# Clinical Implications of Bronchodilator Testing: Diagnosing and Differentiating COPD and Asthma-COPD Overlap

Srinadh Annangi and Angel O Coz-Yataco

**BACKGROUND: Bronchodilation testing is an important component of spirometry testing, and omitting this procedure has potential clinical implications toward diagnosing respiratory diseases. We aimed to estimate the impact of bronchodilator testing in accurately diagnosing COPD and differentiating COPD from asthma-COPD overlap (ACO). METHODS: The National Health and Nutrition Examination Survey data were analyzed from 2007–2012. Airflow limitation was defined by $FEV_1/FVC < 0.7$. Subjects with pre-bronchodilator airflow limitation were classified into pre-but-not-post-bronchodilator airflow limitation and post-bronchodilator airflow limitation groups. Spirometry-confirmed COPD was defined by persistent airflow limitation on post-bronchodilator spirometry. The American Thoracic Society (ATS) and the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) definitions were used to identify possible ACO subjects. RESULTS: We identified 11,763 subjects ≥ 40 y of age eligible for spirometry; 625 of them had a pre-bronchodilator $FEV_1/FVC < 0.7$ and completed post-bronchodilator spirometry that met ATS spirometry quality standards. A total of 244 (39%) of these subjects had only pre-not-post-bronchodilator airflow limitation, thereby not meeting the definition of spirometrically confirmed COPD. The prevalence of ACO was 7.6% using the modified ATS definition and 19.8% using the modified SEPAR criteria. When bronchodilator testing-based criteria were excluded from ATS and SEPAR definitions, the number of ACO subjects decreased by 39.3% and 12.3%, respectively. CONCLUSIONS: Spirometry with bronchodilation is an important element in the accurate diagnosis of ACO and COPD. Spirometry performed without bronchodilator testing may lead to an estimated misclassification of ACO by 7.6% to 19.8% and overdiagnosis of COPD by 39%.** *Key words:* COPD*; asthma; bronchodilation; spirometry; asthma-COPD overlap; ACO*. [Respir Care 2022;67(4):440–447. © 2022 Daedalus Enterprises]

## Introduction

COPD is the fourth leading cause of death and one of the leading causes of morbidity in the United States. Approximately 15.5 million Americans are affected by COPD with an age-adjusted death rate of 40.6 per 100,000 population.[1,2] The economic burden of COPD in 2010 was reported at $32.1 billion, with 16.4 million workdays lost and a projected increase to 49.0 billion by 2020.[3] Early and appropriate diagnosis followed by comprehensive management will help reduce the severity of symptoms, rate of exacerbations, improve quality of life, and decrease health care utilization.[4,5] Bronchodilator testing during spirometry evaluation includes performing an initial spirometry (pre-bronchodilator spirometry) followed by second spirometry (post-bronchodilator spirometry) after the administration of bronchodilator medication. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) document defined COPD as irreversible airflow limitation evidenced by the post-bronchodilator $FEV_1/FVC < 0.70$.[5] Post–bronchodilator spirometry values are better predictors of clinical outcomes and mortality compared to pre-bronchodilator values based on a recent analysis of the COPD gene study population.[6] Despite the recommendation to use post-bronchodilator spirometry values to establish the diagnosis of COPD, spirometry is not always performed with a subsequent bronchodilator testing.[7-15] Data from the National Committee for Quality Assurance in 2004 revealed that approximately only one third of newly diagnosed COPD subjects had spirometry testing, and only half of these had bronchodilator testing performed.[13] Using pre-bronchodilator $FEV_1/FVC$

criteria instead of the post-bronchodilator ratio may overdiagnose COPD, leading to inappropriate treatment and potentially increased health care utilization. The prevalence of airflow limitation was 55% higher when the pre-bronchodilator ratio was used instead of the post-bronchodilator ratio among subjects in the PLATINO study.[16] Similarly, a Norwegian study reported a 27% relative reduction in COPD prevalence when the post-bronchodilator ratio criteria were used.[17] When current COPD treatment guidelines were largely based on severity of airflow limitation, intensity of symptoms, and exacerbation risk, there has been increasing evidence suggesting the role of tailored therapy based of phenotypic variants in COPD. One particular subtype is asthma-COPD overlap (ACO).[18] The proposed criteria to diagnose ACO include atopy, clinical history, and bronchodilator responsiveness.[19,20] If bronchodilator testing is not routinely performed, spirometry-confirmed COPD may be overestimated and cases of ACO may be misclassified as sole COPD.[15] The objectives of our study were to estimate the impact of bronchodilator testing in the diagnosis of COPD and in differentiating COPD from ACO.

