Tuberculosis is Associated with Chronic Hypoxemia among Kenyan Adults (CHAKA): A Case-Control Study

Neelima Navuluri, MD, MPH,[1,2] Peter S. Kussin, MD,[1,2] Joseph R. Egger, PhD[2], Elcy Birgen, BsC[2,3], Sylvia Kitur,[3] Nathan M. Thielman, MD[1,2], Alice Parish, MSPH[4], Cynthia L. Green, PhD[4], Mark M. Janko, PhD,[2] Lameck Diero[5], Kara Wools-Kaloustian, MD[6], David Lagat, MD[5], Loretta G. Que, MD[1]

1. Department of Medicine, Duke University School of Medicine, Durham, NC, United States
2. Duke Global Health Institute, Duke University, Durham, NC, United States
3. Academic Model Providing Access to Healthcare (AMPATH), Eldoret, Kenya
4. Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, NC, United States
5. Moi University School of Medicine & Moi Teaching and Referral Hospital, Eldoret, Kenya
6. Division of Infectious Disease, Department of Medicine, University of Indiana School of Medicine, Indianapolis, IN, United States

Corresponding Author: Neelima Navuluri, Neelima.navuluri@duke.edu; Tel: 919-684-5662; Fax: 919-681-4637

Authors' Contributions: NN contributed to study conceptualization, funding acquisition, methodology, data curation, formal analysis, writing of the original draft, and revising and editing the manuscript. JRE contributed to the methodology, formal analysis and revising and editing the manuscript. EB, SK, and MJ contributed to data collection and revising and editing the manuscript. AP, CG, and KW contributed to the analysis and editing the manuscript. NT, LD, PSK, DL and LQ contributed to the conceptualization, funding acquisition, methodology, supervision of the study and revising and editing manuscript. The authors have no conflicts of interest to disclose.

Funding: NN was supported by a Vanderbilt-Emory-Cornell-Duke Consortium Global Health Fellowship, funded by the National Heart, Lung, and Blood Institute (NHLBI) and the Fogarty International Center (FIC) of the NIH (D43 TW009337), as well as the CHEST Foundation. The views expressed are solely those of the authors and do not necessarily represent the views of the NIH. The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Ethics Committee Approval: All study procedures were approved by the ethical review boards at Duke University (Pro00100397) and Moi University (IREC/2019/72).

Subject Category: 11.6 Treatment of Tuberculosis or Latent Infection

ANNALSATS Articles in Press. Published May 18, 2024 as 10.1513/AnnalsATS.202402-167OC

Abstract:

Rationale: Data on risk factors for chronic hypoxemia in low and middle-income countries are lacking.

Objective: We aimed to quantify the association between potential risk factors and chronic hypoxemia among adults hospitalized in Kenya.

Methods: A hospital-based case-control study was conducted at Moi Teaching and Referral Hospital in Eldoret, Kenya. Adult inpatients were screened on admission and enrolled in a 1:2 case to control ratio. Cases were patients with chronic hypoxemia, defined as a resting oxygen saturation (SpO2) $\leq$ 88% on admission and either a one-month post discharge SpO2 $\leq$ 88% or, if they died prior to follow-up, a documented SpO2 $\leq$ 88% in the 6 months prior to enrollment. Controls were randomly selected, stratified by sex, among non-hypoxemic inpatients. Data were collected via questionnaires and structured chart review. Regression was used to assess the association between chronic hypoxemia and age, sex, smoking status, biomass fuel use, elevation, and self-reported history of tuberculosis and HIV diagnosis. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported.

Results: The study enrolled 108 chronically hypoxemic cases and 240 non-hypoxemic controls. In multivariable analysis, as compared to controls, chronically hypoxemic cases had significantly higher odds of older age (OR 1.2 per 5-year increase; 95% CI: 1.1-1.3), female sex (OR 3.6, 95% CI: 1.8-7.2), current or former tobacco use (OR 4.7, 95% CI: 2.3-9.6) and prior tuberculosis (OR 11.8, 95% CI: 4.7-29.6), but no increase in odds of HIV diagnosis and biomass fuel use.

Conclusion: These findings highlight the potential impact of prior tuberculosis on chronic lung disease in Kenya and the need for further studies on post-tuberculosis lung disease.

ANNALSATS Articles in Press. Published May 18, 2024 as 10.1513/AnnalsATS.202402-167OC

Chronic hypoxemia is a major cause of morbidity and mortality in patients with chronic lung diseases, which are ranked as the 3rd leading cause of death by the World Health Organization (WHO).[1–3] Major etiologies of chronic hypoxemia in high-income countries include chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD), with tobacco use being a key risk factor.[4] However, sparse data are available on risk factors for chronic hypoxemia among patient populations in low- and middle-income countries (LMICs) such as Kenya, where smoking rates are lower, but mortality from lung disease remains high.[5]

For example, studies in Uganda and Kenya demonstrated higher rates of obstructive lung disease among women and patients younger than 40 years of age as compared to high income countries. This suggests that there may unique risk factors for chronic lung disease in these settings.[6] Indoor air pollution from biomass fuel use is a frequently cited risk factor for chronic lung disease, as is HIV and prior lower respiratory tract infections such as tuberculosis (TB).[7,8] However, to our knowledge, none of these studies have focused on chronic hypoxemia, which characterizes advanced or end-stage lung disease and may be influenced by other health conditions such as heart disease. Furthermore, most studies describe cohorts of people living with HIV (PLWH).

Given the paucity of epidemiologic data on chronic hypoxemia and its specific risk factors in LMICs, this study sought to characterize patients with chronic hypoxemia admitted to a national referral hospital in Kenya and assess demographic, environmental, and clinical risk factors for chronic hypoxemia. Oxygen prescription and use among participants with chronic hypoxemia was also assessed. Strong epidemiologic data would provide support for strategies to curb the burden of hypoxemic lung disease in Kenya and direction for future research and funding efforts.

Methods

Study Design and Patients:

A hospital-based case-control study was conducted at Moi Teaching and Referral Hospital (MTRH) in Eldoret, Kenya between September 2019 and March 2022. MTRH is one of two national referral hospitals in the country, offering tertiary care services to a catchment population of over 24 million people across Western Kenya. MTRH consists of several different wards with the general medicine wards being among the largest in the hospital, responsible for caring for adult patients with a wide range of non-surgical issues.

All hospitalized patients in the general medicine wards were eligible for participation in the study regardless of admission diagnosis. Eligible cases included those $\geq$18 years with chronic hypoxemia, which was defined as a resting oxygen saturation (SpO2) $\leq$ 88% on admission and either 1) an SpO2 $\leq$ 88% at one-month post-discharge follow-up study visit or 2) if the patient died prior to follow-up, a documented SpO2 $\leq$ 88% during a previous outpatient visit or on hospital discharge exam in the 6 months prior to the current admission. Since participants were recruited in the hospital but followed post-discharge, patients who were hypoxemic on admission to the hospital and remained hypoxemic for three or more days were enrolled as suspected cases. Case confirmation occurred at time of death or at the one-month post discharge follow-up visit.

