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TUBERCULOSIS

Lack of an Association Between Household Air Pollution Exposure and Previous Pulmonary Tuberculosis

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Abstract

Context Observational studies investigating household air pollution (HAP) exposure to biomass fuel smoke as a risk factor for pulmonary tuberculosis have reported inconsistent results.

Objective To evaluate the association between HAP exposure and the prevalence of self-reported previous pulmonary tuberculosis.

Design We analyzed pooled data including 12,592 individuals from five population-based studies conducted in Latin America, East Africa, and Southeast Asia from 2010 to 2015. We used multivariable logistic regression to model the association between HAP exposure and self-reported previous pulmonary tuberculosis adjusted for age, sex, tobacco smoking, body mass index, secondary education, site and country of residence.

Results Mean age was 54.6 years (range of mean age across settings 43.8–59.6 years) and 48.6% were women (range of % women 38.3–54.5%). The proportion of participants reporting HAP exposure was 38.8% (range in % HAP exposure 0.48–99.4%). Prevalence of previous pulmonary tuberculosis was 2.7% (range of prevalence 0.6–6.9%). While participants with previous pulmonary tuberculosis had a lower pre-bronchodilator FEV_1 (mean −0.7 SDs, 95% CI −0.92 to −0.57), FVC (−0.52 SDs, 95% CI −0.69 to −0.33) and FEV_1/FVC (−0.59 SDs, 95% CI −0.76 to −0.43) as compared to those who did not, we did not find an association between HAP exposure and previous pulmonary tuberculosis (adjusted odds ratio = 0.86; 95% CI 0.56–1.32).

Conclusions There was no association between HAP exposure and self-reported previous pulmonary tuberculosis in five population-based studies conducted worldwide.

Keywords Biomass fuel · Tuberculosis burden · Cross-sectional study

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Background

Tuberculosis is the ninth leading cause of death worldwide, with an estimated 1.3 million tuberculosis-related deaths and it predominantly affects residents in low- and middle-income countries [1]. Being immunocompromised due to HIV and having diabetes are both associated with reactivation of pulmonary tuberculosis [2]. While multiple studies have shown an association between exposure to tobacco smoke and active tuberculosis in a dose-response manner [3–8], they do not definitively show a causal link. Moreover, the mechanism of such a causal link is not well established even if existed. Similarly, household air pollution (HAP) exposure may increase susceptibility to tuberculosis by possibly affecting airway protective mechanisms. Some studies have implicated an association between biomass fuel exposure and tuberculosis compared to exposure to cleaner fuels [9–11]. Population density, continued reliance on readily available biomass fuels, and the rise in ambient air pollution in developing countries might, therefore, appear to undermine efforts to control tuberculosis. However, evidence associating household air pollution exposure from domestic solid fuel use with the risk for developing pulmonary tuberculosis remains inconsistent [12, 13]. Recent systematic reviews and meta-analyses have found that overall, there was no statistically significant association between biomass fuel exposure and tuberculosis [14, 15]. Whereas controlled experiments have revealed increased susceptibility to development of tuberculosis following exposure of macrophages to wood smoke [16, 17], potential confounders and effect modifiers are difficult to adjust for in carrying out observational studies. In resource-limited communities, where a higher proportion of the population in mostly rural environments is primarily dependent on solid fuels for energy, it is plausible that household air pollution exposure would be associated with a higher prevalence of tuberculosis among rural compared to urban residents.

In this study, we sought to investigate the association between HAP exposure and previous pulmonary tuberculosis among 13 diverse low- and middle-income countries by comparing those exposed to HAP to the unexposed.

