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Early View

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A multi-country cohort study evaluating the prevalence, risk factors, lung function and clinical outcomes of chronic bronchitis in low- and middle-income countries

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Running Title: chronic bronchitis in low- and middle-income countries

Keywords: chronic bronchitis, prevalence, risk factors, lung function, low- and middle-income countries

Take Home Message: We found there was a high burden of chronic bronchitis in LMICs with comorbid asthma, second-hand smoke, biomass, and prior TB exposure as chronic bronchitis risk factors. Chronic bronchitis carried increased respiratory symptoms and worse quality of life.

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ABSTRACT

Background: Chronic bronchitis affects up to 40% of individuals with COPD and may serve as an early predictor of the disease and development of COPD. We investigated the prevalence, risk factors, and clinical outcomes associated with chronic bronchitis in three low- and middle-income countries (LMICs).

Methods: We conducted a population-based study of adults aged ≥40 years in Bhaktapur (Nepal), Lima (Peru), and Nakaseke (Uganda). Chronic bronchitis was defined as a productive cough several days per week for over four weeks. Multivariable log-binomial regression identified risk factors and outcomes associated with chronic bronchitis.

Results: Among 9,664 participants (mean age 56.2 years, 51.0% male, 66.9% ever smokers), chronic bronchitis prevalence was 9.7%, with 31.5% of those also having COPD. Significant risk factors included older age (adjusted RR=1.54 per 19.8 years, 95% CI 1.4–1.7), male sex (1.18, 1.05–1.34), prior tuberculosis (1.45, 1.14–1.83), prior asthma diagnosis (2.11, 1.84–2.42), pack-years of tobacco use (1.16 per 10 pack-years, 1.14–1.18), family history of chronic respiratory diseases (1.69, 1.50–1.91), second-hand smoke exposure (1.45, 1.28–1.64), lower socioeconomic status quartile (1.22,1.07–1.39), and indoor biomass exposure (1.45, 1.13–1.64). Participants with chronic bronchitis experienced more breathlessness, worse respiratory health (higher St. George's Respiratory Questionnaire scores), and higher hospitalization rates (all $p<0.001$).

Conclusions: Chronic bronchitis is common in LMIC settings and is associated with multiple modifiable risk factors, including second-hand smoke, biomass exposure, and prior respiratory disease. Addressing these factors may reduce disease burden and improve quality of life.

Word Count: 245

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition with several overlapping phenotypes.[1] One such phenotype is chronic bronchitis, which is characterized by inflammation and irritation of the large airways leading to excessive mucus production and persistent cough. In contrast to COPD, chronic bronchitis is a clinical diagnosis that does not require spirometry for confirmation. It was classically defined as a productive cough for at least three months duration in two consecutive years [2]; however, recent studies have advocated using a simpler definition based on chronic productive cough in an attempt to ease its recognition.[3] In large epidemiological studies, the prevalence of chronic bronchitis varies widely from 6% to 27% [4]; this is in part due to the use of varying definitions, all of which hampers our understanding of the condition.

As a result, variations in the definitions of chronic bronchitis further complicate our understanding of chronic bronchitis and make it difficult to recognize and identify associated risk factors. Prior research has identified risk factors including tobacco smoke exposure rural residence, cooking with biomass, occupational dust exposure, lower educational attainment, and comorbid tuberculosis.[5] Chronic bronchitis risk factors are of disproportionately high prevalence in low- and middle-income country (LMIC) settings and may further influence chronic bronchitis prevalence.[6-9] A prior study in China found a high frequency of underdiagnosis of chronic bronchitis, so better understanding of chronic bronchitis risk factors may lead to further recognition in LMIC settings.[10, 11]

It is well recognized that chronic productive cough may be an important manifestation of COPD; however, not everyone with COPD has chronic bronchitis.[10, 11] While chronic bronchitis may affect up to 40% of patients with COPD, there remains a population of individuals with chronic bronchitis that do not have airflow obstruction.[4, 12-15] Emerging research now suggests that chronic bronchitis may be an early predictor of COPD in some individuals and represent a subgroup of patients with increased risk of developing COPD.[16-19]. In the Latin-American Pulmonary Obstruction Investigation Project (PLATINO) study, chronic cough and sputum production were independent predictors of COPD development, and having chronic bronchitis symptoms was associated with three times the risk of COPD diagnosis compared to those without symptoms.[16] There are limited data identifying populations with chronic bronchitis and evaluating the relationship between chronic bronchitis and COPD development. Identifying this at-risk population for COPD through early detection may impact clinical course.

Early recognition of chronic bronchitis is vital to improve clinical outcomes and improve quality of life. Among patients with COPD, individuals with chronic bronchitis had worse clinical outcomes including lung function decline[20], a higher rate of exacerbations,[14, 16, 21] prolonged length-of-stay for hospitalizations,[22] and higher all-cause mortality.[3, 18, 22] These poor clinical outcomes associated with chronic bronchitis may further impact health-related quality of life [15]. The Burden of Obstructive Lung Disease (BOLD) study found that people with chronic bronchitis had significantly higher physical and mental health impact compared to chronic airflow obstruction and asthma.[23] Aside from the BOLD study, there are limited data of these outcomes in LMIC settings. Emerging research is shifting to focus on environmental factors and clinical outcomes associated with chronic bronchitis. Moreover, limited population-based data evaluating the prevalence of COPD in individuals with or without chronic bronchitis and associated risk factors for the chronic bronchitis phenotype are available.

We sought to examine the prevalence, risk factors, lung function, and clinical outcomes of chronic bronchitis in LMICs by leveraging the population-based multi-national Global Excellence in COPD (GECo) study in three LMIC settings.

MATERIALS AND METHODS

Study setting and design

This study is a secondary analysis of the Global Excellence in COPD outcomes (GECo) study, a multi-national, population-based study aimed at developing cost-effective models of COPD diagnosis and care using data for 10,709 participants from three geographically diverse LMIC settings: Bhaktapur, Nepal; Lima, Peru; and Nakaseke, Uganda.[24, 25] We used available household census data at each site to recruit a random, age- (45–49, 50–54, 55–64, 65–95 years) and sex-stratified sample between January 5, 2018, and March 9, 2020. Only one participant per household was selected to participate in the study. The sample size justification for the parent study was described in detail elsewhere.[24] Eligibility criteria were: age ≥40 years, able and willing to perform spirometry, and full-time resident for at least six months in the study area, not pregnant, absence of active pulmonary tuberculosis, and did not have contraindications to perform spirometry (blood pressure higher than 180/100 mmHg or pulse > 120 beats/min; eye, thoracic surgery or abdominal surgery or a myocardial infarction in the last three months). We obtained written informed consent prior to enrolment in the local language.

Our study was approved by the ethics committees of University College London in the UK, the School of Medicine at Johns Hopkins University in Baltimore, USA, the Nepal Health Research Council in Kathmandu, Nepal, A.B. PRISMA in Lima, Peru, and the Uganda National Council for Science and Technology and the Makerere School of Medicine in Kampala, Uganda.

Data Collection

Trained research personnel collected socio-demographic information, self-reported past medical history, and exposure history. Indoor air pollution was self-reported by participants as harmful pollutants in enclosed spaces such as sources from cooking fuels, tobacco smoke, and household products. Participants self-reported regular medication use of short- and long-acting bronchodilators, anticholinergics, inhaled corticosteroids, and xanthines. We translated study questionnaires into local languages (Nepali in Nepal, Spanish in Peru, and Luganda in Uganda), back translated, and verified by respective research teams. Participants self-reported symptoms and healthcare interactions including hospitalizations or exacerbations requiring medical intervention. We evaluated health-related quality of life with validated questionnaires, the St. George's Respiratory Questionnaire (SGRQ) [26-28] and the EQ-5D.[29-31] Standardized biometric data including height, weight, and vitals were collected in triplicate.

Definition of chronic bronchitis

We defined chronic bronchitis in participants using the SGRQ definition, which was defined as symptoms questions in the SGRQ such as "Over the past four weeks, I have coughed …" and "Over the past four weeks, I have brought up phlegm…," and defined chronic bronchitis in participants who self-reported having both symptoms "almost every day" or "several days a week." The SGRQ definition of chronic bronchitis has been used recently in COPDGene and SPIROMICS studies. [15, 32] We report the classic chronic bronchitis definition in a secondary analysis as self-reported having a productive cough lasting most days in a month lasting for three months duration with at least two of these episodes within a span of two years.[33-35]

Assessment of lung function

We performed spirometry using the Easy-One spirometer (EasyOne Air, ndd, Zurich, Switzerland) following standard guidelines.[36] We conducted post-bronchodilator spirometry 15-20 minutes after administration of 400 mcg of salbutamol. Research assistants encouraged participants to exhale for at least 6 seconds (and preferably longer to meet end of forced expiration) during spirometry testing to maximize the likelihood of obtaining a complete expiratory maneuver, Participants were not excluded based solely on forced expiratory time under six seconds. We calculated Z-scores based on the 2012 Global Lung Function Initiative mixed ethnic reference population [37] and defined COPD as a post-

bronchodilator FEV_1/FVC Z-score < -1.645 standard deviations (SDs). [38] We excluded lung function values less than -6 or greater than 6 SDs as implausible values. In sensitivity analyses, we defined COPD as a post-bronchodilator FEV_1/FVC <0.7. [39]

Development of a socioeconomic status index

Socioeconomic status is an important determinant of chronic respiratory diseases[40]; however, we have yet to identify a simple method to calculate a country-wide index. For this study, we developed site-specific indices using multiple correspondence analyses applied to harmonized household-level indicators of education, assets, and living conditions. Variables that were used in our analyses include information on water and sanitation, cooking and construction characteristics (clean stove, covered floor, no crowding), availability of electricity, health insurance, education, and ownership of assets such as a mattress, chair, table, television, refrigerator, and bank account. Missingness was less than 1% for all variables and 2.5% of participants were missing any of the variables we used in our analysis. We used iterative expectation-maximization (EM) algorithm implemented through the missMDA package. MCA was performed separately for each site to accommodate country-specific variation in asset distributions. For each site, the first principal dimension captured the majority of variance (Peru 13.9%, Uganda 17.0%, Nepal 19.4%) and corresponded to increasing ownership of assets and improved household conditions. The first component score was scaled between 0 and 1, where higher SES index values reflect lower socioeconomic status (worse SES). Finally, each country's SES index was categorized into quartiles, with participants in the upper quartile of the SES index identified as the lowest-SES group for subsequent analyses.

