Assessing the prevalence and impact of preserved ratio impaired spirometry in low-income and middle-income countries: a post-hoc cross-sectional analysis

Trishul Siddharthan, Kyle Grealis, Nicole M Robertson, Min Lu, Sibei Liu, Suzanne L Pollard, Shakir Hossen, Peter Jackson, Natalie A Rykiel, Adaeze C Wosu, Oscar Flores-Flores, Shumonta A Quaderi, Patricia Alupo, Bruce Kirenga, Federico Ricciardi, Julie A Barber, Ram K Chandyo, Arun K Sharma, Santa Kumar Das, Laxman Shresthra, J Jaime Miranda, William Checkley, John R Hurst, on behalf of the GECo Study Investigators*

Summary

Background More than 90% of the morbidity and mortality from chronic respiratory disease occurs in low-income and middle-income countries (LMICs), with substantial economic impact. Preserved ratio impaired spirometry (PRISm) is a prevalent lung function abnormality associated with increased mortality in high-income countries. We aimed to conduct a post-hoc analysis of a cross-sectional study to assess the prevalence of, the risk factors for, and the impact of PRISm in three diverse LMIC settings.

Methods We recruited a random, age-stratified and sex-stratified sample of the population in semi-urban Bhaktapur, Nepal; urban Lima, Peru; and rural Nakaseke, Uganda. Quality-assured post-bronchodilator spirometry was performed to American Thoracic Society standards and PRISm was defined as a forced expiratory volume in one second (FEV_1) of less than 80% predicted with a FEV_1/forced vital capacity ratio of 0·70 or more. We used t tests and χ^2 analyses to assess the relationships between demographic, biometric, and comorbidity variables with PRISm. Multivariable logistic models with random intercept by site were used to estimate odds ratios (ORs) with 95% CIs.

Findings 10 664 participants were included in the analysis, with a mean (SD) age of 56·3 (11·7) years and an equal distribution by sex. The prevalence of PRISm was 2·5% in Peru, 9·1% in Nepal, and 16·0% in Uganda. In multivariable analysis, younger age (OR for each decile of age 0·87, 95% CI 0·82–0·92) and being female (1·37, 1·18–1·58) were associated with increased odds of having PRISm. Biomass exposure was not consistently associated with PRISm across sites. Individuals with PRISm had impairment in respiratory-related quality of life as measured by the St George's Respiratory Questionnaire (OR by decile 1·18, 95% CI 1·10–1·25).

Interpretation The prevalence of PRISm is heterogeneous across LMIC settings and associated with age, female sex, and biomass exposure, a common exposure in LMICs. A diagnosis of PRISm was associated with worse health status when compared with those with normal lung function. Health systems in LMICs should focus on all spirometric abnormalities as opposed to obstruction alone, given the disease burden, reduced quality of life, and size of the undiagnosed population at risk.

Funding Medical Research Council.

Introduction

Morbidity and mortality from chronic respiratory diseases are increasing globally, with the largest increase in low-income and middle-income countries (LMICs).[1,2] The epidemiology of chronic obstructive pulmonary disease (COPD) and asthma in LMICs have been well described, although less is known about the epidemiology of other respiratory conditions.[3,4] The diagnosis of COPD is based on a reduction in the ratio of forced expiratory volume in one second (FEV_1 to forced vital capacity (FVC), but this is not the only pattern of abnormality seen on spirometry. Preserved ratio impaired spirometry (PRISm) is defined as an FEV_1 of less than 80% predicted and a FEV_1/FVC ratio of 0·70 or higher. PRISm has been associated with a range

of deleterious health outcomes in high-income country settings, including higher rates of hospitalisation and mortality than in those with normal lung function (in high-income settings).[5–8] PRISm is additionally associated with decreased quality of life and increased symptoms in high-income countries compared with those with normal lung function.[5–10] PRISm represents a heterogeneous group of conditions with structural and functional airway abnormalities that do not meet criteria for COPD; however, this pattern of abnormality might not be stable over time and can also reflect extra-thoracic alterations in body composition, such as obesity.[9] Therefore, PRISm is also a relevant marker of potential lung injury in LMICs and should be an area of further focus.[5–9,11]

Division of Pulmonary and Critical Care (T Siddharthan MD, K Grealis MSBST, S Hossen MSPH) **and Division of Biostatistics** (M Lu PhD, S Liu MSc), **School of Medicine, University of Miami, Miami, FL, USA; Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, MD, USA** (T Siddharthan, N M Robertson MD MPH, S L Pollard PhD MSPH, N A Rykiel MSc, W Checkley MD PhD); **Virginia Commonwealth University, Richmond, VA, USA** (P Jackson MD); **Department of International Health** (O Flores-Flores MD), **Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA** (A C Wosu PhD MPH, W Checkley); **Centro de Investigación del Envejecimiento (CIEN), Facultad de Medicina Humana, Universidad de San Martin de Porres, Lima, Peru** (O Flores-Flores); **UCL Respiratory** (S A Quaderi MBBS BSc, J R Hurst PhD FRCP) **and Department of Statistical Science** (F Ricciardi PhD, J A Barber PhD), **University College London, London, UK; College of Health Sciences, Makerere University, Kampala, Uganda** (P Alupo MBChB MMED, B Kirenga MMED PhD); **Department of Community Medicine, Kathmandu Medical College, Kathmandu, Nepal** (R K Chandyo PhD); **Institute of Medicine, Tribhuvan University, Kathmandu, Nepal** (A K Sharma MD, S Kumar Das MD,

