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ORIGINAL CONTRIBUTIONS

Pulmonary Function Measures as Predictors and Correlates of Cognitive Functioning in Later Life

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The relation between pulmonary function and cognitive functioning was investigated in a cohort of 3,036 Japanese-American men living in Hawaii. Pulmonary function, as indicated by forced expiratory volume in 1 second (FEV_1), was measured at the baseline examination from 1965 to 1968. Cognitive function was assessed by the Cognitive Abilities Screening Instrument (CASI) test at least 23 years later (1991–1993). Baseline FEV_1 was significantly correlated with follow-up CASI score ($r = 0.22$, $p = 0.0001$). Although the strength of the association was reduced by controlling for the effects of other factors, stepwise multiple linear regression showed that FEV_1 during middle age was a significant predictor of CASI in later life, after taking into account the effects of age, education, stroke, sedentary job activity, nonmanual occupation, height, generation, and Japanese speaking ability. The mean CASI value was significantly greater for men whose FEV_1 exceeded 2.8 liter compared with those whose FEV_1 levels were in the lowest (<2.5 liters) quartile. Furthermore, the test on the effect of interaction between FEV_1 and age was statistically significant ($p = 0.0024$), with subjects less than 55 years of age at the baseline examination showing a stronger direct association of FEV_1 with CASI than the men aged 55 or older. These findings suggest that pulmonary function impairment may be associated with cognitive function impairment in later life. *Am J Epidemiol* 1996;143:750–6.

aging; cognition; forced expiratory volume

It is widely accepted that increasing age (1, 2) and lower educational level (1, 2) are associated with poor performance on tests of cognitive function in older adults. Although dementing illnesses become progressively more common in later life, a large part of the decline in test performance that occurs after age 65 is presumed to be due either to normal aging or to health conditions other than dementia (3, 4).

Very little information exists regarding the possible influence of diseases, health, or general vigor in early or middle life on cognitive function in late life. Efforts to identify predictors of cognitive function in late life have been remarkably unfruitful (1). Exceptions are a history of prior stroke (strongly associated with a greater prevalence of cognitive impairment) and long-standing hypertension (1, 5–7). It has been reported that physically fit elderly adults experienced less profound declines in cognitive function than their less fit contemporaries (8). Although a recent cross-sectional study suggested that previous cardiovascular disease was directly associated with cognitive function impairment independent of the effects of age and education (9), others have failed to demonstrate a significant relation between prior myocardial infarction and late life cognitive impairment (10, 11).

It is intuitively reasonable to expect that health conditions associated with chronic or repeated brain hypoxia might lead to a gradual deterioration of neural integrity and neuropsychological functioning. Consistent with this expectation, some studies (12, 13) have found that deterioration of cognitive performance correlated significantly with nocturnal breathing difficulties, including apnea and hypopnea. Other studies (14, 15) showed that cognitive dysfunction was more com-

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Abbreviations: CASI, Cognitive Abilities Screening Instrument; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second.

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mon in patients with hypoxemic or polycythemic chronic obstructive pulmonary disease (COPD) compared with subjects without COPD. These findings suggest that poor pulmonary function may be directly or indirectly related to impaired cognitive functioning because there is a strong correlation between impaired pulmonary function and COPD (16, 17) or specific respiratory symptoms such as persistent wheeze, chronic cough, chronic phlegm, or dyspnea (18).

Direct attempts to examine relations between pulmonary function and cognitive functioning in the absence of overt disease have been rare. Results from one epidemiologic study conducted in older, community-dwelling residents of East Boston, Massachusetts, indicated a positive ($p < 0.0001$) relation between cognitive function and peak expiratory flow rate (19). We have found no reports linking pulmonary function in middle adult life to level of cognitive function in late life.

The present study was conducted to investigate the relation of pulmonary function (the forced expiratory volume in 1 second (FEV_1)) measured in 1965–1968 to cognitive function at least 23 years later (1991–1993) among Japanese-American men in Hawaii who participated in the Honolulu Heart Program. Analyses are presented that address the hypothesis that midlife pulmonary functioning may be a risk factor for one or more aging-related processes leading to declines in level of cognitive functioning in late life.

