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Research Article

Pulmonary Function in Midlife as a Predictor of Later-Life Cognition: The Coronary Artery Risk Development in Adults (CARDIA) Study

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Abstract

Background: Studies found associations between pulmonary function (PF) and cognition, but these are limited by mostly cross-sectional design and a single measure of PF (typically forced expiratory volume in 1 second [FEV_1]). Our objective was to prospectively analyze the association of repeatedly measured PF with cognition.

Methods: We studied 3 499 participants in the Coronary Artery Risk Development in Young Adults cohort with cognition measured at year 25 (Y25) and Y30, and PF (FEV_1 and forced vital capacity [FVC], reflecting better PF) measured up to 6 times from Y0 to Y20. Cognition was measured via Stroop test, Rey-Auditory Verbal Learning Test [RAVLT], and digit symbol substitution test [DSST], which capture executive function, verbal learning and memory, and attention and psychomotor speed, respectively; lower Stroop, and higher RAVLT and DSST scores indicate better cognition. We modeled linear, cross-sectional associations between cognition and PF at Y30 (mean age 55), and mixed models to examine associations between cognition at Y25–Y30 and longitudinal PF (both annual rate of change, and cumulative PF from Y0 to Y20).

Results: At Y30, FEV_1 and FVC were cross-sectionally associated with all 3 measures of cognition (β = 0.08–0.12, p < .01–.02). Annual change from peak FEV_1/FVC ratio was associated with Stroop and DSST (β = 18.06, 95% CI = 7.71–28.40; β = 10.30, 95% CI = 0.26–20.34, respectively), but not RAVLT. Cumulative FEV_1 and FVC were associated with Stroop and DSST (β = 0.07–0.12, p < .01–.02), but only cumulative FEV_1 was associated with RAVLT (β = 0.07, 95% CI = 0.00–0.14).

Conclusions: We identified prospective associations between measures of PF and cognition even at middle ages, adding evidence of a prospective association between reduced PF and cognitive decline.

Keywords: Aging, Pulmonary function, Cognition

As average life expectancy increases and the population ages (1,2), there is great interest in understanding etiologies of aging trajectories, including age-related cognitive decline (3). Current evidence points to an important role for physical functioning in cognitive aging, with studies demonstrating relationships between a wide variety of measures of cognitive and physical aging (1,4). Several reports also suggest a relationship between decreased pulmonary function and cognitive decline, with poor pulmonary function associated with poor cognitive status (5,6). Plausible mechanisms for this association include poorer cerebral oxygenation (7), decreased physical activity (8), and greater vascular disease (9). However, the literature remains unclear on the temporality of these associations. Lower pulmonary function has been correlated with poor cognitive performance in patient populations, such as those with chronic obstructive pulmonary disease (COPD) (10) and bronchiectasis (11), but less is known about this association among population-based studies.

In addition, there are few studies on whether a decline in pulmonary function during young adulthood is associated with late-life cognition (12). Furthermore, to our knowledge, no studies have examined more complex measures of pulmonary function in relation to cognitive scores in the context of the aging process. For example, the rate of pulmonary function change or decline from peak pulmonary function may be better predictors of cognition in later life compared with pulmonary function measured once, and could potentially even suggest interventions to reduce late-life cognitive impairment by improving midlife pulmonary function, but have generally been understudied due to lack of appropriate longitudinal data (13,14). However, many cohorts do not possess data on peak pulmonary function as enrollment occurs after the peak is reached, reducing the ability of these cohorts to contribute to our understanding of the health impacts of poor pulmonary function over time.

We hypothesized that cumulative pulmonary function would yield a better predictor of cognition than pulmonary function measured once or relative to its peak, as cumulative pulmonary function includes more information than peak or decline from peak pulmonary function measures (eg, exposure to poor pulmonary function throughout early life), and may obviate the need to determine a precise peak pulmonary function. By virtue of this information, cumulative pulmonary function may be a more useful biomarker for long-term cognition, and thus a more useful and/or modifiable target for interventions designed to improve later cognition or prevent cognitive decline earlier in life. Therefore, the objective of this study is to determine, in a large population-based cohort, whether pulmonary function measures (forced expiratory volume in 1 second [FEV$_1$], forced vital capacity [FVC], and FEV$_1$/FVC ratio) are prospectively associated with cognitive decline at midlife. This includes exploring longitudinal measures of pulmonary function, such as the annual rate of pulmonary function change and cumulative pulmonary function, to determine which is most strongly associated with later cognitive function. We hypothesized that poorer lung function would be associated with worse cognitive function at follow-up.

Method

The Coronary Artery Risk Development in Young Adults Study

Coronary Artery Risk Development in Young Adults (CARDIA) is a prospective cohort designed to investigate the development of cardiovascular disease (15). In 1985–1986, 5115 Black and White men and women ages 18–30 were recruited from 4 urban sites in the United States: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. CARDIA participants have been followed for over 30 years since enrollment providing detailed demographic and clinical data including self-reported, anthropometric, and laboratory measures. These data were collected across 8 examination cycles starting at baseline and at study years (Y) 2, 5, 7, 10, 15, 20, 25, and 30. Retention rates have been high throughout these follow-ups (91%, 86%, 81%, 79%, 74%, 72%, 72%, and 71%, respectively). Additional details regarding study design and recruitment, and participant characteristics at baseline, have been reported previously (15). CARDIA was approved by the institutional review boards at all study sites and all participants provided written informed consent.

