Respiratory Symptoms in Young Adults and Future Lung Disease

The CARDIA Lung Study

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Abstract

Rationale: There are limited data on factors in young adulthood that predict future lung disease.

Objectives: To determine the relationship between respiratory symptoms, loss of lung health, and incident respiratory disease in a population-based study of young adults.

Methods: We examined prospective data from 2,749 participants in the CARDIA (Coronary Artery Risk Development in Young Adults) study who completed respiratory symptom questionnaires at baseline and 2 years later and repeated spirometry measurements over 30 years.

Measurements and Main Results: Cough or phlegm, episodes of bronchitis, wheeze, shortness of breath, and chest illnesses at both baseline and Year 2 were the main predictor variables in models assessing decline in FEV₁ and FVC from Year 5 to Year 30, incident

obstructive and restrictive lung physiology, and visual emphysema on thoracic computed tomography scan. After adjustment for covariates, including body mass index, asthma, and smoking, report of any symptom was associated with -2.71 ml/yr excess decline in FEV₁ ($P < 0.001$) and -2.18 in FVC ($P < 0.001$) as well as greater odds of incident (prebronchodilator) obstructive (odds ratio [OR], 1.63; 95% confidence interval [CI], 1.24–2.14) and restrictive (OR, 1.40; 95% CI, 1.09–1.80) physiology. Cough-related symptoms (OR, 1.56; 95% CI, 1.13–2.16) were associated with greater odds of future emphysema.

Conclusions: Persistent respiratory symptoms in young adults are associated with accelerated decline in lung function, incident obstructive and restrictive physiology, and greater odds of future radiographic emphysema.

Keywords: respiratory function tests; respiratory epidemiology; respiratory symptoms; chronic obstructive pulmonary disease

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At a Glance Commentary

Scientific Knowledge on the

Subject: Respiratory symptoms, in particular those of chronic bronchitis, predict accelerated rate of decline in lung function and risk of future obstructive lung physiology in several cohorts of cigarette smokers. We sought to evaluate whether a broader panel of respiratory symptoms portends a poor prognosis in terms of lung health and risk of both physiologic and radiographic lung disease in a population-based cohort of generally healthy young adults.

What This Study Adds to the

Field: We found that the presence of persistent respiratory symptoms in young adults was associated with accelerated decline in lung function and greater risk of incident obstructive and restrictive lung physiology over 30 years of follow-up. Cough-related symptoms were associated with future obstructive physiology and radiographic emphysema. These findings imply that respiratory symptoms in young adults may serve as an easily queried indicator of susceptibility to loss of lung health and future lung disease.

Lung health in generally healthy adults is often defined by attenuation of age-related decline in lung function after it peaks in young adulthood (1). Beyond the known adverse effects of cigarette smoking (2–4), predictors of accelerated decline in lung function are largely undescribed. Reduced lung function, even when in a range considered to be normal and not meeting the criteria for any specific respiratory disease, is associated with adverse health outcomes, including cardiovascular disease and mortality (5, 6). Whether respiratory symptoms in young adulthood, independent of smoking status, portend future impairment in lung health or development of lung disease and its radiologic manifestations over a life course of observation has not been investigated.

In the National Health and Nutrition Examination Survey 2007 to 2010, 21% of adults reported at least one respiratory symptom. Frequent cough, frequent

phlegm, or wheeze were associated with abnormal lung function as well as poor health-related quality of life among those with normal lung function (7). More recent investigations of current and former smokers documented that among individuals without obstructive lung physiology, those with respiratory symptoms had greater activity limitation, lower absolute lung function (albeit often in the normal range), and more airway wall thickening on chest computed tomography (CT) scan than those without symptoms (8, 9). Several factors associated with risk of future chronic obstructive pulmonary disease (COPD) may also be associated with the presence of respiratory symptoms, including asthma, smoking, poor lung development *in utero* and throughout childhood, viral infections, and environmental exposures to vapors, gases, dusts, and fumes (10). Cough and phlegm in particular have inconsistently been found to be predictors of future incident COPD (11–14).

