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Pulmonary Function Impairment May be An Early Risk Factor for Late-Life Cognitive Impairment

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Abstract

Background—Low pulmonary function (PF) is associated with poor cognitive function and dementia. There are few studies of change in PF in mid-life and late-life cognitive status.

Design and Participants—We studied this is 3,665 subjects from AGES-Reykjavik Study who had at least one measure of forced expiratory volume/ 1 sec (FEV_1) and were cognitively tested on average 23 years later. A subset of 1,281 subjects had two or three measures of FEV_1 acquired over a 7.8 year period. PF was estimated as $FEV_1/Height^2$. Rate of PF decline was estimated as the slope of decline over time. Cognitive status was measured with continuous scores of memory, speed of processing, and executive function, and as the dichotomous outcomes of mild cognitive impairment (MCI) and dementia.

Results—Lower PF measured in mid-life predicted lower memory, speed of processing, executive function, and higher likelihood of MCI and dementia 23 years later. Decrease of PF over a 7.8-year period in mid-life was not associated with lower cognitive function or dementia.

Conclusion—Reduced PF measured in mid-life may be an early marker of later cognitive problems. Additional studies characterizing early and late PF changes are needed.

Keywords

Cognition; Dementia; Forced Expiratory Volume; Longitudinal Cohort Studies

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INTRODUCTION

Poor pulmonary function leads to a reduced oxygen supply to the brain.[1,2] Lower pulmonary function (PF) has been correlated with poor cognitive performance in patient populations as well as in community dwelling subjects with a wide range of health status and ethnicities.[1–7] PF has also been shown to be consistently reduced in demented subjects in cross-sectional studies,[8] and is associated with a future risk for dementia.[9–11] These extant studies, based on one measure of PF, may well reflect the strong constitutional and early life environmental factors that affect PF.[12] There are few data on whether a decline in PF in mid-life also contributes to late-life cognitive test scores and risk for MCI and dementia. If change, in addition to level of PF, is also associated with cognition, this would strengthen the evidence that PF has a more direct effect on cognition. This is important to study as preventing poor PF with early interventions, such as education campaigns to stop smoking or increase physical activity, or by treating and preventing pulmonary diseases may reduce late-life cognitive impairment.

METHODS

The population-based AGES-RS study (2002–2006) cohort (5764 men and women) is based on surviving members of the Reykjavik Study initiated in 1967 by the Icelandic Heart Association to prospectively study cardiovascular disease in Iceland.[13] The Reykjavik Study included a random sample of men and women born between 1907 and 1935 and living in Reykjavik area. By design, sub-cohorts of subjects were examined from one to six times from 1967 to 1996.[13]

Pulmonary assessment at mid-life

PF was evaluated at each Reykjavik Study examination with Vitalograph Spirometers (Vitalograph Ltd., Buckingham, UK). The same equipment was used throughout the study and was regularly calibrated with a 1 liter syringe. Three attempts were recorded for each forced expiratory volume in 1 s (FEV_1). PF was calculated as FEV_1 divided by height squared of the subject, as this has been shown in this cohort to be a more stable predictor of outcomes than FEV_1 alone.[14] Height was taken at the time the first spirometry measure was acquired. In analyses using repeat measures of spirometry we used the same baseline height so $FEV_1/height^2$ did not appear to change because of a change in height.

Assessment of cognition, and dementia and MCI later in life (2002–2006)

Cognitive assessment in AGES-RS study has already been detailed.[15] In brief, we administered a battery of six different cognitive tests that included a modified version of the California Verbal Learning Test,[16] the Figure Comparison Test,[17] the Digit Symbol Substitution Test,[18] the Stroop Test,[19] a shortened version of the Cambridge Neuropsychological Test Automated Battery Spatial Working Memory test,[20] and the Digits Backward test.[18] From these tests, three cognitive domain composite Z-scores were calculated: memory, speed of processing and executive function.[15]

Dementia case ascertainment was a three-step process previously described[13] that included a screening based on the Mini-Mental State Examination and the Digit Symbol Substitution Test, a diagnostic neuropsychological test battery, an informant interview, and a neurological examination. A consensus diagnosis of dementia and MCI was made by a panel including a geriatrician, neurologist, neuropsychologist, and neuroradiologist. Dementia was classified according to DSM-IV criteria.[21] MCI was defined as having a borderline score (i.e.< −1.5 SD scores based on the distribution of scores in a cohort sub-sample) in at least

one cognitive domain or as having one abnormal test result in at least two other domains not severe enough to be classified as dementia.[22]