Biostatistical methods

The primary analytical aim was to characterize the prevalence of chronic bronchitis and identify risk factors and clinical outcomes associated with the condition. We first calculated overall and site-, age- and sex-stratified prevalence of chronic bronchitis and stratified by COPD status. We used Welch's analysis of variance (for continuous variables) and chi-square tests (for dichotomous or categorical values) to compare differences in socio-demographic factors by study sites.

We then built exact log-binomial regression models to identify risk factors with chronic bronchitis as the outcome.[41] We used a multivariable exact log-binomial regression with chronic bronchitis as the outcome as a function of *a priori* identified risk factors: age, male sex, self-reported prior diagnosis of asthma, pack-years of tobacco use, second-hand smoke exposure, self-reported history of tuberculosis, family history of chronic respiratory diseases (CRDs), the lowest SES index quartile, and indoor biomass cooking by site. Age and pack-years of tobacco smoking were included as continuous variables and scaled to the interquartile range (in the case of age) or to 10-pack years (in the case of pack-years of tobacco smoking). We obtained relative risk estimates and corresponding 95% confidence intervals (CIs) for each risk factor from the regression coefficients. We acknowledge that risk factors may vary by site. To determine the relative order of risk factor importance by site, we built site-specific conditional random forest analyses [42] and estimated variable relative importance for the nine risk factors. Tuning of the conditional random forest based on classification accuracy resulted in setting the selection of the random set of variables to 2 and number of trees to 2000.

For our secondary analysis, we evaluated the lung function and clinical outcomes stratified by chronic bronchitis status. We compared lung function reported as absolute value (litres) and Z-scores for post-bronchodilator FEV_1, FVC, and FEV_1/FVC. We compared clinical outcomes including (1) respiratory symptoms evaluated by the modified Medical Research Council (mMRC) dyspnea score, (2) respiratory symptoms impeding daily activities in the past year, and lung function questionnaire (LFQ); (2) health-related quality of life assessed by SGRQ and EQ-5D; and (3) hospitalization that was self-reported in the past 12 months as

surrogate measures for clinical outcomes. Clinically significant dyspnea was defined using the minimally clinically important difference [MCID] with an mMRC dyspnea score of ≥2. [30, 43] Similarly, using the MCID a clinically significant EQ-5D of higher health-related quality of life was defined as an EQ-5D score ≥ 0.50.[31] Total LFQ scores of ≤ 18 was utilized as a surrogate measure of symptomatic airway obstruction with prior studies noting negative predictive value of 90% and validation in a cohort study compared to spirometry.[44] Using logistic regression, we evaluated clinical outcomes of chronic bronchitis adjusted for potential confounders (age, sex, employment, education, history of tuberculosis, family history of CRD, tobacco use, and cooking indoors with biomass). We aimed to predict clinical outcomes of chronic bronchitis. Clinical outcomes include hospitalization, LFQ ≤18, mMRC dyspnea score ≥ 2, and respiratory symptoms impeding daily activities in the last year.

We conducted statistical analyses in R version 4.3.2.[45] Statistical outputs and supplementary tables and figures are included in the Online Supplement.

RESULTS

Participant characteristics

We enrolled 10,709 participants. Post-bronchodilator spirometry was missing in 45 (0.4%) participants and 648 (6.1%) did not meet quality criteria for spirometry. Of these 10,008 (90.2%) participants, 344 (3.4%) participants had missing or implausible values and were excluded from analyses with 9,664 (90.2%) participants remaining. There were differences in age (mean 58.7 vs. 56.2 years; p<0.001) and sex distribution (males 34.9% vs. 51.0%; p<0.0001) between the 9,664 participants who were included in the analysis and the 344 participants with missing or implausible values.

We summarized differences in participant characteristics by chronic bronchitis status in **Table 1**. Mean age was 56.2 (SD 11.7) years, 51.0% were male, and 66.9% were smokers. All participants self-reported lifetime biomass exposure. Participants with chronic bronchitis were older, more likely to be male, had a lower BMI, were less educated, unemployed, and had a greater number of years of past biomass exposure and pack-years of tobacco use (**Table 1**). Similar socio-demographic results were observed using the fixed definition of COPD (**Supplemental eTable 1**). Among the 934 participants with chronic bronchitis, participants with concurrent COPD were male, older, had a lower BMI, less educated, and had higher pack-years of tobacco use and years of biomass use (p < 0.05). We also compared the prevalence, key demographic characteristics and lung function between individuals classified with chronic bronchitis using the SGRQ-based definition and the classic definition (**Supplemental eTable 2**) as a sensitivity analysis. Prevalence of chronic bronchitis, sex distribution, and lung function differed significantly (p<0.05). Participants fulfilling the SGRQ-definition of chronic bronchitis had significantly lower lung function compared to the classic definition.

Prevalence of chronic bronchitis and lung function impairment

A total of 934 (9.7%) participants met criteria for chronic bronchitis using the SGRQ definition (**Table 2**). Nepal had the highest prevalence of chronic bronchitis at 21.2% and COPD (7.9%) coupled with the highest frequency of daily tobacco use and second-hand smoke exposure (**Supplemental eTable 3**). In Peru, the prevalence of chronic bronchitis was 5.4% and concurrently had the highest frequency of prior diagnosis of tuberculosis. Uganda had the lowest prevalence of chronic bronchitis at 1.7% with the highest proportion of current biomass use and lowest pack-years of tobacco (**Table 2**). In **Supplemental eTable 4** we include the prevalence, socio-demographic characteristics, and lung function using the GLI-Global reference equation with similar distribution of COPD among participants with chronic bronchitis.

Among participants with chronic bronchitis, 31.5% (n=294) participants had COPD using the lower limit of normal (LLN) definition compared to 36.2% (n=338) using the fixed definition. There was a higher proportion of COPD with older age and among males. Participants with chronic bronchitis with COPD had lower lung volumes including FEV_1 and FVC Z-scores compared to participants with chronic bronchitis without COPD (p<0.001) (**Table 2**).

Risk factors for chronic bronchitis

We summarized the adjusted relative risk of chronic bronchitis in **Figure 1 and Supplemental eTable 5**. In multivariable analysis, older age, male sex, a previous diagnosis of tuberculosis, a self-reported diagnosis of asthma, higher pack years of tobacco use, second-hand smoke exposure, family history of CRD, high SES index (indicating low SES), and indoor biomass exposure were associated with increased risk of chronic bronchitis (**Figure 1**). Indoor biomass exposure had 1.45 times higher risk of chronic bronchitis, which carried similar risk as second-hand smoke exposure. In ranking risk factors by site, the most influential risk factors in order of relative importance were comorbid asthma, pack-years, and age for Nepal; pack-years, prior tuberculosis diagnosis, and male sex for Peru; and prior tuberculosis diagnosis, comorbid asthma, and male sex in Uganda.

Clinical and health-related quality of life outcomes

We summarize respiratory symptoms and quality of life in **Table 3.** Participants with chronic bronchitis had a higher prevalence of respiratory symptoms as evaluated by elevated the mMRC dyspnea scores and reduced LFQ scores (p<0.001). We found that 47.3% (n=442) participants with chronic bronchitis reported clinically significant dyspnea (mMRC dyspnea score of ≥2) compared to 27.3% (n=2384) participants without chronic bronchitis (p<0.001). There was higher frequency of wheezing in the chronic bronchitis group compared to those without chronic bronchitis (34.3% vs. 22.8%, p<0.001).

Participants with chronic bronchitis also reported worse quality of life and clinical outcomes compared to participants without chronic bronchitis as measured by the EQ-5D, SGRQ, and patient-reported hospitalization outcomes. Participants without chronic bronchitis had higher quality of life as (EQ-5D score ≥ 0.50) compared to participants with chronic bronchitis (98.3% vs. 93.1%, respectively, p<0.001). Participants with chronic bronchitis had a higher rate of hospitalization over the past year, higher total and sub-score SGRQ scores, and higher frequency of respiratory symptoms that impede daily activities in the past year (**Table 3**). Uganda had the highest total SGRQ score (higher impairment in quality of life), largest burden of hospitalization, and increased frequency of respiratory symptoms impeded daily activities (**Supplemental eTables 6-8**). Meanwhile, Peru was characterized by the highest frequency of wheezing. Nepal had the lowest frequency of hospitalization and burden of respiratory symptoms impacting daily activities.

Among participants with chronic bronchitis, those with COPD had significantly higher frequency of respiratory symptoms, wheezing, and impediment of daily activities (p<0.05) **(Table 3)**. Among participants with chronic bronchitis, 67.3% of participants with COPD reported clinically significant dyspnea (mMRC dyspnea score ≥2) compared to 38.1% among participants without COPD (p<0.001). Participants with COPD and chronic bronchitis had higher total mean SGRQ scores indicating worse health-related quality of life compared to participants without COPD (p<0.001).

After adjustment, chronic bronchitis was associated with significantly higher odds of patient-reported reported respiratory symptoms that interfered with daily activities (adjusted OR=1.67, 95% CI 1.24–2.22, p<0.001). Chronic bronchitis was associated with clinically significant dyspnea, defined as mMRC dyspnea score ≥ 2 (adjusted OR=1.73, 95% CI 1.49–2.00, p<0.001). Similarly, chronic bronchitis was associated with increased odds of lung function questionnaire score ≤ 18, which is a cut point validated suggesting airflow obstruction (adjusted OR=2.40, 95% CI 2.02–2.85, p<0.001). However, chronic bronchitis

was not associated with increased odds of hospitalization in the past year (adjusted OR=1.28, 95% CI 0.79–1.99, p=0.30).

DISCUSSION

In this study, we found that the overall prevalence of chronic bronchitis in three diverse LMIC settings was 9.7%. Among those with chronic bronchitis, the prevalence of COPD was 31.5%. We identified predictors of chronic bronchitis as older age, male sex, prior tuberculosis diagnosis, diagnosis of asthma, a higher number of pack years of tobacco use, second-hand smoke exposure, family history of chronic respiratory disease, lower SES, and indoor biomass exposure. Furthermore, participants with chronic bronchitis had reduced quality of life, and increased respiratory symptoms compared to those without chronic bronchitis. These indicate results indicate a significant and clinically important burden of chronic bronchitis in LMIC settings.