Using longitudinal data from the CARDIA (Coronary Artery Risk Development in Young Adults) study, a population-based cohort study of young adults aged 18 to 30 years in 1985 to 1986 inclusive of both smokers and nonsmokers, we sought to examine the relationship between baseline respiratory symptoms and change in lung function over the next 30 years, incident obstructive and restrictive lung physiology, and CT scan-measured emphysema. We hypothesized that the presence of respiratory symptoms in young adults is associated with greater decline in lung function and increased risk of incident COPD later in life.

Methods

Study Design and Participants

CARDIA is a prospective cohort study of the evolution of cardiovascular disease risk factors in young adults (15). From 1985 to 1986, 5,115 black and white individuals aged 18 to 30 years were examined in Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. Recruitment achieved nearly equal numbers at each site of race, sex, education (more than high school or high school or less), and age (18–24 yr or 25–30 yr). Fifty percent of invited individuals contacted were examined (47% of black

individuals and 60% of white individuals). Reexamination occurred after 2, 5, 7, 10, 15, 20, 25, and 30 years, with 71% of the surviving cohort returning for the Year 30 examination. Respiratory symptoms were determined using questions adapted from the American Thoracic Society–Division of Lung Diseases 78 questionnaire (16). The questions asked and their groupings into discrete predictor variables are documented in the online supplement (Table E1). We determined a symptom to be persistent, and herein referred to as present, if it was reported at both the baseline and Year 2 examinations.

Outcomes

Lung function was measured at Years 0, 2, 5, 10, 20, and 30. Standard spirometry procedures as recommended by the American Thoracic Society were followed at all examinations (17–20). Change in lung function was calculated as Year 30 minus Year 5 lung function and converted to annualized value by dividing by 25. The Year 5 measurement was the first one selected, to mitigate the effects of increasing lung function between the Year 0 and Year 5 examinations among the younger members of the cohort (*see* Table E2 in the online supplement). Considering the young age of some participants at baseline and the fact that lung function had not yet reached the maximum at Year 5 in all subjects, we also estimated peak lung function as the maximum measured at Year 0, 2, 5, 10, 20, or 30. The details of this analysis and the results of this sensitivity analysis are in the online supplement. Incident obstructive physiology was defined as having a prebronchodilator ratio of FEV₁/FVC less than 70% at Year 30 but not at Year 5, and incident spirometric restriction was defined as FVC less than 80% predicted at Year 30, with FEV₁/FVC greater than 70%, but not at Year 5 (21, 22). The analysis was repeated using post-bronchodilator spirometry, which was only available at Year 30.

Visual assessment of Year 25 CT scans was performed using methods we have previously described for the detection of interstitial lung abnormalities (23–25). Briefly, reader 1 reviewed all the CT scans and categorized them as having centrilobular emphysema and/or paraseptal emphysema, or neither. Reader 2 then reviewed all those CT scans that had emphysema (centrilobular emphysema,

paraseptal emphysema, or both) as well as a random sample of 10% of the remaining CT scans. A third reader then adjudicated cases in which there was a disagreement between readers 1 and 2. An additional objective assessment of the Year 25 CT scan parenchymal features was performed as described previously (26, 27). The details of this method are in the online supplement.

Statistical Analysis

Multivariable linear regression was used to determine the association between respiratory symptoms and annualized decline in prebronchodilator lung function. Covariates included race–sex group, center, height, body mass index (BMI), Year 5 lung function, physician-diagnosed asthma, and baseline smoking status (never, former, current). Multiplicative interactions between asthma and smoking and each symptom were ascertained in the multivariable models.

Generalized estimating equations were used to examine trends in FEV₁, FVC, and FEV₁/FVC as a function of age from the Year 5 to the Year 30 measurement. Covariates were race–sex group, examination year, and baseline height, BMI, smoking status, and physician-diagnosed asthma. Interactions between respiratory symptoms and age were evaluated to assess whether age trends in lung function decline differed between those with or without respiratory symptoms. The model predictions were

then plotted to give a visual representation, using repeated spirometric measures, of how the presence of symptoms is associated with age-related decline in lung function.

