Title: Prevalence, risk factors, and longitudinal outcomes associated with asthma COPD overlap (ACO) in the NHLBI Pooled Cohorts study.

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Introduction

The extent to which asthma and chronic obstructive pulmonary disease (COPD) represent distinct disease entities versus related phenotypes on the spectrum of obstructive lung disease remains a subject of debate. While current clinical guidelines and the majority of prior epidemiologic research have treated asthma and COPD as different diseases, there has been increasing investigation into Asthma COPD Overlap (ACO) in recent years.

The exact prevalence of ACO is unclear. Standard definitions for ACO are lacking, although some have recently proposed guidelines for such definitions (1, 2). Furthermore, most prior studies of ACO have investigated the prevalence of asthma among a population with known COPD, or the prevalence of COPD in a population with known asthma. Accordingly, it is no surprise that the prevalence estimates for ACO vary from 13% to 38% based upon the definitions used and the populations studied (3-7). Administrative data suggests that the prevalence of ACO in the US is approximately 17.4% (8) among those with all obstructive lung disease and 3.2% (9) in the adult population; however, to date, there has not been an assessment in a large, well-characterized, US population-based cohort with spirometry measurements.

Several studies have suggested that individuals with ACO are different phenotypically versus individuals with either asthma or COPD alone. Compared to asthma and COPD patients, those with ACO have been found to be younger (5, 6), to have a greater BMI (6, 10), and to have worse clinical outcomes (3, 6, 7, 10). When compared to those with COPD alone, several studies have shown that patients with ACO have lower smoking burden (5, 6), and yet more respiratory symptoms and dyspnea, poorer quality of life, and higher risk of exacerbations. This
is interesting to consider in the context of some studies demonstrating less severe airflow obstruction (3, 5) and lower mortality (11) in the group with ACO compared to those with COPD alone. Age at disease onset(12) may also be an important modifying factor in ACO prognosis.

To date, there has been no large scale-study of ACO in a large, prospective, US population-based study. We therefore propose to evaluate the prevalence, risk determinants, and prognostic significance of ACO in the NHLBI Pooled Cohorts Study. We will compare the prevalence and correlates of ACO compared to asthma and COPD alone, as well as testing the associations between ACO and prospective respiratory outcomes including decline in lung function and clinical events.

**Research Questions**

1. **ACO prevalence**: What is the prevalence of asthma, COPD, and ACO in the NHLBI Pooled Cohorts Study? To what extent is ACO prevalence impacted by disease definition (e.g., using recently published guidelines versus previous research definitions)?
2. **ACO risk determinants**: Which risk factors are associated with ACO and how are they similar or different from risk factors for asthma or COPD alone (e.g., demographics, environmental exposures, comorbid chronic diseases)? Moreover, which risk factors predict "incident ACO" in persons without ACO at study baseline?
3. **ACO prognosis**: Is ACO associated with a different prognosis versus asthma or COPD alone with respect to longitudinal trajectory of lung function; symptoms; respiratory hospitalization rates; and all-cause and respiratory mortality?

**Data**

**Sample**

We propose to use data from adult participants in nine cohorts that have been harmonized and pooled as part of the NHLBI Pooled Cohorts Study:

1. Atherosclerosis Risk in Communities (ARIC) Study
2. Cardiovascular Health Study (CHS)
3. Coronary Artery Risk Development in Young Adults (CARDIA)
4. Framingham Offspring Study (FHS-O)
5. Health Aging and Body Composition (Health ABC) Study
6. Hispanic Community Health Study/Study of Latinos (HCHS/SOL)
7. Jackson Heart Study (JHS)
8. Multi-Ethnic Study of Atherosclerosis (MESA)
9. Strong Heart Study (SHS)

**COPD Case Definition**: Self-reported physician diagnosis of COPD, emphysema, or chronic bronchitis, AND pre-bronchodilator FEV1/FVC<70%

**Asthma Case Definition**: Self-reported physician diagnosis of asthma

**ACO Case Definition**: meeting criteria for both COPD and Asthma

Incident ACO will be defined in the same manner among persons without ACO at baseline.
In secondary analyses, we will sub-classify asthma and ACO according to age of asthma onset (at <18 versus 18+ years old), and we will evaluate the impact of conditioning COPD diagnosis on reporting 10 or more pack-years, as has been done in some prior studies.(13, 14)

To the extent that additional phenotypic data are available, we will define ACO in sensitivity analyses according to an adaptation of the current Spanish consensus definition and include individuals with COPD (as per our case definition) with both history of asthma and history of atopy.