L Shrestha MD); **CRONICAS Centre of Excellence in Chronic Diseases and School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru** (J Jaime Miranda MD PhD)

Correspondence to:
Dr Trishul Siddharthan, Division of Pulmonary and Critical Care, School of Medicine, University of Miami, Miami, FL 33136, USA
tsiddhar@miami.edu

Research in context

Evidence before this study
On Oct 5, 2023, we searched PubMed, Web of Science, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases with a combination of relevant medical subject heading (MeSH) and free text terms relating to "prevalence" [OR] "risk factors" [OR] "outcomes" [AND] "preserved ratio impaired spirometry" for papers published, without date or language restrictions. After screening, we identified 47 peer-reviewed studies published on preserved ratio impaired spirometry (PRISm) that have primarily been conducted in high-income countries rather than low-income and middle-income countries (LMICs) where chronic respiratory disease risk factors differ and the major burden of chronic respiratory diseases exists. In US and European cohorts, PRISm was found to be associated with female sex, obesity, and previous diagnosis of comorbid conditions. Among the published studies, PRISm prevalence ranges from 7% to 21% with different risk factors identified in different settings.

Added value of this study
This study is one of the first to estimate the prevalence of PRISm in a population-based sample across three diverse LMIC settings, with the prevalence ranging from 2·5% to 16·0%. Furthermore, we identified novel risk factors, whereas previously described risk factors of obesity and tobacco were not associated with PRISm in these LMIC settings. Lastly, we found that PRISm was associated with poor respiratory health, as determined by the St George's Respiratory Questionnaire, when compared with individuals without spirometric impairment.

Implications of all the available evidence
Although the prevalence of PRISm varies between LMIC sites, there is substantial disease burden across settings with risk factors that are more common in LMIC settings. When combined with data from high-income countries showing increased morbidity and mortality among this group, there is increasing evidence to suggest that public health efforts related to respiratory disease should broaden to target all spirometric abnormalities as opposed to addressing airflow obstruction alone.

PRISm has been associated with systemic inflammation, as well as increased cardiopulmonary (and therefore multisystem) morbidity and mortality.[5] Previous population-based studies in high-income countries have estimated the prevalence of PRISm as 7–21%.[5,8–10,12] These studies identified risk factors for PRISm as female (vs male) sex, tobacco use, obesity (vs a normal BMI), truncal fat mass (per kg and per percentage [continuously]), and previous diagnosis of asthma and cardiovascular disease.[5,6,9–11] However, few studies have investigated the population prevalence, risk factors, and development of PRISm in LMIC settings. LMICs have different risk factors and environmental exposures that can predispose individuals to impaired spirometry.[13] Previous studies in Peru have reported the prevalence of a restrictive spirometric pattern (now referred to as PRISm) that was more common in women and in rural (vs urban) settings.[14] The BOLD investigators also reported substantial variation by setting, and overall 16·4% of women and 11·7% of men had restrictive spirometry.[7] However, the study sites within the BOLD study did not include low-income countries and data from the middle-income countries included were limited by a cluster population-based sampling method.[3]

Although different studies have used different definitions for PRISm, this is unlikely to account for all the variation in prevalence that exists across LMICs. Because a substantial portion of patients with PRISm progress to develop spirometric airflow limitation (ie, COPD), identification of populations at high-risk and early clinical diagnosis of PRISm is of the utmost importance.[11] We aimed to test the hypothesis that the prevalence and clinical burden of PRISm in LMICs would be as great as those for COPD, and therefore that LMICs should focus on addressing all patterns of spirometric impairment, to maximise the value from testing in identifying people at risk of poor outcomes. We also hypothesised that the prevalence, risk factors, and burden of PRISm would vary across LMIC settings.

Methods
Study setting and design
This study is a post-hoc analysis of data from the multi-country, population-based Global Excellence in COPD Outcomes (GECo) study, which aims to assess the discriminative accuracy of simple questionnaires and peak expiratory flow to screen for COPD in three diverse LMIC settings, the protocol and primary results of which have been previously published.[15,16]

Nepal is a low-income country located in southeast Asia with a total population of 26·5 million people, of which 82% lived rurally at the time of recruitment (ie, in 2018). In 2017, Nepal's gross domestic product was £49 billion (2018 conversion rate £0·0069=1 Nepalese rupee), with 25% of the population living below the national poverty line (ie, 19262 Nepalese rupees per person per year). The study site was in Bhaktapur, 8 miles east of Kathmandu. The majority of the estimated 80000 inhabitants of Bhaktapur municipality were either craftsmen or businessmen and their families, while many domestic migrants had come to work in the outskirts at brick and carpet factories.

