson et al. 2003). For example, cytokines, low molecular weight proteins, respond to both acute and chronic inflammation and have been used as clinical markers of cardiovascular disease (Feghali and Wright 1997; Pearson et al. 2003). Acute phase proteins including C-reactive protein (CRP) and Serum Amyloid A (SAA) are produced in the liver during inflammation. Expression of circulating CRP in the blood is an indication of inflammatory activity and predictor of future cardiovascular disease (Ridker 2003; Johnson et al. 2004). Cellular-adhesion molecules, such as Intercellular Adhesion Molecule 1 (ICAM-1) and V*ascular Cell*

Adhesion Molecule 1 (VCAM-1), are increased in endothelial inflammation and raised levels are also associated with various cardiovascular diseases (Teixeira et al. 2014; Blann and Lip 2000). There is toxicological and epidemiological evidence from the field of air pollution, including woodsmoke exposure, that increased levels of particulate matter exposure are associated with increased levels of biomarkers of endothelial and systemic inflammation (Allen et al. 2011; R. D. Brook et al. 2010; W. Li et al. 2016; Vossoughi et al. 2014; Calderón-Garcidueñas et al. 2008; van Eeden et al. 2001; Tsai et al. 2012; Y. Li et al. 2012; Lars Barregard et al. 2006; L Barregard et al. 2008). Observational studies from the field of household air pollution also provide evidence for an association between household air pollution and increased inflammatory markers (Caravedo et al. 2016; Dutta, Ray, and Banerjee 2012).

Chronic diseases, such as cardiovascular disease, are difficult to study in household air pollution research. Such research requires a large sample size, is time-consuming, costly, and impractical in many field settings (McDade, Williams, and Snodgrass 2007). In this cross-sectional study among rural Honduran women, we used a minimally invasive method of finger-stick dried blood spots to assess a comprehensive biomarker panel of systemic inflammation and 24-hour average exposure to household air pollution. Additionally, we evaluated the association between household air pollution and systemic inflammation by risk factors associated with cardiovascular disease risk including age, obesity, diabetes status, and high blood pressure (Dubowsky et al. 2006). Our goal was to utilize reproducible, cost-effective, subclinical markers of cardiovascular disease risk in a field setting to improve our understanding of the association between household air pollution exposure and cardiovascular disease risk (Rajagopalan and Brook 2012; E. M. Miller and McDade 2012).

Methods

Study protocols were approved by the Colorado State University Institutional Review Board.

Study Setting

The study was conducted in nine rural communities surrounding a small town of La Esperanza, Honduras. La Esperanza is home to approximately 15,000 people and located in the mountainous region of Western Honduras. Electricity is scarce in the rural villages around La Esperanza and households continue to utilize cookstoves with firewood for their cooking needs. Traditional cookstoves in the communities are typically self-built wood burning stoves, with a metal griddle, and a chimney. Improved *Justa* cookstoves are a common wood-burning stoves in Central America. The *Justa* design includes a rocket-elbow combustion chamber, metal griddle, and chimney (Figure 1).

Participants

The study team visited villages surrounding the town of La Esperanza and presented detailed information about participation in the research study. From 500 households, we selected a convenience sample and visited 170 households from February 9th-April 30th 2015. The female primary cook in each household was recruited to participate in the study. Enrollment criteria required that the primary cook own a traditional or improved *Justa* cookstove (built at least 4 months prior to the interview) and be age 25-56 years, a non-smoker, and not pregnant. Our final sample size was 150 households; eighteen households were excluded as they did not have a female primary cook who met the eligibility criteria and two women chose not to participate. Study

participants provided informed consent and received an incentive of USD$5 worth of food items for their participation.

Exposure to Household Air Pollution

Gravimetric $PM_{2.5}$ was measured using Triplex cyclones with a particle cut size of 2.5µm (BGI by Mesa Labs, Butler NJ, USA). Air was pulled through the cyclone by an external pump (SKC AirCheck XR5000, SCKInc, Eighty Four, PA, USA) that was pre-calibrated daily using a flow meter (DryCal Dc-Lite, Bios International, Mesa Labs, NJ, USA) and set to at a flow rate of 1.5 L/min. $PM_{2.5}$ was collected on 37-mm PFTE-coated glass fiber filters (Fiberfilm^{TM} T60A20, Pall Corporation, Port Washington KY, USA). The filters were equilibrated for at least 24-hours and then pre-weighed at Colorado State University (CSU) using a microbalance (Mettler Toledo Microbalance, model MX5, resolution and repeatability of 1-ug). After collection of the sample, filters were stored at -22°C and then transported to CSU, equilibrated for temperature and relative humidity, and post-weighed. One filter blank was collected every two weeks.

We measured kitchen and personal 24-hour concentrations of $PM_{2.5}$ and black carbon. Kitchen exposure monitors were placed between 76 and 127 centimeters above the stove and away from open windows and doors. In order to capture the personal concentration, the exposure monitor was placed in a small bag that each participant wore over the 24-hour period (except when bathing or sleeping). Women were instructed to place the bag with the monitor next to their bath or bed when not wearing it. The inlet to the cyclone was clipped to a strap near the woman's breathing zone on her chest.

The $PM_{2.5}$ limit of detection (LOD) was calculated as follows: average mass of blank filters plus 3 times the standard deviation (SD) of the sample blank filter masses. All samples with a

concentration less than the LOD (7 kitchen samples and 7 personal samples) were replaced with a value of LOD/√2. We calculated gravimetric $PM_{2.5}$ concentration as the change in filter mass adjusted for the average blank mass. A 24-hour time-weighted average was calculated as the total weight of the filter divided by the air volume sampled (average flow rate times total minutes sampled). Due to a broken DryCal pump needed to calibrate the equipment used for $PM_{2.5}$, we were unable to gather PM exposure measures from the first 41 houses recruited into the study. In addition, other samples were excluded from analysis due to; the AirCheck pumps running for less than 75% of the intended time (<18 hours) (three personal and two kitchen samples), faulty filter weight (one personal $PM_{2.5}$ sample), and missing post-calibration data in the field (one kitchen $PM_{2.5}$ sample).

Black carbon concentrations were estimated based on the optical transmission of light through the air sampling filters (Hansen et al, 1984) using a transmissometer (model OT-21, Magee Scientific, USA). Transmission data were converted to mass concentrations based on published mass-absorption values for combustion aerosols (Chylek et al, 1981) and corrected for a filter loading artifact wherein an underestimation of the estimation occurs at high sample loading (Kirchstetter and Novakov, 2007). The LOD was estimated to be 0.86 $\mu g/m^3$, which corresponds to three times the standard deviation of 54 blank samples (additional blank filters were used from field sampling campaigns conducted within the same year to estimate the reference values for the transmissometer since pre-sampling transmission data were not collected on sample filters). Values below the LOD (3 kitchen samples and 10 personal samples) were substituted by LOD/√2.

We also evaluated exposure to household air pollution using stove type (traditional cookstove or cleaner-burning *Justa* stove).

Markers of Systemic Inflammation

Markers of systemic inflammation were assessed via dried blood (Mei et al. 2001). In order to obtain the dried blood spots (DBS), each woman had her finger pricked with a sterile disposable 1.75 mm point BD Genie^{TM} lancets (BD, Franklin Lakes, USA), and blood was spotted onto a standardized filter paper (See Figure 2) (903 Protein Saver Card, Schleicher & Schuell, NH). The samples were obtained in the morning between the hours of 7:30am and 12:00pm. The samples were dried overnight, placed in baggies with desiccant and humidity indicator cards, frozen at -22°C in Honduras, and then transported and stored at Colorado State University at -80°C. Samples were shipped to the National Health and Environmental Effects Laboratory of the U.S. Environmental Protection Agency for analysis. The Human Pro-Inflammatory-4 II Base Kit (IL-Iβ, TNF-α, IL-6, and IL-8) and the V-PLEX Plus Vascular Injury Panel 2 (human) kit (ICAM-1, VCAM-1, CRP, SAA) were used with the Meso Scale Multiplex instrument (Meso Scale Discovery; Gaithersburg, MD).

Additional Information

To estimate diabetes-related information for our effect modification analyses, we measured glycated hemoglobin (HbA1c) with a 5 µl finger stick sample of blood. The sample was analyzed in the field with the A1CNow+® system (PTS Diagnostics, Indianapolis, USA). We defined prediabetes as participants having a HbA1c ≥5.7% and ≤6.4%, while diabetes was defined as having HbA1c >6.4% (Alberti et al. 2009). Due to a limited number of participants with diabetes based on the HbA1c levels (n=3) we combined prediabetes and diabetes into one category.

Blood pressure was measured using the SphygmoCor XCEL Central Blood Pressure Measurement System (AtCor Medical Pty Ltd, Australia), recorded at the brachial artery on the

woman's right arm with a 23-33 cm cuff. Three consecutive measurements were taken for each participant after a 10-minute rest period. The average of the last two measurements was recorded. We categorized blood pressure into normal blood pressure (systolic <120 mmHg and diastolic <80 mmHg) and borderline high or high blood pressure (systolic ≥120 mmHg and/or diastolic ≥80 mmHg). Blood pressure analyses are reported in Young et al. (under review).

The study team administered in-person demographic surveys in the homes of participants. Responses were recorded on a tablet into an electronic data collection system, Open Data Kit (Brunette et al. 2013). We gathered data on the number of beds per person in the household, years of formal education, access to electricity, the number of assets (cars, bikes, motorbikes, televisions, radios, refrigerators, sewing machines, electricity), and dietary diversity score as indicators of socioeconomic status (SES). For the dietary diversity score, women reported all food eaten in the previous 24-hour period and the number of portions (Arps 2011). The final dietary diversity score was a sum of the number of food groups a woman had eaten at least one portion of in the past 24 hours, ranging from 1 to 10. Surveys were also used to collect information on cooking and exposure to secondhand smoke. Anthropometric data were gathered at the homes of women. We dichotomized body mass index (BMI) into <25.1 or ≥ 25.1 kg/m^2 based on the median value for our effect modification analyses. Women self-reported any medication use at the time of the study.

Statistical Analysis

Data were analyzed using SAS® software version 9.4 (SAS Institute, Inc., Cary, NC, USA). We removed participants who self-reported use of hypertension medications (N=3) or, use of vitamins and/or folic acid (N=22), or anti-inflammatory medications (N=11) as these medications may

decrease levels of inflammation in the body and may interfere with inflammatory marker measurements (Zhou et al. 2010; Reifen 2002; Carroll and Schade 2003; Solini, Santini, and Ferrannini 2006).

We conducted descriptive statistics for the entire population and by stove type used and also calculated Spearman correlation coefficients for the 7 inflammatory markers. We did not explore the association of household air pollution and IL-6 as an inflammatory marker as approximately 89% of samples were below the LOD. We evaluated the association between $PM_{2.5}$ and black carbon with each of the inflammatory markers. We performed multiple linear regression analyses with one biomarker as the dependent variable and one exposure concentration as the independent variable. We natural logarithmically transformed both exposure concentrations as well as all inflammatory markers to meet the assumptions of linear regression. Potential confounding variables were chosen a priori based on previous literature. We evaluated options for a marker of socio-economic status, including dietary diversity score, number of assets, electricity, beds per person, and education level, for predictive ability in crude models with each biomarker. In our final models, we controlled for age, body-mass index, categorical assets (< 2 assets or ≥2 assets), electricity (yes/no) and years of school (< 6 or ≥6 years).

We assessed effect modification of the association between household air pollution and markers of inflammation due to potential risk factors associated with air pollution exposure and cardiovascular disease. We explored effect modification by age (<40 or ≥40), BMI (< 25.1 or ≥ 25.1 units), diabetes status (normal vs. pre-diabetic/diabetic), and hypertension (normal vs. pre-hypertensive/hypertensive) by adding an interaction term in the models.

Results

We enrolled 150 women in our cross-sectional study; 146 women provided blood samples for inflammation analysis. Two participants declined to provide blood samples, and two women had samples that were not valid. Baseline population characteristics are presented in Table 1. The average age of women in the study was 37.3 years (SD: 8.9), average BMI was 25.9 kg/m^2 (SD: 4.1), and about half the population (n=67) had less than 6 years of education. Most variables were similar between the two stove type groups, except for education status where 51.4% of traditional stove users had less than 6 years of education compared to 41.7% *Justa* of stove users.

After removing erroneous samples, the final sample sizes for the pollutant measurements was 105 for personal $PM_{2.5}$, 106 for personal black carbon and kitchen $PM_{2.5}$, and 107 for kitchen black carbon. The four 24-hour averages of the continuous pollutant measures were strongly correlated (Table 2). Within pollutants, there was a positive correlation between kitchen concentrations and personal concentrations to $PM_{2.5}$ (rho=0.80) and kitchen and personal black carbon (rho=0.77). $PM_{2.5}$ and black carbon exposures were correlated among kitchen measurements (rho=0.89) and personal measurements (rho=0.78). Twenty-four hour minimum, maximum, median, 25^{th} and 75^{th} percentile concentrations of each pollutant are shown in Table 3. As expected, kitchen $PM_{2.5}$ was higher than personal $PM_{2.5}$ with median concentration of 132 $\mu g/m^3$ (25^{th} and 75^{th} percentile: 62 $\mu g/m^3$, 374 $\mu g/m^3$) compared to 80 $\mu g/m^3$ (25^{th} and 75^{th} percentile: 51 $\mu g/m^3$, 137 $\mu g/m^3$). The same pattern holds for kitchen and personal black carbon. In addition, women who owned traditional stoves were exposed to higher concentrations of each of the two pollutants than women who owned *Justa* stoves (Table 3).

Overall summary statistics for the seven inflammatory markers measured in DBS are presented in Table 4. ICAM-1 and VCAM-1 had the highest Spearman correlation coefficient (rho =0.71). Other inflammatory markers were moderately correlated: CRP and SAA (0.49), ICAM-1 and TNF-α (0.48), VCAM-1 and TNF-α (0.42), and CRP and ICAM-1 (0.39). All other markers exhibited low or no correlation (Figure 3).

We observed inconsistent associations between $PM_{2.5}$ and black carbon and levels of inflammatory markers in DBS (Table 5). The strongest associations were observed between higher levels of household air pollution and higher levels of CRP and SAA. For example, a 25% increase in personal $PM_{2.5}$ concentrations resulted in a 10.5% (95% CI: 1.2 – 20.6) increase in CRP concentrations after controlling for potential confounders. Similar significant results were observed between higher kitchen concentrations of black carbon and higher CRP concentrations, while there was a suggestive positive association between kitchen $PM_{2.5}$ and personal black carbon. We also observed associations between all four continuous pollutants and SAA (Table 4). A 25% increase in personal $PM_{2.5}$ exposure was associated with an 8.3% increase in SAA concentrations (95% CI: 2.3, 14.7). For both CRP and SAA, the largest increase in DBS concentrations was observed with higher personal concentrations of $PM_{2.5}$ (Table 4). Additionally, a 25% higher kitchen black carbon concentrations was associated with 1.9 % higher IL-8 concentrations (95% CI: 0.4-3.5). We did not observe any associations between household air pollution concentrations and IL-1β, ICAM-1, VCAM-1, and TNF-α.

In general, women who owned traditional cookstoves had higher levels of inflammatory markers in DBS, although ICAM and IL-8 were associated with higher, nonsignificant, levels among

Justa stove users. We observed that women who owned traditional stoves had a 59.8 percent higher SAA concentration compared to women who used a *Justa* cookstove (95% CI: 10.2 – 131.8).

