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Associations of Respiratory Symptoms and Lung Function with Measured Carbon Monoxide Concentrations among Nonsmoking Women Exposed to Household Air Pollution: The RESPIRE Trial, Guatemala

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Running title: HAP and adult respiratory health – RESPIRE trial

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Abstract

Background: With 40% of the World's population relying on solid fuel, household air pollution (HAP) represents a major preventable risk factor for COPD. Meta-analyses have confirmed this relationship, however constituent studies are observational with virtually none measuring exposure directly.

Objectives: We estimated associations between HAP exposure and respiratory symptoms and lung function in young, non-smoking women in rural Guatemala, using measured CO concentrations in exhaled breath and personal air to assess exposure.

Methods: The Randomised Exposure Study of Pollution Indoors and Respiratory Effects (RESPIRE) Guatemala study was a trial comparing respiratory outcomes among 504 women using improved chimney stoves versus traditional cookstoves. The present analysis included 456 women with data from post-intervention surveys including 6-monthly interviews (respiratory symptoms), spirometry and CO (ppm) in exhaled breath measurements. Personal CO was measured using passive diffusion tubes at variable times during the study. Associations between CO concentrations and respiratory health were estimated using random intercept regression models.

Results: Respiratory symptoms (cough, phlegm, wheeze or chest tightness) during the previous six months were positively associated with breath CO measured at the same time of symptom reporting and with average personal CO concentrations during the follow-up period. CO in exhaled breath at the same time as spirometry was associated with lower lung function [average reduction in FEV_1 (in mL) for a 10% increase in CO was 3.33 mL (95% CI: -0.86, -5.81)]. Lung function measures were not significantly associated with average post-intervention personal CO concentrations.

Conclusions: Our results provide further support for the effects of HAP exposures on airway inflammation. Further longitudinal research modelling continuous exposure to particulate matter against lung function will help understand more fully the impact of HAP on COPD.

Introduction

Approximately 2.8 billion people used solid fuels (wood, animal dung, agricultural wastes, charcoal and coal) in 2010 (WHO 2012), little changed since 1980 (Bonjour et al. 2013; Rehfuess et al. 2006). Solid fuel combustion leads to high levels of health-damaging household air pollution (HAP) including carbon monoxide (CO), particulate matter (PM), nitrogen dioxide (NO_2) and polycyclic aromatic hydrocarbons (Naeher et al. 2007). Studies consistently show high HAP levels in households using solid fuels with $PM_{2.5}$ being observed to be 10 to > 50 times the World Health Organisation (WHO) annual average Air Quality Guideline level (Saksena et al. 2003; WHO 2006). Women and young children especially experience high levels of HAP exposure due to traditional gender-based household roles involving more time in proximity to the stove (Torres-Duque et al. 2008).

Globally, HAP from solid fuel use was estimated by the Global Burden of Disease Project 2010 (GBD-2010) to account for 3.5 (95%CI: 2.7-4.4) million deaths and 4.3% (95%CI: 3.4-5.3) of disability adjusted life years in 2010 (Lim et al. 2012). Additionally it has been estimated that 16% of the 3.1 million deaths from outdoor air pollution are attributable to HAP due to its impact on ambient air (Lim et al. 2012). Accordingly, HAP is ranked 4th in terms of global burden when compared to 67 risk factors contributing to the Global Burden of Disease calculations (2nd among women) (Lim et al. 2012). This HAP-related mortality arises from four disease outcomes; chronic obstructive pulmonary disease (COPD), acute lower respiratory infections (ALRI) in children less than 5 years and from cardiovascular disease and lung cancer (Smith et al. 2004; Smith et al. 2014). In addition, whilst there is a paucity of epidemiological investigation, there is evidence of an association between HAP and other health outcomes including cataracts and adverse pregnancy outcomes (Pope et al. 2010; Smith et al. 2014).

Smith et al. (2014) estimated that HAP-related COPD resulted in almost 800,000 premature deaths per year (Smith et al. 2014). Although cigarette smoking among women remains low in most developing countries, women exposed to HAP in such countries develop COPD with clinical characteristics, quality of life and increased mortality similar in degree to that of tobacco smokers (Fullerton et al. 2008). Three published systematic reviews and meta-analyses of HAP and COPD have reported significant pooled effect estimates of OR=2.80 (95% CI: 1.85, 4.00) (Kurmi et al. 2010), OR=2.44 (95% CI: 1.90, 2.33) (Hu et al. 2010) and OR=2.40 (95% CI: 1.47, 3.93) (Po et al. 2011). Recently, a further meta-analysis reported an increased pooled effect of biomass smoke exposure of OR=1.94 (95% CI: 1.62, 2.33) – an estimate used in the comparative risk assessment of HAP for GBD-2010 (Smith et al. 2014). With the majority of studies included in the meta-analyses not directly measuring exposure, the effect estimates were based on exposure determined by fuel type (e.g. 'use of solid fuels' or 'exposure to biomass' compared to 'use of other fuels'). All meta-analyses identified a larger effect in women, the latter reporting a pooled OR of 2.30 (95% CI: 1.73, 2.06) in women compared to 1.90 (95% CI: 1.15, 3.13) in men, reflecting their greater exposure to HAP (Smith et al. 2014).

These systematic reviews highlighted the variability in study quality and considerable methodological and statistical heterogeneity (Hu et al. 2010; Kurmi et al. 2010; Po et al. 2011). In addition, most studies utilised cross-sectional or case-control designs (Hu et al. 2010; Po et al. 2011; Smith et al. 2014), with only one retrospective cohort study (Kurmi et al. 2010) and no prospective cohort studies or intervention designs. Finally, only one study used a direct exposure measure (Liu et al. 2007), the rest using exposure proxies (fuel/ stove type and time spent by fire) (Hu et al. 2010; Kurmi et al. 2010; Po et al. 2011; Smith et al. 2014). Such proxies can lead

to substantial exposure misclassification. Accurate, direct measurement of HAP exposure is required to define exposure-response relationships (Smith-Sivertsen et al. 2009).