Multivariable logistic regression was used to determine the association between symptoms and incident abnormal lung function at Year 30. Covariates were age, race–sex group, center, and baseline BMI, physician-diagnosed asthma, and smoking status (never, former, current). Multivariable logistic regression was used to test the association between symptoms and CT scan–determined emphysema at Year 25. Covariates were the same as those used for incident spirometric abnormalities.

Results

Participant Characteristics

A total of 2,749 participants were included in analyses of baseline symptoms and lung function decline, and 2,954 participants were included in analyses of baseline symptoms and CT scan–measured emphysema. Reasons for exclusion of participants are summarized in Figure 1. Characteristics of participants who were excluded compared with those included are documented in the online supplement (Table E3). Participant characteristics by the presence or absence of each symptom reported at both baseline and Year 2 (that

is, the same symptom reported twice at consecutive examinations) are shown in Table 1. A total of 1,293 participants (43.9%) reported at least one of the symptoms at both the baseline and Year 2 examinations. Current smoking was universally more common among those reporting symptoms than those without. Year 5 and Year 30 lung function were slightly lower among participants with symptoms than those without, but still in the normal range. Frequencies of reporting each symptom at one or both the baseline and Year 2 examinations are shown in the online supplement (Table E4).

Baseline Respiratory Symptoms and Loss of Lung Health

Covariate-adjusted associations between respiratory symptoms and annualized decline in lung function from Year 5 to Year 30 are shown in Table 2. The presence of any respiratory symptom consistently reported at baseline and Year 2 was associated with greater decline in FEV₁ (−2.71 ml/yr), FVC (−2.18 ml/yr), and FEV₁/FVC (−0.05%/yr) compared with the absence of symptoms after adjustment for race–sex group, center, height, Year 5 lung function, baseline BMI, physician-confirmed asthma, and smoking status (never, former, current). For frame of reference regarding these effect sizes, current smoking, the most widely accepted clinical risk factor for future lung health impairment was associated with −3.07 ml/yr ($P < 0.001$) excess decline in FEV₁, −2.25 ml/yr ($P = 0.002$) excess decline in FVC, and −0.04%/yr ($P < 0.001$) excess decline in FEV₁/FVC compared with nonsmokers in these same multivariable models. The combination of cough-related symptoms (cough or phlegm, episodes of bronchitis, or chest illnesses) was associated with greater decline in FEV₁ (−2.57 ml/yr, $P < 0.001$), FVC (−2.12 ml/yr, $P = 0.001$), and FEV₁/FVC (−0.04%/yr, $P < 0.001$) compared with the absence of cough-related symptoms.

When individual symptoms were assessed, cough or phlegm, episodes of bronchitis, wheeze, shortness of breath, and chest illnesses (reported at both baseline and Year 2) were all associated with greater annual decline in FEV₁ and FEV₁/FVC. Only wheeze and chest illness were associated with greater annual decline in FVC (Table 2). A sensitivity analysis was performed evaluating decline from peak

Figure 1. Numbers of participants included in the analyses presented in Tables 2 and 3 based on availability of baseline and Year 2 symptom questionnaires, covariates, pulmonary function measurements, and thoracic computed tomography scans. CT = computed tomography.

