

ORIGINAL RESEARCH

Asthma, Chronic Obstructive Pulmonary Disease, and Mortality in the U.S. Population

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Background: COPD and asthma are common diseases in the U.S. population and can coexist. Our goal was to determine the prevalence of self-reported, physician-diagnosed asthma and COPD in a sample of the U.S. population and their association with lung function impairment and mortality. **Methods:** We used baseline data from NHANES III and the follow-up mortality data. We used logistic regression and Cox Proportional Hazards models, adjusting for age, sex, race/ethnicity, education level, smoking status, and disease stage. **Results:** The sample consisted of 15,203 subjects, of whom 4,542 died during the follow-up period. Coexisting COPD and asthma was reported by 357 (2.7%), COPD by 815 (5.3%), and asthma by 709 (5.3%). Subjects with both conditions had a higher proportion of obstruction (30.9%) than those with COPD (24.3%), asthma (13.3%), or no lung disease (5.4%). In survival models adjusting for all factors except baseline lung function, coexisting COPD and asthma had the highest risk for mortality (Hazard Ratio [HR] 1.83, 95% confidence interval [CI] 1.34, 2.49), followed by COPD only (HR 1.44, 95% CI 1.28, 1.62), and asthma only (HR 1.16, 95% CI 0.94, 1.42). These effects were attenuated after controlling for baseline lung function: coexisting asthma and COPD (HR 1.45, 95% CI 1.06, 1.98), COPD only (1.28, 95% CI 1.13, 1.45), and asthma only (HR 1.04, 95% CI 0.85, 1.27). **Conclusion:** In this analysis, subjects who report coexisting asthma and COPD have a higher risk of obstruction on spirometry and a higher risk of death during follow-up.

Keywords: COPD, Asthma, overlap, airflow obstruction, mortality

BACKGROUND

Asthma and chronic obstructive pulmonary disease (COPD) are the most common obstructive lung diseases (OLD). They constitute a leading cause of morbidity and mortality worldwide, and represent a global economic burden for health-care systems of industrialized and developed countries (1, 2).

COPD is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines on COPD(3, 4), as a disease characterized by airflow limitation that is not fully reversible, progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases (5). COPD affects 210 million people worldwide and is currently the fourth-largest cause of death in the world (projected to become the third by 2030) (6), while in the United States it has surpassed stroke and is now the third leading cause of death (7).

Asthma is defined by the Global Initiative for Asthma (GINA) as “a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment”(8). The WHO estimates that asthma affects 300 million people in the world (24.6 million people in the United States) (9), with reports suggesting that the prevalence of asthma in many parts of the world is still increasing (10), with the potential for an additional 100 million more cases by the year 2025 (8).

Although asthma and COPD represent two distinct entities with different pathogenesis and risk factors, clinical features of both diseases may overlap in adult patients, and large population studies have shown that a high proportion of patients with respiratory problems are diagnosed with more than one OLD (i.e., asthma and chronic bronchitis or emphysema) (11, 12). Moreover, overlapping diagnoses of asthma and COPD occur more commonly in patients more than 50 years of age and its frequency increases with age (11, 13).

Although previous studies suggest that coexistence of asthma and COPD is associated with higher cost and

Conflict of Interest Statement: DMM has received research funding from GlaxoSmithKline, Novartis, Boehringer-Ingelheim, and Pfizer and has worked as a consultant or advisor for GlaxoSmithKline, Novartis, Boehringer-Ingelheim, Astra-Zeneca and Pfizer. EDG and MK declare no conflicts of interest.

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utilization of medical services (12), the natural history and long-term prognosis of patients with overlap asthma and COPD have not been well described. To determine the prevalence of asthma, COPD, and coexisting asthma and COPD in a representative sample of the U.S. population and to determine the extent to which these processes were associated with mortality in up to 18 years of follow-up, we performed an analysis of baseline data from the Third National Health and Nutrition Examination Survey (NHANES III) and the Follow-up mortality Data.

METHODS

The Third National Health and Nutrition Examination Survey (NHANES III) was conducted from 1988 to 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention, Atlanta, GA. In this study a stratified multistage clustered probability design was used to select a sample of the U.S. population. Study participants completed extensive questionnaires in the household and a comprehensive physical examination, including pulmonary function testing, either in the household or at a specially equipped mobile examination center. A total of 81 sites were included in the final sample. The study was approved by the National Center for Health Statistics' Institutional Review Board. A follow-up of the original NHANES III cohort, linking study subjects to the National Death Index, determined vital status in December 2006.