MATERIALS AND METHODS

The subjects for this study are American men of Japanese ancestry, born in the years 1900–1919 and residing on the Hawaiian island of Oahu. They were first identified by the Honolulu Heart Program in 1965 with use of the comprehensive 1942 Selective Service registration files (20). Of the 11,148 identified men, 8,006 (71.8 percent) were interviewed and examined from 1965 to 1968, 180 (1.6 percent) died before they could be examined, and 2,962 (26.6 percent) did not participate in the program.

At the baseline examination (1965–1968), spirometry was performed on a water seal recording spirometer (Respiratory Vitalometer Model P-600; Warren E. Collins, Inc., Boston, Massachusetts) with subjects standing and without noseclips. Each man performed three spirometric tests at examination. Because standards for calculating FEV_1 from spirometric curves have changed since pulmonary function was measured in this cohort, all spirograms were reanalyzed using modified American Thoracic Society standards that included back-extrapolation, correction for body temperature, pressure, and saturation with water vapor, and the use of a computer-linked digitizer (21). Spirograms were assessed for technical acceptability using specific objective criteria (smooth and continuous curve, apparent maximal effort, good start, and no evidence of the following: false starts, excessive hesitation, coughing, glottis closure, early termination, leaks, or obstructed mouthpiece). Measures of forced vital capacity were rejected because very few met the criteria of 6 seconds' duration.

Analyses presented here utilize the following risk factor information collected at baseline in 1965–1968: age and date of birth, education, cigarette smoking history, systolic and diastolic blood pressures, weight, standing height, subscapular skinfold thickness, amount and type of physical activity, present occupation, generation, number of years lived in Japan, Japanese language skills, hematocrit level, and total caloric intake. Body mass index was calculated as weight/height^2. The physical activity index was calculated from answers to questions concerning work and recreational activities, as previously described (22). The history of prior stroke was determined by the Honolulu Heart Program surveillance up to the end of 1993 according to the criteria outline in the earlier study (23). Two definitions were used to identify subjects with the history of prior COPD at the 1991–1993 examination—symptoms of chronic bronchitis (cough and phlegm for 3 or more months of the year lasting 2 or more years) and emphysema diagnosed by a physician and reported by the subject, consistent with a previous study (24).

A total of 3,844 (80 percent of survivors) of the initially examined men returned for reexamination between 1991 and 1993. During the subsequent interview, information was collected on the subject's history of cerebrovascular and cardiovascular disease, and the Cognitive Abilities Screening Instrument (CASI) was successfully administered to 3,734 men. Contents of the CASI have been described in detail elsewhere (25). Briefly, the CASI has a score range of 0–100 and provides quantitative assessment on attention, concentration, orientation, short-term memory, long-term memory, language abilities, visual construction, list-generating fluency, abstraction, and judgment. A Japanese language version was used for study participants who were not fully comfortable with the English language version. A total of 698 men who were reexamined but did not have FEV_1 measures at the first examination were excluded from the analysis. The remaining men totaled 3,036.

Due to the skewed distribution of CASI measurements (most of the values were on the high end, as shown in figure 1), Spearman nonparametric correlations (26) were used to examine the relation between specific lifestyle risk factor variables and CASI. Be-

