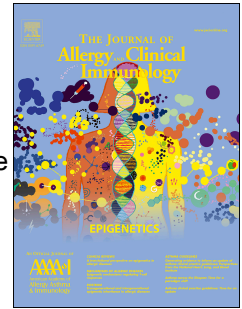


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Epidemiology and Risk Factors of Asthma-COPD Overlap in Low- and Middle-Income Countries

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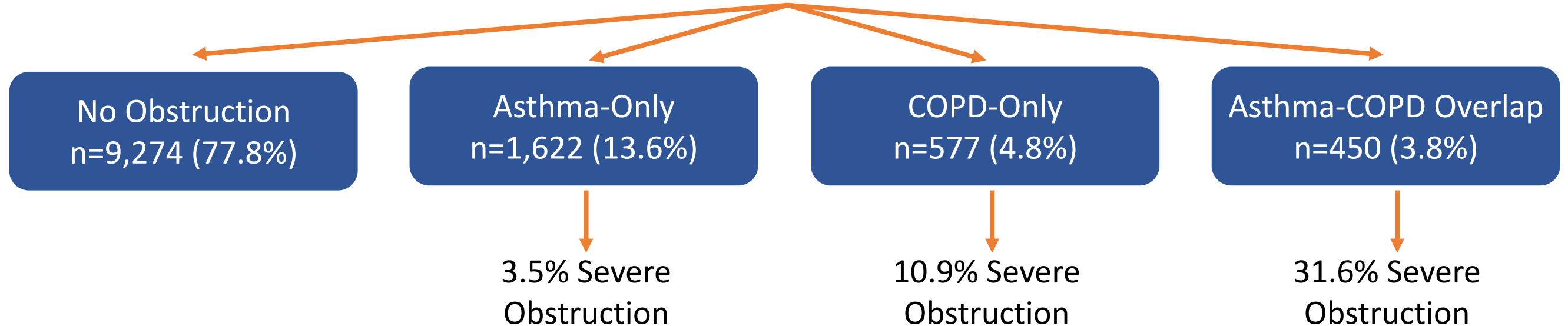
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Asthma-COPD Overlap in Low- and Middle-Income Countries

Multi-country, multi-center analysis
Cross-sectional data from four studies
n=11,923



Epidemiology and Risk Factors of Asthma-COPD Overlap in Low- and Middle-Income Countries

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Declaration of Interests

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Abstract*Background*

Asthma-COPD Overlap (ACO) represents the confluence of bronchial airway hyper reactivity and chronic airflow limitation and has been described as leading to worse lung function and quality of life than found with either singular disease process.

Objective

We aimed to describe the prevalence and risk factors for ACO among adults across six low- and middle-income countries (LMICs).

Methods

We compiled cross-sectional data for 11,923 participants aged 35-92 years from four population-based studies in 12 settings. We defined COPD as post-bronchodilator FEV₁/FVC below the lower limit of normal, asthma as wheeze or medication use in 12 months or self-reported physician diagnosis, and ACO as having both.

Results

The prevalence of ACO was 3.8% (0% in rural Puno, Peru to 7.8% in Matlab, Bangladesh). The odds of having ACO were higher with household exposure to biomass fuel smoke (OR=1.48; 95% CI 0.98–2.23), smoking (OR=1.28 per 10 pack-years; 1.22–1.34), and having primary or less education (OR=1.35; 1.07–1.70) compared to non-obstructed individuals. ACO was associated with severe breathing obstruction (FEV₁ % predicted <50; 31.5% of ACO vs. 10.9% of COPD

alone or 3.5% of asthma alone) and severe spirometric deficits compared to participants with asthma (-1.61 z scores FEV₁; -1.48, -1.75) or COPD alone (-0.94 z scores; -0.78, -1.10).

Conclusion

ACO may be as prevalent and more severe in LMICs than has been reported in high-income settings. Exposure to biomass fuel smoke may be an overlooked risk factor and we favor diagnostic criteria for ACO that include environmental exposures common to LMICs.

Clinical Implications

Due to risk factors common to low- and middle-income countries, such as rapid urbanization and biomass exposure, asthma-COPD Overlap may be as common and more severe than in high-income settings.