Table 1. Baseline Demographic Characteristics by Symptoms Absent or Present

	Cough or Phlegm		Episodes of Bronchitis		Wheeze		Shortness of Breath		Chest Illnesses	
	No (n = 2,398)	Yes (n = 351)	No (n = 2,658)	Yes (n = 91)	No (n = 2,007)	Yes (n = 741)	No (n = 2,502)	Yes (n = 222)	No (n = 2,150)	Yes (n = 599)
Sex, F, n (%)	1,373 (57.3)	199 (56.7)	1,515 (57.0)	57 (62.6)	1,141 (56.9)	430 (58.0)	1,374 (54.9)	181 (81.5)	1,206 (56.1)	366 (61.1)
Race, black, n (%)	1,057 (44.1)	166 (47.3)	1,186 (44.6)	37 (40.7)	934 (46.5)	288 (38.9)	1,081 (43.2)	129 (58.1)	937 (43.6)	286 (47.8)
Age, yr	25.1 (3.6)	25.3 (3.5)	25.2 (3.5)	24.9 (3.7)	25.1 (3.6)	25.3 (3.5)	25.2 (3.5)	25.2 (3.7)	25.2 (3.6)	25.3 (3.5)
Smoking (Year 0), n (%)										
Never	1,572 (65.6)	132 (37.6)	1,665 (62.6)	39 (42.9)	1,348 (67.2)	355 (47.9)	1,594 (63.7)	94 (42.3)	1,407 (65.4)	297 (49.6)
Former	350 (14.6)	31 (8.8)	368 (13.8)	13 (14.3)	276 (13.7)	105 (14.2)	352 (14.1)	26 (11.7)	284 (13.2)	97 (16.2)
Current	476 (19.8)	188 (53.6)	625 (23.5)	39 (42.9)	383 (19.1)	281 (37.9)	556 (22.2)	102 (46.0)	459 (21.4)	205 (34.2)
BMI, kg/m ²	24.3 (4.7)	25.0 (4.9)	24.3 (4.8)	24.6 (4.8)	24.2 (4.6)	24.8 (5.1)	24.2 (4.5)	26.6 (6.6)	24.2 (4.6)	24.8 (5.3)
Asthma, n (%)	101 (4.2)	38 (10.8)	125 (4.7)	14 (15.4)	14 (0.7)	125 (16.9)	113 (4.5)	26 (11.7)	66 (3.1)	73 (12.2)
Year 5 FVC, % predicted	102.0 (12.0)	100.7 (11.9)	102.0 (12.0)	100.1 (12.1)	102.2 (12.0)	101.1 (11.7)	102.3 (11.8)	97.6 (11.9)	102.0 (11.8)	101.6 (12.5)
Year 5 FEV ₁ , % predicted	100.1 (12.5)	97.6 (14.1)	99.9 (12.7)	96.8 (13.7)	100.7 (12.1)	97.1 (14.0)	100.2 (12.5)	95.2 (13.9)	100.1 (12.1)	98.5 (14.6)
Year 5 FEV ₁ /FVC, %	82.2 (6.2)	81.3 (9.7)	82.1 (6.7)	81.2 (7.9)	82.7 (5.9)	80.4 (8.5)	82.0 (6.4)	82.7 (10.2)	82.3 (6.6)	81.3 (7.3)
Year 30 FVC, % predicted	94.3 (14.6)	91.3 (15.8)	94.0 (14.7)	91.0 (15.8)	94.6 (14.6)	92.2 (15.2)	94.5 (14.6)	87.0 (14.9)	94.5 (14.5)	92.1 (15.6)
Year 30 FEV ₁ , % predicted	92.9 (15.7)	87.0 (18.4)	92.4 (16.2)	86.4 (16.9)	93.7 (15.4)	88.0 (17.6)	92.8 (15.9)	84.3 (17.0)	93.1 (15.7)	88.9 (17.6)
Year 30 FEV ₁ /FVC, %	77.2 (6.7)	74.4 (9.0)	76.9 (7.1)	74.4 (8.1)	77.7 (6.2)	74.5 (8.6)	76.9 (7.0)	76.2 (8.6)	77.2 (6.8)	75.6 (8.2)
Decline FVC (Year 5 to Year 30), ml/yr	-30.3 (165)	-33.1 (17.8)	-30.6 (16.6)	-32.5 (19.6)	-30.1 (16.6)	-31.9 (16.8)	-30.7 (16.7)	-30.3 (15.2)	-30.1 (16.4)	-32.5 (17.5)
Decline FEV ₁ (Year 5 to Year 30), ml/yr	-31.7 (14.4)	-35.5 (16.4)	-32.0 (14.7)	-35.0 (17.5)	-31.7 (14.4)	-33.3 (15.7)	-32.2 (14.6)	-31.8 (14.6)	-31.7 (14.1)	-33.7 (16.7)

Definition of abbreviation: BMI = body mass index.

Results are reported as mean (SD) unless otherwise specified. Symptoms present defined as those which are consistently reported at both the baseline and Year 2 examinations.

