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Chronic exposure to biomass fuel smoke and markers of endothelial inflammation

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Abstract

Indoor smoke exposure may affect cardiovascular disease (CVD) risk via lung-mediated inflammation, oxidative stress, and endothelial inflammation. We sought to explore the association between indoor smoke exposure from burning biomass fuels and a selected group of markers for endothelial inflammation. We compared serum concentrations of amyloid A protein, E-selectin, soluble ICAM-1 and VCAM-1, von Willebrand factor (VWF), and high sensitivity C-reactive protein (hs-CRP) in 228 biomass exposed vs. 228 non-exposed participants living in Puno, Peru. Average age was 56 years (SD=13), average BMI was 26.5 kg/m^2 (SD=4.4), 48% were male, 59.4% completed high school and 2% reported a physician diagnosis of CVD. In unadjusted analysis, serum levels of soluble ICAM-1 (330 vs. 302 ng/mL; p<0.001), soluble VCAM-1 (403 vs. 362 ng/mL; p<0.001), and E-selectin (54.2 vs. 52.7 ng/mL; p=0.05) were increased in biomass exposed vs. non-exposed participants, respectively; whereas serum levels of vWF (1148 vs. 1311 mU/mL; p<0.001) and hs-CRP (2.56 vs. 3.12 mg/L; p<0.001) were decreased, respectively. In adjusted analyses, chronic exposure to biomass fuels remained positively associated with serum levels of soluble ICAM-1 (p=0.03) and VCAM-1 (p=0.05) and E-selectin (p=0.05), and remained negatively associated with serum levels of vWF (p=0.02) and hs-CRP (p<0.001). Daily exposure to biomass fuel smoke was associated with important differences in specific biomarkers of

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endothelial inflammation and may help explain accelerated atherosclerosis among those who are chronically exposed.

Keywords

biomass fuel exposure; rural communities; endothelial inflammation biomarkers; household air pollution; cardiovascular disease; epidemiology

INTRODUCTION

Household air pollution (HAP) is the third greatest cause of disability adjusted life years lost worldwide and it is responsible for 3.3 million deaths each year (Lim et al 2015). An increasing body of evidence suggests that HAP may also be responsible for an increased risk of cardiovascular disease (CVD) (Baumgartner et al 2011; Burroughs Pena et al 2015; Clark et al 2011; Dutta et al 2011; McCracken et al 2007; McCracken et al 2011; Lee et al 2012; Painschab et al 2013). Specifically, observational studies have found higher blood pressure (Baumgartner et al 2011; Burroughs Peña et al 2015; McCracken et al 2007); a thicker carotid intima-media complex (Painschab et al 2013), and an increased prevalence of self-reported coronary heart disease, stroke and diabetes in populations chronically exposed to biomass fuel smoke (Lee et al 2012). The mechanisms proposed include lung-mediated inflammation with a systemic release of cytokines (Barregard et al 2006), oxidative stress (Banerjee et al 2012), endothelial dysfunction (Allen et al 2011; Butarak et al 2011) and thrombogenesis (Ray et al 2006), all of which could lead to atherosclerosis and adverse health outcomes (Brevetti et al 2006; Fichtlscherer et al 2004; Verma et al 2002).

A healthy endothelium is necessary for appropriate functioning of the vasculature. Endothelial inflammation as a result of noxious events or activation of the inflammatory cascade is thought to be the initial event for the development of CVD and it is likely mediated by increased expression of several substances involved in the proliferation on smooth muscle, and abnormal function of coagulation and fibrinolysis (Halcox et al 2001; Verma et al 2002; Widlansky et al 2003). Previous studies have found a relationship between exposure to particulate matter (PM) and initiation of endothelial inflammation leading to an increased risk of cardiovascular events (Barregard et al 2006; Helbing et al 2014).