Variability of chronic bronchitis prevalence among the current body of literature may be compounded by the types of definitions used. Prior studies have reported chronic bronchitis prevalence varying from 2 to 27% based on the specific definition employed and setting.[4, 5, 23, 46]

The classic definition likely overestimates chronic bronchitis prevalence compared to the SGRQ definition because it relief on self-reported symptoms without considering their impact on health status or quality of life. The classic definition is based solely on presence of cough and sputum for a defined duration and may not account for symptom severity, variability, or impact on daily function, potentially leading to the inclusion of milder or less clinically significant cases. The SGRQ definition incorporates symptom burden and functional impairment providing a more stringent and clinically relevant measure of disease. In our cohort, we found chronic bronchitis prevalence of 9.7% with SGRQ definition. The SGRQ definition of chronic bronchitis is most widely used in large trials and has been shown to identify more individuals with chronic bronchitis with high sensitivity and specificity [15, 32]. Furthermore, there was inter-site variability in the prevalence of chronic bronchitis, ranging from 21.2% in Bhaktapur and 5.4% in Lima to 1.7% in Nakaseke. A population-based study in Uganda found the age- and sex-stratified prevalence of chronic bronchitis was 3.5% in rural communities and 2.2% in urban communities with a high proportion of biomass use like our sample compared to 5.5% in a sample of five cities in Colombia.[5, 47] However, these estimates of chronic bronchitis may under-recognize its true burden in community settings as was previously reported in a population-based study in China.[10]

The interplay of risk factors of chronic bronchitis that are unique to each setting in LMICs may in part explain the prevalence of chronic bronchitis. Prior asthma diagnosis was consistently one of the most important variables for chronic bronchitis and was the most important risk factor in Nepal. Previous research suggests that a prior diagnosis of asthma, specifically in childhood, can increase the likelihood of developing chronic bronchitis.[48, 49] Childhood asthma has been associated with early reductions in lung function [50] that can persist to adulthood potentially putting the individual at greater risk of further lung injury and COPD development as evidenced prospectively in the Melbourne Asthma Cohort and WHEASE cohort.[51, 52] In the Canadian Cohort of Obstructive Lung disease (CanCOLD), the investigators found that self-reported diagnosis of asthma was associated with higher odds of mild COPD and moderate-severe COPD in a never smoking population.[53] Similarly, in the COPDGene cohort self-reported history of childhood asthma was associated with increased risk of COPD and suggests a possible genetic contribution between prior asthma diagnosis and chronic bronchitis.[54] These results may be extrapolated to chronic bronchitis as a phenotype of COPD. To our knowledge, we are the first to find an associated between self-reported healthcare provider diagnosed asthma and chronic bronchitis in LMICs, which may be explained by lung function decline from early in life and genetic influences that persist into adulthood. It is also possible that chronic bronchitis has been mislabelled as asthma due to barriers to healthcare access. However, this finding should be interpreted with caution as

asthma is a clinical diagnosis, and self-reported asthma diagnosis by a healthcare provider may be prone to misclassification, especially in resource-limited settings where diagnostic capability is variable.

We found that second-hand smoke carried higher odds of chronic bronchitis, but its importance was less than the cumulative exposure of personal tobacco smoking. Therefore, chronic bronchitis has been thought of as a prominent sequela of tobacco use with increased susceptibility and suggested to be a group of increased risk of COPD development. The population-based study in five Latin American cities (PLATINO) study included 5,314 participants in Central and South America found that the prevalence of classic definition chronic bronchitis was 3.1%, which was substantially lower than in our study. Among those with chronic bronchitis (classic definition) 7.4% had COPD and 2.5% did not have COPD.[16] Meanwhile a population-based study throughout China diagnosed chronic bronchitis in 7.4% with COPD and 2.5% without COPD.[10] In contrast to our study with low tobacco use (mean pack-years 2.6), the PLATINO study and population-based study in China had a high prevalence of tobacco use compounded by lower frequency of biomass exposure.[10, 16] Previous studies have also shown variation in prevalence of COPD within-country and between-country due to differences in prevalence of risk factors beyond tobacco smoking. When we analyse the presence of COPD among individuals with chronic bronchitis, we found that Uganda has the highest percentage (42.3%) while the Peru has the lowest (6.2%). The low prevalence of chronic bronchitis and high proportion of COPD among those with chronic bronchitis in Uganda may be due to low prevalence of smoking which is strongly associated with cough and sputum production and more predominant presence of other risk factors.

Smoking alone likely does not account for the higher prevalence of chronic bronchitis in LMIC settings. Male sex was an important predictor for chronic bronchitis in our study. Prior research has suggested that biomass cooking practices in rural LMIC settings primarily affect women may explain differences in chronic bronchitis, but this is an area of debate with conflicting findings by setting.[55, 56] Sex differences in chronic bronchitis have been mixed with male sex reported as a predictor of chronic bronchitis possibly explained by tobacco use patterns or occupational exposures.[10] However, a South African study found female sex as a strong predictor to chronic bronchitis potentially explained by greater biomass cooking exposure due to gender roles.[46] A cross-sectional study in Nigeria found that the mean daily biomass smoke exposure was significantly greater in females than males (1.51 vs. 1.06 hours, $p<0.0001$).[57] Furthermore, differences in intrathoracic deposition between tobacco and biomass smoke may further explain differences in COPD phenotypes and clinical outcomes.[58] Compared to tobacco smoke, biomass exposure is characterized by a slower lung function decline, greater airway involvement, and more respiratory symptoms.[59] While biomass shares many of the same components with tobacco smoke, differences in chemical components may lead to differences in risk and pathophysiological sequelae. We found biomass carried increased risk of chronic bronchitis and was an important risk factor in Uganda, where over 90% of households use solid biomass fuel and there is a high lifetime biomass exposure.[60] In India, prior research has found there is higher risk of developing chronic bronchitis was linked increasing cumulative biomass exposure with a significant dose-response relationship.[61] There is a well-studied association between biomass smoke exposure and COPD with prior meta-analyses finding that biomass exposure carried over two times increased risk of COPD along with biomass exposure associated with lung function decline.[62-64] Earlier research has primarily focused on the link between biomass exposure and the emphysematous phenotype of COPD rather than chronic bronchitis.[65, 66] A case-control study in Mexico found that wood biomass smoke was associated with 3.9 times increased odds of chronic bronchitis compared to healthy individuals.[67] Similarly, a cross-sectional study of 1,827 current smokers found wood smoke exposure was associated 1.64 times higher odds of chronic bronchitis.[68] Further large-scale studies are needed to

characterize the influence on varying levels of biomass exposure and prospective evaluation of development of chronic bronchitis.

There are limited studies in LMICs exploring risk factors of chronic bronchitis unique. Family history of CRDs was implicated as an important risk factor of chronic bronchitis at the three study sites. Early genetic studies have found genome wide association of chronic mucous hypersecretion with SNP on chromosome 3 among a population in the Netherlands.[69] A multinational pooled analysis of the COPDGene, GenKOLS, and ECLIPSE studies found a genome-wide locus of chromosome 11p15.5 among individuals with COPD and chronic bronchitis but this was compared to smoking controls.[70] There may be a genetic component to chronic bronchitis or partially mediated by comorbid asthma, but shared exposure experiences by families including tobacco and biomass smoke may compound the relationship between chronic bronchitis and family history of chronic respiratory diseases. Similarly, the multinational BOLD study found comorbid asthma and family history chronic lung disease were significant predictors of chronic bronchitis.[23] Screening for chronic bronchitis among populations with comorbid asthma or family history of CRDs may be key early intervention.

Research has been shifting towards exploring the overlap between chronic bronchitis phenotype and COPD. A population-based study in China found that 30% of individuals with COPD had chronic bronchitis. Chronic bronchitis is not a benign condition and when coupled with airflow obstruction, prior research found worse lung function, increased exacerbations and higher rates of mortality. [14, 16, 20, 71-73] The COPDGene study found that chronic bronchitis is a better predictor for COPD development than dyspnea further highlighting the importance of chronic bronchitis identification.[74] The PLATINO study reported higher frequency of respiratory symptoms (i.e., wheezing, dyspnea) and exacerbation rate (16.7% vs. 6.6%, respectively) among participants with chronic bronchitis compared to those without chronic bronchitis. While validated QoL measures such as the SGRQ and EQ-5D were not evaluated in PLATINO participants self-reported higher frequency of work limitation and leisure impairment among participants with chronic bronchitis.[16] Negative outcomes associated with chronic bronchitis without COPD further speaks to the clinical importance of chronic bronchitis even without airflow obstruction. We similarly found worse pulmonary and QoL outcomes associated with chronic bronchitis, and particularly chronic bronchitis with comorbid COPD. Participants with chronic bronchitis and COPD had significantly worse health-related QoL and outcomes compared participants with chronic bronchitis alone. Therefore, chronic bronchitis may represent a predictor of worsening lung function prior to COPD development, presenting an opportunity for early detection and intervention.

This study expands on limited research on prevalence of chronic bronchitis prevalence, risk factors, and clinical outcomes in LMICs. Our study of a large population age- and sex-stratified sample included quality controlled pre- and post-bronchodilator spirometry in three diverse settings. A strength is the use of the SGRQ definition of chronic bronchitis rather than the classic definition due to its wider use in both clinical and research settings. An additional advantage of using the SGRQ-based definition is the ease of implementation across large population-based studies, without requiring longitudinal data on symptom duration, which is often unavailable in LMIC settings. This allows for standardized, validated symptom measurement linked to key clinical outcome such as health-related QoL, exacerbation risk, and mortality.[15, 32] However, a disadvantage is the short symptom recall duration (4 weeks), which may reduce specificity for identifying individuals with chronic symptoms. Despite these limitations the SGRQ-based definition enables cross-cohort comparability and aligns with COPDGene and SPIROMICS studies.[15, 32] This study has some potential limitations. Chronic bronchitis diagnosis was self-reported by participants at one time point at the baseline study visit, which was subject to recall bias and cultural understanding. Chronic bronchitis may not be a consistent feature over time.[75] We limited bias by piloting questionnaires with community members during the formative phase to

incorporate culturally acceptable terminology and back-translated questionnaires in the primary language of each study site. Second, although participant occupation was recorded, detailed data on specific occupational exposures (i.e., dust, fumes, chemicals) were not collected, limiting our ability to assess the impact of occupational risk factors on chronic cough. Furthermore, past medical history of comorbid diagnoses diagnosed by a healthcare provided was self-reported by participants. A limitation of symptom-based definitions leads to potential inclusion of participants with other etiologies of cough and sputum production such as asthma, bronchiectasis, acute post-viral illness, or medication side effect (i.e., ACE inhibitor), particularly give 4-week symptom recall period. Diagnostic capabilities are often limited in resource limited settings and may underestimate the presence of comorbid conditions. Finally, we elected to use the SGRQ definition of chronic bronchitis rather than the classic definition[32] due to wider use in both clinical and research settings.[76]

CONCLUSIONS

Our multi-country study conducted in three LMICs found a high burden chronic bronchitis in one out of ten participants and a third of these participants had COPD. Modifiable and non-modifiable risk factors including older age, male sex, prior tuberculosis, prior diagnosis of asthma, higher number of pack-years of tobacco use, second-hand smoke, family history of chronic respiratory diseases, lower SES index, and indoor biomass exposure varied in importance by LMIC setting. Implementing interventions to address modifiable risk factors such as history of tuberculosis, indoor biomass use, and tobacco use may reduce the burden of chronic bronchitis may improve quality of life and reduce respiratory symptoms in populations at-risk of COPD development.