A randomised controlled trial (RCT) of a chimney stove intervention in Mexico, ineligible for these systematic reviews due to outcome definition criteria, found a significant reduction in respiratory symptoms and lung function decline when compared to open fire use only among women (50%) adherent in using the intervention (Romieu et al. 2009). These women had an FEV_1 rate decline of 31mL/ year compared to 61mL/year in open fire users (p=0.012).

The first RCT to investigate the impact of reduced HAP from a chimney cookstove intervention (Plancha) on ALRI in children and the respiratory health of their mothers was carried out in rural Guatemala (Smith et al. 2011) (RESPIRE - Randomised Exposure Study of Pollution Indoors and Respiratory Effects). Intention-to-treat analysis found reductions in the risk of respiratory symptoms. In addition a relationship between symptoms and lung function was found at baseline (Diaz et al. 2007a; Smith-Sivertsen et al. 2009). No significant association with lung function (FEV_1 and FEV_1/ FVC ratio), however, was observed. Exposure levels, assessed using CO as a proxy for $PM_{2.5}$, were significantly reduced in intervention compared to control (open fire) groups; 61.6%; $p<0.0001$, although post-intervention $PM_{2.5}$ exposure remained high with exposure distributions between groups overlapping (Smith et al. 2011; Smith-Sivertsen et al. 2009). The RESPIRE study allows investigation of the relationship between respiratory outcomes (symptoms and lung function) and a continuous measure of post-intervention exposure rather than by intervention and control groups based on the intention-to-treat analysis. Such an analysis would provide further support for the effects of HAP exposure on airway inflammation in this young population.

We present here analysis from the RESPIRE trial modelling HAP exposure as a continuous measure of CO with lung symptoms and function in young non-smoking women exposed to high HAP levels since birth.

Methods

The methods for the adult component of the RESPIRE trial have been published (Smith-Sivertsen et al. 2009) and are briefly described below.

Study population

Women were recruited from 23 indigenous communities in the rural highlands of San Marcos in North West Guatemala. At the time of the study the population primarily spoke Mam and illiteracy was common (Hallman et al. 2006).

The main household fuel is wood, typically burned indoors in a 3-stone open fire. Average levels of particulate matter (PM_{10} and $PM_{2.5}$ – respirable particles with a diameter of ≤10 or ≤2.5 microns) in this setting have been measured to be 717 $\mu g/m^3$ and 528 $\mu g/m^3$, respectively (Naeher et al. 2000). Women spend 5 hours per day on average in a room with a lit open fire (Engle et al. 1998). An additional, concentrated source of exposure is the temazcal (traditional sauna) typically taken one to several times per week and leading to very high levels of CO and PM (Thompson et al. 2004). Smoking is uncommon.

A rapid census survey of 5365 households in this region found 770 houses with children under 4 months and/or a pregnant woman and using open fires eligible for RESPIRE. Of these 534 were recruited to the study and following baseline assessment randomly assigned to an intervention (received the chimney stove) (Smith et al. 2011; Smith-Sivertsen et al. 2009) or control group

(open fire). 504 women (mean age 27.7 years) agreed to participate and were recruited in 2 phases – phase I in October to November 2002 (Group A: 153 intervention and 147 control women) and phase 2 in April to May 2003 (Group B: 106 intervention and 98 control women).

The study was carried out over 2 years (October 2002 to December 2004). Women were surveyed at baseline, before randomisation, and every 6 months until 12 months (Group A), and 18 months (Group B) after randomisation to intervention and control groups (Figure 1). Questionnaires were administered at each survey by a trained bilingual interviewer. Information included age, height, weight, pregnancy status, smoking, respiratory symptoms, and days since the temazcal was last used. Household information included building construction/ layout, number of children, others smoking, and number of consumer goods possessed (radio, television, refrigerator, bicycle, motorcycle and car) combined into an asset index. Lung function and breath CO were measured at the woman's home after the interview, while personal 48-hr CO exposure (diffusion tubes) was assessed at different times (Figure 1).

Meteorological data collected over 6 months at the study centre in San Lorenzo, included rainfall (mm per day) and average, minimum and maximum temperatures (^{o}C). These readings were taken for each survey round after completion of interviews. Household elevation was available from baseline GPS measurement.

Ethical approvals for studies involving human participants were obtained from University of California (Berkeley, CA, USA), Universidad del Valle (Guatemala City, Guatemala), the US Centers for Disease Control and Prevention (Atlanta, GA, USA), the University of Liverpool (Liverpool, UK), and WHO (Geneva, Switzerland). Local, trained fieldworkers visited each recruited household and obtained oral informed consent from the study women.

Assessment of respiratory symptoms and lung function

Questionnaires recorded frequency and duration of respiratory symptoms including cough, phlegm, wheeze, and chest tightness experienced in the previous 6 months. Cough and phlegm are the most recognised symptoms of airway inflammation, and their chronicity was assessed based on the duration of symptoms (> 3 months indicating chronic cough and/or phlegm). Questions were based on standardised instruments (Medical Research Council/ International Union Against Tuberculosis and Lung Disease and International Study of Asthma and Allergies in Childhood) (Abramson et al. 1991; Bai et al. 1998; ISAAC. 1998; Toren et al. 1993), with modification and piloting to improve comprehension (Diaz et al. 2007b). Questionnaires were translated into Mam following Spanish translation, with independent back-translation. A more detailed description of content and development of the study questionnaire has been published (Diaz et al. 2007a; Diaz et al. 2007b). For analysis, respiratory outcomes included (i) presence of cough, phlegm, cough and/or phlegm, wheeze and chest tightness, (ii) presence of any respiratory symptom, (iii) presence of chronic cough (>3 months duration), chronic phlegm, chronic cough and/ or chronic phlegm.

