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SCIENTIFIC INVESTIGATIONS

Sleep problems and associations with cardiovascular disease and all-cause mortality in asthma-chronic obstructive pulmonary disease overlap: analysis of the National Health and Nutrition Examination Survey (2007–2012)

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Study Objectives: The impact of sleep problems (ie, sleep duration and presence of sleep disorders) on cardiovascular morbidity and all-cause mortality in adults with asthma-chronic obstructive pulmonary disease overlap (ACO) is unknown.

Methods: Using the National Health and Nutrition Examination Survey database (2007–2012 cycles) and National Death Index data, we identified 398 persons with ACO. Data on self-reported physician-diagnosed sleep disorders and cardiovascular disease were collected. Sleep duration in hours was categorized as short (≤ 5 hours), normal (6–8 hours), and long (≥ 9 hours). Associations between sleep duration and presence of sleep disorders and cardiovascular disease and all-cause mortality were analyzed in regression models adjusted for age, sex, race, smoking status, and body mass index.

Results: Presence of sleep disorders was more commonly reported in the ACO group (24.7%) compared to all other groups. The ACO group had a higher proportion of short sleepers (27.6%) compared to controls (11.7%) and chronic obstructive pulmonary disease (19.2%) and a higher proportion of long sleepers (6.9%) compared to chronic obstructive pulmonary disease (5.5%). Presence of sleep disorders was associated with increased risk for cardiovascular disease (odds ratio = 2.48; 95% confidence interval, 1.65–3.73) and death (hazard ratio = 1.44; 95% confidence interval, 1.03–2.02); risk did not vary between groups. A stronger association existed between sleep duration and increased risk for cardiovascular and all-cause mortality in ACO compared to chronic obstructive pulmonary disease and controls.

Conclusions: These results suggest that persons with ACO may represent a high-risk group that should be targeted for more aggressive intervention for sleep problems, a modifiable risk factor.

Keywords: sleep disorder, sleep duration, asthma, COPD, mortality

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep problems (ie, short and long sleep duration and sleep disorders) are common in persons with either asthma or chronic obstructive pulmonary disease and have been linked to increased cardiovascular risk and mortality in the general population. The impact of sleep problems on cardiovascular disease and mortality in persons with asthma-chronic obstructive pulmonary disease overlap is unknown.

Study Impact: The majority of previous studies examined the independent effect of pulmonary disease (ie, asthma and chronic obstructive pulmonary disease) or sleep problems on health and mortality. This study used population-level data to find that there is a trend for increased burden of sleep problems in asthma-chronic obstructive pulmonary disease overlap compared to chronic obstructive pulmonary disease, asthma, and controls that can impose important clinical implications, including increased risk for cardiovascular disease and all-cause mortality.

INTRODUCTION

The Global Initiative for Asthma and the Global Initiative for Obstructive Lung Disease characterize asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) as a heterogenous entity by which patients are characterized by persistent airflow limitation (ie, not fully reversible postbronchodilation) and have diagnoses and/or features of both asthma and COPD.[1] Compared with asthma or COPD alone, patients with ACO experience greater symptom burden,[2] more comorbidities,[1–3] a disproportionately higher health care utilization,[4–6] increased mortality,[7] and poorer quality of life.[8] Unlike asthma and COPD, the mechanisms underlying ACO are largely unknown.[9] Emerging evidence implicates smoking history, peripheral blood eosinophil counts, airway and systemic inflammation, and age of asthma onset as factors that predispose patients to ACO.[7,10,11] A recent meta-analysis found the pooled prevalence of ACO among patients with COPD to be 28%.[5] Despite this high prevalence, there is a paucity of evidence to inform management of this patient population.

Patients with asthma or COPD only have an increased risk of cardiovascular disease (CVD) with associated morbidity and mortality effects.[12–15] Estimates of the prevalence of CVD in ACO range between 25% and 50%.[2,16] Retrospective data

found cardiovascular risk was greater in ACO when compared to those without asthma and/or COPD and those with asthma or COPD only.[17,18] These findings suggest that not only do patients with ACO have higher propensity for CVD compared to those without chronic lung disease, but that this association may be more pronounced in ACO compared to asthma and COPD only.

Asthma and COPD have been independently associated with increased sleep problems.[19,20] Among adults, the presence of sleep disorders (ie, obstructive sleep apnea and insomnia) has been linked to increased cardiovascular risk[21–23] and mortality.[24,25] Likewise, in the general population, both short (ie, less than 6 hours) and long (ie, 9 or more hours) sleep duration have well-established associations with adverse health outcomes, including chronic diseases, functional decline, and mortality.[26,27] The few studies that have examined sleep in ACO have focused on the prevalence of sleep disorders or the associations with respiratory symptoms.[28,29] No studies to date have examined the impact of sleep disorders and sleep duration on CVD and mortality in ACO. The present study analyzed data from the National Health and Nutrition Examination Survey (NHANES) to determine the prevalence of sleep problems, defined by sleep duration or the presence of sleep disorders, in persons with ACO. We also determined whether the presence of sleep problems is associated with increased prevalence for cardiovascular disease and increased hazards of mortality in adults with ACO when compared to adults with asthma only, COPD only, and those without either asthma or COPD after controlling for covariates. We hypothesized that these associations are greater in persons with ACO because of potential synergistic effects of asthma and COPD comorbidity.