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CONFLICT OF INTEREST

In the past 36 months, JRH has received support by AstraZeneca for clinical trials along with AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Sanofi-Regeneron, and Takeda for consulting fees, advisory, and educational work. TS has received grants from AstraZeneca, Sanofi, and GlaxoSmithKline and consulting fees from GlaxoSmithKline, Apogee Therapeutics, Vernoa Pharmaceuticals, and AstraZeneca. TS has received equipment, materials, drugs, gifts, or other services from Siemens. OFF is supported by a US National Institutes of Health K43 Global Emerging Fellow training grant. RAW has received research grants from Chiesi, AstraZeneca, and Sanofi and consulting fees from the U.S. Government CMS for consulting fees on COPD and asthma medications. RAW is on the Board of Directors for the COPD Foundation and Scientific Advisory Board for the American Lung Association. RAW in on the Data Safety Monitoring Board at AstraZeneca, Kamada, Bristol Myers Squibb, AbbVie, Puretech, and Pulmonx. RAW is on the Clinical Endpoint Committee for AbbVie, Galderma, Boehringer-Ingelheim, Chiesi, Biontech, and AstraZeneca. The remaining authors have no conflicts of interest to declare.

Table 1. Description of participants with and without chronic bronchitis (St. George's Respiratory Questionnaire (SGRQ) definition), with and without COPD (lower limit of normal definition) using the GLI mixed ethnic reference equation.

Variables	Overall GECo Cohort	Chronic Bronchitis (CB)* (n=934)		No Chronic Bronchitis* (n=8730)	p-value**	p-value***
		COPD (n=294)	Without COPD (n=640)			
Demographics						
Age, years, mean (SD)	56.2 (11.7)	65.3 (10.8)	58.0 (12.0)	55.8 (11.5)	<0.001	<0.001
Sex, n (%) Male Female	 519 (55.6) 415 (44.4)	 184 (62.6) 110 (37.4)	 335 (52.3) 305 (47.7)	 4212 (48.2) 4518 (51.8)	 <0.001 <0.001	 0.004 0.004
BMI, kg/m² mean (SD)		23.3 (4.3)	26.9 (4.7)	26.4 (5.3)	<0.001	<0.001
Employment, n (%)	573 (61.3)	163 (91.6)	410 (95.1)	6331 (96.8)	0.001	0.13
Secondary School Graduation, n (%)	147 (15.7)	22 (20.2)	125 (31.3)	2016 (29.6)	0.80	0.031
Average Household Income (USD), mean (SD)	244.7 (2,265.9)	146.7 (317.5)	188.6 (933.1)	252.5 (2,375.2)	0.33	0.46
Past Medical History						
Self-Reported History of Chronic Bronchitis (CB), * n (%)	14 (1.5)	6 (2.0)	8 (1.2)	96 (1.1)	0.35	0.53
Family History of Chronic Respiratory Disease, n (%)	22 (2.4)	8 (2.8)	14 (2.2)	61 (0.7)	<0.001	0.75

Self-Reported Comorbidities†, n (%)						
Hypertension	192 (20.6)	49 (16.7)	143 (22.3)	1704 (19.5)	0.48	0.057
Coronary Heart Disease	38 (4.1)	11 (3.7)	27 (4.2)	193 (2.2)	0.001	0.87
Diabetes	69 (7.4)	14 (4.8)	55 (8.6)	577 (6.6)	0.40	0.052
COPD	29 (3.1)	25 (8.5)	4 (0.6)	29 (0.3)	<0.001	<0.001
Asthma	106 (11.3)	60 (20.4)	46 (7.2)	280 (3.2)	<0.001	<0.001
History of Treated Tuberculosis	58 (6.2)	26 (8.8)	32 (5.0)	328 (3.8)	<0.001	0.034
Regular Medication Use, n (%)					<0.001	0.44
Short-acting beta-agonists	37 (4.0)	9 (3.1)	28 (4.4)	79 (0.9)	<0.001	0.020
Short-acting muscarinic agents	12 (1.3)	8 (2.7)	4 (0.6)	16 (0.2)	<0.001	<0.001
Long-acting beta-agonists	12 (1.3)	10 (3.4)	2 (0.3)	25 (0.3)	<0.001	0.001
Long-acting muscarinic agents	15 (1.6)	11 (3.7)	4 (0.6)	20 (0.3)	0.035	0.80
Inhaled corticosteroids	4 (0.4)	2 (0.7)	2 (0.3)	9 (0.1)		
Self-Reported Chest Infection in the Past Year, mean (SD)	0.5 (2.9)	0.5 (2.2)	0.4 (1.7)	0.5 (2.9)	0.46	0.34
Exposure History						
Ever Tobacco Use, n (%)	443 (47.4)	163 (55.4)	280 (43.8)	2758 (31.6)	<0.001	0.001
Pack years of tobacco use, mean (SD)	2.6 (8.4)	11.1 (16.5)	5.6 (11.8)	2.0 (7.4)	<0.001	<0.001
Years of Past Biomass Use, mean (SD)	37.3 (18.1)	55.1 (18.8)	41.1 (20.8)	36.9 (17.9)	<0.001	<0.001
Responsible for Household Cooking, n (%)	410 (43.9)	120 (40.8)	290 (45.3)	4814 (55.1)	<0.001	0.22

* St. George's Respiratory Questionnaire chronic bronchitis: over the past four weeks, coughed or brought up phlegm almost every day or several days a week.
** Within the GECo cohort, p-value comparing participants with chronic bronchitis compared to participants without chronic bronchitis
*** Among participants with chronic bronchitis, p-value comparing participants with and without COPD
† : participant self-reported history of diagnosis by a health professional

Table 2. Prevalence of chronic bronchitis by study site, age, and sex using the SGRQ chronic bronchitis definition.

	Overall (N=9664)	Chronic Bronchitis*		p-value**
		With COPD † (n=294)	Without COPD † (n=640)	
Study Site n (%)				<0.001
Nepal	3323 (34.4)	261 (7.9)	444 (13.4)	
Peru	3257 (33.7)	11 (0.3)	166 (5.1)	
Uganda	3084 (31.9)	22 (0.7)	30 (1.0)	
Age, n (%)				<0.001
40-44 years	2316 (24.0)	13 (0.6)	131 (5.7)	
45-49 years	1351 (14.0)	18 (1.3)	83 (6.1)	
50-64 years	3576 (37.0)	102 (2.9)	227 (6.3)	
65-95 years	2421 (25.1)	161 (6.7)	199 (8.2)	
Sex, n (%)				0.004
Male	4731 (49.0)	184(3.9)	335 (7.1)	
Female	4933 (51.0)	110 (2.2)	305 (6.2)	
FEV_1 Z-score mean (SD)				
Pre-bronchodilator	-0.25 (1.41)	-2.34 (1.21)	-0.26 (1.26)	<0.001
Post-bronchodilator	-0.10 (1.39)	-2.09 (1.22)	0.07 (1.25)	<0.001
FVC Z-score mean (SD)				
Pre-bronchodilator	0.05 (1.35)	-0.86 (1.49)	0.07 (1.29)	<0.001
Post-bronchodilator	0.02 (1.31)	-0.56 (1.40)	0.05 (1.26)	<0.001
FEV_1/FVC Z-score mean (SD)				
Pre-bronchodilator	-0.58 (1.10)	-3.10 (0.95)	-0.63 (0.81)	<0.001
Post-bronchodilator	-0.27 (1.08)	-2.99 (0.94)	-0.25 (0.78)	<0.001

* St. George's Respiratory Questionnaire chronic bronchitis: over the past four weeks, coughed or brought up phlegm almost every day or several days a week.
**: p-value comparing chronic bronchitis with and without COPD
† : COPD was defined using the lower limit of normal definition (FEV_1/FVC Z-score less than -1.645 standard deviations)

Table 3. Respiratory symptoms, and quality of life stratified by chronic bronchitis diagnosis in the GECo cohort.

		Chronic Bronchitis* (n=934)		No Chronic Bronchitis (n=8730)	p-value***
		COPD** (n=294)	No COPD** (n=640)		
Respiratory Symptoms					
mMRC, n (%)					
1	Breathlessness with strenuous exercise	96 (32.7)	396 (61.9)	6346 (72.7)	<0.001
2	Shortness of breath hurry on the level or walking up a slight hill	149 (50.7)	211 (33.0)	2167 (24.8)	
3	Walk slower on the level due to breathlessness and stop for breath when walking on own pace	35 (11.9)	24 (3.8)	175 (2.0)	
4	Stop for breath after walking 100 meters or after a few minutes on the level	11 (3.7)	8 (1.2)	37 (0.4)	
5	Too breathless to leave the house or breathlessness when dressing	3 (1.0)	1 (0.2)	5 (0.1)	
Lung Function Questionnaire, mean (SD)		16.2 (3.1)	18.6 (3.1)	20.3 (2.6)	<0.001
Ever Wheezing, n (%)		129 (43.9)	191 (29.8)	1992 (22.8)	<0.001
Quality of Life					
EQ-5D Score, mean (SD)		0.7 (0.2)	0.8 (0.2)	0.9 (0.2)	<0.001
St. George Respiratory Questionnaire, mean (SD)					
	Total Score	27.0 (20.7)	15.4 (14.6)	6.7 (10.3)	<0.001
	Symptoms	39.2 (17.4)	33.4 (14.6)	10.3 (11.5)	<0.001
	Activities	39.9 (26.0)	20.5 (20.9)	10.2 (16.7)	<0.001
	Impacts	16.2 (22.0)	7.6 (15.1)	3.7 (9.5)	<0.001
Hospitalization in Past 12 Months, n (%)		14 (4.8)	14 (2.2)	119 (1.4)	<0.001

Respiratory Symptoms Impeding Daily Activities in the Last Year, n (%)	33 (11.2)	40 (6.2)	310 (3.6)	<0.001

* St. George's Respiratory Questionnaire chronic bronchitis: over the past four weeks, coughed or brought up phlegm almost every day or several days a week.
**COPD was defined using the lower limit of normal definition (FEV_1/FVC Z-score less than -1.645 standard deviations)