**QUICK LOOK**

**Current knowledge**

Bronchodilator testing with spirometry is an important component in diagnosing and differentiating COPD and asthma-COPD overlap (ACO). Despite the recommendation to use post-bronchodilator spirometry values to establish the diagnosis of COPD, spirometry is not always performed with subsequent bronchodilator testing. The clinical implications of not performing bronchodilator testing in potential overdiagnosis of COPD and misdiagnosis of asthma.

**What this paper contributes to our knowledge**

Spirometry performed without bronchodilator testing may lead to an estimated overdiagnosis of COPD by 39%. Potential to misdiagnose subjects with ACO as just COPD by 7.6% to 19.8% was also noted in our analysis.

## Methods

We analyzed the National Health and Nutrition Examination Survey (NHANES) data from 2007–2012.[21] Eligible subjects to undergo spirometry included individuals age 6–79 y. Among those who completed baseline spirometry, subjects with pre-bronchodilator airflow limitation were selected for a follow-up bronchodilator spirometry test.[22,23] The quality of NHANES spirometry studies was graded A–F based on the American Thoracic Society (ATS) and European Respiratory Society task force spirometry standardization guidelines.[24] Blood specimens were analyzed for white blood cell count and differential as per the NHANES procedure manual.[25] The self-reported responses to the medical conditions questionnaire were collected by trained personnel using the computer-assisted personal interviewing system. The NHANES medical conditions questionnaire used in our analysis included the questions: Has a doctor or health care professional "ever told you had asthma?," "ever told you had emphysema?," and "ever told you had chronic bronchitis?" The NHANES respiratory health questionnaire used included "do you usually cough on most days for 3 consecutive months or more during the year?" and "do you bring up phlegm on most days for 3 consecutive months or more during the year?" The frequency of health care utilization questionnaire used the following question: "during the past 12 months, how many times have you seen a doctor or other healthcare professional at a doctor's office, a clinic or some other place?"

Subjects $\geq$ 40 y of age with complete spirometry studies graded as A or B and pre-bronchodilator airflow limitation were included in our analysis. We defined airflow limitation as a $FEV_1/FVC < 0.7$. Study subjects were classified into the pre-not-post–bronchodilator obstruction if airflow limitation is seen only in pre–bronchodilator spirometry but not in post–bronchodilator spirometry testing and spirometry-confirmed COPD group if the airflow limitation is seen in both before and after bronchodilator spirometry testing.[17] Peripheral eosinophilia was defined as blood eosinophil count $\geq$ 300 cells/μL. The $\Delta FEV_1$ constitutes the difference between post-bronchodilator and pre-bronchodilator spirometry $FEV_1$ values. Bronchodilator responsiveness was defined as $\Delta FEV_1$ of 12% and 200 mL with bronchodilator testing. We used 2 different definitions to identify ACO subjects: the ATS roundtable and the modified Spanish Society of Pneumology and Thoracic Surgery (SEPAR) (Table 1).[19,20] Precise information regarding smoking duration or air pollution exposure (ATS major criteria), history of atopy or allergic rhinitis (ATS minor criteria), and serum

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Table 1. Criteria Proposed and Criteria Used in Our Analysis Toward Identifying Subjects With Asthma-COPD Overlap