METHODS

Study population and inclusion criteria

NHANES is a cross-sectional survey assessing the health and nutritional status of adults and children in the United States. A nationally representative sample of approximately 5,000 individuals is selected annually in a complex sampling design to undergo an interview to collect self-report data on demographic, socioeconomic, and health-related information and objective clinical data from a medical examination that includes laboratory testing and physical measurements. Spirometry was performed during the 2007–2012 cycles. Detailed methodology of NHANES is available elsewhere.[30] Written informed consent was obtained from participants, and the National Center for Health Statistics Research Ethics Review Board approved the survey; deidentified data were used for the analyses.

Participants aged 20 years and older with demographic, medical condition, and sleep questionnaire data and who completed spirometry during NHANES 2007–2012 cycles were included in the analyses. Asthma was defined as an affirmative response to the questions, "Has a doctor ever told you that you had asthma?" and "Do you still have asthma?" COPD was defined as participants ≥ 40 years of age that (1) answered "yes" to 1 of the following questions: "Has a doctor ever told you that you had emphysema?" or "Has a doctor ever told you that you had chronic bronchitis?" or (2) had spirometry-confirmed COPD evidenced by a postbronchodilator forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio < 0.70. ACO was defined if participants were ≥ 40 years of age and met criteria for both asthma and COPD. The operational definitions for chronic airway disease used in the current study were previously adopted in other NHANES publications.[2,28] Controls were defined as those participants without asthma or COPD.

Outcomes

The outcomes of interest were presence of CVD and all-cause mortality. Cardiovascular disease was defined as the presence of at least 1 of the following physician-diagnosed conditions: angina, congestive heart failure, hypertension, coronary heart disease, myocardial infarction, or stroke and was identified from the survey as a positive response to the question, "Have you ever been told by a doctor or health professional that you have [condition]?"

Mortality status was determined by linking National Death Index public access files through December 31, 2015 to data of NHANES respondents (details of this data linkage can be found at https://www.cdc.gov/nchs/data-linkage/mortality-public.htm). Although the major cause of death was able to be determined, examination of cause-specific morality, in particular cardiovascular mortality and chronic lower respiratory disease-related mortality, were precluded in this study due to limited numbers of deaths.

Sleep problems

Sleep duration was evaluated by a question that asked, "How much sleep do you usually get on weekdays or workdays?" Responses were entered in hours. Sleep duration was categorized as "short" (≤ 5 hours), "normal" (6–8 hours), and "long" (≥ 9 hours) sleep duration. Presence of sleep disorders was based on a positive response to the question, "Have you ever been told by a doctor or other health professional that you have a sleep disorder?"

Sociodemographic and clinical variables

Sociodemographic variables included age, sex, race, marital status, education, and financial status. Age was reported in years, with values in persons aged 80 years or older censored and recoded as "80" to maintain anonymity. Race/ethnicity were categorized as non-Hispanic White or Other (non-Hispanic Black, Mexican American, Other Hispanic, or Other Race). Marital status was categorized as Married/Partnered or Single/Not Partnered. Educational level was categorized as < high school or ≥ high school. Financial status was determined was determined by the family size-to-household income ratio. Low income was categorized as less than 200% of the federal poverty line determined by federal poverty guidelines. Clinical variables included body mass index (kg/m^2) and smoking status. Smoking status was categorized as nonsmoker, former smoker, or current smoker. Nonsmoker was defined by a "no" response to the question, "Have you smoked at least 100 cigarettes in your entire life?" Former smoker was defined by a "yes" response to this question but a "no" response to the

question, "Do you now smoke cigarettes?" Current smoker was defined as a positive response to both questions.

Statistical analysis

Analyses were conducted using complex survey design functionality in SAS 9.4 (SAS Institute Inc., Cary, NC) incorporating 6-year interview-based survey weights, clustering in primary sampling units, and stratification. Descriptive statistics included the weighted means and standard error for continuous variables and weighted percentages and standard errors for categorical variables. Comparisons between the ACO group and the other groups (control, asthma, and COPD) used linear contrasts with analysis of variance for continuous variables and Rao-Scott chi-square test for categorical variables.

Logistic regression models were fit to assess the associations of sleep duration (reference: normal) and presence of sleep disorders with the presence of CVD. Cox regression models were fit to examine the influence of sleep duration and sleep disorders on risk of all-cause mortality. Both logistic and Cox regression models controlled for age, sex, race/ethnicity, poverty level, smoking status, and body mass index. Separate models were fit for each sleep duration and sleep disorder to assess their unique influences. Models were built as follows: (1) main effects for disease group, sleep duration, and presence of sleep disorders; (2) adding control variables to the main effects models; (3) incorporating interactions between disease groups with sleep duration categories and presence of sleep disorders to assess differential prediction of all-cause mortality and presence of CVD from sleep duration and presence of sleep disorders among disease groups. Odds ratios from logistic regression and hazard ratios from Cox regression are reported as estimates with their corresponding 95% confidence interval (CI).