***p-value comparing chronic bronchitis vs. non-chronic bronchitis groups

REFERENCES

1. Corlateanu A, Mendez Y, Wang Y, Garnica RJA, Botnaru V, Siafakas N. "Chronic obstructive pulmonary disease and phenotypes: a state-of-the-art.". Pulmonology. 2020;26(2):95-100.
2. Definition and classification of chronic bronchitis for clinical and epidemiological purposes; A report to the Medical Research Council by their Committee on the Aetiology of Chronic Bronchitis. Lancet. 1965;285(7389):775-9.
3. Dotan Y, So JY, Kim V. Chronic Bronchitis: Where Are We Now? Chronic Obstr Pulm Dis. 2019;6(2):178-92.
4. Kim V, Criner GJ. Chronic bronchitis and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;187(3):228-37.
5. Siddharthan T, Grigsby M, Morgan B, Kalyesubula R, Wise RA, Kirenga B, et al. Prevalence of chronic respiratory disease in urban and rural Uganda. Bull World Health Organ. 2019;97(5):318-27.
6. Boers E, Barrett M, Su JG, Benjafield AV, Sinha S, Kaye L, et al. Global Burden of Chronic Obstructive Pulmonary Disease Through 2050. JAMA Netw Open. 2023;6(12):e2346598.
7. Abbas AH, Mustafa MA, Abozaid M. Prevalence and risk factors of patients with chronic bronchitis among Iraqi adults. J Med Life. 2023;16(3):419-27.
8. Menezes AM, Perez-Padilla R, Hallal PC, Jardim JR, Muino A, Lopez MV, et al. Worldwide burden of COPD in high- and low-income countries. Part II. Burden of chronic obstructive lung disease in Latin America: the PLATINO study. Int J Tuberc Lung Dis. 2008;12(7):709-12.
9. van Gemert F, Kirenga B, Chavannes N, Kamya M, Luzige S, Musinguzi P, et al. Prevalence of chronic obstructive pulmonary disease and associated risk factors in Uganda (FRESH AIR Uganda): a prospective cross-sectional observational study. Lancet Glob Health. 2015;3(1):e44-51.
10. Lu M, Yao W, Zhong N, Zhou Y, Wang C, Chen P, et al. Chronic obstructive pulmonary disease in the absence of chronic bronchitis in China. Respirology. 2010;15(7):1072-8.
11. Koch M, Butt T, Guo W, Li X, Chen Y, Tan D, et al. Characteristics and health burden of the undiagnosed population at risk of chronic obstructive pulmonary disease in China. BMC Public Health. 2019;19(1):1727.
12. Kim V, Han MK, Vance GB, Make BJ, Newell JD, Hokanson JE, et al. The chronic bronchitic phenotype of COPD: an analysis of the COPDGene Study. Chest. 2011;140(3):626-33.
13. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res. 2010;11(1):122.
14. Burgel PR, Nesme-Meyer P, Chanez P, Caillaud D, Carre P, Perez T, et al. Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD subjects. Chest. 2009;135(4):975-82.
15. Kim V, Criner GJ. The chronic bronchitis phenotype in chronic obstructive pulmonary disease: features and implications. Curr Opin Pulm Med. 2015;21(2):133-41.
16. de Oca MM, Halbert RJ, Lopez MV, Perez-Padilla R, Talamo C, Moreno D, et al. The chronic bronchitis phenotype in subjects with and without COPD: the PLATINO study. Eur Respir J. 2012;40(1):28-36.

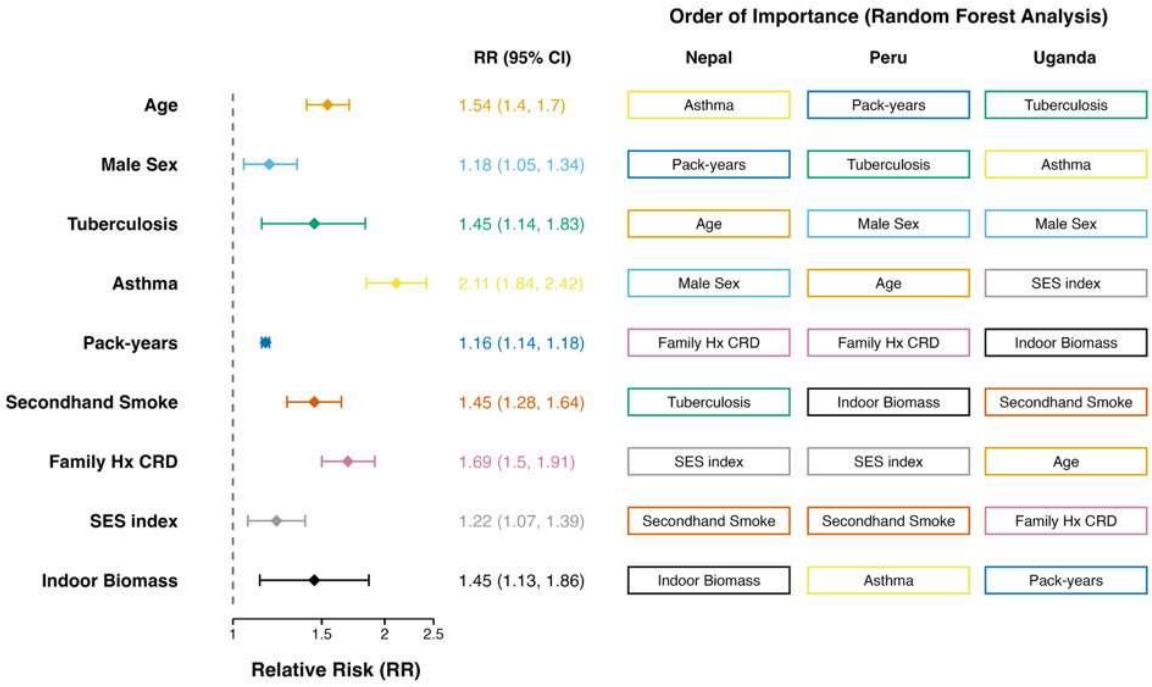
17. Lindberg A, Jonsson AC, Ronmark E, Lundgren R, Larsson LG, Lundback B. Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. Chest. 2005;127(5):1544-52.
18. Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Chronic bronchitis before age 50 years predicts incident airflow limitation and mortality risk. Thorax. 2009;64(10):894-900.
19. Fan J, Fang L, Cong S, Zhang Y, Jiang X, Wang N, et al. Potential pre-COPD indicators in association with COPD development and COPD prediction models in Chinese: a prospective cohort study. Lancet Reg Health West Pac. 2024;44:100984.
20. Vestbo J, Prescott E, Lange P. Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. Copenhagen City Heart Study Group. Am J Respir Crit Care Med. 1996;153(5):1530-5.
21. Choi JY, Yoon HK, Lee SY, Kim JW, Choi HS, Kim YI, et al. Comparison of clinical characteristics between chronic bronchitis and non-chronic bronchitis in patients with chronic obstructive pulmonary disease. BMC Pulm Med. 2022;22(1):69.
22. Pelkonen M, Notkola IL, Nissinen A, Tukiainen H, Koskela H. Thirty-year cumulative incidence of chronic bronchitis and COPD in relation to 30-year pulmonary function and 40-year mortality: a follow-up in middle-aged rural men. Chest. 2006;130(4):1129-37.
23. Mejza F, Gnatiuc L, Buist AS, Vollmer WM, Lamprecht B, Obaseki DO, et al. Prevalence and burden of chronic bronchitis symptoms: results from the BOLD study. Eur Respir J. 2017;50(5).
24. Siddharthan T, Pollard SL, Quaderi SA, Mirelman AJ, Cardenas MK, Kirenga B, et al. Effectiveness-implementation of COPD case finding and self-management action plans in low- and middle-income countries: global excellence in COPD outcomes (GECo) study protocol. Trials. 2018;19(1):571.
25. Siddharthan T, Pollard SL, Quaderi SA, Rykiel NA, Wosu AC, Alupo P, et al. Discriminative Accuracy of Chronic Obstructive Pulmonary Disease Screening Instruments in 3 Low- and Middle-Income Country Settings. JAMA. 2022;327(2):151-60.
26. Morgan BW, Grigsby MR, Siddharthan T, Kalyesubula R, Wise RA, Hurst JR, et al. Validation of the Saint George's Respiratory Questionnaire in Uganda. BMJ Open Respir Res. 2018;5(1):e000276.
27. Sherpa CT, LeClerq SL, Singh S, Naithani N, Pangeni R, Karki A, et al. Validation of the St. George's Respiratory Questionnaire in Nepal. Chronic Obstr Pulm Dis. 2015;2(4):281-9.
28. Vanegas AC, Calvo V. Validation of quality of life questionnaire St George's for patients with respiratory diseases in Colombia, Latin America. European Respiratory Journal. 2012;40(Suppl 56):P3973.
29. Jones PW. St. George's Respiratory Questionnaire (SGRQ): American Thoracic Society; 2021 [updated November 30, 2021. Available from: https://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/sgrq.php.
30. Jones PW. St. George's Respiratory Questionnaire: MCID. COPD. 2005;2(1):75-9.
31. Nolan CM, Longworth L, Lord J, Canavan JL, Jones SE, Kon SS, et al. The EQ-5D-5L health status questionnaire in COPD: validity, responsiveness and minimum important difference. Thorax. 2016;71(6):493-500.