| ACO Diagnostic Criteria | Modified Criteria for Our Analysis |
|---|---|
| American Thoracic Society Roundtable Criteria[19a] | |
| Major Criteria (3 major criteria)<br>(1) Persistent air flow limitation and age ≥ 40 y<br>(2) Documented history of asthma before 40 y of age or bronchodilator responsiveness > 400 mL in $FEV_1$<br>(3) At least 10 pack-years of tobacco smoking or equivalent air pollution exposure | Major Criteria (2 major criteria)<br>(1) Persistent air flow limitation and age ≥ 40 y<br>(2) Documented history of asthma before 40 y of age or bronchodilator responsiveness > 400 mL in $FEV_1$ |
| Minor Criteria (3 minor criteria)<br>(1) Two separate bronchodilator responsiveness ≥ 12% and ≥ 200 mL<br>(2) Blood eosinophil count of ≥ 300/μL<br>(3) Documented history of atopy or allergic rhinitis | Minor Criteria (2 minor criteria)<br>(1) Bronchodilator responsiveness ≥ 12% and ≥ 200 mLc<br>(2) Blood eosinophil count of ≥ 300/μL |
| Modified Spanish Society of Pneumology and Thoracic Surgery Criteria [20b] | |
| Major Criteria (2 major criteria)<br>(1) Bronchodilator response > 400 mL and 15%<br>(2) Previous history of asthma | Major Criteria (2 major criteria)<br>(1) Bronchodilator response > 400 mL and 15%<br>(2) Previous history of asthma |
| Minor Criteria (3 minor criteria)<br>(1) Blood eosinophils > 5%<br>(2) Two separate bronchodilator responsiveness > 12% and > 200 mL<br>(3) Serum IgE > 100 IU/mL or history of atopy | Minor Criteria (2 minor criteria)<br>(1) Blood eosinophils >5%<br>(2) Bronchodilator responsiveness > 12% and > 200 mL[c] |

[a] Proposed definition was presence of all 3 major criteria and at least 1 minor criterion, and definition used in our analysis was presence of all 2 major criteria and at least 1 minor criterion.
[b] Proposed definition was presence of at least 1 major criterion or at least 2 minor criteria in COPD patients, and this definition was used in our analysis.
[c] Proposed minor criteria required positive bronchodilator responsiveness on 2 separate occasions. In our analysis, we modified to positive bronchodilator responsiveness on a single test.
ACO = asthma-COPD overlap
ATS = American Thoracic Society.
SEPAR = Spanish Society of Pneumology and Thoracic Surgery
IgE = immunoglobulin E

immunoglobulin E (IgE) levels (SEPAR minor criteria) was not available in the NHANES data. Since bronchodilator testing in NHANES was performed only once, bronchodilator responsiveness could only be assessed on a single occasion instead of in 2 separate tests (ATS and SEPAR minor criteria). Owing to these limitations, we modified the proposed definitions, allowing us to estimate the number of subjects with possible ACO but not definite ACO. (Table 1).

Modifying ATS and SEPAR definitions limited our analysis to only identify possible but not definite ACO subjects. So we have attempted to impute missing information to estimate definite ACO prevalence among our study population. While imputing the "presence of atopy or allergic rhinitis" minor criterion that was excluded from ATS definition, prevalence estimate of 50–90% was used based on previous studies.[26-28] Similarly while imputing "serum IgE > 100 IU/mL or history of atopy," minor criteria that was excluded from SEPAR definition, prevalence estimates of 33.6% and 40% were used among subjects with positive bronchodilator responsiveness and eosinophil count > 5%, respectively.[29]

Non-weighted samples were analyzed using SPSS version 21 (IBM, Armonk, New York). Descriptive statistics were analyzed for statistical significance using the chi-square test, and a $P$ value of $< .05$ was considered statistically significant.

## Results

We identified 11,763 NHANES participants age ≥ 40 y that were eligible for spirometry testing; 7,144 of them had completed spirometry studies that met ATS standards A or B. A total of 1,332 had pre-bronchodilator airflow limitation and qualified for bronchodilator testing (Fig. 1). Among these, 625 subjects completed bronchodilator testing that met ATS quality standards and were included in our analysis. Only 381 (61%) of these subjects had persistent airflow limitation on the post-bronchodilator spirometry and were classified as spirometry-confirmed COPD, whereas the remaining 244 (39%) had airflow limitation only with pre–bronchodilator but not post-bronchodilator spirometry testing. Study subjects were predominantly male (64.3%) and non-Hispanic Whites (63.8%) (Figure 2). Spirometry-confirmed COPD subjects were significantly older compared to subjects with pre-not-post–bronchodilator airflow limitation (mean age ± SD: 61.6 ± 10.2 vs 58.1 ± 9.9; $P < .05$). Spirometry-confirmed COPD subjects were also more likely to have a doctor-informed