Lung function, without bronchodilator use, (FEV_1, FVC and FEV_1/FVC ratio) was measured with a Micro Medical Microloop turbine spirometer (Micro Medical Ltd., Rochester, United Kingdom), using American Thoracic Society guidelines (ATS. 1995). Quality assurance was maintained through weekly calibration, extensive training and supervision (Diaz et al. 2007a). Regular assessments of inter-observer repeatability were carried out with additional training if required. (Diaz et al. 2007a)

Exposure assessment

The primary measure of personal HAP exposure was CO (Naeher et al. 2000). Two approaches to assessment were available for this analysis: COppm in exhaled breath and 48-hr mean COppm measured with passive diffusion tubes.

Measurements of CO breath were carried out immediately following spirometry using a MicroMedical Micro CO (Micro Medical Ltd., Rochester, United Kingdom). Women performed three measurements outside the home at each survey and the average of the two highest readings was recorded. Quality assurance was maintained through regular instrument comparison, field-worker training, and supervision (Diaz et al. 2007a). Exhaled CO monitors were calibrated against standard CO 49.8ppm span gas every 2–4 weeks during the study period (Diaz et al. 2007a; Smith et al. 2010a). Previous work carried out by Naeher et al (Naeher et al. 2001) in the study region found CO measurements using the passive diffusion tubes were a good proxy for $PM_{2.5}$ in homes using open fires and plancha stoves with a strong correlation between the measures (r= 0.92 for kitchen measurements). In addition when the open fire and Plancha data were pooled, a strong correlation between mother personal CO and child personal CO was observed (r=0.85).

Average 48-hr CO ppm was measured using 1DL CO passive diffusion tubes (Gastec Corp., 6431 Fukaya, Ayase-City, Kanagawa, 252-1195, Japan). Quality assurance in tube reading and validation of the data has been reported (Smith et al. 2010a; Smith et al. 2011). Tube measurement validation included (i) an instrument precision substudy (comparing 50 pairs of Gastec 1DL duplicate tube measures), (ii) an exchangeability substudy (comparing 50 pairs of 1D and 1DL tube measures), and (iii) an external validation substudy (where both the 1D (n=45) and 1DL (n=232) tube types were collocated with a continuous electrochemical CO monitor in

the household kitchens) (Smith et al. 2010b). Exposure measurements using tubes were taken at baseline (prior to randomisation) and three times post-intervention until the study end, but did not coincide with the home visits for assessment of symptoms, lung function and CO in breath (Figure 1). Additional measurements were taken before baseline for Group A (Figure 1). Only post-intervention measurements were used in the current analysis.

Women were asked to wear the CO tubes during the monitoring period and fieldworkers stressed the importance of keeping the tube on or near the woman at all times requesting the tube be kept near their bed during sleeping (Smith et al. 2010b). The women were asked to remove the tubes when using the traditional sauna (temazcal) as very high levels of CO from this exposure saturate the tube reagent. For CO breath, the relatively short half-life of around 5 hours (Crowley et al. 1989) and the varying timing of measurements relative to recent exposure events of varying intensity at successive surveys will have added further within-person random error. In a study of individual and group variability in exposure assessment for children in the RESPIRE trial, child 48-hr CO was found to have a low reliability for measuring predicted long-term CO exposure through mixed modelling (intraclass correlation r=0.33) (McCracken et al. 2009).

Statistical analysis

Analysis of exposure in exhaled CO used individual post-intervention round measurements as these took place at the same time as the survey interviews and spirometry. Analysis of exposure by CO tubes used the mean of all post-intervention measurements for each woman because measurements were not synchronised with home visits for health outcomes (Figure 1). Natural log (Ln) transformation of data from both CO measures was used due to marked positive skew (Figures 2(a) and (b)).

The relationship between CO measures was assessed by correlation, using Spearman rho for untransformed data and Pearson correlation for log-transformed values. For this analysis, we estimated correlations between each CO tube measurement and the breath CO measurement at the next follow-up visit.

We examined the relationship between survey round measurements (Ln(CO) exhaled breath) and average post-intervention exposure (Ln(CO) tube) with lung symptoms experienced in the 6 months preceding each survey using random intercept logistic regression; (xt logit in Stata; Stata Corp, College Station, Tx). The presence or absence of symptoms, during the 6 months prior to the interview, was recorded for each successive survey for repeated measures analysis over the three follow-up periods. Symptoms were defined as 'chronic' if women reported having them for more than 3 months duration.

Because CO in exhaled breath was measured at the same time as spirometry was taken, we examined the relationship between the actual survey round measurements (LnCO ppm) with lung function (FEV_1, FVC and FEV_1/FVC ratio – percentage) as a cross-sectional analysis. For CO measured by the tubes we modelled average post-intervention exposure (LnCO ppm) with lung function. All analysis was conducted using random intercept linear regression; (xt reg in Stata; Stata Corp, College Station, Tx).

Confounding covariates were dealt with in two ways.

(1) Factors that were fixed over time or only estimated once over the study were dealt with as non-time varying covariates (women's age, height, weight, asset index (McCracken et al. 2009), altitude and environmental tobacco smoke exposure). None of the women smoked.

