Author’s response to reviews

Title: Personal carbon monoxide exposure, respiratory symptoms, and the potentially modifying roles of sex and HIV infection in rural Uganda: a cohort study

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Author’s response to reviews:

Reviewer #1

1. Lines 103 to 104: Authors should include a line stating procedures that study participants followed during bathing and sleeping activities within the 48-h of measurement.

We have added the following text to describe bathing and sleeping-related instructions given to participants (Lines 127 through 129):

“Participants were instructed to place the CO monitors at their bedside during sleep and nearby during bathing-related activities.”
2. Was there any method used to test whether participants wore the Lascar CO monitors for all the 48 hours or the for the duration of measurement?

We did not formally test whether participants wore the monitors for all the 48 hours of the measurement period, but we did exclude participants with less than 8 hours of available data from analyses. We also reviewed software-generated graphs of CO levels over time to visually confirm that there was concentration variation over the measurement period in a randomly-selected portion of study participants. We’ve added these details to the Methods section (Lines 130 through 132) and the Limitations section (Lines 340 through 344):

Lines 130 through 132:
“A convenience sample of software-generated graphs of CO concentration over time were reviewed to confirm concentration variation over the sampling period as a surrogate for study procedure compliance.”

Lines 340 through 344:
“Additionally, we did not formally monitor device use compliance, so some participants may not have worn the devices for the entire sampling period. However, we have no reason to believe that non-use would be non-random, so would suggest that the exposure misclassification bias this may have introduced would be most expected to bias our results towards the null, further underscoring the significance of our findings.”

3. Did the authors select a minimum % of the CO data as sufficient to computation/analysis?

We included only sampling periods with at least 8 hours of continuous CO measurements in our statistical analyses, which we specified in Line 171 of the statistical analysis description:

“Participants with less than eight hours of CO data were excluded from these analyses.”

4. How representative is the study site compared to rural areas in SSA?

Our study site is generally similar to other mixed urban/rural settings throughout sub-Saharan Africa. Mbarara Town is the district’s commercial center and would accurately be characterized as urban, while most residents (including our study participants) live in outlying rural areas where the local economy is driven primarily by subsistence agriculture and animal husbandry. Our cohort eligibility criteria and recruitment methods, described below, ensure a representative sampling of the regional population, which we have confirmed by comparison to national
demographic surveys. We added these details in the Methods (Lines 99 through 113) and Results (Lines 213 through 215) of the updated manuscript:

“...The Uganda Non-Communicable Diseases and Aging Cohort (UGANDAC) is a prospective, longitudinal observational cohort study of HIV infected and uninfected adults based in Mbarara District, Uganda.[24-26] Mbarara district, located in southwestern Uganda, includes an urban center and a larger surrounding rural area totaling 1,846 square kilometers. Most residents live in outlying rural areas, have at most a primary school education, and the local economy is dominated by petty trading, subsistence agriculture, and animal husbandry.[27] Food and water insecurity are common.[28, 29] In 2018, Uganda ranked 181st out of 192 for Gross National Income per capita, similar to most other sub-Saharan African countries.[30] The UGANDAC cohort is a mixed cohort of HIV-infected and uninfected adults. HIV-infected participants are at least 40 years of age, have been on antiretroviral therapy for at least three years, and receive their HIV-related care at the Mbarara Regional Referral Hospital’s HIV clinic. The HIV clinic is a prototypical, PEPFAR-supported, government-run HIV clinic. Sex and age-similar (by quartile of the HIV infected sub-group) HIV-uninfected participants were selected at random from a complete population census of a village located within the clinical catchment area and confirmed to be HIV uninfected prior to each annual study visit.”

“The above demographics are similar to the general Ugandan population with the exception of HIV prevalence, which is 5.9% nationally.[42, 43]”

5. Appropriateness of sample size: Was there any basis (i.e. a power calculation, prior preliminary data) used to determine the 260 study participants? Note: The reviewer understands the challenges of field work and recruitment.