Effect Modification

For effect modification analyses, 18 of 110 women reported no high-risk factors. Of those who reported only one risk factor, 13 reported only age ≥40 as a risk factor, 15 had only high BMI (≥25.1), five women had only high blood pressure, and 11 were classified as only high HbA1c (Figure 4). We observed evidence of effect modification between several cardiovascular risk factors and the effect of increased levels of household air pollution on inflammatory markers. For example, the effect of personal $PM_{2.5}$ concentrations and IL-1β was modified by the age of the participants. A 25% higher personal $PM_{2.5}$ concentration was associated with a 0.9% (95% CI: -4.6, 2.9) change in lower IL-1β concentration among women less than 40 years old, but associated with a 5.4% (95% CI: -1.1, 12.4) higher IL-1 β concentrations among women 40 years old or older (p-interaction = 0.1) (Figure 5). The effect of BMI on the association of kitchen $PM_{2.5}$ and IL-8 concentrations was observed only among women with BMI <25.1 (Estimate: 6.3, 95% CI: 2.8, 9.9) (Figure 6).

We observed several instances of effect modification by diabetes status (Figure 7). The positive association observed between higher concentrations of household air pollution and higher levels of CRP was only observed among women who were classified as "normal" compared to the null association in the prediabetic and diabetic group. A 25% higher kitchen $PM_{2.5}$ was associated with a 8.6% (95% CIL 2.6,15.0) higher CRP concentration, while a 25% higher personal $PM_{2.5}$ concentration was associated with a 20.7% higher CRP among non-diabetic women (95% CI: 10.0, 32.4); (p-interaction; kitchen $PM_{2.5}$ = 0.01, personal $PM_{2.5}$ = 0.01) (Figure 8). On the contrary,

higher concentrations of kitchen $PM_{2.5}$, personal $PM_{2.5,}$ and kitchen black carbon were associated with higher IL-8 concentrations among women who were pre-diabetic or diabetic compared to those who were not (p-interaction; kitchen $PM_{2.5}$ = <0.01, personal $PM_{2.5}$ = 0.04, kitchen BC =0.0; (kitchen $PM_{2.5}$: 8.2%, 95% CI: 4.4, 12.2; personal $PM_{2.5}$: 8.3%, 95% CI: 0.0, 17.0; kitchen black carbon: 5.6%, 95% CI: 2.9,8.4).

Finally, among those who were classified as having high blood pressure, a 25% higher kitchen $PM_{2.5}$ was associated with a 13.1% higher SAA concentration (95% CI: 2.1-25.2) compared to a 2.8% higher SAA among those without pre-hypertension or hypertension (95% CI: -1.1-6.8) (p-interaction = 0.08) (Figure 8). Among women who owned a traditional stove, those with BMI ≥25.1 had 9.2 % higher IL-8 concentration (95% CI: -15.9 – 41.6) compared to *Justa* stove owners, while those with BMI < 25.1 had a 24.6 % lower in log IL-8 concentrations compared to *Justa* stove owners (95% CI: -43.1 – 0.2) p-interaction = 0.06).

Discussion

Our cross-sectional analysis points to possible associations between household air pollution, $PM_{2.5}$ and black carbon and increasing levels of systemic inflammatory markers among female primary cooks. These results suggest that inhalation of smoke from cooking with biomass may result in oxidative stress and systemic inflammation and have potential implications for future cardiovascular disease risk. We found that the associations were strongest between household air pollution and the acute phase proteins, CRP and SAA. More specifically, the strongest associations for CRP and SAA were among personal $PM_{2.5}$ concentrations as compared to the kitchen concentrations.

Our results are largely consistent with literature showing associations between air pollution, especially particulate matter, and markers of systemic inflammation. For example, the association between increasing air pollution exposure and markers of systemic inflammation has been observed in the ambient air pollution literature (Delfino et al. 2009; Dubowsky et al. 2006). Although we did not observe associations with TNF-α, ICAM-1 and VCAM-1, several studies have demonstrated these associations with increasing levels of ambient air pollution (Alexeeff et al. 2011; Madrigano et al. 2010; Vossoughi et al. 2014). Additional evidence demonstrates that exposure to wood-smoke has been associated with increased levels of SAA as observed in a controlled exposure study by Barregard et al. (Barregard et al., 2006).

The use of biomarkers of systemic inflammation in household air pollution research is more limited, and the results demonstrate inconsistent associations between various measurements of exposure and inflammatory markers. For example, positive associations have been observed between biomass use and markers of systemic inflammation in India where Dutta et al. observed higher levels of serum CRP, IL-8 and TNF-α among biomass users compared to LPG users (Dutta, Ray, and Banerjee 2012). Another study by Dutta et al. in India evaluated sputum cytology for markers of airway inflammation associated with cookstove exposure and PM_{10}. Women who cooked with biomass fuels had 6.9 times increased levels of TNF-α in the sputum samples compared to women cooking with LPG (86.9 ± 28.1 vs. 12.6 ± 6.2 pg/ml, $p < 0.001$). Similar results were observed for sputum concentrations of IL-8 (26.7 ± 7.4 for biomass users vs. 10.1 ± 3.3 pg/ml for LPG users, $p < 0.001$) (Dutta et al. 2013).

A study in Nigeria evaluated markers of systemic inflammation among pregnant women who were randomized to cook with either ethanol or continue cooking with firewood (Olopade et

al. 2017). After an average of 145 days from baseline to post-randomization, measured levels of serum TNF-α decreased by an average of 6.20 pg/ml (SE: 5.24) among pregnant women switching from firewood to ethanol and increased by 14.03 pg/ml (SE: 5.89) among women continuing to cook with firewood. Women randomized to continue cooking with firewood (control) had 68% higher levels of post-randomized TNF-α compared to women randomized to cook with ethanol. Statistically significant increases in IL-8 and TNF-α were also observed in associations with measured concentrations of $PM_{2.5}$ (both log-transformed); IL-8: 0.24 (95% CI: 0.02, 0.44); TNF-α: 0.18 (95% CI: 0.03, 0.34) (Olopade et al. 2017).

Caravedo et al. compared serum concentrations of SAA, CRP, ICAM-1 and VCAM-1 among 228 biomass-exposed and 228 non-exposed men and women in Peru. Adjusted analyses demonstrated that chronic exposure to biomass fuels was positively associated with increased levels of ICAM-1 and VCAM-1, but was unexpectedly negatively associated with CRP and no association was observed with SAA (Caravedo et al. 2016). In another study using stove type as the exposure variable, Misra et al. explored the association of biomass wood fuel use (vs. electricity) and markers of systemic inflammation (CRP, SAA, IL-8, IL-1β, TNF-α, ICAM-1 and VCAM-1) among 415 women in Southern Africa (Misra et al. 2018). After adjusting for confounders, age, gravidity, caffeine consumption, passive smoking and water source, the authors found only an association among women who used wood mostly indoors and SAA compared to electricity users (estimate: -0.38, 95% CI: -0.68,-0.08). In all other analyses the authors found no associations with levels of inflammatory markers comparing biomass users vs. non-biomass users (Misra et al. 2018). A previous study by our group in Honduras (Clark et al. 2009) did not observe associations between 8-hour average kitchen or personal $PM_{2.5}$ concentrations and CRP.

Although inconsistent, our findings suggest that the observed association between household air pollution and systemic inflammation may be modified by several risk factors thought to increase susceptibility for air pollution-related cardiovascular events (Brook et al., 2010; Dubowsky et al., 2006). There is extensive scientific and mechanistic evidence that obesity, diabetes, age, and hypertension are associated with cardiovascular disease (R. H. Eckel 1997; Ortega, Lavie, and Blair 2016; Leon 2015; Sanidas et al. 2017).

Epidemiologic evidence for effect modification of obesity and diabetes between particulate matter and markers of systemic inflammation, such as CRP, are mixed (Y. Li et al. 2012). Dubowsky et al. observed that associations between $PM_{2.5}$ and CRP were stronger among people classified as diabetic, obese, and hypertensive as compared to those without these conditions. For example, a 6.1 $\mu g/m^3$ increase in 5-day mean $PM_{2.5}$ was associated with a 48% increase in CRP for people with obesity and a 74% increase in people with diabetes, compared to 12% increase among people without the conditions (Dubowsky et al. 2006). Hoffman et al. also observed stronger associations between $PM_{2.5}$ and markers of systemic inflammation among those who were diabetic (Hoffmann et al. 2009). Two household air pollution studies have also examined effect modification by cardiovascular disease risk factors. Carvedo et al. explored effect modification by age categories (35-44 years, 45-54, 55-64, and 65 and over) and sex, but did not observe interaction between stove type and ICAM-1 or VCAM-1 (Caravedo et al. 2016). Additionally, Dutta et al. also evaluated the association of cookstove exposure (biomass vs. LPG) and inflammatory markers, modified by hypertension. After controlling for confounders, CRP concentrations among women with hypertension (systolic blood pressure: > 140 mmHg and diastolic blood pressure ≥

90 mm Hg) were significantly elevated compared to those without hypertensions (OR = 1.14, 95% CI: 1.04-2.29) (Dutta, Ray, and Banerjee 2012).

Our results for effect modification by diabetes status were inconsistent. We observed that women who were not pre-diabetic or diabetic had a stronger effect between higher levels of CRP and increasing concentrations of household air pollution, while pre-diabetic or diabetic women had higher levels of IL-8 with increasing exposure concentrations. Similar to our effect modification results for obesity and the impact of air pollution on IL-8 concentrations, Hoffman et al. observed that the association between particulate matter and inflammation was stronger among women who were not obese (Hoffmann et al. 2009). Our results indicating that higher kitchen $PM_{2.5}$ concentrations are associated with higher SAA concentrations among those with high blood pressure may be influenced by a small sample size.

Strengths and Limitations

Our study demonstrates the ability to collect DBS in the field setting and may provide an alternative to assessing inflammatory markers in serum. Several validation studies have shown high correlations between serum and DBS samples (Skogstrand et al. 2008; Qian 2015; E. M. Miller and McDade 2012; Schmid et al. 2004). Our study utilized measured concentrations of 24-hour average $PM_{2.5}$ and black carbon and provides a more robust quantitative evaluation of exposure without relying on "proxies" of exposure such as stove type.

Our study is limited by the cross-sectional nature of the design; and we cannot determine that exposure preceded systemic inflammation, however women who owned a *Justa* cookstove must have owned the stove for at least 4 months (average 24 months). Selection bias could have occurred due to the recruitment of a convenience sample, however we believe it is unlikely that

selection into the study would be associated with both the exposure and disease. Additionally, our one-time measurement of household air pollution and finger-prick blood spot may not be representative of long-term exposures or chronic systemic inflammation. Although our results indicate that women with cardiovascular risk factors may be more susceptible to the effects of household air pollution, other related factors may play a role in the association. Our results indicate differential impacts of diabetes status with different inflammatory markers (CRP vs. IL8) and additional information regarding potential mechanistic pathways may help elucidate these findings. Finally, generalizability of our stove type results (traditional vs. cleaner-burning *Justa*) may not be generalizable to other populations or stove and fuel types.

Conclusions

There is a growing burden of cardiovascular disease morbidity and mortality in low-and middle-income countries where approximately 80% of the cardiovascular deaths already occur (Bowry et al. 2015). Risk factors for cardiovascular disease include hypertension, tobacco use, dietary factors, obesity and physical inactivity (Lim SS, Vos T, Flaxman AD 2012). In addition, several million people are chronically exposed to high levels of household air pollution. Although air pollution is associated with cardiovascular disease, there is limited understanding of the mechanism pathway to disease. Our results indicate that exposure to household air pollution is associated with several markers of systemic inflammation among women in rural Honduras. These findings support the hypothesis of a pathway from inhaled particles to systemic inflammation. Given the potentially large contribution of household air pollution to cardiovascular disease risk, it is vital that additional research continues to evaluate personal exposure to household air

pollution and markers of systemic inflammation and the potential for cleaner-burning cookstoves to reduce exposure and risk for cardiovascular disease.

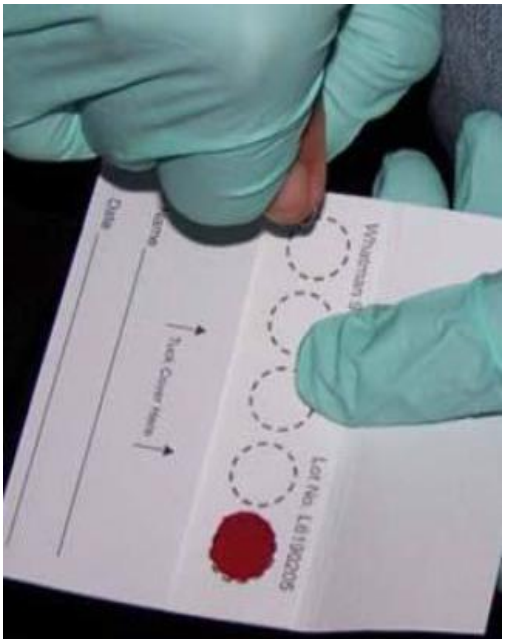

Figure 6.1: Protein saver card and dried blood spot

Table 6.1: Population characteristics among non-smoking primary female cooks using traditional or cleaner-burning *Justa* stoves, rural Honduras (N=146)			
	Total (N=146)	Traditional (N=73)	*Justa* (N=73)
	N (%) or Mean (SD) ; range	N (%) or Mean (SD) ; range	N (%) or Mean (SD) ; range
Age (years)	37.3 (8.9); 25-56	38.4 (9.4); 25-56	36.1 (7.9); 25-56
Body mass index (kg/m^2)	25.9 (4.1); 17.1-37.5	25.8 (4.5); 17.1-37.5	26.0 (3.8); 18.2-33.6
Categorized BMI			
<25.1	67 (46%)	36 (49.3%)	31 (42%)
≥ 25.1	79 (54%)	37 (50.7%)	42 (58%)
Elevation (meters)*	1913 (103); 1729-2158	1990 (91); 1736-2152	1936 (109); 1729-2158
Years of education**			
Less than six years	67 (46.5%)	37 (51.4%)	30 (41.7%)
Six or more years	77 (53.5%)	35 (48.6%)	42 (58.3%)
Electricity*			
No	119 (82.1%	61 (83.6%)	58 (80.6%)
Yes	26 (17.9%)	12 (16.4%)	14 (19.4%)
Number of assets			
Less than 2	69 (47.3%)	33 (45.2%)	36 (49.3%)
Two or more	77 (52.7%)	40 (54.8%)	37 (50.7%)
Years spent cooking with biomass	25.8 (9.7); 9-50	26.8 (10.5); 9-49	24.8 (8.8); 9-50
Self-reported exposure to secondhand smoke	5 (3.4%)	5 (3.6%)	0 (0%)
Systolic blood pressure	118.6 (12.7); 91-160	120.4 (12.2); 97-158	116.8 (13.1); 91-160
Diastolic blood pressure	73.1 (8.6); 55-105	73.8 (9.4); 58-96	72.4 (8.9); 55-105
Pre-hypertension/ hypertension			
No	118 (80.8%)	54 (74%)	64 (88)%
Yes	28 (19%)	19 (26%)	9 (12%)
HbA1c^	5.5 (0.75); 4.1-13.0	5.5 (0.4); 4.7-6.5	5.6 (1.0); 4.1-13.0
Pre-Diabetic or diabetic			
No	104 (74%)	54 (76%)	50 (73%)
Yes	36 (25%)	17 (24%)	19 (27%)

*N=145; Traditional=73, Justa=73

**N=144; Traditional=73, Justa=72

^N=140; Traditional=71, Justa=69

Table 6.2: Spearman rho correlation matrix of kitchen and personal air pollution measurements (N=102)

	Kitchen $PM_{2.5}$	Personal $PM_{2.5}$	Kitchen Black Carbon	Personal Black Carbon
Kitchen $PM_{2.5}$	1	0.80	0.89	0.68
Personal $PM_{2.5}$		1	0.76	0.78
Kitchen Black Carbon			1	0.77
Personal Black Carbon				1