Recent research has focused on identifying markers of early endothelial inflammation which could help assess CVD risk. Serum biomarkers like Von Willebrand factor (vWF), C-reactive protein (CRP), intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) are overexpressed in conditions with evidence of endothelial inflammation (Brevetti et al 2006; Hwang et al 1997; Lawson et al 2009; Ley et al 2001; Sonneveld et al 2015); however, compelling evidence for a link to CVD is lacking. We hypothesized that HAP may lead to endothelial inflammation. We compared serum levels of six selected markers of endothelial inflammation in a group of participants with and without daily exposure to biomass fuel smoke living in Puno, Peru.

METHODS

Study setting

The study population was comprised of adults aged ≥ 35 years living in Puno, Peru and surrounding rural villages (Miranda et al 2012). The Department of Puno has a population of approximately 150,000 inhabitants, and an elevation of 3,825 meters above sea level. Urban participants work primarily in commerce or education, and predominantly cook with clean fuels (liquid-propane gas, kerosene, or electricity). Typical rural participants are subsistence farmers who cook indoors almost exclusively with traditional open-fire stoves and biomass fuels (i.e., wood, animal dung, and crop residue). In a previous study, we documented that rural dwellers lived in households with a greater exposure to indoor particulate matter and carbon monoxide concentrations than did urban dwellers (Pollard et al 2014). All participants provided informed consent. The Institutional Review Boards of Johns Hopkins University in Baltimore, USA, and A.B. PRISMA and Universidad Peruana Cayetano Heredia in Lima, Peru approved the study protocol.

Study Design

We selected a random sample of 456 participants with and without daily exposure to biomass fuels from an ongoing cohort in Puno (Miranda et al 2012). Trained field workers administered a standardized face-to-face questionnaire and comprehensive clinical evaluation as described previously (Miranda et al 2012). Certified phlebotomists collected blood for processing in a centralized testing facility. Blood stored at -70°C was later tested for serum amyloid A (SAA), E-selectin, soluble levels of ICAM-1 and sVCAM-1, vWF at the Johns Hopkins Clinical Research Unit Core Lab. Serum levels of hs-CRP were available for the entire cohort (Miranda et al 2012).

Definitions

Participants were stratified by their history of long-term household cooking with clean vs. biomass fuels. We used dwelling locale as a proxy for long-term or chronic exposure (Pollard et al 2014). We defined presence of CVD as a self-reported history of or current medication use for arrhythmias, angina, myocardial infarction, heart failure, hyperlipidemia or stroke; a history of hypertension as a self-reported history or current anti-hypertensive medication use; diabetes as a self-reported history or anti-hyperglycemic medication use; and, daily smoking as having ≥1 cigarette/day. We calculated an Alcohol Use Disorders Identification Test [AUDIT] score using questions about alcohol consumption (Daeppen et al 2000). We also calculated the homeostasis model of assessment-insulin resistance (HOMA-IR) as the product of fasting glucose (mmol/L) and fasting insulin (μU/mL)/22.5.

Assessment of endothelial function markers

The endothelial inflammation biomarkers selected were E-selectin, soluble ICAM-1 and VCAM-1, SAA, vWF, and hs-CRP. We used a commercially available multiplexed ELISA (Mesoscale Discovery, Gaithersburg, USA) to measure sICAM-1, sVCAM-1 and SAA. Electrochemiluminescent signals from the ELISA plates were detected and standard curves were calculated using a SECTOR Imager 2400 workstation (Mesoscale Discovery,

Gaithersburg, USA). The sensitivities of the multiplex ELISA markers were 0.01 ng/ml, 0.07 ng/ml and 0.09 ng/ml; inter-assay coefficients of variation (CV) were 5.9%, 9.2% and 12.1%; and, intra-assay CVs were 6.48%, 3.78% and 3.21% for sICAM-1, sVCAM-1 and SAA, respectively. We measured hs-CRP using Latex (Tina-quant CRP-HS Roche/Hitachi analyzer, Indianapolis, IN, USA). We used commercial ELISA assays to measure soluble E-selectin (R&D Systems., Minneapolis, USA) and vWF (Novus Biologicals, LLC, Littleton, CO, USA). Assays for E-selectin had a sensitivity of 3 pg/ml, an intra-assay CV of 6.6% and an inter-assay CV of 6.5%, whereas that for vWF had a sensitivity of 2.5 mU/ml, an intra-assay CV of 2.57% and an inter-assay CV of 8.8%.