Methods

Study Settings

Pooled data from multiple, population-based studies involving 13 diverse low- and middle-income country settings was used for this secondary analysis. The specific studies include the CRONICAS Cohort Study [18] in Peru; the Pulmonary Risk in South America (PRISA) study [19] in Chile (Temuco), Argentina (Bariloche, and Marcos Paz), and Uruguay (Canelones); the Center for Control of Chronic Diseases at the International Centre for Diarrheal Disease Research, Bangladesh (icddr, b) [20]; the LINK study (Lung Function Study in Nakaseke and Uganda); and the FRESH AIR (Free Respiratory Evaluation and Smoke-Exposure Reduction by Primary Health Care Integrated Groups) study in Uganda [21].

Study Design

A cross-sectional study design was conducted pooling baseline information from one cross-sectional and four longitudinal studies that aimed to characterize the association between HAP exposure and COPD. CRONICAS and PRISA are longitudinal studies that started in 2010, both using an age- and sex-stratified random sampling [18, 19]. The Bangladesh study is a longitudinal study using simple random sampling of available census data [20]. LINK is an ongoing cohort study that started collecting baseline data in 2015. FRESH AIR Uganda a cross-sectional study that used multilevel sampling and was completed in 2012 [21]. Participants in these primary studies were adults aged ≥ 18 years, had to be permanent residents in the sampling area, and had the ability to provide informed consent. Patients with active pulmonary tuberculosis were excluded. Eligibility for our study was met by participants having both HAP exposure, and previous pulmonary tuberculosis data. Participants without either exposure or tuberculosis information were excluded. All field workers completed confidentiality training, and all studies obtained approval from their respective internal review boards [18–21].

Spirometry

The primary studies at all sites followed joint American Thoracic Society/European Respiratory Society recommendations when performing and grading spirometry. FRESH AIR used Pneumotrac spirometers (Vitalograph Ltd., Buckingham, England, UK), while PRISA, CRONICAS, LINK, and the Bangladesh study used ndd spirometers (ndd, Zurich, Switzerland) [19–22]. Pre-bronchodilator and post-bronchodilator FEV_1 values were obtained for all individuals in PRISA and CRONICAS, whereas other studies only took post-bronchodilator measurements on those who screened positive for obstruction on pre-bronchodilator spirometry ($FEV_1/FVC \leq 0.7$ in FRESH AIR and the Bangladesh studies, and $FEV_1/FVC \leq$ lower limit of normal in LINK).

Definitions

We defined HAP exposure as self-reported previous and current domestic use of solid fuel as the primary source of energy, which included wood, coal, animal dung, and crop residue; clean fuel as electricity, gas, or liquid petroleum products; previous pulmonary tuberculosis as self-reported history of pulmonary tuberculosis that is no longer active; tobacco smoking as a current and prior history of smoking tobacco; hospitalization was as a history of admission to hospital for any medical condition in the preceding one year; and, body mass index (BMI) as weight (in kg) divided by height (in meters) squared. We stratified BMI categories according to World Health Organization classification [23]. Secondary education was defined by the International Standard Classification of Education [24]. We also defined site as the area of residence. Masindi, Matlab, Nakaseke and Rural Puno were classified as rural sites. Chronic obstructive lung disease was defined as a post-bronchodilator FEV_1/FVC z-score ≤ -1.64 SDs of the Global Lung Function Initiative 2012 mixed ethnic reference population [25].