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Controls were selected in a 2:1 ratio to suspected cases using survivor sampling among non-hypoxemic inpatients ≥18 years. Because hospital wards are separated by sex, controls were selected by numbering admission logs for each ward and using a random-number generator to select potential controls to approach for enrollment on the day of admission in each of the two hospital wards. Controls were then enrolled within three days of admission. Equal allocation of controls, by sex, was intended to capture the sex distribution of the population, which was assumed to be roughly equal (i.e., 50:50 male-female).

We powered the study on HIV as a primary exposure. We estimated a 10% prevalence of HIV among controls.[9] With 112 cases and 224 controls, we estimated 80% power to detect a minimum OR of 2.41 with an alpha level of 0.05 for a greater odds of HIV among chronically hypoxemic cases.

Data Collection

Research assistants used structured paper forms to collect participant eligibility information. SpO2 was assessed on all participants (cases and controls) on room air using a Masimo Rad-5v® pulse oximeter with at least two readings. For participants who were on clinically prescribed oxygen supplementation, a standardized operating procedure was used to safely assess SpO2 on both oxygen supplementation and room air.

Data from questionnaires and chart review were collected using Research Electronic Data Capture (REDCap), hosted at Duke University.[10,11] Demographic and self-reported medical history data included education, occupation, tobacco use, biomass fuel use, electricity availability, self-reported medical co-morbidities, and prior hospitalizations. Structured chart review data included admission and discharge characteristics, past medical and surgical history as listed on admission or discharge forms or physician notes, and laboratory results. Medical co-morbidities are presented as aggregates of participant self-report of medical history to research staff and clinician-reported medical history within the patient charts. Tuberculosis history is categorized and reported as prior tuberculosis for participants who reported a prior history of tuberculosis for which they were treated versus active tuberculosis for those who were receiving anti-tuberculosis treatment during the study period. Laboratory results closest to participant's initial admission date were utilized.

A measure of participants' primary residence elevation was constructed using the NASA Shuttle Radar Topographic Mission's 90-meter Digital Elevation Database.[12] Each participant was geocoded to the ward of residence, and their residential ward (third administrative division), and the average elevation of each residential ward was calculated with raster-based GIS tools in R.[13] Average elevation was used because coordinates for study participants were unavailable, and it partially accounts for variability in elevation exposure due to individual local mobility patterns.

Statistical Analysis

Standard summary statistics were used to describe the study population. Univariable logistic regressions and univariate statistical tests, such as the Wilcoxon rank-sum and chi-square, were used to assess the association between chronic hypoxemia and cohort characteristics, as appropriate.

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A multivariable logistic regression model was then used to determine the association between chronic hypoxemia and tuberculosis adjusting for age, sex, smoking status, biomass fuel use, elevation, and HIV history, which were selected a priori. We did not adjust for factors that are thought to be on the causal pathway (mediator) between tuberculosis and chronic hypoxemia, such as COPD. Model assumptions were assessed and a spline for elevation was included in the model, split at <2000m, the median elevation for the entire cohort. Model results are presented as the odds ratio (OR) with 95% confidence interval (CI). Analyses were conducted using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC) and a p-value <0.05 was considered statistically significant.

Results

Baseline Descriptive Characteristics

The study enrolled 211 potential cases, of which 108 (51.2%) were confirmed to be chronically hypoxemic and included in the analysis cohort as cases, and 240 non-hypoxemic controls (Figure 1). Of the 108 cases, 70 (65%) met the case definition based on an SpO2 ≤88% at post-discharge follow-up visit and 38 (35%) based on an SpO2 ≤ 88% on prior outpatient visit or discharge exam in the 6 months prior to admission.

Demographics and medical history are shown in Table 1. Chronically hypoxemic cases were significantly older with a median age of 64 (Q1-Q3: 44-75) years compared to 42 (Q1-Q3: 28-63) years among non-hypoxemic controls (OR 1.04; 95% CI 1.02-1.05). They were also predominantly female as compared to controls (61% vs 44%; OR 1.99, 95% CI 1.25-3.16). A significantly higher proportion of cases had no history of attending school (OR 10.28, 95% CI 2.63-29.13) or having only completed primary school (OR 3.41, 95% CI 1.34-8.67) as compared to controls. In addition, cases had higher odds of being employed as farmers (OR 2.35, 95% CI 1.14-4.83) or in small-business (OR 2.33, 95% CI 1.04-5.25), as compared to controls. The odds of chronic hypoxemia increased 1.33 times for every 100m increase in mean elevation of participant's primary residence up to 2000m (95% CI 1.12-1.58) using regression splines; however, there were no significant differences in the odds of chronic hypoxemia for increasing elevation above 2000m. Chronically hypoxemic cases also had a higher rate of enrollment in the National Health Insurance Fund (NHIF), which is Kenya's universal health coverage insurance plan, as compared to controls (OR 1.74, 95% CI 1.06-2.85).

Compared to controls, chronically hypoxemic cases had higher odds of current or former tobacco use (OR 3.45, 95% CI: 2.11-5.65). Marijuana use was uncommon (<5%) and did not significantly differ between cases and controls (OR 1.12, 95% CI 0.37-3.35). In terms of biomass use, firewood was the most common source of cooking fuel among participants, followed by gas and charcoal (Table 1). Compared to controls, biomass fuel use was higher in the chronic hypoxemic cases, however not statistically significant (firewood: OR 1.66, 95% CI: 0.83-3.32).

Clinical characteristics including medical history and laboratory values on admission are shown in Table 2. Among cases, 34 (31.5%) participants reported a history of prior tuberculosis and 6 (5.6%) were being treated for active tuberculosis while among controls, 13 (5.4%) participants reported prior tuberculosis and 14 (5.8%) were being treated for active tuberculosis. Without adjusting for potential confounders, chronically hypoxemic cases had 8.19 times the relative odds of prior tuberculosis diagnosis

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(95% CI 4.09-16.41), but no significantly increased odds of active tuberculosis (OR 1.34; 95% CI 0.50-3.63). Among cases, other reported medical co-morbidities with significantly higher odds include asthma (OR 13.49, 95% CI 2.94-62.01), chronic obstructive pulmonary disease (OR 81.97, 95% CI 24.70-272.04), lung fibrosis (OR 41.56, 95% CI 5.43-317.91), self-reported pulmonary embolism treated with blood thinners (OR 4.82, 95% CI 1.18-19.64), pulmonary hypertension (OR 52.53, 95% CI 20.05-137.60), heart disease including heart failure or arrythmias (OR 3.54, 95% CI 2.16-5.81), and pneumonia (OR 2.80, 95% CI 1.37-5.73). Cases also had higher odds of prior hospitalization (OR 2.17, 95% CI 1.25-3.79). There were significantly lower odds of anemia (OR 0.24, 95% CI 0.09-0.61), kidney disease (OR 0.38, 95% CI 0.18-0.78), and cancer (OR 0.38, CI 0.19-0.76) among chronically hypoxemic cases as compared to controls. There was no significant association between HIV diagnosis and chronic hypoxemia (OR 1.06, 95% CI 0.52-2.17).