Capsule Summary

Asthma-COPD Overlap is examined in a large, multinational cohort of adults across low- and middle-income settings. Risk factors prevalent in low- and middle-income countries are investigated and ACO is found to be common and severe.

Key Words

Asthma; chronic obstructive pulmonary disease; COPD; overlap; Asthma-COPD Overlap; ACO; epidemiology; risk factors; health outcomes; spirometry; population-based

Abbreviations

ACO – Asthma-COPD Overlap

ALR – Alternating Logistic Regression

ATS/ERS – American Thoracic Society/European Respiratory Society

BMI – Body Mass Index

COPD – Chronic Obstructive Pulmonary Disease

FEV₁ – Forced Expiratory Volume in One Second

FVC – Forced Vital Capacity

GLI – Global Lung Function Initiative

LiNK – Lung Function in Nakaseke and Kampala Study

LMIC – Low- and Middle-Income Country

OR – Odds Ratio

PRISA – Pulmonary Risk in South America Study

Introduction

Asthma-COPD Overlap (ACO) refers to chronic respiratory disease comprised of clinical and biological markers of both asthma and chronic obstructive pulmonary disease (COPD), each of which are leading causes of disability and death worldwide.¹⁻⁴ Although COPD and asthma have been well defined, the mechanism of injury in ACO has not.⁵ COPD is characterized by poorly reversible airflow obstruction via an abnormal inflammatory response in the lungs, marked by innate and adaptive immune responses to noxious exposures such as cigarette smoke.⁶ Asthma is characterized by airway hyper responsiveness and inflammation that results in reversible airway obstruction.⁷ Current opinions largely agree that ACO is not a standalone condition but lack consensus on whether the underlying mechanism of injury represents a synergistic result of unique phenotypes of asthma and COPD or a spectrum of eosinophilic and neutrophilic inflammatory illness.⁸⁻¹¹ In general, ACO has been defined as increased variability of airflow in association with an incompletely reversible airway obstruction, a symptomatic description that could be representative of many underlying physiologies.¹²

To date, research has less often focused on individuals whose illness classification lies in between COPD and asthma. Most randomized controlled trials focusing on COPD and asthma have included only participants with clearly-defined cases of disease, failing to represent the breadth of respiratory disease that exists in populations.¹³⁻¹⁵ ACO refers to people who fail to fall into these strictly-defined sets.

The only known population-based studies of ACO have been performed in high-income settings (Korea, Italy, Norway, the Netherlands) or in metropolitan areas of low- and middle-income countries (LMICs), such as the PLATINO Study.¹⁷⁻²² Little is known about ACO in other resource-poor settings. Since ACO may represent the confluence of eosinophilic and neutrophilic inflammation, risk factors unique to low- and middle-income countries – unplanned urbanization, biomass fuel exposure, and increasing tobacco use – need to be examined to understand the driving forces behind ACO in LMICs.²³⁻²⁶ With these factors in mind, the potential exists for there to be a significant population of undiagnosed ACO in the low- and middle-income world.

A recent workshop led by the American Thoracic Society and the United States National Heart, Lung, and Blood Institute called for further epidemiological investigation of ACO.²⁷ We hypothesize that, due to exposures common to LMIC settings, ACO will be comparably prevalent to high-income areas. To that aim, we characterize ACO in a population-based sample of adults from multiple LMICs, which represent a broad range of geographical settings including wide degrees of urbanization and ethnic diversity. Additionally, we compare individuals with ACO to those without respiratory disease, those with asthma-only, and those with COPD-only, examining risk factors and lifestyle outcomes between groups.

Methods

Study Setting

We compiled data for this analysis from four population-based studies conducted in LMICs under the sponsorship of the United States National Institutes of Health. These included the CRONICAS Cohort Study in Peru,²⁸ the Pulmonary Risk in South America (PRISA) study in Argentina, Chile, and Uruguay;²⁹ a longitudinal study in Bangladesh,³⁰ and the Lung Function in Nakaseke and Kampala (LiNK) study in Uganda.³¹ In total, the data represent 12 sites of varying geography and socioeconomic status in six different LMICs.