Table 2. Association (Covariate-adjusted Linear Regression Coefficient) between Respiratory Symptoms (Reported at Both Year 0 and Year 2; Mean Ages, 25 and 27 Years, Respectively) and Decline in Lung Function from Year 5 to Year 30

Symptom	FEV ₁ (ml/yr)	FVC (ml/yr)	FEV ₁ /FVC (%/yr)
Any symptom*	−2.71, <i>P</i> < 0.001	−2.18, <i>P</i> < 0.001	−0.05, <i>P</i> < 0.001
Cough or phlegm	−2.86, <i>P</i> < 0.001	−1.94, <i>P</i> = 0.03	−0.04, <i>P</i> = 0.07
Episodes of bronchitis	−3.43, <i>P</i> = 0.02	−2.57, <i>P</i> = 0.11	−0.05, <i>P</i> < 0.001
Chest illnesses	−2.07, <i>P</i> = 0.001	−1.93, <i>P</i> = 0.007	−0.03, <i>P</i> = 0.006
Wheeze	−1.94, <i>P</i> = 0.002	−1.09, <i>P</i> = 0.11	−0.04, <i>P</i> < 0.001
Shortness of breath	−1.52, <i>P</i> = 0.11	−0.81, <i>P</i> = 0.46	−0.03, <i>P</i> = 0.04

*Any symptom is defined by any one symptom category being reported at both the baseline and Year 2 examinations (the same symptom being reported at both examinations). Covariates: race–sex group, center, height, Year 5 lung function (FEV₁, FVC, or FEV₁/FVC), baseline body mass index, physician-confirmed asthma, and smoking status (never, former, current).

lung function (rather than Year 5) to Year 30. These results are shown in the online supplement (Table E5).

There was a statistically significant multiplicative interaction between smoking status and episodes of bronchitis (*P* = 0.01) for FEV₁ decline. Stratified analysis by smoking status (never, former, current) for episodes of bronchitis showed excess FEV₁ declines of −1.22 ml/yr (*P* = 0.53), −8.06 ml/yr (*P* = 0.02), and −6.15 ml/yr (*P* = 0.002) in those reporting episodes of bronchitis versus those who did not for baseline never, former, and current smokers, respectively. There were no significant interactions between any of the symptom categories and asthma on change in either FEV₁ or FVC.

The relationship between respiratory symptoms and age-related decline in lung function was assessed by modeling spirometry values from Years 5, 10, 20, and 30 as a function of age in covariate-adjusted generalized estimating equation models (Figure 2). Both cough or phlegm and wheeze were associated with greater age-related decline in FEV₁, FVC, and FEV₁/FVC compared with those without the respective symptom. Episodes of bronchitis were associated with accelerated age-related decline in FEV₁ and FEV₁/FVC, but not FVC. Chest illness was associated with greater age-related decline in FEV₁ and FVC, but not FEV₁/FVC. Shortness of breath was associated with lower FEV₁ and FVC across all age ranges, but not greater age-related decline in lung function (Figure 2).

Respiratory Symptoms and Future Lung Disease

Associations between respiratory symptoms and incident lung disease are shown in

Table 3. The presence of any respiratory symptom was associated with greater odds of both incident prebronchodilator obstructive and restrictive physiology at Year 30. Cough-related symptoms (cough or phlegm, episodes of bronchitis, and chest illnesses) were associated with obstructive but not restrictive physiology. Among the individual symptoms, cough or phlegm, episodes of bronchitis, wheeze, and chest illness were each associated with greater odds of incident obstructive physiology. Shortness of breath was associated with greater odds of incident spirometric restriction but not obstruction (Table 3). There were no statistically significant interactions between baseline smoking status or asthma and any of the symptoms on incident prebronchodilator obstructive or restrictive physiology (all *P* > 0.05). Results for post-bronchodilator obstructive and restrictive physiology are shown in the online supplement (Table E6). The presence of any respiratory symptom was associated with both post-bronchodilator obstructive (odds ratio [OR], 1.62; 95% confidence interval [CI], 1.10–2.40) and restrictive physiology (OR, 1.44; 95% CI, 1.10–1.88). Cough-related symptoms were associated with greater odds of post-bronchodilator obstruction (OR, 1.56; 95% CI, 1.08–2.26) but not restriction (OR, 1.27; 95% CI, 0.96–1.66) (Table E6).