Cognitive Assessments

Full details of the cognitive assessments in CARDIA have been reported previously (16). Briefly, cognition was measured at Y25 and Y30 by certified technicians. This study examined 3 cognitive tests that were administered at each time point: the Stroop test, the Rey-Auditory Verbal Learning Test (RAVLT), and the Digit Symbol Substitution Test (DSST). Raw/untransformed values were used for all 3 tests. The Stroop test measures executive function by requiring the participant to respond to one form of a stimulus (read the name of a color) while inhibiting response to another form of stimulus (the word color itself) and includes 3 subtests; lower scores indicate better performance (17). The RAVLT tests verbal learning and memory; participants are read a list of 15 words and asked to recall them 10 minutes later, with a greater number of words recalled indicating better performance (18). The DSST tests attention and psychomotor speed by asking participants to translate a written sheet of numerals (1–9) into symbols within 2 minutes, with higher scores indicating better performance (19).

Pulmonary Function Measurements

Full details of CARDIA's pulmonary function measurements have been reported previously (20). Briefly, this study used all pulmonary function measurements available (Y0, Y2, Y5, Y10, Y20, and Y30). At each exam, pulmonary function was measured using spirometry procedures as recommended by the American Thoracic Society (21). Pulmonary function measurements included FVC, the volume of air that can be forcibly exhaled after taking the deepest breath possible, and FEV$_1$, the volume of air exhaled in the first second of a forced exhalation maneuver. In addition, the FEV$_1$/FVC ratio was also calculated. FVC can serve as a marker of lung health that encompasses both total lung volume and respiratory muscle strength, FEV$_1$ as a marker of airway disease in the lung, and the FEV$_1$/FVC ratio as a diagnostic marker used to define obstructive airway disease. Higher values for all 3 measures indicate better pulmonary function.

Covariates

Structured questionnaires were used to self-report participants' demographic characteristics (age, sex, race, education, and income), behaviors (eg, use of tobacco), and medical history (including comorbidities) at each CARDIA examination. Physical activity was measured using the validated CARDIA Physical Activity Questionnaire (22,23). Height was measured with a vertical ruler and weight from a calibrated balance beam scale. Seated blood pressure was measured in triplicate after a 5-minute resting period using a random-zero sphygmomanometer and with an automated oscillometric blood pressure monitor (Omron HEM-907XL; Online Fitness, Santa Monica, CA), calibrated to the sphygmomanometer. Blood pressure was determined by averaging the last 2

measurements taken. We defined hypertension as self-reported use of antihypertension medication, or the clinical definition (SBP > 140 mmHg or DBP > 90 mmHg) as of the examination.

Statistical Analyses

We report descriptive characteristics using n (%) or mean (SD) as appropriate. For multivariable analyses, we first examined cross-sectional linear models of Y30 data only (overall and in race and sex strata). Next, we calculated peak pulmonary function prior to the cognitive measurements (ie, Y0–Y20) for each participant, then calculated the annual rate of change from that peak to their last pulmonary function measurement prior to the cognitive measurements (ie, Y20). This was done because 96.0%–99.9% of participants had peak pulmonary function at or before Y20 (Supplementary Table 1), consistent with literature (24). To ensure that these decisions introduced no bias, we conducted a sensitivity analysis analyzing cognition at Y30 versus rate of pulmonary function change from peak to Y30. We then included annualized rate of change from peak as an independent variable in a mixed linear model, with cognition at Y25 and Y30 as the dependent variable of interest. In order to fully examine the repeated cognition measures, we conducted all models with cognition as the outcome averaged across both time measurements using generalized estimating equations (GEEs) with exchangeable correlation structures and robust variance estimators to combine (average) the Y25 and Y30 measures of cognition in our models. GEEs capture within-individual variation over the repeated cognition measurements in our study, and effectively allow for a larger sample size and thus more precise estimates of our associations of interest, averaged across 2 repeated measurements and with minimal underlying assumptions. We also report race- and sex-stratified results for this analysis.

We next calculated cumulative pulmonary function for subjects with at least 3 measures during Y0–Y20: one at Y0, one at Y20, and one or more between Y0 and Y20. Each of these measurements was multiplied by the time interval between 2 consecutive examinations and added together to generate cumulative measures of FEV_1, FVC, and the FEV_1/FVC ratio. This ensures that all cumulative pulmonary function measures are on the same scale, regardless of the number of measurements used to calculate it. Participants missing lung function data were excluded from analysis.

To demonstrate the potential advantage offered by cumulative measures in terms of predicting cognitive function, we compared prospective associations of both pulmonary function decline and cumulative pulmonary function with all 3 cognitive test scores. To perform this proof-of-concept analysis we selected 2 subgroups to maximize the difference between cumulative pulmonary function and decline from peak: similar FEV_1 at Y0 and Y20 but different FEV_1 in-between (Y2, Y5, and Y10, corresponding to mean FEV_1 of 3.51, 3.48, and 3.38 liters, respectively). Thus, group 1 ($n = 54$) consists of those who had an FEV_1 greater than the mean at each of Y2, Y5, and Y10, while Group 2 ($n = 87$) consists of those who had an FEV_1 less than the same means. To illustrate these 2 subgroups (Figure 1), we calculated the 20-year slope of FEV_1 and the 20-year annualized cumulated FEV_1. We then conducted 2 separate linear regressions to examine the associations of the slope of FEV_1 and cumulative FEV_1 with Y25 cognitive test scores adjusting for age, sex, race, center, height, and weight. These were followed by a final mixed linear model regressing cognition at both Y25 and Y30 on cumulative pulmonary function.