This analysis was limited to subjects aged 25 years and older who completed the baseline survey and their vital status determined at the end of follow-up.

Baseline lung function

Predicted values from NHANES III were used in the analysis (14). We used age, sex, height and race/ethnicity to determine the predicted values. The study participants were classified into "Lung function status", using the pre-bronchodilator lung function (post-bronchodilator values were not obtained in this survey), into categories based on a modification of COPD classification criteria: obstructed ($FEV_1/FVC < 70\%$ and $FEV_1 < 80\%$ predicted), restricted ($FEV_1/FVC \geq 70\%$ and $FVC < 80\%$ of predicted), symptoms only (no obstruction or restriction but reporting symptoms of cough, wheeze, or dyspnea), normal (no obstruction or restriction and no symptoms), and no pulmonary function obtained (regardless of whether they reported symptoms) (15).

Definitions

Data included in this analysis were sex, age, body mass index (BMI), educational status, race/ethnicity, smoking status, history of respiratory disease, and disease stage (as noted here). Age was classified at baseline and was categorized for use in tables (25–44, 45–54, 55–64, 65–74, 75–84, and 85 and older), and was used as a continuous variable in the survival analyses. BMI was classified at baseline and was categorized into 5 categories (missing, < 18.5 , 18.5 – 24 , 25 – 29 , and ≥ 30 kg/m²). Education status was stratified into three levels (< 12 years, 12 years, and > 12 years). We defined subjects as being

current smokers, former smokers, or never smokers based on their responses to series of questions. One had to have smoked more than 100 cigarettes to qualify as a former or current smoker. Race/ethnicity was classified as White, Black, Mexican-American, or other.

Subjects were asked "Has a doctor ever told you that you have asthma?" with similar questions asked about "chronic bronchitis" and "emphysema." We classified those with a positive response to these questions as "Asthma only" and "COPD only" respectively, and as COPD/Asthma if they had a positive response to both.

Statistical analysis

Data analysis was completed using statistical software (Statistical Analysis Software, version 9.2; SAS Institute; Cary, NC and SUDAAN version 10.1; RTI, Research Triangle Park, NC, and SPSS 17, Somers, NY). NHANES III weights were used in all of the analyses. We calculated the deaths per 1,000 person years of follow-up for our key covariates.

We determined the relation between reported respiratory disease and disease stage (as determined by lung function). We used logistic regression, predicting obstructive spirometric findings ($FEV_1/FVC < 70\%$ and $FEV_1 < 80\%$ predicted), with reported respiratory disease as our main predictor and adjusting for age, sex, body mass index, education level, race/ethnicity, and smoking status. We repeated this analysis examining the interaction between smoking status and reported respiratory disease.

Our primary outcome of interest in the survival models was mortality by 2006. Cox proportional hazard regression models were developed using the SUDAAN procedure SURVIVAL to account for differential follow up in cohort participants. Time of follow-up was used as the underlying time metric. Censoring occurred at the date of death certificate or date the participant was last known to be alive. Plots of the log-log survival curves for each covariate were produced to evaluate the proportional hazards assumptions. Age, sex, race/ethnicity, smoking status, education level, body mass index, reported respiratory disease, and disease stage were included in the adjusted models.

RESULTS

Our study cohort consisted of 15,203 subjects aged 25 and older, of whom 4,542 (29.9%) died by the end of 2006. The characteristics of the population at baseline, person-years of follow-up, and deaths per 1,000 person-years are displayed in Table 1.