Associations between respiratory symptoms and the presence of visual emphysema on CT scan 25 years later are shown in Table 3. The presence of any respiratory symptom at Years 0 and 2 was not associated with increased odds of centrilobular or paraseptal emphysema (although was associated with a composite

outcome of either centrilobular and/or paraseptal emphysema). In contrast, cough-related symptoms were associated with both centrilobular and paraseptal emphysema. Among the individual symptoms, cough or phlegm, wheeze, and chest illnesses were associated with future emphysema. The results of objective parenchymal features–based measures of emphysema and interstitial change are reported in the online supplement (Table E7). Cough or phlegm and episodes of bronchitis were associated with greater objective emphysema on the basis of the local histogram. None of the individual symptoms were associated with greater objective interstitial change (Table E7).

Incident Lung Disease and Sustained Respiratory Symptoms

Among the 291 participants with incident prebronchodilator obstructive physiology at Year 30, 28.9% did not report symptoms at baseline or Year 30, 18.2% reported symptoms only at baseline, 13.0% reported symptoms only at Year 30, and 39.9% reported symptoms at both baseline and Year 30 (Table E8). Some 53% of participants with incident obstructive physiology reported at least one symptom at the Year 30 examination. Among the 329 participants with incident prebronchodilator restrictive physiology, 26.4% did not report symptoms at either the baseline or Year 30 examinations, 14.3% reported symptoms only at baseline, 21.9% reported symptoms only at Year 30, and 37.4% reported symptoms at both baseline and Year 30. A total of 59.3% of participants with incident restrictive physiology reported at least one symptom at Year 30 (Table E9).

Discussion

In this population-based cohort study inclusive of both smokers and nonsmokers, we report that respiratory symptoms determined between the ages of 18 and 32 years are associated with impairment in lung health over the subsequent 30 years, as determined by accelerated age-related decline in lung function and greater risk of incident lung disease determined through both physiologic testing and CT imaging of the lung parenchyma. These associations were adjusted for typical risk factors of asthma and smoking status (both determined at the time of symptom report),

Figure 2. Relationships between baseline respiratory symptoms and age-related decline in lung function modeled through generalized estimating equations. Lung function performed at CARDIA (Coronary Artery Risk Development in Young Adults) study visits at Years 5, 10, 20, and 30 were used to determine mean lung function for each age according to whether symptoms were present at both the baseline and Year 2 examinations. Model covariates include: race–sex group, baseline height, body mass index, smoking status, and physician-diagnosed asthma. Tests of statistical significance reflect a difference in the slopes of age-related change in lung function between the symptom-present versus symptom-absent groups.

indicating that the presence of respiratory symptoms may serve as a prognostic marker for future impairment in lung health and lung disease. In adjusted models, the presence of respiratory symptoms was associated with similar effect sizes for decline in lung function to those of the well-established predictive biomarker of current cigarette smoking, magnifying the clinical significance of these findings. This implies that simple assessments of respiratory symptoms in young adults could lend

prognostic information regarding future lung health.

One interesting aspect of our study is that the nature of the symptoms being reported impacts the future manifestations of lung disease. Cough-related symptoms were associated with incident obstructive lung physiology and emphysema, whereas shortness of breath was associated with restrictive lung physiology. When placed in clinical context, these are not surprising. Cough or phlegm and episodes of

bronchitis may be more “exposure-driven” (including exposures beyond merely cigarette smoking, such as dusty work environments or air pollution) and point to susceptibility to future COPD or emphysema, whereas the more nonspecific shortness of breath may reflect either metabolic derangements associated with obesity and future restrictive physiology or impaired cardiopulmonary fitness. Indeed, we have previously reported in CARDIA that impaired fitness

Table 3. Association between Respiratory Symptoms at Baseline (Present at Both Year 0 and Year 2; Mean Ages, 25 and 27 Years, Respectively) and Incident Prebronchodilator Obstructive or Restrictive Physiology over 30 Years and Presence of Visual Emphysema on Computed Tomography Scan 25 Years Later (Mean Age, 50 Years)