Biostatistical methods

Our primary objective was to compare markers of endothelial inflammation in participants with and without chronic exposure to biomass fuel smoke. In exploratory analyses, we found that several of the endothelial inflammation markers were non-normally distributed. Therefore, we used the Box-Cox Power transform to identify the best transformation for each biomarker (Table 1). We then used multivariable linear regressions to model each of the transformed biomarkers as a function of chronic exposure to biomass fuel smoke, and adjusted for age, sex, BMI, LDL/HDL, log HOMA-IR, log hemoglobin A1c, whether or not the participant completed high school, the number of people sleeping in the house, whether the participants had a self-reported history of hypertension, cardiovascular disease, or diabetes, and the AUDIT score. Finally, we calculated standardized coefficients as a means to contrast the association between chronic exposure to biomass fuel smoke and endothelial inflammation for each of the transformed biomarkers. We calculated 95% bootstrap confidence intervals for the standardized coefficients using 250 samples with replacement. We used t-tests to compare continuous variables between groups if normally distributed and Mann-Whitney U tests if non-normally distributed. We used chi-square or Fisher exact tests, when appropriate, to compare categorical variables between groups. We conducted all statistical analyses in R (www.r-project.org).

RESULTS

Participant Characteristics

We measured selected markers of endothelial inflammation in a subset of 456 participants from the original cohort. Overall daily smoking prevalence was low at 1.4%. We did not find differences in age (p=0.09), sex (p=0.68), site (p=0.60), body mass index (p=0.56), systolic blood pressure (p=0.34), or level of education (p=0.64) between participants who were included in the subset for this analysis and those who were not. We summarized participant characteristics stratified by fuel exposure status in Table 2. Participants who used biomass fuels daily were slightly older, were more likely to be female, and had a lower socioeconomic status than did those who used clean fuels. They were also thinner, and had a higher blood pressure, a lower prevalence of self-reported cardiovascular disease history, a lower LDL to HDL ratio, and a lower level of insulin resistance.

Association between pairs of markers for endothelial inflammation

In Figure 1, we show the correlation matrix between pairs of markers of endothelial inflammation. We found positive correlation between hs-CRP and SAA (Spearman r=0.56; p<0.001) and between soluble levels of ICAM-1 and VCAM-1 (Spearman r=0.74; p<0.001). All other correlations were either weak or non-significant. In particular, vWF did not appear to be correlated with any of the other selected markers.

Chronic exposure to biomass fuel and markers of endothelial inflammation

In Table 3, we summarized biomarkers of endothelial inflammation by fuel exposure status. Serum levels of soluble ICAM-1 and VCAM-1, and E-selectin, were significantly higher in participants who used biomass fuels daily compared to those who used clean fuels, whereas vWF and hs-CRP were significantly lower. On the other hand, serum levels of SAA were similar. In Figure 2, we summarized mean serum levels by age and fuel exposure categories to explore for age by fuel exposure status interactions. In general, most markers appeared to increase with age regardless of fuel exposure status with the exception of serum levels of vWF among the group of participants who used biomass fuels daily. Soluble levels of ICAM-1 and VCAM-1 were consistently elevated among participants who used biomass fuel daily vs. clean fuel regardless of age category, whereas there appeared to be more variability in levels of E-selectin, SAA, vWF and hs-CRP by fuel exposure status and age.