Potential confounding and moderating variables

In addition to age and sex, analyses were adjusted for factors associated with both PF and cognitive outcomes.[23] Variables measured concurrently with the first PF measure included education level (> high school yes/no), occupation (manual, intermediate and professional), BMI and moderate to vigorous physical activity in youth and midlife. Variables measured in the late-life exam concurrently with cognition included: presence of depressive symptoms measured by the 15-point Geriatric Depression Scale;[24] self-reported history of a doctor's diagnosis of coronary heart disease; chronic obstructive pulmonary disease (COPD); hypertension by doctor's report, use of anti-hypertensive medication, or measured systolic and diastolic blood pressure; diabetes by doctor's report, use of anti-diabetic drugs, or fasting glucose levels; and life-time history of smoking (never, former, current).

Based on previous reports we investigated whether presence of the Apolipoprotein E ε*4 allele,[25] a genetic susceptibility factor for dementia, modified the association of PF to dementia. Apolipoprotein E (Apo E) genotype was determined by standard DNA amplification and a restriction isotyping method.[26] Subjects were classified as having no Apo E ε4 alleles or having 1 or 2 Apo E ε4 alleles.

Analytical sample

We excluded baseline spirometry assessments made before March 1, 1976 (n=1,522) because, as described previously, there were a significant number of outlier measurements from that period;[14] measures made between 1991 and 1996 (n=51) by subjects who were older than 70 years of age;[13] subjects with no PF assessments (n=8), and those with incomplete cognitive data (n=518). These exclusions resulted in an analytical sample of 3,665 subjects with complete data on PF and cognitive status (see supplemental figure). Compared to subjects not included in the analysis, those included were younger, more likely to be women, were less likely to be depressed or smokers and more often had a manual occupation.

The 3,665 included 128 MCI and 288 demented subjects. Of the 3,665, 1,281 subjects (of which 1,151 were not demented or had MCI) had multiple PF assessments to estimate change in PF; 874 subjects had two and 407 had three assessments. Differences between those with one compared to those with multiple measures are shown in supplementary table 1. Analyses on cognitive domains included only subjects with no dementia or MCI (n=3,249 for the first PF assessment and n=1,151 for the change in PF); analyses on dementia and MCI included all subjects (n=3,665 for the first PF assessment and n=1,281 for the change in PF).

Statistical analysis

For the baseline analyses, descriptive comparisons and hypothesis testing were examined by quartile of PF, using analysis of variance or logistic regression. The change in PF was estimated by the coefficient of PF linearly regressed against age in each of the 1281 subjects who had at least two pulmonary assessments corresponding to the change in FEV_1 per year. The change results are expressed as the change in cognitive score, or likelihood of dementia or MCI associated with each standard deviation change in PF. All models were first adjusted for age and sex (Model 1) and then further adjusted for the aforementioned potential confounders (Model 2). We entered into model 1, the PF and Apo E ε4 main effect terms and their cross product to test the interaction between the two variables. Analyses were

conducted with the statistical software package SAS Version 9.1 (SAS Institute Inc., Cary, N.C., USA). In all analyses, the 2 sided α–level of 0.05 was considered significant

RESULTS

The sample of 3,665 subjects had a mean age of 76 years and 33 percent were male. Mean age at the first spirometry assessment was 52 years (SD 5.3), which was on average 23 years prior to the cognitive assessment. Low $FEV_1/height^2$ was associated with older age, lower education, less mid-life physical activity; and presence of COPD, diabetes, high blood pressure and smoking (Table 1). Among subjects with multiple PF assessments, PF decreased by an average of 1.9% per year.

Level of PF and cognition

Among the 3, 249 non-demented subjects, performance in the three cognitive domains increased as $FEV_1/height^2$ quartile increased (*P* for linear trend < 0.001 for all three cognitive domains). Coefficients were slightly attenuated after adjustments for demographic and cardiovascular risk factors and disease (Model 2, Table 2). The interaction between the presence of Apo E ε4 and PF was not significant (*P* >0.15) for any of the cognitive domains.