Biostatistical Methods

Our primary analytical aim was to examine the association between HAP exposure and previous pulmonary tuberculosis. We used multiple logistic regression to model the association between HAP exposure and previous pulmonary tuberculosis adjusted for age, sex, BMI, tobacco smoking, and secondary education with multilevel mixed random effects to account for within-site and within-country nested correlations. BMI and age were modelled as continuous variables, tobacco smoking, sex and secondary education as dichotomous variables, and site and country were treated as categorical variables. The final model included these covariates which were selected a priori because they were considered biologically relevant. In sensitivity analyses, we stratified by age (< 60 years vs. age ≥ 60 years), sex, urbanization status, tobacco smoking, prevalence of HAP exposure (≥ 90% of participants with HAP exposure vs. < 90%) to determine if age, sex, tobacco smoking, site and percentage of participants with HAP exposure influenced the exposure–outcome relationship. We also estimated unadjusted and adjusted odds ratios of the association between HAP exposure and previous tuberculosis stratified by site using logistic regression. We used the Firth bias adjustment for sites with fewer than 10 cases of previous pulmonary tuberculosis in either the HAP exposed or non-exposed groups [26]. In secondary analyses, we used multivariable linear mixed-effects models with random intercepts by site to study the association between previous pulmonary tuberculosis and pre-bronchodilator FEV_1 values accounting for an interaction with age and adjusting for HAP exposure and the previously mentioned covariates. We also used multiple logistic regression to model the association between prior hospitalizations and previous pulmonary tuberculosis adjusted for age, sex, BMI, tobacco smoking, and secondary education with multilevel mixed random effects to account for within-site and within-country nested correlations. Individuals with missing tuberculosis or HAP exposure information were dropped from our analysis. We used STATA (Version 15, College Station, Texas, USA) and R (www.r-project.org) for our statistical analysis.

Results

Population Characteristics

Data were collected across five countries spanning South America, Southeast Asia, and Sub-Saharan Africa from 2010 to 2015. A total of 13,023 participants were included across all studies; however, 12,592 met eligibility criteria and were included in our analysis. A total of 220 participants (1.7%) were missing information on previous pulmonary tuberculosis and 214 (1.6%) were missing information on HAP exposure. Participants had an average (± SD) age of 54.6 ± 11.2 years, 48.6% ($n = 6122$) were women, 38.1% ($n = 4800$) had a secondary education or higher, and 12.3% ($n = 1546$) of the population smoked tobacco.

Across all settings, 38.8% ($n = 4884$) of the population were exposed to HAP (Fig. 1), and 52.7% ($n = 2575$) were women. More participants under 60 years of age reported HAP exposure by 46% ($n = 2246$), while 33% ($n = 1329$) more participants age 60 years and above used clean fuel. The proportions of participants who smoked tobacco were equal in both fuel use categories (11.3% in HAP exposed vs. 12.9% in non exposed). Seventy-eight percent ($n = 3848$) of those exposed to HAP did not have a secondary school education. Underweight and normal weight participants were 37.8% more likely to be exposed to HAP than their counterparts with higher weights. Matlab, Nakaseke, Kampala, Masindi, and Rural Puno reported the highest HAP exposures (Table 1).

Pulmonary Tuberculosis Outcomes

The overall prevalence of previous pulmonary tuberculosis was 2.7% (range of prevalence across sites, 0.6–6.9%). We plotted the prevalence of household air pollution (HAP) exposure against the prevalence of previous pulmonary tuberculosis at each site in Fig. 1. Participants with previous pulmonary tuberculosis had lower lung function than those who did not have previous pulmonary tuberculosis (Fig. 2). Specifically, previous pulmonary tuberculosis was associated with lower adjusted pre-bronchodilator z-scores

