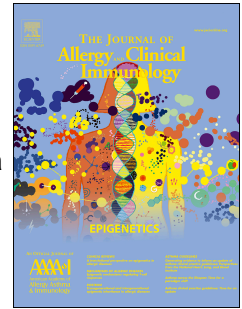


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A burning need to redefine airways disease: Biomass smoke exposure identified as a unique risk factor for ACO in low- and middle- income countries

Amir A. Zeki, MD, MAS, Cameron H. Flayer, BS, Angela Haczku, MD, PhD



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Editorial

For the article JACI-D-18-00090

Title: Epidemiology and Risk Factors of Asthma-COPD Overlap in Low- and Middle-Income Countries by Morgan et al. (JACI 2018)

A burning need to redefine airways disease: Biomass smoke exposure identified as a unique risk factor for ACO in low- and middle- income countries

Amir A. Zeki, MD, MAS; Cameron H. Flayer, BS; Angela Haczku, MD, PhD

Division of Pulmonary, Critical Care, and Sleep Medicine

Department of Internal Medicine

University of California, Davis

ADDRESS FOR CORRESPONDENCE:

Angela Haczku, MD, PhD

Professor of Medicine

School of Medicine, University of California, Davis

#6510 GBSF

One, Shields Avenue, Davis CA 95616

haczku@ucdavis.edu; Phone: 530-754-6932; Fax: 530-752-8632

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35 *"In theory, theory and practice are the same. In practice, they are not."* (Yogi Berra)

36
37 Asthma-Chronic Obstructive Pulmonary Disease Overlap (ACO), formerly known as
38 asthma-COPD overlap syndrome (ACOS), has emerged as an important clinical entity in the
39 arena of obstructive airway diseases. ACO is a chronic pulmonary disease composed of clinical
40 and biochemical markers of both asthma and COPD¹. Patients with 'overlap' typically have
41 increased respiratory symptoms, more severe and more frequent exacerbations, and worse
42 quality of life scores than asthma or COPD alone. Although no widely-accepted definition exists,
43 the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung
44 Disease (GOLD) have developed a descriptive definition of ACO to guide clinicians
45 (<http://www.ginasthma.org> <http://www.goldcopd.org>). In addition, there have been several
46 studies and expert panel statements attempting to better define this distinguishable phenotype
47 of airway disease with a recent workshop report developed jointly by the American Thoracic
48 Society (ATS) and the National Heart, Lung, and Blood Institute (NHLBI)². Today most experts
49 agree that ACO is likely a heterogeneous cluster of several clinical sub-phenotypes but there is
50 still no consensus on whether unique pathological mechanisms underlie ACO, or if there are
51 shared endotypes at some level between asthma, COPD, and ACO. We presently lack the
52 basic science and clinical data to support a single, widely-accepted definition. The challenge
53 lies, at least partially, in the fact that clinical trials have historically excluded patients with
54 features of overlapping asthma and COPD and that relevant animal models for ACO have just
55 started to be developed.

56 ACO can be thought of in two basic ways: (1) the combination of asthma and COPD due
57 to two different chronic inhalational insults (i.e. smoke inhalation) combined with prolonged
58 allergen sensitization and exposure, occurring at different times. (2) ACO as a cluster of several
59 heterogeneous sub-phenotypes that reflect a clinical phenotype that cannot be easily
60 distinguished as asthma or COPD alone. For example, ACO of this second group may include

sub-groups such as severe asthma with fixed airflow obstruction or incomplete reversibility post-bronchodilator, childhood asthma that progresses to adult 'COPD-like' asthma, adult asthmatics with other inhaled noxious exposure(s) (e.g. air pollution, chemical fumes, etc.), eosinophilic COPD, and obese steroid-resistant asthma with fixed airflow obstruction, to name a few. ACO belonging to the first group may be more straightforward, e.g. a smoker with atopy/allergic symptoms and/or eosinophilia, while that of the second group is not only seemingly more complex, but it is also more intriguing in terms of pathogenesis and the natural history of disease. Because the etiology of the disease is largely unknown, efforts need to be made to identify unique risk factors for ACO that may distinguish it from asthma or COPD. This recognition has led to a multitude of studies from around the world including from the United States, United Kingdom, Japan, Korea, Spain, Italy, Switzerland, Norway, the Netherlands, among others that described patients with features of both asthma and COPD³⁻⁸. However, a significant population of potentially undiagnosed ACO likely exists in the lesser studied low- and middle-income countries (LMICs) where disease maybe driven by unique risk factors. In this issue of JACI, Morgan *et al.* reported a study characterizing ACO in a population-based sample of adults from multiple LMICs, representing a broad range of geographical settings including wide degrees of urbanization and ethnic diversity. They compared individuals with ACO to those without respiratory disease, those with asthma-only, and those with COPD-only, examining risk factors and lifestyle outcomes between groups⁹.

Environmental exposures play a big role in the etiology of many lung diseases. Emerging literature importantly suggests that there are inflammatory and immune cell differences between biomass- and tobacco-smoke related airways disease¹⁰. There are approximately 3 billion people worldwide who rely on coal and other biomass fuels for heating and cooking. Biomass smoke exposure has been associated with multiple different chronic lung diseases including COPD, asthma, bronchitis and interstitial lung disease, to name a few.