RESULTS

Characteristics of the study population

There were 7,616 adults 20 years and older in our national sample from 2007 to 2012. Weighted estimates of demographic characteristics of the sample stratified by individuals with asthma (6.26%), COPD (12.76%), ACO (4.35%), and those without asthma or COPD (ie, controls [76.63%]) are presented in **Table 1**. Overall, participants in the ACO group were more likely to have CVD and a higher body mass index than the other groups (all P values < .05). Compared to COPD, the ACO group was younger, more likely female, living below the poverty level, and less likely to be non-Hispanic White (all P values < .05). Compared to the asthma group, the ACO group was older and more likely to be non-Hispanic White, married, a former smoker, and have less than a high school education (all P values ≤ .002). The ACO group was older, more likely female, non-Hispanic White, have less than a high school education, and be a current or former smoker compared to controls (all P values < .001).

Sleep problems

Physician-diagnosed sleep disorder was more commonly reported in the ACO group (24.7%) compared to the asthma (10.7%), COPD (13.5%), and control (4.6%) groups (**Table 1**). On average, the ACO group reported a shorter sleep duration in hours per night (6.6 hours) compared to the control (7.0 hours) and asthma (6.7 hours) groups. There was no difference in self-reported sleep duration between the ACO and COPD groups. **Figure 1** depicts the percentage of short (≤ 5 hours), normal (6 to 8 hours), and long (≥ 9 hour) sleep duration within each group. The ACO group had a higher proportion of short sleepers (27.6%) compared to controls (11.7%) and COPD (19.2%) and a higher proportion of long sleepers (6.9%) compared to COPD (5.5%); no differences were noted between ACO and asthma groups.

Sleep, CVD, and mortality

Results from the logistic regression models for the presence of CVD are displayed in relation to sleep duration category (**Table 2**) and to the presence of sleep disorders (**Table 3**). In fully adjusted models (**Table 2**), when compared to participants with normal sleep duration, short sleepers had a higher likelihood of having CVD (odds ratio = 1.70; 95% CI, 1.26–2.30). Long sleep duration trended toward higher risk but did not reach significance. Likewise, participants with sleep disorders, compared to those without sleep disorders (**Table 3**), had a greater likelihood of having CVD (odds ratio = 2.48; 95% CI, 1.65–3.73). From interaction models, relative to the ACO group, long sleepers in all the other disease groups had extremely lower odds for CVD (**Table 2**); however, the influence of sleep disorders on CVD did not vary significantly between disease groups (**Table 3**). In a main effect model together with sleep duration, the presence of sleep disorders remained a significant predictor of CVD (odds ratio = 2.36; 95% CI, 1.57–3.57); adjusted risk did not differ between groups (**Table S1** in the supplemental material).

Results from the Cox regression models for the risk of all-cause mortality are displayed in relation to sleep duration category (**Table 4**) and to the presence of sleep disorders (**Table 5**). Relative to the ACO group with normal sleep (**Table 4**), both short and long sleepers in either the control (hazard ratio [HR] = 0.19; 95% CI, 0.07–0.47 and HR = 0.07; 95% CI, 0.02–0.35, respectively) or COPD (HR = 0.38; 95% CI, 0.19–0.77 and HR = 0.24; 95% CI, 0.12–0.51, respectively) groups had lower risks of all-cause mortality. In covariate adjusted models (**Table 5**), the presence of sleep disorders predicted significantly higher risks for all-cause mortality (HR = 1.44; 95% CI, 1.03–2.02); however, the prediction of risk from sleep disorders did not significantly differ between disease groups. To check the robustness of the sleep duration by disease group interaction effect and main effect of sleep disorder on all-cause mortality risks, a model was fit including both these terms along with covariates. Both the main effect of sleep disorder and disease group by sleep duration interactions remained significant (**Table S2**). **Figure 2** displays the estimated hazards (ie, risks of all-cause mortality) within controls, ACO, and COPD disease groups relative to both sleep duration and presence of sleep disorder. Individuals in the ACO group having long or short sleep duration appear to have increased hazards compared to COPD and controls.

Table 1—Weighted sociodemographic and clinical characteristics of the study population, NHANES 2007–2012.