Our choice of sample size was defined by the size of the parent cohort, which had enrolled approximately 300 study participants who were being evaluated at yearly study visits. Our screening period began when the manuscript’s first author was awarded a pilot grant to introduce pulmonary-focused study measures including ambulatory CO monitoring to this pre-existing study cohort, and successfully captured CO data at all participant study visits between September 2015 and October 2017. Thus, our power was determined by a pre-existing cohort size.

6. Lines 120 - 122: The authors explain that they elected to quantify exposure using the 1-hour and 8-hour TWA to capture exposures of shorter duration such as meal-related biomass
smoke yet participants did not complete time-activity analyses as stated in line 293. I think authors should add examples of other possible determinants which could have led to the exposures captured.

Meal-related biomass smoke is likely to affect mostly the

We agree and have added discussion of shorter-duration exposures that may contribute to total CO exposure (Lines 150 through 153). While cooking-related exposures disproportionately influence women’s exposure, other biomass-related exposures such as home heating and lighting (recently demonstrated to influence indoor air pollution in the same study region) and traffic-related exposures are not predicted to have sex-based differences.

“We elected to use 1-hour TWA to define exposure in our cohort because the most likely sources of CO in the study setting - traffic-related exposures while traveling on foot or by car and biomass exposures related to cooking, heating and lighting[36] activities - are generally shorter-term exposures.”

Reviewer #2:

1. The HIV status of the study population was determined but not the Tuberculosis status. The authors state in the conclusion: "Alternatively, air pollution exposure may increase the risk of pulmonary tuberculosis through smoke-induced endothelial and alveolar damage that facilitates mycobacterial infection[53, 54] and/or altered antimycobacterial innate immunity.[55] Thus, air pollution exposure may potentiate baseline tuberculosis risk among PLWH,[56] which may underlie the increased respiratory symptom burden among PLWH as compared to HIV-uninfected participants exposed to air pollution. We did not test for tuberculosis in the cohort, so we could not evaluate the potentially mediating effect of pulmonary tuberculosis on the relationship between CO exposure and respiratory symptoms." The test for tuberculosis should have been done. Then the data could be analysed as: co-infection with HIV and TB; TB infected only; etc. TB is the biggest driver of respiratory issues.

We agree with the reviewer that it is possible that undiagnosed active tuberculosis among our participants could be a principal driver of our findings. However, we believe that the likelihood of undiagnosed active TB within our cohort is low for the following reasons. First, the World Health Organization estimates that TB incidence in Uganda in 2017 was only 200 per 100,000 people (0.2% of the population), which makes undiagnosed TB unlikely in our HIV-uninfected participants. Second, HIV-infected participants in our cohort were on antiretroviral therapy for a median of 9 years (interquartile range 8 – 10 years) and almost all participants were virally suppressed (94% with undetectable viral loads; 80% with CD4 counts ≥ 350 cells/mm3). Nonetheless, we acknowledge that the inability to rule out active tuberculosis is a weakness of our analysis, and include this weakness in the updated manuscript (Lines 349 through 352):
“Additionally, sputum samples were not available for analysis, so we were unable to evaluate participants for active tuberculosis. However, the degree of viral control and the TB incidence in Uganda make undiagnosed active tuberculosis less likely.[72, 73]”

Importantly, e-value calculations lend further support to our assertion that active tuberculosis is unlikely to be confounding the relationship between CO exposure and respiratory symptoms in our cohort. As elaborated by VanderWeele and Ding (Ann Intern Med. 2017;167:268-74), the e-value quantifies the minimum strength of association that an unobserved confounder (like tuberculosis) would need to have with both the exposure (CO) and outcome (respiratory symptoms) in order to fully explain the estimated association. For example, our measured association between CO exposure and increased odds of respiratory symptoms among women (AOR = 3.3, 95% CI 1.1 – 10.0; Table 5) has a corresponding e-value of 3.03, meaning that relatively strong confounding associations would be needed to completely explain our findings.