In Figure 3, we summarized standardized coefficients for the adjusted relationship between chronic exposure to biomass fuels and transformed values of selected markers of endothelial inflammation. Specifically, in multivariable analyses, we found that serum levels of soluble ICAM-1, soluble VCAM-1, and E-selectin remained significantly higher in participants who used biomass fuels daily, and vWF and hs-CRP remained significantly lower. We did not find age by fuel exposure category interactions for E-selectin (p=0.38), soluble ICAM-1 (p=0.95) or VCAM-1 (p=0.52), SAA (p=0.92), vWF (p=0.15), or hs-CRP (p=0.33). We also did not find sex by fuel exposure category interactions for E-selectin (p=0.06), soluble ICAM-1 (p=0.65) or VCAM-1 (p=0.49), SAA (p=0.88), vWF (p=0.17), or hs-CRP (p=0.42).

DISCUSSION

We measured a select group of serum biomarkers as a proxy of endothelial health. While none of these markers have been proven to be a direct expression of endothelial function, they may provide some insights into local inflammation that occurs at the level of endothelial cells (Felmeden and Lip 2005). In this study, we compared endothelial inflammation biomarkers in participants with and without daily exposure to biomass fuels. Specifically, we found that serum levels of soluble ICAM-1 and VCAM-1, and E-selectin were elevated in participants with daily biomass fuel use vs. those who used clean fuels, whereas vWF and hs-CRP were lower. These relationships were unaffected even after adjusting for well-recognized factors that contribute to endothelial dysfunction such as age, sex, body mass index, HDL, and self-reported history of hypertension, cardiovascular disease, and diabetes, and alcohol use.

While there is strong evidence that higher levels of ambient air pollution are linked to an increased risk of CVD, epidemiological evidence for a link between biomass fuel smoke exposure and CVD risk is still emerging. For example, Dutta *et al* found that both fine ($PM_{2.5}$) and coarse (PM_{10}) concentrations were positively related to increase CVD risk in rural India (Dutta et al 2011). Exposure to biomass fuel smoke has been linked to higher blood pressure in China (Baumgartner et al 2011), Guatemala (McCracken et al 2007), and Peru (Burroughs Peña et al 2015). Our group also reported that daily exposure to biomass fuel was associated with a thicker carotid intima media and a higher prevalence of plaques (Painschab et al 2013).

Our biomarker results are consistent with previous studies that address the relationship between ambient air pollution and endothelial health. Alexeeff *et al* found that levels of ICAM-1 were positively correlated with higher concentrations of black carbon exposure (Alexeeff et al 2011). Bind *et al* found higher serum levels of ICAM and VCAM were associated with higher exposures to traffic related pollutants (Bind et al 2012). Few studies, however, have examined the relationship between household air pollution from burning biomass fuels and endothelial function markers. One recent study by Buturak *et al* found that flow mediated dilation and endothelial-independent vasodilation were reduced in individuals with biomass fuel exposure (Butarak et al 2011).

The negative relationship found between either vWF or hs-CRP and biomass exposure status does not match with our expectations. Indeed, we would have anticipated finding positive associations between these markers and daily exposure to biomass fuel smoke. Nonetheless, other studies have reported similar findings. In the MESA study, investigators reported a lack of association between CRP and long-term exposure to traffic related pollutants (Hajat et al 2015). A double blind randomized study involving healthy individuals vs. those with metabolic syndrome who were exposed to either filtered air or diesel air residuals showed non-significant increase in cytokines, ICAM or VCAM (Krishnan et al 2013; Davel et al 2012). Other investigators like Hildebrant *et al* found that decreased serum levels of vWF were association with higher levels of almost all measured pollutants. These investigators suggested that vWF was a non-specific biomarker that can change in response to several other factors (Hildebrandt et al 2009). A similar phenomenon may be occurring with CRP. Specifically, hs-CRP is an inflammatory marker that responds to acute exposures. In contrast, to biomass fuel smoke was chronic exposure among our participants, which could lead to compensatory pathways and thus lowering values of serum hs-CRP. Finally another plausible explanation the observed lower hs-CRP levels could be that rural participants who used biomass fuels daily have higher levels of physical activity due to farming activities compared to the urban participants (Plaisance et al., 2006).

