Undiagnosed Obstructive Lung Disease in the United States

Associated Factors and Long-term Mortality

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Abstract

Rationale: Understanding factors associated with undiagnosed obstructive lung disease and its impact on mortality could inform the ongoing discussions about benefits and risks of screening and case finding.

Objectives: To define factors associated with undiagnosed obstructive lung disease and its long-term mortality.

Methods: Cross-sectional analysis of participants, aged 20 to 79 years, in two National Health and Nutritional Examination Surveys (NHANES), NHANES III (1988–1994) and NHANES 2007–2012, with longitudinal follow-up of NHANES III participants.

Measurements and Main Results: We classified participants with spirometry-confirmed obstructive disease, based on the fixed ratio definition ($FEV_1/FVC < 0.7$), as "diagnosed" (physician diagnosis of either asthma or chronic obstructive pulmonary disease), and "undiagnosed" (no recorded physician diagnosis). For the longitudinal analysis of NHANES III participants, mortality was the outcome of interest. We tested the contribution of self-reported health status and comorbidity burden (exposure) to the odds of being undiagnosed using logistic models adjusted for demographics, smoking status, and lung function. We estimated hazard ratios (HRs) for all-cause mortality for diagnosed and undiagnosed subjects participating in NHANES III who had spirometry using Cox- proportional regression analysis. Among those with spirometry-defined obstruction, 71.2% (SE, 1.8) in NHANES III and 72.0% (SE, 1.9) in NHANES 2007–2012 were undiagnosed. In multivariate models, undiagnosed obstructive disease was consistently associated in both surveys with self-reported good/excellent health status, lower comorbidity burden, higher lung function, and being of racial/ethnic minority. Among NHANES III participants (median follow up, 14.5 yr), both undiagnosed (HR, 1.23; 95% confidence interval, 1.08–1.40) and correctly diagnosed participants (HR, 1.74; 95% confidence interval, 1.45–2.09) had higher risk for all-cause mortality than participants without obstruction.

Conclusions: Undiagnosed obstructive lung disease is common among American adults and remained unchanged over 2 decades. Although undiagnosed subjects appear healthier than those with a diagnosis, their risk of death was increased compared with subjects without obstruction. These findings need to be considered when judging the implications of case-finding programs for obstructive lung disease.

Keywords: obstructive lung disease; health status; comorbidities; chronic obstructive pulmonary disease; asthma

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The prevalence of obstructive lung disease in the United States is close to 15% and has remained stable over the last 20 years (1). Despite this high prevalence, analysis of the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) showed that more than 60% of adults with obstructive disease and low lung function ($FEV_1 < 50\%$ predicted) do not report a diagnosis of obstructive disease (i.e., asthma or chronic obstructive pulmonary disease [COPD]) (1, 2). Conversely, in the same period the societal impact of obstructive lung diseases continue growing; COPD is currently the third cause of mortality in adults in America (3), and asthma prevalence has increased from 3.0% in the 1970s to 7.0% in 2007 (4).

Understanding factors that contribute to undiagnosed obstructive lung disease is critical, because undiagnosed obstruction is also associated with negative economic and health effects. Specifically, undiagnosed COPD (5, 6) and asthma (7), the two major obstructive lung diseases, have been associated with increased health care cost and accruing more cardiovascular risk factors (7). Although the reasons for obstructive disease to be undiagnosed are likely multifactorial, it is conceivable that people who seem to have good health status and less comorbidity might be overlooked even when they have been exposed to risk factors (e.g., smoking) for COPD or asthma. Furthermore, the impact of the lack of diagnosis on mortality is unknown.

In this study, we tested the hypothesis that good self-reported health status and lower comorbidity burden are associated with undiagnosed obstructive lung disease and examined whether the associations have changed in the last 20 years. We also sought to assess the impact of undiagnosed disease on long-term mortality. We used data from NHANES III (1989–1994) and NHANES 2007–2012 because these survey cycles included spirometry data plus questions about physician-diagnosed asthma and COPD. NHANES III and its Linked Mortality File afforded us the opportunity to test long-term mortality of undiagnosed obstructive disease. Some of the results of this study have been previously reported in the form of an abstract (8).