Overall, 5.3% of subjects reported asthma alone, 5.3% reported COPD alone, and 2.7% reported both asthma and COPD (Table 1). Among those reporting both asthma and COPD, 30.9% were obstructed, compared to 24.3% of those with COPD only, 13.3% of those with asthma only, and 5.4% of those with no reported respiratory disease (Table 2). Other characteristics of the population, stratified by respiratory disease status, are displayed in Table 2, including mean age, which was highest among those with COPD only (56.0 years), lowest among those with asthma only (44.9 years), and

Table 1. Characteristics of analyzed population at baseline (n = 15,203) with deaths (n = 4,542) at up to 18 years of follow-up

	N	% (weighted)	Person-Years of Follow-up	Deaths per 1,000 Person Years (weighted)
Sex				
Female	8,093	52.5	105,557	14.1
Male	7,110	47.5	89,247	14.8
Age Group, Years				
25–44	6,577	51.8	96,975	2.4
45–54	1,990	15.9	28,372	8.5
55–64	2,147	13.3	28,283	19.0
65–74	2,260	11.6	25,233	45.6
75–84	1,669	5.9	12,839	103.3
85 +	560	1.5	3,104	172.7
Body Mass Index, kg/m ²				
< 18.5	255	1.9	2,837	21.4
18.5–24	4,925	38.3	64,293	11.4
25–29	4,978	31.8	64,807	13.9
> = 30	3,701	22.1	49,434	14.6
Missing	1,344	6.0	13,434	39.5
Education, Years				
< 12	6,645	26.6	80,772	25.4
12	4,178	30.6	54,782	14.2
> 12	4,380	42.8	59,250	8.4
Race/Ethnicity				
White	6,691	77.4	80,683	15.3
Black	4,121	10.6	53,663	16.0
Mexican-American	3,804	4.9	52,652	8.4
Other	587	7.4	7,806	7.4
Smoking Status				
Never	7,126	44.0	92,826	14.1
Former	3,987	26.6	47,832	19.9
Current	4,090	29.4	54,147	11.6
Respiratory Disease				
COPD/Asthma	357	2.7	4,028	28.3
COPD only	815	5.3	8,735	36.1
Asthma only	709	5.3	9,187	11.7
None	13,322	86.7	172,854	13.1
Lung Function Status*				
Obstructed	1,205	7.5	12,169	45.2
Restricted	1,635	7.7	19,717	25.1
Symptoms	3,727	26.4	48,717	13.5
No Testing	2,045	10.2	21,445	34.3
Normal	6,591	48.3	92,757	6.3

*Lung function status, as defined in methods.

intermediate among those with both asthma and COPD (50.9 years).

Logistic regression among 13,871 subjects who had lung function testing and body mass index determined showed that male sex, increasing age, low body mass index, white race/ethnicity, and current or former smoking status increased the risk of having obstruction on spirometry. Compared to those with no reported lung disease, those reporting both COPD and asthma had the highest risk (odds ratio [OR] 7.64, 95% confidence interval [CI] 5.08, 11.49), followed by those with asthma only (OR 3.70, 95% CI 2.67, 5.13) and COPD only (OR 3.50, 95% CI 2.52, 4.85). (Table 3). Figure 1 displays the interaction between reported respiratory disease and smoking status as predictors of obstructive spirometry in fully adjusted models. Reported asthma only, COPD only, or asthma and COPD were predictors of obstruction regardless of smoking status.

In survival models adjusting for all factors except baseline lung function, reported coexisting COPD and asthma

had the highest risk for mortality (Hazard Ratio [HR] 1.83, 95% confidence interval [CI] 1.34, 2.49), followed by current COPD (HR 1.44, 95% CI 1.28, 1.62), and current asthma (HR 1.16, 95% CI 0.94, 1.42) (Table 4). These affects were attenuated after controlling for baseline lung function: coexisting asthma and COPD (HR 1.45, 95% CI 1.06, 1.98), current COPD (1.28, 95% CI 1.13, 1.45), and current asthma (HR 1.04, 95% CI 0.85, 1.27) (Table 4). Figures 2 and 3 display the survival curves before (Figure 2) and after (Figure 3) adjusting for lung function status at baseline.

DISCUSSION

The concept of COPD representing an overlap between different obstructive lung diseases has been discussed since the time of the Ciba symposium in 1959 (16). Subsequent studies have consistently shown that the diagnoses of asthma, chronic bronchitis and emphysema may converge

Table 2. Characteristics of analyzed population at baseline (n = 15,203) by respiratory disease status