Table 6.3: 24-hour average kitchen and personal fine particulate matter and black carbon concentrations, traditional and *Justa* stove users, rural Honduras

	All Participants						Traditional Stove Users						*Justa* Stove Users					
	N	Min	25th	Median	75th	Max	N	Min	25th	Median	75th	Max	N	Min	25th	Median	75th	Max
24–hour average kitchen $PM_{2.5}$ *(µg/m³)*	*106*	18	62	132	374	1654	*62*	18	91	181	511	1654	*44*	18	38	71	159	1134
24–hour average personal $PM_{2.5}$ *(µg/m3)*	*105*	18	51	80	137	346	*62*	18	65	115	154	346	*43*	18	39	52	81	174
24–hour average kitchen Black Carbon *(µg/m3)*	*107*	1	9	21	82	1172	*63*	1	15	44	114	1172	*44*	1	4	11	19	469
24–hour average personal Black Carbon *(µg/m3)*	*106*	1	4	7	18	123	*62*	1	7	14	32	123	*44*	1	1	4	9	47

$PM_{2.5}$: fine particulate matter

Table 6.4: Levels of inflammatory markers by participant characteristics and potential risk factors for cardiovascular disease among rural Honduran female participants

		Median (25th, 75th percentiles)						
	N (%)	CRP	SAA	IL-8	IL-1β	TNF-a	ICAM-1	VCAM-1
All participants	110	13.6 (5.8, 27.5)	28.9 (17.9, 52.8)	5.8 (4.9, 8.2)	0.20 (0.1, 0.20)	0.06 (0.04, 0.07)	6.9 (5.9, 8.5)	11.2 (9.8, 13.3)
Age (years)								
< 40	70 (64%)	13.4 (5.0, 22.0)	30.4 (19.3, 57.5)	5.7 (4.5, 8.0)	0.15 (0.12, 0.19)	0.06 (0.04, 0.09)	6.8 (5.9, 8.1)	11.0 (9.9, 12.7)
≥ 40	40 (36%)	17.8 (6.4, 35.9)	25.2 (15.9, 40.4)	6.3 (5.1, 8.6)	0.16 (0.13, 0.21)	0.06 (0.04, 0.09)	7.7 (6.2, 9.8)	12.2 (9.1, 15.4)
BMI								
< 25.1	51 (46%)	8.5 (3.6, 21.4)	27.9 (17.8, 46.5)	6.5 (5.2, 11.0)	0.15 (0.11, 0.18)	0.06 (0.04, 0.08)	7.6 (6.2, 9.1)	11.7 (9.8, 14.0)
≥ 25.1	59 (54%)	17.2 (10.3, 32.0)	29.5 (17.9, 56.6)	5.5 (4.5, 7.2)	0.16 (0.12, 0.25)	0.06 (0.04, 0.08)	6.8 (5.9, 8.3)	11.0 (9.5, 13.1)
Diabetes/Pre-Diabetes								
No	82 (75%)	14.2 (5.0, 28.9)	28.0 (17.5, 54.1)	5.6 (4.9, 7.9)	0.15 (0.12, 0.20)	0.05 (0.04, 0.07)	7.0 (5.9, 9.1)	11.4 (10.1, 13.1)
Yes	28 (25%)	12.6 (6.4, 24.3)	29.9 (20.5, 47,2)	6.5 (4.8, 10.9)	0.15 (0.12, 0.20)	0.06 (0.04, 0.08)	6.8 (6.2, 8.3)	10.6 (8.6, 13.7)
Hypertension								
No	87 (79%)	11.5 (4.5, 23.5)	28.6 (17.9, 54.1)	5.5 (4.6, 7.8)	0.15 (0.12, 0.19)	0.05 (0.04, 0.07)	6.9 (5.8, 8.2)	10.9 (9.5, 13.0)
Yes	23 (21%)	21.4 (13.4, 50.9)	29.5 (16.8, 52.8)	7.7 (5.3, 9.8)	0.12 (0.14, 0.28)	0.07 (0.05, 0.08)	7.8 (6.6, 9.3)	12.5 (10.7, 14.3)

***Concentrations presented per 1000 pg/ml**

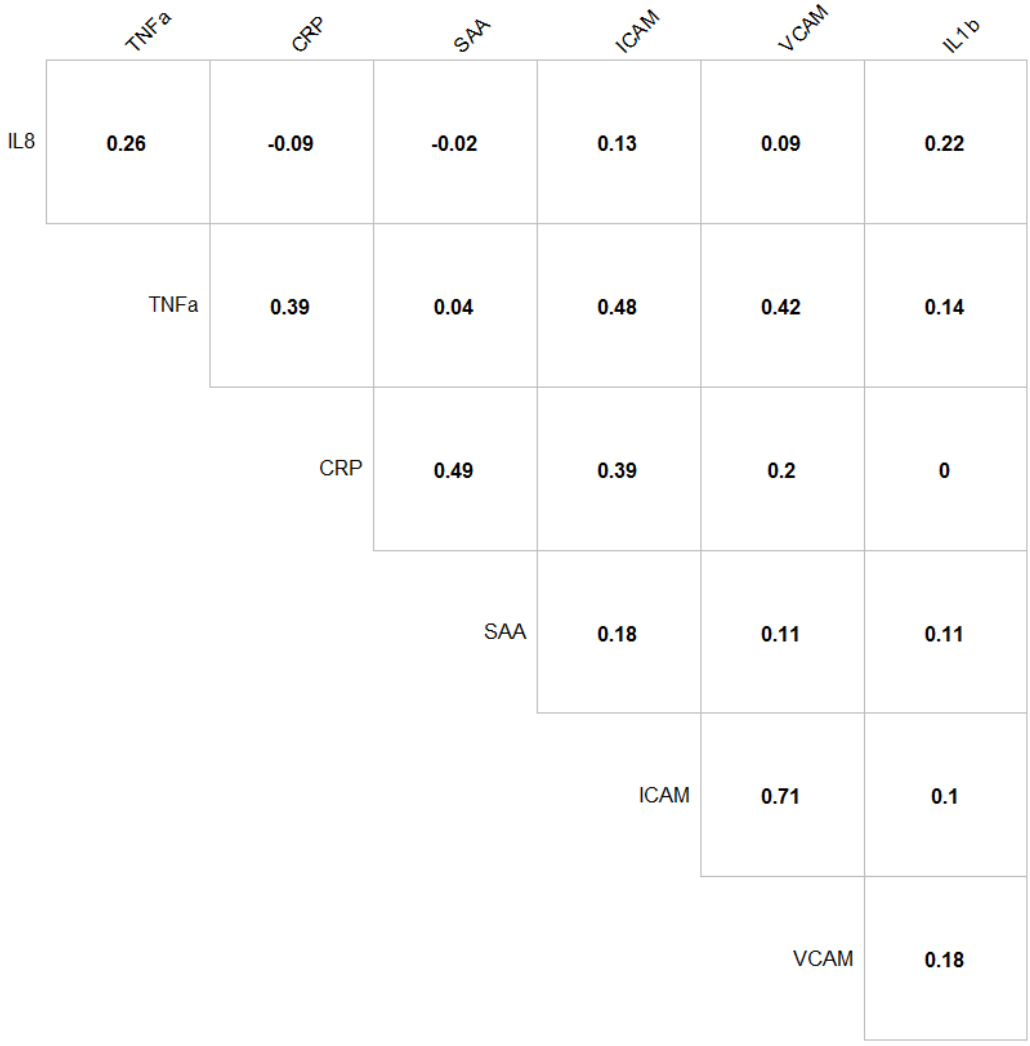

Figure 6.2: Spearman rank correlation between inflammatory markers (N=110)

Table 6.5: Estimated adjusted[1] percentage difference in inflammatory marker per 25% increase in 24-hour average measured pollution, or by stove type) among traditional and *Justa* stove users, rural Honduras

CRP			*N*	*Percentage Difference*	*95% CI*
Kitchen $PM_{2.5}$ ($\mu g/m^3$)[2]			74	4.2	-1.1, 9.7
Personal $PM_{2.5}$ ($\mu g/m^3$)			73	10.5	1.2, 20.6
Kitchen BC ($\mu g/m^3$)			75	3.9	0.1, 7.8
Personal BC ($\mu g/m^3$)			73	4.2	-0.5, 9.1
Stove type†					
	Traditional		54	24.6	-33.4, 133.1
	Justa	*ref*	56		
SAA			*N*	*Percentage Difference*	*95% CI*
Kitchen $PM_{2.5}$ ($\mu g/m^3$)			74	3.9	0.6, 7.5
Personal $PM_{2.5}$ ($\mu g/m^3$)			73	8.3	2.3, 14.7
Kitchen BC ($\mu g/m^3$)			75	3.6	1.1, 6.1
Personal BC ($\mu g/m^3$)			73	4.1	1.1, 7.2
Stove type†					
	Traditional		54	59.8	10.2, 131.8
	Justa	*ref*	56		
IL-8			*N*	*Percentage Difference*	*95% CI*
Kitchen $PM_{2.5}$ ($\mu g/m^3$)			74	2.0	-0.1, 4.2
Personal $PM_{2.5}$ ($\mu g/m^3$)			73	0.6	-3.1, 4.4
Kitchen BC ($\mu g/m^3$)			75	1.9	0.4, 3.5
Personal BC ($\mu g/m^3$)			73	0.5	-1.3, 2.5
Stove type†					
	Traditional		54	-5.89	-26.2, 19.9
	Justa	*ref*	56		
IL-1β			*N*	*Percentage Difference*	*95% CI*
Kitchen $PM_{2.5}$ ($\mu g/m^3$)			74	1.6	-0.3, 3.6
Personal $PM_{2.5}$ ($\mu g/m^3$)			73	0.8	-2.5, 4.2
Kitchen BC ($\mu g/m^3$)			75	1.1	-0.3, 2.5

Personal BC (µg/m^3)			73	0.5	-1.2, 2.2
Stove type†					
	Traditional		54	3.99	-17.55, 31.14
	Justa	*ref*	56		

TNF-α			*N*	*Percentage Difference*	*95% CI*
Kitchen $PM_{2.5}$ (µg/m^3)			74	-0.16	-2.51, 2.24
Personal $PM_{2.5}$ (µg/m^3)			73	1.11	-2.92, 5.31
Kitchen BC (µg/m^3)			75	0.27	-1.44, 2.02
Personal BC (µg/m^3)			73	-0.36	-2.44, 1.76
Stove type†					
	Traditional		54	4.50	-21.34, 38.84
	Justa	*ref*	56		
ICAM-1			*N*	*Percentage Difference*	*95% CI*
Kitchen $PM_{2.5}$ (µg/m^3)			74	-0.48	-1.68, 0.75
Personal $PM_{2.5}$ (µg/m^3)			73	0.54	-1.54, 2.66
Kitchen BC (µg/m^3)			75	-0.29	-1.17, 0.59
Personal BC (µg/m^3)			73	-0.25	-1.32, 0.83
Stove type†					
	Traditional		54	-6.79	-19.08, 7.36
	Justa	*ref*	56		
VCAM -1			*N*	*Percentage Difference*	*95% CI*
Kitchen $PM_{2.5}$ (µg/m^3)			74	-0.13	-1.16, 0.91
Personal $PM_{2.5}$ (µg/m^3)			73	0.28	-1.48, 2.07
Kitchen BC (µg/m^3)			75	-0.14	-0.90, 0.62
Personal BC (µg/m^3)			73	-0.02	-0.93, 0.90
Stove type†					
	Traditional		54	6.02	-6.01, 19.59
	Justa	*ref*	56		

Cl: Confidence interval; PM2.5: fine particulate matter; CRP (C-reactive protein); SAA (serum amyloid-a); IL-8 (interleukin-8); IL-1ß (interleukin 1ß); TNF-α (tumor necrosis factor-α); ICAM-1 (intercellular adhesion molecule 1); VCAM-1 (intercellular molecule 1).

1: Models were adjusted for age, body mass index (BMI), number of assets (<2 or ≥2), electricity (yes/no), years of education (<6 or ≥6)

2: In continuous exposure models, inflammatory markers and measured pollution were both natural log transformed. Beta coefficients were entered into the formula ((1.25^ß)-1) and multiplied by 100. We can interpret the estimate of the continuous pollution exposures as a percent increase in inflammatory marker for each 25% increase in exposure. Example: There is a 10.49% higher CRP level with a 25% higher personal PM2.5 concentration.

*†Inflammatory markers were log-transformed. Categorical variable beta coefficients were entered into the formula (e^ß-1)*100). The estimates for the categorical measures of exposure can be interpreted as the percent difference in inflammatory marker when comparing traditional stove to the reference (Justa stove).*

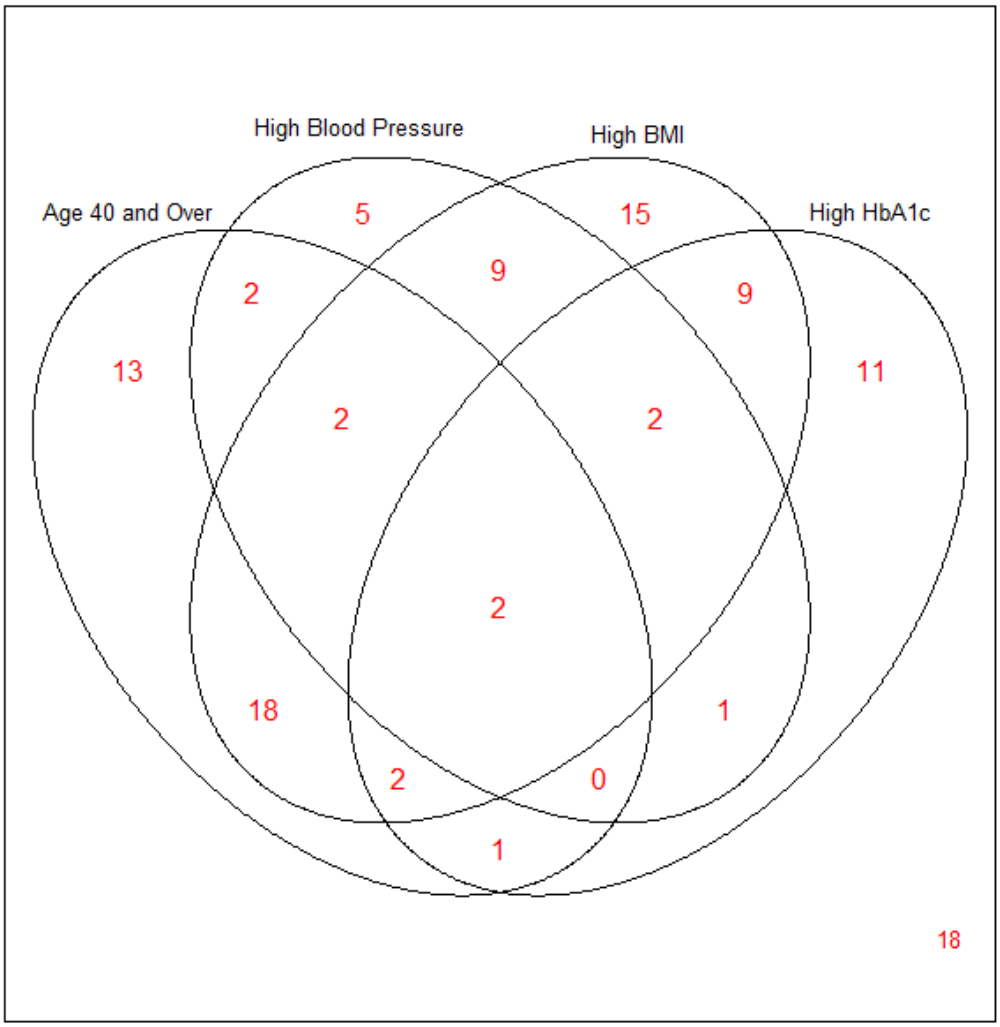

Figure 6.3: Venn diagram of risk factors for cardiovascular disease among women using traditional and Justa cookstoves (N = 110)