All multivariable analyses adjusted for age at cognitive examination, sex, race, center, and height; both mixed-effects models
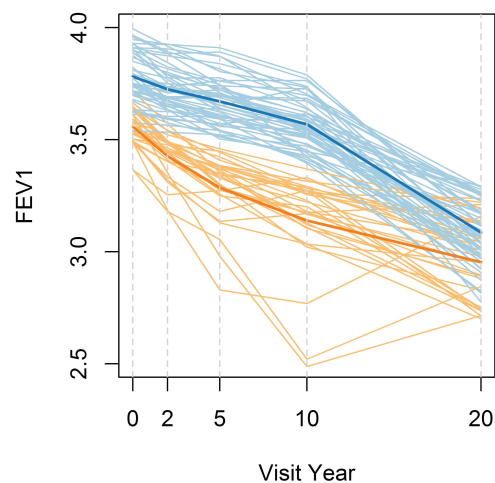
Figure 1. Spaghetti plot of FEV_1 trajectory across 20-y follow-up for 2 groups featured by different decline patterns. The light gray (blue in the online version) group is characterized by an accelerated decline after Y10 ($n = 54$), compared with the dark gray (orange in the online version) group characterized by a steadily decline ($n = 87$). Each light-colored line represents one individual, with each bolded line representing the mean for each group.

additionally adjusted for peak pulmonary function (Model 1). We also report a second set of models (Model 2) additionally adjusted for smoking status and a third set (Model 3) additionally adjusted for education, income, weight, physical activity, COPD (yes/no), stroke or transient ischemic attack (TIA; yes/no), asthma (yes/no), and hypertension (yes/no). Finally, we conducted sensitivity analyses replacing change from peak pulmonary function with 2 different calculations of age at peak pulmonary function (one using peak pulmonary function from Y0 to Y20 and one using peak pulmonary function from Y0 to Y30). We also calculated model fit statistics using Model 1 to compare decline versus cumulative FEV_1 and FVC.

Results

Characteristics of the full CARDIA sample at baseline were reported previously (15). Table 1 shows the characteristics of our study population ($N = 3\ 499$ at Y25 and $N = 3\ 358$ at Y30; 3 033 participants had cognition data at both time points). Briefly, our population at Y25 had mean age 50 and was majority female (57%), Black (53%), and never-smokers (61%). At Y30, mean FEV_1 was 2.70 L (SD: 0.75 L), mean FVC 3.53 L (0.98 L), and the mean FEV_1/FVC ratio 76.8% (7.1%). Supplementary Table 1 shows the distribution of peak pulmonary function by study year; most subjects peaked by Y5 (range 75%–92%), corresponding to mean age 30. Figure 1 shows our analysis of pulmonary function decline ($n = 3\ 397$ measurements) versus cumulative pulmonary function ($n = 3\ 221$ measurements); we found that cumulative pulmonary function was a better predictor of the Stroop score than pulmonary function decline (see Supplementary Table 2 for full results), but not for the other 2 scores.

Table 2 shows our cross-sectional results. In Model 1, Y30 FEV_1 was associated with all 3 measures of cognition at Y30 including better cognition as measured Stroop (β: −1.94, 95% CI: −2.75, −1.12), RAVLT (β: 0.45, 95% CI: 0.32, 0.58), and DSST (β: 4.26, 95% CI: 2.98, 5.55). Adjusting for smoking (Model 2) only slightly attenuated these associations; in Model 3, these associations were attenuated further but persisted. Y30 FVC had similar associations (Supplementary Table 3). Y30 FEV_1/FVC ratio was only associated

Table 1. Characteristics of CARDIA Participants at Year 25 and Year 30 With Non-missing Cognition Data

	Y25	Y30
N*	3 499	3 358
Age†, mean (*SD*), y	50.2 (3.6)	55.1 (3.6)
Female, *n* (%)	1 980 (56.6)	1 913 (57.0)
Education, mean (*SD*), y	15.1 (2.7)	15.1 (2.6)
Race, *n* (%)		
White	1 640 (46.9)	1 605 (47.8)
Black	1 859 (53.1)	1 753 (52.2)
Center, *n* (%)		
Birmingham, AL	818 (23.4)	757 (22.6)
Chicago, IL	826 (23.6)	773 (23.0)
Minneapolis, MN	878 (25.1)	830 (24.7)
Oakland, CA	977 (27.9)	997 (29.7)
Smoking status, *n* (%)		
Never	2 106 (61.1)	2 079 (62.8)
Former	750 (21.8)	769 (23.2)
Current	589 (17.1)	463 (14.0)
Physical activity (total intensity score)	337.9 (275.6)	321.5 (271.6)
Height, mean (*SD*), cm	170.3 (9.4)	169.9 (9.4)
Weight, mean (*SD*), kg	87.4 (22.0)	88.0 (21.9)
COPD, *n* (%)	43 (1.2)	71 (2.1)
Stroke, *n* (%)	69 (2.0)	107 (3.2)
Asthma, *n* (%)	267 (7.7)	323 (9.7)
Hypertension, *n* (%)	1 320 (37.7)	1 472 (43.8)
Pulmonary function:		
FEV_1, mean (*SD*), L	—	2.7 (0.8)
FVC, mean (*SD*), L	—	3.5 (1.0)
Raw FEV_1/FVC ratio, mean (*SD*), %	—	76.8% (7.1%)
Percent predicted FEV1, mean (*SD*)	—	92.0% (16.3%)
Percent predicted FVC, mean (*SD*)	—	93.9% (14.8%)
Cognition raw scores		
Stroop, median (P_{25}, P_{75})	21 (16, 27)	20 (16, 27)
RAVLT, median (P_{25}, P_{75})	9.0 (7.6, 10.4)	9.2 (7.8, 10.4)
DSST, median (P_{25}, P_{75})	70 (59, 81)	67 (55, 78)

