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Household air pollution and blood markers of inflammation: A cross-sectional analysis

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Abstract

Household air pollution (HAP) from biomass stoves is a leading risk factor for cardiopulmonary outcomes; however, its toxicity pathways and relationship with inflammation markers are poorly

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CONFLICT OF INTEREST

The authors declare they have no actual or potential competing financial interests.

Cardiopulmonary outcomes and Household Air Pollution (CHAP) trial Investigators present in Appendix 1.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

PEER REVIEW

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understood. Among 180 adult women in rural Peru, we examined the cross-sectional exposure-response relationship between biomass HAP and markers of inflammation in blood using baseline measurements from a randomized trial. We measured markers of inflammation (CRP, IL-6, IL-10, IL-1β, and TNF-α) with dried blood spots, 48-h kitchen area concentrations and personal exposures to fine particulate matter ($PM_{2.5}$), black carbon (BC), and carbon monoxide (CO), and 48-h kitchen concentrations of nitrogen dioxide (NO_2) in a subset of 97 participants. We conducted an exposure-response analysis between quintiles of HAP levels and markers of inflammation. Markers of inflammation were more strongly associated with kitchen area concentrations of BC than $PM_{2.5}$. As expected, kitchen area BC concentrations were positively associated with TNF-α (pro-inflammatory) concentrations and negatively associated with IL-10, an anti-inflammatory marker, controlling for confounders in single- and multi-pollutant models. However, contrary to expectations, kitchen area BC and NO_2 concentrations were negatively associated with IL-1β, a pro-inflammatory marker. No associations were identified for IL-6 or CRP, or for any marker in relation to personal exposures.

Keywords

biomass stoves; black carbon; exposure-response; fine particulate matter; household air pollution; markers of inflammation

1 | INTRODUCTION

Household air pollution (HAP) from biomass stoves was attributed to 2.3 million deaths and 91.5 million disability-adjusted life-years (DALYs) lost in 2019.[1] HAP from biomass stoves is among the largest environmental risk factors for preventable disease.[2–5] Exposure to HAP is a leading risk factor for bronchitis, chronic obstructive pulmonary disease, lung cancer, childhood pneumonia, acute lower respiratory infections, cardiovascular events, and low birthweight.[6–8] In particular, cardiovascular disease accounted for the majority of deaths and disability-adjusted life-years from ambient air pollution in the Global Burden of Disease study and it has been estimated to cause a similar amount of deaths and DALYs due to HAP.[1,5,9] Cardiovascular disease is the leading cause of morbidity and mortality worldwide, and over 80% of premature cardiovascular disease deaths occur in low- and middle-income countries (LMICs).[10]

Pollutants commonly monitored in HAP studies include carbon monoxide (CO) and particulate matter (PM). Chronic exposure to ambient CO has been associated with congestive heart failure, ischemic heart disease, cardiovascular disease, as well as low birthweight, congenital defects, stroke, and asthma in epidemiological studies.[11] Fine particles, smaller than 2.5 micrometers in aerodynamic diameter ($PM_{2.5}$), are small enough to deposit in the alveoli, initiate inflammatory cascades, and may enter the pulmonary circulation.[12] Extensive epidemiological studies have found strong associations between ambient particulate air pollution and respiratory symptoms, lung cancer, and increased risk of cardiopulmonary-related morbidity and mortality in adults and children.[7,13–19,19–24]

Existing research on PM toxicity suggests that inflammation is likely involved in the pathways of cardiovascular disease development.[25] Ambient and traffic-related PM

exposure have been associated with pulmonary systemic pro-oxidant and pro-inflammatory effects.[12,26,27] In particular, relationships between air pollution and markers of inflammation (including C-reactive protein or CRP, and inflammation cytokines such as TNF-α, IL-1β, and IL-6) have been identified in animal models and human studies.[27–35] Inflammatory cytokines may induce a systemic response that contributes to the pathogenesis of adverse cardiopulmonary health effects associated with ambient PM exposure.[36–38]

Black carbon (BC) is a main component of $PM_{2.5}$ from the incomplete combustion of carbonaceous materials and may play an important role in cardiovascular disease development.[33,39] BC is thought to elicit cardiovascular endpoints through inflammation pathways.[25,27,40,41] Several literature reviews suggest that BC might have stronger associations with cardiopulmonary outcomes than with total PM or other $PM_{2.5}$ components.[25,33,39,40,42] The effect of BC from traffic-related exposures has been shown to be more robust than the effect of total PM on mortality, hospital admissions, and emergency department visits, both in healthy adults and in older, susceptible populations.[25,33,39,40] In addition, the association between ambient BC concentration and cardiorespiratory-related hospital admissions in adult populations seems to be significantly stronger than associations with most single elements of PM.[42–47] However, toxicity studies of PM and its components have focused on diesel exhaust particles, urban air pollution,[12,16,18,20,41] and short-term wildfire events.[25,48]

The pathways between HAP from biomass stoves and cardiovascular outcomes have not been fully explored.[49] However, prior evidence suggests that inflammation plays an important role in disease development from biomass smoke exposure.[50] PM from biomass fuel burning seems to alter the innate immune system through alveolar macrophage-driven inflammation, recruitment of neutrophils, and disruption of barrier defenses.[36] Furthermore, acute biomass PM exposure appears to induce different inflammatory profiles depending on the fuel type (dung or wood) and duration of the exposures.[36,38,51]

Few studies have investigated the relationship of HAP with markers of inflammation in the HAP literature.[52–57] These existing studies have evaluated the impact of different types of stoves on markers of inflammation or cardiovascular health, for example, comparing biomass stove use with clean fuel use [53–57] or comparing use of stoves with and without chimneys.[52] Furthermore, no HAP studies have explored the association of BC and inflammation markers in multi-pollutant models. In light of these knowledge gaps, we sought to examine the exposure-response relationship between BC, $PM_{2.5}$, CO, and NO_2 with markers of inflammation among adult women who use primarily biomass stoves in rural Peru.