	COPD/Asthma n = 357 % (weighted)	COPD Only n = 815 % (weighted)	Asthma Only n = 709 % (weighted)	None n = 13,322 % (weighted)
Sex				
Female	62.0	61.3	50.6	51.7
Mean Age (Standard Error)	50.9 (1.1)	56.0 (0.8)	44.9 (0.8)	47.0 (0.4)
Body Mass Index, kg/m ²				
< 18.5	2.5	4.1	2.6	1.7
18.5–24	33.1	37.6	34.7	36.7
25–29	24.5	25.6	31.2	32.5
> = 30	32.4	23.0	24.6	21.5
Missing	7.5	9.7	6.9	5.7
Education, Years				
<12	35.4	38.2	25.7	25.7
12	32.3	34.6	27.7	30.5
>12	32.3	27.2	46.6	43.8
Race/Ethnicity				
White	78.6	88.2	79.1	76.6
Black	9.5	7.0	10.9	10.9
Mexican-American	2.2	2.2	3.3	4.9
Other	9.7	2.7	6.8	7.6
Smoking Status				
Never	41.0	40.9	31.6	28.2
Former	31.4	35.8	25.5	26.0
Current	27.6	23.2	42.9	45.8
Lung Function Status*				
Obstructed	30.9	24.3	13.3	5.4
Restricted	8.5	8.2	7.5	7.7
Symptoms	44.0	38.0	46.4	23.9
No Testing	8.2	12.3	10.7	10.1
Normal	8.4	17.3	22.0	53.0

*Lung function status, as defined in methods.

Table 3. Results from logistic regression model predicting the presence of Stage 2 obstruction (FEV₁/FVC < 70% and FEV₁ < 80% predicted) in 13,871 subjects

	Odds Ratio (95% Confidence Interval)
Sex	
Male	1.29 (1.04, 1.61)
Female	1
Age	1.06 (1.05, 1.07)
Body Mass Index, kg/m ²	
<18.5	2.62 (1.59, 4.29)
18.5–24	1
25–29	0.78 (0.62, 1.00)
>= 30	0.95 (0.75, 1.20)
Education, Years	
<12	1.41 (1.13, 1.78)
12	1.46 (1.15, 1.86)
>12	1
Race/Ethnicity	
White	1
Black	0.76 (0.60, 0.96)
Mexican-American	0.58 (0.43, 0.77)
Other	1.16 (0.65, 2.08)
Smoking Status	
Never	1
Former	2.03 (1.60, 2.58)
Current	4.30 (3.24, 5.71)
Respiratory Disease	
COPD/Asthma	7.64 (5.08, 11.49)
COPD only	3.50 (2.52, 4.85)
Asthma only	3.70 (2.67, 5.13)
None	1.00 (1.00, 1.00)

at population level, with many patients presenting with mixed COPD-like phenotypes (11, 17, 18). Nevertheless, the natural history of some of these “overlap phenotypes” has not been well characterized. By analyzing a large sample of subjects from the general population in the United States, we observed that the overlap of asthma and COPD is associated with a higher risk for airflow obstruction and mortality.

Previous research suggests that patients with overlap OLD present higher degree of airflow obstruction (11). In addition, coexisting asthma and COPD has been associated with a higher disease severity score (18, 19), health care utilization and cost (12, 19), and an elevated mortality risk (20). Our results are in agreement with previous findings in that airflow obstruction is more common among people reporting concomitant diagnoses of asthma and COPD.

Development of incompletely reversible airflow obstruction may occur in patients with long standing asthma – these patients tend to be older and have an increased risk of death from respiratory diseases (21, 22). Studies have also shown that subjects with active asthma have a greater risk of developing COPD as compared with subjects with no asthma, and that this risk is increased by smoking status (23). Moreover, it is known that a large proportion of older adults with COPD report a history of asthma, and that subjects with asthma are more likely to report coexisting COPD compared to subjects without asthma (24). It is then expected that overlap of asthma and COPD occurs more frequently in older individuals, particularly in those with history of tobacco use.