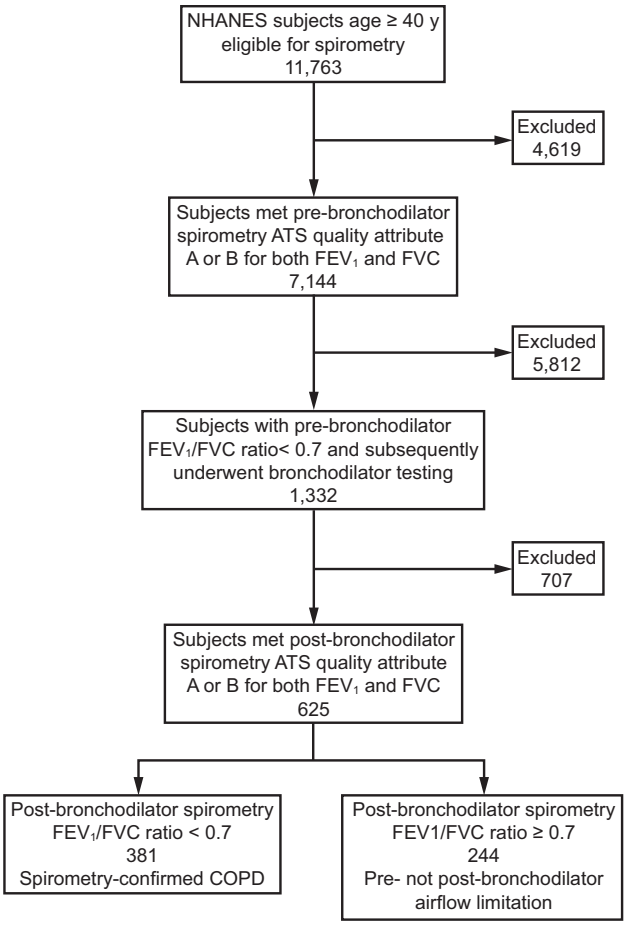



Fig. 1. Flow diagram of the study population. NHANES = National Health and Nutrition Examination Survey. ATS = American Thoracic Society.

history of emphysema (5.0% vs 1.2%, $P = .01$), be a current smoker (37.0% vs 21.3%, $P < .001$), experience cough (15.5% vs 9.4%, $P = .03$), and more likely to have required health care (88.2% vs 81.6%, $P = .03$). No significant differences were noted between these 2 groups with respect to the history of doctor-informed chronic bronchitis (8.1% vs 6.1%, $P = .43$) or asthma (17.8% vs 17.2%, $P = .93$) (Table 2). The proportion of subjects without airflow limitation in post–bronchodilator spirometry was significantly higher among females compared to males (47.5% vs 34.3%, $P < .05$) and in the 40–49 y age group compared to all other age groups (53.3%, $P < .05$) (Figure 2). Such proportion was higher among Mexican Americans; however, it was not statistically significant ($P = .08$).

The 381 subjects with spirometry-confirmed COPD were further analyzed to determine the prevalence of possible ACO. After excluding 12 subjects with missing blood eosinophil counts and one subject with unknown asthma history, 368 subjects were further analyzed. Using the ATS criteria, 56 subjects met both of the modified major criteria. Among these, 13 had only peripheral eosinophilia, 9 had only positive bronchodilator responsiveness, and 6 met both the minor criteria, totaling 28 subjects with possible ACO (7.6%) with ATS criteria (Figure 3). When the SEPAR criteria were used, 69 subjects met major criteria as 60 had only a history of asthma, 5 had only $\Delta FEV_1 > 400$ mL and >15%, and 4 subjects met both criteria. When the remaining 299 subjects who did not meet any of the major criteria were analyzed for minor criteria, 4 met both minor criteria qualifying for possible ACO. Therefore, the total number of subjects with possible ACO was 73 (19.8%) with modified SEPAR criteria (Figure 3).