Chronically hypoxemic cases had a significantly higher median hemoglobin concentration (14.2 vs 11.1 g/dL) than controls, but a lower mean creatinine (0.8 vs 0.9 mg/dL). Among the subset of participants who had a blood gas assessed, chronically hypoxemic cases also had a significantly higher partial pressure of carbon dioxide (PaCO2; 48.6 vs 25.0 mmHg). Other laboratory values including white blood cell count, platelets, and albumin did not different significantly between cases and controls (Table 3).

In terms of hospital duration and mortality, chronically hypoxemic cases had a longer median length of stay (11 vs 8 days; p=0.014) but there was no significant difference in inpatient mortality (16.7% vs 13.8%; p=0.48) as compared to controls (Table 3). However, phone follow-up at one-month post-discharge showed significantly higher mortality rates (16.7% vs 10.2%) and re-hospitalization (15.6% vs 4.9%) among cases who survived initial hospitalization compared to controls (p=0.002).

Multivariable analysis

In multivariable analysis, we found cases were at nearly 12 times higher relative odds of having had prior tuberculosis (OR 11.75; 95% CI 4.67-29.61) and 4 times higher odds (OR 4.02; 95% CI 1.18-13.74) of having active tuberculosis compared to non-hypoxemic controls (Figure 2). Additionally, after controlling for other factors hypoxemic cases were significantly older (OR 1.19 per 5-year increase; 95% CI 1.09-1.29), more frequently female (OR 3.59; 95% CI 1.79-7.21), and current or former tobacco users (OR 4.65; 95% CI 2.25-9.63) compared to controls.

The average elevation of the ward of primary residence was associated with chronic hypoxemia at elevations <2000 meters above sea level (OR 1.40 per 100m increase; 95% CI 1.13-1.74), but was not meaningfully associated with chronic hypoxemia for participants living above 2000 meters (OR 0.97; 95% CI 0.82-1.16). Chronically hypoxemic cases did not have significant differences in cooking fuel type (OR 0.80 for charcoal vs firewood; 95% CI 0.28-2.29) or positive HIV test results (OR 0.64; 95% CI 0.24-1.69) as compared to controls. Adding chronic lung disease and chronic heart disease to the model had limited effect on the strengths of these associations (Supplementary Material).

Follow-Up Characteristics and Resource Availability of Chronically Hypoxemic Patients

Oxygen use, home oxygen prescription and availability, and hypoxemia on follow-up among the subset of chronically hypoxemic cases were also analyzed (Table 4). Their mean SpO2 on room air was 75.9% ± 9.0 on admission, 80.2% ± 7.2 at discharge, and 79.2% ± 6.3 at follow-up. At the time of screening

ANNALSATS Articles in Press. Published May 18, 2024 as 10.1513/AnnalsATS.202402-167OC

and enrollment into the study, only 63 (58.3%) chronically hypoxemic participants were receiving supplemental oxygen therapy, with a median of 6 liters per minute (Q1-Q3: 5-10). In terms of home oxygen use, only 10 (9.3%) of chronically hypoxemic cases were using oxygen at home at the time of admission. At discharge, 41 (45.6%) cases had home oxygen discussed with them by someone from their care team, of which only 13 (31.7%) were able to obtain home oxygen prior to discharge.

In order to assess feasibility of home oxygen concentrators in this population, availability of electricity was surveyed. Only 48 (44.4%) of chronically hypoxemic cases had electricity in their homes, among whom 45 (93.7%) participants reported at least 1-2 power outages per week. The majority of participants (55.5%) reported an average outage duration ≤4 hours, though 13 (28.9%) had an average duration >8 hours.

Discussion

In this cohort of adults admitted to a tertiary referral hospital in Kenya, tuberculosis and female sex were strongly associated with chronic hypoxemia in addition to more well-established risk factors such as older age, tobacco use, and altitude. Chronically hypoxic cases were at nearly 4-fold higher odds of being women and nearly 12-fold higher odds of having prior tuberculosis as compared to controls. These findings highlight important areas of future investigation regarding post-tuberculosis lung disease (PTLD) and sex-disparities in lung health.

PTLD is defined as evidence of a "chronic respiratory abnormality with or without symptoms, attributable at least in part to previous tuberculosis," and encompasses obstructive lung disease, restrictive lung disease, and pulmonary hypertension, all of which may lead to chronic hypoxemia.[14] The size and strength of the association between both active and prior tuberculosis in this study underscores the important role that tuberculosis plays in chronic hypoxemia among this population. This is in contrast to patient populations in the United States and Europe receiving home oxygen for chronic hypoxemia, where age and tobacco use are the major risk factors.[4,15] Our findings are congruent with the current understanding of how tuberculosis disease, and the immune response to tuberculosis, likely leads to lung injury and remodeling, and therefore various phenotypes of chronic lung disease.[16]The estimates of higher odds for asthma, COPD, lung fibrosis, and pulmonary hypertension align with current understanding of the pathophysiology of chronic hypoxemia in this population. Indeed, clinical and epidemiological studies of patients treated for tuberculosis have found increased risk of obstructive airway disease, bronchiectasis, pulmonary hypertension, and low forced vital capacity pattern on spirometry compared to those without a history of tuberculosis.[17–19] Further prospective studies are needed to better understand how the pathophysiology, risk factors, and outcomes for these varying phenotypes of lung disease may be similar or different in individuals with prior tuberculosis. These studies will also need to account for the increased risk of tuberculosis disease in individuals with COPD.[20]

Additionally, chronically hypoxemic cases had significantly higher odds of being female. In fact, identifying eligible female controls for enrollment into the study was difficult because many females identified by the random generator were hypoxemic on initial screening and thus ineligible to be selected as part of the control group. Future studies on chronic hypoxemia and PTLD should explore potential biological, social, and environmental mechanisms for sex differences in chronic lung disease in-line with

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ongoing work on sex-differences in asthma, COPD, pulmonary hypertension and cystic fibrosis.[21,22] Given that biomass fuel use and type (i.e., firewood vs charcoal vs gas/kerosene) were not significantly different between our cases and controls, future studies should also move beyond differential exposure to indoor air pollution and biomass fuel use as the primary rationale for sex differences in lung disease across East Africa or include more precise individual indoor and outdoor air pollution exposure assessments such as particulate matter measurements.[6,23,24]

The odds of living at higher elevations up to 2000m was increased among chronically hypoxemic cases, but the odds were not different between cases and controls above 2000m. The impact of increasing elevation on hypoxemia is well established and helps explain the findings up to 2000m. The lack of an association beyond 2000m may be due to residual confounding or selection bias as patients with chronic hypoxemia may move to lower elevations to help with symptoms.