Our study has several strengths. First, this is the largest study of markers of endothelial inflammation and chronic exposure to biomass fuel smoke. Second, we were able to measure several biomarkers thought to be related to endothelial inflammation that could help us elucidate specific mechanisms involved in endothelial damage. Third, our study derived its samples from a population-based study in a high altitude setting in two disparate socioeconomic settings, allowing for increased environmental, dietary, and lifestyle variability. Our study also has some potential shortcomings. First, we used dwelling location

as a proxy for chronic biomass exposure which could increase the risk of confounding bias. However, in a previous study we measured household particulate matter and carbon monoxide of a representative subset of homes and confirmed that rural households in our study area had significantly higher levels of indoor environmental exposures than did urban households (Pollard et al 2014). Second, although endothelial inflammatory biomarkers are positively associated with cardiovascular disease, it is unclear how high altitude may affect many of these biomarkers. Third, socioeconomic status can be related to endothelial inflammation and adverse cardiovascular outcomes (Hong et al 2006), and there may be unmeasured confounders that are defined by dwelling location including physical activity and time spent indoors. Fourth, while we did not find interactions between age or sex by fuel exposure, biomass exposed and non-exposed groups differed both in age and sex which could affect our overall findings. Finally, even though inflammatory biomarkers have been related to endothelial damage and dysfunction, direct methods to measure endothelial function like flow-mediation dilation are still needed to establish a direct link.

CONCLUSION

In summary, we found that specific biomarkers related to endothelial inflammation — namely serum levels of soluble ICAM-1, VCAM-1, and E-selectin — were positively associated with daily exposure to biomass fuels in our study population. We postulate that these markers may be useful surrogates to measure improvements in endothelial health in relation to reductions in household air pollution levels. Nonetheless, longitudinal studies measuring endothelial inflammatory biomarkers with pollutant concentrations, or assessment of biomarkers in field intervention trials that use improved cookstoves or clean fuels are necessary to further determine the applicability of these biomarkers.

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PRACTICAL IMPLICATIONS

Specific biomarkers related to endothelial inflammation (soluble ICAM-1, VCAM-1, and E-selectin) were positively associated with daily exposure to biomass fuels in our study population. These markers may be useful surrogates to measure improvements in endothelial health in response to reductions in household air pollution levels.