When $\Delta FEV_1$ and bronchodilator responsiveness–based major and minor criteria were excluded from the ATS and SEPAR definitions, the prevalence of estimated ACO decreased significantly. Using the ATS criteria, 48 subjects met major criteria; and 17 of them had peripheral eosinophilia, decreasing the estimated prevalence of ACO from 7.6–4.6%. When the SEPAR criteria were used, 64 met major criteria and none met minor criteria, thereby decreasing the estimated prevalence of ACO from 19.8–17.4%. (Figure 4).

ATS definition requires the presence of 2 major criteria along with any one minor criteria to qualify as having ACO. Imputation analysis was performed among 28 subjects that met the required major criteria but did not meet any minor criteria, thereby not qualifying for ACO. After imputation, 14–25 of them would have allergic rhinitis, thereby meeting the minor criteria and subsequently qualifying as potentially having ACO diagnosis. Including these additional 14–25 subjects would increase the total number of ACO subjects to approximately 42–53, with an estimated prevalence of around 11.4–14.4% based on ATS definition (Figure 6). Similarly, SEPAR definition requires presence on any one major criteria or presence of any 2 minor criteria to qualify as having ACO. After performing imputation analysis, 11 additional subjects with bronchodilator responsiveness and 17 subjects with eosinophil count > 5% would have elevated IgE levels. Therefore, an additional 28 subjects would meet the criteria for ACO based on the presence of 2 minor criteria, increasing the total number of ACO subjects to 101, with a prevalence estimate of 27.4% using SEPAR definition. (Figure 5).

## Discussion

COPD is a heterogeneous disease with different clinical phenotypes including ACO.[30-34] Our study highlights the importance of bronchodilator testing to prevent COPD overdiagnosis. Since the proportion of subjects with pre-not-post–bronchodilator airflow limitation was higher among females and individuals age 40–49, they may be more vulnerable for COPD overdiagnosis. Even though women were less likely to exhibit reversibility in their

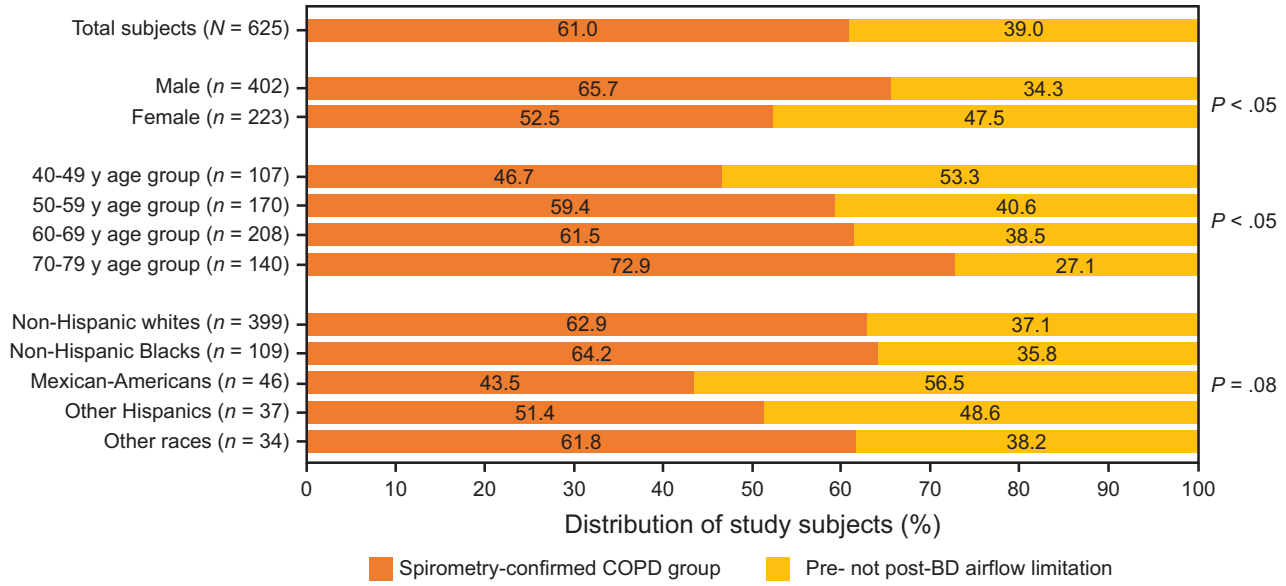



Fig. 2. Distribution of study subjects across spirometry-confirmed CPOD group and pre-but-not-post–bronchodilator airflow limitation group.