Interestingly, cases did not show a significantly higher prevalence of HIV compared to controls, despite the known independent association between HIV and chronic lung disease.[25–27] HIV prevalence among both cases and controls are consistent with known prevalence rates of HIV among the general inpatient population at MTRH and the majority of both cases (100%) and controls (86.2%) were on antiretroviral therapy, suggesting that unknown testing status or major differences in viral suppression likely do not explain this negative finding.[9] Possible explanations include that data regarding the association between HIV and lung disease come from studies in the US and Europe, where rates of tuberculosis are significantly lower, HIV rates from intravenous drug use are higher, and environmental exposures differ as compared to Kenya which may have a differential impact on HIV and lung disease.[28,29] Also, many of the initial studies on HIV and lung disease were conducted among populations who were not universally on treatment from the time of diagnosis, an era in which tuberculosis was a major cause of death among people living with HIV.[30,31] Our lack of an association may reflect the beneficial impact of advancements in HIV treatment on severity of chronic lung disease.[30]

Other notable findings include significantly higher odds of less than secondary school education and employment as farmers or small-business owners/self-employed among chronically hypoxemic cases in univariable analysis. This suggests that occupational lung disease, certain environmental exposures, or socioeconomic status may play an important role in this population. Furthermore, the higher hemoglobin and hematocrit levels among chronically hypoxemic cases can be readily explained by normal physiologic responses to hypoxemia. However, the higher creatinine levels and relative anemia among controls is noteworthy, and may be explained by high rates of chronic kidney disease and cancer among controls. These high rates of kidney disease and cancer among our non-hypoxemic controls are most likely due to the fact MTRH is a tertiary referral hospital with some of the only publicly available dialysis and cancer services in the region.

Finally, healthcare utilization among chronically hypoxemic cases is high, with cases having higher rates of prior hospitalizations in the last year, longer admission length-of-stay, and higher rates of re-hospitalization at one-month follow-up. While there was no difference in mortality at discharge, there was higher mortality among chronically hypoxemic cases post-discharge. The lack of difference in mortality rates at discharge may be influenced by our case definition in that we were not able to confirm chronic hypoxemia among 29 participants who died prior to discharge due to lack of prior documentation

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of SpO2s. Higher mortality rates at follow-up may be linked to our findings that less than 10% of chronically hypoxemic participants used home oxygen prior to admission, less than half were prescribed home oxygen by the care team prior to discharge, and only about one-third were able to maintain existing or obtain new home oxygen at discharge. Given that long-term oxygen therapy is a well-established cornerstone of management of chronic hypoxemia and improves mortality and morbidity, it will be critical to increase availability and utilization of home oxygen among patients in western Kenya.[32,33] This task will be further complicated by limited access to electricity and frequent power outages as seen in our study.

Strengths of this study include a rigorous epidemiological study design with a hospital-based control group and comprehensive data collection including measurement on elevation of study participants. There was also a high rate of phone and in-person follow-up among patients who survived past hospital discharge, which limits potential selection bias of the odds ratio due to attrition. The study is, however, not without limitations. First, while MTRH covers a large catchment area in Kenya, this is a single-center study and the measures of association may not be generalizable to other clinical contexts. Furthermore, since MTRH is a large referral hospital seeing high acuity patients, the findings in regards to mortality and other outcomes may also not be generalizable to lower acuity settings. Second, individual air pollution exposures were imprecisely assessed, and there may be recall bias in participants' reporting of clinical history, such as prior tuberculosis, both of which could lead to exposure misclassification; though this was likely to be non-differential between cases and controls which would lead to an attenuation of the odds ratio estimate towards the null. Self-reported history of tuberculosis may also not be clinically accurate, given the potential for misdiagnosis or erroneous attribution of respiratory symptoms or abnormal chest imaging to tuberculosis by clinicians.[34]. Future studies should consider including more definitive tuberculosis diagnosis and history verification, as well as more precise measures of individual-level indoor and outdoor air pollution exposures. Third, missing elevation data may have impacted the precision of estimates in the multivariable model, especially for the odds of active tuberculosis among cases and controls. We previously reported the results of a multivariable model that does not include elevation for comparison.[35] Fourth, our study was powered on HIV as a primary exposure, which may have contributed to the wide confidence intervals we found. A larger sample size may have provided more precise estimates. Finally, since the study utilized survival sampling, there is potential for Berkson's bias.[36,37] For example, our estimate of the association between sex and chronic hypoxemia may be an over-estimate if the true odds of being female in the cohort is closer to 1. If the true odds of being female is 1, then our estimated odds ratio for female sex would be attenuated from 1.99 to 1.57.

In conclusion, in this hospital-based case-control study of adults admitted to a tertiary referral hospital in Kenya, tuberculosis, female sex, age, tobacco use, and altitude were significantly associated with chronic hypoxemia even when accounting for HIV status and biomass fuel use. Despite high rates of hospital admission and readmission, longer length of stay, and high mortality rates post-discharge, participants with chronic hypoxemia face significant challenges in obtaining long-term oxygen therapy which could improve their morbidity and mortality. Future directions for research include prospective studies on PTLD and sex-disparities in lung health, as well as further work and implementation studies on home oxygen therapy in Kenya and other resource-limited settings.

ANNALSATS Articles in Press. Published May 18, 2024 as 10.1513/AnnalsATS.202402-167OC

Acknowledgements: Our immense gratitude to the individuals who were willing to participate in this study and provide their time and energy during and after their hospitalization. We thank the incredible nursing and medical records staff on the inpatient medicine wards at MTRH who made this study possible. We also thank the Duke Hubert-Yeargan Center for Global Health, the Academic Model Providing Access to Healthcare (AMPATH) Consortium, and the AMPATH Research Office for their support.

ANNALSATS Articles in Press. Published May 18, 2024 as 10.1513/AnnalsATS.202402-167OC

