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Current respiratory symptoms and risk factors in pregnant women cooking with biomass fuels in rural Ghana

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ABSTRACT

Background: More than 75% of the population in Ghana relies on biomass fuels for cooking and heating. Household air pollution (HAP) emitted from the incomplete combustion of these fuels has been associated with adverse health effects including respiratory effects in women that can lead to chronic obstructive pulmonary disease (COPD), a major contributor to global HAP-related mortality. HAP is a modifiable risk factor in the global burden of disease, exposure to which can be reduced.

Objective: This study assessed the prevalence of respiratory symptoms, as well as associations between respiratory symptoms and HAP exposure, as measured using continuous personal carbon monoxide (CO), in nonsmoking pregnant women in rural Ghana.

Methods: We analyzed current respiratory health symptoms and CO exposures upon enrollment in a subset ($n = 840$) of the population of pregnant women cooking with biomass fuels and enrolled in the GRAPHS randomized clinical control trial. Personal CO was measured using Lascar continuous monitors. Associations between CO concentrations as well as other sources of pollution exposures and respiratory health symptoms were estimated using logistic regression models.

Conclusion: There was a positive association between CO exposure per 1 ppm increase and a composite respiratory symptom score of current cough (lasting > 5 days), wheeze and/or dyspnea (OR: 1.2, $p = 0.03$). CO was also positively associated with wheeze (OR: 1.3, $p = 0.05$), phlegm (OR: 1.2, $p = 0.08$) and reported clinic visit for respiratory infection in past 4 weeks (OR: 1.2, $p = 0.09$). Multivariate models showed significant associations between second-hand tobacco smoke and a composite outcome (OR: 2.1, $p < 0.01$) as well as individual outcomes of cough > 5 days (OR: 3.1, $p = 0.01$), wheeze (OR: 2.7, $p < 0.01$) and dyspnea (OR: 2.2, $p = 0.01$). Other covariates found to be significantly associated with respiratory outcomes include involvement in charcoal production business and dyspnea, and involvement in burning grass/field and wheeze. Results suggest that exposure to HAP increases the risk of adverse respiratory symptoms among pregnant women using biomass fuels for cooking in rural Ghana.

1. Introduction

Household air pollution (HAP) from use of solid fuels (biomass and coal) presents a major global public health threat resulting in an estimated 1.6 million deaths annually (GBD 2017, 2018). The incomplete combustion of plant-based fuels (primarily wood, charcoal and agricultural crops) emits a mixture of health-damaging air pollutants including carbon monoxide (CO), polycyclic aromatic hydrocarbons (PAH), nitrogen dioxide (NO_2) and respirable particulate matter (Naeher et al., 2007). Women and children are disproportionally exposed to these harmful chemical compounds due to increased time involved in cooking (Torres-Duque et al., 2008).

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While 2.8 billion people, or 40% of the world's population, rely on solid fuels, more than 75% of households in Ghana use these fuels as their main source of domestic energy (Bonjour et al., 2013; WHO, 2018b). In rural areas of Ghana specifically, the reliance on biomass fuels for cooking is very high (94%) (WHO, 2018b). Chronic exposure to biomass smoke has been associated with multiple adverse health effects, including chronic bronchitis, COPD, ALRI, lung cancer, reduced birth weight and cataracts (Dherani et al., 2008; Perez-Padilla et al., 2010; Pierson et al., 1989; Smith et al., 2014; Torres-Duque et al., 2008; Zhou et al., 2014). Specifically, use of biomass fuel is a significant risk factor for respiratory disease, and HAP-related COPD has been estimated to result in 800,000 premature deaths per year globally (Smith et al., 2014; Kurmi et al., 2014a; Gordon et al., 2014).

While there is evidence for an association between COPD and HAP, fewer studies have examined acute and current respiratory symptoms such as cough, phlegm, wheeze, and dyspnea (shortness of breath) as early indicators of airway inflammation and asthma in women exposed to biomass (Diaz et al., 2007; Pope et al., 2014). Further, these studies are often hampered by the use of exposure proxies such as fuel type and years cooked, rather than a quantitative measure of HAP exposure (i.e. CO or fine particulate matter, $PM_{2.5}$) (Ekici et al., 2005; Ezzati and Kammen, 2002; Liu et al., 2007; Rinne et al., 2007; Shrestha and Shrestha, 2005; Zhong et al., 2007). HAP is a preventable risk factor in the global burden of disease, and identification and treatment of acute and current respiratory health symptoms as indicators of chronic respiratory disease are critical in disease prevention.