Peru is an upper-middle-income country located in South America with a population of 30·5 million people, 10 million of whom were living in the capital (Lima), and 79% of whom lived in urban areas at the time of recruitment. Peru's gross domestic product was £145 billion, and 26% of the population lived below the national poverty line (poverty rate at £1·61 or $2·15 a day [2017 purchasing power parity], 8·24% of the population in 2010). The minimum wage in Peru was 850 soles per month (ie, £186, conversion rate £0·2284 per 1 sole). We recruited in Pampas de San Juan de Miraflores, a peri-urban community in southern Lima.

Uganda is a low-income country located in east Africa with a total population of 37 million people, and a large rural population (>80%) at the time of recruitment. Uganda's gross domestic product was £19 billion with 20% living below the national poverty line (ie, 2666 Ugandan shillings per day per capita). The study was carried out in the Nakeseke District of Uganda. Most of the inhabitants (75%) were subsistence farmers.

We enrolled an age-stratified and sex-stratified random sample of full-time residents of the study areas in Nepal, Peru, and Uganda using established census data from each site. Within each site, a sampling frame of potentially eligible individuals was generated in eight strata in categories of age (40–44, 45–54, 55–64, and 65–95 years) and sex (male and female). Trained field workers attempted to contact participants up to three times. If a participant was unable to be located, refused to participate, or did not meet inclusion criteria, they were randomly replaced with another participant from the same sampling frame. Once a sampling frame was exhausted, a new sampling frame of potentially eligible individuals was selected from those remaining in the census. This study was reviewed and approved by the University College London Research Ethics Committee (9661/001), Johns Hopkins School of Medicine (IRB00139901), Uganda National Council for Science and Technology, Makerere School of Medicine (SOMREC 2017–096), Nepal Health Research Council (136/2017), and AB PRISMA (CE2147.17).

Data collection

Data collection relevant to this analysis was performed between January, 2018, and March, 2020, and included baseline demographic characteristics, medical history, and self-reported exposure history to cigarettes and household air pollution (ie, asking participants, do you use biomass fuels for cooking or heating daily?). Trained research assistants collected biometric data including height, weight, and blood pressure. Quality-assured post-bronchodilator spirometry was performed according to American Thoracic Society standards. Participants reported health-related quality of life measures with the EQ-5D and the St George's Respiratory Questionnaire (SGRQ), and symptom burden with the modified Medical Research Council questionnaire, previously validated in these settings.[17–19]

Definitions

PRISm was defined as a post-bronchodilator FEV_1 of less than 80% predicted with post-bronchodilator FEV_1/FVC of 0·70 or more using the Global Lung Initiative Mixed Ethnic reference values.[20] We further stratified PRISm severity based on post-bronchodilator FEV_1: mild was considered to be 50% or more but less than 80% predicted; moderate was considered 30% or more but less than 50%; and severe was considered less than 30%.[6] COPD was defined as a post-bronchodilator FEV_1/FVC of less than 0·70 using the Global Lung Initiative Mixed Ethnic reference values. Normal lung function was defined as the absence of COPD or PRISm. Participant characteristics included current biomass exposure (yes or no), education level (primary school incomplete, primary school, secondary school, or higher education) and comorbidities (previous diagnosis of heart disease [yes or no], treated pulmonary tuberculosis [yes or no], or diabetes [yes or no]).

Data analysis

Our primary analysis was to characterise the prevalence of PRISm. We conducted secondary analyses to assess risk factors for PRISm and the health impact of PRISm by investigating the associations between PRISm and quality of life and symptom burden.

Characteristics of those with and without PRISm were compared using standard two sample tests (*t* tests and χ^2 test). We used multivariable logistic regression models to further investigate the association between the odds of PRISm and various risk factors: age, sex, daily biomass exposure (yes or no), daily cigarette smoking (yes or no), previous infection with tuberculosis, BMI, comorbid conditions (heart disease or diabetes), and secondary education. We then used multivariable logistic regression models with random intercept by site to assess the association between PRISm and respiratory health status (SGRQ total and component scores) in separate comparisons against those with normal spirometry and those with COPD adjusted for previously identified risk factors. Linear regression was used to compare quality of life scores between those with and without PRISm.