To address this knowledge gap, we are currently enrolling participants from this cohort in a study that collects CT chest imaging, which we anticipate will allow us to investigate the influence of tuberculosis on respiratory morbidity within our cohort. In the meantime, despite the above weakness, this analysis is one of the first studies to evaluate ambulatory CO monitoring as an inexpensive, technically feasible method to quantify air pollution exposure in resource-limited settings, and thus extends the scientific literature in important ways. The results of our work provide a foundation on which future studies of pollution-associated health risks can be developed, including future explorations of potential confounding or effect modification by tuberculosis, which will further elucidate the pathophysiologic mechanisms by which air pollution influences respiratory morbidity in sub-Saharan Africa.

2. Please check list of references because in some instances page numbers for articles are missing.

We have updated our references to include the full citations, inclusive of page numbers.

Reviewer #3:

1. This is a very small detail, but in your abstract, you begin the results paragraph with a number. This should be written out or the sentence should be rearranged.

We have corrected this oversight by writing out the number at the beginning of this sentence (Line 39):

“Two hundred and sixty study participants completed 419 sampling periods.”
2. Your title references the "modifying role of sex and HIV infection," but examining effect modification is not listed in your introduction as one of your hypotheses. The effect modification analysis seems like an exploratory analysis, so I think it should be mentioned in the introduction and identified as such. I would also recommend changing your title to be more in line with the main aim of the study.

Thank you for identifying these inconsistencies in our title, abstract and analytic approach. Sex- and HIV-stratified analyses were specified a priori, so we have modified our abstract background (Lines 25 through 27), abstract methods (Lines 35 through 37) and the stated aims in the main manuscript background section (Lines 92 through 96) accordingly:

Abstract Background (Lines 25 through 27):

“Most of the global burden of pollution-related morbidity and mortality is believed to occur in resource-limited settings, where HIV serostatus and sex may influence the relationship between air pollution exposure and respiratory morbidity.”

Abstract Methods (Lines 35 through 37):

“We fit generalized mixed effects models to identify correlates of CO exposure exceeding international air quality thresholds, quantify the relationship between CO exposure and respiratory symptoms, and explore potential effect modification by sex and HIV serostatus.”

Manuscript Background (Lines 92 through 96):

“To test our hypothesis, we assessed the feasibility of using ambulatory CO monitoring to measure personal air pollution exposure in rural southwestern Uganda, identified correlates of higher CO exposure, and explored whether relationships between CO exposure and chronic respiratory symptoms differed based on sex or HIV serostatus.”

The manuscript title has been edited to reflect that assessment of effect modification was not the primary aim of the study:

“Title: Personal carbon monoxide exposure, respiratory symptoms, and the potentially modifying roles of sex and HIV infection in rural Uganda: a cohort study.”

3. The introduction is well-written, but I think it is missing some information about the motivations of the study. I would recommend including some information about previously-identified correlates of CO exposure. Also, the background mentions nothing about potential effect modifiers in the CO-respiratory symptoms association. A mention of why you chose to look at certain factors would be helpful. In the conclusion, you include some of this and I think some of it should be moved to the introduction.
We now include information regarding known correlates of CO exposure (Lines 88 through 90) and the potentially modifying roles of both sex and HIV serostatus in the Introduction (Lines 66 through 76) to provide support for the aims of our analysis.

Lines 88 through 90:

“Carbon monoxide (CO) is a byproduct of the partial combustion of carbon-containing materials, and the major sources of CO exposure in RLS include biomass burning and traffic-related emissions.[14-17]”

Lines 66 through 76:

“Most of the one billion people with chronic respiratory disease globally live in RLS such as sub-Saharan Africa,[4] where the convergence of the air pollution and HIV epidemics may underlie the disproportionate regional burden of disease. Although people living with HIV (PLWH) are more likely to have chronic lung disease due to virally-mediated lung damage and higher susceptibility to lung infections,[5, 6] air pollution may synergistically increase lung disease risk in co-exposed populations through shared inflammatory pathways[7] and/or increased tuberculosis risk.[8] Recent data also suggest that the higher burden of air pollution-related respiratory symptoms among women in RLS – often attributed to higher exposure among women due to cooking-related biomass burning – may at least partially result from sex hormone-based differences in the pulmonary effects of inhaled pollutants.[9, 10] Despite these plausible relationships, little is known about whether these potentially vulnerable populations are at heightened risk for pollution-associated respiratory morbidity.”