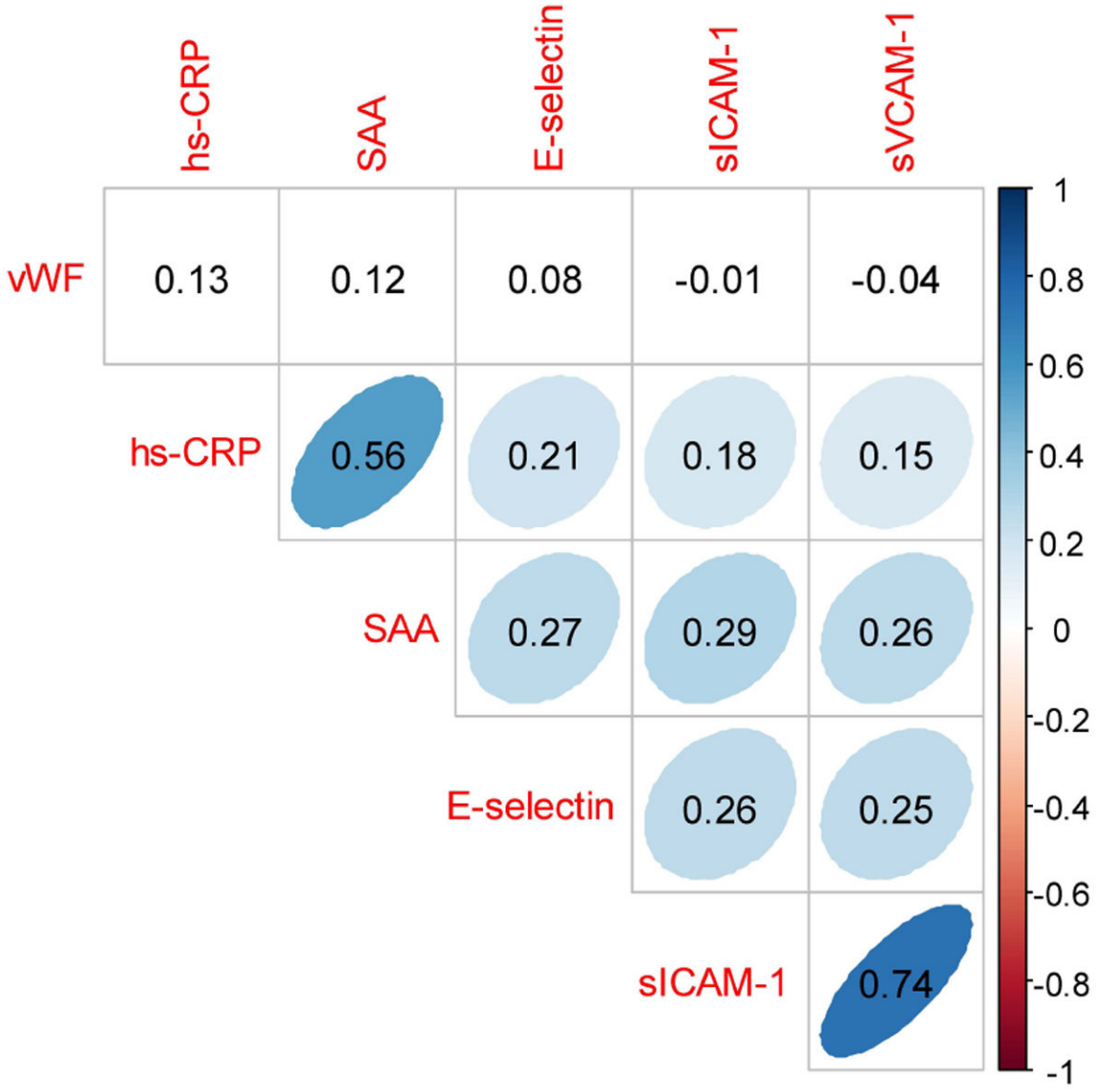

Figure 1. Correlations among markers for endothelial inflammation

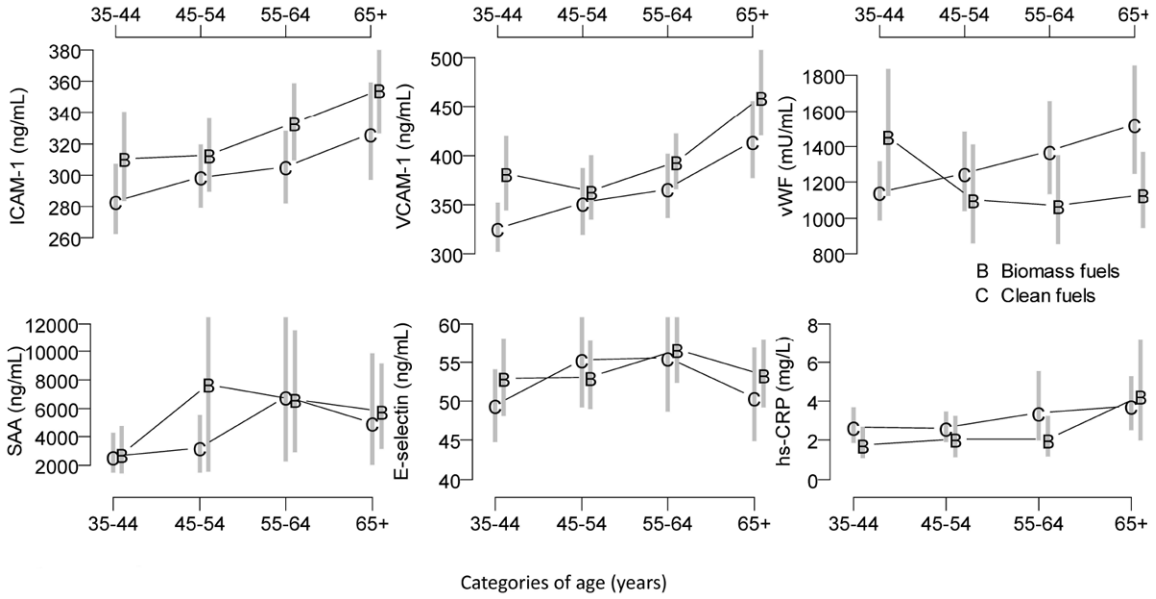

Figure 2. Relationship between biomarkers and age for exposed and non-exposed groups

Mean and 95% confidence interval for serum biomarker concentrations in the biomass fuel (B) and clean fuel (C) groups. Vertical grey segments represent 95% bootstrap percentile confidence intervals.