The objective of this study was to assess cross-sectional associations between respiratory health symptoms and personal CO exposure from biomass smoke, as well as other risk factors of respiratory health, in a well-defined cohort of pregnant women in rural Ghana.

2. Materials and methods

2.1. Study design

The Ghana Randomized Air Pollution and Health Study (GRAPHS) is a community-level clustered randomized cookstove intervention trial in rural Ghana which has been described elsewhere (Jack et al., 2015). Between August 2013 and March 2016, non-smoking, pregnant women were recruited from communities in Kintampo North and Kintampo South areas, located in the Brong-Ahafo region of central Ghana. Participants were enrolled if they were in their first or second trimester of pregnancy as established by ultrasound with a singleton fetus, and presented as the primary cook of the household (Jack et al., 2015). Pregnancies with gestational age > 28 weeks, as determined via ultrasound, were excluded (Boamah et al., 2014).

At the time of enrollment following the woman's first prenatal visit to the Kintampo clinic, and prior to the intervention, trained interviewers administered a total of four questionnaires (i.e. maternal enrollment form, including the respiratory symptom module; baseline economic status survey; household cooking practices survey; and a daily exposure monitoring survey) to collect data on smoking, socioeconomic status, education level, fuel use, kitchen and cooking characteristics, as well as the participants' current respiratory symptoms. The study protocols were approved by the Institutional Review Boards of Columbia University Medical Center, Massachusetts General Hospital/Partners Healthcare, the Ghana Health Service Ethical Review Committee, and the Kintampo Health Research Centre Institutional Ethics Committee. Potential participants in this analysis included women enrolled in GRAPHS to whom a respiratory survey had been administered, and an initial CO measurement session had been conducted by September 2014 (n = 1183).

2.2. Exposure monitoring

Immediately following enrollment into GRAPHS, women were outfitted at the clinic with a lightweight Lascar (Lascar Electronics, London, UK) EL-CO-USB electrochemical data logging CO monitor, and personal measurements were collected over the subsequent 72 h period. The CO monitors were attached to the participant's clothing near her breathing zone during the day and located near the participant during sleeping hours. Trained fieldworkers visited the women every 24 h to record the previous day's cooking events, to assess wearing compliance, and troubleshoot possible issues with the monitor. The CO monitor was set to record measurements every 10 s, and report CO concentrations between 0 and 100 ppm (ppm). Instrument precision is + −6% (as reported by manufacturer). The CO monitors were tested at the Kintampo Health Research Centre (KHRC) laboratory approximately every six weeks against certified span gas (50 ppm CO in zero air). Individual monitoring sessions were adjusted to account for drift CO in sensor readings. Given the logistical difficulty of shipping CO span gas to Ghana, it was not feasible to test sensors prior to every deployment (Jack et al., 2015). All CO data were downloaded at KHRC and post-processed to account for a monitor- and time-specific correction factor derived from the calibration between the CO monitors and the National Institute of Standards and Technology (NIST) standard. In this analysis, CO exposure was calculated over every minute of each personal monitoring session (which ranged from 44 to 90 h, with a mean of 71.4 h). The mean of the minute-averaged CO was then used as the metric representing exposure to cooking smoke. CO data used in this analysis passed three QA/QC validity criteria: (1) "high" confidence in the unit-specific Lascar CO monitor correction factor (between 0.6 and 1.2 as calculated from the CO gas span procedure), (2) CO monitoring session duration of > 44 h, and (3) coding of "1" or "high" confidence of validity from a visual evaluation of the tracing of the minute-wise CO data (Quinn et al., 2016).

2.3. Assessment of respiratory outcomes

A questionnaire administered during the enrollment clinic visit, and translated at the time of administration, recorded current respiratory symptoms including current cough (lasting > or < 5 days), wheeze, phlegm, dyspnea, as well as physician-diagnosed tuberculosis (TB) or asthma (or other chronic breathing problems). Participants were also asked whether they had sought health care for a respiratory infection in the previous 4 weeks (see Appendix). The six respiratory symptoms analyzed in this study are: 1) cough > 5 days, 2) wheeze, 3) dyspnea (shortness of breath), 4) any of these three symptoms (i.e. composite symptom score), 5) phlegm (with cough), and 6) clinic visit for a respiratory infection in the past 4 weeks.

2.4. Covariates

At enrollment, gestational age was determined via ultrasound. Maternal height and weight were measured during this first hospital visit, at the same time the self-reported medical history survey was administered. Marital status, level of education, and socioeconomic indicators (e.g. occupation, asset ownership, housing construction) were reported by questionnaire during a home visit following enrollment. Other possible sources of pollution exposure beyond cooking smoke (e.g. mosquito coils, smoking in household) and activities that may have influenced exposure during the 72 h monitoring session (e.g. charcoal production, roadside food sales) were recorded by questionnaire, after the 24 h and 72 h CO monitoring sessions.