**18 participants did not have any risk factor*

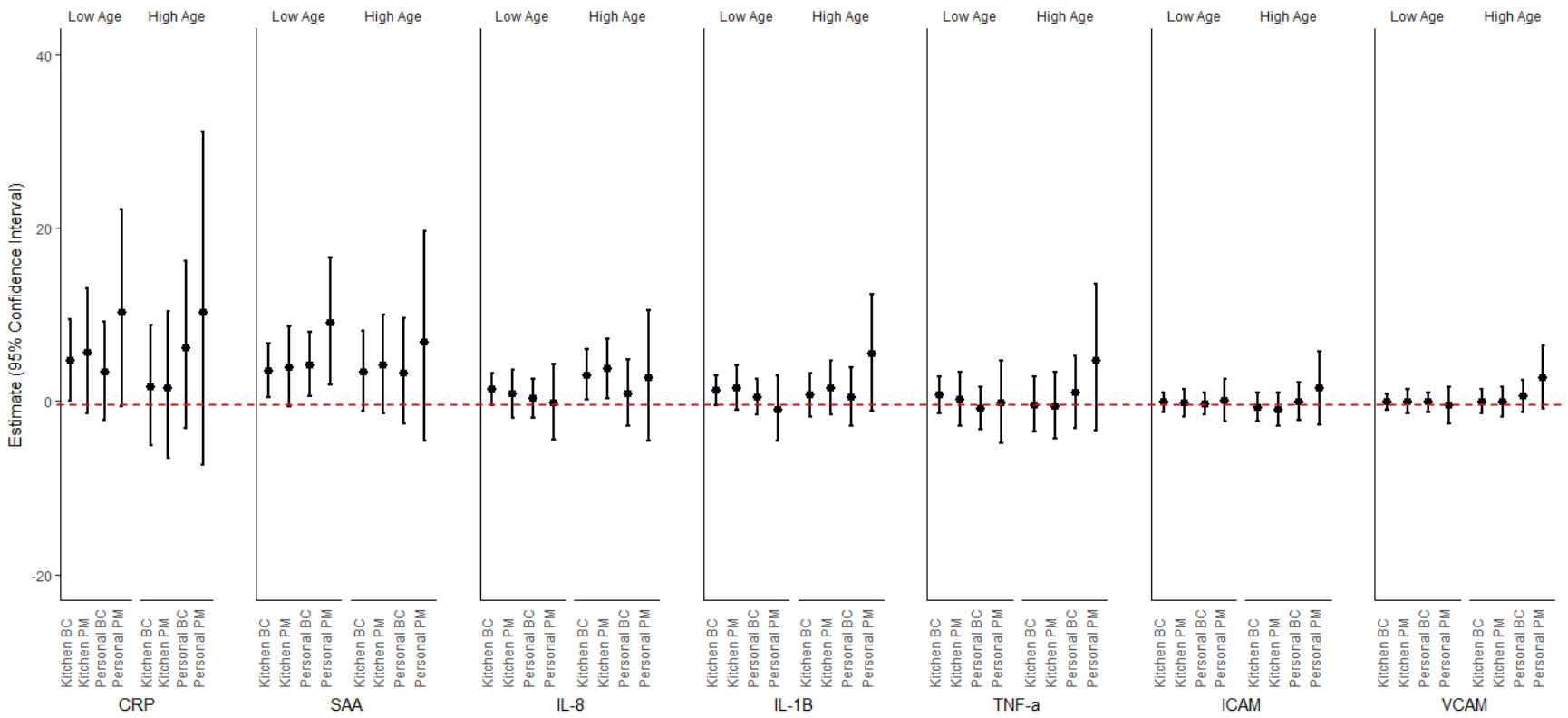

Figure 6.4: Associations between 24-hour average pollution concentrations and levels of inflammatory markers stratified by age <40 or ≥40

Low age = <40 years old (N =47 kitchen PM, N= 48 for personal PM, kitchen BC and personal BC); high age = ≥40 years old (N = 27 for kitchen PM and kitchen BC, N=25 for personal PM and personal BC)

PM= particulate matter; BC=black carbon; SAA (serum amyloid-a); IL-8 (interleukin-8); IL-1β (interleukin 1β); TNF-α (tumor necrosis factor-α); ICAM-1 (intercellular adhesion molecule 1); VCAM-1 (intercellular molecule 1).

In continuous exposure models, inflammatory markers and measured pollution were both natural log transformed. Beta coefficients were entered into the formula ((1.25^β)-1) and multiplied by 100. We can interpret the estimate of the continuous pollution exposures as a percent increase in inflammatory marker for each 25% increase in exposure.

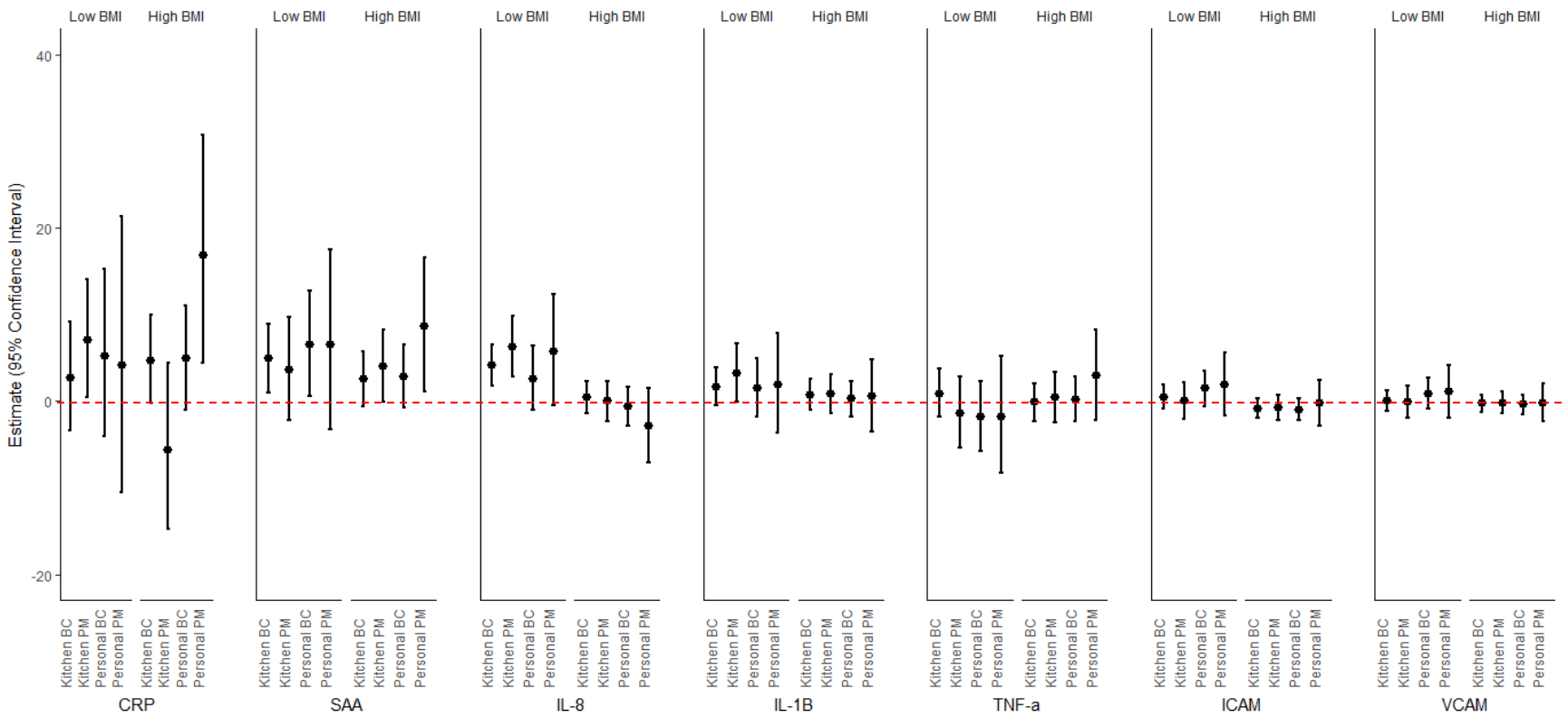

Figure 6.5: Associations between 24-hour average pollution concentrations and levels of inflammatory markers stratified by BMI (<25.1 or ≥ 25.1)

Low BMI = BMI <25.1 kg/m^3 (N = 31 for kitchen PM and kitchen BC, N=30 for personal PM and personal BC); high BMI = ≥ 25.1 kg/m (N =44 kitchen BC, N= 43 for personal PM, kitchen BC and personal BC)

PM= particulate matter; BC=black carbon; SAA (serum amyloid-a); IL-8 (interleukin-8); IL-1ϐ (interleukin 1ϐ); TNF-α (tumor necrosis factor-α); ICAM-1 (intercellular adhesion molecule 1); VCAM-1 (intercellular molecule 1).

In continuous exposure models, inflammatory markers and measured pollution were both natural log transformed. Beta coefficients were entered into the formula ((1.25^ϐ)-1) and multiplied by 100. We can interpret the estimate of the continuous pollution exposures as a percent increase in inflammatory marker for each 25% increase in exposure.

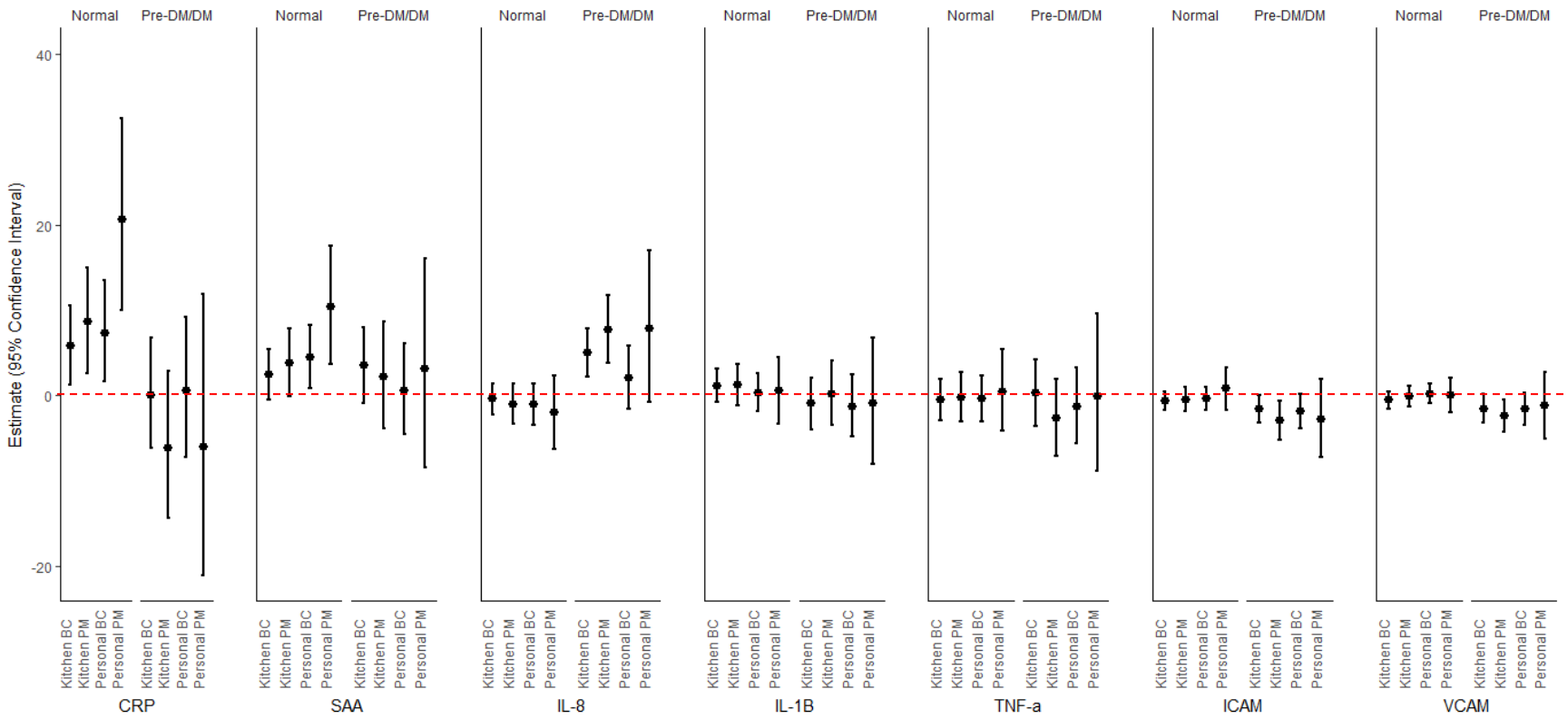

Figure 6.6: Associations between 24-hour average pollution concentrations and levels of inflammatory markers stratified by diabetes status

**Normal = <6.4% (N = 61 for kitchen PM and kitchen BC, N=60 for personal PM and personal BC); Pre DM/DM = prediabetes or diabetes status, HbA1c ≥6.4% (N =14 kitchen BC, N= 13 for kitchen PM, personal PM, and kitchen BC)*

PM= particulate matter; BC=black carbon; SAA (serum amyloid-a); IL-8 (interleukin-8); IL-1β (interleukin 1β); TNF-α (tumor necrosis factor-α); ICAM-1 (intercellular adhesion molecule 1); VCAM-1 (intercellular molecule 1).

In continuous exposure models, inflammatory markers and measured pollution were both natural log transformed. Beta coefficients were entered into the formula ((1.25^β)-1) and multiplied by 100. We can interpret the estimate of the continuous pollution exposures as a percent increase in inflammatory marker for each 25% increase in exposure.