Table 2. Prevalence of Comorbidities

| Comorbidity | Spirometry-Confirmed COPD ($n = 381$) | Pre-Not-Post–Bronchodilator Airflow Limitation ($n = 244$) | $P$ |
|---|---|---|---|
| History of emphysema | 19 (5.0) | 3 (1.2) | .01 |
| History of asthma | 68 (17.8) | 42 (17.2) | .91 |
| History of chronic bronchitis | 31 (8.1) | 15 (6.1) | .43 |
| Current smokers | 141 (37.0) | 52 (21.3) | < .001 |
| Cough most of the days for 3 consecutive months | 59 (15.5) | 23 (9.4) | .03 |
| Phlegm with cough over the last 3-month period | 51 (13.4) | 23 (9.4) | .16 |
| Received health care at least once in the last year | 336 (88.2) | 199 (81.6) | .03 |

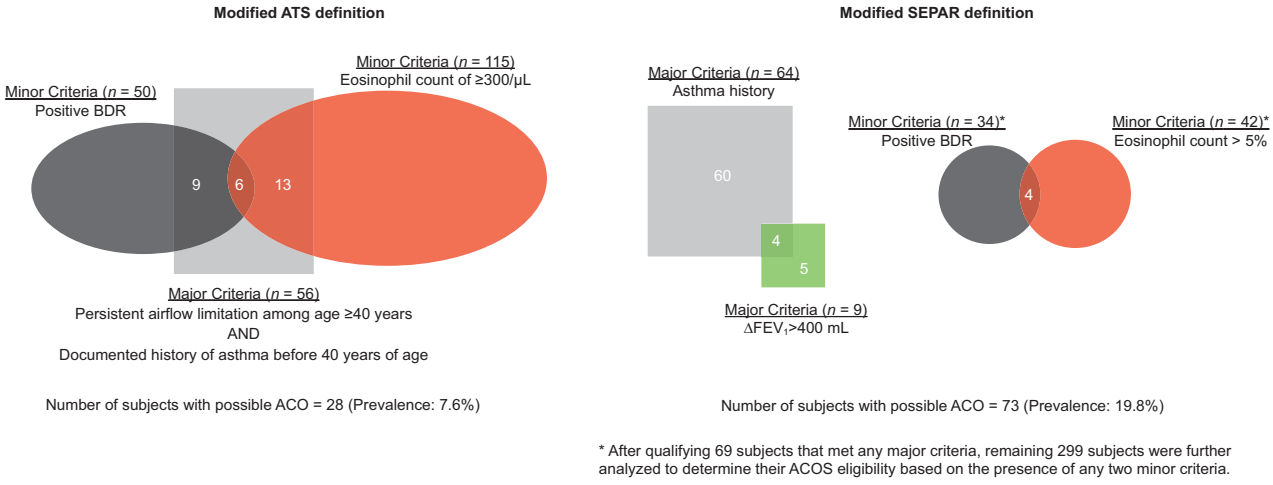
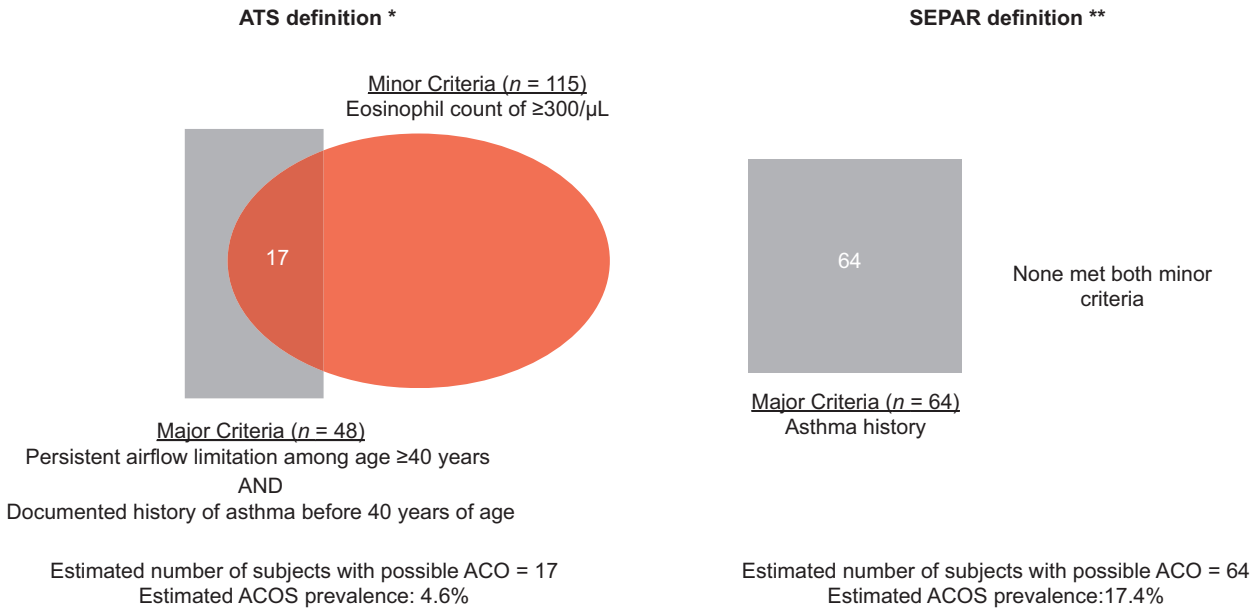