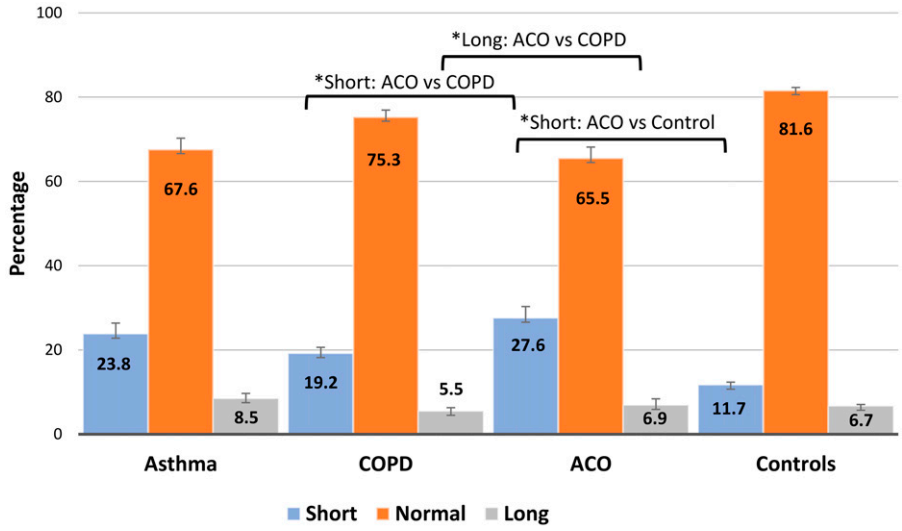
	Controls	Asthma	COPD	ACO	*P* Values*		
	n = 5,729	n = 483	n = 1,006	n = 398			
	Estimate (SE)[a]	Estimate (SE)[a]	Estimate (SE)[a]	Estimate (SE)[a]	ACO vs Controls	ACO vs Asthma	ACO vs COPD
Age, mean	30.8 (0.24)	30.0 (0.47)	60.1 (0.40)	59.5 (0.62)	< .001	< .001	.047
Male sex, %	50.9 (0.65)	35.6 (2.92)	54.7 (2.05)	38.1 (3.88)	.001	.654	< .001
Race/ethnicity, %					< .001	< .001	.009
Non-Hispanic White	60.3 (2.29)	65.4 (3.60)	83.4 (1.89)	78.2 (2.55)			
Other	39.7 (2.29)	34.6 (3.60)	16.6 (1.89)	21.8 (2.55)			
Marital status, %					.525	< .001	.248
Married/partnered	57.4 (1.44)	47.4 (2.89)	63.7 (2.94)	59.2 (3.01)			
Single/not partnered	42.6 (1.44)	52.6 (2.89)	36.3 (2.94)	40.8 (3.01)			
Poverty level, %					.166	.516	< .001
< 200%	47.2 (1.64)	56.3 (3.41)	36.4 (2.56)	53.2 (4.06)			
≥ 200%	52.8 (1.64)	43.7 (3.41)	63.6 (2.56)	46.8 (4.06)			
Education, %					< .001	.002	.375
Less than high school	16.7 (0.92)	16.1 (2.07)	22.8 (1.87)	25.9 (3.41)			
High school and above	83.3 (0.92)	83.9 (2.07)	77.2 (1.87)	74.1 (3.41)			
Smoking status, %					< .001	< .001	.094
Current	24.8 (1.07)	32.6 (3.01)	26.1 (1.90)	31.2 (3.61)			
Former	14.6 (0.86)	14.8 (1.97)	37.6 (2.22)	34.0 (3.40)			
Never	60.6 (1.35)	52.6 (2.90)	36.4 (2.25)	34.8 (2.98)			
BMI, mean	27.8 (0.15)	29.8 (0.37)	28.8 (0.26)	31.3 (0.44)	.001	< .001	< .001
Cardiovascular disease, %							
Angina	0.27 (0.07)	0.54 (0.34)	5.2 (0.79)	10.9 (2.00)	< .001	< .001	< .001
Stroke	0.51 (0.12)	1.04 (0.45)	6.5 (1.04)	9.3 (1.74)	< .001	< .001	.095
Congestive heart failure	0.36 (0.08)	1.7 (0.63)	6.3 (0.89)	13.2 (2.64)	< .001	< .001	.003
Hypertension	12.3 (1.02)	19.9 (4.46)	41.3 (2.90)	57.4 (5.49)	< .001	< .001	.006
Myocardial infarction	0.50 (0.12)	0.95 (0.38)	8.08 (0.88)	14.5 (2.05)	< .001	< .001	< .001
Coronary artery disease	0.31 (0.08)	0.10 (0.10)	8.4 (1.08)	13.2 (2.51)	< .001	< .001	.052
Presence of CVD	15.4 (1.16)	26.2 (4.53)	60.1 (3.45)	76.0 (4.30)	< .001	< .001	.002
Presence of sleep disorders, %	4.6 (0.35)	10.7 (1.74)	13.5 (1.18)	24.7 (2.82)	< .001	< .001	< .001
Sleep duration h, mean	7.0 (0.03)	6.7 (0.17)	6.7 (0.07)	6.6 (0.12)	.003	< .001	.184

Data are presented as weighted percentage (%) and standard error for categorical variables and weighted means and standard error for continuous variables. *Based on Rao-Scott chi-square test for categorical variable and linear contrast *t* tests from weighted ANOVA for continuous variables. ACO = asthma-COPD overlap, ANOVA = analysis of variance, BMI = body mass index, COPD = chronic obstructive pulmonary disease, CVD = cardiovascular disease, NHANES = National Health and Nutrition Examination Survey, SE = standard error.

DISCUSSION

We examined the prevalence of sleep problems and their associations with CVD and mortality in a nationally representative sample of adults with ACO compared to those with asthma, COPD, and controls (those without either asthma or COPD). We hypothesized that the associations would be greater in persons with ACO. The main findings of this study are as follows: (1) the prevalence of sleep disorders in ACO was approximately 2 times higher than rates in persons with asthma or COPD and over 5 times higher than controls; (2) a higher proportion of short sleepers was found in ACO compared to COPD and controls and a higher proportion of long sleepers compared to COPD; (3) the presence of sleep disorders imposes increased risk for CVD and death; however, its influence does not depend on disease group; and (4) in partial support of our hypothesis, a stronger association existed between sleep duration and increased risk for CVD and all-cause mortality in ACO compared to COPD and controls. These results suggest that persons with ACO may represent a high-risk group that should be targeted for more aggressive intervention of sleep problems, a modifiable risk factor.