A household asset index was constructed previously as a proxy for socioeconomic status, using housing characteristics (materials of walls and floor), ownership of household durables (e.g. tables, mattresses, radios, phones and TV), and household's primary source type of drinking water and toilet facility. A higher score indicates a higher household socioeconomic status (Quinn et al., 2016).

Potential confounders included age, body mass index (BMI), education, marital status, religion, ethnicity, land/home ownership, occupation, and gestational age. Advanced age, cigarette smoking, and low socioeconomic status are known risk factors for chronic obstructive diseases (Higgins et al., 1984). The following potential confounders were selected based on previous research (Higgins et al., 1984; Kurmi et al., 2014b) and were controlled for in all logistic regression models: age, BMI, gestational age, secondhand smoke, and asset index. Since exposure to second-hand smoke may influence CO exposure, a binary indicator variable for tobacco smoking by anyone in the household or compound was included.

Other covariates that may influence pollution exposure were included such as kitchen characteristics (fuel and stove type), cooking location (outdoor/indoor), number of meals prepared, other households cooking nearby (neighborhood effect), and household size (as a proxy for number of people cooked for). Other smoke exposures included as binary variables were mosquito coil, kerosene lantern, candles, grass burning, charcoal production, and commercial food preparation. A combined variable for exposure to burning of trash/toilet paper, busy vehicle road, charcoal production, fish smoking, and restaurant/chop bar was also included.

2.5. Statistical analysis

We analyzed associations between respiratory symptoms and CO among 840 of 1183 subjects potentially available for analysis. Reasons for missing data included a) missing covariate data (n = 22), b) smoking status, i.e. current or past smokers (n = 5), and c) CO measurements outside the CO-QA/QC criteria described in Section 2.2 (n = 316).

Statistical analyses were performed using Stata (v12.1, College Station, TX, USA). Baseline demographic characteristics were compared between the population included in the CO analysis (n = 840) and the population excluded after application of criteria described above (n = 343). Multivariate logistic regression was employed to calculate odds ratios (ORs) for the association between the respiratory symptoms and exposure, as measured by personal CO, as well as other covariates. Cluster-robust variance estimates were calculated to account for the clustering of individual observations within communities. Differences in CO and covariates were assessed using analysis of variance (ANOVA). Covariates not associated with the main respiratory outcome of interest in the univariate analyses ($p < 0.1$) were not included in the final models. Specifically, if a covariate was associated ($p < 0.1$) with a respiratory symptom, it was included in the initial multivariate logistic regression analysis, and if it remained associated with the respiratory outcome variable at $p < 0.1$ in the multivariate model, it was included in the final multivariate model. In addition to the covariates controlled for in all models, we included the following covariates in models for specific outcomes: "exposure to burning of field/grass" for wheeze, "involvement in charcoal business" for dyspnea, and "occupation" for phlegm. Logistic regression diagnostics were performed to test for specification error, goodness of fit, collinearity, and influential observations. One influential observation was removed from the adjusted wheeze, dyspnea, and composite outcome regression models, while an additional observation was removed from the final model for cough (> 5 days).

3. Results

Table 1 summarizes the demographic characteristics of the 840 women in the CO analyses. The baseline characteristics of the women included in our analysis did not differ statistically from women excluded due to invalid CO data, missing covariate data and current/past smoking status (n = 343). The only significant difference between the two groups was smoking status (current/past), however, this is attributable to the deliberate exclusion of smokers from our analysis (see Methods). The prevalence of respiratory symptoms also did not differ significantly between the two subpopulations.

Table 1
Demographic data comparing subpopulations of women in the GRAPHS cohort (n = 1183).