4. Are most of the HIV-infected individuals in your cohort virally-suppressed? What percentage are on ART?

All HIV-infected study participants were on ART, 94% were virally suppressed, and 80% had CD4 T-cell counts of at least 350 cells/mm3. Our updated Table 1 now includes details on viral control among the HIV-infected participants, and we included a summative sentence in the updated Results section (Lines 207 through 210):

“Among the 131 participants with HIV, 122 (94%) had undetectable HIV viral loads, 105 (80%) had CD4 T-cell counts of at least 350 cells/mm3, and all had been taking antiretroviral therapy for a median of 9 years (interquartile range [IQR] 8-10).”

5. In lines 115-116, can you mention the specific tests used? In your table 1, you presented descriptives by sex and this should be mentioned.
We updated the manuscript text to include our statistical tests of association. In Table 1, we now summarize cohort characteristics by HIV serostatus rather than by sex, pursuant to the reviewer’s suggestion below, which we now mention in the manuscript text as well (Lines 139 through 143):

Lines 139 through 143:

“We first summarized cohort characteristics by HIV serostatus using Wilcoxon rank sum, chi-squared and Fisher’s exact tests, as appropriate. We evaluated for selection bias by comparing cohort characteristics between those who did versus those who did not complete at least one CO sampling session during the study period using Wilcoxon rank sum, chi-squared or Fisher’s exact tests, as appropriate.”

6. In general, I found your description of the primary outcome of interest a little bit hard to follow (starting in L113). It would be easier to understand if mentioned the two outcomes at the beginning, and then went into more detail about how they were calculated. It would also be helpful if you could mention why you chose 2 different time frames for the outcome.

We have clarified the description of how we identified our chosen CO exposure threshold of interest (the maximum 1-hour time-weighted average [TWA] CO exposure during each sampling period). In the updated Methods section (Lines 144 through 173) we now begin by first describing why we chose the 1-hour TWA rather than the 8-hour TWA as our primary outcome of interest, then how we calculated the 1-hour TWA, followed by our multivariable logistic regression model building approach, and ending with our planned sensitivity analysis evaluating the robustness of our results by substituting the 1-hour TWA for the 8-hour TWA.

7. In line 130-131, you should mention the characteristics of interest. I'm also a little bit confused about the purpose of the analysis mentioned here. How is this different from the analysis described in line 133? I think addressing my above comment will help clarify this difference.

We have greatly simplified the description of our methods, as noted in response to Comment # 6 above. In short, the analytic details in lines 130 – 131 and beginning again in Line 133 of the original manuscript described the same analysis. This has been clarified, and the details can be found in Lines 144 through 173 of the updated manuscript, as noted above.
8. Do you have any information about compliance with wearing the personal monitors? I might suggest including some of this. It is probably not necessary to include this, but why do some participants have multiple sampling periods, while some only have one?

We evaluated compliance with wearing the personal monitors by spot-checking the software-generated graphs of CO concentration over time, assuming that variations in CO concentration over time correlated with compliance. We did not perform any more formal compliance assessments, which we have included as a study limitation. We include this information in Methods (Lines 128 through 130) and Discussion (Lines 340 through 344) of the updated manuscript:

Lines 130 through 132:

“A convenience sample of software-generated graphs of CO concentration over time were reviewed to confirm concentration variation over the sampling period as a surrogate for study procedure compliance.”

Lines 340 through 344:

“Additionally, we did not formally monitor device use compliance, so some participants may not have worn the devices for the entire sampling period. However, we have no reason to believe that non-use would be non-random, so would suggest that the exposure misclassification bias this may have introduced would be most expected to bias our results towards the null, further underscoring the significance of our findings.”

Regarding the multiple sampling periods: this study was a sub-study of an ongoing longitudinal study in which participants were seen yearly. Depending on individual study participant visit schedules and whether they agreed to or declined CO measurement study procedures, our study duration (September 2015 – October 2017) captured anywhere from one to three annual study visits per participant.

