Low Lung Function in Young Adult Life Is Associated with Early Mortality

To the Editor:

Low levels of lung function are known to be a significant predictor of cardiopulmonary mortality in the adult general population (1–6). This association may be the consequence of an accelerated decline of lung function during adult life (e.g., in response to cigarette smoking), but it can also result from tracking of low levels of lung function achieved by early adulthood, possibly as a result of impaired lung growth during childhood and/or *in utero*. The goal of this study was to test the latter hypothesis by using TESAOD (Tucson Epidemiological Study of Airway Obstructive Disease) to determine the relation of levels of lung function achieved in young adulthood to subsequent mortality risk. Some of the results of this study have been previously reported in the form of an abstract (7).

TESAOD is a population-based prospective cohort study of non-Hispanic white households initiated in Tucson, Arizona, in 1972 (8). At the initial survey and in 12 follow-up surveys completed approximately every 2 years up to 1996, participants completed a standardized respiratory questionnaire and, with the exception of survey 4, spirometric lung function tests (9). During the follow-up, newborns and spouses of participants were also recruited into the study.

For this study, we defined as “baseline survey” the first survey at which participants were 21–35 years old and completed lung function tests. At the baseline survey, 1,412 participants also had available information for covariates and did not report having cystic fibrosis or having had any chest or lung surgery.

Percentage predicted values for spirometric indices were computed using reference equations by Knudson and colleagues (10). For participants with available follow-up, 10-year within-subject slopes of FEV₁ decline were also computed by regressing FEV₁ values against age at each lung function test that was completed within 10 years of the baseline survey. Slopes of FVC and FEV₁/FVC ratio were computed using similar methods.

Vital status was updated during the study follow-up through direct contact with family and next of kin and collection of death certificates. In addition, a systematic review of mortality as of January 1, 2011, was completed through linkage with the National Death Index. Causes of death were determined on the basis of death certificates for events up to 1978 and on National Death Index records for events after 1978. For this study, we analyzed four causes of death: heart disease, chronic obstructive pulmonary disease (COPD), cancer, and external causes (mainly accidents, homicides, and suicides). Because of the small number of deaths resulting from COPD ($n = 7$), these events were combined with deaths resulting from heart disease into the category of cardiopulmonary mortality, as done previously (11).

Cox proportional hazards models were used to estimate hazard ratios for all-cause mortality and cause-specific mortality while adjusting for covariates. Separate models were used to test the effects of baseline levels of FEV₁, FVC, and FEV₁/FVC ratio. FEV₁ and FVC were tested both as percentage predicted and as crude values. Time to event was defined as the time from the baseline survey to the date of death for deceased participants and to January 1, 2011, for subjects who were still alive at that time. In secondary analyses, models were further adjusted for the decline of the specific lung function index of interest during the first 10 years after the baseline survey. As a consequence, for these models, follow-up for time to event began 10 years after the baseline survey.

The 1,412 participants included in this study had a mean age of 26 years at baseline, with 52% females and 51% ever-smokers. Smokers had an average of 8.4 pack-years at baseline. The mean percentage predicted FEV₁ at baseline was 100.5%. The mean follow-up period for the main mortality analyses was 32.5 ± 6.7 years. By January 1, 2011, 122 participants (8.6%) had died (17 by heart disease, 7 by COPD, 42 by cancer, 24 by external causes, and 32 by other causes).

Table 1 shows associations of lung function with all-cause and cause-specific mortality. Baseline FEV₁, but not FVC, was associated with all-cause mortality. However, both FEV₁ and FVC were associated with heart and cardiopulmonary mortality. In models adjusted for sex, age, body mass index, smoking status, and pack-years at baseline (Table 1), every 10% decrease in baseline FEV₁ percentage predicted levels was associated with an increase in mortality risk of 15% ($P = 0.052$) for all causes, 72% ($P = 0.002$) for heart disease, and 67% ($P = 0.002$) for cardiopulmonary mortality. These associations were also confirmed when crude FEV₁ levels were used ($P = 0.02$, 0.001, and <0.001 ; respectively). Similarly, every 10% decrease in baseline FVC percentage predicted levels was associated with a 69% ($P = 0.006$) increase in heart disease and a 54% ($P = 0.01$) increase in cardiopulmonary mortality. Results were confirmed in Cox models that were further adjusted for the 10-year slope of lung function decline during the follow-up (Table 1). To rule out potential overadjustment in models on percentage predicted values, we also confirmed results for percentage predicted FEV₁ and FVC after removing sex and age from covariates (data not shown).