Characteristic	Included in analysis (n = 840)	Excluded from analysis (n = 343)	p-value
Age (years); mean (SD)	27.3 (7.1)	27.8 (7.6)	0.26
Body mass index (kg/m2); mean (SD)	23.4 (3.4)	23.3 (3.2)	0.58
Height (cm); mean (SD)	155.3 (6.4)	155.7 (6.8)	0.37
Weight (kg); mean (SD)	56.4 (8.3)	56.4 (8.1)	0.98
Gestational age (weeks); mean (SD)	15.9 (4.3)	15.9 (4.4)	0.94
Asset Index; mean (SD)	−0.01 (2.2)	0.052 (2.3)	0.67
Ever smoker (current/past); n (%)	0 (0)	5 (1.5)	0.00
Smoker in household or compound; n (%)	177 (21)	68 (20)	0.35
Years cooked	6.6 (6)	6.8(6)	0.65
Education level; n (%)			0.29
None	317 (38)	144 (42)	
Primary school	225 (27)	79 (23)	
Middle school	247 (29)	96 (28)	
Middle school or above	43 (5)	12 (4)	
NA	8 (1)	12 (4)	
Marital status; n (%)			0.27
Married	441 (53)	188 (55)	
Living with partner (unmarried)	270 (32)	106 (31)	
Widowed/divorced/separated/single	121 (14)	37 (11)	
NA	8 (1)	12 (4)	
Employment status; n (%)			0.17
None	260 (31)	97 (28)	
Trader/food seller/businesswoman	174 (21)	58 (17)	
Farmer/laborer/domestic worker	326 (39)	144 (42)	
Seamstress/hairdresser	45 (5)	26 (8)	
Other	27 (3)	6 (2)	
NA	8 (1)	12 (4)	
Cooking location; n (%)			0.49
Open/Outdoor	493 (59)	186 (54)	
Partially enclosed	120 (14)	41 (12)	
Fully enclosed	162 (19)	63 (18)	
NA	65 (8)	53 (16)	
Fuel Type; n (%)			0.27
Wood	800 (95)	302 (88)	
Crop Residue	1 (0)	0 (0)	
Charcoal	34 (4)	15 (4)	
LPG	2 (0)	4 (1)	

Approximately one-fifth (21%) of the women included in the main analysis were exposed to secondhand tobacco smoke in the household or compound. Subjects had a mean of 27 years of age (SD 7.1) and were early in their gestational period (mean 15.9 weeks, SD 4.3). A small percentage of participants was educated beyond middle school (5%), and the majority of women classified themselves as farmers, laborers or domestic workers (39%), or not employed outside the home (31%). Regarding cooking characteristics, the majority of women (59%) cooked in outdoor settings, while approximately one-fifth (19%) cooked in fully enclosed kitchens, and 14% of households reported cooking in various semi-enclosed kitchen locations. The predominant fuel type used for cooking was wood (95%) followed by a small fraction of charcoal users (4%), while one woman reported crop residue as her main fuel, and two women reported using LPG as their primary cooking fuel.

The mean CO measured in this population was 1.6 ppm (SD 1.3; median: 1.3 ppm; IQR: 0.7–2.2) and ranged from 0.04 to 15 ppm (Fig. 1). The mean duration of CO monitoring sessions was 71.4 h (range 44.2–90.3). Compliance with the CO monitoring protocol was high; field workers reported women were wearing the devices 94% of the time at the time the field worker arrived for the daily check-up visits.

Table 2 presents prevalence of current respiratory symptoms across

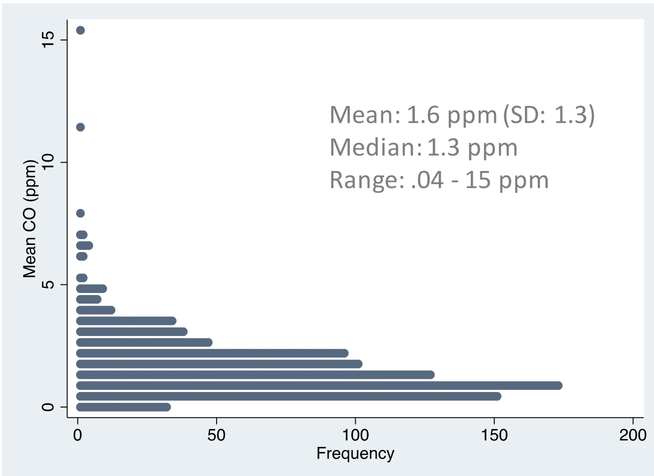

Fig. 1. Mean CO (ppm) distribution/frequency.

the 840 women. Phlegm (with cough) was the most frequent respiratory symptom reported (9.6%), while cough > 5 days was reported by 6.2% of the women, wheeze by 4.8%, dyspnea by 4.6% of the participants, and 1.7% of women reported seeking health care for respiratory infection in the past 4 weeks. The composite outcome of cough (> 5 days), wheeze and/or dyspnea was reported by 9.5% of women. Prevalence rates of other reported respiratory symptoms not included in this study are presented in Table S1.