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Figure 1: Consort Diagram

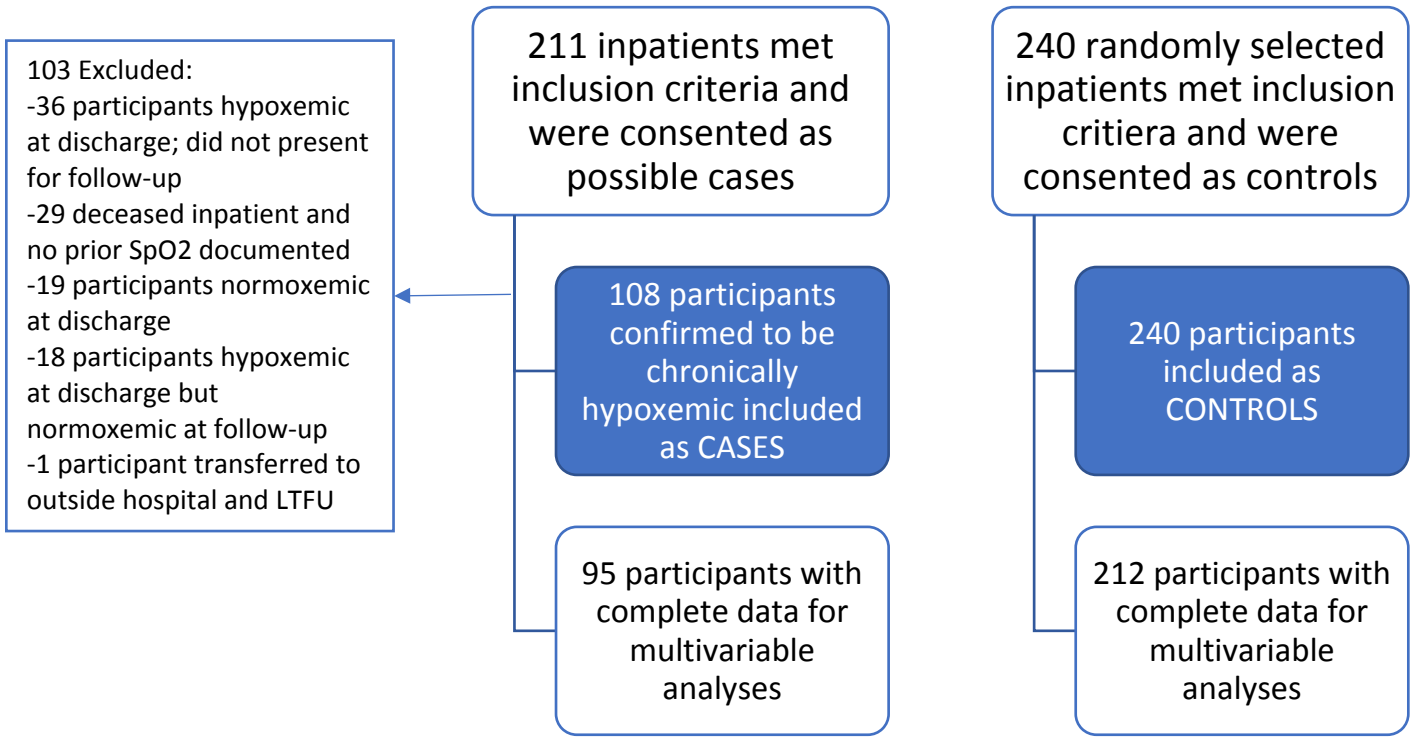

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Table 1: Baseline Characteristics of Non-Hypoxemic Controls and Chronically Hypoxemia Cases*

Variable	Non-Hypoxemic Controls (N=240)	Chronically Hypoxemic Cases (N=108)	Unadjusted Odds Ratio (95% CI)
Age, years	42.2 (28.1, 63.2)	63.6 (43.8, 74.9)	**1.20 (1.13-1.27) per 5-year increase**
Sex			
Male	134 (55.8%)	42 (38.9%)	ref
Female	106 (44.2%)	66 (61.1%)	**1.99 (1.25-3.16)**
BMI, kg/m²,	n=187	n=91	
	21.3 (18.9, 23.5)	20.8 (16.8, 25.5)	1.02 (0.97-1.07) per 1-unit increase
Insured via NHIF	143 (59.6%)	77 (72.0%)	**1.74 (1.06-2.85)**
Marital Status			
Single	69 (28.8%)	14 (13.0%)	ref
Married	130 (54.2%)	58 (53.7%)	**2.20 (1.14-4.22)**
Divorced/Separated	10 (4.2%)	6 (5.6%)	2.96 (0.92-9.47)
Widowed	31 (12.9%)	30 (27.8%)	**4.77 (2.22-10.23)**
Highest Level of Education			
None	18 (7.5%)	30 (27.8%)	**10.28 (3.63-29.13)**
Primary School	85 (35.4%)	47 (43.5%)	**3.41 (1.34-8.67)**
Secondary School	96 (40.0%)	22 (20.4%)	1.41 (0.53-3.76)
College/University	37 (15.4%)	6 (5.6%)	ref
Unknown	4 (1.7%)	3 (2.8%)	--
Occupation/Type of Work, n	240	107	
Farmer	69 (28.8%)	49 (45.8%)	**2.35 (1.14-4.83)**
Small-Business/Self-Employed	34 (14.2%)	24 (22.4%)	**2.33 (1.04-5.25)**
Unemployed	43 (17.9%)	13 (12.1%)	ref
Skilled labor	28 (11.7%)	10 (9.3%)	1.18 (0.46-3.06)
Student	21 (8.8%)	1 (0.9%)	0.16 (0.02-1.29)
Driver (bus, car, motorcycle)	13 (5.4%)	2 (1.9%)	0.51 (0.10-2.55)
Casual labor	12 (5.0%)	5 (4.7%)	1.38 (0.41-4.64)
Teacher	6 (2.5%)	1 (0.9%)	0.55 (0.06-5.01)
Healthcare worker	4 (1.7%)	0 (0.0%)	--
Retired	10 (4.2%)	2 (1.9%)	0.66 (0.13-3.41)
Tobacco Use			
Never smoked	192 (80.0%)	58 (53.7%)	ref
Current or Former	48 (20.0%)	50 (46.3%)	**3.45 (2.11-5.65)**
If yes, amount (sticks/day)	7.5 (2.5, 20.0)	7.0 (4.0, 20.0)	
Marijuana use			
No	230 (95.8%)	103 (95.4%)	ref
Yes	10 (4.2%)	5 (4.6%)	1.12 (0.37-3.35)
Primary cook for household			
No	35 (14.6%)	21 (19.4%)	1.41 (0.78-2.57)
Yes	205 (85.4%)	87 (80.6%)	ref
Cooking Fuel Type			
Firewood	175 (72.9%)	87 (80.6%)	1.66 (0.83-3.32)
Charcoal	25 (10.4%)	9 (8.3%)	1.20 (0.44-3.26)

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Other	40 (16.7%)	12 (11.1%)	ref
Gas	38 (15.8%)	11 (10.2%)	--
Kerosene or Electricity	2 (0.8%)	1 (0.9%)	--
Elevation of ward of primary residence (meters), n	212	95	
	1944.2 (1768.2, 2114.8)	2015.3 (1905.8, 2242.7)	**100m increase (<2000m): 1.33 (1.12-1.58)** 100m increase (>2000m): 0.99 (0.87-1.13)

Data presented as count (percentage) or median (Q1,Q3)
BMI = body mass index; NHIF = National Health Insurance Fund;

***Baseline characteristics stratified by sex are available in Supplementary Material**

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Table 2: Clinical Variables for Chronically Hypoxemic Cases & Non-Hypoxemic Controls*