Symptom	Obstructive Physiology (n = 291)	Restrictive Physiology (n = 329)	Centrilobular Emphysema (n = 129)	Paraseptal Emphysema (n = 162)	Any Visual Emphysema (n = 209)
Any symptom*	1.63 (1.24–2.14)	1.40 (1.09–1.80)	1.48 (0.98–2.23)	1.37 (0.94–1.99)	1.54 (1.10–2.16)
Cough-related symptoms†	1.65 (1.26–2.16)	1.18 (0.91–1.54)	1.58 (1.07–2.32)	1.46 (1.02–2.09)	1.56 (1.13–2.16)
Cough or phlegm	1.40 (1.00–1.97)	1.28 (0.90–1.81)	1.34 (0.86–2.09)	1.54 (1.03–2.32)	1.57 (1.09–2.26)
Episodes of bronchitis	2.04 (1.19–3.52)	1.19 (0.62–2.25)	1.88 (0.86–4.07)	1.64 (0.77–3.51)	1.93 (0.99–3.74)
Chest illnesses	1.41 (1.05–1.89)	1.10 (0.82–1.46)	1.62 (1.08–2.41)	1.50 (1.03–2.19)	1.64 (1.17–2.30)
Wheeze	1.61 (1.21–2.14)	1.07 (0.80–1.43)	1.84 (1.23–2.75)	1.50 (1.02–2.19)	1.61 (1.15–2.27)
Shortness of breath	0.99 (0.61–1.59)	1.84 (1.26–2.67)	1.00 (0.55–1.83)	0.94 (0.52–1.70)	1.02 (0.61–1.69)

Data presented as covariate-adjusted odds ratio (95% confidence interval). Obstructive physiology: FEV₁/FVC < 70%; restrictive physiology: FVC < 80% and FEV₁/FVC ≥ 70%. Covariates: age, race–sex group, center, baseline body mass index, physician-confirmed asthma, and smoking status (never, former, current).

*Any symptom is defined by any one of the symptom categories being reported at both the baseline and Year 2 examinations (the same symptom being reported at both examinations).

†Cough-related symptoms are defined as cough or phlegm, episodes of bronchitis, or chest illnesses being reported at both the baseline and Year 2 examinations (the same symptom being reported at both examinations).

is associated with accelerated decline in lung function (28).

In a previous study of European adults between the ages of 20 and 44 years, cough or phlegm was associated with incident COPD over 8 years of follow-up (11). In a British birth cohort, chronic bronchitis among smokers in adult life was associated with greater FEV₁ decline and higher risk of subsequent obstructive lung physiology (13). Our report extends these findings by evaluating a broader panel of respiratory symptoms, assessing smokers and nonsmokers alike, reporting on both decline in lung function and incident lung disease exclusively from young adulthood, taking advantage of spirometric measures at multiple time points and documenting the presence of emphysema on CT scan. We also report on not only risk of obstructive lung physiology and emphysema but also decline in lung health in general (loss of both FEV₁ and FVC) as well as incident spirometric restrictive physiology. Indeed, the transition to impaired lung health can be marked by the development of obstructive or restrictive physiology, and both patterns of impairment have significant clinical implications for both cardiovascular and respiratory outcomes (6, 29, 30).

There is a large body of literature demonstrating the transient nature of symptoms in both adolescence and adulthood across all fields of clinical care. This has been well recognized for a number

of years in respiratory disease, as exemplified by chronic bronchitis, which mandates that symptoms be present for at least 2 years (31). The required durability of symptoms is needed, in part, to ensure that the symptoms reflect a true biologic process and not a transient affliction. With this in mind, and to ensure that our main predictors are reflective of a true biologic risk factor and not transient phenomena, we required that the same symptom be reported by a participant at both the baseline and Year 2 examinations.