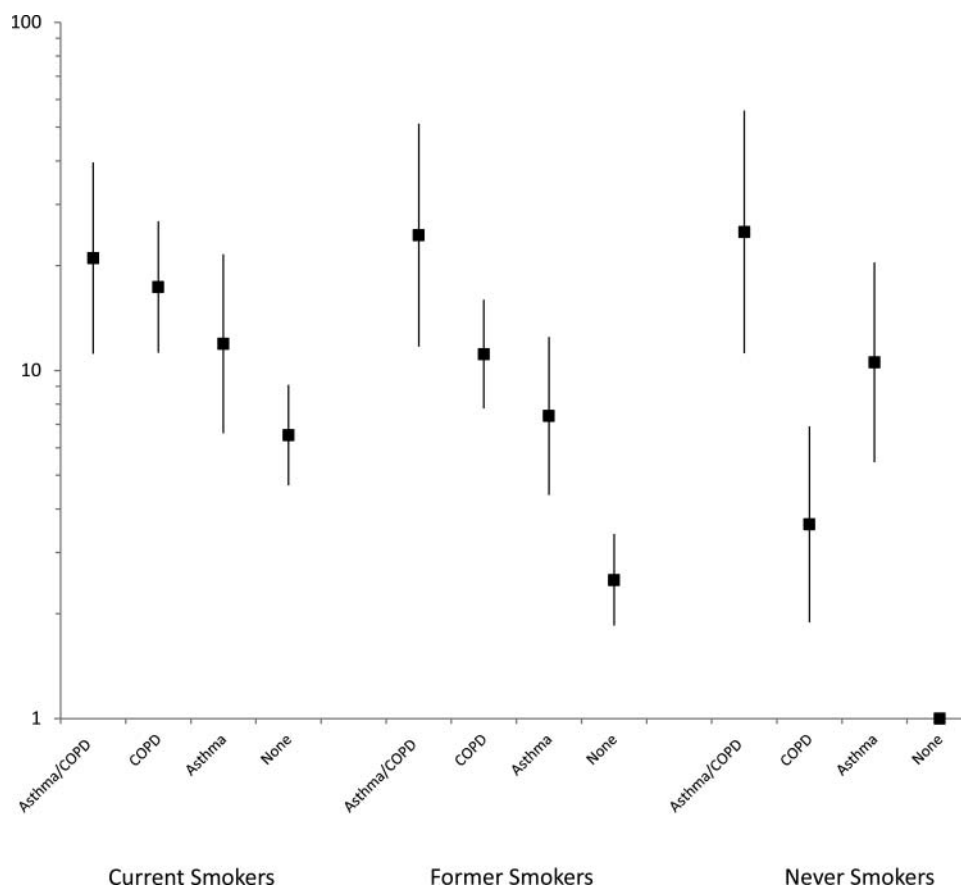


Figure 1. Results from adjusted logistic regression model predicting the presence of Stage 2 obstruction ($FEV_1/FVC < 70\%$ and $FEV_1 < 80\%$ predicted), demonstrating the interaction between smoking status and reported lifetime history of asthma, COPD, or both.

In our analysis, subjects with coexisting asthma and COPD were older than those with asthma only (50.9 vs. 44.9 years, Table 2), but younger than those with COPD only (56.0 years). Recent increasing trends in asthma prevalence may

modify this relation in the future, as a higher proportion of asthma patients age (9).

Additionally, it is also well known that the amount of lifetime exposure to cigarette smoking as well as aging are

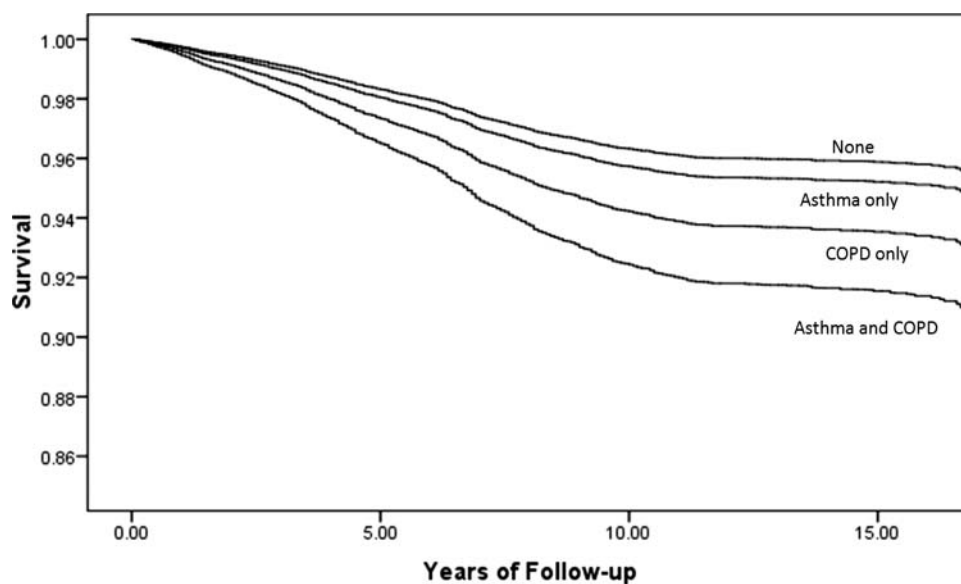


Figure 2. Results from Cox proportion hazard models. Curves are adjusted for sex, age, body mass index, education, race/ethnicity, and smoking status at baseline.