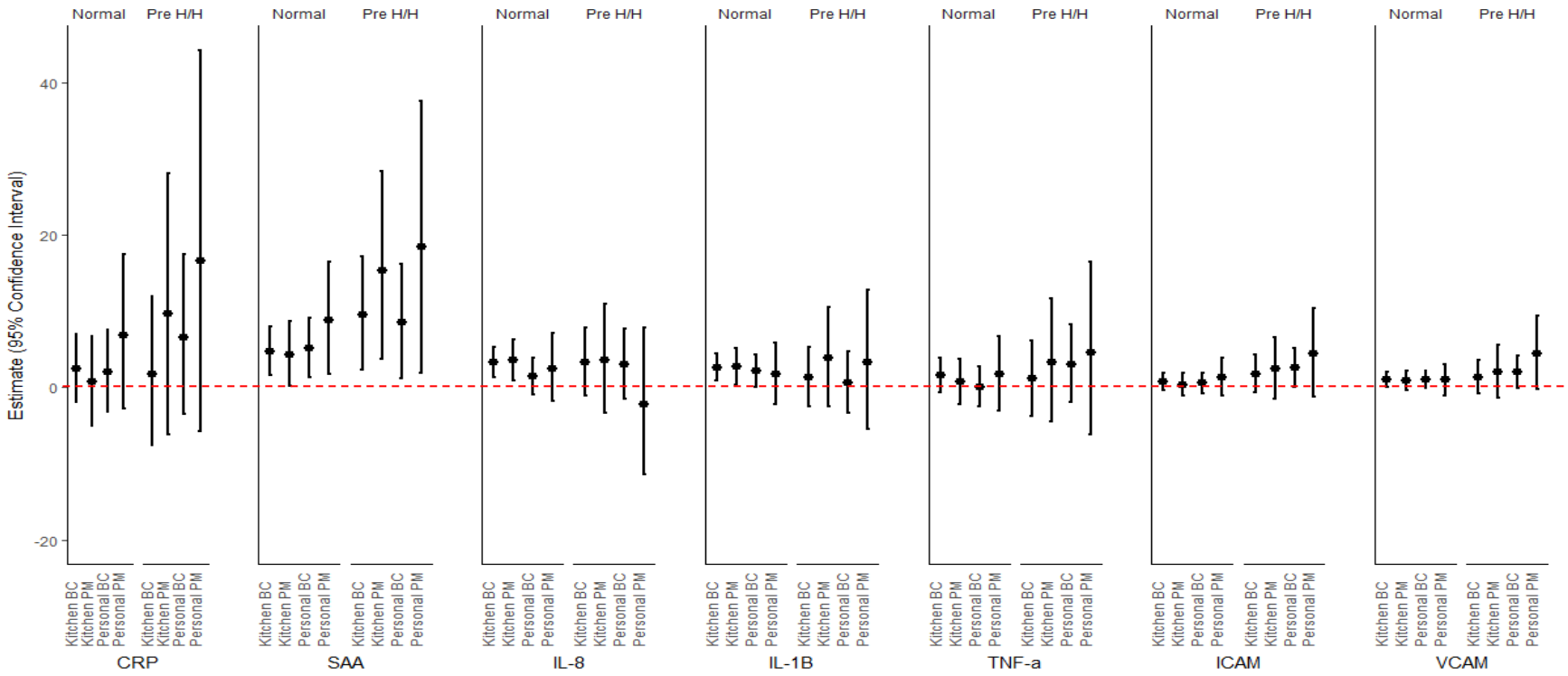

Figure 6.7: Associations between 24-hour average pollution concentrations and levels of inflammatory markers stratified by high blood pressure

Normal = normal blood pressure (systolic <120 mmHg and diastolic <80 mmHg) (N = 53 for kitchen PM, personal PM, and personal BC, N= 54 for kitchen BC); Pre H/H = borderline high or high blood pressure (systolic ≥120 mmHg and/or diastolic ≥80 mmHg) (N=19 for kitchen PM and kitchen BC, N=18 for personal PM and personal BC)

PM= particulate matter; BC=black carbon; SAA (serum amyloid-a); IL-8 (interleukin-8); IL-1β (interleukin 1β); TNF-α (tumor necrosis factor-α); ICAM-1 (intercellular adhesion molecule 1); VCAM-1 (intercellular molecule 1).

In continuous exposure models, inflammatory markers and measured pollution were both natural log transformed. Beta coefficients were entered into the formula ((1.25^β)-1) and multiplied by 100. We can interpret the estimate of the continuous pollution exposures as a percent increase in inflammatory marker for each 25% increase in exposure

Chapter 7: Conclusions

Approximately 41% of the world's population, nearly 3 billion people, relies on solid biomass fuels for cooking (Bonjour et al. 2013) and household air pollution is the 10th leading factor for morbidity and mortality worldwide (Gakidou et al. 2017). Cleaner-burning cookstoves aim to decrease harmful emissions in order to reduce the burden of disease from household air pollution. The degree to which cleaner-burning stoves can reduce the burden of disease however, especially long-term chronic disease such as cardiovascular disease, is not well understood. The goal of this dissertation was to improve scientific knowledge of the exposure-response relationship of household air pollution and disease by addressing the following gaps identified in the literature. (i) a need to characterize the size distribution and sub-daily temporal variability of household air pollution; most studies calculate a 24 or 48 hour average exposure (Northcross et al. 2015), (ii) a lack of direct exposure assessment in epidemiological household air pollution studies; the majority of studies utilize a binary proxy for exposure such as fuel type (Thomas et al. 2015; Bruce et al. 2015) (iii) an absence of direct measurements of personal exposure for epidemiological models; personal exposure is often lower than kitchen exposure as women do not spend 100% of their time indoors, and (iv) a need to identify and utilize biomarkers of health indicative of chronic disease risk.

In this study, we evaluated real-time concentrations of $PM_{2.5}$ and ultrafine particles among a sample of households using traditional biomass and cleaner-burning *Justa* stoves in rural Honduras. We also evaluated $PM_{2.5}$ mass and black carbon and the cross-sectional association with biomarkers of airway and systemic inflammation. Results from our study provide fundamental new

knowledge regarding levels of household air pollution exposure from traditional and cleaner-burning biomass cookstoves and the association with markers of inflammation.

Exposure

Overall, we observed lower 24-hour average $PM_{2.5}$, black carbon, and ultrafine particle number concentrations in the kitchens of cleaner-burning *Justa* stoves compared to traditional stoves. Additionally, personal concentrations of $PM_{2.5}$ and black carbon were lower among those who cooked with *Justa* stoves compared to those who cooked with traditional stoves. For example, the median 24-hour average kitchen $PM_{2.5}$ concentration was 40% lower among households with *Justa* stoves compared to traditional cookstoves. In addition, twenty-four hour average kitchen $PM_{2.5}$ and black carbon concentrations were highly correlated.

The use of real-time monitors demonstrated that the 24-hour average concentrations of $PM_{2.5}$ and PNC were highly variable over the course of the monitoring period. The maximum values of various averaging windows (1-minute, 5-minute, 15-minute, and 60-minute) were highly correlated with the 24-hour averages for both $PM_{2.5}$ and PNC. On average, $PM_{2.5}$ concentrations were over 100 $\mu g/m^3$ for several hours for both traditional and cleaner-burning biomass cookstoves. Furthermore, the top 5% of $PM_{2.5}$ kitchen concentrations contributed 75% of the 24-hour mean value.

Our use of real-time data to evaluate kitchen $PM_{2.5}$ concentrations has several implications for future evaluations of household air pollution. First, the high correlation between $PM_{2.5}$ shorter-term averaging windows and 24-hour average indicates that the 24-hour average may be a sufficient and cost-effective, quantification of exposure, especially when evaluating chronic-disease outcomes. Real-time data however, may reveal stove use patterns and adoption behaviors

useful in evaluating cookstove interventions. The overall highest 5% of $PM_{2.5}$ concentrations contributed substantially to the overall 24-hour average, and may indicate that improving combustion or changing cooking habits in order to reduce the highest concentrations will decrease overall average concentrations.

Our study with the DiSCMini ultrafine particle monitor is only the second to quantify ultrafine particle number concentrations in kitchens from biomass cookstoves. It is the first study to characterize 24-hour concentrations of real-time $PM_{2.5}$ and ultrafine PNC from traditional and cleaner burning biomass cookstoves and offers several interesting findings. The median of the 24-hour average PNC in kitchens with *Justa* stoves was 70% lower than the median of the 24-hour average PNC kitchen concentration in kitchens with traditional stoves. Our study is limited by a relatively small sample size and further research is needed to determine if cleaner-burning biomass cookstoves truly emit lower PNC in a field setting. The 24-hour average $PM_{2.5}$ and ultrafine PNC concentrations among all stoves were highly correlated, however when stratifying the analysis by stove type, the correlation was lower among *Justa* stove households. Additional research with a larger sample size of traditional and cleaner-burning stoves is needed before we can determine if monitoring ultrafine PNC will add useful information in models of exposure and health outcomes for various stove types.

The exposure portion of the study has several limitations. First, measuring ultrafine PNC was limited by several technical issues of the DiSCMini instrument. Primarily, the DiSCMini is not built to monitor the very high concentrations of particles observed in the homes, which resulted in instrument clogging and reduced air flow. At this time, we are unable to quantify these impacts on the data. Future lab testing should be conducted in order to quantify the impact of the clogged

inlet and low flow on PNC measurements. Additional guidelines and study protocols would also be useful to standardize future data collection. Finally, all kitchen and personal concentrations were measured for only one 24-hour period and we cannot be certain we captured a "typical" concentration for the kitchens or personal measurements. Repeated measurements of these concentrations may elucidate how variable kitchen and personal concentrations are over time.

Biomarkers and Chronic Disease

Aims 2 and 3 add to the body of literature evaluating the health impacts of household air pollution. Among adults, there is evidence that exposure to household air pollution is associated with chronic obstructive pulmonary disease (COPD), lung cancer, cataracts, tuberculosis, adult lower respiratory infections, and adverse pregnancy outcomes (Smith et al. 2014b). The underlying mechanisms of pulmonary diseases associated with air pollution are not well understood; however, evidence suggests that exposure may result in increased reactive oxygen species and production of proinflammatory cytokines, leading to airway inflammation (Bernstein et al. 2004; Holgate et al. 2003; van Eeden et al. 2001). Previous household air pollution studies have focused on COPD, acute lower respiratory diseases, and forced expiratory volume; however, other pulmonary impacts, such as asthma and airway inflammation, have not been well studied. Although evidence is available for increased blood pressure and ischemic heart disease, the association between exposure to household air pollution and cardiovascular disease requires additional investigation to clarify the mechanisms of disease (R. D. Brook et al. 2010).

In aim 2, we did not observe an association between kitchen or personal concentrations of $PM_{2.5}$ or black carbon and a marker of airway inflammation, FeNO. Our study was limited to the use of a portable instrument that captured airway inflammation in the proximal airways. We were

unable to assess the association between household air pollution concentrations and distal airway inflammation. Future studies should consider the assessment of airway inflammation from household air pollution at both the proximal and distal airways.

In aim 3, we observed inconsistent associations between levels of household air pollution and 7 markers of systemic inflammation. Results of the association of household air pollution on markers of systemic inflammation were largely inconsistent, however we observed associations between C - reactive protein (CRP) and serum amyloid-A (SAA). Several inflammatory markers, such as ICAM-1, VCAM-1, TNF-α were consistent with the null. The results of effect modification analyses by risk factors associated with cardiovascular disease risk were also inconsistent. Several associations did not support our original hypotheses that higher concentrations of household air pollution would result in stronger increases in markers of systemic inflammation among women who had cardiovascular disease risk factors. For example, risk factors such as older age (≥40 years) and high blood pressure in general had no impact on the association between household air pollution and markers of systemic inflammation. When stratifying by BMI, we observed that higher concentrations of household air pollution often resulted in lower concentrations of markers of systemic inflammation compared to women with high BMI (≥25.1). Additionally, when categorizing women into those with pre-diabetes or diabetes vs. normal, we also observed inconsistent associations; sometimes higher concentrations of household air pollution were associated with higher concentrations of inflammatory markers among women who were pre-diabetic or diabetic (IL-8), while other times higher concentrations of household air pollution were associated with higher concentrations of systemic inflammation among women without pre-

diabetes or diabetes (CRP, SAA, ICAM, VCAM). Several of these results for effect modification do not support our hypotheses, and make interpreting the overall results difficult.

Our inconsistent results may be due to the complex mechanisms of air pollution on inflammation and cardiovascular disease. Additionally, each marker of systemic inflammation plays a slightly different role in the possible inflammation pathways. For example, cytokines (such as IL-8, IL-1β, and TNF-α) play a role in mediating acute inflammatory reactions and are involved in the activation of the other markers of inflammation we studied (CRP, SAA, ICAM-1 and VCAM-1). CRP and SAA are synthesized in the liver in response to increases of cytokines and cellular adhesion molecules (ICAM-1 and VCAM-1) are also induced by cytokines at the endothelium. It is unclear how the cascade of inflammatory response may influence levels of the various markers. For example, higher household air pollution concentrations were generally associated with decreased ICAM-1 and VCAM-1, however the confidence intervals were wide and results were not significant. Our results demonstrating that higher concentrations of household air pollution are associated with higher acute phase proteins, CRP and SAA, supports previous epidemiological air pollution literature findings. The similar effect estimates of the two markers also supports evidence of the immune response function that the two proteins act in a similar way. In order to interpret our inconsistent results, additional exploration is needed to further reveal the mechanistic pathways of inflammation and biomarkers indicative of various stages of cardiovascular disease risk. Similar investigation is needed into the role of other risk factors for cardiovascular disease risk, such as obesity and diabetes status.

Study Limitations

Our epidemiological study of household air pollution and measurements of inflammation is limited by the cross-sectional nature of the study design. We cannot establish whether exposure preceded disease. We attempted to address this potential limitation by including only women who had been using a cleaner-burning cookstove for more than four months (average length of *Justa* stove ownership was just under two years). Additionally, we only measured household air pollution concentrations and markers of inflammation from one point of time. We make the assumption that these measurements are representative of typical exposures and corresponding inflammation in order to represent long-term disease risk. Finally, the markers of systemic inflammation are non-specific markers of inflammation. Levels of inflammatory markers may be attributable to sources other than high concentrations of household air pollution. We controlled for possible confounding such as BMI, age, and socioeconomic factors associated with both household air pollution and increased inflammation. There may be residual confounding if we were unable to control for other confounders or improperly measured confounding variables with our questionnaire (such as SES) (Armstrong 1998). Participants who self-reported medication use such as anti-inflammatory medications were removed from the analysis. If however, women in the analysis were taking medications and did not report it, and their health status was associated with stove use and household air pollution concentrations differently than healthy women, we may also have residual confounding.

We utilized several techniques to reduce measurement error in the health outcomes. For example, the sample collection of FeNO and DBS was completed in the morning following the 24-hour exposure period for all participants. Many cytokines exhibit a strong diurnal pattern that peak

in the early morning (Zhou et al. 2010). Additionally, all DBS samples were frozen to minimize the degradation of the samples (most cytokines are stable at -80 degrees Celsius for up to 2 years). We believe any error would be non-differential error with respect to the biomarkers of inflammation.

It is possible that the study could have been subject to selection bias. Given that participants were recruited from a convenience sample of women at community meetings, if women who did not attend were older or sicker, we may not be able to generalize our results to the full community population. Results of this study may also not be generalizable to all populations or other cleaner-burning cookstove designs.

Future Directions

This dissertation adds to the limited evidence of household air pollution $PM_{2.5}$, black carbon, and ultrafine particle concentrations from traditional and cleaner-burning biomass cookstoves. Additionally, we utilized novel markers to explore the association of household air pollution of both airway and systemic inflammation. Future studies would benefit from combining the approaches from the three aims of this dissertation. For example, future studies should consider larger samples sizes and repeated measurements within participants of both household air pollution and biomarkers. Studies should evaluate ultrafine particle concentrations from various stove and fuel combinations and consider the implications of cleaner-burning stoves on household air pollution. If we find that ultrafine particles are different than $PM_{2.5}$ concentrations between various stove types or under certain stove conditions, epidemiological studies should also consider adding ultrafine particle exposure measurements to health studies in order to explore the health impact. Given the global burden due to cardiovascular disease, future studies

should also continue to explore the association of household air pollution and cardiovascular disease risk. Using biomarkers of systemic inflammation may provide critical insight into future cardiovascular disease risk.