Morgan *et al.* conducted their cross-sectional investigation on a large, multi-national cohort of participants with asthma and COPD. To describe the prevalence ACO risk factors among adults across six LMICs (Peru, Argentina, Chile, Uruguay, Bangladesh, Uganda), the authors included 11,923 participants from four population-based studies in twelve different settings, and reported that biomass air pollution is a novel risk factor for ACO⁹. Risk factors for ACO in high-, middle-, and low- income countries have not been previously compared since most studies came from relatively high-income countries.

In their study populations, COPD was defined as a post-bronchodilator FEV1/FVC below the lower limit of normal (defined as the lowest 5th percentile) of the reference population. Asthma was defined as having wheezing, asthma medication use in the past 12 months, or self-reported physician diagnosis of asthma. ACO was defined as having both asthma and COPD. One of the potential limitations of this study is with the definition of asthma itself. Because “wheezing” was one of three criteria used to identify asthmatics, this symptom (or physical finding) can also be observed in those with COPD, perhaps milder forms that could be misclassified based on spirometric criteria. If so, then this could result in an over-estimation of the prevalence of ACO, i.e. those with COPD who wheeze have this symptom incorrectly attributed to asthma rather than COPD itself, and therefore, are classified as ACO rather than lone COPD. It is not clear what proportion of patients fall under this category. Nonetheless, the findings from this study are supported by most other published work, i.e. that patients with ACO are generally sicker than those with lone COPD or asthma¹.

The authors report that the prevalence of ACO was 3.8% (ranging from 0% to 7.8%), and the odds of having ACO were higher with household exposure to biomass fuel smoke, smoking, and low education status (primary school or less) as compared to non-obstructed subjects. ACO was also associated with severe airflow obstruction (FEV1 <50% predicted). Patients with ACO had significantly higher adjusted odds of hospitalization compared to non-obstructed subjects (OR=32.4, 95% CI 17.3-60.8), and much higher than asthma or COPD. Life

impairment was also markedly higher in ACO subjects compared to non-obstructed controls (OR=21.8, 95% CI 16.2-29.3), and much greater than asthma or COPD. Lung function including pre- and post-bronchodilator ratios of FEV1/FVC (and Z scores) were also lower in ACO as compared to controls and those with asthma or COPD. Among ACO subjects, 31.6% had severe obstruction compared with 10.9% of COPD and 3.5% of asthma subjects. Interestingly, ACO was associated with worse outcomes than would be expected by adding the effects of asthma and COPD alone, which suggests a synergy of dysregulated molecular mechanisms that ultimately manifest in the ACO clinical phenotype.

Key risk factors for ACO in this study included age, pack-years of smoking, low educational status and biomass fuel exposure. Prevalence increased with age regardless of gender but with a male-predominance until age 75 after which it become female-predominant. It is noteworthy that while higher BMI was the only risk factor for ACO when compared to COPD, in comparison with non-obstructed or asthma only groups higher BMI was protective against ACO. The biological effects of higher BMI in populations living in LMICs may be different than individuals with higher BMI living in high-income countries perhaps due to host-gene-environment interactions. Alternatively, higher BMI could instead represent other hidden co-variables not examined in the study that are somehow protective and worthy of further study.

ACO epidemiology studies are scarce in LMICs, so studying novel geographical regions characterized by lower income was a major strength of the Morgan *et al.* study. Importantly, the present work highlights the risks and higher ACO prevalence associated with biomass fuel exposure in LMICs as compared to high-income countries. Indeed, ACO may not only be more severe but it may be more like COPD rather than asthma in LMICs in comparison with ACO reported in high-income nations and identifies biomass fuel as an important novel risk factor in the development of ACO. Figure 1 shows how risk factors for ACO vary in different geographical regions. Morgan *et al.* found that biomass smoke exposure was a novel risk factor in LMICs in a geographical region that was not studied before and that had the lowest income per country

138 compared with other geographical and income regions. This knowledge has significant
139 implications for the health of citizens in lower income and developing countries, creating an
140 opportunity for prevention and intervention around the globe.

141 Rethinking obstructive airway diseases in this technological “-omics” age will be
142 necessary to advance the field, and ultimately, provide better patient care. Based on the
143 classical understanding of eosinophilic versus neutrophilic airway inflammation, and the more
144 recent ‘molecular phenotyping’ of type 2 (T2) versus non-T2 (or T2-low) airway inflammation, we
145 will eventually update our airway disease nomenclature to reflect the reality of overlap.
146 However, as the study by Morgan et al. illustrates, this should take into consideration the
147 differences in environmental exposures including biomass smoke as this could arguably lead to
148 a unique sub-phenotype of ACO, different from just aeroallergen and cigarette smoke exposure
149 as is typically observed in higher-income societies. In the coming years, theory will hopefully
150 meet practice as we implement these new ways of thinking about and diagnosing complex
151 airway disorders.

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FIGURE LEGEND:

Figure 1. Risk factors for asthma COPD overlap (ACO) vary by geographical area. Risk factors for ACO (bubbles) from 6 major epidemiological studies (identified by number in yellow squares as listed below) are superimposed on a geographical map of the world that is colored by Income Groups. Morgan *et al.* showed that ACO patients from South America tended to be male and smoked more, while participants from Africa tended to be younger, have less obesity, be exposed to more biomass, and have less education. ACO patient participants from Asia had less obesity, were exposed to more biomass smoke and had less education than others in the study.

1: Morgan *et al.* South America, Uganda, Bangladesh⁹

2: Menezes *et al.* South America⁷

3: de Marco *et al.* Italy⁶

4: de Marco *et al.* Europe⁴

5: Henriksen *et al.* Norway³

6: Chung *et al.* South Korea⁵

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