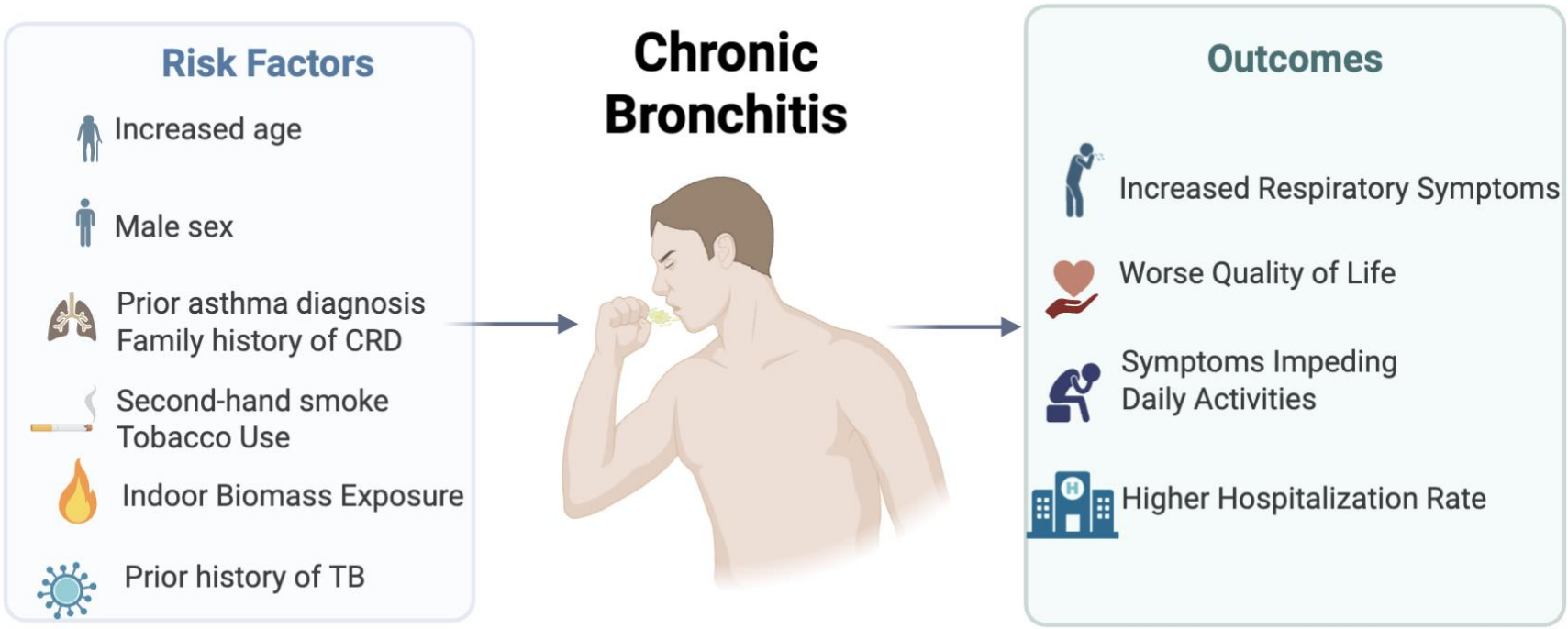
32. Kim V, Crapo J, Zhao H, Jones PW, Silverman EK, Comellas A, et al. Comparison between an alternative and the classic definition of chronic bronchitis in COPDGene. Ann Am Thorac Soc. 2015;12(3):332-9.
33. Widysanto AM, G. Chronic Bronchitis. StatPearls. 2024(Jan).
34. Agusti A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. Eur Respir J. 2023;61(4).
35. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS, Committee GS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001;163(5):1256-76.
36. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999;159(1):179-87.
37. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.
38. Vaz Fragoso CA, Concato J, McAvay G, Van Ness PH, Rochester CL, Yaggi HK, et al. The ratio of FEV1 to FVC as a basis for establishing chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2010;181(5):446-51.
39. Agusti A, Anzueto A, Celli BR, Mortimer K, Salvi S, Vogelmeier CF, et al. GOLD 2023 Executive Summary: responses from the GOLD Scientific Committee. Eur Respir J. 2023;61(6).
40. Grigsby M, Siddharthan T, Chowdhury MA, Siddiquee A, Rubinstein A, Sobrino E, et al. Socioeconomic status and COPD among low- and middle-income countries. Int J Chron Obstruct Pulmon Dis. 2016;11:2497-507.
41. Zhu CH, DW; Stankovich, J; Willis, K; Blizzard, L. Refinements on the exact method to solve the numerical difficulties in fitting the log binomial regression model for estimating relative risk. Communications in Statistics- Theory and Methods. 2024;53(23):8359-75.
42. Strobl C, Boulesteix AL, Kneib T, Augustin T, Zeileis A. Conditional variable importance for random forests. BMC Bioinformatics. 2008;9:307.
43. Jones PW, Forde, Yvonne. St. George's Respiratory Questionnaire Manual: St. George's University of London; 2022 [updated Marh 2022. Available from: https://www.sgul.ac.uk/research/research-operations/research-administration/st-georges-respiratory-questionnaire/docs/SGRQ-Manual-March-2022.pdf.
44. Mintz ML, Yawn BP, Mannino DM, Donohue JF, Hanania NA, Grellet CA, et al. Prevalence of airway obstruction assessed by lung function questionnaire. Mayo Clin Proc. 2011;86(5):375-81.
45. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Viennna, Austria2022.
46. Ehrlich RI, White N, Norman R, Laubscher R, Steyn K, Lombard C, et al. Predictors of chronic bronchitis in South African adults. Int J Tuberc Lung Dis. 2004;8(3):369-76.
47. Gonzalez-Garcia M, Caballero A, Jaramillo C, Torres-Duque CA. Chronic bronchitis: High prevalence in never smokers and underdiagnosis- A population-based study in Colombia. Chron Respir Dis. 2019;16:1479972318769771.

48. McGeachie MJ. Childhood asthma is a risk factor for the development of chronic obstructive pulmonary disease. Curr Opin Allergy Clin Immunol. 2017;17(2):104-9.
49. Ali KM. Childhood asthma as a risk factor for adult chronic obstructive pulmonary disease: a systematic review and meta-analysis. Expert Rev Respir Med. 2022;16(4):461-7.
50. Hancox RJ, Gray AR, Poulton R, Sears MR. The Effect of Cigarette Smoking on Lung Function in Young Adults with Asthma. Am J Respir Crit Care Med. 2016;194(3):276-84.
51. Tai A, Tran H, Roberts M, Clarke N, Wilson J, Robertson CF. The association between childhood asthma and adult chronic obstructive pulmonary disease. Thorax. 2014;69(9):805-10.
52. Tagiyeva N, Devereux G, Fielding S, Turner S, Douglas G. Outcomes of Childhood Asthma and Wheezy Bronchitis. A 50-Year Cohort Study. Am J Respir Crit Care Med. 2016;193(1):23-30.
53. Tan WC, Sin DD, Bourbeau J, Hernandez P, Chapman KR, Cowie R, et al. Characteristics of COPD in never-smokers and ever-smokers in the general population: results from the CanCOLD study. Thorax. 2015;70(9):822-9.
54. Hayden LP, Cho MH, Raby BA, Beaty TH, Silverman EK, Hersh CP, et al. Childhood asthma is associated with COPD and known asthma variants in COPDGene: a genome-wide association study. Respir Res. 2018;19(1):209.
55. Panigrahi AP, B. Chronic bronchitis and airflow obstruction is associated with household cooking fuel use among never-smoking women: a community-based cross-sectional study in Odisha, India. BMC Public Health. 2018;18(924).
56. Sreedevi SR, Holla R, Vishak AK, Unnikrishnan B, Rekha T, Mithra PP, et al. COPD in females- Seeing through the smoke. Lung India. 2025;42(1):40-6.
57. Thacher JD, Emmelin A, Madaki AJ, Thacher TD. Biomass fuel use and the risk of asthma in Nigerian children. Respir Med. 2013;107(12):1845-51.
58. Nicolaou L, Checkley W. Differences between cigarette smoking and biomass smoke exposure: An in silico comparative assessment of particulate deposition in the lungs. Environ Res. 2021;197:111116.
59. Ortiz-Quintero B, Martinez-Espinosa I, Perez-Padilla R. Mechanisms of Lung Damage and Development of COPD Due to Household Biomass-Smoke Exposure: Inflammation, Oxidative Stress, MicroRNAs, and Gene Polymorphisms. Cells. 2022;12(1).
60. Kansiime WM, RK. Atusingwize, E; Wafula, ST; Nsereko, V; Ssekamatte, T; Nalugya, A; Coker, ES; Ssempebwa, JC; Isunju JS;. Use of biomass fuels predicts indoor particulate matter and carbon monoxide concentrations; evidence from an informal urban settlement in Fort Portal city, Uganda. BMC Public Health. 2022;22:1723.
61. Mahesh PA, Jayaraj BS, Prabhakar AK, Chaya SK, Vijaysimha R. Identification of a threshold for biomass exposure index for chronic bronchitis in rural women of Mysore district, Karnataka, India. Indian J Med Res. 2013;137(1):87-94.
62. Hu G, Zhou Y, Tian J, Yao W, Li J, Li B, et al. Risk of COPD from exposure to biomass smoke: a metaanalysis. Chest. 2010;138(1):20-31.
63. Po JY, FitzGerald JM, Carlsten C. Respiratory disease associated with solid biomass fuel exposure in rural women and children: systematic review and meta-analysis. Thorax. 2011;66(3):232-9.

64. Kurmi OP, Devereux GS, Smith WC, Semple S, Steiner MF, Simkhada P, et al. Reduced lung function due to biomass smoke exposure in young adults in rural Nepal. Eur Respir J. 2013;41(1):25-30.
65. Rivera RM, Cosio MG, Ghezzo H, Salazar M, Perez-Padilla R. Comparison of lung morphology in COPD secondary to cigarette and biomass smoke. Int J Tuberc Lung Dis. 2008;12(8):972-7.
66. Camp PG, Ramirez-Venegas A, Sansores RH, Alva LF, McDougall JE, Sin DD, et al. COPD phenotypes in biomass smoke- versus tobacco smoke-exposed Mexican women. Eur Respir J. 2014;43(3):725-34.
67. Perez-Padilla R, Regalado J, Vedal S, Pare P, Chapela R, Sansores R, et al. Exposure to biomass smoke and chronic airway disease in Mexican women. A case-control study. Am J Respir Crit Care Med. 1996;154(3 Pt 1):701-6.
68. Sood A, Petersen H, Blanchette CM, Meek P, Picchi MA, Belinsky SA, et al. Wood smoke exposure and gene promoter methylation are associated with increased risk for COPD in smokers. Am J Respir Crit Care Med. 2010;182(9):1098-104.
69. Dijkstra AE, Smolonska J, van den Berge M, Wijmenga C, Zanen P, Luinge MA, et al. Susceptibility to chronic mucus hypersecretion, a genome wide association study. PLoS One. 2014;9(4):e91621.
70. Lee JH, Cho MH, Hersh CP, McDonald ML, Crapo JD, Bakke PS, et al. Genetic susceptibility for chronic bronchitis in chronic obstructive pulmonary disease. Respir Res. 2014;15(1):113.
71. Fuhrman C, Roche N, Vergnenegre A, Chouaid C, Zureik M, Delmas MC. [Chronic bronchitis: prevalence and quality of life. Analysis of data from the French Health Interview Survey 2002-2003]. Rev Mal Respir. 2009;26(7):759-68.
72. Miravitlles M, Guerrero T, Mayordomo C, Sanchez-Agudo L, Nicolau F, Segu JL. Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis. The EOLO Study Group. Respiration. 2000;67(5):495-501.
73. Ekberg-Aronsson M, Pehrsson K, Nilsson JA, Nilsson PM, Lofdahl CG. Mortality in GOLD stages of COPD and its dependence on symptoms of chronic bronchitis. Respir Res. 2005;6(1):98.
74. Meek PM, Petersen H, Washko GR, Diaz AA, Klm V, Sood A, et al. Chronic Bronchitis Is Associated With Worse Symptoms and Quality of Life Than Chronic Airflow Obstruction. Chest. 2015;148(2):408-16.
75. Rosenberg SR, Kalhan R. Chronic Bronchitis in Chronic Obstructive Pulmonary Disease. Magnifying Why Smoking Cessation Still Matters Most. Ann Am Thorac Soc. 2016;13(7):999-1000.
76. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. The Presence of Chronic Mucus Hypersecretion across Adult Life in Relation to Chronic Obstructive Pulmonary Disease Development. Am J Respir Crit Care Med. 2016;193(6):662-72.