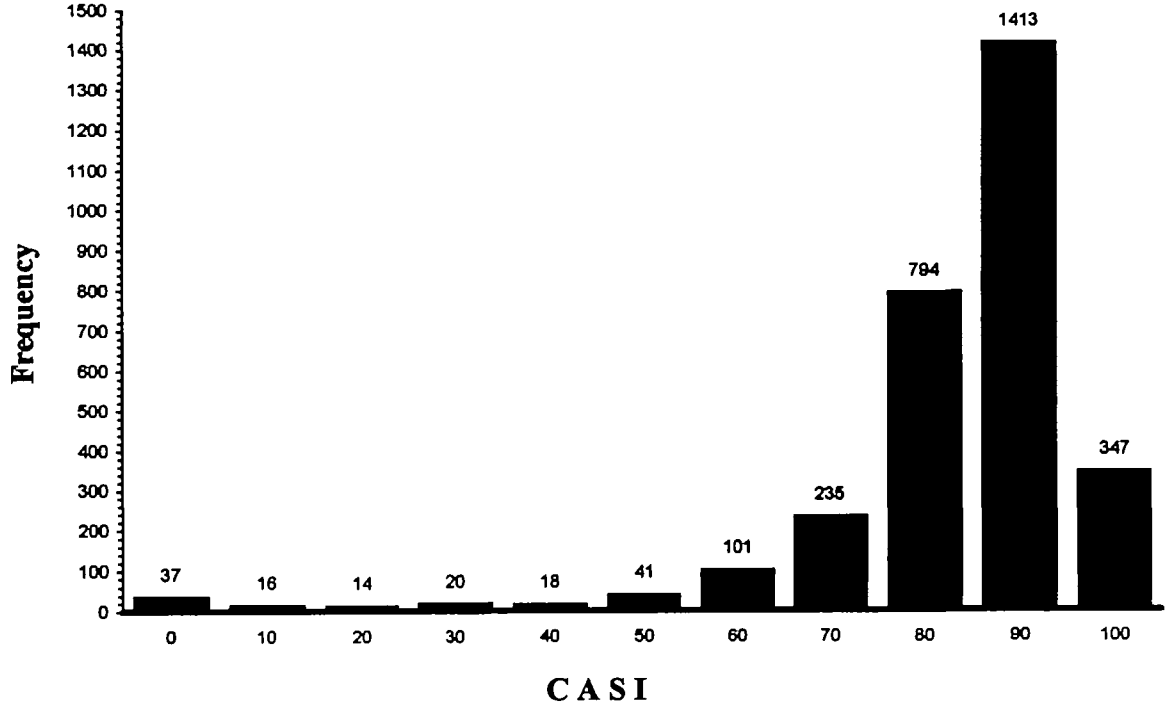

FIGURE 1. Distribution of Cognitive Abilities Screening Instrument (CASI) scores of Japanese-American men who participated in the Honolulu Heart Program in 1965–1968.

cause the distribution of CASI scores was skewed, we considered several transformations using $(CASI)^2$ or $(CASI)^3$, which resulted in a more (approximately) normal distribution for statistical tests. Stepwise multiple linear regression analysis (27) was performed to determine whether FEV_1 along with other explanatory variables were significantly ($p < 0.05$) related to the CASI score. Some of the explanatory variables were selected because of known association with cognitive functioning, e.g., age, education, physical activity, blood pressure, and history of prior stroke. Others (e.g., height, smoking, generation) were selected because of a plausible association with some aspect of brain structure, function, disease, or aging. Means of CASI scores were then calculated according to quartile of FEV_1, with adjustment for other significant predictors of CASI resulting from the stepwise selection. Adjustment for covariates was done using one-way unbalanced analyses of covariance (28). Similar analyses were performed using stratification by age at initial examination to test for the possible effect of interaction between age and FEV_1 on CASI scores.

Our analyses showed that the relation between FEV_1 and CASI was not significantly altered by the power transformations of CASI compared with the untransformed CASI. For ease of interpretation, we reported only the results using untransformed CASI scores.

RESULTS

In table 1, the means of specific lifestyle characteristics for participants and for nonparticipants are summarized. Compared with the participants, nonparticipants were significantly ($p < 0.05$) older and shorter and reported having smoked for fewer total years. There were no significant differences in other characteristics for the two groups.

Spearman correlation coefficients (r) for CASI score (1991–1993 examination) and FEV_1 and other specific lifestyle characteristics (1965–1968 examination) are presented in table 2. FEV_1 was positively correlated with CASI score ($r = 0.22$, $p = 0.0001$). In addition, education, hours spent in sedentary activity, weight, height, subscapular skinfold thickness, hematocrit level, and total daily caloric intake (all determined at the baseline examination) were each significantly and positively correlated with CASI. On the other hand, there were significantly negative associations between CASI score and age, years smoked, systolic blood pressure, physical activity index, various types of daily physical activity (with the exception of sedentary type), and years lived in Japan.

To explore the relations between CASI and FEV_1, we performed a stepwise multiple linear regression analysis employing age, education, occupation, blood pressure, and other selected sociodemographic and

TABLE 1. Age-adjusted means of specific lifestyle characteristics of male Japanese-American participants and nonparticipants ascertained at baseline examination, Honolulu Heart Program, 1965–1968