Figure 1—Percentage of sample with short, normal, or long sleep duration by chronic lung disease category.



Percentage of the sample with short, normal, or long sleep duration by disease group (COPD, asthma, ACO, and controls [those without COPD and asthma]). *Statistical significance, $P < .05$. ACO = asthma-COPD overlap, COPD = chronic obstructive lung disease.

We found the prevalence of a physician-diagnosed sleep disorder was highest in the ACO group, while the proportion of both short and long sleepers was higher than the COPD group. Data from a national survey of U.S. adults identified self-reported short sleep duration (< 7 hours per night) in approximately 80% of persons with ACO,[28] an estimate much higher compared to the 27.5% found in the current study, which used a cutoff of ≤ 5 hours to define short sleep duration. Unlike the current study, no difference in prevalence of short sleep duration was found between the asthma and ACO groups, potentially due to small group sizes resulting in the lack of statistical power to detect group differences. Yang et al[31] found similar rates of self-reported short sleep duration (< 5 hours) in asthma (23%) vs individuals without asthma (12.7%). We found adults with ACO were also more likely to report having a physician-diagnosed sleep disorder (24.7%) compared to the asthma (10.7%), COPD (13.5%), and control (4.6%) groups. These results are comparable to another population-based study comparing incidence of obstructive sleep apnea in ACO vs COPD only.[32] However, Lal et al[28] found a lower prevalence of physician-diagnosed sleep disorder (15.7%) among 70 adults with ACO. The pathogenesis of sleep problems in ACO is multifactorial and likely consequent to 1 or more of the following: anxiety, medication use (ie, corticosteroid use, bronchodilators), inflammation, nicotine use, sleep hygiene, and comorbid disorders (eg, gastroesophageal reflux and primary sleep disorders).[33,34] Likewise, sleep disorders and subsequent sleep loss have been shown to increase inflammation and decrease lung function, which may lead to asthma and COPD exacerbations and frequent awakenings.[35,36] These results suggest that adults with ACO may benefit from regular evaluation of sleep problems.

The findings of an overall main effect for sleep disorder that leads to a greater risk for CVD and all-cause mortality among all disease groups were in line with related studies, but our results expand on previous research by including a previously unexamined population of patients with ACO. Previous studies have shown an association between presence of comorbid sleep disorder and cardiovascular morbidity and all-cause mortality among persons with COPD.[37–39] Kendzerska et al[38] assessed the combined presence of COPD and suspected obstructive sleep apnea on cardiovascular events and mortality and reported increased hazard (HR = 1.91) of outcomes among those with co-occurring COPD and nocturnal hypoxemia. Although NHANES data do not allow for type of sleep disorder to be determined, we did find a similar high HR for presence of sleep disorders on all-cause mortality (HR = 1.44) that did not differ between COPD, asthma, ACO, and controls. Prior investigations have also demonstrated higher risk for mortality among those with asthma or COPD and comorbid sleep disorders compared to those without sleep disorders.[37,40] Although not specific to asthma or COPD, 2 meta-analyses reported an association between insomnia and increased risk of developing CVD and cardiovascular mortality among adults.[23,41] The proposed mechanisms linking CVD and mortality to sleep disorders (eg, obstructive sleep apnea and insomnia) likely have some overlap with asthma and COPD and include elevated levels of inflammatory cytokines, systemic inflammation, oxidative stress, and exaggerated sympathetic excitation.[35] The resultant adverse cardiac changes seem to be driven by the burden of hypoxemia, especially during sleep.[38,42] More research is needed to determine mechanisms linking sleep disorders and clinical outcomes in ACO.

Sleep duration has not been examined in adults with ACO. We found that after controlling for confounders, short sleep duration was associated with increased risk for CVD. Additionally, significant interactions existed that indicated a U-shape relationship with all-cause mortality. When compared to the

Table 2—Weighted results of the adjusted binary logistic regression assessing the association between sleep duration and presence of cardiovascular disease among all participants (n = 7,616).

	Model I: Main Effects			Model II: Control for Covariates			Model III: Interaction Effect		
		95% CI			95% CI			95% CI	
Predictor	Odds Ratio	Lower Bound	Upper Bound	Odds Ratio	Lower Bound	Upper Bound	Odds Ratio	Lower Bound	Upper Bound
Disease group (ref. ACO)									
Controls	0.07[a]	0.05	0.090	0.64	0.38	1.07	0.49	0.20	1.22
Asthma	0.11[a]	0.08	0.17	1.01	0.57	1.78	0.74	0.31	1.79
COPD	0.72	0.51	1.02	0.76	0.49	1.17	0.48[a]	0.24	0.96
Sleep duration (ref. normal)									
Short sleep duration	1.70[a]	1.34	2.15	1.70[a]	1.26	2.30	1.60	0.65	3.89
Long sleep duration	0.98	0.73	1.33	1.12	0.85	1.47	600790[a]	201249	1793537
Age	—	—	—	1.08[a]	1.07	1.10	1.08[a]	1.07	1.10
BMI	—	—	—	1.09[a]	1.08	1.11	1.09[a]	1.07	1.11
Female sex (ref. male)	—	—	—	0.85	0.69	1.03	0.93	0.73	1.19
Other race (ref. non-Hispanic White)	—	—	—	1.13	0.85	1.50	1.01	0.81	1.25
Smoking status (ref. nonsmoker)									
Former smoker	—	—	—	1.57[a]	1.16	2.12	1.24	0.82	1.86
Current smoker	—	—	—	1.19	0.91	1.56	1.85[a]	1.23	2.79
Poverty level (ref. < 200%)	—	—	—	0.70[a]	0.54	0.91	1.04	0.76	1.41
Interaction effect									
COPD × long sleep duration	—	—	—	—	—	—	< 0.01[a]	< 0.01	< 0.01
Asthma × long sleep duration	—	—	—	—	—	—	< 0.01[a]	< 0.01	< 0.01
Controls × long sleep duration	—	—	—	—	—	—	< 0.01[a]	< 0.01	< 0.01
COPD × short sleep duration	—	—	—	—	—	—	0.67	0.29	1.55
Asthma × short sleep duration	—	—	—	—	—	—	0.76	0.28	2.06
Controls × short sleep duration	—	—	—	—	—	—	0.83	0.31	2.20