Table 3 presents results of the crude and adjusted odds ratios with cluster-robust variance estimates for one unit (ppm) increase in CO exposure and respiratory outcomes. Overall, CO exposure was associated with the composite outcome (i.e. cough > 5 days, wheeze, and/or dyspnea) as well as with wheeze. There were also slight associations between personal CO and phlegm (with cough), report of seeking health care for respiratory infection (previous 4 weeks), and cough. We did not find an association between CO exposure and dyspnea.

Specifically, wheeze was associated with CO exposure in the adjusted model (OR 1.3, $p = 0.05$). Exposure to secondhand smoke from someone smoking in the participant's household or compound was associated with a 2.7 greater odds of reporting wheeze, compared to women who did not report secondhand smoke exposure ($p < 0.01$). Additionally, women who reported proximity to, or involvement with "burning fields or grass" had an odds ratio of 2.7 when also reporting wheeze ($p = 0.08$), compared to women who did not report this activity.

A 1 ppm unit increase in mean 72 h CO exposure was associated with a 20% increase in odds of having the composite outcome of cough > 5 days, wheeze, and/or dyspnea (OR 1.2, $p = 0.03$). Both the inclusion of phlegm in the composite outcome in sensitivity analyses (i.e. cough > 5 days, wheeze, dyspnea and/or phlegm) and removal of wheeze from the composite outcome attenuated the association (OR 1.1, $p < 0.05$, for both). Analysis based on symptom severity (i.e. cough > 5 days, and phlegm, and wheeze) found no association with CO and severity of symptoms, however, the number of people reporting all three symptoms was low ($n = 15$). Lastly, regression models were run to test type of cough (dry vs. wet) and duration of cough (< and > 5 days), and associations with CO were found only for cough < 5 days (OR 1.2, $p = 0.02$), and dry cough (OR 1.3, $p = 0.01$). Secondhand smoke remained a significant predictor of the composite respiratory outcome in the multivariate logistic regression model with CO (OR 2.1, $p < 0.01$).

While report of phlegm (with cough) was weakly associated with CO exposure (OR: 1.2, $p = 0.08$), a significant predictor of phlegm in this population was women who reported their occupation as "trader, food seller or businesswoman", which seemed to have a protective effect (OR 0.4, $p = 0.03$). This may have been due to chance or might reflect a socioeconomic effect. CO exposure was associated with women who reported a clinic visit for a respiratory infection in the previous 4 weeks, such that a 1 ppm increase in CO exposure increases the odds by 20% that women report seeking health care for a respiratory infection compared to women who did not report seeking health care (OR 1.2, $p = 0.09$).

While CO exposure was weakly associated with cough > 5 days (OR: 1:05, $p = 0.69$), we found a null association for shortness of breath/dyspnea (Table 3). However, cigarette smoke (in the household or compound) during the monitoring period was associated with increased odds of a cough > 5 days (OR: 3.1, $p = 0.01$), and two predictors for increased odds of reporting dyspnea were involvement in charcoal business (OR 2.7, $p < 0.01$) and secondhand smoke (OR 2.2; $p = 0.01$).

We controlled for secondhand smoke since it is a source of CO. Sensitivity analyses were conducted to include women who had reported past or current smoking ($n = 5$), however, the adjusted models did not differ significantly from the final models run on the subpopulation ($n = 840$) without current or past smoking status. Since no women reported having received a diagnosis of tuberculosis (TB), and only one participant reported having doctor-diagnosed asthma or other chronic breathing problems, TB and asthma were not included as respiratory outcomes in this analysis (see Table S1).

Table 2
Prevalence of current respiratory symptoms in 840 women in GRAPHS.

Respiratory symptom	n (%)
Cough > 5 days	52 (6.2)
Wheeze	40 (4.8)
Dyspnea (shortness of breath)	39 (4.6)
Composite: cough > 5 days, wheeze, dyspnea	80 (9.5)
Phlegm (with cough)	81 (9.6)
Clinic visit for respiratory infection past 4 weeks	14 (1.7)

4. Discussion

This study analyzed prevalence of respiratory symptoms and associations between HAP exposure (using continuous CO measurement) in nonsmoking pregnant women in rural Ghana prior to any HAP intervention. To our knowledge, this is the first study in Africa to assess current respiratory symptoms and HAP exposure, as measured by personal CO, in pregnant women dependent on biomass fuels. Acute respiratory symptoms alone may be early indicators of chronic airway disease and early identification of these symptoms would allow for preventative care and intervention (Woodruff et al., 2016).