Notes: COPD = chronic obstructive pulmonary disease; DSST = digit symbol substitution test; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; RAVLT = Rey-Auditory Verbal Learning Test.

*Three thousand and thirty-three participants had complete cognition data at both Y25 and Y30.

†Participants were ages 18–30 at baseline (Y0).

with better RAVLT in Model 1 (β: 1.26, 95% CI: 0.37, 2.15), and no measures of cognition in Model 2 or Model 3. Our stratified results (Supplementary Table 4) revealed few differences by race or by sex.

Table 3 shows our model results of annual pulmonary function decline. The rate of FEV_1 change was associated with better cognition primarily in Model 1 (β: −30.69, 95% CI: −48.77, −12.61 for Stroop; β: 6.62, 95% CI: 3.49, 9.74 for RAVLT; and β: 94.91, 95% CI: 68.05, 121.76 for DSST); only DSST remained significant in Model 3 (β: 43.09, 95% CI: 17.09, 69.09). FVC had similar associations (Model 3 DSST: β = 22.61, 95% CI: 0.37, 44.85). FEV_1/FVC ratio was associated with better Stroop and DSST in all 3 models, but not with RAVLT (for Model 3, β: −198.83, 95% CI: −315.19, −82.48 for Stroop, and β: 193.83, 95% CI: 27.06, 360.60 for DSST). Supplementary Table 5 shows our sensitivity analysis of pulmonary function change from peak to Y30; these results were similar to those of pulmonary function change from peak to Y20. Supplementary Table 6 shows our

race- and sex-stratified results; longitudinal associations were generally consistent across strata, but Black and female participants had some stronger associations than White and male participants (respectively) in fully adjusted models (Model 3).

Table 4 shows the results of cumulative FEV_1 and cumulative FVC, and cognition. Cumulative FEV_1 was associated with better cognition in Model 3 using 2 measures (β: −1.08, 95% CI: −1.87, −0.29 for Stroop; and β: 1.34, 95% CI: 0.22, 2.46 for DSST). Cumulative FVC followed a similar pattern, and was associated with better cognition in Model 3 with the same 2 measures (β: −0.82, 95% CI: −1.48, −0.16 for Stroop and β: 0.96, 95% CI: 0.02, 1.90 for DSST). Cumulative FEV_1/FVC ratio was only associated with better DSST in Models 1 and 2 (β: 9.30, 95% CI: 0.48, 18.11). Supplementary Table 7 shows our analysis of peak pulmonary function from Y0- to 20 and cognition at Y25 and Y30. Supplementary Table 8 shows our comparison of model fit statistics, with cumulative FEV_1 and FVC each offering modest improvements in model fit relative to their respective rates of decline, regardless of the measure of model fit or of cognition.

Discussion

In this study, we found small but robust associations between pulmonary function at various points during midlife and cognition measured in later midlife. Our cross-sectional associations were modest but consistent with other studies in older populations (25), while our longitudinal findings suggest that pulmonary function may be a useful predictor of cognition. Our findings on cumulative pulmonary function suggest a potentially longer-term relationship between pulmonary function and cognition than previously studied. This may provide useful information for future studies of cognition with repeated pulmonary function measurements and for testing potential mechanisms of this association. In contrast to prior studies of older and/or unwell individuals, our findings add new evidence in a relatively young and healthy population that reduced pulmonary function is a risk factor for later-life cognitive decline.

Our cross-sectional models identified modest associations between both FEV_1 and FVC and each measure of cognition. These are consistent with studies of clinical outcomes (26–28) and of FEV_1 and cognition throughout adulthood (29); our null findings with FEV1/FVC were also consistent with prior studies (25,30). One possible explanation for these findings is that overall pulmonary function, rather than obstructive or restrictive lung impairment specifically, may drive associations with cognition. This is consistent with similar findings regarding cognition and other breathing disorders such as sleep apnea (31) and poor respiratory muscle function (32). Thus, our findings suggest that pulmonary-associated cognitive declines can begin in midlife well before clinical lung disease, highlighting the importance of pulmonary function as a potential risk factor for cognitive impairment and the need to test it in at-risk populations.