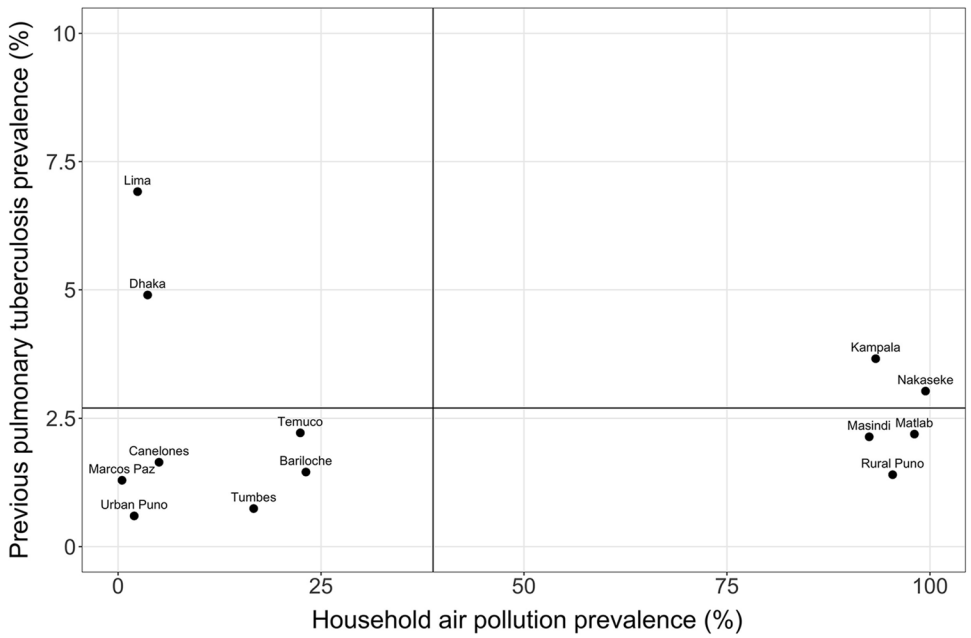

Fig. 1 Prevalence of previous pulmonary tuberculosis and household air pollution (HAP) exposure by site. We plotted the ecological relationship between the prevalence of HAP exposure against the prevalence of previous pulmonary tuberculosis across each site. The *y*-gridline represents the mean prevalence (%) of previous pulmonary tuberculosis, the *x*-gridline represents the mean prevalence (%) of HAP exposure across all sites in Argentina, Bangladesh, Chile, Peru, Uganda, and Uruguay from primary studies conducted between 2010 and 2015

Table 1 Population baseline characteristics by household air pollution exposure

	Household air pollution exposure ($n=4884$)	No household air pollution exposure ($n=7708$)	Overall
Women, % (*n*)	52.7 (2575)	46.0 (3547)	48.6 (6122)
Age, % (*n*)			
< 60 years	73.0 (3565)	65.0 (1071)	68.2 (8589)
≥ 60 years	27.0 (1319)	35.0 (2648)	31.8 (4003)
Tobacco smoke, % (*n*)	11.3 (955)	12.9 (551)	12.3 (1546)
Hospitalization, % (*n*)	0.7 (31)	0.8 (58)	75.0 (89)
Secondary education, % (*n*)	21.2 (1037)	48.9 (3763)	38.1 (4800)
Body mass index, % (*n*)			
Underweight	14.5 (707)	2.6 (203)	7.2 (910)
Normal	52.1 (2547)	26.2 (2015)	36.2 (4562)
Overweight	21.5 (1050)	39.5 (3046)	32.6 (4096)
Obese	11.9 (580)	31.7 (2444)	24.0 (3024)
Site, % (*n*)			
Urban areas			
Bariloche	5.2 (255)	11.0 (849)	8.8 (1102)
Canelones	0.9 (43)	10.0 (809)	6.8 (852)
Dhaka	1.3 (61)	21.0 (1613)	13.3 (1674)
Kampala	12.0 (586)	0.5 (42)	5.0 (628)
Lima	0.5 (24)	13.0 (974)	7.9 (998)
Marcos Paz	0.1 (6)	16.0 (1233)	9.8 (1239)
Temuco	4.7 (233)	10.4 (805)	8.2 (1038)
Tumbes	3.2 (158)	10.2 (788)	7.5 (946)
Urban Puno	0.2 (10)	6.4 (493)	4.0 (503)
Rural areas			
Masindi	10.6 (519)	0.6 (42)	4.5 (561)
Matlab	36.7 (1790)	0.5 (35)	14.5 (1825)
Nakaseke	14.8 (722)	0.1 (4)	5.8 (726)
Rural Puno	9.8 (477)	0.3 (23)	3.9 (500)
Previous pulmonary tuberculosis % (*n*)	2.3 (114)	2.9 (220)	2.7 (334)