Methods

Study Design and Data Source

NHANES 2007–2012 (response rate for interview, 78%; response rate for examination, 75% in 2007–2008 survey cycle, 79 and 77% in 2009–2010, and 73% and 70% in 2011–2012) and NHANES III (response rates, 86 and 78%) were selected due to availability of spirometry as part of the participant's examination. NHANES methodology has been extensively described elsewhere (9, 10); briefly, participants are invited for an interview after being selected using a multistratified, multistage sampling design, resulting in a representative sample of the noninstitutionalized U.S. population. Participants are interviewed at home and invited to have an examination component in a mobile examination center. NHANES III included a passive follow-up for death through December 31, 2006 in the Linked Mortality File (11). NHANES data are deidentified and publically available, making the current investigation exempt from human subject review.

Population

Participants 20 to 79 years old were selected based on having all the following criteria: (*1*) participation in the mobile examination assessment with a valid spirometry performed; (*2*) complete data on self-reported physician-diagnosed asthma, emphysema, or chronic bronchitis; and (*3*) complete data on covariates detailed below. We conducted our main analyses using only participants who met obstructive

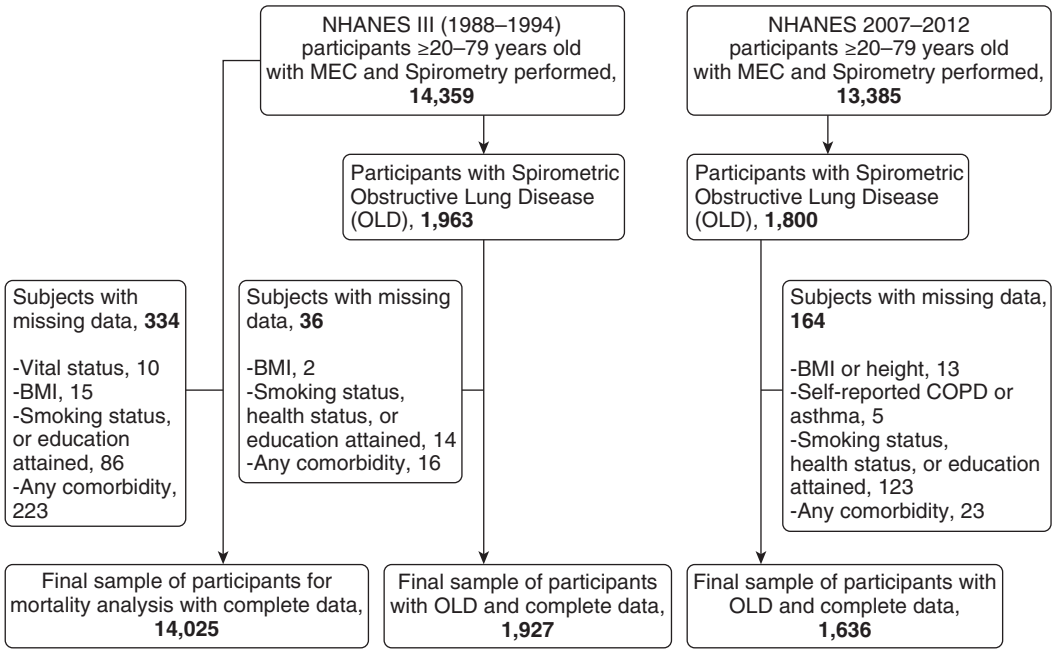

Figure 1. Flow of participants in National Health and Nutritional Examination Survey (NHANES) IIII (1988–1994) and NHANES 2007–2012. BMI = body mass index; COPD = chronic obstructive pulmonary disease; MEC = Mobile Examination Center.

lung disease criteria in both NHANES III and NHANES 2007–2012. The analysis for mortality used all NHANES IIII participants meeting the inclusion criteria, regardless of the diagnosis of obstructive disease, and with vital status ascertained.

Spirometry and Obstructive Disease Definition

NHANES offered spirometry to all adults (NHANES III) and to all participants in the 6 to 79 years age range (NHANES 2007–2012). Spirometry was obtained using an Ohio 822/827 dry-rolling seal volume spirometer following similar protocols across surveys (except for the number of maneuvers: up to eight in NHANES III versus three acceptable maneuvers in NHANES 2007–2012). NHANES reported prebronchodilator values of FEV_1 and FVC in milliliters. FEV_1% predicted values were computed using predictive equations. In NHANES 2007–2012 surveys more exclusions to spirometry testing were added, particularly exclusion of those requiring supplement oxygen. Obstruction was defined, as per modified Global Initiative for Obstructive Lung Disease criteria, as FEV_1/FVC less than 0.7 (12).