[a]Indicates a significant association, all *P* values < .05. ACO = asthma-COPD overlap, BMI = body mass index, CI = confidence interval, COPD = chronic obstructive pulmonary disease.

Table 3—Weighted results of the adjusted binary logistic regression assessing the association between presence of sleep disorders and presence of cardiovascular disease among all participants (n = 7,616).

	Model I: Main Effects			Model II: Control for Covariates			Model III: Interaction Effect		
		95% CI			95% CI			95% CI	
Predictor	Odds Ratio	Lower Bound	Upper Bound	Odds Ratio	Lower Bound	Upper Bound	Odds Ratio	Lower Bound	Upper Bound
Disease group (ref. ACO)[b]									
Controls	0.07[a]	0.06	0.10	0.65	0.41	1.04	0.51	0.19	1.32
Asthma	0.13[a]	0.08	0.19	1.02	0.60	1.74	0.72	0.25	2.10
COPD	0.79	0.57	1.09	0.80	0.53	1.21	0.44[a]	0.22	0.91
Presence of sleep disorders (ref. no sleep disorders)[a]	2.98[a]	2.05	4.33	2.48[a]	1.65	3.73	2.90	0.70	12.05
Age[a]	—	—	—	1.08[a]	1.07	1.10	1.08[a]	1.07	1.10
BMI[a]	—	—	—	1.09[a]	1.08	1.11	1.08[a]	1.06	1.10
Female sex (ref. male)	—	—	—	0.85	0.69	1.04	0.94	0.74	1.19

(continued on following page)

Table 3—Weighted results of the adjusted binary logistic regression assessing the association between presence of sleep disorders and presence of cardiovascular disease among all participants (n = 7,616). (*Continued*)

	Model I: Main Effects			Model II: Control for Covariates			Model III: Interaction Effect		
		95% CI			95% CI			95% CI	
Predictor	Odds Ratio	Lower Bound	Upper Bound	Odds Ratio	Lower Bound	Upper Bound	Odds Ratio	Lower Bound	Upper Bound
Other race (ref. non-Hispanic White)	—	—	—	1.17	0.89	1.56	1.04	0.83	1.30
Smoking status (ref. nonsmoker)									
Former smoker[a]	—	—	—	1.59[a]	1.18	2.17	1.23	0.83	1.82
Current smoker	—	—	—	1.22	0.92	1.62	1.85[a]	1.27	2.70
Poverty level (ref. < 200%)[a]	—	—	—	0.69[a]	0.54	0.90	0.99	0.72	1.36
Interaction effect									
COPD × sleep disorder	—	—	—	—	—	—	0.87	0.18	4.21
Asthma × sleep disorder	—	—	—	—	—	—	0.63	0.11	3.48
Controls × sleep disorder	—	—	—	—	—	—	0.82	0.18	3.74

[a]Indicates a significant association, all *P* values < .05. ACO = asthma-COPD overlap, BMI = body mass index, CI = confidence interval, COPD = chronic obstructive pulmonary disease.

Table 4—Univariate and multivariate Cox regression analyses to determine association between sleep duration and all-cause mortality in sample participants (n = 7,616).