(2) Factors which varied over time and were re-assessed at each successive survey were dealt with as time-varying covariates by including the survey-specific values. These included (i) pregnancy status, (ii) season [dry and cold (Nov-Feb); dry and warm (Mar-Apr); wet (May-Oct)], (iii) rainfall (mm/24 hrs), (iv) day of the week (to account for market days), (v) daily minimum, maximum and average temperatures (^{o}C)), (vi) fieldworker (based on the code for the fieldworker carrying out the interview/ spirometry), (vii) recruitment group (coded as A or B; Figure 1) and (viii) days since last temazcal use (this was included as a covariate for CO tube modelling but not for CO breath which incorporates exposure to all recent combustion sources). The covariates were included in multivariable models for adjustment if they modified effect estimates for associations between the exposure variables (CO breath and tube) and the outcome variables (respiratory symptoms and lung function) by at least 5%. For models of lung function age and height were automatically included.

Results

Table 1 shows the number of women providing exposure measurements (CO in exhaled breath and CO measured by tube) at each post intervention survey round by recruitment group. In addition the total number of repeat measurements available for analysis of each CO indicator is shown. For CO measured in breath more than 90% of women provided at least one measurement for both recruitment groups. For CO measured by tube 93% of women in Group A and 88% of women in Group B provided at least one exposure measurement. The average/ median number of repeat measures was 2 for CO tubes (for both group A and B) and 2 and 3 for CO breath for group A and B respectively. The correlations between CO breath and CO tube measurements taken prior to each survey were low (Table 2) with r values ranging from 0.17 to 0.36. The

correlation between average post-intervention CO breath and CO tube was low (Spearman's rho = 0.33; $p<0.001$).

Table 3 shows odds ratios for associations between Ln-transformed breath CO at individual visits and symptoms during the previous 6 months, and odds ratios for associations between symptoms during each 6-month period and the Ln-transformed average of all post-intervention personal CO measurements. CO breath was positively associated with phlegm, chronic phlegm (> 3 months), cough and phlegm, chronic cough and chronic phlegm (> 3 months), wheezing and chest tightness, although only univariate associations with wheeze and chronic phlegm were statistically significant ($p<0.05$).

For CO tube measurements there was a positive association with the majority of respiratory symptoms, with the presence of any respiratory symptom (adjusted OR=1.35 (95%CI: 1.01, 1.81)), phlegm (unadjusted OR= 1.51 (95%CI: 1.01, 2.27)) and combination of cough and phlegm (adjusted OR=1.63 (95%CI: 1.00, 2.66)) and wheeze (adjusted OR=1.57 (95%CI: 1.07, 2.30)) achieving statistical significance.

For lung function (Table 4), only exhaled CO showed an association, specifically with FEV_1, with an adjusted value of -35 mL (95% CI -9, -61) associated with each unit increase in Ln transformed CO breath (adjusted p=0.008).

Discussion

To our knowledge, this is the first study to examine relationships between a continuous measure of HAP (albeit a proxy for exposure measured by CO) and prevalence of respiratory symptoms and lung function in young, non-smoking women in a rural biomass fuel-dependent population. Our results found exposure to CO (ppm in exhaled breath and passive diffusion tubes) associated

with common respiratory symptoms, particularly phlegm (tubes), cough and phlegm (tubes) and wheeze (exhaled breath and tubes). Although based on relatively small numbers, more chronic symptoms (> 3 months duration) appeared to have a larger positive association with CO. In addition CO in exhaled breath was significantly associated with lower lung function measured at the same time after adjusting for covariates; the average reduction in FEV_1 (in mL) for a 10% increase in CO being 3.33ml (95% CI: -0.86, -5.81)).

The average breath COppm levels in this study were 6.91 (sd±3.33), 6.59 (sd±2.97) and 6.90 (sd±3.42) at 6, 12 and 18 months. A study of healthy smokers, passive smokers and non-smokers found average levels of COppm of 17.13 (sd±8.50), 5.20 (sd±3.38) and 3.61 (sd±2.15) respectively (Deveci et al. 2004). The levels observed in these relatively young non-smoking women therefore fall between those for active and passive smokers and are greater than the published WHO 24 hour air quality guideline for CO of 6ppm (WHO 2010). Although cigarette smoking is the leading cause of COPD in the developed world, HAP exposure is likely to be an important preventable cause in Lower and Middle Income Countries (LMIC), especially in women (Salvi and Barnes 2010).

The global health impact of HAP-related COPD is large with GBD-2010 estimating that HAP accounted for 783,000 COPD deaths in 2010 (Smith et al 2014). Although there is strong quantitative evidence for an increased risk of COPD from HAP (Hu et al. 2010; Po et al. 2011; Smith et al. 2014) this is largely based on observational data (typically cross-sectional and case-control studies). Increased exposure to biomass combustion has been associated with reduced lung function in cross-sectional studies of populations from Brazil (da Silva et al. 2012), Malawi (Fullerton et al. 2011) and Nepal (Pandey et al. 1985). Our findings provide evidence that may be used to better quantify the respiratory health effects of exposure to HAP.

The strengths of this study are the ability to compare directly measured exposure to a pollutant designated a good proxy for particulate matter (rather than other weaker proxies such as self-reported fuel use or time spent cooking) with objectively assessed lung function measured using standardised spirometry with repeated assessments of exposures and outcomes over 18 months. In addition, information on a range of covariates (both constant and time-varying) was available for multivariable modelling of adjusted associations. (Smith et al. 2011)

There did not appear to be a consistent pattern in the relationship between the two measures of CO with respiratory symptoms and lung function. For CO tubes (averaged over the three post-intervention periods) there was no association with lung function (reduced FEV_1) however for CO breath (analysed for each of the three post-intervention periods) exposure was significantly associated with a lower FEV_1.