Outcomes

Main outcomes were undiagnosed obstructive disease and all-cause mortality. Undiagnosed obstruction was defined as a combination of an obstructive spirometry pattern with no self-reported prior physician diagnosis of COPD and asthma. Self-reported physician diagnosis of COPD and asthma was based on a positive answer to the following questions: "Have you ever been told by a doctor or other health care professional that you had chronic bronchitis or emphysema?" and "Have you ever been told by a doctor or other health care professional that you had asthma?" We determined participant death using the NHANES III Linked Mortality File, which matches participants with records from the National Death Index (NDI).

Covariates

The presence and number of comorbidities was based on a combination of questionnaire and examination data (13), selecting conditions for which surveys of NHANES III and NHANES 2007–2012 used the same wording. Positive response to the question "Have you ever been told by a doctor or other health care professional that you had…[condition name]?" was considered as self-reported comorbid condition, including arthritis, cancer, chronic heart failure, heart coronary disease, and stroke. Diabetes was considered present if the participant responded "yes" to the self-report question and was receiving treatment. Hypertension was considered present based on either a systolic blood pressure greater than or equal to140 mm Hg, diastolic blood pressure greater than or equal to 90 mm Hg, or a positive response to the question: "Are you currently taking medication to lower your blood pressure?" We used the collected comorbidities in two additional ways: as a count of comorbidities (recoded

Table 1. Comparison of subjects diagnosed and undiagnosed with obstructive lung disease in two different NHANES surveys

	NHANES III (1988–1994)			NHANES 2007–2012		
	Diagnosed (*n = 517*)	Undiagnosed (*n = 1,410*)	*P* Value*	Diagnosed (*n = 463*)	Undiagnosed (*n = 1,173*)	*P* Value*
Demographics						
Male sex	53.6 (2.3)	59.5 (1.9)	0.0614	53.4 (3.4)	63.6 (2.2)	0.01
Age, mean (SE), yr	55.6 (1.0)	56.5 (0.8)	0.37	54.5 (0.8)	57.1 (0.6)	0.006
Race and ethnicity						
Non-Hispanic white	85.4 (2.0)	84.7 (1.2)	0.61	84.8 (2.2)	82.7 (1.9)	0.32
African American	7.8 (0.9)	7.3 (0.7)	0.54	7.7 (1.2)	7.7 (1.2)	0.98
Mexican American	1.4 (0.3)	2.3 (0.3)	0.007	1.6 (0.5)	2.8 (0.5)	0.09
Other	5.4 (1.6)	5.7 (1.0)	0.85	6.0 (1.4)	6.8 (1.3)	0.54
High school graduate or beyond	31.9 (3.8)	35.3 (2.1)	0.38	80.0 (2.5)	81.7 (1.8)	0.54
No access to health care	16.3 (2.4)	18.5 (1.7)	0.46	8.5 (1.6)	10.8 (1.3)	0.26
BMI, kg/m^2, mean (SE)	26.1 (0.3)	26.6 (0.2)	0.30	28.9 (0.4)	27.9 (0.2)	0.001
Respiratory symptoms						
Dyspnea	64.3 (2.5)	27.6 (1.7)	<0.0001	60.1 (3.4)	31.7 (2.2)	<0.0001
Cough	33.3 (2.2)	13.1 (1.6)	<0.0001	21.9 (2.2)	13.0 (1.5)	0.0008
Wheezing	65.4 (3.3)	17.0 (1.5)	<0.0001	51.2 (4.1)	12.2 (1.3)	<0.0001
Phlegm	26.3 (2.1)	12.3 (1.3)	<0.0001	21.5 (2.5)	11.4 (1.4)	0.0004
Any symptom	84.8 (2.0)	43.5 (2.0)	<0.0001	75.5 (3.0)	39.3 (2.3)	<0.0001
Smoking status						
Never	27.7 (3.1)	23.0 (1.6)	0.20	25.6 (2.7)	29.9 (2.0)	0.18
Former	35.3 (2.6)	37.8 (1.9)	0.46	35.2 (3.1)	35.8 (2.1)	0.88
Current	37.0 (2.9)	39.3 (2.0)	0.52	39.2 (3.4)	34.0 (1.9)	0.21
Lung function						
FEV_1, mean (SE)	2,104.6 (49.7)	2,558.8 (34.5)	<0.0001	2,325.8 (54.1)	2,700.9 (33.3)	<0.0001
FEV_1% predicted, mean (SE)	67.8 (1.2)	81.0 (0.6)	<0.0001	71.9 (1.1)	83.5 (0.6)	<0.0001