Our findings do raise the question of what, exactly, is causing respiratory symptoms in this population of generally healthy young adults. Both current smoking and physician-diagnosed asthma were predictably more common across each symptom category compared with those without symptoms. There were, however, a substantial proportion of individuals reporting symptoms who did not report smoking or asthma. Several other factors could be associated with the presence of respiratory symptoms, including premature birth; antenatal exposure to tobacco; environmental tobacco smoke exposure; childhood respiratory infections or illnesses; occupational exposures to vapors, gases, dusts, or fumes; or exposure to air pollution. Each of these exposures has been associated with risk of future COPD (10). Nonsmoking exposures, however, are difficult to ascertain and quantify in both clinical practice and epidemiologic studies

like ours. This challenge magnifies the potential impact of ascertaining respiratory symptoms in young adults even in the absence of clearly apparent exposures: our data would indicate that the mere presence of sustained symptoms in young adults carries prognostic importance and possibly heralds a susceptibility to loss of lung health, and, in some cases, future lung disease.

The importance and consequence of respiratory symptoms has recently been documented in older populations of current and former smokers with preserved lung function. In SPIROMICS (the Subpopulations and Intermediate Outcome Measures in COPD Study), current and former smokers with average age 60 years old who reported significant respiratory symptoms had a higher rate of respiratory exacerbations and greater activity limitation and airway wall thickening without emphysema than asymptomatic smokers (8). In the COPDGene (Genetic Epidemiology of COPD) study, current and former smokers with symptoms but normal lung function had worse quality of life, more frequent respiratory exacerbations, shorter 6-minute-walk distance, and greater CT scan abnormalities than never-smoking control subjects (9). Our work is importantly different from these prior studies by evaluating symptoms occurring in young adulthood—a time most would consider peak lung health—which allows us to evaluate how respiratory symptoms are associated with subsequent decline in lung

function and future incident disease. Our work also illustrates that the subsequent impact of those symptoms on lung health is comparable to the well-studied effect of smoking.

Our study has several strengths. The population-based nature of CARDIA distinguishes it from other studies of the health impacts of respiratory symptoms, as it is free from participation bias that is implicit in the COPD-focused studies described above. Furthermore, the measurement of symptoms in the period of peak lung health in young adults speaks to the novel health implications of symptoms being reported before any chronic respiratory disease is typically diagnosed. The ability to ascertain serial lung function and its decline from young adulthood over 30 years is a unique feature of our analysis, as is our ability to assess incident COPD and emphysema on thoracic CT scans, which, when consistent, as they are for cough or phlegm, lends particular credence to our findings and allows us to tie the physiologic measure of obstructive lung physiology to a deeper mechanistic underpinning for airspace dilation and lung parenchymal remodeling.

There are some potential weaknesses in our study. As discussed earlier, symptom

reporting probably changes in individuals and could be inconsistent over time. To address this, we only considered symptom to be “present” if it was reported consistently at both the baseline and Year 2 examinations. Our inability to ascertain and adjust for etiologies of respiratory symptoms beyond asthma or smoking could be viewed as a weakness that is inherent in any observational epidemiologic study such as ours. In addition, the possibility of residual confounding by asthma (which may be undiagnosed at the early examinations when symptoms were determined) or smoking status (which may change over time in individual participant after the baseline examination) exists. We rely on spirometric measures rather than static lung volumes to define restrictive physiology, which could be viewed as a limitation. Obtaining static lung volumes, however, has not typically been done in community-based epidemiologic studies such as CARDIA. Retention can be a challenge in any long-term cohort study such as CARDIA. Participants who were lost to follow-up in CARDIA had greater burden of respiratory symptoms at baseline than those included in the current analysis. Given our findings of respiratory

symptoms association with future impairment in lung health, we believe this pattern of missing data would bias toward a null finding, and, therefore, our ability to still demonstrate associations between baseline symptoms and future lung health is reassuring.

Conclusions

In a large, population-based cohort study of generally healthy adults, we found that report of respiratory symptoms between the ages of 18 and 32 years was associated with decline in lung function, incident COPD, and, in the case of cough or phlegm and episodes of bronchitis, radiographic emphysema over 30 years of follow-up independent of smoking status or asthma diagnosis. These findings indicate that respiratory symptoms, among susceptible individuals, precede the onset of physiologic or radiographic disease, and identification of individuals with sustained respiratory symptoms in routine clinical practice could be helpful for identification of individuals at greatest risk for future lung disease. ■

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

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