2 | METHODS

2.1 | Study design and setting

This study was nested within the Cardiopulmonary Outcomes and Household Air Pollution (CHAP) trial, a randomized controlled trial of a cleaner energy intervention.[58] We used baseline data collected from 180 women who were enrolled in the trial, aged 25–64 years from rural communities surrounding the city of Puno, Peru. Puno is located in

southeastern Peru, near the shore of Lake Titicaca at 3825 meters above sea level. We enrolled women who were the primary cook of their household and reported daily use of biomass fuels for cooking. At baseline, we measured kitchen area concentrations and personal exposures to HAP, collected dried blood spot samples (DBS), and recorded basic demographic information. We also collected duplicate anthropometric measurements of weight and height and used the mean of the two measurements to estimate BMI for each participant. Socioeconomic status was evaluated through asset ownership, and participants were assigned to a national wealth quintile defined by the Demographic and Health Survey (DHS).[59] Additional information about the trial has been previously published.[58]

2.2 | Exposure assessment

We collected 48-h samples of kitchen area concentrations and personal exposures to $PM_{2.5}$, CO, and BC among the 180 participants, and kitchen area NO_2 concentrations in a subset of 97 households.

We measured CO using the direct-reading EL-USB-CO data logger (Lascar Electronics, Erie, PA, USA). CO monitors were calibrated by co-locating all monitors in a sealed chamber every 3–4 months. The monitors were exposed to clean air (nitrogen gas) and a CO concentration of 100 ppm in the chamber. Individual slopes and intercepts were estimated for each device at each co-location timepoint to correct any drift in the devices. The limit of detection (LOD) for the CO monitors was estimated as 1 ppm, which was three times the standard deviation of concentrations logged during the regular clean air calibration checks in the field.

We used the ECM aerosol monitor (RTI Inc., Research Triangle Park, NC, USA) that simultaneously measures both continuous-time $PM_{2.5}$ concentrations and integrated gravimetric samples collected on a filter using a pump at 0.3 L/min flow rate. Humidity-corrected nephelometric concentrations of every sample were calibrated using the sample-specific gravimetric time-weighted average filter samples. The ECM also logs temperature, relative humidity, and flow rate and has an accelerometer that measures movement which was used to estimate wearing compliance.[60] ECM pumps were calibrated daily with a TSI 4100 flowmeter (TSI Incorporated 500 Cardigan Road Shoreview, MN, USA). We recorded the flow rate before and after each sample collection. Gravimetric $PM_{2.5}$ samples were collected using 15-mm Teflon filters with a 2-μm pore size (Measurement Technology Laboratories LLC, Minneapolis, MN, USA). Filters were pre- and post-weighed at Johns Hopkins University in a humidity- and temperature-controlled room using a MT5 microbalance (Mettler Toledo, Columbus, OH, USA). All $PM_{2.5}$ samples included 10% blanks and all reported concentrations were blank-corrected. The LOD for $PM_{2.5}$ samples was estimated as three times the standard deviation of the mass measured from field blanks. For $PM_{2.5}$, the LOD was estimated to be 20 μg for the initial 6 months of the study and 9.8 μg for the subsequent 6 months. This change was due to a reduction of filter handling by pre-loading filters into individual ECM cassettes before shipping the filters to the field site.

BC concentrations were determined from the $PM_{2.5}$ gravimetric samples by measuring optical attenuation on filters using a Magee OT21 Sootscan transmissometer (Magee Scientific, Berkeley, CA). The LOD for BC samples was estimated as three times the

standard deviation of the attenuation readings recorded from field blanks. The LOD for BC was 1.4 μg. For all pollutants, the concentrations below the LOD were replaced by the LOD divided by the square root of two.

We monitored kitchen area NO_2 concentrations for 48 h in a subset of households (n = 97) using Aeroqual Series 500 portable direct-reading monitors with NO_2 sensor heads (Aeroqual Limited, Auckland, New Zealand). Measurements were recorded at 1-min intervals over 48 h, with support from two auxiliary batteries to extend the sampling duration due to the lack of electricity in many households. The LOD was calculated as three times the standard deviation (SD) of two devices reading a zero concentration. We estimated an LOD of 20 ppb. As 15% of NO_2 sample durations were more than 24 h but <48 h, we used only data from the initial 24 h of sampling to calculate a 24-h mean. Additional details of the baseline NO_2 assessments have been previously published.[61]

Kitchen area concentrations were measured by placing NO_2, CO, and $PM_{2.5}$ monitors approximately one meter from the combustion zone and 1.5 meters above the floor (representing the breathing zone), and at least one meter from doors and windows (when possible). Personal exposures to CO and $PM_{2.5}$ were measured by placing the monitors near each participant's breathing zone in an adapted apron commonly used by women in the study area and provided to the participants.[58] Measures of $PM_{2.5}$, CO, and NO_2 were logged at 1-min intervals. BC concentrations were later measured after sample collection from the $PM_{2.5}$ filter samples. All kitchen area samples included 10% duplicates.