Frequency of respiratory symptoms in this study ranged from nearly 2% of women seeking health care for respiratory infection in the previous 4 weeks to ~5% reporting symptoms of dyspnea or wheeze, and nearly 10% reporting phlegm (with cough) or the composite outcome (i.e. cough > 5 days, wheeze and/or dyspnea). The respiratory frequencies reported in our population were similar to those found in Mexico, where 6% of women using biomass fuel reported cough, 5% reported wheeze, 7% reported dyspnea, and 13% reported phlegm (Romieu et al., 2009). A study in Malawi which measured a 48 h median personal CO exposure of 1.23 ppm, found lower reported respiratory symptom frequencies compared to our study (Nightingale et al., 2018). Yet other studies also using a direct exposure measure,

Table 3

Crude and adjusted odds ratios for respiratory symptoms and exposure to CO.

Respiratory symptom	Crude		Adjusted	
	OR	(95% CI)	OR	(Robust 95% CI)
Cough > 5 days	1.00	(0.81, 1.24)	1.05	(0.83, 1.32)
Wheeze	1.19	(1.00, 1.42)	1.27	(1.00, 1.63)[a]
Dyspnea (shortness of breath)	1.01	(0.79, 1.29)	0.99	(0.67, 1.47)[b]
Composite: cough > 5 days, wheeze, dyspnea	1.17	(1.01, 1.35)	1.21	(1.02, 1.45)
Phlegm (with cough)	1.12	(0.96, 1.30)	1.15	(0.98, 1.35)[c]
Clinic visit for respiratory infection past 4 weeks	1.16	(0.88, 1.54)	1.19	(0.97, 1.44)

All models adjusted for age, BMI, gestational age, secondhand smoke, asset index.

[a] Model additionally adjusted for "burning grass/fields".

[b] Model additionally adjusted for "involvement in charcoal business".

[c] Model additionally adjusted for "occupation".

reported higher frequencies of respiratory symptoms overall, compared to our study (Clark et al., 2009; Diaz et al., 2007; Kurmi et al., 2014b; Regalado et al., 2006; Fullerton et al., 2011). One explanation for this may be the relatively lower mean personal exposure level (CO) measured in our study, compared to the studies also measuring CO, which could be due to the predominance of outdoor cooking in our cohort (Clark et al., 2009; Diaz et al., 2007; Kurmi et al., 2014b; Smith, 2000). While the majority (59%) of this study population cook outdoors, however, our previous pilot research found that outdoor cooking does not necessarily predict lower exposures (Van Vliet et al., 2013). Initial personal $PM_{2.5}$ concentrations measured in GRAPHS suggest there may be lower personal exposure concentrations measured in this cohort compared to the smaller pilot population ($n \sim 30$). The pilot research did not measure CO levels and therefore we cannot compare concentrations between the two studies.

In this study, we observed associations between CO exposure and respiratory symptoms of wheeze, the composite outcome (cough > 5 days, wheeze and/or dyspnea), cough, phlegm and clinic visit in the past 4 weeks for respiratory infection. We did not observe an association for dyspnea. While other studies found an increased association between household air pollution and cough, our study found a higher odds ratio of phlegm and wheeze (Diaz et al., 2007; Regalado et al., 2006). A study in Turkey found women cooking with biomass fuel had increased odds ratios for acute cough, dyspnea, and wheeze when compared to women cooking with LPG (Ekici et al., 2005), although direct comparison is difficult due to urban-rural population split in that study and use of an exposure proxy of years cooking. In Nepal, women using biomass fuels as measured by mean 24-hour kitchen concentrations of CO, found elevated odds ratios for 'ever' wheeze and wheeze on 'most days and nights'. Furthermore, all respiratory symptoms in the Nepal study were positively and significantly associated with the peak quantitative measure of exposure (> 2 SD of 24-hour mean $PM_{2.5}$). While this does not imply that peaks are more important than mean exposures, we do note other studies have suggested that peak exposures may have particular importance (Kurmi et al., 2014b; Van Vliet et al., 2013).

Our findings suggest that in addition to CO exposure, other exposure factors were associated with an increase in respiratory symptoms. In the present study, significant predictors ($p < 0.05$) of respiratory symptoms include second hand smoke, as expected, for cough > 5 days (OR: 3.1), wheeze (OR: 2.7), dyspnea (OR: 2.2) and the composite outcome (OR: 2.1), as well as involvement in charcoal production for dyspnea (OR: 2.7), and grass/field burning for wheeze (OR: 2.7).

While not significant in the final adjusted models, kerosene lamp use was associated in this study with presence of phlegm and women reporting seeking health care for respiratory infection in the previous 4 weeks. Kerosene fuels are enriched in black carbon (Lam et al., 2012; Van Vliet et al., 2013) and preliminary research suggests kerosene lamps may be an important independent risk factor for respiratory health in general and for tuberculosis (TB) specifically (Pokhrel et al., 2010; Lin et al., 2007). We were unable to assess this relationship since no women in the present study reported having TB. While history of TB was found to be the most common risk factor for COPD, overall incidence of TB in Ghana is quite low (Torres-Duque et al., 2008; WHO, 2018a).