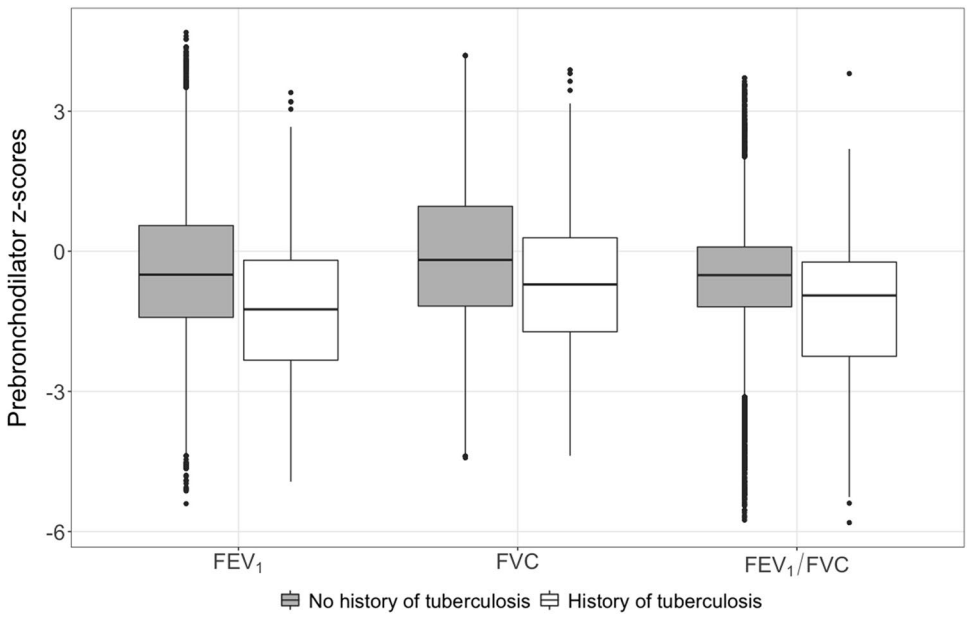

Fig. 2 Pre-bronchodilator lung function *z*-scores by previous pulmonary tuberculosis status. Pre-bronchodilator FEV_1 (forced expiratory volume in one second), FVC (forced vital capacity), ratio (FEV_1/FVC ratio), are presented for participants with and without previous pulmonary tuberculosis from primary studies conducted in Argentina, Bangladesh, Chile, Peru, Uganda, and Uruguay between 2010 and 2015

for FEV_1 (mean −0.7 SDs, 95% CI −0.92 to −0.57), FVC (−0.52 SDs, 95% CI −0.69 to −0.33) and FEV_1/FVC (−0.59 SDs, 95% CI −0.76 to −0.43).

In multiple variable analyses accounting for clustering by country and site, HAP exposure was not associated with the odds of having previous pulmonary tuberculosis (adjusted OR = 0.86; 95% CI 0.56–1.32) (Table 2). Women had 42% lower odds of previous pulmonary tuberculosis than men (adjusted OR = 0.58; 95% CI 0.47–0.74). A higher body mass index was associated with 7% lower odds of having previous pulmonary tuberculosis (adjusted OR = 0.93 per 1 kg/m^2; 95% CI 0.90–0.95). Additionally, participants who reported prior hospitalizations (a variable not selected a priori and hence not included in the final model) had threefold higher odds of having previous pulmonary tuberculosis than their non-hospitalized counterparts in both unadjusted (OR = 3.01; 95% CI 1.28–7.07) and adjusted analyses (OR = 3.28, 95% CI 1.39–7.74). There was no association between tobacco smoking, age, and secondary education with previous pulmonary tuberculosis (Table 2). The odds of tuberculosis were homogenous across strata of age, sex, urbanization status, HAP exposure, and tobacco smoking. Multivariable regression models on rural versus urban sites, sites with high (≥90%) versus low (<90%) HAP exposure prevalence showed no difference in odds of previous tuberculosis in either setting (Table 3). Lima, Dhaka, and Kampala had the highest prevalence of previous pulmonary tuberculosis while urban Puno, Tumbes, and rural Puno had the least (Fig. 3).