Sensitivity analysis was conducted using the Global Lung Function 2012 Caucasian reference value. Additionally, race-neutral reference values were used to determine if the findings were consistent regardless of the reference chosen. All p values were two sided, and we used $p < 0.05$ as the threshold for statistical significance. Each analysis used all available data and those with missing values were excluded. All analysis was performed using R (version 4.2.1) and SAS Studio (version 9.4).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.
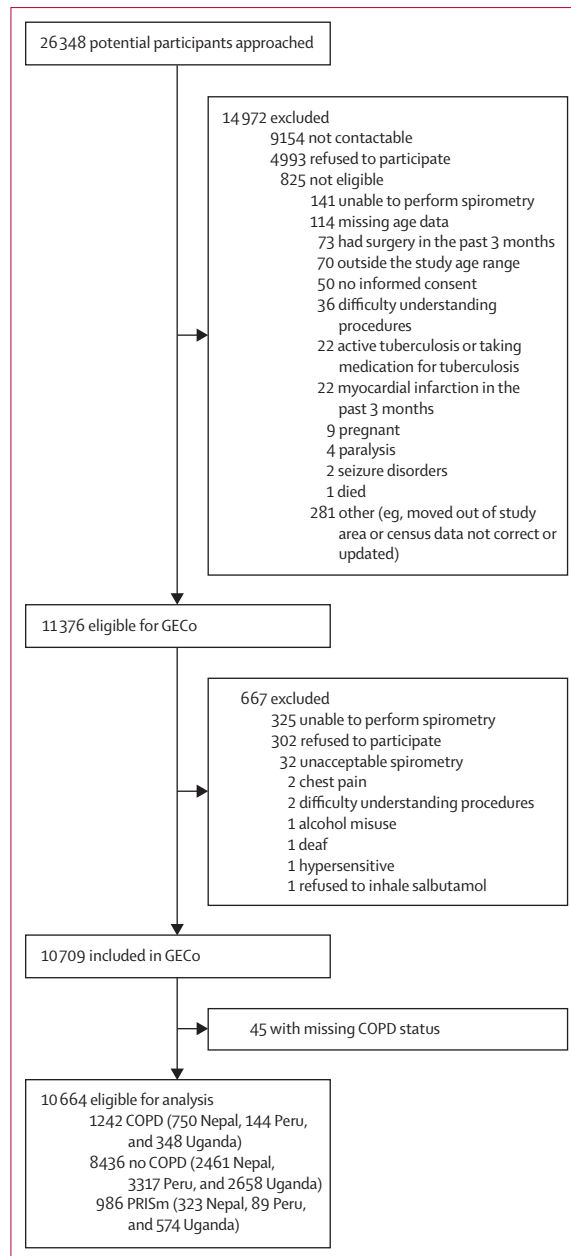
Figure 1: Trial profile
COPD=chronic obstructive pulmonary disorder. PRISm=preserved ratio impaired spirometry.

Results

10 664 participants with complete data were included in the analysis (figure 1). The mean age of the cohort was 56·3 (SD 11·7) years with an equal sex distribution (5359 [50·3%] being female; table). The unweighted prevalence of PRISm using our primary definition across the sites was 9·2% (986/10 664) but varied between 2·5% (89/3550) in Peru, 9·1% (323/3534) in Nepal, and 16·0% (574/3580) in Uganda (figure 1; appendix 1 p 5). The unweighted prevalence of COPD was

21·2% (750/3534) in Nepal, 4·1% (144/3550) in Peru, and 9·7% (348/3580) in Uganda (appendix 1 p 5). When stratifying PRISm by disease severity the majority (966 [98·0%] of 986) of the sample had mild restriction. The highest prevalence of more severe disease was in Peru, with 4·5% (4/89) of PRISm cases classified as severe.

Risk factors for PRISm when compared with normal lung function by individual site, are reported in figure 2 and appendix 1 (pp 2–3). Across sites, individuals with PRISm were more likely to be younger (odds ratio [OR] for each decile of age=0·87, 95% CI 0·82–0·92) and female (1·37, 1·18–1·58). Biomass fuel use was found to have negative association with PRISm in Uganda (OR 0·58, 0·35–0·75); however, this finding was not consistent across sites (OR 0·85, p=0·40 for Nepal and 2·68, p=0·35 for Peru). Higher level of education (OR 0·50, 0·41–0·61) showed lower association with PRISm than other levels of education, as did current smoking (0·71, 0·56–0·89) compared with those who have never smoked. Although there was a higher prevalence of PRISm among those with self-reported disease (appendix 1 p 5) there was no significant association between PRISm and self-reported asthma (OR 0·91, 0·62–1·29), COPD (1·23, 0·47–2·71), and tuberculosis (0·95, 0·66–1·34).

When comparing individuals with PRISm to those with normal spirometry, PRISm was associated with greater impairment in respiratory-related health status as measured by the overall SGRQ (OR by decile 1·18, 95% CI 1·10 to 1·25), activity (1·08, 1·03 to 1·14), impact (1·17, 1·08 to 1·26), and symptom (1·14, 1·06 to 1·21). Activity, impact, and symptoms are domains of the SGRQ. Furthermore, when assessing PRISm severity based on FEV_1, there was a worsening of SGRQ total score with increasing PRISm severity (β=–0·01, 95% CI –0·01 to –0·01; p<0·01). However, when comparing those with PRISm to only those with COPD, individuals with PRISm were overall less symptomatic (OR 0·67, 95% CI 0·61 to 0·73) and with less effects on the activity (0·77, 0·72 to 0·83), impact (0·79, 0·72 to 0·87), and symptom components (0·69, 0·63 to 0·75).

In sensitivity analysis, using a definition of PRISm based on the lower limit of normal using race neutral reference equations, 138 participants with COPD were reclassified with PRISm. The overall prevalence of PRISm decreased to 6·4% (685/9979) with 6·7% (238/3296) in Nepal, 1·6% (58/3492) in Peru, and 10·9% (389/3191) in Uganda. We found similar results with using race neutral and and National Health and Nutrition Examination Survey III equations (appendix 1 p 8).

Discussion

In this analysis of a multi-site LMIC cohort recruited using random population screening, we found variation in the prevalence of PRISm across sites, with risk factors

varying by site. However, we noted similar and clinically significant impact of PRISm on respiratory symptoms and quality of life when compared with normal spirometry. PRISm was associated with female sex, younger age, and had no associations with current smoking or BMI, when compared with those with normal spirometry. Previous studies have shown that PRISm is associated with comorbidities; however, no associations between comorbidities and PRISm were found, likely a result of the limitations with using self-reported non-communicable disease diagnoses in LMICs. These results show the high prevalence and potential burden of PRISm in LMIC settings and support considering all patterns of impairment on spirometry to maximise the value of identifying people at risk of poor outcomes in such settings.