In our study, the FEV_1/FVC rate of change was most strongly associated with the Stroop test, which measures executive function. Savage et al. observed that COPD patients experienced greater atrophy of brain regions associated with executive function as measured via MRI (33). However, this same study also found atrophy in a region associated with verbal memory, which in our study (as measured by the RAVLT) was not associated with change from peak pulmonary function. These and other findings (34,35) point to different domains of cognition being differentially associated with reduced pulmonary function in midlife. Future research should explore this possibility further and validate change from peak pulmonary function as a risk factor for reduced cognition.

Table 2. Cross-sectional Associations Between Pulmonary Function and Cognition at Y30

Cognition	N	FEV$_1$ (100 mL)		Raw FEV$_1$/FVC Ratio	
		β (95% CI)	P	β (95% CI)	P
Stroop					
Model 1	2 961	−0.19 (−0.28, −0.11)	<.01*	−3.83 (−9.41, 1.75)	.18
Model 2	2 932	−0.17 (−0.25, −0.08)	<.01*	−0.55 (−6.28, 5.18)	.85
Model 3	2 850	−0.10 (−0.19, −0.02)	.02*	0.62 (−5.28, 6.52)	.84
RAVLT					
Model 1	3 021	0.05 (0.03, 0.06)	<.01*	1.26 (0.37, 2.15)	.01*
Model 2	2 991	0.04 (0.02, 0.05)	<.01*	0.54 (−0.37, 1.45)	.25
Model 3	2 907	0.02 (0.01, 0.04)	<.01*	0.32 (−0.59, 1.23)	.49
DSST					
Model 1	3 019	0.43 (0.3, 0.56)	<.01*	7.65 (−1.14, 16.4)	.09
Model 2	2 989	0.37 (0.24, 0.5)	<.01*	0.86 (−8.14, 9.86)	.85
Model 3	2 902	0.20 (0.07, 0.33)	<.01*	−3.36 (−12.54, 5.81)	.45

Notes: CI = confidence interval; DSST = digit symbol substitution test; FEV$_1$ = forced expiratory volume in 1 s; FVC = forced vital capacity; RAVLT = Rey-Auditory Verbal Learning Test.

*Statistically significant at $p < .05$. Beta coefficients represent the average change in raw cognition score associated with each 100-mL increase in FEV$_1$ and each one-unit increase in FEV$_1$/FVC ratio.

Model 1: Adjusted for age at Y30, sex, race, center, and height.

Model 2: Additionally adjusted for smoking status.

Model 3: Additionally adjusted additionally for education, income, weight, physical activity, chronic obstructive pulmonary disease (yes/no), stroke or transient ischemic attack (yes/no), asthma (yes/no), and hypertension (yes/no).

Table 3. Longitudinal Associations Between Annual Pulmonary Function Change From Peak to Y20 and Cognitive Function at Y25 and Y30

Cognition	N	FEV$_1$ (100 mL/y)		FVC (100 mL/y)		Raw FEV$_1$/FVC Ratio	
		β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Stroop							
Model 1	3 144	−3.07 (−4.88, −1.26)	<.01*	−2.21 (−3.74, −0.68)	<.01*	−248.46 (−364.42, −132.49)	<.01*
Model 2	3 136	−2.73 (−4.54, −0.92)	<.01*	−2.02 (−3.55, −0.50)	<.01*	−218.57 (−334.92, −102.21)	<.01*
Model 3	3 105	−0.58 (−2.40, 1.25)	.54	−0.22 (−1.77, 1.34)	.79	−198.83 (−315.19, −82.48)	<.01*
RAVLT							
Model 1	3 144	0.66 (0.35, 0.97)	<.01*	0.59 (0.33, 0.86)	<.01*	15.61 (−4.63, 35.84)	.13
Model 2	3 136	0.58 (0.27, 0.89)	<.01*	0.54 (0.28, 0.80)	<.01*	11.57 (−8.62, 31.76)	.26
Model 3	3 105	0.23 (−0.08, 0.54)	.14	0.26 (0.00, 0.52)	.05	0.46 (−19.24, 20.16)	.96
DSST							
Model 1	3 144	9.49 (6.81, 12.18)	<.01*	6.02 (3.72, 8.31)	<.01*	420.11 (247.02, 593.19)	<.01*
Model 2	3 136	8.39 (5.73, 11.05)	<.01*	5.48 (3.21, 7.74)	<.01*	345.74 (173.68, 517.81)	<.01*
Model 3	3 105	4.31 (1.71, 6.91)	<.01*	2.26 (0.04, 4.49)	.046*	193.83 (27.06, 360.60)	.02*

Notes: CI = confidence interval; DSST = digit symbol substitution test; FEV$_1$ = forced expiratory volume in 1 s; FVC = forced vital capacity; RAVLT = Rey-Auditory Verbal Learning Test.

Linear mixed models were used to model cognitive function at both Y25 and Y30.

*Statistically significant at $p < .05$. Beta coefficients represent the average change in raw cognition score associated with each 100 mL/y average annual change of FEV$_1$ and FVC, and each 1-unit/year average annual change in FEV$_1$/FVC ratio.

Model 1: Adjusted for peak pulmonary function as well as age at cognitive exam, sex, race, center, and height.

Model 2: Additionally adjusted for smoking status.