Discussion

Our analysis pooled data from population-based observational studies across a diversity of low- and middle-income country settings. There was no association between HAP exposure and previous pulmonary tuberculosis. This relationship was consistent even after we performed multilevel mixed regression analysis considering urbanization status, age, and sex strata, or restricting to sites with the highest household air pollution exposures, or tuberculosis prevalence. Our data shows rural sites, and Kampala the only urban site mostly used biomass as their primary fuel source. However, participants in Matlab, Masindi, and

Table 2 Crude and adjusted multilevel mixed logistic regression models for tuberculosis, coefficients reported as odds ratios

	Crude odds ratio	95% CI	Adjusted odds ratio	95% CI
Household air pollution exposure	0.95	0.62–1.46	0.86	0.56–1.32
Women vs. men	0.52	0.41–0.66	0.58	0.46–0.74
Tobacco smoking	1.34	0.95–1.88	1.00	0.71–1.42
Age (per decade)	1.08	0.97–1.19	1.04	0.94–1.15
Body mass index (per kg/m^2)	0.92	0.89–0.94	0.93	0.90–0.95
Secondary education	1.01	0.79–1.28	0.96	0.76–1.24

Table 3 Sensitivity analysis with crude and adjusted multilevel mixed logistic regression models for tuberculosis, coefficients reported as odds ratios

	Unadjusted OR	95% CI	Adjusted OR	95% CI
Age				
< 60 years	1.06	0.66–1.69	0.97	0.61–1.54
≥ 60 years	0.79	0.46–1.37	0.69	0.39–1.21
Sex				
Male	1.01	0.64–1.59	0.88	0.56–1.39
Female	0.95	0.56–1.62	0.85	0.50–1.45
Urbanization status				
Rural	0.99	0.60–1.62	0.96	0.59–1.56
Urban	0.69	0.21–2.28	0.67	0.20–2.20
Household air pollution exposure				
Low exposure (< 90% of participants)	0.86	0.48–1.52	0.80	0.46–1.45
High exposure (≥ 90% of participants)	0.91	0.32–2.52	0.96	0.34–2.70
Tobacco smoking				
No	0.93	0.59–1.45	0.86	0.56–1.34
Yes	1.09	0.53–2.26	0.89	0.43–1.84