In our relatively young non-smoking female population there were no COPD cases according to Global Initiative for Chronic Obstructive Lung Disease criteria (FEV_1: FVC < 70) (Lenfant and Khaltaev 2005). Typically HAP-associated COPD is seen in elderly women born in rural areas with lifelong HAP exposure from solid fuel use (Perez-Padilla et al. 2010). Whilst we did not observe an association between repeated measures of 48hr personal exposure to CO (as a proxy for PM) and repeated lung function measurements, we did find significant associations with acute and chronic respiratory symptoms, albeit based on small numbers for the latter. In addition we observed a significant association between CO in exhaled breath (a proxy for more recent exposure) and lower FEV_1 measured at the same time. Further follow-up of the study women would be needed to fully understand this relationship.

Carbon monoxide (CO) as an indicator for health-damaging constituents of HAP

CO was used to represent HAP exposure due to the practicality of measurement using passive diffusion tubes and in exhaled breath (at the same time spirometry was carried out). A wide range of pollutants will contribute to respiratory symptoms and lung function deficit leading to COPD, particularly respirable particulate matter (Ling and van Eeden 2009). Whilst CO has been demonstrated cross-sectionally to be a reliable proxy for $PM_{2.5}$ in kitchens where biomass is the primary fuel, little is known about this relationship for personal exposure (McCracken et al. 2013). The RESPIRE study quantified the relationship within this study population. Repeated measures (216 measures) of 24-hour $PM_{2.5}$ and COppm (passive diffusion tubes) in 116 women found CO explained 78% of between-subject variance in personal $PM_{2.5}$ suggesting that CO is a reliable surrogate for individual's exposure to respirable particulates (McCracken et al. 2013).

Mechanisms

It is likely that HAP exposure causes an inflammatory response and increased oxidative stress in the respiratory tract, particularly in lower airways (Barregard et al. 2006; Barregard et al. 2008; Swiston et al. 2008). Evidence from animal models involving rats suggest biomass smoke exposure from cow dung and wood can lead to chronic bronchitis, bronchiolitis and peribronchial fibrosis (Hu et al. 2013; Rai et al. 1982). Research summarising the potential adverse health effects of individual constituents of air pollution from woodsmoke identified exposure to nitrogen dioxide as being associated with toxicological effects including pulmonary edema, bronchoconstriction and increased respiratory infection rates and exposure to particulate matter as (i) being associated with decreased lung function in children and (ii) having mutagenic properties within the lower respiratory tract (Pierson et al. 1989). In a controlled experiment where 20 healthy individuals were exposed to woodsmoke combustion with $PM_{2.5}$ levels ranging

from 165-303 μg/m³ and 205-662 μg/m³ for low and high exposure, respectively, significant mucosal irritation was detected, assessed using a standardized self-reported rating scale of irritation of the throat, nose and eyes (Riddervold et al. 2011). Acute exposure to particulate matter from ambient air pollution episodes has been found to be associated with reduced lung function in children in the US and the Netherlands, with declines in lung function associated with episodic exposure to suspended particles occurring rapidly and persisting for up to three weeks before recovery (Pierson et al. 1989). In a US study of exposure to ambient particulate matter and respiratory effects in asthmatic children, levoglucosan (a marker of woodsmoke) was measured outside and found to be significantly associated with a decrease in measured lung function (FEV_1) (Allen et al. 2008). In a sample of 45 women from the RESPIRE population, we found exposure to indoor biomass smoke to be associated with higher gene expression of multiple mediators of airway inflammation and remodeling. These mechanisms could explain some of the observed association between prolonged biomass smoke exposure and COPD (Guarnieri et al. 2014). In a study comparing COPD patients exposed to woodsmoke and tobacco smoke with controls for matrix metalloproteinases (MMP) activity and expression, researchers found significant increases in MMP-2 and MMP-9 in both exposed groups and concluded that such increased activity from wood smoke exposure could produce lung damage similar to COPD associated with tobacco smoke (Montano et al. 2004). In addition an imbalance of oxidants/antioxidants caused by pollutants such as those derived from biomass combustion could play a role COPD pathogenesis by regulating redox-sensitive transcription factors (e.g., NF-κB), autophagy and unfolded protein response leading to chronic lung inflammatory response (Yao and Rahman 2011). CO has been implicated as a possible indicator of lung and/or systemic inflammation and breath CO has been widely studied as a putative inflammatory marker

of disease in relation to asthma, COPD, cystic fibrosis, bronchiectasis in addition to systemic conditions (sepsis and diabetes) (Ryter and Choi 2013). Our study identified an increased risk of common and chronic respiratory symptoms with higher CO exposure measured by tube and in breath (although the majority only reached statistical significance for the former), consistent with acute mucosal irritation and inflammatory response. There are a number of limitations in the current study that should be considered when interpreting the findings. Firstly, given the observational nature of the analysis (despite being part of a randomised trial) there is likely to be some confounding. We attempted to account for this by adjusting for a variety of covariates collected as part of the trial, however there is the potential for residual confounding or confounding where the covariates were not adequately controlled. Secondly, there might be some differential misclassification between women who received the intervention (less exposed) and those who were controls in terms of the self-reporting of respiratory symptoms. Finally, for some of the respiratory outcomes confidence intervals were wide reflecting low precision due to small numbers of women reporting symptoms (particularly those that were chronic).