Figure 1. Forest plot displaying the relative risk of chronic bronchitis with associated 95% confidence intervals of participants in the Global Excellence in COPD Outcomes (GECo) study for each of the nine risk factors within a binomial logistic regression analysis (left pane). A random forest analysis displays the order of importance of the nine risk factors as stratified by study site (right pane).





SUPPLEMENTAL INFORMATION

Supplemental eTable 1. Description of participants with and without St. George's Respiratory Questionnaire (SGRQ) definition of chronic bronchitis using the fixed definition of COPD

Variables	Chronic Bronchitis (CB)* (n=934)		No Chronic Bronchitis* (n=8730)
	COPD** (n=338)	Without COPD** (n=596)	
Demographics			
Age, years mean (SD)	66.8 (10.1)	56.6 (11.6)	55.8 (11.5)
Sex, n (%)			
Male	220 (65.1)	299 (50.2)	4212 (48.2)
Female	118 (34.9)	297 (49.8)	4518 (51.8)
BMI, kg/m² mean (SD)	23.3 (4.1)	27.2 (4.7)	26.4 (5.3)
Employment, n (%)	186 (92.1)	387 (95.1)	6331 (96.8)
Secondary School Graduation, n (%)	25 (19.8)	122 (31.9)	2016 (29.6)
Average Household Income (USD), mean (SD)	137.3 (300.8)	196.8 (964.3)	252.5 (2375.2)
Past Medical History			
Self-Reported History of Chronic Bronchitis (CB),* n (%)	6 (1.8)	8 (1.3)	96 (1.1)
Family History of Chronic Respiratory Disease, n (%)	10 (3.1)	12 (2.1)	61 (0.7)
Self-Reported Comorbidities†, n (%)			
Hypertension	65 (19.2)	127 (21.3)	1704 (19.5)
Coronary Heart Disease	14 (4.1)	24 (4.0)	193 (2.2)
Diabetes	15 (4.4)	54 (9.1)	577 (6.6)
COPD	26 (7.7)	3 (0.5)	29 (0.3)
Asthma	66 (19.5)	40 (6.7)	280 (3.2)
History of Treated Tuberculosis	32 (9.5)	26 (4.4)	328 (3.8)
Regular Medication Use, n (%)			
Short-acting beta-agonists	13 (3.8)	24 (4.0)	79 (0.9)
Short-acting muscarinic agents	8 (2.4)	4 (0.7)	16 (0.2)
Long-acting beta-agonists	10 (3.0)	2 (0.3)	25 (0.3)
Long-acting muscarinic agents	12 (3.6)	3 (0.5)	25 (0.3)
Inhaled corticosteroids	2 (0.6)	2 (0.3)	9 (0.1)
Self-Reported Chest Infection in the Past Year, mean (SD)	0.6 (2.5)	0.4 (1.4)	0.5 (2.9)
Exposure History			
Ever Tobacco Use, n (%)	192 (56.8)	251 (42.1)	2758 (31.6)
Pack years of tobacco use, mean (SD)	11.5 (16.8)	5.0 (10.9)	2.0 (7.4)
Years of Past Biomass Use, mean (SD)	54.4 (18.8)	40.2 (20.9)	36.9 (17.9)

Responsible for Household Cooking, n (%)	132 (39.1)	278 (46.6)	4814 (55.1)

* based on responses from the St. George's Respiratory Questionnaire responding both cough and sputum production "almost every day" or "several days a week" over the past 4 weeks

** fixed definition of COPD defined as $FEV_1/FVC \leq 0.70$

Supplemental eTable 2. Description of participants with and without classic definition of chronic bronchitis using the lower limit of normal definition of COPD comparing St. George's Respiratory Questionnaire (SGRQ) based definition compared to classic definition

	No CB (Both Definitions) n=6918	Classic Definition of CB n=2467	SGRQ Definition of CB n=934	CB by Both Definitions n=655	p-value*
Chronic Bronchitis Prevalence	--	2467 (25.5)	934 (9.7)	655 (6.8)	<0.001
Study Site n (%)					<0.001
Nepal	1912 (19.8)	1208 (12.5)	705 (7.3)	502 (5.2)	
Peru	2198 (22.7)	995 (10.3)	177 (1.8)	113 (1.2)	
Uganda	2808 (29.1)	264 (2.7)	52 (0.5)	40 (0.4)	
Age, n (%)					0.48
40-44 years	1786 (18.5)	473 (4.9)	144 (1.5)	87 (0.9)	
45-49 years	1031 (10.7)	280 (2.9)	101 (1.0)	61 (0.6)	
50-64 years	2588 (26.8)	897 (9.3)	329 (3.4)	238 (2.5)	
65-95 years	1513 (15.7)	817 (8.5)	360 (3.7)	269 (2.8)	
Sex, n (%)					0.010
Male	3362 (34.8)	1215 (12.6)	519 (5.4)	365 (3.8)	
Female	3556 (36.8)	1252 (13.0)	415 (4.3)	290 (3.0)	
FEV_1 Z-score mean (SD)					
Pre-bronchodilator	-0.19 (1.33)	-0.39 (1.58)	-0.92 (1.58)	-1.09 (1.59)	<0.001
Post-bronchodilator	-0.05 (1.32)	-0.21 (1.55)	-0.70 (1.56)	-0.88 (1.58)	0.001
FVC Z-score mean (SD)					
Pre-bronchodilator	0.04 (1.32)	0.08 (1.42)	-0.22 (1.42)	-0.33 (1.44)	0.022
Post-bronchodilator	-0.01 (1.30)	0.10 (1.36)	-0.14 (1.34)	-0.24 (1.35)	0.090
FEV_1/FVC Z-score mean (SD)					
Pre-bronchodilator	-0.44 (0.98)	-0.92 (1.29)	-1.41 (1.43)	-1.58 (1.48)	<0.001
Post-bronchodilator	-0.12 (0.93)	-0.62 (1.31)	-1.11 (1.52)	-1.29 (1.58)	<0.001

* p-value comparing chronic bronchitis St. George's Respiratory Questionnaire (SGRQ) and classic definitions of chronic bronchitis (CB). The classic definition of CB was defined as productive cough lasting most days in a month lasting for three months duration with at least two of these episodes within a span of two years. The SGRQ definition of CB was defined as productive cough at least several days a week for at least 4 weeks.

Supplemental eTable 3. Overall and site-specific sociodemographic and exposure risk factors in the Global Excellence in COPD outcomes study.

	Overall (n=9664)	**Nepal** (n=3323)	**Peru** (n=3257)	**Uganda** (n=3084)	**p-value**
Sociodemographic Factors					
Age, years, mean (SD)	56.2 (11.7)	56.0 (11.7)	56.6 (11.3)	56.0 (12.0)	0.046
Male sex, n (%)	4731 (49.0)	1631 (49.1)	1609 (49.4)	1491 (48.3)	0.690
Socioeconomic status index, mean (SD)	0.3 (0.3)	0.2 (0.2)	<0.1 (0.1)	0.8 (0.1)	<0.0001
Chest infection in the past year, n (%)	1548 (16.0)	102 (3.1)	485 (14.9)	961 (31.2)	<0.0001
Diagnosis of tuberculosis, n (%)	386 (4.0)	105 (3.2)	248 (7.6)	33 (1.1)	<0.0001
Diagnosis of asthma, n (%)	386 (4.0)	122 (3.7)	238 (7.3)	26 (0.8)	<0.0001
Family history of chronic respiratory disease, n (%)	2102 (21.8)	1044 (31.4)	786 (24.1)	272 (8.8)	<0.0001
Exposure History					
Daily tobacco use, n (%)	1469 (15.2)	687 (20.7)	514 (15.8)	268 (8.7)	<0.0001
Pack-years, mean (SD)	2.6 (8.4)	5.3 (11.5)	1.1 (6.4)	1.1 (4.7)	<0.0001
Second-hand smoke, n (%)	1368 (14.2)	861 (25.9)	427 (13.1)	80 (2.6)	<0.0001
Past biomass fuel exposure, n (%)	9663 (>99.9)	3322 (>99.9)	3257 (100.0)	3084 (100.0)	0.390
Current biomass fuel exposure, n (%)	2740 (28.4)	175 (5.3)	16 (0.5)	2549 (82.7)	<0.0001

Supplemental eTable 4. Description of participants with and without chronic bronchitis (St. George's Respiratory Questionnaire (SGRQ) definition), with and without COPD (lower limit of normal definition) using the GLI Global reference equation.