Model 3: Additionally adjusted for education, income, weight, physical activity, chronic obstructive pulmonary disease (yes/no), stroke or transient ischemic attack (yes/no), asthma (yes/no), and hypertension (yes/no).

Finally, we identified associations between cumulative FEV$_1$ and cognition. Prior longitudinal studies, including a meta-analysis, found associations between midlife pulmonary function and later-life cognition (36). While cumulative FEV$_1$ was less strongly associated with cognition than cross-sectional or rate of change in FEV$_1$, associations with all 3 cognition measures persisted even in fully adjusted models for cumulative pulmonary function but not rate of change. Thus, both measures may serve complimentary roles, with rate of change offering a more clinically actionable biomarker while cumulative pulmonary function may provide useful information for long-term preventive care even in the presence of competing risks (ie, confounding factors). Little is known about the effects of chronic reduced pulmonary function on cognition in the absence of lung disease, but one study suggested white matter damage in COPD cases (37). Alternatively, this relationship may be similar to the cumulative damage done to the cardiovascular system by, for example, chronic elevated blood pressure or other cardiovascular conditions that might affect brain oxygenation, or oxidative damage induced through systemic inflammation. Cumulative FEV$_1$/FVC ratio was associated with DSST only, only in Models 1 and 2. As this measure is difficult to interpret, future

Table 4. Annualized Longitudinal Associations Between Cumulative FEV_1 and Cumulative FVC from Y0 to Y20 and Y25 to Y30 Cognition

Cognition	N	Cumulative FEV_1 (100 mL/y)		Cumulative FVC (100 mL/y)		Cumulative raw FEV1/FVC ratio (per y)	
		β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Stroop							
Model 1	2 985	−0.17 (−0.25, −0.09)	<.001*	−0.12 (−0.19, −0.05)	<.001*	−4.00 (−9.94, 1.97)	0.19
Model 2	2 978	−0.16 (−0.24, −0.08)	<.001*	−0.12 (−0.19, −0.05)	<.001*	−1.62 (−7.62, 4.37)	0.60
Model 3	2 949	−0.11 (−0.19, −0.03)	.007*	−0.08 (−0.15, −0.02)	.01*	−0.44 (−6.38, 5.50)	0.88
RAVLT							
Model 1	2 985	0.02 (0.01, 0.04)	<.001*	0.02 (0.01, 0.03)	.006*	0.73 (−0.30,1.77)	0.17
Model 2	2 978	0.02 (0.01, 0.04)	.003*	0.02 (0.00, 0.03)	.007*	0.38 (−0.66,1.42)	0.47
Model 3	2 949	0.01 (0.00, 0.02)	.12	0.01 (0.00, 0.02)	.14	0.06 (−0.94,1.06)	0.90
DSST							
Model 1	2 985	0.29 (0.17, 0.41)	<.001*	0.18 (0.08, 0.28)	.0006*	14.67 (5.81,23.52)	<.01*
Model 2	2 978	0.25 (0.14, 0.37)	<.001*	0.18 (0.08, 0.28)	.0004*	9.30 (0.48,18.11)	.04*
Model 3	2 949	0.13 (0.02, 0.25)	.02*	0.10 (0.00, 0.19)	.04*	4.86 (−3.56,13.28)	.26

Notes: CI = confidence interval; DSST = digit symbol substitution test; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; RAVLT = Rey-Auditory Verbal Learning Test.

*Statistically significant at $p < .05$. Beta coefficients represent the average change in raw cognition score associated with each 100 mL/y increase in annualized cumulative FEV_1 and FVC.

Model 1: Adjusted for age at cognitive exam, sex, race, center, and height.

Model 2: Additionally adjusted for smoking status.

Model 3: Additionally adjusted for education, income, weight, physical activity, chronic obstructive pulmonary disease (yes/no), stroke or transient ischemic attack (yes/no), asthma (yes/no), and hypertension (yes/no).

research using more detailed measures of pulmonary function may help shed light on its associations (if any) with cognition. If validated, these findings demonstrate that interventions to improve pulmonary function could be useful even at younger ages for preventing cognitive decline. These findings also inform studies of exposures that affect pulmonary function (eg, pollution, smoking); previous cross-sectional studies have found that the pulmonary function–cognition link tended to be independent of known confounding variables. This may be due to earlier exposures that influence cumulative pulmonary function and in so doing affect later-life pulmonary function and cognition. Future research should likewise explore this possibility.

This study is subject to several limitations of note. First, although CARDIA was designed to be representative of the United States, it is geographically limited to 4 study sites and only 2 racial subpopulations. Our findings should be validated in additional diverse populations. However, in general, our findings did not differ substantially across race and sex strata. Further replication of these associations is warranted, particularly for subgroups not represented in CARDIA. Second, cognition was only assessed via 3 instruments. Other domains of cognition, as well as risk of dementia and other forms of cognitive impairment, were beyond the scope of this study. Also, the small associations identified may not readily translate into a clinically significant risk factor; additional longitudinal studies of populations with diagnosed cognitive impairment will help place these results in their clinical context. Third, our analysis of annualized rate of pulmonary function assumed a linear relationship between it and cognition. While this was necessary due to the structure of our data and scope of this study, future research should explore possible nonlinear relationships. Finally, the lack of cognitive assessments prior to Y25 limits our ability to draw inferences on longer-term patterns of cognition as they relate to changes in longitudinal pulmonary function. This, coupled with the observational study design, limit the ability of this study to infer a causal relationship between pulmonary function and cognition. Future research in larger, more diverse cohorts with pulmonary and cognition measures spanning a longer time period and a greater range of potential exposures, mediators, and confounders is necessary to establish a causal relationship.