Definition of abbreviations: BMI = body mass index; NHANES = National Health and Nutritional Examination Survey.
Data presented as percentage (SE) unless otherwise specified.
**P* value represents comparison between correct diagnosis and underdiagnosed obstructive lung disease groups' characteristics in each survey.

Table 2. Multivariate models show, in both surveys, self-reported good-to-excellent health status, lower comorbidity burden, and preserved lung function associated with an increased odds of undiagnosed obstructive disease

Factor	NHANES III	NHANES 2007–2012
Comorbidity burden		
0	Ref.	Ref.
1–2	0.81 (0.50–1.30)	0.81 (0.50–1.11)
3 or more	0.47 (0.25–0.91)	0.60 (0.37–0.95)
Health status		
Fair/poor	Ref.	Ref.
Excellent/very good/good	1.89 (1.35–2.65)	1.77 (1.0–3.12)
Demographics		
Male sex	Ref.	Ref.
Female sex	2.02 (1.37–2.99)	1.37 (0.93–2.26)
Age, by year increment	1.05 (1.03–1.07)	1.06 (1.04–1.08)
Race and ethnicity		
Non-Hispanic white	Ref.	Ref.
African American	1.66 (1.25–2.22)	1.82 (1.20–2.74)
Mexican American	2.64 (1.63–4.27)	2.17 (1.01–4.67)
Other	2.04 (1.00–4.17)	1.00 (1.00–1.01)
BMI		
Normal or overweight	Ref.	Ref.
Obese ($\geq$30 kg/m^2)	1.22 (0.86–1.72)	0.81 (0.59–1.11)
Education		
Below high school	Ref.	Ref.
High school and beyond	0.88 (0.61–1.28)	0.94 (0.61–1.44)
Access to health care		
Regular access	Ref.	Ref.
Lack of regular access	1.23 (0.80–1.89)	1.24 (0.68–2.27)
Smoking status		
Never	Ref.	Ref.
Former	1.33 (0.82–2.16)	1.24 (0.81–1.91)
Current	1.80 (1.08–3.03)	0.78 (0.50–1.21)
Lung function		
FEV_1, per 100-ml increase	1.12 (1.08–1.15)	1.10 (1.06–1.14)
Comorbidity group*		
Cardiovascular	0.53 (0.34–0.82)	0.83 (0.58–1.18)
Mobility related	0.69 (0.52–0.91)	0.49 (0.34–0.66)

Definition of abbreviations: BMI = body mass index; NHANES = National Health and Nutritional Examination Survey.
All entries are odds ratio (95% confidence interval).
*Cardiovascular comorbidity includes chronic heart failure and heart attack. Mobility-related comorbidity includes arthritis and stroke.

as zero, one to two, or three or more, out of the seven possible comorbid conditions included) and also as comorbidities by system/impact (responses to questions about chronic heart failure and heart coronary disease combined as "cardiovascular disease"; and arthritis and stroke grouped as "mobility-related conditions"). Obesity was defined as body mass index (BMI) greater than or equal to 30 and included as a separate comorbidity.

Baseline self-rated health status was based on the previously validated CDC health-related quality of life instrument (using response to the question "Would you say your health in general is…", with response options ranging from excellent to poor, which were coded dichotomously as excellent/very good/good vs. fair/poor health).

We included the following demographic and socioeconomic covariates: age (as a continuous variable), sex, education level (high school graduated and beyond vs. less than complete high school education as the reference; thereafter, high education level), BMI ($\geq$30 [obesity] vs. $<$30), lifetime smoking status (smoking status was classified as never-smoking and ever-smoking based on whether or not the participant smoked at least 100 cigarettes in his/her lifetime). Ever-smokers were further considered as current smokers or former smokers based on smoking status at the time of the interview. Regular access to health care was based on the answer to the question "Is there a place that you usually go when you are sick or you need advice about your health?"