Characteristics	Participants† (n = 3,036)	Nonparticipants (n = 808)
Age (years)—unadjusted	52.5	53.6*
FEV_1‡ (liters)	2.82	2.82§
Education (years)	10.5	10.3
Nonmanual occupation (%)	46	44
Smokers (%)	68	65
Cigarettes/day	18.3	17.8
Years smoked	19.6	18.3*
Systolic blood pressure (mmHg)	130.2	129.6
Diastolic blood pressure (mmHg)	81.4	81.1
Physical activity index	32.9	32.9
Weight (kg)	63.9	63.8
Height (m)	1.634	1.627*
Body mass index (kg/m²)	23.9	24.0
Subscapular skinfold (cm)	16.6	16.6
Years lived in Japan	1.7	2.0
Speak Japanese (%)	84	86
Read/write Japanese (%)	33	35
Hematocrit level	44.7	44.6
Total caloric intake	2,359	2,343
CHD‡ prevalence (%)	16	18
Stroke prevalence (%)	6	4

* $p < 0.05$.
† Referent group for mean comparison.
‡ FEV_1, forced expiratory volume in 1 second; CHD, coronary heart disease.
§ Only 89 nonparticipants had FEV_1 values measured at baseline examination.

TABLE 2. Spearman's correlation coefficients between CASI† score (ascertained in 1991–1993) and other variables of Japanese-American men who participated in the Honolulu Heart Program, 1965–1968

	CASI	FEV_1†
FEV_1 (liters)	0.22*	1.00
Age (years)	−0.33*	−0.26*
Education (years)	0.44*	0.15*
Cigarettes/day	−0.02	−0.10*
Years smoked	−0.09*	−0.15*
Systolic blood pressure (mmHg)	−0.09*	−0.12*
Diastolic blood pressure (mmHg)	−0.02	−0.04*
Physical activity index	−0.23*	−0.04*
On-job physical activity/day	−0.23*	−0.07*
Off-job physical activity/day	−0.04*	−0.02
Hours spent in no activity/day	−0.06*	−0.01
Hours spent in sedentary activity/day	0.24*	0.05*
Hours spent in slight activity/day	−0.05*	−0.03
Hours spent in moderate activity/day	−0.20*	−0.02
Hours spent in heavy activity/day	−0.07*	−0.02
Weight (kg)	0.14*	0.19*
Height (m)	0.23*	0.43*
Body mass index (kg/m²)	0.03	−0.03
Subscapular skinfold (cm)	0.06*	−0.09*
Years lived in Japan	−0.13*	−0.01
Hematocrit level	0.05*	−0.04*
Total caloric intake	0.07*	0.09*

* $p < 0.05$.
† CASI, Cognitive Abilities Screening Instrument; FEV_1, forced expiratory volume in 1 second.

lifestyle characteristics as independent variables, with CASI score as the dependent variable. The results from this analysis are shown in table 3. Of the 32 predictor variables examined, only FEV_1, age, education, prior stroke (at the time of CASI testing), nonmanual occupation, hours spent in sedentary activity, height, generation, and Japanese speaking ability were significantly ($p < 0.05$) associated with CASI score. Also shown in table 3 is that on the average, the CASI score would be expected to increase 1.39 units for every 1-liter increase in FEV_1, provided that other predictor variables are held constant. By comparison, 10 years of age would be associated with a change of 7 CASI score units and 6 years of education, with a change of 6 CASI score units. Some of these 32 variables were highly correlated, e.g., cigarettes/day and years of smoking ($r = 0.72$), systolic and diastolic blood pressures ($r = 0.79$), physical activity index and hours spent in moderate ($r = 0.90$) or sedentary ($r = -0.79$) activity, and body mass index and body weight ($r = 0.85$) or subscapular skinfold thickness ($r = 0.70$). However, separate consideration for these variables in the stepwise linear regression models did not meaningfully alter the results.

In table 4, the means of CASI scores according to quartile of FEV_1 are shown. We observed a significantly greater mean CASI for subjects whose FEV_1 exceeded 2.8 liter compared with those whose FEV_1 levels were in the lowest (<2.5 liter) quartile. In addition, the overall linear trend in mean CASI score by FEV_1 quartiles was statistically significant ($p = 0.0001$). This positive relation persisted ($p = 0.029$) even after controlling for the effects of other predictors of CASI found in table 3.

The possible effect of interaction between FEV_1 and age on CASI was analyzed. The age boundary of 55 years was selected on the basis of the mean age (mean = 54 years, range = 45–68 years) at initial examination. A strong direct association of FEV_1 with CASI was present only for men younger than 55 years of age, as shown in table 5. These findings were confirmed by a statistically significant test for interaction between continuous FEV_1 and continuous age ($p = 0.0024$).