9. In the paragraph that starts in line 146, I don't see which models were used. You also mention that you explored interaction, but you do not say how this was done. Interaction terms? Stratified analysis? Both?

We have clarified our description of our model building approach in the updated manuscript (Lines 174 through 185). In brief, we used the same model building approach to identify correlates of self-reported respiratory symptoms as we used in our models identify correlates of CO exposure above WHO standards. We also now state specifically that we explored interactions by first including the product term in our multivariable logistic regression models and then stratifying models by the covariate of interest (Lines 186 through 193):
To evaluate the relationship between personal CO exposure and respiratory symptoms, we fitted generalized mixed effects models, with a random effect intercept to account for repeated measures of CO within the same participant, in the same manner as described above. We defined respiratory symptoms as self-reported chronic cough, dyspnea on exertion, or wheezing. In this model, 1-hour TWA CO exposure above WHO thresholds was the primary explanatory variable of interest. We identified potential correlates of interest based on the scientific plausibility of their relationship with either the outcome (respiratory symptoms) or primary explanatory variable of interest (CO exposure). These included age, sex, smoking status, socioeconomic status (household asset index), HIV serostatus, and season (dry versus rainy). We then used the same multivariable logistic regression model building technique as described above whereby we included all candidate covariates with a p-value < 0.2 in the final multivariable regression model, with the exception that we forced smoking status into the final model based on established relationships between smoking and respiratory morbidity.

We then evaluated for evidence of interaction between CO exposure and sex because of anticipated differences in CO exposure concentrations [20] and for evidence of interaction between CO exposure and HIV serostatus because of anticipated differences in respiratory symptom burden.[37-39] Beginning with the adjusted multivariable logistic regression model established through the above-described model building approach, we first conducted formal tests of interaction whereby we added CO*sex and CO*HIV interaction terms, independently, to the final model and evaluated their statistical significance. We then stratified models by HIV serostatus and by sex, respectively, to look for differential relationships between CO exposure and respiratory symptoms within strata.

We updated our Introduction with a summary of why individuals with HIV and women may be at higher risk of air pollution-related respiratory morbidity, including pertinent references (Lines 66 through 76), and have updated the references cited in support of our interactions of interest in the Methods section (Lines 186 through 188):

Most of the one billion people with chronic respiratory disease globally live in RLS such as sub-Saharan Africa,[4] where the convergence of the air pollution and HIV epidemics may
underlie the disproportionate regional burden of disease. Although people living with HIV (PLWH) are more likely to have chronic lung disease due to virally-mediated lung damage and higher susceptibility to lung infections,[5, 6] air pollution may synergistically increase lung disease risk in co-exposed populations through shared inflammatory pathways[7] and/or increased tuberculosis risk.[8] Recent data also suggest that the higher burden of air pollution-related respiratory symptoms among women in RLS – often attributed to higher exposure among women due to cooking-related biomass burning – may at least partially result from sex hormone-based differences in the pulmonary effects of inhaled pollutants.[9, 10] Despite these plausible relationships, little is known about whether these potentially vulnerable populations are at heightened risk for pollution-associated respiratory morbidity.”

Lines 186 through 188:

“We then evaluated for evidence of interaction between CO exposure and sex because of anticipated differences in CO exposure concentrations [20] and for evidence of interaction between CO exposure and HIV serostatus because of anticipated differences in respiratory symptom burden.[37-39]”

11. In the paragraph that start in line 195, what were models adjusted for? The same things as other models? Also, did you only use stratified models, or do you have some formal test of interaction? If the former, I think this adds to my comment about the slightly misleading title. I would recommend running some formal interaction analyses. I am not convinced your results are due to the statistical precision gained by having higher levels of the exposure and outcome in HIV infected individuals and women, compared to other individuals.

The multivariable logistic regression model evaluating correlates of chronic respiratory symptoms was adjusted for sex, HIV serostatus, CO exposure and smoking history. We clarified this in the updated Results section (Lines 238 through 243) and clarified the description of our tests of interaction in the updated Methods section (Lines 186 through 193).