Statistical Analysis

Descriptive statistics with proportions or means were used when appropriate. The age-standardized prevalence of obstructive disease was computed using the 2000 U.S. population as a reference. Differences in the prevalence of obstructive disease diagnosis, comorbidities, and other proportions between NHANES III and NHANES 2007–2012 were compared using linear or logistic regression analyses as appropriate using cycle survey as predictor (14). The association of comorbidities and health status with diagnosis of obstructive lung disease was assessed using multivariate logistic analysis. Models included age, sex, race/ethnicity, education level, smoking status, access to health care, and FEV_1 (in liters) as covariates. Differences in all-cause mortality between NHANES III participants without obstruction (reference group) and undiagnosed and diagnosed obstructive lung disease were assessed using Cox proportional hazard models. Time to event for all-cause mortality was censored at date of death certificate or at December 31, 2006 (time of last follow-up).

Survival analysis was also conducted among those with obstructive disease only. Survival models were adjusted for sex, age, race/ethnicity, lifetime smoking status, education level, and BMI, and further sensitivity analyses included adjustment for comorbidities and FEV_1 (in liters). All analyses incorporated appropriate sampling weights to account for the complex study design, sampling, and nonresponse and were performed using callable SUDAAN 10.1 (RTI International, Research Triangle Park, NC) and SAS 9.3 (SAS Institute, Cary, NC) statistical software.

Results

Frequency and Characteristics of Undiagnosed Obstructive Disease

Among participants of NHANES III (n = 14,359) and NHANES 2007–2012 (n = 13,835) aged 20 to 79 years with spirometry and complete data, obstructive lung disease was present by spirometry in 1,927 (13.4%) and

Table 3. Models for all-cause mortality for National Health and Nutritional Examination Survey III participants (N = 14,248)

Factor	Model 1*	Model 2†	Model 3‡
Diagnostic group			
No obstruction	Ref.	Ref.	Ref.
Undiagnosed obstruction	1.23 (1.08–1.40)	1.25 (1.10–1.42)	0.99 (0.87–1.14)
Diagnosed obstruction	1.74 (1.45–2.08)	1.61 (1.32–1.95)	1.03 (0.83–1.27)
Demographics			
Age, by yr increment	1.10 (1.09–1.10)	1.09 (1.08–1.09)	1.07 (1.06–1.08
BMI, by kg/m^2 increment	1.02 (1.01–1.03)	1.01 (0.99–1.02)	1.00 (0.99–1.01)
Sex			
Female	Ref.	Ref.	Ref.
Male	1.40 (1.26–1.55)	1.41 (1.27–1.56)	2.32 (2.03–2.64)
Race and ethnicity			
Non-Hispanic white	Ref.	Ref.	Ref.
African American	1.49 (1.29–1.72)	1.40 (1.22–1.60)	1.17 (1.04–1.32)
Mexican American	1.15 (0.95–1.39)	1.15 (0.95–1.38)	1.06 (0.88–1.26)
Smoking status			
Never	Ref.	Ref.	Ref.
Former	1.29 (1.10–1.52)	1.28 (1.09–1.50)	1.27 (1.08–1.49)
Current	2.32 (1.99–2.70)	2.32 (1.99–2.71)	2.07 (1.77–2.43)
Education			
Below high school	Ref.	Ref.	Ref.
High school and beyond	0.73 (0.64–0.83)	0.75 (0.66–0.86)	0.81 (0.71–0.93)
Comorbidity count			
0	Ref.	Ref.	Ref.
1–2 comorbidities		1.53 (1.28–1.82)	1.46 (1.22–1.75)
⩾3 comorbidities		2.82 (2.30–3.45)	2.56 (2.11–3.11)
Lung function			
FEV_1, per 100-ml increment			0.94 (0.93–0.95)

Definition of abbreviation: BMI = body mass index.
Data presented as hazard ratio (95% confidence interval). The survival model incorporated sampling weights. There is an association between undiagnosed obstructive lung disease and mortality. Data from National Health and Nutritional Examination Survey III, Third National Health and Nutrition Examination Survey (1988–1994) and its Linked Mortality File, National Center for Health Statistics. Analysis based on 2,660 deaths identified; 10 subjects with missing vital status.
*Model 1 adjusted for demographics, education, and smoking status.
†Model 2: Model 1 additionally adjusted for comorbidity count.
‡Model 3: Model 2 additionally adjusted for FEV.