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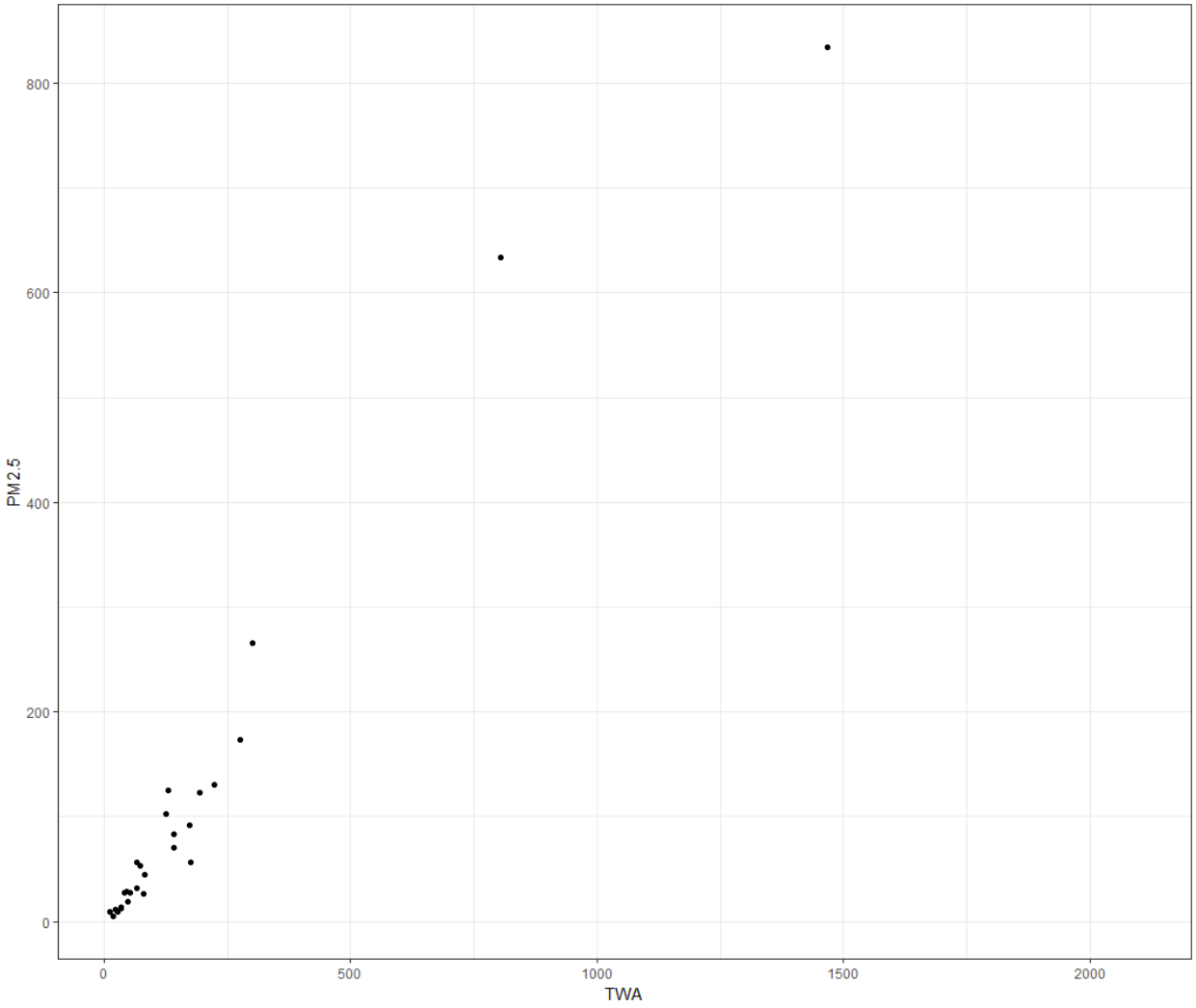
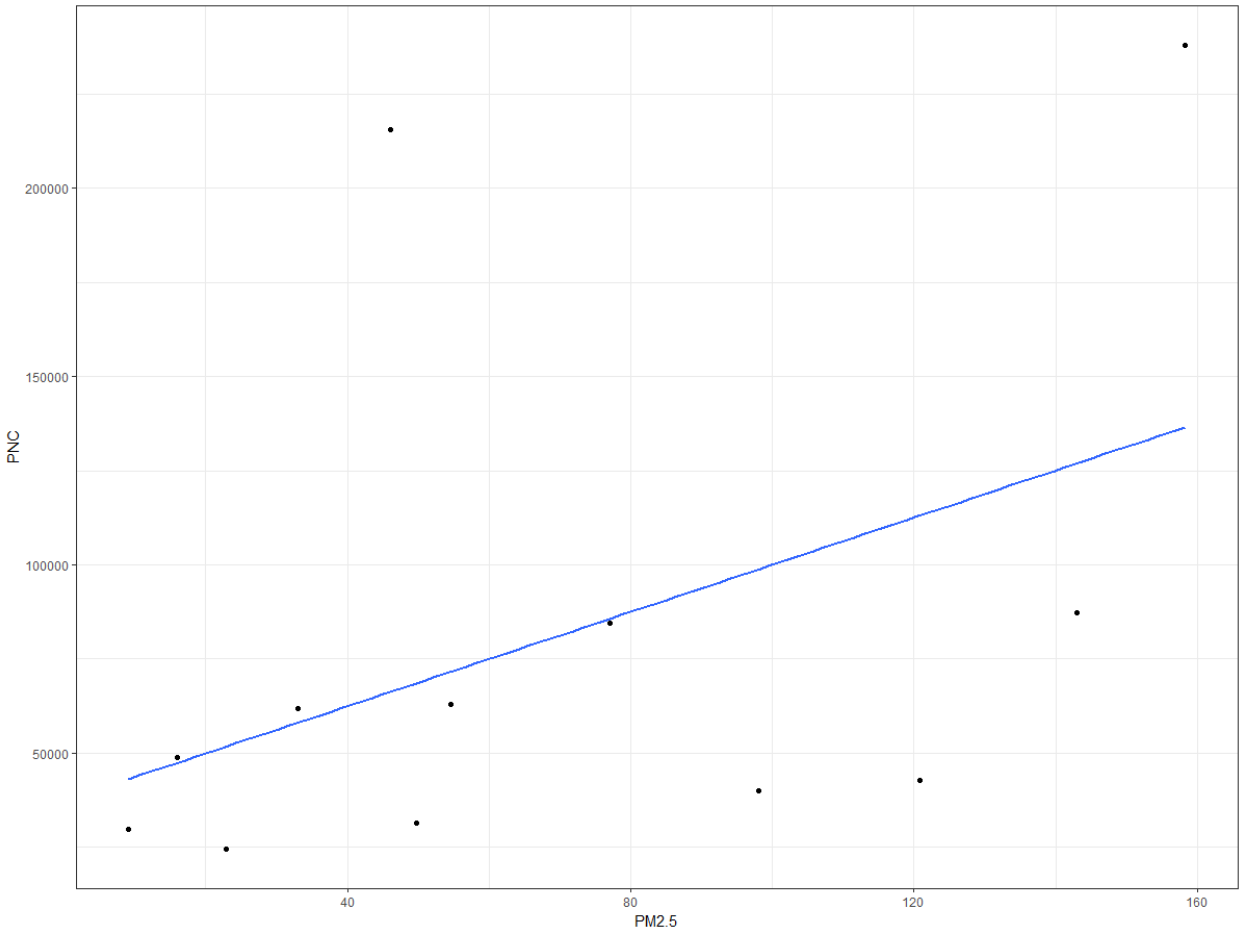
Appendices

Appendix 4.1: Observed Spearman rank correlation between optical real-time nephelometer and integrated gravimetric $PM_{2.5}$



(Spearman rho = 0.93 n =27). In this plot the nephelometer data has not been corrected using the time-integrated gravimetric filter measurement.

Appendix 4.2: $PM_{2.5}$ and PNC for kitchens with a *Justa* stove



Appendix 6.1: Distribution of pollution concentrations stratified by cardiovascular disease risk factors

	N	Kitchen PM	N	Personal PM	N	Kitchen BC	N	Personal BC
		median (25th, 75th)		median (25th, 75th)		median (25th, 75th)		median (25th, 75th)
Age < 40	69	129 (61,236)	69	74 (44,127)	70	18 (7, 59)	70	8 (4, 17)
Age ≥ 40	37	188 (75,476)	36	101 (52, 145)	37	34 (11, 101)	36	7 (4, 27)
BMI < 25.1	46	130 (71, 243)	46	94 (62, 144)	46	22 (11, 69)	46	10 (5, 27)
BMI ≥ 25.1	60	137 (54, 408)	59	74 (43, 125)	61	19 (7, 92)	60	6 (2, 15)
Normal	80	134 (64, 284)	81	75 (48, 130)	81	19 (8, 67)	81	7 (4, 15)
Pre-diabetes/ Diabetes	26	123 (58, 476)	24	97 (51, 145)	26	32 (10, 141)	25	9 (5, 35)
Normal	90	116 (61, 243)	89	75 (51, 133)	90	18 (8, 62)	90	7 (3, 15)
Pre-Hypertension/ Hypertension	16	341 (93, 764)	16	111 (53, 154)	17	68 (17, 188)	16	10 (3, 40)

Appendix 6.2: Crude and Adjusted Percent Difference in Inflammatory Markers Associated with Concentrations of Household Air Pollution Stratified By Age

CRP		N	Crude Estimate (pg/mL)	95% CI	95% CI	P-value	Adjusted Estimate (pg/mL)	95% CI	95% CI	P-value
Area PM										
	Age < 40	47	4.3	-3.2	12.4	0.49	5.6	-1.4	13.1	0.48
	Age ≥ 40	27	0.0	-8.7	9.6		1.6	-6.6	10.4	
Personal PM										
	Age < 40	48	8.2	-3.3	21.1	0.62	10.2	-0.6	22.1	1.00
	Age ≥ 40	25	2.6	-14.5	23.2		10.2	-7.4	31.2	
Area BC										
	Age < 40	48	3.3	-1.6	8.5	0.58	4.7	0.1	9.5	0.73
	Age ≥ 40	27	0.8	-6.4	8.7		1.6	-5.1	8.8	
Personal BC										
	Age < 40	48	2.7	-3.2	8.9	0.90	3.3	-2.1	9.1	0.63
	Age ≥ 40	25	2.0	-7.2	12.1		6.1	-3.1	16.1	
Stove Type										
Justa (ref)										
Traditional	Age < 40	30	6.2	-6.9	21.2	0.87	31.3	-24.8	129.1	0.92
	Age ≥ 40	24	4.3	-12.5	24.4		37.1	-35.6	191.9	
SAA										
Area PM										
	Age < 40	47	2.7	-2.1	7.8	0.94	3.9	-0.6	8.6	0.95
	Age ≥ 40	27	3.0	-2.9	9.3		4.1	-1.3	9.9	
Personal PM										
	Age < 40	48	7.0	-0.6	15.2	0.44	9.0	1.9	16.6	0.76
	Age ≥ 40	25	1.2	-10.3	14.2		6.8	-4.6	19.7	

Area BC										
	Age < 40	48	2.4	-0.9	5.8	0.99	3.5	0.5	6.6	0.97
	Age ≥ 40	27	2.3	-2.7	7.6		3.4	-1.1	8.2	
Personal BC										
	Age < 40	48	3.9	0.0	8.0	0.40	4.2	0.6	8.0	0.79
	Age ≥ 40	25	0.8	-5.2	7.2		3.3	-2.6	9.5	
Stove Type										
Justa (ref)										
Traditional	Age < 40	30	69.1	11.3	156.8	0.87	69.8	13.3	154.5	0.83
	Age ≥ 40	24	59.8	-8.6	179.3		83.3	5.8	217.4	
IL8										
Area PM										
	Age < 40	47	0.9	-1.8	3.7	0.13	0.8	-1.9	3.6	0.19
	Age ≥ 40	27	4.2	0.9	7.7		3.7	0.3	7.3	
Personal PM										
	Age < 40	48	0.2	-4.1	4.8	0.21	-0.1	-4.4	4.3	0.50
	Age ≥ 40	25	5.7	-1.6	13.6		2.7	-4.5	10.5	
Area BC										
	Age < 40	48	1.5	-0.3	3.4	0.24	1.4	-0.5	3.3	0.34
	Age ≥ 40	27	3.5	0.7	6.4		3.0	0.2	6.0	
Personal BC										
	Age < 40	48	0.3	-2.0	2.6	0.30	0.3	-1.9	2.6	0.79
	Age ≥ 40	25	2.6	-1.2	6.4		0.9	-2.8	4.8	
Stove Type										
Justa (ref)										
Traditional	Age < 40	30	2.1	-16.2	24.4	0.96	3.2	-18.9	31.2	0.76
	Age ≥ 40	24	1.3	-22.2	31.9		9.9	-20.7	52.3	

TNFa										
Area PM										
	Age < 40	47	0.3	-2.8	3.4	0.78	0.2	-2.9	3.4	0.76
	Age ≥ 40	27	-0.4	-4.1	3.4		-0.6	-4.3	3.3	
Personal PM										
	Age < 40	48	-0.1	-4.6	4.6	0.30	-0.1	-4.8	4.7	0.31
	Age ≥ 40	25	4.6	-3.0	12.7		4.7	-3.3	13.5	
Area BC										
	Age < 40	48	0.7	-1.6	2.9	0.89	0.7	-1.4	2.8	0.56
	Age ≥ 40	27	-0.1	-4.5	4.4		-0.4	-3.6	2.8	
Personal BC										
	Age < 40	48	-0.9	-3.3	1.5	0.42	-0.8	-3.3	1.7	0.47
	Age ≥ 40	25	0.9	-2.9	4.9		1.0	-3.1	5.3	
Stove Type										
Justa (ref)										
Traditional	Age < 40	30	-10.0	-29.7	15.4	0.59	-7.1	-27.5	18.9	0.95
	Age ≥ 40	24	0.5	-27.8	40.0		-8.2	-34.4	28.5	
Il-1β										
Area PM										
	Age < 40	47	1.2	-1.3	3.8	0.98	1.5	-1.0	4.1	1.00
	Age ≥ 40	27	1.1	-1.9	4.3		1.5	-1.6	4.7	
Personal PM*										
	Age < 40	48	-1.4	-5.1	2.4	0.18	-0.9	-4.6	2.9	0.10
	Age ≥ 40	25	3.6	-2.6	10.3		5.4	-1.1	12.4	
Area BC										
	Age < 40	48	0.9	-0.8	2.6	0.71	1.2	-0.5	2.9	0.73
	Age ≥ 40	27	0.3	-2.2	2.9		0.7	-1.9	3.3	

Personal BC										
	Age < 40	48	0.3	-1.7	2.3	0.80	0.5	-1.6	2.5	0.99
	Age ≥ 40	25	-0.2	-3.4	3.1		0.5	-2.9	3.9	
Stove Type										
Justa (ref)										
Traditional	Age < 40	30	2.1	-16.2	24.4	0.96	1.4	-17.0	23.8	0.89
	Age ≥ 40	24	1.3	-22.2	31.9		3.6	-21.0	35.8	
ICAM										
Area PM										
	Age < 40	47	-0.2	-1.8	1.3	0.61	-0.2	-1.8	1.4	0.58
	Age ≥ 40	27	-0.9	-2.7	1.0		-0.9	-2.9	1.0	
Personal PM										
	Age < 40	48	0.0	-2.3	2.4	0.57	0.1	-2.3	2.6	0.58
	Age ≥ 40	25	1.3	-2.5	5.3		1.5	-2.7	5.8	
Area BC										
	Age < 40	48	-0.1	-1.2	0.9	0.61	-0.13	-1.20	0.95	0.58
	Age ≥ 40	27	-0.6	-2.2	0.9		-0.68	-2.28	0.96	
Personal BC										
	Age < 40	48	-0.3	-1.5	0.9	0.82	-0.29	-1.57	1.01	0.84
	Age ≥ 40	25	0.0	-2.0	1.9		-0.04	-2.16	2.13	
Stove Type										
Justa (ref)										
Traditional	Age < 40	30	-5.4	-16.7	7.5	0.48	-4.84	-16.51	8.46	0.56
	Age ≥ 40	24	2.1	-13.9	21.1		1.55	-14.97	21.28	
VCAM										
Area PM										
	Age < 40	47	0.1	-1.3	1.5	1.00	-0.02	-1.41	1.38	0.97
	Age ≥ 40	27	0.1	-1.6	1.8		-0.06	-1.75	1.66	

Personal PM										
	Age < 40	48	-0.4	-2.4	1.6	0.11	-0.48	-2.52	1.61	0.13
	Age ≥ 40	25	2.7	-0.6	6.1		2.68	-0.85	6.35	
Area BC										
	Age < 40	48	0.0	-0.9	0.9	0.98	-0.07	-1.01	0.87	0.95
	Age ≥ 40	27	0.0	-1.4	1.4		-0.02	-1.44	1.41	
Personal BC										
	Age < 40	48	-0.1	-1.2	0.9	0.43	-0.12	-1.22	0.98	0.53
	Age ≥ 40	25	0.7	-1.0	2.4		0.56	-1.26	2.42	
Stove Type										
Justa (ref)										
Traditional	Age < 40	30	3.5	-7.9	16.2	0.36	2.62	-7.96	14.41	0.47
	Age ≥ 40	24	13.2	-3.1	32.2		9.68	-5.38	27.12	

Cl: Confidence interval; PM2.5: fine particulate matter; CRP (C-reactive protein); SAA (serum amyloid-a); IL-8 (interleukin-8); IL-1β (interleukin 1β); TNF-α (tumor necrosis factor-α); ICAM-1 (intercellular adhesion molecule 1); VCAM-1 (intercellular molecule 1).