Conclusion

RESPIRE Guatemala (the first RCT studying the effect of HAP on health) has allowed examination of relationships between directly measured personal HAP exposure (COppm) and risk of respiratory symptoms and levels of lung function in young, non-smoking women – evidence previously missing from the literature. Common respiratory symptoms (including cough, phlegm, wheeze and chest tightness) were increased in association with CO concentrations measured in exhaled breath and by passive diffusion tube. Chronic symptoms (> 3 months) were also associated, although based on a small number of observations. In addition, CO in exhaled breath was significantly associated with lower lung function at the same time after

adjusting for covariates with an average reduction in FEV_1 (in ml) for a 10% increase in CO of 3.33mL (95% CI: -0.86, -5.81)). Given the limitations of our study in relation to the potential for uncontrolled confounding, misclassification and random error, confirmation of these findings require further prospective studies to examine changes in COPD incidence following interventions to decrease HAP exposure from solid fuel use, and will require larger sample sizes and/or duration of follow-up.

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Table 1. Number (%) of exposure measurements available for women post intervention, for CO tube and CO breath by recruitment group and survey round.

	CO tube		CO Breath	
	Group A (n=300)	**Group B (n=204)**	**Group A (n=300)**	**Group B (n=204)**
6 month survey	270 (90.0)	65 (31.9)	271 (90.3)	185 (90.7)
12 month survey	196 (65.3)	152 (74.5)	257 (85.7)	181 (88.7)
18 month survey	--	170 (83.3)	--	176 (86.3)
Number of measurements				
0	22 (7.3)	24 (11.8)	25 (8.3)	14 (6.9)
1	90 (30.0)	22 (10.8)	22 (7.3)	9 (4.4)
2	188 (62.7)	109 (53.4)	253 (84.3)	10 (4.9)
3	--	49 (24.0)	--	171 (83.8)

Table 2. Pearson Correlation of CO tube and CO breath at each post-intervention follow-up round (based on ln transformed values).

Survey round	Recruitment Group A		Recruitment Group B	
	Coef.	p value	Coef.	p value
6 months	0.23	0.0002	0.36	0.005
12 months	0.18	0.015	0.17	0.042
18 months	--	--	0.32	<0.0005

Table 3. Results of random intercept logistic regression for effect of exposure (CO breath – round measurements and CO tubes – post intervention average values) on respiratory symptoms: all post-intervention survey rounds.

Symptoms	CO breath (n=465 – at least one measurement)			CO tube (n=458 – at least one measurement)		
	No.[a]	OR[b] (95% CI)	p-value	No.[a]	OR[b] (95% CI)	p-value
Symptom experienced in the last 6 months						
Cough (unadjusted)	114	1.01 (0.46, 2.20)	0.98	106	1.22 (0.88, 1.70)	0.23
Cough (adjusted)[c]	(141)	0.96 (0.44, 2.10)	0.91	(131)	1.15 (0.82, 1.61)	0.41
		age			age, temazcal	
Phlegm (unadjusted)	68	1.82 (0.72, 4.60)	0.21	63	1.51 (1.01, 2.27)	0.05
Phlegm (adjusted)[c]	(83)	1.57 (0.61, 4.06)	0.35	(78)	1.47 (0.98, 2.21)	0.06
		age, fieldworker, group, asset[d], altitude, weight			age	
Cough or phlegm (unadjusted)	135	0.95 (0.45, 2.01)	0.90	126	1.24 (0.91, 1.69)	0.17
Cough or phlegm (adjusted)[c]	(169)	0.88 (0.42, 1.86)	0.75	(158)	1.20 (0.88, 1.65)	0.25
		age			age, fieldworker, group	
Cough & phlegm (unadjusted)	46	2.62 (0.90, 7.63)	0.08	42	1.67 (1.03, 2.72)	0.04
Cough & phlegm (adjusted)[c]	(55)	2.32 (0.73, 7.40)	0.15	(49)	1.63 (1.00, 2.66)	0.05
		age, fieldworker, group, asset[d], rainfall, height, weight, pregnancy			age	
Wheeze (unadjusted)	67	2.65 (1.12, 6.26)	0.03	62	1.64 (1.12, 2.39	0.01
Wheeze (adjusted)[c]	(78)	2.28 (0.94, 5.52)	0.07	(72)	1.57 (1.07, 2.30)	0.02
		age, fieldworker, asset[d], altitude, max temp, weight			age	
Chest tightness (unadjusted)	82	2.20 (0.92, 5.25)	0.08	75	1.38 (0.95, 2.01)	0.09
Chest tightness (adjusted)[c]	(101)	1.71 (0.69, 4.23)	0.25	(94)	1.31 (0.90, 1.91)	0.16
		age, fieldworker, altitude, weight, temazcal			age	
Any symptom (unadjusted)	184	1.32 (0.67, 2.62)	0.42	170	1.40 (1.04, 1.88)	0.03
Any symptom (adjusted)[c]	(250)	1.16 (0.57, 2.34)	0.68	(232)	1.35 (1.01. 1.81)	0.04
		age, fieldworker, ETS[e]			age	
Symptom experienced in the last 6 months for > 3 months						
Cough (unadjusted)	57	1.45 (0.61, 3.50)	0.40	53	1.19 (0.84, 1.68)	0.34
Cough (adjusted)[c]	(78)	1.11 (0.46, 2.67)	0.82	(73)	1.21 (0.85, 1.74)	0.29
		age, height, weight, ETS[e], season, rainfall, min temp			age, fieldworker, group	
Phlegm (unadjusted)	36	3.28 (1.02, 10.54)	0.05	34	1.37 (0.82, 2.29)	0.23
Phlegm (adjusted)[c]	(42)	2.56 (0.83, 7.93)	0.10	(40)	1.31 (0.77, 2.22)	0.32
		age, asset[d], altitude, height, weight			age, fieldworker, group, height	
Cough or phlegm (unadjusted)	73	1.56 (0.67, 3.62)	0.30	69	1.19 (0.83, 1.69)	0.34
Cough or phlegm (adjusted)[c]	(85)	1.29 (0.54, 3.09)	0.57	(80)	1.21 (0.83, 1.76)	0.32
		age, fieldworker, height, ETS[e]			age, fieldworker, group, height	
Cough & phlegm (unadjusted)	23	3.15 (0.87, 11.42)	0.08	21	1.58 (0.87, 2.89)	0.13
Cough & phlegm (adjusted)[c]	(26)	2.66 (0.66, 10.79)	0.17	(24)	1.59 (0.84, 3.01)	0.15
		age, asset[d], height, weight, rainfall, pregnancy			age, height, weight, pregnancy	