We also stratified our analyses by smoking status and found no significant interaction of smoking and FEV_1 with CASI score (data not shown).

TABLE 3. Stepwise multiple linear regression analysis of selected variables for predicting CASI† scores for Japanese-American men based on 1965–1968 data from the Honolulu Heart Program

Variable*	Beta coefficient	Standard error	p value
Intercept	90.80	7.59	0.0001
Age	−0.76	0.05	0.0001
Education	1.03	0.08	0.0001
Prevalence of stroke	−12.08	0.96	0.0001
Nisei generation	2.69	0.68	0.0001
Speak Japanese	−2.12	0.62	0.0006
FEV_1†	1.39	0.54	0.0106
Nonmanual occupation	1.29	0.51	0.0123
Hours spent in sedentary activity/day	0.20	0.08	0.0129
Height	0.25	0.11	0.0270

* Other variables considered in the stepwise regression analysis but not included in the final model were: smoking status (current vs. never, past vs. never), cigarettes/day, years smoked, pack-years of cigarettes smoked, systolic blood pressure, diastolic blood pressure, physical activity index, various types of daily physical activity (except sedentary type), body mass index, weight, subscapular skinfold, hematocrit level, years lived in Japan, read/write Japanese, total caloric intake, generation (kibei vs. issei), and prevalence of coronary heart disease at baseline or during the study period.

† CASI, Cognitive Abilities Screening Instrument; FEV_1, forced expiratory volume in 1 second.

DISCUSSION

Pulmonary function measured at least 23 years earlier was identified as an important predictor of cognitive function in elderly Japanese-American men. Compared with men who had normal or greater than normal pulmonary function, those who had the poorest FEV_1 (<2.5 liters) achieved a significantly lower CASI score. Although much of the association disappeared after other important factors were controlled for, there remained a significant direct association that was independent of age, education, occupation, history of prior stroke, generation, Japanese language skills, and height.

Our findings are in agreement with those of a cross-sectional study of 3,812 elderly (aged 65 years and older) men residing in East Boston (19). In that study, peak expiratory flow rate was strongly ($p < 0.0001$) and positively associated with each of the three simple measures of cognitive function, including performance on the Short Portable Mental Status Questionnaire and brief tests of immediate (story) memory and attention. To our knowledge, there have been no previous epidemiologic studies that have directly investigated midlife pulmonary function in relation to late life cognitive functioning.

The pathophysiologic and biologic mechanisms that could explain the effects of impaired pulmonary function on the subsequent development of cognitive function impairment are unclear. Some researchers support the commonsense notion that a cognitive disorder in subjects with severely impaired FEV_1 may be caused, at least in part, by insufficient oxygenation of brain tissue (14) because all neurochemical systems are oxygen dependent and some may be vulnerable to minor degrees of hypoxia. One study proposed that mild hypoxia impairs brain function because it adversely affects the metabolism of central neurotransmitters, including acetylcholine (29). In addition, it has been suggested that subjects with significantly low FEV_1 may suffer from COPD, lung cancer, heart disease, or other diseases that have the potential to compromise cerebral function. A study on the neuropsychological assessment of COPD found that the patients with COPD were more impaired in their cognitive ability than their healthy counterparts (14). Furthermore, a significant negative relation between hemoglobin and cognitive function impairment was also reported (14). A cross-sectional study conducted in the Netherlands showed that previous vascular events, presence of plaques in the carotid arteries, and peripheral arterial atherosclerotic disease were each associated with im-

TABLE 4. Mean CASI* scores by quartiles of FEV_1 for Japanese-American men based on 1965–1968 data from the Honolulu Heart Program

FEV_1 (liters)	No.	CASI		Covariate-adjusted† CASI	
		Mean ± SE	p value‡	Mean ± SE	p value§
<2.5	715	78.0 ± 0.6		82.4 ± 0.5	
2.5 to <2.8	701	81.6 ± 0.6	0.0001	83.4 ± 0.5	0.1414
2.8 to <3.1	831	84.8 ± 0.5	0.0001	84.6 ± 0.4	0.0007
≥3.1	789	85.9 ± 0.6	0.0001	83.6 ± 0.5	0.0834
p for trend		0.0001		0.0285	

* CASI, Cognitive Abilities Screening Instrument; FEV_1, forced expiratory volume in 1 second.

† Adjusted for age, education, prevalence of stroke, occupation (nonmanual vs. manual), hours spent in sedentary activity/day, height, generation, and Japanese speaking ability.