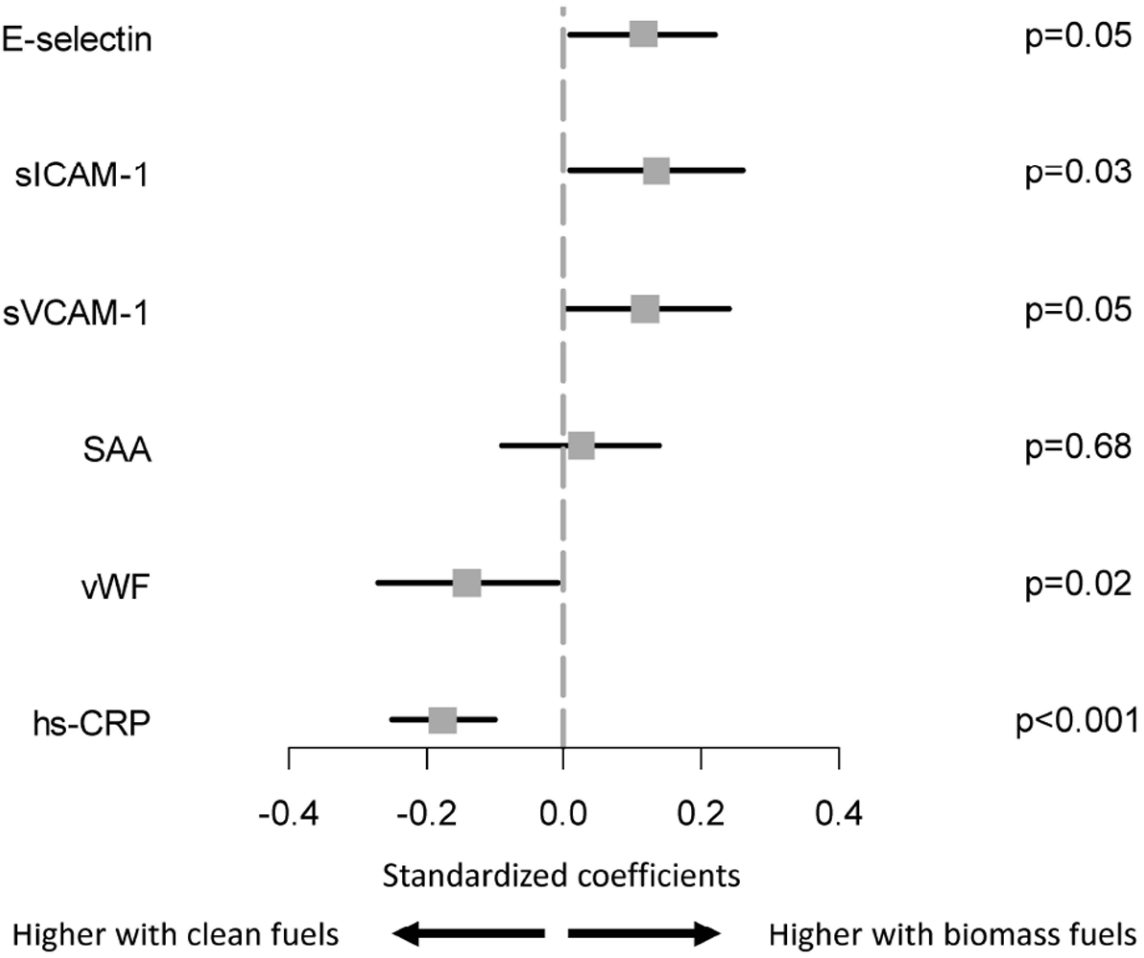

Figure 3. Standardized coefficients obtained multivariable regression to measure the association between chronic exposure to biomass fuel use and selected endothelial function markers

Table 1

Markers of endothelial inflammation and selected transformations for non-normal distributions.

Biomarkers	Selected transformation
E-selectin (ng/mL)	log(E-selectin)
sICAM-1 (ng/mL)	log(sICAM-1)
sVCAM-1 (ng/mL)	$\frac{1}{\sqrt{sVCAM1}}$
Serum amyloid A (ng/mL)	log(serum amyloid A)
vWf (mU/mL)	log(vWF)
hs-CRP (mg/L)	log(hs-CRP)

Table 2

Population Characteristics

	Biomass fuels (n=228)	Clean fuels (n=228)	P value
Demographics			
Age in years, mean (SD)	58.1 (12.5)	53.9 (12.2)	<0.01
Sex, % male (n)	42% (95)	53% (121)	0.01
Completed high school, % (n)	29.6% (67)	89% (202)	<0.01
Number of people per house, mean (SD)	3.1 (1.9)	4.3 (2)	<0.01
Clinical Characteristics			
BMI in kg/m^2, mean (SD)	25.2 (4.2)	27.8 (4.2)	<0.01
SBP in mmHg, mean (SD)	117.7 (17.8)	111.8 (17.5)	<0.01
Self-reported history, % (n)			
Hypertension	7.0% (16)	17.2% (39)	<0.01
Diabetes	3.1% (7)	6.6% (15)	0.08