[a]Odds ratio for a one unit increase in CO exposure (ln transformed) – all adjusted for non-independency of data for repeated measures within individuals. [b]Number of women with exposure data reporting a symptom on at least one occasion (number in parentheses is the total number of times the symptom was reported post intervention). [c]Covariates included in adjusted model indicated for each analysis. [d]Asset index based on number of consumer goods possessed (radio, television, refrigerator, bicycle, motorcycle and car). [e]Environmental tobacco smoke.

Table 4. Results of random effects linear regression for effect of exposure (CO breath – all post intervention survey rounds (maximum n=3 per woman); CO tube – post intervention average) on lung function.

Measure of lung function	CO breath (n=465)[a] (round values)		CO tube (n=458)[a] (post intervention average)	
	Coeff[b] (95% CI)	p-value	Coeff[b] (95% CI)	p-value
FEV_1 (L)				
unadjusted	-0.031 (-0.056, -0.006)	0.02	0.012 (-0.030, 0.053)	0.58
adjusted[c]	-0.035 (-0.061, -0.009)	0.01	0.015 (-0.019, 0.050)	0.39
	age, fieldworker, group, asset[d], weight, altitude, season, min temp, day of week		age, height, group, asset[d], weight, altitude, season, min temp, day of week, temazcal	
FVC (L)				
unadjusted	-0.024 (-0.055, 0.007)	0.13	0.027 (-0.021, 0.075)	0.27
adjusted[c]	-0.026 (-0.057, 0.006)	0.11	0.028 (-0.010, 0.064)	0.14
	age, weight, altitude, season, min temp, day of week		age, height, group, asset[d], weight, altitude, season, rainfall, min temp, day of week	
FEV1/FVC Ratio (%)				
unadjusted	-0.401 (-0.963, 0.162)	0.16	-0.319 (-0.853, 0.215)	0.24
adjusted[c]	-0.356 (-0.932, 0.221)	0.23	-0.272 (-0.823, 0.268)	0.32
	age, height, fieldworker, weight, altitude, season, min temp, day of week		age, height, group, asset[d], weight, altitude, season, rainfall, min temp, day of week, temazcal	

[a]Of the 465 women providing at least one CO breath measurement, 458 (98%) provided measurements from spirometry. Of the 458 providing at least one CO tube measurement 431 (94%) provided measurements from spirometry. [b]Beta coefficient represents the difference in lung function in litres associated with a 1 unit increase in CO (ln transformed) – all adjusted for time. [c]Covariates included in adjusted model indicated for each analysis. [d]Asset index based on number of consumer goods possessed (radio, television, refrigerator, bicycle, motorcycle and car).

Figure Legends

Figure 1. Timing of assessment of personal exposure using CO-tubes and of symptoms, lung function and CO-breath, in relation to the instalment of the chimney stove, for recruitment groups A and B. Q1-Q4 = yearly quarters (3 month intervals). B = baseline; PI = post-intervention.

Figure 2a. Average Post Intervention CO tube (untransformed and Ln transformed).

Figure 2b. CO exhaled breath at 12 month follow-up (untransformed and Ln transformed).

Figure 1.