Study Design

Multi-stage age- and sex-stratified random sampling was used in PRISA and CRONICAS, whereas the Bangladesh study used simple random sampling. LiNK used population proportional to size sampling, as outlined by the WHO.^{32, 33} Recruitment began in 2010 for CRONICAS, in 2011 for PRISA and Bangladesh, and in 2015 for LiNK. The lower age cutoffs were 35 years for LiNK and CRONICAS and 40 years for the Bangladesh study with no upper limit, whereas PRISA included participants aged 45 to 75 years. Each study required residency of the area and the ability to give informed consent. Common exclusion criteria included pregnancy, active pulmonary tuberculosis, recent myocardial infarction, and recent surgery of the chest, lungs, heart, or eyes. Each study limited enrollment to one person per household. Field workers completed confidentiality training and informed consent was collected for all research participants. Each study obtained research approval from their local and international internal review boards.

Field workers performed spirometry following American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines using flow-based, portable Easy-On-PC spirometers (CRONICAS and LiNK) and EasyOne spirometers (Bangladesh and PRISA), both of which use the same technology developed by ndd Medical Technologies (Zurich, Switzerland).³⁴ Lung function was recorded as Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV₁), and FEV₁/FVC ratio. These measures were transformed into z scores based on the Global Lung Function Initiative (GLI) mixed-ethnic reference population.³⁵ Post-bronchodilator spirometry was conducted 15 minutes after inhaled salbutamol in Bangladesh, LiNK, and CRONICAS while albuterol was used in PRISA. CRONICAS and PRISA conducted post-bronchodilator assessment on all participants, while LiNK and the Bangladesh study only conducted post-bronchodilator testing on participants who were obstructed following initial testing. Specific methods for collection of other data are outlined in previous publications.²⁸⁻³¹

Outcome Measures

We defined COPD as a post-bronchodilator FEV₁/FVC ratio below the lower limit of normal (defined as the lowest 5th percentile) of the GLI mixed-ethnic reference population; asthma as fulfilling one of three criteria: self-report of wheezing in one year, self-report of medication use for asthma in one year, or self-report of a physician diagnosis of asthma; and ACO as the presence of both conditions.^{20, 21, 36-38} Based on these criteria, participants were then categorized into four groups: participants without asthma or COPD (non-obstructed), participants with asthma and no COPD (asthma-only), participants with COPD and no asthma (COPD-only), and participants with both (Asthma-COPD Overlap).

We defined hospitalization as self-report of hospitalization for primarily pulmonary reason and lifestyle impairment as self-report of impairment with daily activities due to breathing, both over the last year. Percent of reversibility was defined as the post-bronchodilator FEV₁ over the pre-bronchodilator FEV₁. Bronchodilator reversibility (as a dichotomous outcome) was defined as $\geq 12\%$ improvement and ≥ 200 mL increase in FEV₁ or FVC according to ATS/ERS criteria.³⁹ Severe obstruction on spirometry was defined as an FEV₁ less than 50% of predicted based on reference values.⁴⁰

Risk factors

We defined low education as having completed primary schooling or less. We defined exposure to biomass fuel smoke as belonging to a household that burns natural solid fuels (wood, charcoal, crop waste, or similar) for heating or cooking. Tobacco exposure history was quantified by pack-years of smoking. We defined one pack-year as having smoked, on average, 20 cigarettes per day for one year. We defined history of tuberculosis as self-report of post-treatment pulmonary tuberculosis. We calculated body mass index (BMI) as weight/height² (kg/m²) and defined obesity as ≥ 30 kg/m².