1,636 (11.8%), respectively (Figure 1). Of those with obstructive disease, only 26.8 and 28.3% (age-adjusted proportion) had physician-diagnosed disease in NHANES III and NHANES 2007–2012, respectively. Study populations showed a change in some health determinants between the two periods evaluated. Overall, compared with NHANES III, participants in NHANES 2007–2012 had higher education level, improved access to health care, and smoked less (Table 1).

In both surveys, compared with those with correct diagnosis of obstructive lung disease, undiagnosed subjects were generally older, less frequently reported dyspnea or other respiratory symptoms, and had better lung function, as measured by FEV_1% predicted (Table 1). Among undiagnosed participants, 5 and 3% had severe or very severe airway obstruction (FEV_1% predicted < 50%), compared with 23 and 14% of those with correct diagnosis in NHANES III and NHANES 2007–2012, respectively. In both surveys, compared with those with correct diagnosis, undiagnosed participants also described better health status and reported a lower count of comorbidities, including lower frequency of cardiovascular and mobility-related diseases (*see* Table E1 in the online supplement).

Undiagnosed Obstructive Disease Is Associated with a Healthier Profile

Multivariate models of the impact of demographics, comorbidities, and health status on the risk of being undiagnosed showed that similar factors were associated with undiagnosed obstructive disease in both surveys, spanning a 20-year time frame (Table 2). For example, in both surveys, having self-reported good-to-excellent health status, a lower comorbidity burden, and preserved lung function were all associated with increased odds of being undiagnosed. Similarly, being of a race/ethnic minority (African American or Mexican American) and older age also increased the odds of being undiagnosed. However, female sex and being a current smoker were independently associated with undiagnosed obstructive disease only in NHANES III. No associations were found between undiagnosed disease and obesity, access to health care, or education level in either survey.

Factors Associated with Undiagnosed Obstruction Are Maintained in Subgroup Analyses

We performed *post hoc* subgroup analyses, testing whether the associations between health status or comorbidities and undiagnosed obstructive disease were maintained in those with more severe disease ($FEV_1 \leqslant 80$%) and separately in ever-smokers. Under those scenarios, the associations were generally maintained, with self-reported good health increasing the odds, and higher count of extrapulmonary comorbidities decreasing the odds of being undiagnosed, both in NHANES III and NHANES 2007–2012 (Table E2).

Mortality Differs by Diagnostic Group

Among 14,359 NHANES III participants who had examination and spirometry performed, 14,025 make up the sample for mortality analysis. Details on missing data are shown in Figure 1. Of these 14,025 participants, 2,617 (18.7%) died during a median follow-up of 14.5 years. In models adjusted for demographics, BMI, education, and smoking status, the risk for all-cause mortality in both undiagnosed and diagnosed obstructive lung disease was significantly higher than that of participants without obstruction (hazard ratio for the undiagnosed group, 1.23; 95% confidence interval [CI], 1.08–1.40; hazard ratio for the diagnosed group, 1.74; 95% CI, 1.45–2.08) (Model 1 in Table 3 and Figure 2), and further adjustment for comorbidity count (Model 2 in Table 3) did not change the associations between diagnosis group and mortality (hazard ratio for the undiagnosed group, 1.25; 95% CI, 1.10–1.42; hazard ratio