‡ To compare the two mean values by analysis of variance using the lowest FEV_1 quartile as reference.

§ Comparison of the two mean values by analysis of covariance using the lowest FEV_1 quartile as reference.

TABLE 5. Covariate-adjusted* mean CASI† values by quartiles of FEV_1† and age of Japanese-American men based on 1965–1968 data from the Honolulu Heart Program

FEV_1 (liters)	CASI					
	<55 years old			≥55 years old		
	No.	Mean ± SE	*p* value‡	No.	Mean ± SE	*p* value‡
<2.5	389	84.8 ± 0.5		301	76.0 ± 0.9	
2.5 to <2.8	478	85.5 ± 0.5	0.3004	200	77.2 ± 1.1	0.4122
2.8 to <3.1	615	86.8 ± 0.4	0.0032	192	78.7 ± 1.2	0.0714
≥3.1	657	86.5 ± 0.4	0.0131	116	75.5 ± 1.5	0.7901
p for trend		0.0035			0.9900	

* Adjusted for age, education, prevalence of stroke, occupation (nonmanual vs. manual), hours spent in sedentary activity/day, height, generation, and Japanese speaking ability.
† CASI, Cognitive Abilities Screening Instrument; FEV_1, forced expiratory volume in 1 second.
‡ Comparison of the two mean values by analysis of covariance using the lowest FEV_1 quartile as reference.

paired cognitive function (9). In the present study, however, the direct FEV_1-CASI relation persisted ($p = 0.02$) after excluding 107 men with COPD (chronic bronchitis or emphysema) at the time of CASI testing. Additional exclusion of subjects who had had lung cancer ($n = 14$), stroke ($n = 181$), and coronary heart disease ($n = 496$) at the time of CASI testing and adjustment for the effects of baseline hematocrit measurements did not affect our major findings. It is nonetheless possible that abnormal pulmonary function in midlife is associated with other yet unidentified clinically inapparent conditions associated with deterioration in cognitive function in late life.

Several methodological limitations may have influenced the results of this study. A total of 808 nonparticipants were excluded from the study because of missing data. It is not certain whether the FEV_1-CASI relation would become stronger or weaker if nonparticipants were included. However, compared with the participants, these men were older and shorter but smoked fewer cigarettes per day and for a shorter duration, as shown in table 1. There was no difference in FEV_1 between the two groups; however, the small number of nonparticipants who underwent pulmonary function testing makes proper evaluation difficult. As shown, age was inversely related to both cognitive function (1, 2) and FEV_1 (30).

Another possible bias involves an association of participation with survival and good health. This investigation included only 3,844 (80 percent of survivors) of 8,006 initially examined men inasmuch as the deaths of 3,201 men during the follow-up period precluded their examination. Our data showed that these nonsurviving men had lower age-adjusted mean FEV_1 (2.60 vs. 2.74 liters, respectively; $p = 0.0001$) and less education (10.14 vs. 10.31 years, $p = 0.02$) but greater mean age (56.7 vs. 53.2 years, $p = 0.0001$) and age-adjusted prevalence of stroke (17.4 vs. 4.8 percent, $p = 0.0001$) compared with the surviving men.

Because no cognitive function testing was done at baseline, there can be no certainty that the relation of late life CASI scores with midlife FEV_1 is not at least partly attributable to a lifelong association between poorer pulmonary functioning and poorer cognitive functioning. However, our data further indicated that the association between low pulmonary function and low CASI was much stronger for the younger (<55 years) age group than for the older age group. This finding can be partially explained by the association of FEV_1 with either age or total mortality or both. For example, in previous analyses reported from the Honolulu Heart Program, FEV_1 was inversely associated with age (30), whereas poor FEV_1 at baseline (31) or a decline in FEV_1 (32) was positively related to total mortality. Moreover, it is also possible that the lack of a statistically significant association between FEV_1 and CASI among the older age group might in part reflect the higher cohort attrition rate compared with the younger age group. Alternatively, it may be that declining cognitive function occurs as part of biologic aging, and this biologic aging process might emerge as a much more progressive pathologic alteration of cognitive function for men who suffered from pulmonary function impairment chronologically earlier in life (≤55 years old at baseline) than for those who suffered later. This idea represents the interesting possibility that accelerated aging of the lung might predict accelerated aging of the brain.

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