Although COPD is increasingly studied in LMIC settings, few studies have sought to assess the prevalence and burden of PRISm. LMIC settings can have distinct risk factors for respiratory disease that can result in PRISm that are less common in high-income countries.[13,14] Mannino and colleagues provided initial assessments of PRISm in the BOLD cohort and found this pattern of abnormality to be prevalent, with risk factors including diabetes, heart disease, and hypertension.[7] These factors are more commonly diagnosed in high-income country settings where adequate primary care infrastructure exists.[21] The present results show a protective effect of previous comorbid diagnoses such as cardiovascular disease in pooled analysis, which might represent higher socioeconomic status among individuals with self-reported disease. Although previous studies have shown an association between biomass exposure and PRISm, our findings did not show similar associations.[7,14]

Notably, there was a higher prevalence of PRISm among those with self-reported asthma, COPD, and tuberculosis than those without these conditions. This could be a result of misdiagnosis and emphasises the need to improve access to spirometry in LMIC settings, to support differential diagnosis. When comparing the health impact of PRISm to that in people with COPD, individuals with PRISm had less impairment in respiratory health-related quality of life as assessed by SGRQ, although there was reduced quality of life in PRISm compared with those with normal spirometry. Previous studies have shown increased symptom burden among those with PRISm, as well as an increased risk of mortality.[5] PRISm has been shown to be a precursor to early obstructive or restrictive disease in some studies.[8] This finding is likely related to the importance impaired FEV_1 has as a marker of respiratory health, irrespective of the ratio of FEV_1/FVC.

One area of focus from previous studies related to PRISm is the relevance of exposures. Although tobacco exposure was protective for PRISm, it remains a leading risk factor for airway obstruction. Previous studies have shown an association between biomass exposure and PRISm. Biomass fuel exposure was not found to be

	Nepal (n=3534)	Peru (n=3550)	Uganda (n=3580)	Total (n=10 664)
Age, years	56·2 (11·7)	56·6 (11·3)	56·1 (12·1)	56·3 (11·7)
Sex				
Female	1769 (50·1%)	1767 (49·8%)	1823 (50·9%)	5359 (50·3%)
Male	1765 (49·9%)	1783 (50·2%)	1757 (49·1%)	5305 (49·7%)
Sitting height, cm	82·4 (5·1)	81·1 (6·9)	80·1 (27·7)	81·2 (16·8)
Smoker				
Ever smoked	1148 (32·5%)	1975 (55·6%)	591 (16·5%)	3714 (34·8%)
Current smoker	727 (20·6%)	559 (15·7%)	355 (9·9%)	1641 (15·4%)
Missing data	0	1 (<0·1%)	3 (0·1%)	4 (<0·1%)
Biomass				
Current biomass	187 (5·3%)	16 (0·5%)	2932 (81·9%)	3135 (29·4%)
Missing data	0	2 (<0·1%)	16 (0·4%)	18 (0·2%)
BMI, kg/m²	26·1 (4·1)	29·7 (4·7)	23·1 (4·7)	26·3 (5·3)
Underweight	97 (2·7%)	9 (0·3%)	447 (12·5%)	553 (5·2%)
Healthy	1364 (38·6%)	486 (13·7%)	2149 (60·0%)	3999 (37·5%)
Overweight	1501 (42·5%)	1559 (43·9%)	686 (19·2%)	3746 (35·1%)
Obese	551 (15·6%)	1387 (39·1%)	276 (7·7%)	2214 (20·8%)
Severe obesity	8 (0·2%)	109 (3·1%)	20 (0·6%)	137 (1·3%)
Missing data	13 (0·4%)	0	2 (0·1%)	15 (0·1%)
Employment				
Employed	2522/2925 (86·2%)	1964/2793 (70·3%)	3128/3218 (97·2%)	7614/8936 (85·2%)
Unemployed	68/2925 (2·3%)	137/2793 (4·9%)	48/3218 (1·5%)	253/8936 (2·8%)
Education level				
Never attended school	1686 (47·7%)	133 (3·7%)	730 (20·4%)	2549 (23·9%)
Primary school incomplete	544 (15·4%)	569 (16·0%)	1948 (54·4%)	3061 (28·7%)
Primary school complete	464 (13·1%)	720 (20·3%)	622 (17·4%)	1806 (16·9%)
Secondary or high school complete	566 (16·0%)	1599 (45·0%)	183 (5·1%)	2348 (22·0%)
Any higher education	273 (7·7%)	521 (14·7%)	77 (2·2%)	871 (8·2%)
Missing data	1 (<0·1%)	2 (<0·1%)	3 (0·1%)	6 (0·1%)
EQ-5D	6·6 (1·6)	6·1 (1·9)	5·8 (1·5)	6·2 (1·7)
St George's Respiratory Questionnaire total	6·0 (1·9–11·2)	2·8 (0·8–7·9)	2·4 (1·1–8·2)	3·5 (1·5–9·6)
Self-reported medical history				
Asthma	131 (3·7%)	255 (7·2%)	27 (0·8%)	413 (3·9%)
Chronic obstructive pulmonary disease	55 (1·6%)	5 (0·1%)	3 (0·1%)	63 (0·6%)
Previous tuberculosis	113 (3·2%)	279 (7·9%)	38 (1·1%)	430 (4·0%)
Previous heart disease	86 (2·4%)	147 (4·1%)	15 (0·4%)	248 (2·3%)
Missing data	0	2 (<0·1%)	2 (0·1%)	4 (<0·1%)
Lung function Z score				
Forced expiratory volume in 1 s Z score	–0·5 (1·2)	0·8 (1·3)	–0·5 (1·2)	–0·1 (1·4)
Forced vital capacity Z score	–0·2 (1·1)	0·8 (1·2)	–0·5 (1·2)	0·1 (1·3)