Biostatistical methods

Our primary aim was to estimate the prevalence and risk factors for ACO. To test for differences between sites and respiratory health groups, categorical and continuous data were compared via chi-squared and ANOVA tests, respectively. Due to the clustered nature of our data, we

used multivariable alternating logistic regression (ALR) for binary outcomes and mixed effects models with random intercepts for continuous outcomes to account for correlation within sites. ALR is a variant of generalized estimating equations where the association between participants for a particular site is modeled with log odds ratios instead of correlations.⁴¹ These were used to characterize ACO against asthma-only, COPD-only, non-obstructed, and general non-ACO groups. For risk factors, all multivariable models for ACO were adjusted by age, sex, BMI, education, biomass exposure, and pack-years of smoking. For lifestyle outcomes, the selected measure was modeled as the independent variable while respiratory health status was included with the same set of predictors to reduce confounding. Interquartile odds ratios compare the odds of having the outcome at the 75th percentile of the variable range to the odds at the 25th percentile. As a secondary analysis, we calculated mean percent of reversibility and the proportion fulfilling ATS/ERS reversibility criteria for each respiratory health group, as well as their corresponding 95% confidence intervals. Sensitivity analyses for spirometric outcomes were conducted among those studies that included post-bronchodilator spirometry for all participants (n=7,277). Further sensitivity analyses were conducted according to other studies' definitions of COPD, asthma, and ACO. Analyses were performed in STATA 13 (StataCorp, College Station, USA) and R (www.r-project.org).

Results

Participant Characteristics

The four studies contributed a total of 12,435 participants, 11,923 (95.9%) of which were included in this analysis. Of those excluded, 13 were missing basic demographic information, an additional 47 fell outside the spirometry reference or individual study inclusion criteria for age, and a final 452 were missing data required to classify respiratory health status. Participants excluded from this analysis were younger, more likely to be female, less likely to be obese, more likely to be exposed to biomass fuel smoke, had fewer pack-years of smoking history, and had lower education than those who remained (E-Table 1 in the Online Repository). A summary of participant demographics can be found in Table 1. For the full sample, we found a 3.8% (95% CI 3.4% to 4.1%) prevalence of ACO which varied from 0% in Rural Puno, Peru to 7.8% in Matlab, Bangladesh (Figure 1, E-Table 2 in the Online Repository). Participants with ACO were older, less likely to be female or obese, more likely to smoke, more likely to be exposed to biomass fuel smoke, and had less education than the non-obstructed or asthma-only population (Table 2). Nearly half (43.8%) of those with COPD and 21.7% of those with asthma had ACO.

Risk Factors for ACO

Risk factors for ACO compared to the non-obstructed, asthma-only, COPD-only, and general non-ACO population are outlined in Figure 2 and E-Table 3 (in the Online Repository). Age, pack-years smoking, low education, and biomass exposure were all risk factors for ACO compared to the asthma, non-obstructed, and general population groups while higher BMI was

protective. Higher BMI was the only risk factor for ACO when compared to COPD. The prevalence of ACO was higher with older age: 1.1% (95% CI 0.8% to 1.7%) for those <45 years old, 3.9% (3.4% to 4.4%) for those aged 45-59 years, 4.9% (4.2% to 5.7%) for those aged 60-74 years, and 5.7% (3.9% to 8.3%) for those aged ≥ 75 years (E-Figure 1 in the Online Repository).

Lifestyle Impairment and ACO

Measures of lifestyle impairment for participants with ACO can also be seen in E-Table 3 (in the Online Repository). In unadjusted comparisons, 6.6% (95% CI 4.6% to 9.3%) of participants with ACO reported being hospitalized for breathing difficulty in one year compared to 1.9% (1.3% to 2.7%) of those with asthma-only and 0.5% (0.2% to 1.6%) of those with COPD-only. Among those with ACO, 44.7% (95% CI 40.1% to 49.3%) reported impairment of daily activities due to breathing compared to 29.6% (27.4% to 31.9%) of those with asthma-only and 8.1% (6.2% to 10.7%) of those with COPD-only. Additionally, participants with ACO reported higher adjusted odds of hospitalization compared to non-obstructed participants (OR=32.4, 95% CI 17.3 to 60.8) than those with COPD-only (OR=1.62, 0.47 to 5.63) or asthma-only (OR=8.30, 4.75 to 14.5). Similarly, the odds of an ACO participant reporting life impairment compared to a non-obstructed participant were higher (OR=21.8, 95% CI 16.2 to 29.3) than the COPD-only (OR=1.46, 1.02 to 2.11) or asthma-only (OR=7.29, 6.13 to 8.67) groups. ACO was associated with around a 2.5 z score deficit in pre-bronchodilator FEV₁/FVC ratio compared to the non-obstructed, asthma-only, and general population groups and a 0.61 z score deficit compared to the COPD-only group (Figure 3, E-Table 3 in the Online Repository). The difference in FEV₁/FVC ratio z score between the ACO group and the non-obstructed population was higher than the