1: Models were adjusted for age, body mass index (BMI), number of assets (<2 or ≥2), electricity (yes/no), years of education (<6 or ≥6)

2: In continuous exposure models, inflammatory markers and measured pollution were both natural log transformed. Beta coefficients were entered into the formula ((1.25^β)-1) and multiplied by 100. We can interpret the estimate of the continuous pollution exposures as a percent increase in inflammatory marker for each 25% increase in exposure. Example: There is a 10.49% higher CRP level with a 25% higher personal PM2.5 concentration.

*†Inflammatory markers were log-transformed. Categorical variable beta coefficients were entered into the formula (e^β-1)*100). The estimates for the categorical measures of exposure can be interpreted as the percent difference in inflammatory marker when comparing traditional stove to the reference (Justa stove).*

Appendix 6.3: Crude and Adjusted Percent Difference in Inflammatory Markers Associated with Concentrations of Household Air Pollution Stratified By BMI

CRP		N	Crude Estimate (pg/mL)	95% CI	95% CI	P-value	Adjusted Estimate (pg/mL)	95% CI	95% CI	P-value
Area PM										
	BMI < 25.1	31	-1.4	-9.7	7.6	0.16	7.1	0.4	14.1	0.16
	BMI ≥ 25.1	43	6.5	-0.1	13.5		-5.7	-14.8	4.4	
Personal PM										
	BMI < 25.1	30	0.7	-12.5	15.9	0.10	4.2	-10.5	21.3	0.22
	BMI ≥ 25.1	43	16.9	4.7	30.7		16.9	4.5	30.7	
Area BC										
	BMI < 25.1	31	2.0	-3.8	8.1	0.56	2.7	-3.4	9.2	0.61
	BMI ≥ 25.1	44	4.3	-0.6	9.4		4.8	-0.3	10.0	
Personal BC										
	BMI < 25.1	30	3.6	-5.2	13.2	0.31	5.2	-4.1	15.3	0.96
	BMI ≥ 25.1	43	4.8	-1.0	10.8		4.9	-0.9	11.1	
Stove Type										
Justa (ref)										
Traditional	BMI < 25.1	26	21.7	-36.3	132.7	0.68	20.7	-37.1	131.6	0.53
	BMI ≥ 25.1	28	46.4	-19.9	167.5		59.2	-13.0	191.3	
SAA										
Area PM										
	BMI < 25.1	31	-0.4	-6.4	6.0	0.42	3.6	-2.2	9.8	0.91
	BMI ≥ 25.1	43	2.7	-1.8	7.5		4.0	-0.1	8.3	
Personal PM										
	BMI < 25.1	30	-2.3	-11.8	8.2	0.16	6.6	-3.2	17.5	0.76
	BMI ≥ 25.1	43	7.1	-1.2	16.1		8.6	1.1	16.6	

Area BC										
	BMI < 25.1	31	2.4	-1.9	6.8	0.63	4.9	1.0	9.0	0.34
	BMI ≥ 25.1	44	1.0	-2.4	4.6		2.5	-0.6	5.7	
Personal BC										
	BMI < 25.1	30	2.8	-3.5	9.4	0.89	6.5	0.6	12.7	0.30
	BMI ≥ 25.1	43	2.2	-1.8	6.4		2.9	-0.7	6.6	
Stove Type										
Justa (ref)										
Traditional	BMI < 25.1	26	68.1	2.4	175.8	0.68	91.7	18.8	209.6	0.60
	BMI ≥ 25.1	28	46.4	-7.7	132.1		61.7	3.7	152.1	
IL8										
Area PM*										
	BMI < 25.1	31	6.5	3.2	9.9	0.00	6.3	2.8	9.9	0.00
	BMI ≥ 25.1	43	0.1	-2.2	2.4		0.0	-2.3	2.4	
Personal PM*										
	BMI < 25.1	30	7.8	1.9	14.0	0.01	5.7	-0.5	12.3	0.03
	BMI ≥ 25.1	43	-2.6	-6.9	1.8		-2.8	-7.1	1.6	
Area BC*										
	BMI < 25.1	31	4.2	1.9	6.5	0.02	4.2	1.8	6.6	0.02
	BMI ≥ 25.1	44	0.6	-1.2	2.5		0.5	-1.4	2.3	
Personal BC										
	BMI < 25.1	30	3.4	-0.3	7.1	0.08	2.6	-1.1	6.4	0.15
	BMI ≥ 25.1	43	-0.5	-2.7	1.8		-0.6	-2.8	1.7	
Stove Type										
Justa (ref)										
Traditional	BMI < 25.1	26	-1.1	-24.9	30.2	0.50	-1.2	-25.5	31.1	0.62
	BMI ≥ 25.1	28	12.4	-13.0	45.3		8.6	-16.4	41.2	

TNFa										
Area PM										
	BMI < 25.1	31	-0.2	-4.0	3.7	0.73	-1.4	-5.4	2.8	0.47
	BMI ≥ 25.1	43	0.6	-2.2	3.5		0.4	-2.4	3.3	
Personal PM										
	BMI < 25.1	30	-0.5	-6.6	6.0	0.35	-1.8	-8.3	5.2	0.27
	BMI ≥ 25.1	43	3.3	-1.7	8.6		3.0	-2.1	8.3	
Area BC										
	BMI < 25.1	31	0.7	-1.4	2.8	0.41	0.9	-1.8	3.7	0.55
	BMI ≥ 25.1	44	-0.4	-3.6	2.8		-0.1	-2.3	2.1	
Personal BC										
	BMI < 25.1	30	-1.1	-4.9	2.8	0.54	-1.8	-5.7	2.3	0.40
	BMI ≥ 25.1	43	0.3	-2.1	2.8		0.3	-2.3	2.8	
Stove Type										
Justa (ref)										
Traditional*	BMI < 25.1	26	-18.2	-38.6	9.0	0.14	-24.6	-43.1	-0.2	0.06
	BMI ≥ 25.1	28	9.6	-16.1	43.1		9.1	-15.9	41.6	
Il-1β										
Area PM	BMI < 25.1	31	2.7	-0.4	6.0	0.29	3.2	-0.1	6.7	0.23
	BMI ≥ 25.1	43	0.6	-1.7	2.9		0.8	-1.5	3.2	
Personal PM	BMI < 25.1	30	0.4	-4.7	5.8	0.96	1.9	-3.7	7.8	0.71
	BMI ≥ 25.1	43	0.6	-3.5	4.9		0.6	-3.5	4.9	
Area BC	BMI < 25.1	31	1.4	-0.7	3.6	0.50	1.7	-0.5	3.9	0.52
	BMI ≥ 25.1	44	0.5	-1.3	2.2		0.8	-1.0	2.5	
Personal BC	BMI < 25.1	30	1.1	-2.1	4.3	0.64	1.5	-1.7	5.0	0.52
	BMI ≥ 25.1	43	0.2	-1.8	2.2		0.3	-1.8	2.4	

Stove Type										
Justa (ref)										
Traditional	BMI < 25.1	26	6.7	-14.9	34.0	0.66	7.2	-15.1	35.3	0.66
	BMI ≥ 25.1	28	-0.3	-19.3	23.1		0.1	-19.3	24.2	
ICAM										
Area PM	BMI < 25.1	31	0.6	-1.4	2.6	0.37	0.1	-2.0	2.2	0.51
	BMI ≥ 25.1	43	-0.6	-2.0	0.9		-0.7	-2.2	0.7	
Personal PM	BMI < 25.1	30	2.1	-1.2	5.5	0.31	1.9	-1.6	5.6	0.32
	BMI ≥ 25.1	43	0.0	-2.6	2.6		-0.3	-2.8	2.4	
Area BC	BMI < 25.1	31	0.7	-0.6	2.0	0.14	0.5	-0.9	1.9	0.14
	BMI ≥ 25.1	44	-0.6	-1.6	0.5		-0.8	-1.9	0.3	
Personal BC*	BMI < 25.1	30	1.5	-0.5	3.5	0.05	1.4	-0.6	3.5	0.05
	BMI ≥ 25.1	43	-0.8	-2.0	0.5		-1.0	-2.2	0.3	
Stove Type										
Justa (ref)										
Traditional	BMI < 25.1	26	2.6	-11.9	19.5		-0.8	-14.6	15.3	
	BMI ≥ 25.1	28	-3.6	-16.4	11.1	0.55	-4.8	-17.2	9.4	0.68
VCAM										
Area PM	BMI < 25.1	31	0.3	-1.4	2.0		-0.1	-1.9	1.8	
	BMI ≥ 25.1	43	0.0	-1.2	1.2	0.78	-0.1	-1.4	1.1	0.95
Personal PM	BMI < 25.1	30	1.2	-1.6	4.0		1.1	-1.9	4.2	
	BMI ≥ 25.1	43	-0.1	-2.2	2.1	0.49	-0.2	-2.4	2.1	0.50
Area BC	BMI < 25.1	31	0.3	-0.9	1.4		0.0	-1.2	1.2	
	BMI ≥ 25.1	44	-0.1	-1.1	0.8	0.57	-0.2	-1.2	0.7	0.72
Personal BC	BMI < 25.1	30	1.0	-0.7	2.7		0.9	-0.9	2.7	
	BMI ≥ 25.1	43	-0.3	-1.4	0.8	0.21	-0.4	-1.5	0.7	0.23

Stove Type										
Justa (ref)										
Traditional	BMI < 25.1	26	4.3	-8.9	19.3	0.55	1.0	-10.8	14.3	0.52
	BMI ≥ 25.1	28	10.2	-2.8	24.9		6.6	-5.0	19.7	

Cl: Confidence interval; PM2.5: fine particulate matter; CRP (C-reactive protein); SAA (serum amyloid-a); IL-8 (interleukin-8); IL-1β (interleukin 1β); TNF-α (tumor necrosis factor-α); ICAM-1 (intercellular adhesion molecule 1); VCAM-1 (intercellular molecule 1).

1: Models were adjusted for age, body mass index (BMI), number of assets (<2 or ≥2), electricity (yes/no), years of education (<6 or ≥6)

2: In continuous exposure models, inflammatory markers and measured pollution were both natural log transformed. Beta coefficients were entered into the formula ((1.25^β)-1) and multiplied by 100. We can interpret the estimate of the continuous pollution exposures as a percent increase in inflammatory marker for each 25% increase in exposure. Example: There is a 10.49% higher CRP level with a 25% higher personal PM2.5 concentration.

*†Inflammatory markers were log-transformed. Categorical variable beta coefficients were entered into the formula (e^β-1)*100). The estimates for the categorical measures of exposure can be interpreted as the percent difference in inflammatory marker when comparing traditional stove to the reference (Justa stove)*

Appendix 6.4: Crude and Adjusted Percent Difference in Inflammatory Markers Associated with Concentrations of Household Air Pollution Stratified By Blood Pressure

CRP		N	Crude Estimate (pg/mL)	95% CI	95% CI	P-value	Adjusted Estimate (pg/mL)	95% CI	95% CI	P-value
Area PM										
	Normal	61	-1.1	-7.0	5.1	0.45	0.7	-5.0	6.8	0.31
	Pre-Hypertension/ Hypertension	13	5.7	-10.3	24.5		9.6	-6.2	28.1	
Personal PM										
	Normal	60	2.8	-7.0	13.6	0.40	6.9	-2.7	17.5	0.46
	Pre-Hypertension/ Hypertension	13	13.9	-8.8	42.3		16.6	-5.7	44.2	
Area BC										
	Normal	61	0.6	-3.9	5.2	0.95	2.4	-1.9	7.0	0.89
	Pre-Hypertension/ Hypertension	14	0.9	-8.7	11.6		1.7	-7.7	12.0	
Personal BC										
	Normal	60	0.2	-5.2	5.8	0.42	2.0	-3.2	7.5	0.45
	Pre-Hypertension/ Hypertension	13	5.0	-5.2	16.4		6.5	-3.5	17.5	
Stove Type										
Justa (ref)										
Traditional	Normal	38	14.1	-31.8	91.1	0.92	18.4	-27.5	93.1	0.84
	Pre-Hypertension/ Hypertension	16	21.5	-58.8	257.7		34.1	-52.0	274.4	
SAA										
Area PM*										
	Normal	61	0.8	-3.4	5.2	0.11	2.8	-1.1	6.8	0.08
	Pre-Hypertension/ Hypertension	13	11.2	-0.6	24.5		13.1	2.1	25.2	
Personal PM										
	Normal	60	3.0	-4.0	10.4	0.24	7.0	0.4	14.1	0.31
	Pre-Hypertension/ Hypertension	13	13.9	-2.5	33.0		16.0	0.5	33.8	
Area BC										

	Normal	61	1.2	-1.9	4.5	0.11	3.2	0.2	6.2	0.24
	Pre-Hypertension/ Hypertension	14	7.8	0.5	15.7		7.6	0.9	14.7	
Personal BC										
	Normal	60	2.1	-1.7	6.1	0.29	3.5	-0.1	7.2	0.43
	Pre-Hypertension/ Hypertension	13	6.6	-0.7	14.5		6.6	-0.2	13.9	
Stove Type										
Justa (ref)										
Traditional	Normal	38	66.7	14.1	143.7	0.80	82.9	26.8	163.8	0.73
	Pre-Hypertension/ Hypertension	16	49.2	-32.7	230.6		57.4	-27.0	239.3	
IL8										
Area PM										
	Normal	61	2.5	0.1	5.0	0.88	2.0	-0.5	4.5	0.99
	Pre-Hypertension/ Hypertension	13	2.0	-4.3	8.7		2.1	-4.4	8.9	
Personal PM										
	Normal	60	2.5	-1.6	6.8	0.30	1.1	-3.0	5.3	0.38
	Pre-Hypertension/ Hypertension	13	-2.7	-11.3	6.6		-3.4	-11.9	6.0	
Area BC										
	Normal	61	2.3	0.5	4.1	0.63	1.8	-0.1	3.7	0.98
	Pre-Hypertension/ Hypertension	14	1.2	-2.8	5.3		1.7	-2.3	6.0	
Personal BC										
	Normal	60	0.6	-1.6	2.9	0.76	0.1	-2.2	2.4	0.57
	Pre-Hypertension/ Hypertension	13	1.4	-2.9	5.8		1.5	-2.7	5.9	
Stove Type										
Justa (ref)										
Traditional	Normal	38	-1.1	-20.3	22.8	0.40	-1.6	-20.4	21.7	0.43
	Pre-Hypertension/ Hypertension	16	22.3	-22.3	92.5		19.9	-23.1	87.1	
TNFa										
Area PM										
	Normal	61	-0.5	-3.1	2.2	0.46	-0.6	-3.4	2.2	0.55