Data are n (%), mean (SD), or median (IQR).

Table: **Characteristics of study participants by normal spirometry, chronic obstructive pulmonary disease, and preserved ratio impaired spirometry**
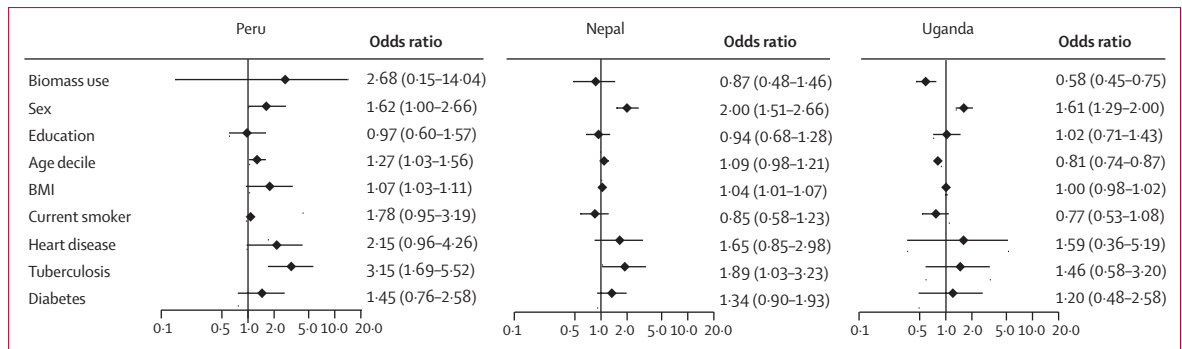
Figure 2: Risk factors associated with PRISm stratified by site
Estimates from multiple regression adjusting for age (decile), sex (male or female), BMI (continuous), daily cigarette smoking (yes or no), biomass use (yes or no), and comorbidities (yes or no). PRISm=preserved ratio impaired spirometry.

consistently associated with PRISm in our site-specific analysis in the pooled analysis. This could be a result of collinearity between biomass and other risk factors of low socioeconomic status at each of the individual sites, and the skewed distribution of both biomass and prevalence of PRISm at each individual site.

This study has several strengths including age-stratified and sex-stratified population-based sampling across sites, as well as quality assured spirometry. Study sites represent diversity in degrees of urbanisation, socioeconomic status, and environmental exposure. Notably, the present data included a rural site, which are generally poorly described in the literature.

The present study also has several limitations. First, the definition of PRISm varies with some studies using fixed cutoffs and others using the lower limit of normal to define disease. Using different definitions of PRISm (percent predicted and fixed ratio for FEV_1/FVC) altered the estimated prevalence of disease; however, this did not change the OR estimates of risk factors or respiratory symptom burden among this population. Most of the individuals misclassified between different definitions had milder disease. Furthermore, prediction equations that inform the predicted FEV_1 might not be representative of the study population. While the present analysis uses mixed ethnic equations from the Global Lung Initiative, we have additionally included race-neutral equations that might be more generalisable across settings. Notably, the results are cross-sectional and there remains an urgent need to understand the stability of PRISm in LMIC settings over time, to better understand the progression of PRISm, the progression to COPD, or reversion to normal spirometry, all of which have been reported in high-income country settings.[9] Although the random population-based sample aimed to limit bias, higher-income, employed individuals might have been less likely to participate, as recruitment occurred during the working day.

The present results suggest a need for a broader consideration of chronic respiratory disease based on all patterns of spirometric impairment in LMIC settings.

While testing and treatment for COPD is expanding in LMIC settings, there is a need to address chronic respiratory diseases more comprehensively.[22] By understanding the risk factors associated with PRISm, clinicians in LMICs can designate patient populations who are at high risk and monitor respiratory symptoms and quality of life in these populations; however, further work is needed to identify risk factors across settings. There remains a crucial scarcity of access to pulmonary function testing, as well as trained clinicians to conduct and interpret tests in primary care across LMIC settings. Although diseases such as COPD and asthma have well defined global guidelines, there is limited understanding of interventions to improve outcomes among patients with PRISm, and further work is needed to understand harm reduction, diagnostic strategies, and treatments for this pattern of spirometric impairment.