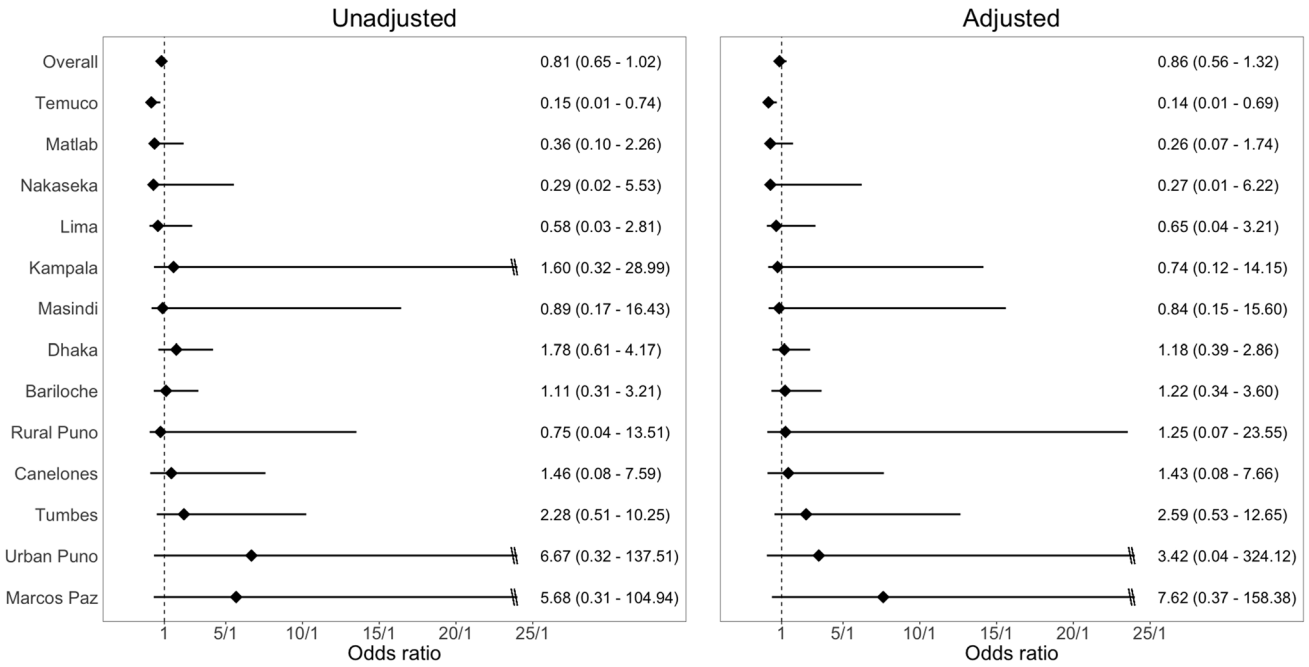

Fig. 3 Association between household air pollution exposure and pulmonary tuberculosis outcomes obtained from a multivariable regression model adjusted for age, sex, tobacco smoke, BMI, and secondary education obtained for the overall cohort of participants and stratified by site. Unadjusted (left panel) and adjusted (right panel) overall and site-specific odds ratios with corresponding 95% confidence intervals are represented by diamonds and lines, respectively. Data were collected in Argentina, Bangladesh, Chile, Peru, Uganda, and Uruguay from primary studies conducted between 2010 and 2015

Rural Puno had low odds of having previous pulmonary tuberculosis despite reporting some of the highest domestic biomass fuel use. The increased odds of tuberculosis in Lima, and Dhaka do not correlate with their levels of reported HAP exposure. Women were more exposed to HAP than men but reported lower proportions of previous pulmonary tuberculosis.

Multiple observational studies have suggested an association between exposure to household air pollution and active pulmonary tuberculosis [10, 27–33]. In a systematic review, tuberculosis cases were more likely to have been exposed to domestic biomass than healthy controls [27]. This potential causal relationship is conceivable as ecologic studies have suggested an association between coal, and combustible

pollutants with tuberculosis [34, 35]. However, some studies have showed no significant biomass–tuberculosis association [36–39]. Limitations of prior studies conducted to date include, inadequate sample sizes, selection bias, low-tuberculosis prevalence, inaccurate tuberculosis ascertainment, misclassification of exposure, failure to adjust for significant covariates such as occupational exposures, and various socioeconomic, and demographic determinants. A study of Nepalese women by Pokhrel et al. found a positive association with biomass exposure from heating rather than cooking [32], while other studies did not control for tobacco smoking [30], or directly measure biomass exposure [28, 33].

Urbanization is common in these communities and is associated with high rates of migration, overcrowding, inefficient healthcare infrastructure, and HIV [40]. All these contribute to morbidity and mortality from pulmonary tuberculosis in resource-poor settings. Furthermore, households may have more than one residence typically living in a rural setting while traveling to work in an urban environment. This poses practical difficulty in isolating site-specific pulmonary tuberculosis risk and delineating domestic from occupational exposures to biomass fuels. Reasons other than exposure to biomass might also appear to explain why some sites or men might have a higher propensity for pulmonary tuberculosis. Across settings, men are more likely to smoke tobacco, and engage in high-risk occupations such as coal mining. Cultural, and religious reasons might hinder women's access to healthcare preventing diagnosis.