	Model I: Main Effects			Model II: Control for Covariates			Model III: Interaction Effect		
		95% CI			95% CI			95% CI	
Predictor	Hazard Ratio	Lower Bound	Upper Bound	Hazard Ratio	Lower Bound	Upper Bound	Hazard Ratio	Lower Bound	Upper Bound
Disease group (ref. ACO)									
Controls	0.07[a]	0.05	0.10	0.60	0.33	1.11	1.02	0.57	1.80
Asthma	0.19[a]	0.10	0.38	1.63	0.64	4.17	0.27	0.03	2.18
COPD	0.74	0.51	1.09	0.65[a]	0.45	0.95	1.01	0.67	1.54
Sleep duration (ref. normal)									
Short sleep duration	1.30	0.92	1.83	1.32	0.91	1.92	2.59[a]	1.49	4.52
Long sleep duration	1.82[a]	1.07	3.10	1.41	0.86	2.31	4.16[a]	2.11	8.23
Age[a]	—	—	—	1.08[a]	1.06	1.10	1.08[a]	1.06	1.10
BMI	—	—	—	1.01	0.99	1.03	1.01	0.99	1.03
Female sex (ref. male)	—	—	—	0.54[a]	0.40	0.74	0.55[a]	0.40	0.74
Other race (ref. non-Hispanic White)	—	—	—	1.31	0.99	1.73	1.31	0.99	1.72
Smoking status (ref. nonsmoker)									
Former smoker	—	—	—	1.70[a]	1.14	2.54	1.74[a]	1.17	2.59
Current smoker	—	—	—	2.39[a]	1.54	3.71	2.45[a]	1.57	3.82
Poverty level (ref. < 200%)	—	—	—	0.51[a]	0.37	0.71	0.52	0.37	0.73
Interaction effect									
COPD × long sleep duration	—	—	—	—	—	—	0.24[a]	0.12	0.51
COPD × short sleep duration	—	—	—	—	—	—	0.38[a]	0.19	0.77
Asthma × long sleep duration	—	—	—	—	—	—	5.60	0.45	80.05
Asthma × short sleep duration	—	—	—	—	—	—	10.35	0.62	172.96
Controls × long sleep duration	—	—	—	—	—	—	0.07[a]	0.02	0.35
Controls × short sleep duration	—	—	—	—	—	—	0.19[a]	0.07	0.47

[a]Indicates a significant association, all *P* values < .05. ACO = asthma-COPD overlap, BMI = body mass index, CI = confidence interval, COPD = chronic obstructive pulmonary disease.

Table 5—Univariate and multivariate Cox regression analyses to determine association between presence of sleep disorder and all-cause mortality in sample participants (n = 7,616).

	Model I: Main Effects			Model II: Control for Covariates			Model III: Interaction Effect		
		95% CI			95% CI			95% CI	
Predictor	Hazard Ratio	Lower Bound	Upper Bound	Hazard Ratio	Lower Bound	Upper Bound	Hazard Ratio	Lower Bound	Upper Bound
Disease group (ref. ACO)									
Controls	0.07[a]	0.05	0.10	0.62	0.35	1.09	0.68	0.36	1.28
Asthma	0.21[a]	0.10	0.41	1.68	0.67	4.23	2.96	0.62	14.20
COPD	0.77	0.52	1.14	0.68[a]	0.46	0.99	0.76	0.34	1.69
Presence of sleep disorder	1.55[a]	1.09	2.21	1.44[a]	1.03	2.02	1.67	0.93	3.01
Age[a]	—	—	—	1.08[a]	1.07	1.10	1.08[a]	1.06	1.10
BMI	—	—	—	1.01	0.99	1.03	1.01	0.99	1.03
Female sex (ref. male)	—	—	—	0.54[a]	0.40	0.74	0.54[a]	0.39	0.75
Other race (ref. non-Hispanic White)	—	—	—	1.32	1.00	1.74	1.29	0.97	1.72
Smoking status (ref. nonsmoker)									
Former smoker	—	—	—	1.70[a]	1.14	2.54	1.68[a]	1.11	2.55
Current smoker	—	—	—	2.41[a]	1.56	3.72	2.37[a]	1.49	3.77
Poverty level (ref. < 200%)	—	—	—	0.50[a]	0.36	0.69	0.50[a]	0.36	0.70
Interaction effect									
COPD × sleep disorder	—	—	—	—	—	—	0.76	0.34	1.69
Asthma × sleep disorder	—	—	—	—	—	—	2.96	0.62	14.20
Controls × sleep disorder	—	—	—	—	—	—	0.35	0.04	2.84

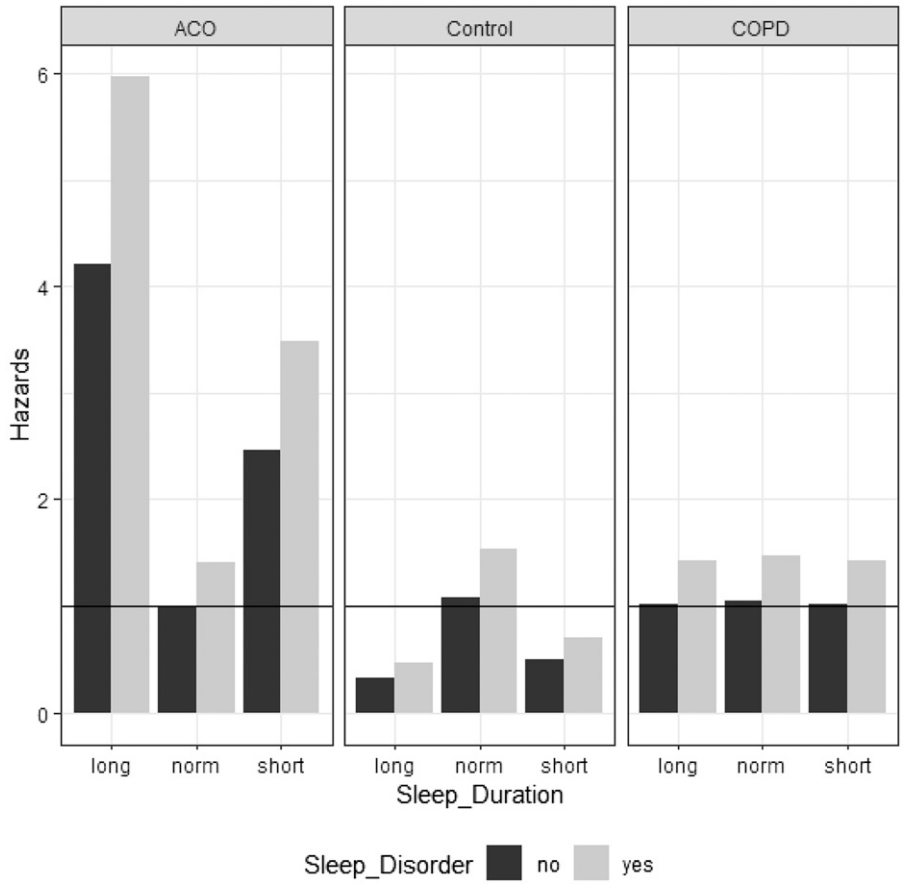
[a]Indicates a significant association, all *P* values < .05. ACO = asthma-COPD overlap, BMI = body mass index, CI = confidence interval, COPD = chronic obstructive pulmonary disease.