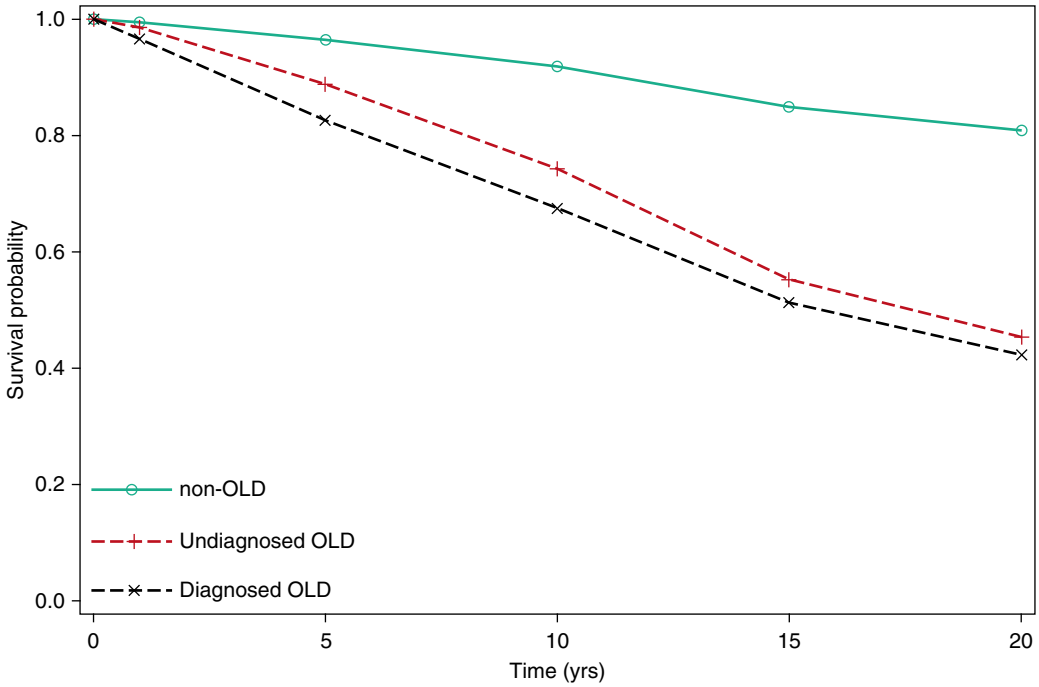

Figure 2. Survival curves for participants in National Health and Nutritional Examination Survey (NHANES) III by obstructive lung disease (OLD) category. Participants undiagnosed (*red*) and diagnosed (*black*) with obstructive disease had a significantly higher mortality risk than those without obstruction (*green*) in unadjusted models.

for the diagnosed group, 1.61; 95% CI, 1.32–1.95). However, when the models where additionally adjusted for lung function (Model 3 in Table 3), the associations were not significant. This result suggests that the increased risk of death in those with either diagnosed or undiagnosed obstructive disease may be influenced by lung function.

To clarify the diagnosis group–by–lung function relations we tested interaction terms between both variables and found that the interaction was significant. In a subsequent step we performed stratified analyses, based on tertiles of lung function, measured by FEV_1 (in liters). We found that the effect of diagnosed and undiagnosed obstructive disease was maintained, but varied by FEV_1 tertiles (Table E3), with diagnosed obstructive disease influencing mortality among those with lower levels of lung function and undiagnosed obstruction having a stronger association with mortality among those with higher levels of lung function (upper FEV_1 tertile).

Discussion

This analysis of two nationally representative health examination surveys demonstrates that more than 70% of Americans aged 20 to 79 years with spirometry-confirmed obstruction were not diagnosed as having asthma or COPD and that this high rate of underdiagnosis has not changed over 2 decades. Although participants with undiagnosed obstructive disease reported good/excellent health, exhibited better lung function and fewer comorbidities, and had a lower risk of all-cause mortality, relative to diagnosed participants, their risk of death was still 23% greater than among those without obstruction. Our findings confirm and extend to the general U.S. population the substantial frequency of undiagnosed obstructive lung diseases seen in studies derived from other national representative samples (e.g., 76% in Sweden [15]), a pooled analysis of international surveys (81.4% [16]), primary care patients (67% in Canada [17]), and the U.S. COPDGene clinic cohort (18). Collectively, these results indicate, despite decreasing U.S. smoking rates, increasing education and awareness about tobacco-related diseases, and established guidelines for asthma diagnosis and treatment, how much more needs to be done to increase awareness of obstructive lung diseases.

Our results provide novel data on the previously unanswered question of whether undiagnosed airflow obstruction impacts survival (19). The relationship we found between increased mortality and low FEV_1 extends similar associations, especially for cardiovascular deaths, previously seen among NHANES participants (20) and in other cohorts (21–23). Hence, undiagnosed obstructive disease represents missed opportunities for prevention, modification of other risk factors (24), and close monitoring of lung function decline (25), particularly among smokers. Additionally, undiagnosed subjects frequently had functional limitations, including need for help with some activities necessary for self-care (26). Our findings point to the desirability of an individualized approach to diagnosis, including further education of physicians and patients about the diagnosis of obstructive diseases and reinforcement about the consequences of tobacco smoking.