The prevalence of PRISm is heterogeneous across LMIC settings and associated with several risk factors that are more common in LMIC than high-income country settings. PRISm is associated with impaired respiratory-related quality of life compared with participants with normal spirometry. Holistic assessments of spirometric impairment are necessary in LMICs to identify those at greatest risk of respiratory morbidity.

GECo Study Investigators
Trishul Siddharthan (Division of Pulmonary and Critical Care, School of Medicine, University of Miami, Miami, FL, USA and Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, MA, USA); Kyle Grealis (Division of Pulmonary and Critical Care, School of Medicine, University of Miami, Miami, FL, USA); Nicole M Robertson (Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, MA, USA); Min Lu (Division of Biostatistics, University of Miami, Miami, FL, USA); Sibei Lu (Division of Biostatistics, University of Miami, Miami, FL, USA); Suzanne L Pollard (Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, MA, USA); Shakir Hossen (Division of Pulmonary and Critical Care, School of Medicine, University of Miami, Miami, FL, USA); Peter Jackson (Virginia Commonwealth University, Richmond, VA, USA); Natalie A Rykiel (Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, MA, USA); Adaeze C Wosu (Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MA, USA); Oscar Flores-Flores (Department of

International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA and Centro de Investigación del Envejecimiento (CIEN), Facultad de Medicina Humana, Universidad de San Martin de Porres, Lima, Peru); Shumonta A Quaderi (UCL Respiratory, University College London, London, UK); Patricia Alupo (College of Health Sciences, Makerere University, Kampala, Uganda); Bruce Kirenga (College of Health Sciences, Makerere University, Kampala, Uganda); Federico Ricciardi (Department of Statistical Science, University College London, London, UK); Julie A Barber (Department of Statistical Science, University College London, London, UK); Ram K Chandyo (Department of Community Medicine, Kathmandu Medical College, Kathmandu, Nepal); Arun K Sharma (Institute of Medicine, Tribhuvan University, Kathmandu, Nepal); Santa Kumar Das (Institute of Medicine, Tribhuvan University, Kathmandu, Nepal); Laxman Shresthra (Institute of Medicine, Tribhuvan University, Kathmandu, Nepal); J Jaime Miranda (CRONICAS Centre of Excellence in Chronic Diseases and School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru); William Checkley (Division of Pulmonary and Critical Care, School of Medicine and Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MA, USA); John R Hurst (UCL Respiratory, University College London, London, UK); Susan Michie (University College London, London, UK); Zachos Anastasiou (University College London, London, UK); Robert A Wise (Johns Hopkins University, Baltimore, MD, USA); Karbir Nath Yogi (Institute of Medicine, Baltimore, MD, USA); Denis Mawanda (Makerere University, Kampala, Uganda); Faith Nassali (Makerere University, Kampala, Uganda); Robert Kalyesubula (Makerere University, Kampala, Uganda); Elisa Romani-Huacani (AB PRISMA, Lima, Peru); Adithya Cattamanchi (University of California San Francisco, San Francisco, CA, USA); Marta Soares (York University, York, UK); Maria Cardenas (University of Cayetano, Lima, Peru); Sakshi Mohan (York University, York, UK).

Contributors
TS, SLP, JAB, BK, JJM, WC, and JRH contributed to the conception and design of the study. TS, SLP, ML, KG, SH, SAQ, NAR, ACW, PA, JAB, RKC, OF-F, BK, JJM, FR, AKS, SKD, LS, WC, JRH, and SL contributed to the acquisition, analysis, or interpretation of data. TS, NMR, JRH, and SL contributed to the drafting of the manuscript. TS, KG, NMR, SLP, SH, PJ, NAR, ACW, OF-F, SAQ, PA, BK, FR, LS, JJM, WC, JRH, and SL contributed to the critical revision of the manuscript for important intellectual content. ML, SH, and KG contributed to the statistical analysis. TS, SLP, JAB, BK, JJM, WC, and JRH contributed to the obtained funding. TS, SLP, SAQ, NAR, ACW, PA, RKC, OF-F, BK, JJM, AKS, LS, WC, and JRH contributed to the administrative, technical, or material support. TS, SLP, SAQ, NAR, ACW, PA, JAB, RKC, OF-F, BK, JJM, AKS, SKD, LS, WC, and JRH provided supervision. TS, JRH, and ML had full access to all the data in the study and verified the data. All authors had full access to all the data.

Equitable partnership declaration
The authors of this paper have submitted an equitable partnership declaration (appendix 2). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health*'s broader goal to decolonise global health.

Declaration of interests
TS reports grants or contracts from the Australian Lung Health Initiative; consulting fees from Verona Pharmaceuticals; and a leadership or fiduciary role in board, society, committee, or advocacy groups for 4D Medical. OF-F reports a Global Emerging Leader Award grant from the Fogarty International Centre. JJM reports grant support and payments made to their institution from the Alliance for Health Policy and Systems Research, Bloomberg Philanthropies, FONDECYT via CIENCIACTIVA and CONCYTEC, the British Council, British Embassy, the Newton-Paulet Fund, the UK Department for International Development, the UK Medical Research Council, the Wellcome Global Health Trials partnership, the Fogarty International Center, Grand Challenges Canada, the International Development Research Center Canada, Inter-American Institute for Global Change Research, the National Cancer Institute, National Heart, Lung, and