2.3 | Biomarker assessment

Dried blood spot (DBS) samples were collected from participants at the end of the 48-h HAP monitoring period. DBS samples were collected using Guthrie DBS cards from a finger on the non-dominant hand swabbed with a sterile alcohol wipe. A sterile lancet was used to puncture the skin and the initial drop of blood was wiped away with an alcohol swab. The following large drops of blood from the finger were then applied onto to five standard spots on a Guthrie DBS card. Cards were labeled and dried at room temperature on a drying rack for at least 10 h. Dried cards were placed in individually labeled Ziploc bags with a desiccant pouch and a humidity indicator card. Once dried, all samples were kept at −20°C and were shipped to Emory University (Atlanta, USA) for analysis.

Inflammation markers (pro-inflammatory: CRP, IL-6, IL-1β, and TNF-α and anti-inflammatory IL-10) were analyzed in duplicate through immunoassay methods. A 6-mm punch was collected from each DBS card and was eluted with 250 μl phosphate-buffered saline (PBS). IL-10, IL-6, IL-1β, and TNF-α samples were analyzed in replicate on a MSD Multiplex Proinflammatory 96-well plate (Meso Scale Discovery Rockville, MD, USA). For CRP, a small aliquot of the initial elute was further diluted 1:10 with PBS, and 100 μl of the diluted eluate was placed in replicate on an MSD Multiplex Vascular Injury 96-well plate (MSD, Meso Scale Discovery Rockville, MD, USA). Conjugate solution was added and allowed to react at 23°C for 120 min after which MSD Read buffer was added (buffer containing tripropylamine as a co-reactant for light generation in electrochemiluminescence immunoassays).[62] Plates were immediately analyzed using electrochemiluminescence on an MSD Multiplex Immunoassay reader with proprietary wavelengths. Concentrations were

calculated based on the absorbance measurements using an external standard calibration plot. We assumed a DBS volume of 70 μl and 100% extraction efficiency from the card to estimate biomarker concentrations.

For all assays, a 10-point calibration curve, a blank, and two quality control materials were analyzed simultaneously with samples. Values of duplicates were averaged and relative standard deviations (RSDs) were required to be within 10% for the analysis to be considered valid. Similarly, quality control materials were required to be within 20% of the expected values and the recovery of calibrants was 100% of the expected value. Whenever those quality control parameters were not met, the analysis was repeated. The LODs of the methods were 13.8 pg/ml for CRP; 0.089 pg/ml for IL-10; 0.181 pg/ml for IL-6; 0.135 pg/ml for IL-1β; and 0.081 for TNF-α pg/ml. Typical RSDs were less than 10% in QC samples and calibrants. Concentrations below the LOD were replaced by the LOD divided by the square root of 2.

2.4 | Statistical analysis

We developed exposure-response linear regression models for CRP, IL-6, IL-10 IL-1β, and TNF-α concentrations (outcome variables) with pollutants (explanatory variables; $PM_{2.5}$, CO, BC, NO_2). We evaluated the association with single-pollutant and multi-pollutant models. We used 48-h means of pollutant measurements, estimated by averaging the consecutive individual 24-h means for $PM_{2.5}$ and CO. A 24-h sample was considered missing if the sample had <20 h of measurements to ensure that each 24-h period was representative (ie, capturing a typical number of cooking events each day). We used the initial 24 h of the sample if the consecutive second 24-h sample was missing for $PM_{2.5}$ and CO. We estimated 24-h means for NO_2 from the initial 24 h of sampling. For BC, we used 48-h means estimated from the integrated time-weighted average concentration from the time-integrated filter-based $PM_{2.5}$ samples (for all samples at least 20 h in duration).

We estimated quintiles of personal exposure and kitchen area concentrations of CO, $PM_{2.5}$, and BC to use as our explanatory variables in separate models for each inflammation marker. We also estimated quintiles from the kitchen area 24-h NO_2 concentrations in a subset of 97 samples. We controlled for body mass index (BMI) and age as continuous variables and wealth quintile in all of our models. We also incorporated the type of fuel used (dung only vs. wood and dung) and season (December to March as rainy vs. dry) into the models, given that different fuel types could cause differential inflammation responses and rainy season can be a risk factor for inflammation. All of the participants reported that they were non-smokers. P-values of linear trends of exposures were obtained using t tests on the log-transformed markers of inflammation and log-transformed continuous pollutant concentrations controlling for confounders.

We log-transformed all inflammation marker variables to help meet linear regression assumptions, given that the distributions were right-skewed. Residual plots were assessed to confirm that linear regression assumptions were met on every model. Because most samples for IL-10 and IL-6 were below LOD (67% and 77%, respectively), we also performed logistic regression models treating IL-10 and IL-6 as binary variables, for samples above

versus below their respective LOD. All data analyses were conducted with MATLAB (The MathWorks, R2019a, Inc., Natick, MA) and STATA (StataCorp. 14.2, College Station, TX).