284 difference between COPD-only (-2.03, 95% CI -2.11 to -1.95) and asthma-only (-0.24, -0.29 to -
285 0.19) subsets compared to the same. Sensitivity testing with post-bronchodilator z scores
286 (n=7,277) revealed very similar results (E-Table 3 in the Online Repository).

287
288 Among those with ACO, 31.6% (95% CI 27.4% to 36.0%) of participants had severe obstruction
289 on pre-bronchodilator spirometry compared to 10.9% (8.6% to 13.7%) of those with COPD-only
290 and 3.5% (2.7% to 4.5%) of those with asthma-only. In adjusted models of pre-bronchodilator
291 FEV₁/FVC ratio among the full sample, both age and disease status remained independently
292 associated factors (E-Table 4 in the Online Repository).

293
294 In sensitivity analyses, 23.0% (95% CI 17.6% to 29.4%) of those with ACO had severely restricted
295 breathing after administration of a bronchodilator compared to 5.8% (3.7% to 8.9%) of those
296 with COPD-only and 0.4% (0.1% to 1.2%) of those with asthma-only. Post-bronchodilation,
297 mean reversibility of FEV₁ was 10.8% (95% CI 8.6% to 13.0%) for ACO, 5.6% (4.4% to 6.7%) for
298 COPD-only, and 4.3% (3.8% to 4.8%) for the asthma-only group. With respect to ATS/ERS
299 criteria, 37.8% (95% CI 31.2% to 44.8%) of those with ACO displayed reversibility of their
300 breathing compared to 22.5% (18.3% to 27.3%) of those with COPD-only and 10.8% (8.8% to
301 13.1%) of those with asthma-only. Including those who were classified in the overlap group,
302 16.2% (14.0% to 18.6%) of all of those with asthma and 28.2% (24.5% to 32.2%) of all of those
303 with COPD displayed airways reversibility.

Discussion

In this multi-study analysis, we estimated the prevalence of Asthma-COPD Overlap in a sample of nearly 12,000 adults in LMICs and compared risk factors and lifestyle impairment outcomes between participants with ACO and those with asthma-only or COPD-only. Although comparisons with previous studies are difficult due to variable case definitions and differing reference populations, our data indicate that there may be a high prevalence of ACO found in LMICs: settings which are known to include environmental risk factors strongly linked to asthma and COPD, such as biomass fuel smoke exposure, rapid urbanization, increasing tobacco smoking, and peri-urban sprawl.^{23, 25, 42}

There are limited data on ACO prevalence and risk factors in LMICs. In a 2014 analysis of the PLATINO cohort, Menezes *et al.* report a 1.8% prevalence of ACO over five Latin and South American sites; however, only urban centers were sampled and a more restrictive definition of asthma was used (including reversibility of breathing). Using the same criteria among studies that conducted universal post-bronchodilator spirometry, we found a prevalence of ACO of 0.71% (n=6,916), although it should be noted that the prevalence of asthma would be expected to be higher in urban settings.²⁵ An analysis of the large ECRHS survey in Europe reported ACO in 3.1% of participants.¹⁹ It is notable that this population was younger when compared those most at risk for COPD and ACO (mean age 34.3 years) but were located in high-income settings, which increased the likelihood of ever having had an asthma diagnosis by a physician.¹⁹ Our data are consistent with a previous analysis of the general population of Italy, which found a prevalence of ACO with older age.¹⁸ In our analysis, 43.8% of participants with COPD had ACO,

which is higher than previous estimates of 13-20% from high-income populations, barring Norway, which stands out at 56% using self-report criteria.^{22, 43-47}

Our participants with ACO were of similar age to those with COPD-only and were around four years older than those with asthma-only, results which have varied in previous research.^{19, 20, 47,}