Variables	Chronic Bronchitis (CB)* (n=934)		No Chronic Bronchitis* (n=8730)	p-value**	p-value***
	COPD (n=281)	Without COPD (n=653)			
Demographics					
Age, years, mean (SD)	65.7 (10.7)	58.0 (12.0)	55.8 (11.5)	<0.001	<0.001
Sex, n (%)					
Male	177 (63.0)	342 (52.4)	4212 (48.2)	<0.001	0.003
Female	104 (37.0)	311 (47.6)	4518 (51.8)	<0.001	0.003
BMI, kg/m² mean (SD)	23.2 (4.1)	26.9 (4.7)	26.4 (5.3)	<0.001	<0.001
Employment, n (%)	152 (91.6)	421 (95.0)	6331 (96.8)	0.001	0.16
Secondary School Graduation, n (%)	19 (18.4)	128 (31.6)	2016 (29.6)	0.800	0.012
Average Household Income (USD), mean (SD)	146.0 (320.6)	188.1 (924.1)	252.5 (2,375.2)	0.332	0.47
Past Medical History					
Self-Reported History of Chronic Bronchitis (CB), * n (%)	6 (2.1)	8 (1.2)	96 (1.1)	0.352	0.45
Family History of Chronic Respiratory Disease, n (%)	7 (2.6)	15 (2.3)	61 (0.7)	<0.001	1.00
Self-Reported Comorbidities†, n (%)					
Hypertension	47 (16.7)	145 (22.2)	1704 (19.5)	0.475	0.070
Coronary Heart Disease	10 (3.6)	28 (4.3)	193 (2.2)	0.001	0.74
Diabetes	14 (5.0)	55 (8.4)	577 (6.6)	0.403	0.088
COPD	25 (8.9)	4 (0.6)	29 (0.3)	<0.001	<0.001
Asthma	60 (21.4)	46 (7.0)	280 (3.2)	<0.001	<0.001
History of Treated Tuberculosis	26 (9.3)	32 (4.9)	328 (3.8)	<0.001	0.017

Regular Medication Use, n (%)					
Short-acting beta-agonists	9 (3.2)	28 (4.3)	79 (0.9)	<0.001	0.55
Short-acting muscarinic agents	8 (2.8)	4 (0.6)	16 (0.2)	<0.001	0.014
Long-acting beta-agonists	10 (3.6)	2 (0.3)	25 (0.3)	<0.001	<0.001
Long-acting muscarinic agents	11 (3.9)	4 (0.6)	25 (0.3)	<0.001	0.001
Inhaled corticosteroids	2 (0.7)	2 (0.3)	9 (0.1)	0.035	0.75
Self-Reported Chest Infection in the Past Year, mean (SD)	0.6 (2.3)	0.4 (1.7)	0.5 (2.9)	0.462	0.26
Exposure History					
Ever Tobacco Use, n (%)	156 (55.5)	287 (44.0)	2758 (31.6)	<0.001	0.001
Pack years of tobacco use, mean (SD)	11.4 (16.7)	5.6 (11.8)	2.0 (7.4)	<0.001	<0.001
Years of Past Biomass Use, mean (SD)	55.2 (18.9)	41.3 (20.7)	36.9 (17.9)	<0.001	<0.001
Responsible for Household Cooking, n (%)	113 (40.2)	297 (45.5)	4814 (55.1)	<0.001	0.16
Lung Function					
FEV_1 Z-score mean (SD)					
Pre-bronchodilator	-2.4 (1.2)	-0.3 (1.3)	-0.2 (1.4)	<0.001	<0.001
Post-bronchodilator	-2.1 (1.2)	-0.1 (1.3)	0.0 (1.4)	<0.001	<0.001
FVC Z-score mean (SD)					
Pre-bronchodilator	-0.9 (1.5)	0.1 (1.3)	0.1 (1.3)	<0.001	<0.001
Post-bronchodilator	-0.6 (1.4)	0.0 (1.3)	0.0 (1.3)	<0.001	<0.001
FEV_1/FVC Z-score mean (SD)					
Pre-bronchodilator	-3.2 (0.9)	-0.7 (0.8)	-0.5 (1.0)	<0.001	<0.001
Post-bronchodilator	-3.0 (0.9)	-0.3 (0.8)	-0.2 (1.0)	<0.001	<0.001

* St. George's Respiratory Questionnaire chronic bronchitis: over the past four weeks, coughed or brought up phlegm almost every day or several days a week.
** Within the GECo cohort, p-value comparing participants with chronic bronchitis compared to participants without chronic bronchitis
*** Among participants with chronic bronchitis, p-value comparing participants with and without COPD
† : participant self-reported history of diagnosis by a health professional

Supplemental eTable 5. Univariable and multivariable logistic regression of risk factors of chronic bronchitis in the GECo cohort

	GECo Cohort			
	Univariable		Multivariable	
	RR (95% CI)	p-value	RR (95% CI)	p-value
Age	1.74 (1.58, 1.91)	<0.001	1.54 (1.40, 1.70)	<0.001
Male sex	1.30 (1.15, 1.47)	<0.001	1.18 (1.05, 1.34)	0.006
Prior history of TB	1.59 (1.25, 2.03)	<0.001	1.45 (1.14, 1.83)	0.002
Diagnosis of asthma	3.08 (2.58, 3.66)	<0.001	2.11 (1.84, 2.42)	<0.001
Pack-years of tobacco use	1.18 (1.17, 1.19)	<0.001	1.16 (1.14, 1.18)	<0.001
Second-hand smoke	1.67 (1.45, 1.93)	<0.001	1.45 (1.28, 1.64)	<0.001
Family history of CRD	1.67 (1.47, 1.90)	<0.001	1.69 (1.50, 1.91)	<0.001
Socioeconomic Status Index	1.28 (1.12, 1.46)	<0.001	1.22 (1.07, 1.39)	0.003
Indoor Biomass Exposure	1.76 (1.35, 2.31)	<0.001	1.45 (1.13, 1.86)	0.003

Supplemental eTable 6. Respiratory symptoms and quality of life stratified by chronic bronchitis diagnosis in Nepal

		Nepal		
		Chronic Bronchitis*		No Chronic Bronchitis* (n=3080)
		COPD** (n=11)	No COPD** (n=166)	
Respiratory Symptoms				
mMRC, n (%)				
1	Breathlessness with strenuous exercise	92 (35.2)	278 (62.6)	1591 (60.8)
2	Shortness of breath hurry on the level or walking up a slight hill	135 (51.7)	155 (34.9)	974 (37.2)
3	Walk slower on the level due to breathlessness and stop for breath when walking on own pace	27 (10.3)	11 (2.5)	47 (1.8)
4	Stop for breath after walking 100 meters or after a few minutes on the level	5 (1.9)	0 (0)	6 (0.2)
5	Too breathless to leave the house or breathlessness when dressing	2 (0.8)	0 (0)	0 (0)
Lung Function Questionnaire, mean (SD)		16.5 (2.9)	19.2 (2.7)	20.6 (2.6)
Ever Wheezing		103 (39.5)	65 (14.6)	188 (7.2)
Quality of Life				
EQ-5D score, mean (SD)		0.7 (0.2)	0.8 (0.2)	0.8 (0.2)
St. George Respiratory Questionnaire, mean (SD) Total Score Symptoms Activities Impacts		 24.6 (19.0) 37.1 (16.1) 38.3 (25.4) 13.2 (19.4)	 11.9 (8.3) 27.8 (9.2) 20.0 (16.5) 2.9 (6.8)	 6.6 (7.6) 7.0 (9.2) 14.8 (15.5) 1.7 (5.7)
Hospitalization in Past 12 months		9 (3.4)	7 (1.6)	25 (1.0)
Respiratory symptoms impeding daily activities in the last year		22 (8.4)	9 (2.0)	28 (1.1)

* based on responses from the St. George's Respiratory Questionnaire responding both cough and sputum production "almost every day" or "several days a week" over the past 4 weeks

**COPD was defined using the lower limit of normal definition (FEV_1/FVC Z-score less than -1.645 standard deviations)

Supplemental eTable 7. Respiratory symptoms and quality of life stratified by chronic bronchitis in Peru

		Peru		
		Chronic Bronchitis*		No Chronic Bronchitis* (n=3080)
		COPD** (n=11)	No COPD** (n=166)	
Respiratory Symptoms				
mMRC, n (%)				
1	Breathlessness with strenuous exercise	2 (18.2)	99 (59.6)	2377 (77.2)
2	Shortness of breath hurry on the level or walking up a slight hill	6 (54.5)	48 (28.9)	639 (20.7)
3	Walk slower on the level due to breathlessness and stop for breath when walking on own pace	3 (27.3)	11 (6.6)	46 (1.5)
4	Stop for breath after walking 100 meters or after a few minutes on the level	0 (0)	7 (4.2)	16 (0.5)
5	Too breathless to leave the house or breathlessness when dressing	0 (0)	1 (0.6)	2 (0.1)
Lung Function Questionnaire, mean (SD)		13.0 (4.0)	16.9 (3.2)	19.8 (2.6)
Ever Wheezing		17 (77.3)	117 (70.5)	1428 (46.4)
Quality of Life				
EQ-5D score, mean (SD)		0.8 (0.2)	0.8 (0.3)	0.9 (0.2)
St. George Respiratory Questionnaire, mean (SD) Total Score Symptoms Activities Impacts		39.8 (21.4) 51.0 (14.0) 44.9 (28.2) 33.7 (24.4)	23.8 (21.2) 46.8 (16.9) 22.1 (28.5) 18.3 (21.9)	6.4 (10.4) 11.0 (12.6) 7.5 (16.1) 4.5 (9.5)
Hospitalization in Past 12 months		2 (18.2)	6 (3.6)	39 (1.3)
Respiratory symptoms impeding daily activities in the last year		4 (36.4)	25 (15.1)	150 (4.9)

* based on responses from the St. George's Respiratory Questionnaire responding both cough and sputum production "almost every day" or "several days a week" over the past 4 weeks

**COPD was defined using the lower limit of normal definition (FEV_1/FVC Z-score less than -1.645 standard deviations)

Supplemental eTable 8. Respiratory symptoms and quality of life stratified by chronic bronchitis in Uganda

		Uganda		
		Chronic Bronchitis*		No Chronic Bronchitis* (n=3032)
		COPD** (n=22)	No COPD** (n=30)	
Respiratory Symptoms				
mMRC, n (%)				
1	Breathlessness with strenuous exercise	2 (9.1)	19 (63.3)	2378 (78.4)
2	Shortness of breath hurry on the level or walking up a slight hill	8 (36.4)	8 (26.7)	554 (18.3)
3	Walk slower on the level due to breathlessness and stop for breath when walking on own pace	5 (22.7)	2 (6.7)	82 (2.7)
4	Stop for breath after walking 100 meters or after a few minutes on the level	6 (27.3)	1 (3.3)	15 (0.5)
5	Too breathless to leave the house or breathlessness when dressing	1 (4.5)	0 (0)	3 (0.1)
Lung Function Questionnaire, mean (SD)		13.0 (4.0)	18.1 (3.2)	20.5 (2.5)
Ever Wheezing		17 (77.3)	9 (30.0)	376 (12.4)
Quality of Life				
EQ-5D score, mean (SD)		0.7 (0.2)	0.8 (0.1)	0.9 (0.1)
St. George Respiratory Questionnaire, mean (SD) Total Score Symptoms Activities Impacts		49.2 (25.0) 58.7 (19.5) 56.1 (26.9) 42.4 (28.9)	21.9 (21.4) 41.1 (14.2) 20.1 (27.9) 17.6 (22.7)	7.1 (12.2) 12.5 (11.4) 8.9 (17.4) 4.6 (11.6)
Hospitalization in Past 12 months		3 (13.6)	1 (3.3)	55 (1.8)
Respiratory symptoms impeding daily activities in the last year		7 (31.8)	6 (20.0)	132 (4.4)