Our confidence that the associations between pollutants and markers of inflammation were not due to chance was higher if the following were true: 1) The direction of the association was consistent within pollutant quintiles. 2) The direction of the associations was consistent between pollutants, regardless of statistical significance. 3) The strength of the association was statistically significant or stronger in multi-pollutant models compared to single-pollutant models after controlling for confounders (BMI, age, rainy season, fuel type, and wealth). 4) An association in a single-pollutant model remained consistent in the multi-pollutant model, that is, after adjusting for levels of other pollutant exposures.

Since 12% of inflammation marker samples were collected a few days before or after pollutant sample collection, we performed a sensitivity analysis restricting to participants where DBS collection was done at the end of the 48-h HAP sample collection. We also explored associations with personal concentrations restricting to samples where personal monitors were being worn more than 70% of awake time during the sampling period.

3 | RESULTS

We enrolled 180 female participants, with a mean age of 48 years (standard deviation [SD] 10 years) and an average BMI of 26.8 kg/m^2 (SD 4.2 kg/m^2). Ninety-four percent of participants were in the two lowest national wealth quintiles. Sixty-three percent of our participants reported having only primary school or no education at all, and 37% of our participants had secondary level education. All of the participants used dung as their primary fuel and 42% reported the use of wood in addition to dung (Table 1).

We collected a total of 169, 178, 178, and 97 kitchen area samples of CO, $PM_{2.5}$, BC, and NO_2, respectively. Concentrations for HAP levels and inflammation biomarkers are summarized in Table 1. Kitchen area median concentrations were as follows: 39 ppm (inter-quartile range, IQR: 19–70 ppm) for CO; 982 $\mu g/m^3$ (IQR: 422–1824 $\mu g/m^3$) for $PM_{2.5}$; 171 $\mu g/m^3$ (IQR: 84–282 $\mu g/m^3$) for BC; and 100 ppb (IQR: 53–178 $\mu g/m^3$) for NO_2. Moderate correlations were observed between concentrations of the different kitchen area air pollutants (Table 2). We were able to obtain concentrations of CRP for 166 participants and TNF-α, IL-1β, IL-10, and IL-6, for 179 participants. CRP concentrations for most participants were below 3 mg/L (95%), which is a common threshold used for high cardiovascular risk.[63]

3.1 | Household air pollution and inflammation markers

We found significant associations between kitchen concentrations of BC and TNF-α, IL-1β, and IL-10 and between kitchen concentration of NO_2 and IL-1β in single- and multi-pollutant models (Tables 3–5 and Table S1). We did not identify statistically significant associations between CO or $PM_{2.5}$ and any markers of inflammation (Tables S2 and S3). We found a positive association between households in the highest quintile of BC kitchen concentrations and the pro-inflammatory marker TNF-α (Figure 1) in single- and multi-pollutant models.

The kitchen area BC concentrations in the fourth and fifth quintiles (medians of 260 and 380 μg/m^3) were associated with a 19% and 13% increase in TNF-α levels compared to the lowest BC quintile (median of 36 μg/m^3) in the single-pollutant model adjusted for age, BMI, rainy season, wealth quintiles, and type of fuel used (95% CIs: −2 to 46% and −8 to 39%, respectively; Table 3). In multi-pollutant models, when further adjusting by CO and $PM_{2.5}$ concentrations, we observed stronger effect estimates and narrower confidence intervals with the association between BC and TNF-α compared with the single-pollutant model (Table 4). After controlling for other pollutants, TNF-α concentrations were associated with an increase of 36% and 27% (95% CIs: 5 to 76% and −4 to 68%, respectively) in the two highest BC concentration quintiles compared to the lowest quintile.

The third, fourth, and fifth quintiles of kitchen area BC concentrations (median concentrations of 171 μg/m^3, 260 μg/m^3, and 380, respectively) were associated with 29%, 26%, and 18% reductions in the anti-inflammatory marker IL-10 compared to the lowest BC quintile (median BC concentration: 36 μg/m^3). In the multi-pollutant model, the negative association between BC concentration quintiles and IL-10 (−36% 95% CI: −56 to −7% and −31% 95% CI: −54 to −4%, for the fourth and fifth quintiles, respectively) were stronger and had narrower confidence intervals than the single-pollutant model (Tables 3 and 4). We observed consistent and stronger associations when using logistic regression models classifying IL-10 as above or below the LOD (Tables S6 and S7). In the multi-pollutant model, we observed significant negative associations between IL-10 and BC third, fourth, and fifth concentration quintiles (p-values <0.01) compared to the first quintile (Table S6).

Contrary to what we expected, the highest quintiles of kitchen area BC concentrations were negatively associated with pro-inflammatory marker IL-1β (Figure 1). This negative association of IL-1β and BC in the kitchen area highest quintile levels (fourth and fifth) became stronger in the multi-pollutant model adjusting for $PM_{2.5}$ and CO (−39% 95% CI: −66 to 11% and −31% 95% CI: −64 to 31%; Table 4). Concentrations of NO_2 were also negatively associated with IL-1β both in single- and multi-pollutant models and after adjusting for other pollutants (Table 5 and Table S1). No associations were observed with other markers of inflammation and NO_2 (Table S1). Interestingly, when using only data from participants in the NO_2 subsample, the associations of BC with TNF-α and IL-10 (Table 5) were statistically significant and consistent with results observed for models involving all participants (Table 4). Although not statistically significant, the direction of the associations between $PM_{2.5}$ quintiles and IL-1β and IL-10 were consistent with the trends observed for BC in single-pollutant models (Table S2).