These findings are also relevant to the continued controversy about the role of screening or case-finding strategies for obstructive lung diseases. In 2008, the U.S. Preventive Task Force recommended against the use of screening spirometry (27)

for COPD, and a similar opinion is presented in a draft recommendation statement currently posted for online discussion (28). The recommendation against screening is based on evidence that early diagnosis could result in additional harms and minimal benefits. Indeed, without screening or early case-finding programs, some degree of underdiagnosis is expected and may even be appropriate, given the current absence of disease-modifying pharmacologic therapy for COPD (12). Thus, our findings of better overall health profiles among undiagnosed subjects with obstructive lung diseases might be used as support against screening and early case identification. However, we believe that such nihilism is unfounded, for two reasons. First, it is crucial to note that almost 40% of undiagnosed NHANES participants still reported respiratory symptoms, and a high proportion already have low lung function ($FEV_1 < 80\%$), a factor also associated with mortality in our cohort and other studies, indicating that they could be candidates for pharmacological or nonpharmacological treatments (12). In particular, there might be therapeutic value in actively seeking those with low lung function ($FEV_1\%$ predicted $< 50\%$), which was present in almost 10% of those undiagnosed. Second, because the NHANES survey was not limited to users of tobacco products, a portion of these participants may have asthma, for which the benefits of pharmacological therapy are better established.

The reasons for this continued high rate of underdiagnosis remain incompletely defined. Although socioeconomic differences are often related to disparities in the prevalence of chronic diseases (29), in disease perception, and in disease impact (13), neither education level nor health care access was associated in our models with undiagnosed obstructive disease. Interestingly, we did find an association with two other factors associated with health care disparities—increasing age and belonging to a racial/ethnic minority—which merits future investigation. Patient and physician awareness of disease is another potential explanation, and here our data provide some insight. Compared with those with physician-diagnosed asthma or COPD, the undiagnosed group reported fewer respiratory symptoms and comorbidities, had higher FEV_1, and believed their overall health status to be good to excellent, all associations that were maintained in fully adjusted multivariate analysis.

Hence, participants with obstructive disease could remain undiagnosed, even if they are part of a population at high risk for respiratory disease (e.g., ever-smokers), if they reported no other medical conditions affecting their health status. This possibility was supported by our subgroup analyses. Thus, failing to recognize the silent nature of early disease stages, both individuals and their physicians may not suspect obstructive disease among these "healthy-appearing smokers."

Our study has the strength of being based on a large, nationally representative sample of the noninstitutionalized adult population, with robust findings in surveys performed 2 decades apart. Limitations include the absence of detailed information about health care use and other measures of impact of undiagnosed disease among our participants. As is customary in this type of survey, our analyses are based on self-reported diagnosis of comorbid conditions, presenting a risk of misclassification. However, we selected as comorbidities of interest prevalent chronic conditions, for which the predictive value of NHANES surveys is high, as has been replicated and used in other studies (1, 2, 26).

Additionally, NHANES asked participants about clinician diagnosis of asthma, emphysema, or chronic bronchitis but did not include less frequent types of obstructive disease, such as bronchiectasis. We used the fixed-ratio definition of airway obstruction, but acknowledge that there is a potential for overdiagnosis among older adults. To address this, we also tested the frequency of undiagnosed obstruction using the lower limit of normal values adjusted for age (30); we found that using lower limit of normal definitions resulted in age-related differences in the frequency of undiagnosed obstruction only in NHANES III (participants aged 20–39 yr had 71.9 vs. 61.3% for those aged 60–79 yr; $P = 0.018$). No age-related differences in undiagnosed disease were found in NHANES 2007–2012. Finally, as there are differences in exclusion criteria between the two NHANES cycles (NHANES 2007–2012 surveys excluded participants with supplementary oxygen requirement), we may have overestimated the undiagnosed rate for the recent surveys.

Conclusions

At the population level, undiagnosed obstructive lung disease (spirometry confirmed but without clinical diagnosis) remains surprisingly frequent. Those with undiagnosed obstruction were more likely to have less severe disease and fewer comorbidities and to perceive their overall health as better than those with a clinical diagnosis of asthma or COPD. Nevertheless, undiagnosed NHANES participants over 2 decades still had a higher mortality risk than that of the general population. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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