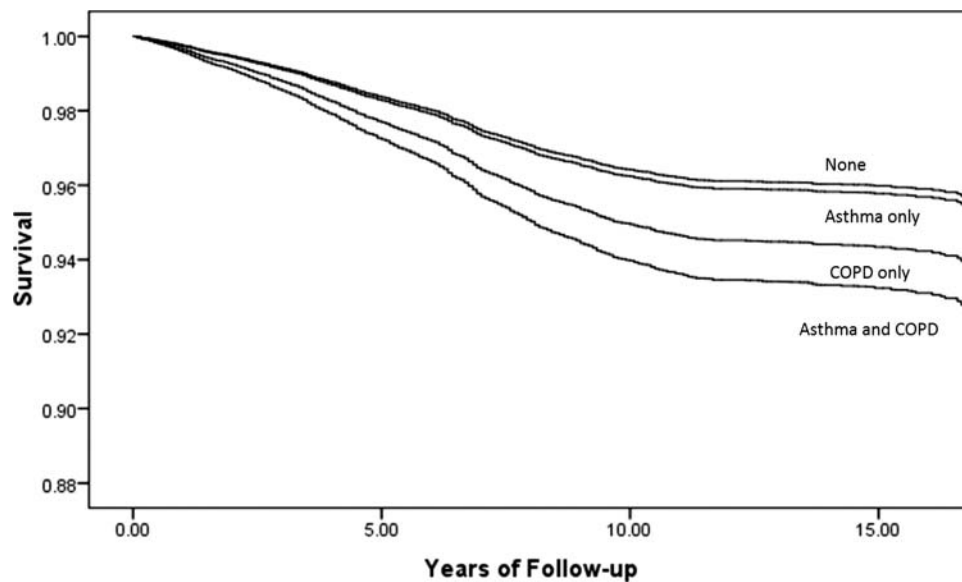


Figure 3. Results from Cox proportion hazard models. Curves are adjusted for sex, age, body mass index, education, race/ethnicity, smoking status and lung function status at baseline.

strongly associated with higher degrees of airflow limitation in patients with asthma or COPD (25, 26). As was expected, increase in age, low body mass index, White race/ethnicity, and current or former smoking status increased the risk for airflow obstruction. Nevertheless, the association between higher degree of obstruction and overlapping asthma and COPD persisted after adjusting for these covariates.

More importantly, we report that the association between co-existing asthma and COPD and higher frequency of airflow obstruction results in increased mortality after long term follow-up. Our results contrast with previous reports suggesting that a concomitant diagnosis of asthma and COPD is not associated with increased mortality. For example, Soriano et al. described unchanged survival of newly diagnosed COPD patients who had an asthma diagnosis from the UK General Practice Research Database (27). That report included only a short follow-up period (3 years) and the determinant of disease was based on administrative data rather than survey data.

Also, Mapel et al. reported longitudinal studies of two cohorts of patients with COPD, among whom a concurrent diagnosis of asthma was associated with better survival. Both of those studies were comparing treatments of active COPD, whereas treatment was not a part of our analysis (28, 29). A study of patients from the Veterans Healthcare Administration database found that a concomitant diagnosis of asthma had a protective mortality effect among those discharged with a recent COPD exacerbation (30). That study was limited to patients with a COPD hospitalization, so it is possible, for example, that co-morbid asthma might increase the risk for hospitalization more than it does for death, potentially explaining the differences between our findings.

Other reports using data from administrative databases in the United States have shown that, when compared to pa-

tients with asthma or COPD alone, patients with concomitant asthma and COPD present higher illness scores, and have almost double risk for requiring emergency department use or hospitalization related to respiratory events (12, 19, 31). Although finding an increased mortality in patients with overlapping OLD may not be surprising (considering that these patients tend to be older and therefore may have an increased number of co-morbidities), our findings highlight the importance of recognizing these patients' elevated risks, and provide further insight into the natural history of airflow obstruction in these patients.