Clinical Variable	Non-Hypoxemic Controls (N=240)	Chronically Hypoxemic Cases (N=108)	Unadjusted Odds Ratio (95% CI)
Diagnosis of Tuberculosis			
No	213 (88.8%)	68 (63.0%)	ref
Yes, Current Active Tuberculosis	14 (5.8%)	6 (5.6%)	1.34 (0.50-3.63)
Yes, Prior Tuberculosis	13 (5.4%)	34 (31.5%)	**8.19 (4.09-16.41)**
HIV Testing Results			
Never done/unavailable	100 (41.7%)	37 (34.3%)	0.77 (0.37-1.61)
Negative	111 (46.3%)	57 (52.8%)	1.06 (0.52-2.17)
Positive	29 (12.1%)	14 (13.0%)	ref
On Anti-retroviral therapy	25 (86.2%)	14 (100%)	
Anemia	41 (17.1%)	5 (4.6%)	**0.24 (0.09-0.61)**
Asthma	2 (0.8%)	11 (10.2%)	**13.49 (2.94-62.01)**
Chronic obstructive pulmonary disease (COPD)/ Emphysema	3 (1.3%)	55 (50.9%)	**81.97 (24.70-272.04)**
Cancer	55 (22.9%)	11 (10.2%)	**0.38 (0.19-0.76)**
Diabetes	36 (15.0%)	8 (7.4%)	0.45 (0.20-1.01)
Heart disease (including heart failure, rheumatic disease, congenital, arrythmias, etc)	47 (19.6%)	50 (46.3%)	**3.54 (2.16-5.81)**
Hypertension	66 (27.5%)	32 (29.6%)	1.11 (0.67-1.83)
Kidney disease	51 (21.3%)	10 (9.3%)	**0.38 (0.18-0.78)**
Lung fibrosis	1 (0.4%)	16 (14.8%)	**41.56 (5.43-317.91)**
Pneumonia	16 (6.7%)	18 (16.7%)	**2.80 (1.37-5.73)**
Pulmonary Embolus, treated	3 (1.3%)	6 (5.6%)	**4.82 (1.18, 19.64)**
Pulmonary Hypertension/ Cor Pulmonale	5 (2.1%)	57 (52.8%)	**52.53 (20.05-137.60)**
Sickle Cell Anemia	2 (0.8%)	0 (0.0%)	--
Stroke	16 (6.7%)	5 (4.6%)	0.68 (0.24-1.91)
Thyroid disease	5 (2.1%)	3 (2.8%)	1.34 (0.32-5.72)
Prior Hospitalization, n	239	108	
Yes	160 (66.9%)	88 (81.5%)	**2.17 (1.25-3.79)**
Number in the last year	1 (0,2)	1 (1, 3)	
Same problem as current admission	104 (65.4%)	71 (80.7%)	
Laboratory Values (Continuous)			**p-value**
WBC (x 10^9/L), n	236	105	0.26
	7.7 (5.4, 11.2)	7.0 (5.3, 9.6)	
Hemoglobin (gm/dl), n	236	105	**<0.001**
	11.1 (8.6, 13.6)	14.2 (12.4, 16.4)	
Hematocrit (%), n	236	104	**<0.001**
	32.9 (24.9, 40.0)	42.5 (37.5, 49.7)	
Platelets (per mm^3), n	235	104	0.11
	244.0 (164.0, 345.0)	220.0 (159.0, 298.5)	
Creatinine (mg/dL), n	234	106	**0.011**
	0.9 (0.6, 1.5)	0.8 (0.6, 1.1)	
Albumin (g/dL), n	195	88	0.39
	3.3 (2.7, 3.8)	3.4 (3.0, 3.7)	
PaCO2 (mmHg), n	39	37	**<0.001**

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	25.0 (20.3, 32.2)	48.6 (34.0, 55.9)	

Data presented as count (percentage) or median (Q1,Q3)

*Baseline characteristics stratified by sex are available in Supplementary Material

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Table 3: Association of Chronic Hypoxemia with Discharge and Mortality Outcomes

Outcome	Non-Hypoxemic Controls (N=240)	Chronically Hypoxemic Cases (N=108)	p-value
Admission Length of Stay (days)	8 (4, 15)	11 (6, 18.5)	**0.014**[1]
Mortality Rate at Discharge	33 (13.8%)	18 (16.7%)	0.48[1]
Outcome at 1-month phone follow-up, n	206*	90	**0.002**[2]
Alive and at home	175 (84.9%)	61 (67.8%)	
Alive, but re-hospitalized	10 (4.9%)	14 (15.6%)	
Deceased	21 (10.2%)	15 (16.7%)	
Time to phone follow-up from discharge (days)	34 (29, 46)	32 (28, 38)	0.033[1]

Data presented as median (Q1,Q3) or count (percentage).
*1 participant with missing follow-up status due to lack of phone or contacts

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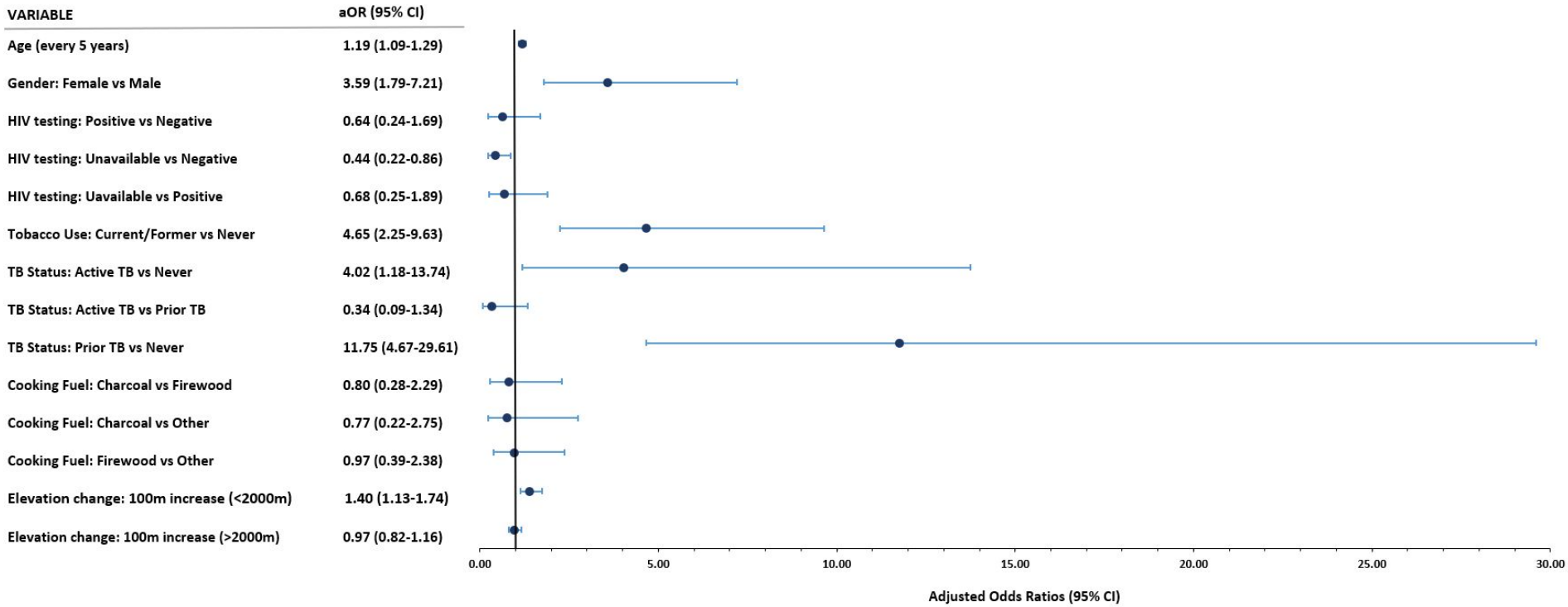
Figure 2: Forest plot showing results of multivariable logistic regression model estimating the odds of each exposure, comparing chronically hypoxemic cases to non-hypoxemic controls



*Model includes age, gender, HIV testing results, tobacco use, tuberculosis (TB) status, cooking fuel type, and elevation change.