**Correlates/Covariates:**
- **Socio-demographics:** age, sex, race/ethnicity, educational attainment
- **Anthropometrics:** height, weight, BMI
- **Smoking:** smoking status, cigarettes per day, pack-years, pipe/cigar
  **Medical history:** cardiovascular disease (CAD/MI/revascularization, heart failure, arrhythmia), diabetes, metabolic syndrome, obesity, allergic disease/allergic rhinitis, chronic kidney disease, cerebrovascular disease, arthritis, malignancy (other than nonmelanoma skin cancer), liver disease, depression, anxiety.
- **Medications:** inhalers, oral steroids
- **Quality of life questionnaires**
- **Other exposures:** occupational history/exposures, air pollution exposure (as available)

**Clinical Endpoints**
- Symptoms: Self-reported respiratory symptoms including dyspnea, wheeze, cough.
- Lung function: Initial and annual decline in FEV1, FVC, FEV1/FVC, using spirometry data that has been validated, harmonized, and pooled by the NHLBI Pooled Cohorts Study (15).
- Events
  - All-cause mortality.
  - Respiratory hospitalization: hospitalizations adjudicated or administratively coded as caused by COPD, chronic bronchitis, or emphysema (ICD-9 490-492, 496, 506.4; ICD-10 J40-J44), pneumonia (ICD-9 480-487, ICD-10 J18), or interstitial lung disease (ICD-9 516, ICD-10 J84).
  - Respiratory mortality: deaths adjudicated or administratively coded as caused by respiratory disease (ICD-9 and ICD-10 codes as specified above) Events will be sub-classified by code position (primary diagnosis code or underlying cause of death versus any code position)
  - Incident lung cancer: first hospitalization or death adjudicated as primarily or secondarily attributable to lung cancer (16).
  - Incident pneumonia: first hospitalization or death adjudicated as primarily attributable to pneumonia.
  - Heart disease: classified by adjudication of prospectively ascertained hospitalizations and mortality, and defined among participants without prevalent cardiovascular disease at baseline.
    - Incident coronary heart disease: adjudication as physician-adjudicated MI, resuscitated cardiac arrest, or CHD death.
    - Incident heart failure: adjudicated, where available.
Of note, data from all cohorts have already been obtained, harmonized, and pooled under the auspices of approved paper/ancillary study proposals relating to other specific biological hypotheses.

**Analysis plan.**

**Research question 1**

We propose to compare the prevalence of asthma, COPD, and ACO using different case definitions as outlined above.

**Research question 2**

We will tabulate baseline participant characteristics according to case status. We will then test associations between case status and potential risk determinants via multi-variable adjusted generalized linear regression models in order to calculate adjusted and standardized prevalence ratios\(^{(17)}\). Associations with incident ACO will be tested in Cox proportional hazards models adjusted for significant correlates identified in the cross-sectional analysis, with time-to-event defined as biological age at event and left-truncation for age at study entry, and cohort treated as a stratum term.

**Research question 3**

- Associations between ACO and longitudinal lung function will be assessed using generalized linear mixed models to characterize population mean changes in lung function over time. In the pooled data, we will use a cohort-specific unstructured covariance matrix.
- Associations between ACO and incident symptoms and events will be analyzed via survival models, as described above.
- Models will be sequentially adjusted for *a priori* confounders and precision variables (age, sex, height, weight, smoking, race/ethnicity, educational attainment, baseline disease status), as well as additional correlates identified in Research Question 2.
- Effect modification will be assessed by multiplicative interaction terms and in stratified models.

**References**

2. GOLD Ga. Diagnosis of Diseases of Chronic Airflow Limitation: Asthma, COPD, and Asthma-COPD Overlap Syndrome (ACOS); 2015.