While our study assessed only current symptoms, it is also of interest to consider chronic symptoms. COPD is one of the most important contributors of the global burden of disease in adults (Torres-Duque et al., 2008; Gordon et al., 2014), however, evidence supporting the association between HAP and COPD is conflicting. While many studies have shown an increased risk of COPD, chronic bronchitis, chronic airway disease and airflow obstruction from biomass smoke (Hu et al., 2010; Dennis et al., 1996; Pandey, 1984; Behera and Jindal, 1991; Shrestha and Shrestha, 2005; Perez-Padilla et al., 2010; Smith et al., 2014; Bruce et al., 1998; Ekici et al., 2005; Regalado et al., 2006; Ellegård, 1996; Liu et al., 2007; Zhong et al., 2007; Siddharthan et al., 2018), with one study suggesting wood smoke may explain 50% of all cases of obstructive airway disease in women (Dennis et al., 1996), a recent large-scale meta-analysis of 25 BOLD (Burden of Obstructive Lung Disease) study sites found no association between COPD (measured by air flow obstruction) and solid fuels. The BOLD analysis did find that chronic phlegm was more likely to be reported among female non-smokers and those who had been exposed to HAP for 20 years or more (Amaral et al., 2017). Many of these studies are hampered by the lack of quantitative exposure measure (i.e. proxy exposure is determined by self-reported fuel type, or the product of hours/day and years cooked), which can lead to exposure misclassification, and therefore direct measurement of HAP exposure is necessary to assess exposure-response relationship (Balmes and Eisen, 2018; Pope et al., 2014; Smith-Sivertsen et al., 2009). Additionally, the resources to perform successful spirometry to assess lung function necessary to classify COPD may not be available. Research suggests that presence of acute symptoms during exposure to biomass smoke may be important predictors of chronic airway disease (Ekici et al., 2005). Therefore, assessing current acute respiratory symptoms as early indicators of chronic respiratory disease serves an important and non-invasive method to provide opportunity for preventive intervention.

Regarding potential mechanisms, exposure to biomass smoke may cause an inflammatory response and increase oxidative stress in the respiratory tract, especially the lower airways (Barregard et al., 2008;

Pope et al., 2014; Swiston et al., 2008). Overall toxicological effects from wood smoke include pulmonary edema, bronchoconstriction, and increased respiratory infection rates, and particulate matter from biomass smoke has been associated with bronchial inflammation, increased reactivity, reduced mucocilliary clearance and macrophage response, as well as decreased lung function in children and mutagenic properties within the lower respiratory tract (Pierson et al., 1989; Kurmi et al., 2014b; Kurmi et al., 2013). Chemical constituents of HAP, i.e. particulate matter and other pollutants, are deposited in the nasopharynx and continue through the respiratory pathway and fine and ultrafine PM reach the alveolus (Gordon et al., 2014). These deposited compounds may disrupt cellular membranes, depress macrophage activity, destroy ciliated, secretory and respiratory epithelial cells and cause biochemical changes (Gordon et al., 2014; Larson and Koenig, 1994).

Although this study measures personal CO measure as a proxy for exposure to pollution from cookstoves including particulate matter, CO has not been shown consistently to be a valid surrogate for $PM_{2.5}$ exposure. The relationship between CO and $PM_{2.5}$ has been found to vary across study sites, stove/fuel types and seasons (Carter et al., 2017). The GRAPHS study measured co-located CO and $PM_{2.5}$ on a subset of participants, therefore allowing for a correlation assessment between the two exposure measures at the end of the study. Exposure to CO itself, however, has also been found to lead to adverse cardiovascular and respiratory outcomes, and a recent finding in the GRAPHS cohort suggests that infants born to mothers with higher HAP CO exposures during pregnancy may be at increased risk for impaired lung function (Chee et al., 2008; Lee et al., 2018). While CO is known to be toxic at high concentrations through displacing hemoglobin (Hb) and binding to intracellular enzymes leading to pulmonary lung damage (Kurmi et al., 2014b; Sørhaug et al., 2006), respiratory effects from low dose chronic exposure to CO are less elucidated. One proposed mechanism is that CO binds to the oxygen receptor, which may interact with the pulmonary neuroendocrine system (Haddad, 2002). While the mean CO level measured in our study population is below the US EPA and WHO standards (9 ppm and 8.6 ppm for 8 h, respectively), our highest measurement of 15 ppm exceeds these levels, however, we note that since our study measures 72 h + multi-day averages, these levels are not directly comparable to ambient standards.