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Table 4: Follow-Up Characteristics & Resource Availability of Chronically Hypoxemic Cases

Variable	Chronically Hypoxemic Cases (N=108)
Receiving supplemental oxygen on admission	
No	45 (41.7%)
Yes	63 (58.3%)
Amount of supplemental oxygen (LPM)	6 (5, 10)
Oxygen Saturation (SpO2) on Room Air	
On Admission, n	108
	75.9 (9.0)
At Discharge, n	84
	80.2 (7.2)
At Follow-Up Visit, n	70
	79.2 (6.3)
Using home oxygen on admission	10 (9.3%)
Did anyone from your care team discuss home oxygen with you?	n=90
No	49 (54.4%)
Yes	41 (45.6%)
Ability to obtain home oxygen	n=41
No, cannot afford oxygen	7 (17.1%)
Yes, it has been purchased	13 (31.7%)
Maybe, will try to obtain	16 (39.0%)
Other	5 (12.2%)
Electricity in participant's home	
No	60 (55.6%)
Yes	48 (44.4%)
Power outages per week	
None	3 (6.3%)
1-2 times per week	36 (75.0%)
3-4 times per week	4 (8.3%)
5-6 times per week	5 (10.4%)
Every day	0 (0.0%)
Average duration of power outages	n=45
< 1 hour	10 (22.2%)
1-4 hours	15 (33.3%)
4-8 hours	7 (15.6%)
> 8 hours	13 (28.9%)
Owns generator	3 (2.8%)

Data presented are count (percentage) or mean (SD)

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Online Data Supplement

Tuberculosis is Associated with Chronic Hypoxemia among Kenyan Adults (CHAKA): A Case-Control Study

Neelima Navuluri, MD, MPH, Peter S. Kussin, MD, Joseph R. Egger, PhD, Elcy Birgen, BsC, Sylvia Kitur, Nathan M. Thielman, MD, Alice Parish, MSPH, Cynthia L. Green, PhD, Mark M. Janko, PhD, Lameck Diero, Kara Wools-Kaloustian, MD, David Lagat, MD, Loretta G. Que, MD

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Table E1: Baseline Characteristics of Non-Hypoxemic Controls and Chronically Hypoxemia Cases, Stratified by Sex

Variable	Male Non-Hypoxemic Controls (N=134)	Female Non-Hypoxemic Controls (N=106)	Male Hypoxemic Cases (N=42)	Female Hypoxemic Cases (N=66)
Age, years	42.2 (29.9, 63.8)	41.8 (27.8, 61.8)	51.8 (41.7, 66.6)	68.2 (46.8, 80.9)
BMI, kg/m²	N=99	N=88	N=39	N=52
	20.5 (19.0, 22.8)	21.5 (18.8, 25.1)	19.2 (16.3, 25.0)	22.4 (17.7, 26.5)
Insured via NHIF	80 (59.7%)	63 (59.4%)	33 (78.6%)	44 (67.7%)
Marital Status				
Single	41 (30.6%)	28 (26.4%)	4 (9.5%)	10 (15.2%)
Married	80 (59.7%)	50 (47.2%)	30 (71.4%)	28 (42.4%)
Divorced/Separated	4 (3.0%)	6 (5.7%)	3 (7.1%)	3 (4.5%)
Widowed	9 (6.7%)	22 (20.8%)	5 (11.9%)	25 (37.9%)
Highest Level of Education				
None	9 (6.7%)	9 (8.5%)	6 (14.3%)	24 (36.4%)
Primary School	44 (32.8%)	41 (38.7%)	20 (47.6%)	27 (40.9%)
Secondary School	59 (44.0%)	37 (34.9%)	11 (26.2%)	11 (16.7%)
College/University	22 (16.4%)	15 (14.2%)	4 (9.5%)	2 (3.0%)
Unknown	0 (0.0%)	4 (3.8%)	1 (2.4%)	2 (3.0%)
Occupation/Type of Work	N=134	N=106	N=42	N=65
Farmer	32 (23.9%)	37 (34.9%)	10 (23.8%)	39 (60.0%)
Small-Business/Self-Employed	18 (13.4%)	16 (15.1%)	12 (28.6%)	12 (18.5%)
Unemployed	18 (13.4%)	25 (23.6%)	5 (11.9%)	8 (12.3%)
Skilled labor	22 (16.4%)	6 (5.7%)	8 (19.0%)	2 (3.1%)
Student	11 (8.2%)	10 (9.4%)	1 (2.4%)	0 (0.0%)
Driver (bus, car, motorcycle)	13 (9.7%)	0 (0.0%)	2 (4.8%)	0 (0.0%)
Casual labor	8 (6.0%)	4 (3.8%)	2 (4.8%)	3 (4.6%)
Teacher	3 (2.2%)	3 (2.8%)	0 (0.0%)	1 (1.5%)
Healthcare worker	2 (1.5%)	2 (1.9%)	0 (0.0%)	0 (0.0%)
Retired	7 (5.2%)	3 (2.8%)	2 (4.8%)	0 (0.0%)
Tobacco Use				
Never smoked	92 (68.7%)	100 (94.3%)	14 (33.3%)	44 (66.7%)
Current or Former	42 (31.3%)	6 (5.7%)	28 (66.7%)	22 (33.3%)
If yes, amount (sticks/day)	6.0 (2.0, 15.0)	15.0 (8.0, 20.0)	12.5 (4.5, 20.0)	5.0 (4.0, 8.0)
Marijuana use				
No	125 (93.3%)	105 (99.1%)	37 (88.1%)	66 (100.0%)

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Yes	9 (6.7%)	1 (0.9%)	5 (11.9%)	0 (0.0%)
Primary cook for household				
No	32 (23.9%)	3 (2.8%)	14 (33.3%)	7 (10.6%)
Yes	102 (76.1%)	103 (97.2%)	28 (66.7%)	59 (89.4%)
Cooking Fuel Type				
Firewood	94 (70.1%)	81 (76.4%)	32 (76.2%)	55 (83.3%)
Charcoal	15 (11.2%)	10 (9.4%)	6 (14.3%)	3 (4.5%)
Other				
Gas	23 (17.2%)	15 (14.2%)	3 (7.1%)	8 (12.1%)
Kerosene or Electricity	2 (1.4%)	0 (0.0%)	1 (2.4%)	0 (0.0%)
Elevation of ward of primary residence (meters)	N=118	N=94	N=37	N=58
	1920.8 (1767.1, 2095.4)	1960.4 (1786.8, 2138.5)	2024.2 (1864.1, 2261.9)	2015.2 (1920.3, 2215.8)