Results (Lines 238 through 243):

“In models adjusted for sex, HIV serostatus, CO exposure and smoking status, the odds of self-reported respiratory symptoms were higher among women as compared to men (AOR 4.0, 95% CI 2.1 to 7.5, p<0.001), and those with CO exposure over WHO guidelines had over twice the odds of any respiratory symptoms compared to those whose CO exposure did not exceed WHO guidelines (AOR 2.1, 95% CI 1.0 – 4.7, p=0.06; Table 4).”

Methods (Lines 186 through 193):
“We then evaluated for evidence of interaction between CO exposure and sex because of anticipated differences in CO exposure concentrations [20] and for evidence of interaction between CO exposure and HIV serostatus because of anticipated differences in respiratory symptom burden.[37-39] Beginning with the adjusted multivariable logistic regression model established through the above-described model building approach, we first conducted formal tests of interaction whereby we added CO*sex and CO*HIV interaction terms, independently, to the final model and evaluated their statistical significance. We then stratified models by HIV serostatus and by sex, respectively, to look for differential relationships between CO exposure and respiratory symptoms within strata.”

Lastly, given that product terms were not statistically significant – though our cohort size may have limited our power to detect statistically significant interactions – we modified our title to allow for the uncertainty surrounding our findings:

“Title: Personal carbon monoxide exposure, respiratory symptoms, and the potentially modifying roles of sex and HIV infection in rural Uganda: a cohort study”

12. Again, I think some of your conclusions about effect modification by sex and HIV infection status are overstated, especially since it was not one of your hypotheses identified at the beginning of the study (at least as-written) and no normal interaction analyses were performed.

As noted in response the reviewer’s above concerns, effect modification was a planned aspect of our original statistical analysis plan, and we have clarified the text throughout our Abstract, Introduction, and Methods to more accurately reflect our intentions. While we acknowledge that our formal tests of interaction were not statistically significant, the subgroup analyses do provide hypothesis-generating results, as our cohort size limits the power we had to conduct formal tests of interaction. Nevertheless, we have softened the language around the certainty of our results in the Discussion and Conclusion sections, and highlight the need for future research into the potentially interactive relationships between air pollution exposure and both sex and HIV serostatus.

Discussion (Lines 289 through 290):

“This is among the first studies to suggest that the relationship between air pollution and respiratory symptoms may differ by HIV serostatus.”

Discussion (Lines 318 through 321):

“Respiratory symptoms are thought to be more prevalent among women in RLS because women are generally responsible for meal preparation and thus exposed to more indoor air pollution. The results of this work may challenge that assumption because the relationship between female sex and respiratory symptoms persisted even after adjusting for personal CO exposure.”
Discussion (Lines 352 through 355):

“Though we identified differences in the relationship between CO exposure and respiratory symptoms in analyses stratified by sex and HIV serostatus, the associated tests for interaction were not statistically significant, so further work is necessary to explore whether sex or HIV serostatus modify the relationship between air pollution and respiratory morbidity.”

Conclusion (Lines 360 through 363):

“In summary, our data offer proof-of-concept that ambulatory CO monitoring is a low-cost and feasible means of assessing personal air quality in a rural sub-Saharan African region, identify biomass smoke as an important source of ambulatory CO exposure, and explore potential differences in pollution-associated respiratory morbidity based on HIV serostatus and sex.”

Conclusion (Lines 367 through 368):

“Future work is needed to formally evaluate the potentially interactive relationships between air pollution and both sex and HIV serostatus.”

13. In the conclusion, I would mention something about your biomass-CO finding.

We’ve expanded the first sentence in our Conclusion section to include our biomass-CO findings (Lines 360 through 363):

“In summary, our data offer proof-of-concept that ambulatory CO monitoring is a low-cost and feasible means of assessing personal air quality in a rural sub-Saharan African region, identify biomass smoke as an important source of ambulatory CO exposure, and explore potential differences in pollution-associated respiratory morbidity based on HIV serostatus and sex.”

Tables:

1. I am curious why your table one stratified by sex. It might be interesting to see an HIV-status stratified table, especially since the populations were recruited from two difference sources. Differences in demographic characteristics could definitely explain the higher CO levels in the HIV-infected subgroup.