A major strength of this study was the use of a direct quantitative measure of exposure, i.e. continuous measure of personal CO, rather than self-reported proxy for fuel use or years of exposure. Another strength of this study is the extensive data captured by the GRAPHS questionnaires on a range of covariates, thereby enabling the examination of other sources of CO exposure, and HAP in general, as well as predictors of respiratory disease.

Limitations of this study arise from the fact that the GRAPHS study was not designed or powered to assess adult respiratory symptoms. Although the design of the questionnaire did not allow for the ability to assess chronicity of respiratory symptoms, i.e. chronic airway disease or chronic bronchitis defined as chronic cough and chronic phlegm on most days in previous 3 to 6 months (in accordance with the British Medical Research Council), assessing acute and current symptoms is important for early preventative intervention, prior to development of chronic respiratory disease. Another limitation present in any questionnaire-based analysis is that all symptoms are based on self-report without subsequent clinical assessment, therefore resulting in possible misclassification (Kurmi et al., 2014b; Ekici et al., 2005). Furthermore, respondents may underreport symptoms, which is not uncommon in low-income countries where people may consider wheeze, dyspnea, and bringing up phlegm as normal (Kurmi et al., 2014b), or not report if symptoms are mild or moderate (*personal communication*, *KHRC*). Another reason for underreporting symptoms may be the knowledge of participating in an intervention study, i.e. they anticipated they would place in the intervention arm (Khushk et al., 2005). Overall, underreport may underestimate true risk. Another limitation of respiratory surveys in non-English speaking settings is that direct translation of respiratory symptoms into local language/dialects (i.e. wheeze) has been proven to be difficult (Diaz et al., 2007; Kurmi et al., 2014b). In this study, the respiratory questionnaire was in English and administered/translated to the local language (Twi) by trained field workers in the field. While the respiratory terminology in the survey seems to be relatively common in Twi (*personal communication*, *KHRC*), the translation by the field worker of the symptoms at the time the questionnaire is administered may introduce bias, and specifically, could lead to sampling bias as field workers may use different words/vocabulary for the same symptom. Respondents may also have difficulty comprehending time-duration patterns (Diaz et al., 2007), however since our instrument only measured current symptoms, this is less of a concern. Due to the cross-sectional design of this study, the associations between CO and current respiratory symptoms may not be causal. Finally, while pregnant women represent a vulnerable population and pregnancy is a relevant time period to look at health effects from household air pollutants, generalizability to non-pregnant women of these findings is uncertain.

5. Conclusion

Chronic respiratory diseases such as COPD, asthma, and tuberculosis present a major burden of disease, especially in Africa (WHO, 2015). Exposure to HAP, as measured by continuous CO, and covariates such as secondhand smoke, charcoal production and field/grass burning, were positively associated with respiratory symptoms in pregnant women using biomass fuels for cooking in rural Ghana. This study adds to the previous findings of increased respiratory symptoms in women cooking with biomass fuels, using a quantitative measure of exposure rather than a proxy for personal exposure. Results from this study and our previous pilot research (Van Vliet et al., 2013) underscore possible risk factors that include other smoke sources (i.e. charcoal production, mosquito coils and kerosene lamps), as well as cultural determinants of exposure (i.e. ethnicity, religion). Current respiratory symptoms may be early indicators of more chronic respiratory disease, and early identification of these symptoms would allow for preventive care. Further research is needed to assess both HAP and non-HAP related risk factors to inform the development of cost-effective strategies aimed at improving respiratory health.

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Appendix

1. Do you have a cough? ……………………....................................			1. Yes	2. No		
2. For how long have you had this cough?...	1. Less than 3 days	2. 3-5 days	3. More than 5 days		9. NA, No cough
3. Is the cough dry or wet?..............................………………………..			1. Dry	2. Wet	9. NA, No cough
4. Do you produce any phlegm (sputum) with the cough?......................			1. Yes	2. No	9. NA, No cough
5. When is the cough worst?......................	1. Morning	2. Midday	3. Evening/Night		9. NA, No cough
6. Do you wheeze (produce noise when you breath out)?......……...			1. Yes	2. No	9. NA, No cough
7. Do you experience difficulty in breathing/shortness of breath?…….			1. Yes	2. No	9. NA, No cough
8. Have you sought health care for a respiratory infection in the last 4 weeks?			1. Yes	2. No	9. NA, Not sick

GRAPHS respiratory symptoms module.

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