Data presented as count (percentage) or median (Q1,Q3)
BMI = body mass index; NHIF = National Health Insurance Fund;

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Table E2: Clinical Variables for Chronically Hypoxemic Cases & Non-Hypoxemic Controls, Stratified by Sex

Clinical Variable	Male Non-Hypoxemic Controls (N=134)	Female Non-Hypoxemic Controls (N=106)	Male Hypoxemic Cases (N=42)	Female Hypoxemic Cases (N=66)
Diagnosis of Tuberculosis				
No	123 (91.8%)	98 (92.5%)	25 (59.5%)	46 (69.7%)
Yes, Current Active Tuberculosis	6 (4.5%)	8 (7.5%)	4 (9.5%)	2 (3.0%)
Yes, Prior Tuberculosis	10 (7.5%)	3 (2.8%)	16 (38.1%)	18 (27.3%)
HIV Testing Results				
Never done/unavailable	53 (39.6%)	47 (44.3%)	14 (33.3%)	23 (34.8%)
Negative	69 (51.5%)	42 (39.6%)	23 (54.8%)	34 (51.5%)
Positive	12 (9.0%)	17 (16.0%)	5 (11.9%)	9 (13.6%)
Anemia	24 (17.9%)	17 (16.0%)	3 (7.1%)	2 (3.0%)
Asthma	2 (1.5%)	0 (0.0%)	5 (11.9%)	6 (9.1%)
Chronic obstructive pulmonary disease (COPD)/ Emphysema	2 (1.5%)	1 (0.9%)	18 (42.9%)	37 (56.1%)
Cancer	33 (24.6%)	22 (20.8%)	4 (9.5%)	7 (10.6%)
Diabetes	15 (11.2%)	21 (19.8%)	3 (7.1%)	5 (7.6%)
DVT or Pulmonary Embolus (PE)	6 (4.5%)	8 (7.5%)	0 (0.0%)	8 (12.1%)
Heart disease (including heart failure, rheumatic disease, congenital, arrythmias, etc)	22 (16.4%)	25 (23.6%)	22 (52.4%)	28 (42.4%)
Hypertension	35 (26.1%)	31 (29.2%)	12 (28.6%)	20 (30.3%)
Kidney disease	33 (24.6%)	18 (17.0%)	6 (14.3%)	4 (6.1%)
Lung fibrosis	1 (0.7%)	0 (0.0%)	8 (19.0%)	8 (12.1%)
Pneumonia	8 (6.0%)	8 (7.5%)	7 (16.7%)	11 (16.7%)
Pulmonary Hypertension/ Cor Pulmonale	2 (1.5%)	3 (2.8%)	19 (45.2%)	38 (57.6%)
Sickle Cell Anemia	1 (0.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Stroke	7 (5.2%)	9 (8.5%)	1 (2.4%)	4 (6.1%)
Thyroid disease	3 (2.2%)	2 (1.9%)	0 (0.0%)	3 (4.5%)
Prior Hospitalization, n	134	105	42	66
Yes	90 (67.2%)	70 (66.7%)	38 (90.5%)	50 (75.8%)
Number in the last year	1 (0,2)	1 (0,2)	1 (0,3)	1 (0,2)
Same problem as current admission	59 (66.3%)	45 (64.3%)	34 (89.5%)	37 (74.0%)
Laboratory Values (Continuous)				
WBC (x 10^9/L), n	131	105	39	66

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	7.3 (5.4, 10.6)	7.9 (5.2, 11.9)	7.1 (5.0, 10.1)	6.9 (5.4, 9.5)
Hemoglobin (gm/dl), n	131	105	39	66
	10.9 (8.4, 14.3)	11.2 (9.5, 13.2)	14.2 (12.1, 15.1)	14.7 (12.4, 16.5)
Hematocrit (%), n	131	105	39	65
	32.7 (23.9, 41.2)	33.6 (26.2, 38.9)	41.9 (37.6, 48.5)	44.1 (37.4, 50.0)
Platelets (per mm^3), n	131	104	39	65
	226.0 (149.0, 298.0)	276.0 (210.0, 406.5)	228.0 (145.0, 297.0)	215.0 (160.0, 301.0)
Creatinine (mg/dL), n	130	104	40	66
	1.0 (0.7, 2.2)	0.7 (0.6, 1.1)	0.8 (0.7, 1.2)	0.8 (0.6, 1.0)
Albumin (g/dL), n	109	86	35	53
	3.4 (2.8, 4.0)	3.1 (2.6, 3.6)	3.3 (2.8, 3.7)	3.4 (3.0, 3.8)
PaCO2 (mmHg), n	22	17	15	22
	27.5 (21.4, 33.2)	24.2 (17.3, 26.5)	42.1 (27.6, 61.4)	50.5 (36.4, 55.9)
Data presented as count (percentage) or median (Q1,Q3)				

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Table E3: Demographic and Co-Morbidity Risk Factors for Chronic Hypoxemia, Sensitivity Analysis to Include Chronic Lung and Heart Disease

	Hypoxemic Cases (n=108)	Non-hypoxemic Controls (n=240)	Multivariable OR (95% CI)
Age, years (*per 5-year increase for OR*)	60.5 (19.7)	46.0 (19.6)	**1.09 (1.00, 1.04)**
Female (versus Male)	66 (61.1%)	106 (44.2%)	**2.97 (1.27, 6.98)**
Current or Former Tobacco Use (versus Never smoked)	50 (46.3%)	48 (20.0%)	1.77 (0.70, 4.44)
Biomass Fuel Use			
Firewood	87 (80.6%)	175 (72.9%)	1.33 (0.38, 4.60)
Charcoal	9 (8.3%)	25 (10.4%)	0.97 (0.19, 5.02)
Other *(gas, kerosene, electric*)	12 (11.1%)	40 (16.7%)	reference
Tuberculosis History			
Active Tuberculosis	6 (5.6%)	14 (5.8%)	2.83 (0.75, 10.74)
Prior Tuberculosis	34 (31.5%)	13 (5.4%)	**6.35 (2.09, 19.29)**
No Tuberculosis Ever	68 (63.0%)	213 (88.8%)	reference
HIV Diagnosis			
Positive	14 (13.0%)	29 (12.1%)	0.6 (0.3, 1.6)
Unknown	37 (34.3%)	100 (41.7%)	0.5 (0.3, 1.0)
Negative	57 (52.8%)	111 (46.3%)	reference
Chronic Lung Disease (including asthma, COPD, lung fibrosis and/or pulmonary hypertension)	81 (75.0%)	9 (3.75%)	**46.98 (18.84, 117.12)**
Chronic Heart Disease	50 (46.3%)	47 (19.6%)	1.46 (0.63, 3.36)

Model includes age, sex, tobacco use, biomass fuel use, tuberculosis history, HIV diagnosis, chronic lung disease, and chronic heart disease.

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