ACO group with normal sleep, both long and short sleepers in COPD and controls had lower hazards of death, while long sleepers in all other groups also had lower risk for CVD. Moreover, individuals in the ACO group having long or short sleep duration appeared to have increased hazards compared to COPD and controls. Similarly, 2 recent meta-analyses revealed associations between both short and long sleep duration and mortality and between short sleep duration and CVD in adults; however; unlike the current study, they also found an association with incident CVD and long sleep duration.[26,27] Among persons with asthma only, short sleep duration has been associated with more frequent asthma attacks, poorer health-related quality of life, and increased risk of overnight hospitalizations.[43] Likewise, Yang et al[31] found both short and long sleep durations to be associated with reduced lung function (FEV1, FVC, and FEV1/FVC) in persons with asthma. Impaired pulmonary function is a predictor of overall mortality in those with or without chronic lung disease.[44,45] It is important to note that asthma and COPD were self-identified in NHANES and that disease control was not assessed; thus, severity of disease and level of disease control could not be controlled for in the analyses and may have influenced the association between sleep duration and mortality. Further research on the effect of sleep duration on mortality in ACO is warranted.

Strengths of this study are its large representative sample of U.S. adults with chronic lung disease and the use of weighted percentages to represent population-level parameters that permit unbiased estimates and minimize sampling error. Some of the limitations of this study are intrinsic to the use of secondary data that were not specifically collected for our research questions. The operational definitions used to identify the disease groups, which have been used in prior NHANES studies, are likely to overestimate or underestimate the prevalence of these disorders; however, there exists a lack of clarity in clinically differentiating between asthma, COPD, and ACO. Type of sleep disorder was unable to be determined. No objective measure of sleep was included in the selected cohorts of NHANES, and important details, such as whether participants with sleep disorders were currently treated, are not included. Sleep duration may be underestimated because the survey did not query average sleep duration on nonworkdays or weekends. Errors in recall on the health surveys may have affected participants' responses. Additionally, the small number of participants in some of the subgroups such as the long sleepers prove problematic for inference, limiting the generalizability of the results.

We have demonstrated that there is a trend for increased burden of sleep problems in ACO compared to COPD, asthma, and controls that can impose important clinical implications.

Figure 2—Risk of all-cause mortality within disease groups relative to sleep duration and presence of sleep disorders.



Risk of all-cause mortality (ie, hazards) within each the ACO, COPD, and control groups relative to sleep duration and presence of sleep disorders. The asthma group is excluded as it did not exhibit a significant interaction with sleep duration. Each stacked bar chart corresponds to the long, normal, and short sleep duration groups with fill representing hazards relative to presence (yes) or absence (no) of sleep disorders. The horizontal reference line represents the base hazards given as relative to individuals in the ACO group with normal sleep duration and no sleep disorder. ACO = asthma-COPD overlap, COPD = chronic obstructive lung disease.

After controlling for covariates, we found that the presence of sleep disorders was associated with increased risk for CVD and all-cause mortality; however, its influence does not depend on disease group. Short sleep duration was associated with increased risk for CVD and death while long sleep duration was associated only with increased risk of death. A stronger association existed between sleep duration and increased risk for CVD and all-cause mortality in ACO compared to COPD and controls. The current findings suggest that persons with ACO may represent a high-risk group that should be targeted for assessment and treatment of sleep problems, a modifiable risk factor. Future research is needed to explore the prognostic impact of normalizing sleep duration to 7–8 hours per night, possibly through screening and subsequent treatment of a sleep disorder, on risk for CVD and mortality in persons with ACO.

ABBREVIATIONS

ACO, asthma-COPD overlap
CVD, cardiovascular disease
CI, confidence interval
COPD, chronic obstructive pulmonary disease
FEV, forced expiratory volume
FVC, forced vital capacity
HR, hazard ratio
NHANES, National Health and Nutrition Examination Survey

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All authors have seen and approved this manuscript. Work for this study was performed at the University of Pittsburgh and at the Veterans Affairs Pittsburgh Healthcare System. The views expressed in this article are those of the authors and do not necessarily reflect the views of the U.S. Department of Veterans Affairs or the U.S. government. The authors report no conflicts of interest.