The prevalence of dementia among the 3,665 subjects was 5.6 percent in the lowest quartile of $FEV_1/height^2$ and 1.9 percent in the highest $FEV_1/height^2$ quartile (Table 1) and the prevalence of MCI was 10.5 and 4.8 percent respectively. Mean $FEV_1/height^2$ was 0.93 (SD=0.22) in dementia cases, 0.97 (0.20) in MCI cases, and 1.01 (0.20) in the other subjects. For every increase of one SD of $FEV_1/height^2$, there was a decreased likelihood of MCI (0.78 (95% confidence interval, 0.68, 0.89) or dementia (0.68; 0.55, 0.83).(Table 2). The Apo E ε4 and PF interaction was not significant for the presence of dementia or MCI (*P*=0.64).

Change in pulmonary function

For the 1,281 subjects (1,151 with no MCI or dementia) with at least two assessments of PF, the mean loss of $FEV_1/Height^2$ was 1.92 (1.61) percent per year, over an average 7.8-year (2.6) period (total loss of 14.3 percent). In this sub-sample, the association of the baseline $FEV_1/height^2$ to cognition was similar to that in the total sample (memory: β=0.08 (SE=0.03), *P*=0.02, speed: β=0.06 (SE=0.03), *P*=0.02 and executive function: β=0.10 (SE=0.03), *P*=0.003). However, there were no significant associations of change in $FEV_1/Height^2$ to memory (*P*=0.88), speed of processing (*P*=0.80) or executive function (*P*=0.97) among the non-demented subjects (Table 2). Compared to the normal subjects, subjects with MCI had a smaller decline in PF (*P*=0.04); no relationship was found with dementia (*P*=0.39).

DISCUSSION

We found subjects with lower $FEV_1/height^2$ at mid-life were more likely, 23 years later, to have lower cognitive test scores or to develop MCI or dementia. Adjustments for a range of factors associated with cerebro-vascular disease or PF, including smoking status, mid-life physical activity and occupation, and late-life COPD attenuated the association of PF to memory, but otherwise did not change the associations of interest. The change in PF over a 7.8-year period was, however, not significantly associated with our cognitive outcomes, with the exception of subjects with MCI, who had a smaller change in PF on average than the subjects who were not MCI or demented.

Strengths of this study include a particularly well-described cohort[13] and the availability of multiple cognitive test-scores, aggregated into three normally distributed cognitive

domains.[15] The dementia and MCI assessment was a multidisciplinary process that was based on a standardized adjudication process.[13] Pulmonary assessments were made according to a standardized protocol administered on average 23 years before the measure of cognitive status. Variability due to the spirometry equipment was minimized by maintaining and using the same equipment over time. Not only does this give us insight into early PF characteristics of persons with later cognitive decline it also reduces the error introduced to PF measures when subjects are cognitively impaired and may not be able to fully comply with the protocol. We were also able to control for important confounding factors including cardiovascular risk factors and disease, although residual confounding cannot be excluded.

The predictive value of mid-life PF for cognitive performance later in life has been reported elsewhere.[9–11] Based on previous studies on this topic the mechanism through which PF may affect cognitive function is generally thought to be related to poor oxygen supply to the brain. The brain only accounts for 2% of the total body weight, yet it consumes 20% of the body energy,[27] almost exclusively through complete oxidation of glucose.[28] Subtle variations of the cerebral blood flow and oxygen saturation are likely to have a significant effect on brain function. Moreover, PF doesn't only reflect lung disease, but also heart disease and other vascular disorders, which in turn could be the cause of cognitive deficits by themselves. However, studies suggest the mechanism is complicated by the complex effects of constitutional and environmental factors that both contribute to pulmonary and cognitive development.[29,30] Indeed, a relationship between PF and cognition can already be observed very early in life, among pre-teens[31] and young adults.[5] In the British 1946 birth cohort,[32] the relationship between PF at 43 years old and the cognitive ability 10 years later was no longer significant when the model was adjusted for cognitive ability at 15 years old suggesting the importance of early life exposures and experiences on late-life functioning. Emery et al. found in the cross-twin correlation analyses of 222 Swedish twin pairs, that FEV_1 was associated with cognition at baseline and six years later, and concluded that the genetic effects accounted for more than the environmental effects.[12]