⁴⁸ In agreement with Menezes *et al.* and Chung *et al.*, our ACO and COPD populations had a lower BMI than non-obstructed or asthma-only participants.^{20, 21, 36, 48} Women comprised a higher percentage of our ACO population than the COPD-only group, but less than the asthma-only or non-obstructed groups, in line with other population-based studies.¹⁹⁻²¹

Many studies have characterized ACO by clinical or quality of life outcomes, often describing participants with overlap as more disabled than those with either asthma or COPD alone.^{18, 20, 21, 36, 47, 49-51} In our sample, ACO was also associated with greater reductions in spirometric outcomes and higher odds of hospitalization or impairment of daily activities compared to the asthma-only and COPD-only populations, seen in some but not all previous studies.^{19-21, 36, 47, 51,}

⁵² Moreover, the presence of both asthma and COPD in a participant (the overlap group) was associated with worse outcomes than would be expected by combining the effects of asthma and COPD alone, an effect not seen in an analysis of high-income countries by de Marco *et al.*¹⁹ For example, the ACO group had worse lung function by pre-bronchodilator FEV₁/FVC than expected when adding the deficits associated with having COPD-only and asthma-only compared to the non-obstructed population. This remained the case for post-bronchodilator testing. Our data agree with the pattern of higher prevalence of severe obstruction on

spirometry in ACO compared to asthma- or COPD-only populations noted by Chung *et al.*;
however, the prevalence in our sample of LMIC settings was much higher than in their South
Korean sample (31.8% vs. 12%).²¹ It should be noted that these estimates were produced via
different reference populations, making for an imperfect comparison.

It is known that cross-sectional lung function is lower in older ages and due to our finding of an
association between age and ACO prevalence, we investigated the possibility of confounding.
We conducted a sensitivity analysis whereby lung function was modeled on both disease status
(categorical) and age (continuous) among other factors noted above. We found that both
remained independently associated factors and no confounding was seen. Our finding of a 0.18
unit decline in FEV₁/FVC ratio per year falls closely in line with previously published reference
values.⁵³

As an observation, we call for the consideration of biomass fuel as an environmental exposure
in future case definitions of ACO. Some publications, including a recent Spanish consensus
document, have included a history of tobacco smoking as a criterion for the diagnosis of ACO.^{19,}
⁵⁴⁻⁵⁶ In many settings, biomass exposure is a prevalent and important risk factor of chronic
respiratory illness, even eclipsing daily smoking in population attributable fraction.⁵⁷ Golpe *et*
al. concluded that exposure to biomass raises systemic inflammation in a manner similar to
tobacco smoking.⁵⁸ Other studies have shown raised pulmonary inflammation profiles due to
biomass exposure.^{59, 60} Our analysis shows both tobacco smoking and biomass fuel smoke
exposure to be risk factors for the development of ACO compared to non-obstructed

populations. We favor inclusive criteria such as those found in the 2015 GINA/GOLD guidelines – which take into account exposures to any respiratory risk factor – as a more globally-focused set of guidelines.⁶¹

Strengths of this analysis include a large and demographically-diverse sample of adults living in LMICs across the southern hemisphere, benefitting from high-quality data collection and spirometry. The diversity of our sample, which covered a wide range of ages (35-92 years) and settings (rural areas and cities of all sizes on three continents) leads us to believe that our results are generalizable to other LMIC settings. However, this analysis has some potential shortcomings. First, we presented pre-bronchodilator spirometry testing for our main analysis of lung function outcomes because post-bronchodilator measurements were not available across the entire study sample. This allowed us to analyze a larger sample and potentially increase the heterogeneity among participants. Sensitivity testing with a smaller sample of post-bronchodilator tests validated those results, although it should be noted that the studies that provided bronchodilators to every participant were both located in South America and, therefore, results from our sensitivity analyses should be compared to the full cohort with care. Second, due to the challenges in collating data across different studies, we were also limited in our ability to investigate asthma-specific risk factors as well as a wider variety of health outcomes, such as quality of life questionnaires. Additionally, among studies over the past decade, the prevalence and characteristics of ACO has varied, in large part due to variable case definitions.¹⁷ Our definition of ACO was limited by an inability to optimally diagnose asthma as outlined by the Global Initiative for Asthma.⁶² It is not feasible for studies of this nature to