	Pre-Hypertension/ Hypertension	13	2.4	-4.6	9.9		1.7	-5.5	9.6	
Personal PM										
	Normal	60	0.3	-3.9	4.7	0.50	0.3	-4.1	5.0	0.64
	Pre-Hypertension/ Hypertension	13	4.0	-5.5	14.3		3.0	-7.0	14.1	
Area BC										
	Normal	61	0.4	-1.7	2.5	0.67	0.2	-1.9	2.3	0.87
	Pre-Hypertension/ Hypertension	14	1.6	-6.4	10.3		-0.3	-4.8	4.5	
Personal BC										
	Normal	60	-1.3	-3.5	1.0	0.23	-1.2	-3.6	1.2	0.30
	Pre-Hypertension/ Hypertension	13	1.7	-2.6	6.2		1.5	-3.1	6.4	
Stove Type										
Justa (ref)										
Traditional	Normal	38	-11.0	-28.6	11.0	0.43	-11.8	-29.2	9.8	0.74
	Pre-Hypertension/ Hypertension	16	9.5	-31.1	73.9		-3.8	-39.3	52.6	
Il-1β			0.7	-1.4	3.0	0.59	1.3	-1.0	3.6	0.76
Area PM	Normal	61	2.5	-3.3	8.6		2.2	-3.7	8.5	
	Pre-Hypertension/ Hypertension	13								
			-0.7	-4.2	3.0	0.43	0.3	-3.4	4.1	0.76
Personal PM	Normal	60	2.9	-5.0	11.4		1.7	-6.4	10.6	
	Pre-Hypertension/ Hypertension	13								
			0.6	-1.0	2.2	0.96	1.2	-0.5	2.9	0.54
Area BC	Normal	61	0.7	-2.9	4.4		-0.1	-3.7	3.7	
	Pre-Hypertension/ Hypertension	14								
			0.1	-1.8	2.1	0.90	0.7	-1.3	2.8	0.50
Personal BC	Normal	60	-0.1	-3.7	3.6		-0.8	-4.5	3.1	
	Pre-Hypertension/ Hypertension	13								

Stove Type										
Justa (ref)										
Traditional	Normal	38	2.5	-13.7	21.8	0.30	3.8	-12.9	23.7	0.24
	Pre-Hypertension/ Hypertension	16	-16.7	-41.9	19.4		-18.6	-43.6	17.7	
ICAM										
Area PM	Normal	61	-0.8	-2.1	0.6	0.30	-0.9	-2.3	0.5	0.34
	Pre-Hypertension/ Hypertension	13	1.3	-2.3	5.0		1.0	-2.7	4.9	
Personal PM	Normal	60	0.0	-2.2	2.3	0.28	0.0	-2.4	2.3	0.34
	Pre-Hypertension/ Hypertension	13	3.0	-1.9	8.2		2.8	-2.5	8.3	
Area BC	Normal	61	-0.5	-1.4	0.5	0.41	-0.6	-1.6	0.5	0.46
	Pre-Hypertension/ Hypertension	14	0.6	-1.7	2.8		0.4	-2.0	2.8	
Personal BC	Normal	60	-0.7	-1.8	0.5	0.16	-0.8	-2.0	0.5	0.19
	Pre-Hypertension/ Hypertension	13	1.2	-1.1	3.5		1.1	-1.3	3.5	
Stove Type										
Justa (ref)										
Traditional	Normal	38	-6.1	-16.2	5.3	0.20	-6.9	-16.9	4.4	0.31
	Pre-Hypertension/ Hypertension	16	11.8	-12.1	42.1		6.7	-15.9	35.5	
VCAM										
Area PM	Normal	61	-0.3	-1.5	0.8	0.35	-0.5	-1.7	0.7	0.49
	Pre-Hypertension/ Hypertension	13	1.2	-1.8	4.4		0.6	-2.5	3.9	
Personal PM	Normal	60	-0.3	-2.2	1.5	0.13	-0.4	-2.3	1.6	0.19
	Pre-Hypertension/ Hypertension	13	3.2	-1.0	7.5		2.9	-1.6	7.5	

Area BC	Normal	61	-0.2	-1.0	0.7	0.62	-0.3	-1.2	0.6	0.83
	Pre-Hypertension/ Hypertension	14	0.4	-1.6	2.3		-0.1	-2.1	2.0	
Personal BC	Normal	60	-0.2	-1.3	0.8	0.34	-0.3	-1.4	0.8	0.46
	Pre-Hypertension/ Hypertension	13	0.8	-1.1	2.8		0.6	-1.5	2.6	
Stove Type										
Justa (ref)										
Traditional	Normal	38	6.0	-4.5	17.6	0.84	4.1	-5.4	14.5	0.82
	Pre-Hypertension/ Hypertension	16	8.7	-12.6	35.2		1.5	-16.9	24.0	

Cl: Confidence interval; PM2.5: fine particulate matter; CRP (C-reactive protein); SAA (serum amyloid-a); IL-8 (interleukin-8); IL-1β (interleukin 1β); TNF-α (tumor necrosis factor-α); ICAM-1 (intercellular adhesion molecule 1); VCAM-1 (intercellular molecule 1).

1: Models were adjusted for age, body mass index (BMI), number of assets (<2 or ≥2), electricity (yes/no), years of education (<6 or ≥6)

2: In continuous exposure models, inflammatory markers and measured pollution were both natural log transformed. Beta coefficients were entered into the formula ((1.25^β)-1) and multiplied by 100. We can interpret the estimate of the continuous pollution exposures as a percent increase in inflammatory marker for each 25% increase in exposure. Example: There is a 10.49% higher CRP level with a 25% higher personal PM2.5 concentration.

*†Inflammatory markers were log-transformed. Categorical variable beta coefficients were entered into the formula (e^β-1)*100). The estimates for the categorical measures of exposure can be interpreted as the percent difference in inflammatory marker when comparing traditional stove to the reference (Justa stove)*

Appendix 6.5: Crude and Adjusted Percent Difference in Inflammatory Markers Associated with Concentrations of Household Air Pollution Stratified By Diabetes Status

CRP		N	Crude Estimate (pg/mL)	95% CI	95% CI	P-value	Adjusted Estimate (pg/mL)	95% CI	95% CI	P-value
Area PM*										
	Normal	53	7.1	0.7	14.0	0.03	8.6	2.6	15.0	0.01
	Pre-diabetes/ Diabetes	19	-5.7	-14.5	4.1		-6.1	-14.3	2.8	
Personal PM*										
	Normal	53	18.3	7.1	30.6	0.01	20.7	10.0	32.4	0.01
	Pre-diabetes/ Diabetes	18	-10.7	-25.9	7.7		-6.0	-21.0	11.9	
Area BC										
	Normal	54	4.7	-0.1	9.6	0.25	5.8	1.3	10.5	0.16
	Pre-diabetes/ Diabetes	19	-0.3	-7.1	6.9		0.1	-6.2	6.8	
Personal BC										
	Normal	53	5.3	-0.7	11.7	0.45	7.4	1.7	13.4	0.19
	Pre-diabetes/ Diabetes	18	1.1	-7.2	10.3		0.6	-7.3	9.2	
Stove Type										
Justa (ref)										
Traditional	Normal	41	69.6	-1.4	191.6	0.15	48.9	-10.8	148.4	0.32
	Pre-diabetes/ Diabetes	12	-22.4	-68.7	92.4		-11.0	-63.2	115.5	
SAA										
Area PM										
	Normal	53	2.0	-2.1	6.2	0.93	4.4	0.5	8.3	0.67
	Pre-diabetes/ Diabetes	19	1.6	-4.8	8.5		2.8	-3.1	9.1	
Personal PM										
	Normal	53	6.3	-0.7	13.8	0.55	10.8	4.2	17.9	0.31
	Pre-diabetes/ Diabetes	18	1.7	-10.6	15.8		3.8	-7.6	16.5	
Area BC										

	Normal	54	0.9	-2.1	4.1	0.41	3.0	0.2	6.0	0.68
	Pre-diabetes/ Diabetes	19	3.3	-1.4	8.2		4.1	-0.1	8.5	
Personal BC										
	Normal	53	3.3	-0.5	7.4	0.47	5.1	1.5	8.8	0.24
	Pre-diabetes/ Diabetes	18	0.8	-4.7	6.7		1.2	-3.8	6.6	
Stove Type										
Justa (ref)										
Traditional	Normal	41	55.1	6.0	127.1	0.71	81.9	24.9	165.0	0.65
	Pre-diabetes/ Diabetes	12	34.8	-28.8	155.1		53.4	-19.9	193.8	
IL8										
Area PM*										
	Normal	53	0.1	-2.1	2.4	0.00	-0.3	-2.6	2.0	0.00
	Pre-diabetes/ Diabetes	19	8.0	4.3	12.0		8.2	4.4	12.2	
Personal PM*										
	Normal	53	0.1	-4.2	4.5	0.06	-1.3	-5.4	3.0	0.04
	Pre-diabetes/ Diabetes	18	9.1	0.6	18.3		8.3	0.0	17.4	
Area BC*										
	Normal	54	0.7	-1.1	2.4	0.01	0.3	-1.5	2.1	0.00
	Pre-diabetes/ Diabetes	19	5.4	2.7	8.2		5.6	2.9	8.4	
Personal BC										
	Normal	53	0.3	-2.1	2.8	0.33	-0.3	-2.7	2.1	0.18
	Pre-diabetes/ Diabetes	18	2.5	-1.1	6.2		2.7	-0.9	6.4	
Stove Type										
Justa (ref)										
Traditional	Normal	41	8.5	-14.5	37.5	0.89	10.7	-11.3	38.0	0.55
	Pre-diabetes/ Diabetes	12	5.0	-29.5	56.3		-3.1	-33.9	42.0	
TNFa										

Area PM										
	Normal	55	0.9	-1.8	3.6	0.36	0.5	-2.3	3.4	0.35
	Pre-diabetes/ Diabetes	19	-1.4	-5.5	2.9		-2.0	-6.3	2.5	
Personal PM										
	Normal	55	1.6	-2.8	6.1	0.90	1.2	-3.4	6.0	0.91
	Pre-diabetes/ Diabetes	18	1.0	-7.3	9.9		0.6	-8.1	10.1	
Area BC										
	Normal	54	0.4	-1.6	2.4	0.92	0.1	-2.0	2.2	0.91
	Pre-diabetes/ Diabetes	19	0.6	-2.4	3.6		0.3	-2.8	3.5	
Personal BC										
	Normal	53	-0.4	-2.9	2.1	0.73	-0.5	-3.0	2.2	0.87
	Pre-diabetes/ Diabetes	18	0.4	-3.3	4.1		-0.1	-3.9	3.9	
Stove Type										
Justa (ref)										
Traditional	Normal	41	4.2	-17.6	31.7	0.46	-6.6	-25.7	17.3	0.79
	Pre-diabetes/ Diabetes	12	-12.1	-40.6	30.2		-11.9	-40.6	30.6	
Il-1β										
Area PM	Normal	55	1.5	-0.8	3.7	0.83	1.9	-0.4	4.2	0.66
	Pre-diabetes/ Diabetes	19	1.0	-2.5	4.6		0.9	-2.7	4.7	
Personal PM	Normal	55	0.4	-3.2	4.1	0.92	1.2	-2.5	5.1	0.73
	Pre-diabetes/ Diabetes	18	0.0	-6.8	7.3		-0.2	-7.3	7.3	
Area BC	Normal	54	1.3	-0.3	2.9	0.35	1.8	0.2	3.5	0.19
	Pre-diabetes/ Diabetes	19	-0.1	-2.4	2.3		-0.1	-2.5	2.3	
Personal BC	Normal	53	1.1	-0.9	3.1	0.64	1.6	-0.5	3.7	0.24
	Pre-diabetes/ Diabetes	18	-0.2	-3.1	2.8		-0.6	-3.6	2.5	

Stove Type										
Justa (ref)										
Traditional	Normal	41	9.5	-8.6	31.2	0.43	4.6	-13.1	25.9	0.62
	Pre-diabetes/ Diabetes	12	-5.0	-29.8	28.6		-4.5	-30.7	31.5	
ICAM										
Area PM*	Normal	53	0.4	-1.0	1.8	0.15	0.2	-1.2	1.7	0.07
	Pre-diabetes/ Diabetes	19	-1.5	-3.7	0.7		-2.2	-4.4	0.1	
Personal PM	Normal	53	1.5	-0.8	3.9	0.25	1.4	-1.0	4.0	0.18
	Pre-diabetes/ Diabetes	18	-1.3	-5.6	3.1		-2.1	-6.5	2.5	
Area BC	Normal	54	0.2	-0.9	1.2	0.50	0.1	-1.0	1.1	0.35
	Pre-diabetes/ Diabetes	19	-0.5	-2.0	1.1		-0.9	-2.4	0.8	
Personal BC	Normal	53	0.3	-1.0	1.6	0.48	0.3	-1.1	1.7	0.24
	Pre-diabetes/ Diabetes	18	-0.6	-2.5	1.4		-1.2	-3.1	0.9	
Stove Type										
Justa (ref)										
Traditional	Normal	41	1.5	-10.5	15.2	0.62	-2.3	-13.2	10.0	0.74
	Pre-diabetes/ Diabetes	12	-4.7	-22.8	17.7		-6.1	-23.5	15.3	
VCAM										
Area PM*	Normal	55	0.7	-0.4	1.9	0.08	0.5	-0.6	1.7	0.05
	Pre-diabetes/ Diabetes	19	-1.2	-3.0	0.6		-1.7	-3.5	0.2	
Personal PM	Normal	55	0.7	-1.2	2.6	0.85	0.7	-1.3	2.7	0.59
	Pre-diabetes/ Diabetes	18	0.3	-3.3	4.1		-0.5	-4.2	3.4	

Area BC	Normal	54	0.4	-0.5	1.3	0.35	0.2	-0.7	1.2	0.25
	Pre-diabetes/ Diabetes	19	-0.4	-1.7	1.0		-0.8	-2.1	0.6	
Personal BC*	Normal	53	0.5	-0.6	1.6	0.22	0.5	-0.6	1.6	0.10
	Pre-diabetes/ Diabetes	18	-0.7	-2.2	0.9		-1.2	-2.8	0.5	
Stove Type										
Justa (ref)										
Traditional	Normal	41	7.0	-4.3	19.6	0.78	3.5	-6.1	14.1	0.89
	Pre-diabetes/ Diabetes	12	10.2	-8.5	32.8		4.8	-11.4	24.1	

Cl: Confidence interval; PM2.5: fine particulate matter; CRP (C-reactive protein); SAA (serum amyloid-a); IL-8 (interleukin-8); IL-1β (interleukin 1β); TNF-α (tumor necrosis factor-α); ICAM-1 (intercellular adhesion molecule 1); VCAM-1 (intercellular molecule 1).

1: Models were adjusted for age, body mass index (BMI), number of assets (<2 or ≥2), electricity (yes/no), years of education (<6 or ≥6)

2: In continuous exposure models, inflammatory markers and measured pollution were both natural log transformed. Beta coefficients were entered into the formula ((1.25^β)-1) and multiplied by 100. We can interpret the estimate of the continuous pollution exposures as a percent increase in inflammatory marker for each 25% increase in exposure. Example: There is a 10.49% higher CRP level with a 25% higher personal PM2.5 concentration.

*†Inflammatory markers were log-transformed. Categorical variable beta coefficients were entered into the formula (e^β-1)*100). The estimates for the categorical measures of exposure can be interpreted as the percent difference in inflammatory marker when comparing traditional stove to the reference (Justa stove)*