Fig. 3. Prevalence of asthma-COPD overlap (ACO) based on modified American Thoracic Society (ATS) and the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) definitions.




*- Δ FEV1 > 400 mL from major criteria AND positive BDR from minor criteria were excluded.
**- Δ FEV1 > 400 mL & 15% from major criteria AND positive BDR from minor criteria were excluded.

Fig. 4. Prevalence estimates of asthma-COPD overlap (ACO) after excluding $\Delta FEV_1$ and bronchodilator responsiveness from major and minor criteria. ATS = American Thoracic Society. SEPAR = Spanish Society of Pneumology and Thoracic Surgery. ACOS = asthma-COPD–overlap syndrome.

airflow limitation, these findings are not consistent in prior studies.[35,36]

Patients with ACO have lower health-related quality of life, higher number of exacerbations, and increased health care cost utilization compared to individuals with COPD alone.[37-44] Unlike COPD, early initiation of inhaled steroids among cases with ACO is recommended and is shown to produce a greater improvement in $FEV_1$.[45,46] The GOLD statement proposed a list of features that makes ACO more likely than COPD or asthma, but no clear guidance was provided with respect to the number of features to be fulfilled to diagnose ACO.[5] ATS and SEPAR proposed different criteria to aid the clinician in the identification of patients with ACO. Differentiating COPD from ACO is of critical importance owing to the difference in clinical management and outcomes.[18] The prevalence of possible ACO using modified ATS in our analysis was 7.6%, much lower than the prevalence estimate of 19.8% using SEPAR definition. The noted difference prevailed after imputation analysis, with 11.4–14.4% using ATS definition and 27.4% using SEPAR definition. Whereas the differences in the criteria used explain the varied prevalence estimates, the accuracy of these definitions in identifying clinically relevant subset of COPD subjects with ACO needs to be further evaluated. Not only there is a difference in the prevalence estimate, the dependence of these definitions on bronchodilator testing-based criteria including bronchodilator responsiveness and $\Delta FEV_1$ also varied. In our analysis, the ATS criteria relied more on these elements than the SEPAR criteria to identify ACO subjects. Exclusion of bronchodilator test-based criteria decreased the number of ACO subjects by 39.3% and 12.3% if using the ATS and SEPAR definitions, respectively.