Our results suggest that poorer pulmonary function during may be associated with later cognition. We confirmed cross-sectional associations between pulmonary function and cognition in a younger, healthier population and identified multiple prospective associations. These findings add new longitudinal evidence to the hypothesis that pulmonary function affects cognition (rather than the reverse) and highlight the importance of addressing pulmonary function at younger ages. Our findings also suggest that studies and interventions targeting lung function decline be implemented at younger ages, before clinical symptoms, to potentially help forestall declines in cognition. Maintaining pulmonary function at or close to peak may be particularly useful for preventing or delaying cognitive impairment at older ages, conversely cumulative pulmonary function may serve as a better biomarker of cognitive risks in younger (ie, middle aged and older) populations. If validated in additional populations, pulmonary function may be a clinically useful risk factor for reduced cognition in clinical settings and future research. Studies should also examine the utility of pulmonary function interventions for improving cognitive impairment.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Author Contribution

B.T.J. designed the study, led the analysis, and prepared the manuscript. X.C., T.G., and Y.Z. conducted data analysis and assisted with manuscript preparation. B.E.H., K.M.K., and L.H. assisted with study design, data analysis, and manuscript preparation. K.Y., R.K., G.W., B.T., M.G., D.R.J., D.L.-J., K.L., and S.S. assisted with data collection and manuscript preparation.

Conflict of Interest

None declared.

References

1. Ortman JM, Velkoff VA, Hogan H. *An Aging Nation: The Older Population in the United States*. Washington, DC: United States Census Bureau, Economics and Statistics Administration, US Department of Commerce; 2014.

2. Petrini M, Cirulli F, D'Amore A, Masella R, Venerosi A, Carè A. Health issues and informal caregiving in Europe and Italy. *Ann Ist Super Sanita*. 2019;55(1):41–50. doi:10.4415/ANN_19_01_08

3. Hohman TJ, Tommet D, Marks S, Contreras J, Jones R, Mungas D; Alzheimer's Neuroimaging Initiative. Evaluating Alzheimer's disease biomarkers as mediators of age-related cognitive decline. *Neurobiol Aging*. 2017;58:120–128. doi:10.1016/j.neurobiolaging.2017.06.022

4. Tolea MI, Chrisphonte S, Galvin JE. Sarcopenic obesity and cognitive performance. *Clin Interv Aging*. 2018;13:1111–1119. doi:10.2147/CIA.S164113

5. Emery CF, Finkel D, Pedersen NL. Pulmonary function as a cause of cognitive aging. *Psychol Sci*. 2012;23(9):1024–1032. doi:10.1177/0956797612439422

6. Bors M, Tomic R, Perlman DM, Kim HJ, Whelan TP. Cognitive function in idiopathic pulmonary fibrosis. *Chron Respir Dis*. 2015;12(4):365–372. doi:10.1177/1479972315603552

7. Somaini G, Stamm A, Müller-Mottet S, et al. Disease-targeted treatment improves cognitive function in patients with precapillary pulmonary hypertension. *Respiration*. 2015;90(5):376–383. doi:10.1159/000439227

8. Parekh PI, Blumenthal JA, Babyak MA, et al.; INSPIRE Investigators. Gas exchange and exercise capacity affect neurocognitive performance in patients with lung disease. *Psychosom Med*. 2005;67(3):425–432. doi:10.1097/01.psy.0000160479.99765.18

9. Dodd JW, Getov SV, Jones PW. Cognitive function in COPD. *Eur Respir J*. 2010;35(4):913–922. doi:10.1183/09031936.00125109

10. Singh-Manoux A, Fau-Singh-Manoux A, Dugravot A, et al. Association of lung function with physical, mental and cognitive function in early old age. *Age (Dordrecht, Netherlands)*. 2011;33(3):385–392. doi:10.1007/s11357-010-9189-x

11. Gülhan PY, Bulcun E, Gülhan M, Çimen D, Ekici A, Ekici M. Low cognitive ability in subjects with bronchiectasis. *Respir Care*. 2015;60(11):1610–1615. doi:10.4187/respcare.03905

12. Vega JN, Newhouse PA. Mild cognitive impairment: diagnosis, longitudinal course, and emerging treatments. *Curr Psychiatry Rep*. 2014;16(10):490. doi:10.1007/s11920-014-0490-8

13. Jackson B, Kubzansky LD, Cohen S, Weiss S, Wright RJ; CARDIA Study. A matter of life and breath: childhood socioeconomic status is related to young adult pulmonary function in the CARDIA study. *Int J Epidemiol*. 2004;33(2):271–278. doi:10.1093/ije/dyh003

14. Angevaren M. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Lib*. 2008;3:1. doi:10.1002/14651858.CD005381.pub3

15. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol*. 1988;41(11):1105–1116. doi:10.1016/0895-4356(88)90080-7

16. Bancks MP, Carnethon MR, Jacobs DR Jr, et al. Fasting glucose variability in young adulthood and cognitive function in middle age: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Diabetes Care*. 2018;41(12):2579–2585. doi:10.2337/dc18-1287

17. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935;18:643. doi:10.1037/h0054651

18. Rosenberg SJ, Ryan JJ, Prifitera A. Rey Auditory-Verbal Learning Test performance of patients with and without memory impairment. *J Clin Psychol*. 1984;40(3):785–787. doi:10.1002/1097-4679(198405)40:3<785::aid-jclp2270400325>3.0.co;2-4

19. Wechsler D. *The measurement of adult intelligence*. Williams & Wilkins Co, Baltimore, MD, 1939. doi:10.1037/10020-000; 1939

20. Cuttica MJ, Colangelo LA, Dransfield MT, et al. Lung function in young adults and risk of cardiovascular events over 29 years: the CARDIA study. *J Am Heart Assoc*. 2018;7(24):e010672. doi:10.1161/JAHA.118.010672

21. Miller MR, Crapo R, Hankinson J, et al.; ATS/ERS Task Force. General considerations for lung function testing. *Eur Respir J*. 2005;26(1):153–161. doi:10.1183/09031936.05.00034505

22. Jacobs DR Jr, Hahn LP, Haskell WL, Pirie P, Sidney S. Validity and reliability of short physical activity history: CARDIA and the Minnesota Heart Health Program. *J Cardiopulm Rehabil*. 1989;9(11):448–459. doi:10.1097/00008483-198911000-00003

23. Dubbert PM, Carithers T, Ainsworth BE, Taylor HA Jr, Wilson G, Wyatt SB. Physical activity assessment methods in the Jackson Heart Study. *Ethn Dis*. 2005;15(4 Suppl 6):S6–56.

24. Bush A. Lung development and aging. *Ann Am Thorac Soc*. 2016;(13 Suppl 5):S438–S446. doi:10.1513/AnnalsATS.201602-112AW

25. Cahana-Amitay D, Lee LO, Spiro A 3rd, Albert ML. Breathe easy, speak easy: pulmonary function and language performance in aging. *Exp Aging Res*. 2018;44(5):351–368. doi:10.1080/0361073X.2018.1521374

26. Aiken-Morgan AT, Gamaldo AA, Wright RS, Allaire JC, Whitfield KE. Stability and change in cognitive status classification of black older adults. *J Am Geriatr Soc*. 2018;66(1):179–183. doi:10.1111/jgs.15225

27. Lutsey PL, Chen N, Mirabelli MC, et al. Impaired lung function, lung disease and risk of incident dementia. *Am J Respir Crit Care Med*. 2018;199(11):1385–1396. doi:10.1164/rccm.201807-1220OC

28. Yoon S, Kim JM, Kang HJ, et al. Associations of pulmonary function with dementia and depression in an older Korean population. *Psychiatry Investig*. 2015;12(4):443–450. doi:10.4306/pi.2015.12.4.443

29. Anstey KJ, Windsor TD, Jorm AF, Christensen H, Rodgers B. Association of pulmonary function with cognitive performance in early, middle and late adulthood. *Gerontology*. 2004;50(4):230–234. doi:10.1159/000078352

30. Vasilopoulos T, Kremen WS, Grant MD, et al. Individual differences in cognitive ability at age 20 predict pulmonary function 35 years later. *J Epidemiol Community Health*. 2015;69(3):261–265. doi:10.1136/jech-2014-204143

31. Jackson ML, Howard ME, Barnes M. Cognition and daytime functioning in sleep-related breathing disorders. *Prog Brain Res*. 2011;190:53–68. doi:10.1016/B978-0-444-53817-8.00003-7

32. Hashim NA, Ismail NA, Emad EM. Evolving relationship between respiratory functions & impairment in sleep and cognition in patients with multiple sclerosis. *Mult Scler Relat Disord*. 2020;46:102514. doi:10.1016/j.msard.2020.102514

33. Savage CC, Dixey PHA, Pennington C, Dodd JW. Visual rating assessment of cerebral atrophy and its relationship with cognitive function in chronic obstructive pulmonary disease. *BMJ Open Respir Res*. 2018;5(1):e000310. doi:10.1136/bmjresp-2018-000310

34. Vidal JS, Aspelund T, Jonsdottir MK, et al. Pulmonary function impairment may be an early risk factor for late-life cognitive impairment. *J Am Geriatr Soc*. 2013;61(1):79–83. doi:10.1111/jgs.12069

35. Finkel D, Reynolds CA, Emery CF, Pedersen NL. Genetic and environmental variation in lung function drives subsequent variation in aging of fluid intelligence. *Behav Genet*. 2013;43(4):274–285. doi:10.1007/s10519-013-9600-3

36. Duggan EC, Piccinin AM, Clouston S, et al. A multi-study coordinated meta-analysis of pulmonary function and cognition in aging. *J Gerontol A Biol Sci Med Sci*. 2019;74(11):1793–1804. doi:10.1093/gerona/glz057

37. Dodd JW, Chung AW, van den Broek MD, Barrick TR, Charlton RA, Jones PW. Brain structure and function in chronic obstructive pulmonary disease: a multimodal cranial magnetic resonance imaging study. *Am J Respir Crit Care Med*. 2012;186(3):240–245. doi:10.1164/rccm.201202-0355OC