In the multi-pollutant model, participants who reported primary use of both wood and dung as fuel had 13% lower TNF-α concentrations (95% CI: −25 to 0.1%) and 69% greater IL-1β concentrations (95% CI: 22 to 134%) than participants who used only dung (Table 4), controlling for covariates. When restricting the models to only participants who reported the use of wood as a secondary fuel (Table 6), BC kitchen concentration quintiles were strongly and positively associated with TNF-α and negatively associated with IL-1β. Among participants who used wood, the fourth and fifth quintiles of kitchen area BC concentrations had 46% and 32% greater concentrations of TNF-α (95% CI: 14 to 87% and 0.1 to 75%, respectively) compared to the lowest quintile (Table 6).

We were not able to detect any consistent and significant trends with IL-6 and pollutant concentrations. Twelve percent of DBS samples were collected a few days before or after HAP concentration measurements instead of concurrently with the HAP monitoring period. When restricting models to only paired samples (n = 145), the direction and magnitude of the results remained consistent as those observed for all participants (Table S4). Low correlations were observed within markers of inflammation (Table S5). Finally, we did not find clear trends or statistically significant associations between inflammation markers and personal exposures to any of the monitored pollutants (results not shown).

4 | DISCUSSION

Black carbon from kitchens that use biomass stoves in high altitude rural Puno was related to pro-inflammation markers TNF-α and IL-1β and anti-inflammation marker IL-10. As expected, indoor air pollutants were positively associated with TNF-α and negatively associated with IL-10; an unexpected result was the negative association of pollutants with IL-1β. We found that BC is more strongly related to these markers of inflammation than $PM_{2.5}$ and that these results were robust to adjustment for $PM_{2.5}$ in multi-pollutant models. These results are similar to what has been suggested in the urban air pollution literature [64]; the association between several health outcomes, including inflammation markers in the blood, is stronger with BC than with $PM_{2.5}$. These results add strength to the hypothesis that BC may be one of the components of $PM_{2.5}$ driving inflammatory responses that lead to adverse health outcomes.[65]

The positive associations we found between TNF-α and kitchen area BC concentrations from biomass stoves are consistent with previous literature. Studies in Guatemala,[52] India,[54,55] and Nigeria [66] have reported positive associations between the pro-inflammatory cytokines TNF-α, IL-8, and IL-6 and biomass stove use compared to use of stoves burning cleaner fuels or advanced, cleaner-burning biomass stoves. Others have reported null associations between markers of inflammation such as TNF-α and HAP levels in Nicaragua [56] and South Africa.[57]

Consistent with an inflammatory response, we also observed a reduction of the anti-inflammatory cytokine IL-10 with increasing levels of HAP. This association between BC and IL-10 remained robust in logistic regression models and in multi-pollutant models that included the smaller subsample of participants with NO_2 measurements. IL-10 inhibits the production of pro-inflammatory cytokines including IFN-γ, IL-2, IL-3, TNF-α, TNF-β, and pro-inflammatory responses.[67] Previous studies have shown that PM from woodsmoke is associated with reductions in IL-10, IL-4, and IL-13 while promoting the release of pro-inflammatory cytokines including TNF-α.[36] IL-10 production was also found to be lower after exposure to PM from wood burning and after exposure to PM from dung burning in the lungs of mice.[38]

Contrary to what we expected, BC and NO_2 concentrations were negatively associated with IL-1β. This negative association of BC with IL-1β seems to be driven by the participants who reported using wood as fuel. Studies have shown that the inflammatory profiles shift dramatically between PM from wood or PM from cow dung regarding neutrophilic

and eosinophilic responses [36,38]; however, we do not fully understand the reason for these negative associations with IL-1 β. Previous HAP studies examining inflammatory markers do not report measuring IL-1β.[52,54,55,66] Yet, inconsistent results with other pro-inflammation markers have been previously observed in a recent HAP study in Nigeria,[66] which found that $PM_{2.5}$ was positively associated with TNF-α but not IL-6. Most HAP studies that have reported positive associations with TNF-α also report positive associations with IL-6.[54,55] PM and NO_2 have been positively associated with IL-1β and urban air pollution.[12,68,69] However, a few short-term air pollution studies [34,70] and ambient air pollution studies [71,72] have also reported inverse associations of PM and NO_2 with markers of inflammation. Nonetheless, associations with markers of inflammation and biomass stove use are more heterogeneous compared to ambient air pollution.[36,73] Thus, it is important to further explore the inflammation pathways in various settings to better understand how different fuel types may differentially affect inflammation pathways.

We consider it unlikely that our findings of an association between BC and TNF-α, IL-1β, and IL-10, and between kitchen concentration of NO_2 and IL-1β are due to chance since we observed that the direction of the associations were consistent within pollutant quintiles and consistent between pollutants regardless of significance; the associations were present in both single and multi-pollutant models; and the associations became stronger in multi-pollutant models.