Participants who reported prior hospitalization had a higher prevalence of pulmonary tuberculosis. In resource-limited settings, where individuals might present to hospital only when compelled to, one could infer an underlying chronic medical condition increased their risk for tuberculosis. Individuals who use solid fuels were more likely underweight, they also had a higher prevalence of tuberculosis. Conversely, overweight individuals in these communities are more likely to afford healthier living environments including cleaner fuels. This interplay may further highlight the challenge, the interaction between poverty, malnutrition, and tuberculosis presents in the ecologic evaluation of the HAP-tuberculosis exposure–disease relationship.

The primary strength of our study is the large population-based sample pooled from cohorts in diverse geographic settings. Our findings can, therefore, be representative of our target population in low- and middle-income countries. However, various factors might explain our negative study findings. First, previous pulmonary tuberculosis was self-reported. We did not have confirmatory information about the disease diagnosis, severity, multi-drug resistance, or about anti-tuberculosis treatment course. However, study participants with a history of tuberculosis may have accurately reported previous pulmonary tuberculosis which is a known risk factor for airway obstruction [41]. This assumption is supported by the observation that our spirometry findings revealed those with previous tuberculosis had obstructive lung disease physiology. Second, household air pollution exposure was self-reported with no direct measure of the quantity and duration of exposure. Direct measurements of household air pollution, however, would only give the degree of exposure at the time of measurement. Furthermore, there is no metric for chronic biomass exposure. Therefore, self-report of biomass fuel use remains as the only viable approach to retrospectively capture long-term exposure. Third, pulmonary tuberculosis may have happened many years prior to the time of household air pollution exposure, our questionnaires were unable to disentangle temporality of the events. Fourth, most of the primary studies also excluded patients with active pulmonary tuberculosis due to the potential risks of contamination during spirometry, and may have affected our estimate of the relationship between household air pollution exposure and pulmonary tuberculosis. Because the misclassification of the outcome (i.e. pulmonary tuberculosis) would have been non-differential, the bias would have been towards the null. However, we would expect this effect to be modest because pulmonary tuberculosis is a rare event. Fifth, misclassification of controls may occur from ambient air pollution exposure, especially in population-dense settings. Our studies did not measure environmental exposures. Sixth, we did not have other potentially confounding variables such as living with another household member who has had active pulmonary tuberculosis or the background prevalence of pulmonary tuberculosis in our study areas. Finally, we were limited to low- and middle-income countries and results may not be comparable to other settings where biomass fuel is used exclusively for household heating. In the face of these limitations, a lack of an association is important to report.

Among the limitations we encountered were the inability to differentiate pulmonary from extrapulmonary tuberculosis from our available data. The general population may not easily distinguish between treatment for latent and active pulmonary tuberculosis. We assumed respondents implied active pulmonary tuberculosis as it is the most diagnosed and treated in these settings. Furthermore, the definition of HAP exposure was not uniform across datasets with variations being history of, current, or current daily biomass use. While the specific type of solid fuel used was identified, data on the stove type, kitchen location, ventilation, household size, history of close contact with an index case of tuberculosis, HIV, and occupational exposures, were not collected. Secondary education is an inadequate measure of social economic status and could lead to residual confounding. Therefore, high-quality research is needed to further explore the association between HAP exposure and pulmonary tuberculosis.

Conclusion

HIV, tobacco smoking, low-socioeconomic status with associated overcrowding, are risk factors for pulmonary tuberculosis. Evidence for exposure to HAP as a contributor to tuberculosis is limited. Our study contributes to the evidence of a lack of association between household air pollution exposure and pulmonary tuberculosis. Further research that better measures HAP exposure while accounting for potential confounders is needed.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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