Thank you for this suggestion. We have now stratified our Table 1 based upon HIV serostatus. While this change highlights that HIV-infected participants have higher self-reported charcoal use compared to firewood and a higher proportion live in urban rather than rural areas – both of which would be expected to increase personal pollution exposure – fewer HIV-infected participants use polluting home lighting sources and fewer HIV-infected participants were
current smokers – both of which would be expected to decrease personal pollution exposure. We’ve included these details in the updated Discussion section (Lines 292 through 296):

“This finding is unlikely to be related solely to demographic-related differences in CO exposure because although PLWH were more likely to self-report home charcoal use and live in urban areas (both of which would increase personal CO exposure), they were also less likely to use biomass-based home lighting fuels or be current smokers (both of which would decrease personal CO exposure).”

2. A small detail, but I would take the Female sex row out of your Table 1, since your table is sex-stratified.

Now that our updated Table 1 is stratified by HIV serostatus, we have retained the female sex row and removed the HIV serostatus row.

3. In the footnotes in Table 2, I would include the statistical tests used to obtain p-values. It might also be helpful to include n’s in Table 2.

We now include the statistical test used to obtain p-values (Wilcoxon rank sum tests) and n’s in Table 2.

4. In Table 3, why are some of the coefficients missing? I’m guessing this because they were removed from the final model?

Yes, the coefficients that are missing from the adjusted model column were excluded because they were excluded from the final model based upon our model-building approach described in Lines 174 through 185 of the updated Methods section:

“To evaluate the relationship between personal CO exposure and respiratory symptoms, we fitted generalized mixed effects models, with a random effect intercept to account for repeated measures of CO within the same participant, in the same manner as described above. We defined respiratory symptoms as self-reported chronic cough, dyspnea on exertion, or wheezing. In this model, 1-hour TWA CO exposure above WHO thresholds was the primary explanatory variable of interest. We identified potential correlates of interest based on the scientific plausibility of their relationship with either the outcome (respiratory symptoms) or primary explanatory variable of interest (CO exposure). These included age, sex, smoking status, socioeconomic status (household asset index),[31] HIV serostatus, and season (dry versus rainy). We then used the same multivariable logistic regression model building technique as described above whereby we included all candidate covariates with a p-value < 0.2 in the final multivariable regression
model, with the exception that we forced smoking status into the final model based on established relationships between smoking and respiratory morbidity.”

5. I'm not sure I follow why some of the correlates of respiratory symptoms are missing from Tables 5-6. Why is this? I think this might become clear when you include more detail about your stratified models in the results section.

Tables 5 and 6 detail our stratified model results. Some of the correlates are missing because we based our stratified models upon our final adjusted multivariable logistic regression model from Table 4, which included only sex, HIV serostatus, personal CO exposure and smoking status. We describe our stratified analyses in more detail in the updated Methods section (Lines 186 through 193):

“We then evaluated for evidence of interaction between CO exposure and sex because of anticipated differences in CO exposure concentrations [20] and interaction between CO exposure and HIV serostatus because of anticipated differences in respiratory symptom burden.[37-39] Beginning with the adjusted multivariable logistic regression model established through the above-described model building approach, we first conducted formal tests of interaction whereby we added CO*sex and CO*HIV interaction terms, independently, to the final model and evaluated their statistical significance. We then stratified models by HIV serostatus and by sex, respectively, to look for differential relationships between CO exposure and respiratory symptoms within strata.”

6. It seems like Table 7 might be unnecessary, and a mention in the text is probably sufficient.

We have removed Table 7, and describe these results only in the Results text (Lines 247 through 250):

“When considering each respiratory symptom individually, the relationship between higher CO exposure and respiratory symptoms was driven by dyspnea on exertion (AOR 3.4, 95% CI 1.3 – 9.0, p=0.01), as no relationship was present with higher CO exposure and either cough or wheeze.”

7. Another small detail, but in Figure 2, change "gender" to "sex."

We have changed Figure 2 accordingly.