Cardiovascular disease	0.4% (1)	3.5% (8)	<0.05
Daily smoking % (n)	2.8% (6)	0% (0)	0.03
AUDIT score, mean (SD)	3.3 (4.9)	3.0 (4.4)	0.45
Laboratory profile, mean (SD)			
LDL/HDL	2.8 (1.2)	3.2 (1.3)	<0.01
log(HbA1c) in %	1.8 (0.1)	1.8 (0.1)	0.4
log(HOMA-IR)	0.25 (0.2)	0.32 (0.3)	<0.01

Table 3

Serum levels of specific markers of endothelial inflammation.

Biomarker, mean (SD)	Biomass fuel group (n=228)	Clean fuel group (n=228)	p value
E-selectin			
E-selectin (ng/mL)	54.2 (16.8)	52.7 (22.1)	
log(E-selectin)	3.95 (0.29)	3.89 (0.39)	0.05
Soluble ICAM-1			
sICAM-1 (ng/mL)	330.9 (99.5)	302.3 (88.7)	
log(sICAM-1)	5.76 (0.28)	5.67 (0.28)	<0.001
Soluble VCAM-1			
sVCAM-1 (ng/mL)	403.3 (141.7)	361.8 (121.0)	
$\frac{1}{\sqrt{sVCAM1}}$	0.051 (0.007)	0.054 (0.008)	<0.001
Serum amyloid A (SAA)			
SAA (ng/mL)	6031 (22774)	4295 (13825)	
log(SAA)	7.50 (1.24)	7.44 (1.07)	0.57
Von Willebrand factor (vWF)			
vWF (mU/mL)	1148 (974)	1311 (888)	
log(vMF)	6.83 (0.62)	7.02 (0.53)	<0.001
High-sensitivity C-reactive protein			
hs-CRP (mg/L)	2.56 (7.05)	3.12 (9.01)	
log(hs-CRP)	-0.14 (1.17)	0.45 (1.06)	<0.001