No significant associations were found between FEV₁/FVC and mortality. No significant associations or trends were found with mortality by cancer or external causes for any of the lung function indices.

Figure 1 shows the association of tertiles of FEV₁ percentage predicted at baseline with cardiopulmonary mortality.

Our findings demonstrate that individuals who achieve low levels of FEV₁ and FVC by the beginning of adult life are at increased risk for early cardiopulmonary mortality. Associations appeared stronger for FEV₁ than FVC, possibly because the former is able to capture deficits related to both obstructive and restrictive patterns. We observed consistent trends of association between low lung function and mortality for both heart disease and COPD, but the number of deaths with COPD as underlying cause was too small to test this disease separately. Interestingly, low levels of maximally achieved FEV₁ in young adulthood have been shown to account for a significant proportion of incident COPD cases at

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Table 1. Association of Baseline Levels of Lung Function (FEV₁, FVC, and FEV₁/FVC) with All-Cause and Cause-Specific Mortality during Follow-up in Tucson Epidemiological Study of Airway Obstructive Disease Participants

	All-Cause			Heart Disease			Cardiopulmonary			Cancer			External Causes			Other Causes		
	HR (95% CI)	P Value		HR (95% CI)	P Value		HR (95% CI)	P Value		HR (95% CI)	P Value		HR (95% CI)	P Value		HR (95% CI)	P Value	
Cox proportional hazards models* (n = 1,412)	Deaths = 122			Deaths = 17			Deaths = 24			Deaths = 42			Deaths = 24			Deaths = 32		
FEV ₁ % predicted: 10% decrease at baseline	1.15 (1.00–1.32)	0.052		1.72 (1.23–2.43)	0.002		1.67 (1.21–2.30)	0.002		1.15 (0.91–1.45)	0.244		1.05 (0.74–1.47)	0.798		0.97 (0.75–1.25)	0.800	
FEV ₁ crude values: 100-ml decrease at baseline	1.04 (1.01–1.08)	0.023		1.16 (1.07–1.27)	0.001		1.15 (1.07–1.24)	<0.001		1.03 (0.97–1.10)	0.325		1.03 (0.95–1.11)	0.462		0.99 (0.93–1.07)	0.879	
FVC % predicted: 10% decrease at baseline	1.07 (0.93–1.23)	0.337		1.69 (1.16–2.46)	0.006		1.54 (1.10–2.18)	0.013		1.08 (0.87–1.34)	0.503		0.91 (0.62–1.32)	0.602		0.96 (0.75–1.23)	0.751	
FVC crude values: 100-ml decrease at baseline	1.02 (0.99–1.05)	0.192		1.12 (1.04–1.22)	0.004		1.11 (1.03–1.19)	0.007		1.01 (0.96–1.07)	0.685		0.99 (0.92–1.06)	0.778		1.00 (0.95–1.06)	0.924	
FEV ₁ /FVC: 10% decrease at baseline	1.22 (0.96–1.56)	0.110		1.18 (0.48–2.92)	0.722		1.39 (0.75–2.57)	0.298		1.28 (0.85–1.94)	0.241		1.36 (0.81–2.27)	0.246		0.97 (0.58–1.62)	0.901	
Cox proportional hazards models further adjusted for subsequent decline of lung function [†] (n = 1,058)	Deaths = 89			Deaths = 12			Deaths = 18			Deaths = 35			Deaths = 14			Deaths = 22		
FEV ₁ % predicted: 10% decrease at baseline	1.17 (0.99–1.38)	0.060		1.91 (1.30–2.80)	0.001		1.87 (1.32–2.64)	<0.001		1.18 (0.91–1.51)	0.208		0.92 (0.67–1.26)	0.613		0.90 (0.63–1.29)	0.568	
FEV ₁ crude values: 100-ml decrease at baseline	1.04 (0.99–1.08)	0.111		1.21 (1.09–1.35)	<0.001		1.18 (1.07–1.31)	0.001		1.03 (0.95–1.11)	0.455		0.97 (0.88–1.07)	0.568		0.97 (0.88–1.06)	0.505	
FVC % predicted: 10% decrease at baseline	1.17 (0.98–1.40)	0.074		1.95 (1.28–2.97)	0.002		1.73 (1.23–2.44)	0.002		1.10 (0.86–1.42)	0.445		1.21 (0.80–1.82)	0.365		0.96 (0.68–1.34)	0.796	
FVC crude values: 100-ml decrease at baseline	1.03 (0.99–1.08)	0.106		1.18 (1.07–1.29)	0.001		1.13 (1.04–1.23)	0.006		1.01 (0.94–1.08)	0.773		1.03 (0.93–1.13)	0.589		1.00 (0.93–1.07)	0.976	
FEV ₁ /FVC: 10% decrease at baseline	1.00 (0.73–1.38)	0.987		0.87 (0.24–3.15)	0.828		1.30 (0.56–2.98)	0.541		1.21 (0.76–1.94)	0.414		0.61 (0.28–1.30)	0.202		0.79 (0.38–1.64)	0.535	