review medical records or even collect post-bronchodilator reversibility on every participant. However, our strategy of combining appropriate and available indicators across studies to identify probable asthma cases (such as self-report of wheeze and past physician diagnosis of asthma) has been used in past large-scale studies of ACO.^{20, 21, 36} As opposed to those studies, which used a fixed FEV₁/FVC ratio cutoff of 0.7 to diagnose COPD, we opted to define COPD as an FEV₁/FVC ratio below the lower limit of normal based on the GLI mixed-ethnic reference population. Finally, although an established international reference population was used for this analysis, it cannot function as the best reference for our entire, diverse study sample. As with variable case definitions, the use of different reference populations across studies makes direct comparisons between our analysis and existing literature difficult. However, until validated references exist for each population, we decided it was a reasonable option.

In the first large-scale, population-based analysis of ACO in diverse areas of LMICs, we found a high prevalence of severe respiratory disease – marked by increased hospitalization and deficits in lung function – that varied by site and was higher with older age. Importantly, we found an increased proportion of those with asthma or COPD who show features consistent with overlap and a high rate of severe obstruction among those with ACO. Thus, the results of this analysis indicate that ACO may be as prevalent and the associated respiratory deficits more severe in LMICs, which are experiencing the simultaneous burdens of biomass exposure and high rates of urbanization and sprawl, than in high-income countries. Research should focus on more accurately defining ACO or the underlying continuum of respiratory illness that it represents.

415 Additionally, important exposures common in LMICs, such as biomass fuel use, should be
416 considered for diagnostic criteria.

417
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Table 1: Comparison of demographic factors between field sites. *P* value refers to inequality of metric across all site groups based on ANOVA or chi-squared tests.

	Lima (8.4%, n=997)	Tumbes (7.9%, n=946)	Urban Puno (4.2%, n=503)	Rural Puno (4.2%, n=503)	Marcos Paz (10.4%, n=1,240)	Bariloche (9.2%, n=1,094)	Temuco (8.9%, n=1,059)	Canelones (7.8%, n=935)	Dhaka (14.6%, n=1,746)	Matlab (15.3%, n=1,829)	Kampala (4.2%, n=498)	Nakaseke (4.8%, n=573)	Overall (n=11,923)	<i>p</i> value
Demographics: % (n) or median (IQR)														
Age	54.7 (45.3, 63.7)	54.7 (44.6, 64.3)	54.8 (44.9, 64.4)	54.8 (45.1, 63.9)	58.4 (51.7, 65.4)	56.6 (51.0, 63.5)	51.6 (58.8, 66.1)	59.1 (52.3, 66.4)	50 (44, 58)	53 (47, 63)	41.1 (36.8, 48.1)	46.8 (40.3, 56.2)	54.2 (47, 63.0)	<0.001
Female	50.7% (505)	49.8% (471)	50.5% (254)	52.7% (265)	40.1% (497)	39.0% (427)	45.4% (481)	40.0% (374)	54.7% (955)	53.9% (986)	50.2 (250)	52.7% (302)	48.4% (5,767)	<0.001
Body Mass Index (kg/m ²)	28.0 (25.3, 31.1)	27.9 (25.1, 30.8)	27.5 (25.1, 30.2)	24.7 (22.5, 27.5)	29.5 (26.1, 33.4)	28.3 (24.9, 32.2)	28.7 (26.0, 31.5)	29.0 (25.5, 32.6)	24.4 (21.3, 27.4)	20.1 (18.1, 22.9)	25.0 (22.0, 29.4)	22.8 (20.6, 26.0)	26.2 (22.4, 30.0)	<0.001
Obese (BMI ≥30 kg/m ²)	32.4% (323)	31.5% (298)	26.4% (133)	10.7% (54)	46.5% (576)	37.8% (414)	36.5% (386)	42.4% (396)	12.5% (218)	1.6% (29)	21.5 (107)	9.8% (56)	25.1% (2,990)	<0.001
Pack-Years Smoking	0 (0, 0.2)	0 (0, 0.3)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 9.2)	0 (0, 9.5)	0 (0, 0)	0 (0, 0)	0 (0, 0.24)	<0.001
Daily Smoker	3.2% (32)	5.6% (53)	2.2% (11)	0.2% (1)	22.8% (283)	23.6% (258)	15.2% (161)	21.8% (204)	6.2% (109)	9.0% (165)	8.6% (43)	8.0% (46)	11.5% (1,366)	<0.001
Household Using Biomass	2.4% (24)	16.7% (158)	2.0% (10)	95.2% (479)	0.5% (6)	23.2% (253)	22.3% (231)	5.1% (43)	3.7% (61)	98.1% (1,789)	93.1% (461)	99.7% (570)	34.9% (4,085)	<0.001
Primary Education or Less	54.2% (540)	64.0% (605)	34.8% (175)	66.6% (335)	65.7% (814)	50.1% (547)	29.3% (310)	50.0% (466)	56.0% (978)	81.2% (1,485)	79.1% (394)	92.5% (530)	60.2% (7,179)	<0.001