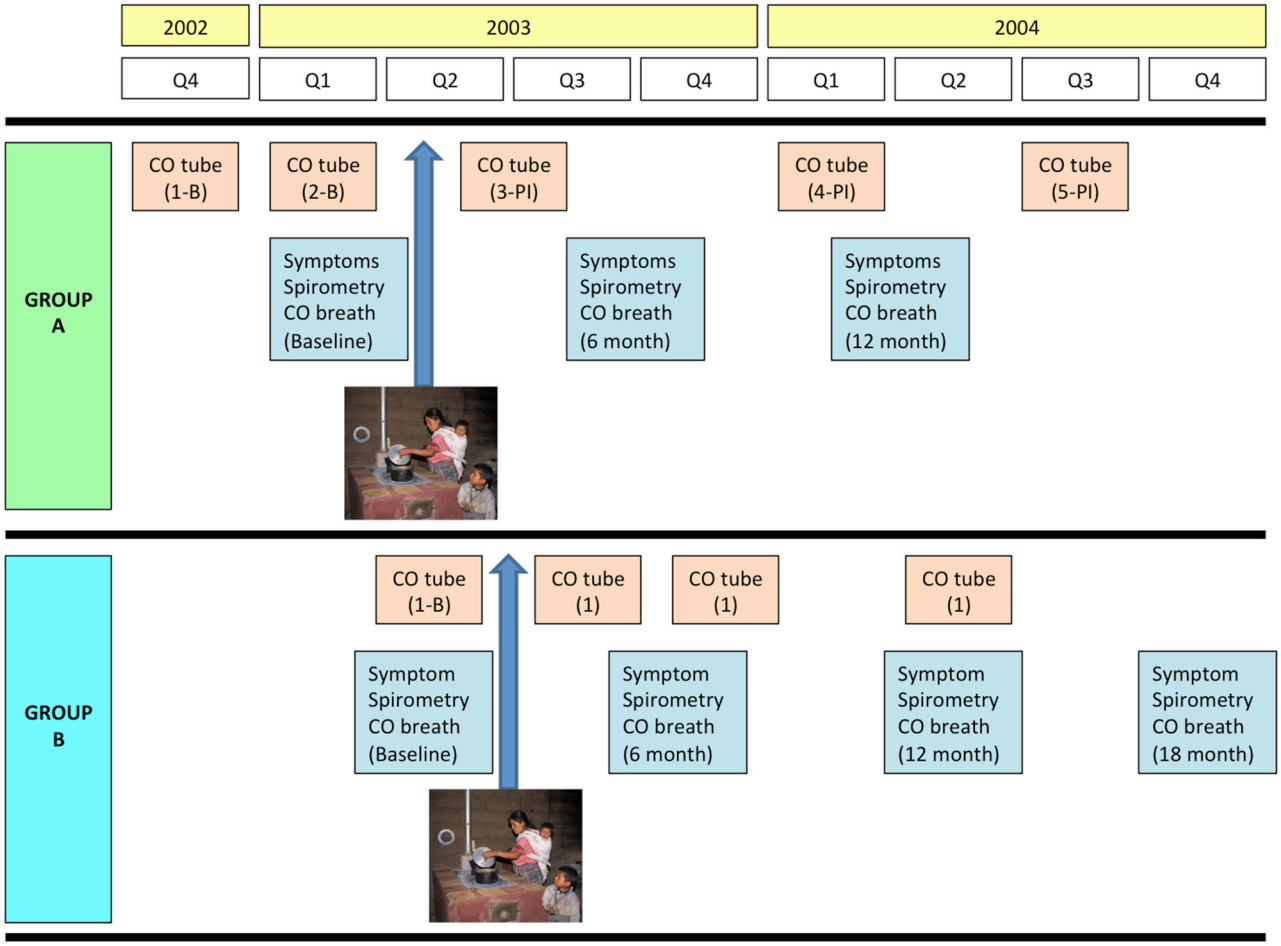
2002
2003
2004
Q4
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4
GROUP A
CO tube (1-B)
CO tube (2-B)
CO tube (3-PI)
CO tube (4-PI)
CO tube (5-PI)
Symptoms Spirometry CO breath (Baseline)
Symptoms Spirometry CO breath (6 month)
Symptoms Spirometry CO breath (12 month)
GROUP B
CO tube (1-B)
CO tube (1)
CO tube (1)
CO tube (1)
Symptom Spirometry CO breath (Baseline)
Symptom Spirometry CO breath (6 month)
Symptom Spirometry CO breath (12 month)
Symptom Spirometry CO breath (18 month)

Figure 2a: Average Post Intervention CO tube (untransformed and Ln transformed)

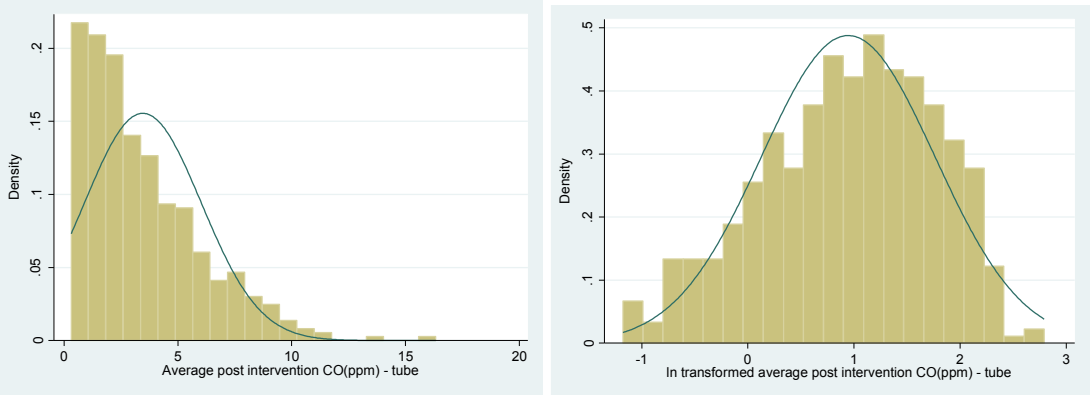
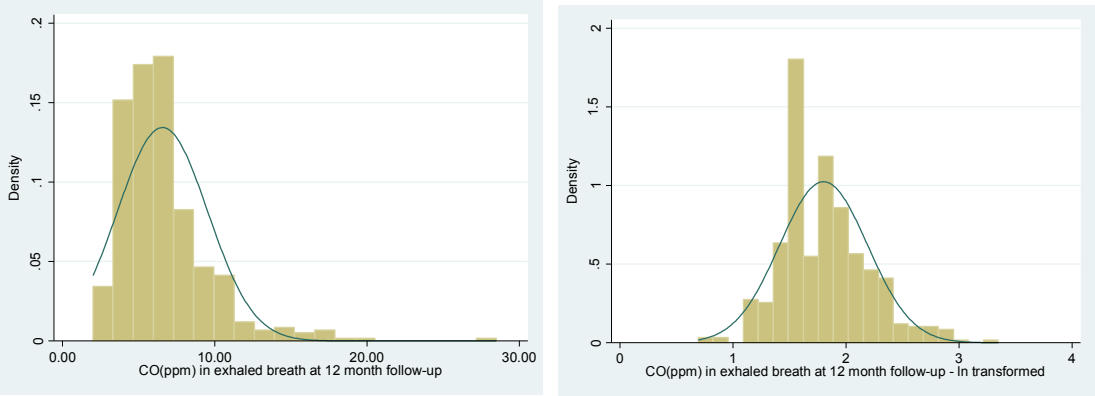
Figure 2b: CO exhaled breath at 12 month follow-up (untransformed and Ln transformed)