This study has several limitations. First, despite high standards for data collection, NHANES examination and laboratory data are still subject to sampling and non-sampling errors. Second, the responses to the questionnaire included in our analysis are based on self-reporting and subject to recall bias. Asthma history in our analysis was identified using the question "Has a doctor or healthcare professional ever told that you have asthma?" Even though this was the most-used definition in previous studies to define asthma, this cannot be used as a surrogate for clinically confirmed asthma.[47] Third, using lower limit of the normal range-predicted criteria instead of GOLD fixed-ratio criteria will alter the prevalence estimates reported in our analysis but does not contradict our conclusion regarding the importance of using post-bronchodilator spirometry values toward accurately diagnosing COPD. Lastly, the ACO prevalence estimates in our analysis are not based on the proposed ATS and SEPAR definitions, as we have modified these definitions by excluding the criteria not available in the NHANES database. Though we attempted to overcome this limitation, the imputed prevalence

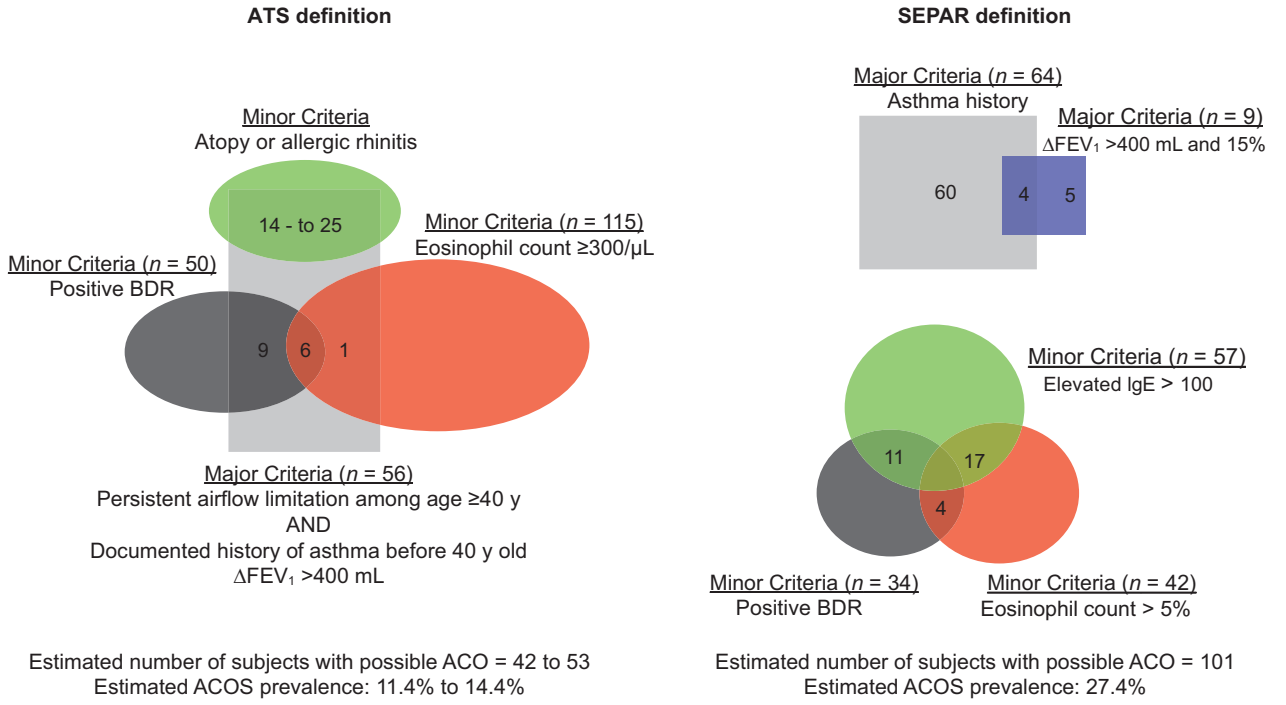



Fig. 5. Prevalence estimates of asthma-COPD overlap (ACO) after imputing the excluded minor criteria. ATS = American Thoracic Society. SEPAR = Spanish Society of Pneumology and Thoracic Surgery.

estimates for those excluded criteria might not reflect their actual prevalence in our population.

## Conclusions

Spirometry with bronchodilator testing is an important element in diagnosing COPD and differentiating COPD from ACO. The estimated number of subjects with ACO that may be misclassified was 7.6% and 19.8% if the modified ATS and SEPAR criteria are used, respectively. The absence of bronchodilator testing may lead to an overdiagnosis of COPD by 39%.

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