These findings further support the hypothesis that asthma and COPD can merge in a proportion of patients during adult life. Our findings suggest that the natural history of coexistent asthma and COPD may be different compared to other classic phenotypes (asthma or COPD alone). Another possibility is that early manifestations of COPD may, in fact, look like and be diagnosed as asthma. Our findings also add evidence to support the argument to include patients with concomitant asthma and COPD in randomized clinical trials to evaluate the impact of pharmacological interventions in the natural history of overlap phenotypes.

Our analysis is not without limitations. The NHANES III is a survey of self-reported physician diagnoses and conditions by the participants, and these diagnoses are not independently validated. Therefore misclassification of both asthma and COPD is possible as many patients may have been diagnosed based on clinical features without considering other criteria. In addition, post-bronchodilator spirometry values was not available, therefore overestimation of airflow obstruction severity is possible. However, our results relating the presence of obstruction to diagnoses, and diagnoses to mortality, suggest these potential limitations have not had a major influence on our findings.

Table 4. Results from Cox Proportional hazards survival models on baseline sample- mortality follow-up of up to 18 years.

	Hazards Ratio (95% Confidence Interval)	Hazards Ratio (95% Confidence Interval)
Sex	A	B
Male	1.35 (1.23, 1.49)	1.35 (1.23, 1.48)
Female	1	1
Age	1.10 (1.09, 1.11)	1.10 (1.09, 1.10)
Body Mass Index, kg/m ²		
<18.5	1.96 (1.46, 2.63)	1.71 (1.24, 2.36)
18.5–24	1	1
25–29	0.93 (0.83, 1.04)	0.92 (0.81, 1.03)
>= 30	1.11 (0.99, 1.24)	1.04 (0.92, 1.17)
Missing	1.57 (1.37, 1.80)	1.74 (1.39, 2.19)
Education, Years		
<12	1.36 (1.18, 1.57)	1.31 (1.14, 1.50)
12	1.42 (1.25, 1.60)	1.37 (1.22, 1.55)
>12	1	1
Race/Ethnicity		
White	1	1
Black	1.32 (1.19, 1.47)	1.34 (1.20, 1.49)
Mexican-American	1.01 (0.87, 1.18)	0.94 (0.81, 1.10)
Other	0.71 (0.59, 0.87)	0.68 (0.56, 0.82)
Smoking Status		
Never	1	1
Former	1.28 (1.14, 1.44)	1.22 (1.09, 1.37)
Current	2.06 (1.83, 2.31)	1.82 (1.62, 2.04)
Respiratory Disease		
COPD/Asthma	1.83 (1.34, 2.49)	1.45 (1.06, 1.98)
COPD only	1.44 (1.28, 1.62)	1.28 (1.13, 1.45)
Asthma only	1.16 (0.94, 1.42)	1.04 (0.85, 1.27)
None	1	1
Lung Function Status *		
Obstructed		2.07 (1.80, 2.37)
Restricted		1.95 (1.69, 2.25)
Symptoms		1.32 (1.18, 1.49)
No Testing		1.25 (1.01, 1.55)
Normal		1

*Lung function status, as defined in methods.

Model A adjusts for all factors except Disease Stage and Model B adjusts for all factors.

CONCLUSIONS

Patients with concomitant asthma and COPD are at increased risk for mortality, and this risk is independent of baseline lung function or smoking status. The recent increases seen in asthma prevalence around the world may result in more people with the asthma/COPD overlap syndrome in the future. As overlap syndromes become more common in adults, it will be important to develop strategies to detect and treat patients with different OLD phenotypes.

ACKNOWLEDGMENTS

The authors would like to thank Ms. Susan Mittenzwei and Ms. Rebecca Copeland for their assistance in this project. The analysis and development of this manuscript was supported by a research grant from GlaxoSmithKline Pharmaceuticals.

DECLARATION OF INTERESTS

Dr. Mannino was responsible for developing the analytic concept, running the data analysis, interpreting the results and writing the manuscript. Dr. Khorsravi and Dr. Diaz-Guzman were responsible for interpreting the results and writing the manuscript. Drs. Mannino and Diaz-Guzman are guarantors of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

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