Definition of abbreviations: CI = confidence interval; HR = hazard ratio.

Hazard ratios are from multivariate Cox proportional hazards models. Cause-specific mortality analyses were completed treating death events resulting from causes other than the specific cause of interest as censored observations. All models used household clustered sandwich estimators of SEs to control for family clustering.

*Adjusted for sex, age, body mass index categories (underweight, <18.5 kg/m²; normal weight, ≥18.5 and <25 kg/m²; overweight, ≥25 and <30 kg/m²; and obese, ≥30 kg/m²), smoking status, and pack-years at baseline. Models on crude values were also adjusted for height. Time to event was defined as the time from the baseline survey to the date of death for deceased participants and to January 1, 2011, for subjects who were still alive at that time.

[†]Adjusted for sex, age, body mass index categories, smoking status, pack-years at baseline, and decline of the specific lung function index during the first 10 years of study follow-up. Models on crude values were also adjusted for height. Time to event began 10 years after the baseline survey and was defined as the time to the date of death for deceased participants and to January 1, 2011, for subjects who were still alive at that time.

Figure 1. Survival curves for cardiopulmonary mortality by tertiles of FEV₁ percentage predicted at baseline. Low tertile: FEV₁ percentage predicted, <95.19%; medium tertile: FEV₁ percentage predicted, ≥95.19% and <106.36%; high tertile: FEV₁ percentage predicted, ≥106.36%.

the population level (12). Larger studies will be required to determine whether this is also the case for COPD mortality.

We cannot exclude that the association between low lung function in young adult life and subsequent mortality is partly the result of an early acceleration of lung function decline between the ages of 21 and 35 years. However, consistent trends were also found in analyses restricted to individuals younger than 30 years (data not shown), at which age the relative contribution of lung function decline is expected to be smaller. In addition, the effects of baseline lung function levels on mortality were confirmed in Cox models that included the slope of their subsequent decline.

Among the strengths of our study are the population-based nature of our cohort, the availability of multiple prospective lung function tests, and the extensive data on mortality events collected over nearly 40 years of follow-up.

In conclusion, in a long-term population-based cohort, we found that low levels of FEV₁ and, to a lesser extent, FVC achieved by the age of 21–35 years predict risk of early cardiopulmonary mortality. ■

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