We did not identify any clear associations with CRP. Although some studies have found positive associations between HAP and CRP,[54,56] others have also found null associations.[57,74,75] Two previous studies in Puno did not identify CRP associations with biomass stove users.[53,76] However, lifestyle differences (ie, more physical activity among rural participants who primarily worked as farmers) may have contributed to the lower concentrations of CRP observed among rural participants.[53] In addition, chronic continuous exposures to HAP could also lead to development of compensatory pathways that may reduce CRP levels not observed in other populations with more acute exposure profiles.[53] It is possible that the participants in this community have better cardiovascular health despite what would be expected due to their HAP exposures.[6,77]

We did not identify associations between markers of inflammation and personal exposures to HAP when considering all personal samples or when restricting to samples with high wearing compliance of personal monitors. We did not observe clear trends in the direction of the associations or consistent discernable trends within pollutants and inflammation markers. It is possible that when restricting to samples with high wearing compliance of personal monitors the sample size, and therefore the power to detect meaningful associations, was limited. Thus, larger samples of participants highly compliant in wearing personal monitors may be required to identify significant effects. Other cross-sectional studies have similarly detected associations between kitchen area concentrations and markers of cardiovascular health such as blood pressure[78] and markers of inflammation,[56] but found no association between personal concentrations and these markers.

Our study has some limitations. Validation studies comparing DBS and venous-drawn blood samples have shown strong correlations for some markers such as CRP, although weaker

correlations have been observed with other markers including inflammatory cytokines such as those we measured.[79–81] It is possible that DBS might not be a good substitute for serum samples for some of the markers measured in this study. DBS tends to be a fraction of typical serum concentrations, limiting comparability with results from studies using different methodologies. We also assumed a DBS volume of 70 μL to estimate concentrations and 100% extraction efficiency, which can vary from sample to sample in practice.[80,82] Further research regarding the validity of several inflammation markers from DBS is needed including methods to improve the current protocols.[56] We were not able to measure other cytokines that have been related to biomass stove use such as IL-8, or other markers of inflammation. Measuring additional markers might help confirm consistency of results compared to other population studies and lead to better understanding of the different profiles associated with biomass smoke from wood versus dung. Finally, we did not have any information on other potential sources of inflammation responses such as a gastro-intestinal or other temporary illness that might confound the association of HAP and markers of inflammation.

Our study has many strengths. This study is among the first to identify exposure-response associations between BC and NO_2 concentrations and inflammation markers, in addition to relationships between inflammation markers and PM and CO from biomass stoves [36,83]. This evidence is among the first to suggest that BC from biomass stoves may play a more important role in the inflammation response than $PM_{2.5}$. Collecting samples using DBS facilitated the logistics of sample collection and transport from our LMIC rural setting. This method also increased participation among our population, who have expressed reluctance to provide venous-drawn blood samples. An additional strength of our study is that, although all of our participants reported the use of dung as their primary fuel, we were able to detect differences in inflammatory markers among the participants who also used wood. These differences in inflammation profiles should be further investigated in population studies that use biomass stoves.

5 | CONCLUSIONS

Household air pollution from biomass stoves was associated with some markers of inflammation. These observations are consistent with an inflammatory response for TNF-α and IL-10 found in previous studies. In our analysis of women who use biomass stoves in rural Peru, the exposure-response association between inflammation markers and HAP appears to be stronger for BC than $PM_{2.5}$. Our results support previous evidence that biomass smoke from wood and dung induces different profiles of inflammation markers that need to be further investigated in population studies. These results can inform future elucidation of the pathways through which exposure to HAP induces adverse health effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Practical implications

- Black carbon, one of the primary components of fine particulate matter from biomass combustion, is suspected to elicit adverse cardiovascular outcomes through inflammatory pathways; however, evidence from household air pollution (HAP) exposures is limited.
- Consistent with the literature, HAP from biomass stoves was associated with blood inflammatory markers TNF-α and IL-10; however, HAP was negatively associated with the pro-inflammatory maker IL-1β.
- We observed stronger exposure-response associations between blood inflammation markers and BC than with $PM_{2.5}$, suggesting BC may be one of the components of $PM_{2.5}$ driving inflammation responses that could lead to adverse health outcomes.
- Our results highlight potential pathways through which exposure to HAP may induce adverse health effects and suggest the need for further research on inflammation responses from HAP exposures due to biomass stove use.