Table 2: Comparison of demographic factors between disease statuses. *P* value refers to inequality of metric across all disease status groups from ANOVA or chi-squared tests.

	Non-Obstructed (77.8%, n=9,274)	Asthma-Only (13.6%, n=1,622)	COPD-Only (4.8%, n=577)	ACO (3.8%, n=450)	<i>p</i> value
Demographics: % (<i>n</i>) or median (<i>IQR</i>)					
Age	53.9 (46.7, 62.9)	53.9 (46.8, 62)	59 (51, 66.9)	58 (51.6, 66)	<0.001
Female	49.2% (4,561)	49.6% (804)	37.1% (214)	41.8% (188)	<0.001
Body Mass Index (kg/m ²)	26.4 (22.8, 30.1)	26.6 (22.5, 30.6)	23.4 (19.3, 27.6)	23.1 (19.0, 28.5)	<0.001
Obese (BMI ≥30 kg/m ²)	25.5% (2,465)	28.9% (469)	13.0% (75)	18.0% (81)	<0.001
Pack-Years Smoking	0 (0, 0)	0 (0, 2.8)	0.3 (0, 19.7)	0 (0, 20.3)	<0.001
Daily Smoker	9.8% (904)	13.6% (220)	22.9% (132)	24.4% (110)	<0.001
Household Using Biomass	34.5% (3,148)	31.3% (492)	44.7% (257)	42.7% (188)	<0.001
Primary Education or Less	59.5% (5,513)	59.3% (961)	67.1% (387)	70.7% (318)	<0.001

Figure 1: Health status by site. Since ACO is defined in this analysis as a combination of fulfilling the criteria for both asthma and COPD, categories are not discrete; an individual may only fall into one category. The prevalence of asthma and COPD as separate conditions (along with ACO) can be found in E-Table 2 (in the Online Repository).

Figure 2: Forest plot of risk factors for ACO. Risk factors are presented as odds ratios for presence of ACO compared to reference populations represented by each panel (ACO vs. COPD-Only, ACO vs. Asthma-Only, ACO vs. Non-Obstructed, and ACO vs. all without ACO). Odds ratios are represented by black diamonds while the 95% Confidence Interval is represented by horizontal bars. Site-specific estimates are represented by grey triangles directly under the overall estimate. Overall estimates were generated via alternating logistic regressions, which accounted for clustering by site. All models included each risk factor presented here.

Figure 3: Box plots of pre- and post-bronchodilator spirometry z scores by disease status. The top and bottom of the box represents the 75th and 25th percentile values of the distribution, respectively, while the center line represents the median. The circles on the top and bottom represent outlying values. Z scores were calculated based on the GLI mixed-ethnic reference population and are presented here unadjusted. FEV₁ refers to the maximum volume of air exhaled in one second. FVC refers to the maximum total volume of air exhaled. FEV₁/FVC refers to their ratio. FEV₁ and FVC may come from different qualifying spirometry trials.