Blood Institute, National Institute of Mental Health, the Swiss National Science Foundation, the UK Research and Innovation (UKRI) Biotechnology and Biological Sciences Research Council, the UKRI Engineering and Physical Sciences Research Council, the UKRI Medical Research Council, the Wellcome Trust, and the World Diabetes Foundation; a contract from Health Action International; consulting fees from the Pan American Health Organization and Bloomberg Philanthropies; participation on data safety monitoring or advisory boards for the Nigeria Sodium Study, the Intensive care bundle with blood pressure Reduction in Acute Cerebral haemorrhage Trial, the Latin American Brain Health institute, Universidad Adolfo Ibáñez (Chile), Programa de Gastronomía, Facultad de Estudios Interdisciplinarios, Pontificia Universidad Católica del Perú, and the InterAmerican Heart Foundation; being Co-chair of the Independent Group of Scientists, 2023 Global Sustainable Development Report, UN; being a member of the Scientific Expert Committee, Global Data Collaborative for CV Population Health, the World Heart Federation, Microsoft, and Novartis Foundation; being a member of the Scientific and Technical Advisory Committee for the Alliance for Health Policy and Systems Research, WHO; being a member of WHO's Technical Advisory Group on non-communicable disease-related research and innovation, Non-communicable Diseases Department, WHO; and being a member of the Advisory Scientific Committee, Instituto de Investigación Nutricional, Peru. All other authors declare no competing interests.

Data sharing
Individual participant data that underlie the results reported in this Article, after de-identification (text, tables, figures, and appendices) will be made available to anyone who requests access by emailing the corresponding author.

References
1   Burney P, Jarvis D, Perez-Padilla R. The global burden of chronic respiratory disease in adults. *Int J Tuberc Lung Dis* 2015; **19:** 10–20.
2   Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392:** 1736–88.
3   Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007; **370:** 741–50.
4   Menezes AMB, Perez-Padilla R, Jardim JRB, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet* 2005; **366:** 1875–81.
5   Wan ES, Castaldi PJ, Cho MH, et al. Epidemiology, genetics, and subtyping of preserved ratio impaired spirometry (PRISm) in COPDGene. *Respir Res* 2014; **15:** 89.
6   Schwartz A, Arnold N, Skinner B, et al. Preserved ratio impaired spirometry in a spirometry database. *Respir Care* 2021; **66:** 58–65.
7   Mannino DM, McBurnie MA, Tan W, et al. Restricted spirometry in the Burden of Lung Disease Study. *Int J Tuberc Lung Dis* 2012; **16:** 1405–11.
8   Wijnant SRA, De Roos E, Kavousi M, et al. Trajectory and mortality of preserved ratio impaired spirometry: the Rotterdam Study. *Eur Respir J* 2020; **55:** 1901217.
9   Higbee DH, Granell R, Davey Smith G, Dodd JW. Prevalence, risk factors, and clinical implications of preserved ratio impaired spirometry: a UK Biobank cohort analysis. *Lancet Respir Med* 2022; **10:** 149–57.
10 Heo IR, Kim HC, Kim TH. Health-related quality of life and related factors in persons with preserved ratio impaired spirometry: data from the Korea National Health and nutrition examination Surve. *Medicina (Kaunas)* 2020; **57:** 4.
11 Wan ES, Balte P, Schwartz JE, et al. Association between preserved ratio impaired spirometry and clinical outcomes in US adults. *JAMA* 2021; **326:** 2287–98.
12 Çolak Y, Nordestgaard BG, Vestbo J, Lange P, Afzal S. Prognostic significance of chronic respiratory symptoms in individuals with normal spirometry. *Eur Respir J* 2019; **54:** 1900734.

13   Jackson P, Siddharthan T. The global significance of PRISm: how data from low- and middle-income countries link physiology to inflammation. *Eur Respir J* 2020; **55:** 2000184.

14   Siddharthan T, Grigsby M, Miele CH, et al. Prevalence and risk factors of restrictive spirometry in a cohort of Peruvian adults. *Int J Tuberc Lung Dis* 2017; **21:** 1062–68.

15   Siddharthan T, Pollard SL, Quaderi SA, 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:** 571.

16   Siddharthan T, Pollard SL, Quaderi SA, et al. Discriminative accuracy of chronic obstructive pulmonary disease screening instruments in 3 low- and middle-income country settings. *JAMA* 2022; **327:** 151–60.

17   Morgan BW, Grigsby MR, Siddharthan T, et al. Validation of the Saint George's Respiratory Questionnaire in Uganda. *BMJ Open Respir Res* 2018; **5:** e000276.

18   Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20:** 1727–36.

19   Williams N. The MRC breathlessness scale. *Occup Med (Lond)* 2017; **67:** 496–97.

20   Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005; **26:** 319–38.

21   Masekela R, Zurba L, Gray D. Dealing with access to spirometry in Africa: a commentary on challenges and solutions. *Int J Environ Res Public Health* 2018; **16:** 62.

22   Hurst JR, Buist AS, Gaga M, et al. Challenges in the implementation of COPD guidelines in low- and middle-income countries: an ATS workshop report. *Ann Am Thorac Soc* 2021; **18:** 1269–77.