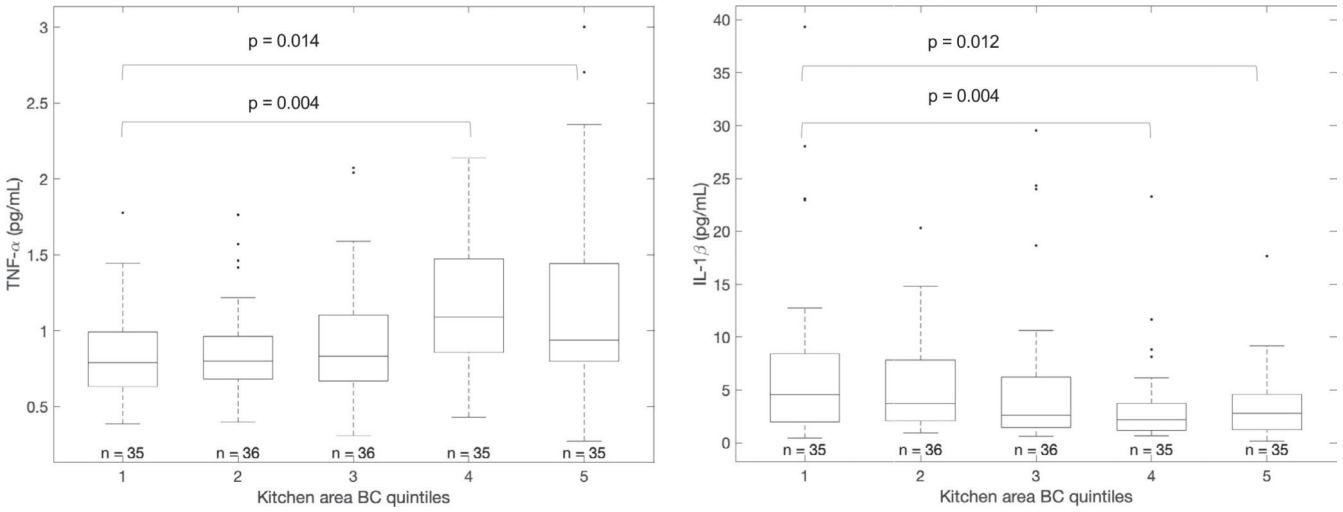

FIGURE 1.

Exposure-response relationship of TNF-α and IL-1β levels using box plots by quintiles of BC kitchen area concentrations. *p*-values are shown comparing quintiles four and five with first quintile using *t* tests on log-transformed TNF-α and IL-1β data

TABLE 1

Baseline participant characteristics

Participant characteristics	**Number (%) or mean (standard deviation)**		
Mean age (years)	48.3 (10.1)		
Mean BMI (kg/m^2)	26.8 (4.2)		
Education level: without education or preschool only	7 (4%)		
Education level: primary	106 (59%)		
Education level: secondary	67 (37%)		
Education level: non-university superior or university	0 (0%)		
Wealth quintile 1 (lowest)	101 (56%)		
Wealth quintile 2	69 (38%)		
Wealth quintile 3	10 (6%)		
Wealth quintile 4 and 5 (highest)	0 (0%)		
Fuel used for cooking: wood & dung	75 (42%)		
Fuel used for cooking: dung only	179 (99%)		
Number of samples during rainy season	62 (34%)		
	Number	**Median**	**Interquartile range**
Inflammation markers[b]			
CRP (mg/L); 0%<LOD	166	0.29	(0.15–0.55)
IL-10 (pg/ml); 67%<LOD	179	0.06	(0.06–0.10)
IL-1β (pg/ml); 0%<LOD	179	2.96	(1.64–6.48)
TNF-α (pg/ml); 0%<LOD	179	0.89	(0.68–1.21)
IL-6 (pg/ml); 77%<LOD	179	0.13	(0.13–0.13)
Kitchen area concentrations			
CO (ppm)	169	39	(19–70)
PM (μg/m^3)	178	982	(422–1824)
BC (μg/m^3)	178	171	(84–282)
NO_2 (ppb)	97	100	(53–178)
Personal concentrations			
CO (ppm)	160	3.5	(1.8–8.4)
PM (μg/m^3)	180	72	(39–130)

BC (μg/m^3)	180	16	(8–30)

Abbreviations: BC, black carbon; BMI, body mass index; CO, carbon monoxide; CRP, associated with a pro-inflammatory response; IL-10, anti-inflammation marker; NO_2, nitrogen dioxide; $PM_{2.5}$, fine particulate matter; TNF-α and IL-1β, pro-inflammation markers.

*b*Inflammation maker assumptions: dried blood spot volume of 70 μl to estimate concentrations and 100% extraction efficiency. Limit of detection values for markers of inflammation: 13.8 pg/ml for CRP; 0.089 pg/ml for IL-10; 0.181 pg/ml for IL-6; 0.135 pg/ml for IL-1β; and 0.081 for TNF-α pg/ml.

TABLE 2

Correlations matrix for kitchen area household air pollutants using Spearman correlation coefficients

	CO	$PM_{2.5}$	BC
$PM_{2.5}$	0.80		
BC	0.65	0.63	
NO_2	0.56	0.58	0.44

TABLE 3

Percent change in markers of inflammation levels by quintile of kitchen BC 48-h means in single-pollutant models[a]

		TNF-α (*n* = 177)				IL-1β (*n* = 177)				IL-10 (*n* = 177)				CRP (*n* = 164)			
BC quintile medians		**Change (%)**	**95%**	**CI**	***p*-value**	**Change(%)**	**95%**	**CI**	***p*-value**	**Change(%)**	**95%**	**CI**	***p*-value**	**Change(%)**	**95%**	**CI**	***p*-value**
Kitchen BC (μg/m^3)																	
1	36	Reference															
2	94	1	−17	22	0.923	−20	−47	22	0.295	−10	−31	16	0.414	−12	−48	47	0.623
3	171	−1	−18	21	0.948	−8	−41	42	0.697	−29	−46	−7	0.014	−31	−60	19	0.179
4	260	19	−2	46	0.085	−36	−59	0.5	0.052	−26	−44	−2	0.037	−30	−60	22	0.206
5	380	13	−8	39	0.235	−20	−49	26	0.335	−18	−39	8	0.158	−27	−59	29	0.274
Linear trend significance[b]		0.129				0.083				0.126				0.188			

Note: Participants are grouped into quintiles of BC 48-h mean levels. Results shown from each model correspond to quintiles of BC levels as the independent variable and each marker of inflammation as the outcome variable.

Abbreviations: BC, black carbon; BMI, body mass index; IL-10, anti-inflammation marker; TNF-α, IL-1β, and CRP, markers associated with a pro-inflammatory response.

[a]Each marker of inflammation model includes the following covariates: BC quintiles, age, BMI, wealth quintile, season, and type of fuel.

[b]*p*-values of linear trends were obtained using t tests on log-transformed continuous BC concentrations.

TABLE 4

Percent change in markers of inflammation by quintiles of kitchen BC 48-h mean in multi-pollutant models controlling for $PM_{2.5}$ and CO[a]

		TNF-α (*n* = 167)				IL-1β (*n* = 167)				IL-10 (*n* = 167)			
BC quintile medians		**Change(%)**	**95 %**	**CI**	***p*-value**	**Change (%)**	**95 %**	**CI**	***p*-value**	**Change (%)**	**95 %**	**CI**	***p*-value**
Kitchen BC (μg/m^3)													
1	36	Reference											
2	94	5	−16	32	0.657	−19	−52	36	0.422	−18	−41	13	0.227
3	171	7	−17	38	0.600	−14	−52	54	0.608	−37	−56	−9	0.014
4	260	36	5	76	0.022	−39	−66	11	0.102	−36	−56	−7	0.019
5	380	27	−4	68	0.098	−31	−64	31	0.257	−31	−54	4	0.075
Linear trend significance[b]		0.053				0.025				0.027			
Use of wood		−13	−25	0.1	0.052	69	22	134	0.002	−14	−30	5	0.146

Abbreviations: BC, black carbon; BMI, body mass index; CO, carbon monoxide; IL-10, anti-inflammation marker; $PM_{2.5}$, fine particulate matter; TNF-α and IL-1β, markers associated with a pro-inflammatory response.

[a]Each marker of inflammation model includes the following covariates: age, BMI, wealth quintile, season, type of fuel (use of wood and dung vs. only dung) and quintiles of BC, $PM_{2.5}$, and CO; results shown include quintiles of BC levels as the independent variable and each marker of inflammation as the outcome variable.

[b]*p*-values of linear trends were obtained using t tests on log-transformed continuous BC concentrations.

TABLE 5

Percent change in markers of inflammation by quintiles of kitchen area BC and NO_2 in multi-pollutant model in subsample of 92 participants[a]

TNF-α (*n* = 92)				**IL-1β (*n* = 92)**				**IL-10 (*n* = 92)**			
Change (%)	**95 %**	**CI**	***p*-value**	**Change (%)**	**95 %**	**CI**	***p*-value**	**Change (%)**	**95 %**	**CI**	***p*-value**
Kitchen NO_2											
Reference											
0	−25	34	0.997	−58	−77	−23	0.006	15	−13	51	0.318
6	−23	47	0.709	−33	−66	31	0.233	5	−23	42	0.768
−7	−38	39	0.719	−70	−87	−31	0.005	8	−26	58	0.669
0	−33	49	0.985	−58	−82	−3	0.043	35	−7	96	0.113
Linear trend significance[b]	0.737			0.347				0.678			
Kitchen BC											
Reference											
7	−23	47	0.687	74	−11	239	0.105	−28	−46	−2	0.036
−8	−38	34	0.648	−16	−62	86	0.660	−43	−60	−18	0.003
33	−12	99	0.172	−15	−63	99	0.709	−35	−55	−5	0.028
42	−8	120	0.113	6	−57	161	0.905	−35	−57	−2	0.041
Linear trend significance[b]	0.140			0.221				0.030			

Abbreviations: BC, black carbon; BMI, body mass index; CI, confidence interval; CO, carbon monoxide; IL-10, anti-inflammation marker; NO_2, nitrogen dioxide; $PM_{2.5}$, fine particulate matter; TNF-α and IL-1β, markers associated with a pro-inflammatory response.

[a]Each marker of inflammation model includes the following covariates: age, BMI, wealth quintile, season, type of fuel (use of wood and dung vs. only dung), and quintiles of BC, NO_2, $PM_{2.5}$, and CO.

[b]*p*-values of linear trends were obtained using t tests on log-transformed continuous pollutant concentrations.

TABLE 6

Percent change in markers of inflammation by quintile of BC among wood users[a]

		TNF-α (*n* = 73)				IL-1β (*n* = 73)			
BC quintile medians (μg/m^3)		**Change (%)**	**95 %**	**CI**	***p*-value**	**Change (%)**	**95 %**	**CI**	***p*-value**
1	36	Reference							
2	94	13	−5	35	0.157	−33	−62	19	0.165
3	171	20	−3	50	0.091	−32	−67	38	0.282
4	260	46	14	87	0.003	−56	−81	−2	0.046
5	380	32	0.1	75	0.049	−54	−82	15	0.096

Note: p-values of linear trends were obtained using *t* tests on log-transformed continuous BC concentrations.

Abbreviations: BC, black carbon; BMI, body mass index; CI, confidence interval; TNF-α and IL-1β, markers associated with a pro-inflammatory response.

[a]Each marker of inflammation model includes the following covariates: BC quintiles, age, BMI, wealth quintile, season.