We found no association between *change* in PF and late life cognitive scores. Apart from constitutional factors, other factors may explain this lack of association. Our follow-up duration of 7.8 years may have been too short to capture an association, even though PF decreased by 1.9% per year, which is slightly higher than the 1% per year reported in the literature for non-smoking adults.[33] The change in PF was measured on average 23 years before the cognitive assessment and patterns of differential change during the interval may have obscured the relationship. Also, since PF predicts mortality in this cohort,[14] survival effects may also play a role. For instance, if subjects with fast declining PF died earlier than those with slower declines in PF, those potentially at the highest risk for cognitive impairment would not have survived to the AGES-RS baseline. Lastly, two measurement issues that could have influenced the results are regression to the mean and a 'floor effect'. Regression to the mean would overall reduce the amount of change PF and a floor effect would truncate the change because subjects with low baseline PF could not substantially decline. These measurement errors may explain the finding that persons with MCI had a slower rate of decline in PF than cognitively normal subjects.

In summary this study shows, subjects with lower mid-life PF had on average lower cognitive scores, and were more often diagnosed with MCI and dementia 23 years later. On the other hand the decrease of PF at mid-life was not associated with cognitive performance, MCI or dementia. These data suggest early efforts to maintain pulmonary health may have a positive influence on late life cognition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

PF	pulmonary function
AGES	Age Gene/Environment-Reykjavik Study
FEV_1	forced expiratory volume in 1 sec
MCI	mild cognitive impairment
SD	standard deviation
BMI	body mass index
COPD	chronic obstructive pulmonary disease

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Table 1

Cohort Characteristics by Quartiles of Mid-life Forced Expiratory Volume in 1 Second / Height^2: AGES-Reykjavik Study

General characteristics	Forced Expiratory Volume in 1 second / Height^{2a} 1st Quartile (low) 2nd Quartile 3rd Quartile 4th Quartile (high)				P^b
	N=919	N=917	N=912	N=917	
Mid-life variables,^{c}M (SD)					
Age at 1st pulmonary assess.	54.2 (5.6)	53.2 (5.4)	52.1 (5.2)	49.7 (5.2)	<.0001
BMI	25.3 (4.0)	25.5 (3.7)	25.4 (3.5)	243.9 (3.4)	0.21
FEV_1/Height^2	0.77 (0.12)	0.95 (0.09)	1.07 (0.09)	1.24 (0.12)	-
Past physical activity, %	26.4	30.2	35.3	36.1	0.00002
Occupation Class, %					
Manual work	57.9	55.4	56.6	55.2	
Intermediate	30.0	31.2	27.9	29.5	0.30
Professional	12.1	13.4	15.5	15.3	
Late-life variables,^{d}M (SD)					
Age	77.6 (5.2)	76.8 (5.2)	76.0 (5.2)	74.4 (5.0)	<.0001
Men, %	32.7	32.8	32.8	32.7	-
Higher education, %	21.3	24.1	27.3	30.2	0.0001
Ever smoker, %	64.6	55.9	51.2	51.1	<.0001
Height	165.2 (9.1)	165.7 (9.3)	166.1 (9.1)	166.2 (9.0)	0.16
Weight	73.5 (14.9)	75.1 (14.5)	75.9 (14.4)	75.2 (14.3)	0.30
Depression (GDS >=6), %	9.0	5.6	6.4	6.3	0.03
Previous CHD, %	23.0	20.8	18.6	17.5	0.02
COPD, %	6.6	3.7	1.8	2.0	<.0001
Diabetes, %	12.8	10.9	11.4	8.2	0.01
High Blood Pressure, %	85.4	83.0	81.0	74.4	<.0001
Coronary Artery Calcium^e	737 (1019)	643 (987)	621 (1011)	561 (991)	0.37
APOE 4 carrier, %	26.4	27.0	27.5	29.2	0.57
Cognition, M (SD)					
Memory ^{f}	−0.22 (0.95)	−0.07 (0.98)	0.07 (0.99)	0.22 (1.01)	0.0002

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General characteristics	Forced Expiratory Volume in 1 second / Height^{2a}				p^b
	1st Quartile (low)	2nd Quartile	3rd Quartile	4th Quartile (high)	
	N=919	N=917	N=912	N=917	
Speed ^{f}	−0.25 (1.11)	−0.08 (1.04)	0.09 (0.92)	0.24 (0.85)	<.0001
Working ^{f}	−0.19 (1.02)	−0.11 (0.99)	0.07 (0.97)	0.23 (0.95)	<.0001
Cognitive status, %					
MCI	10.6	8.9	7.5	4.6	0.0006
Dementia	5.6	4.4	2.1	1.9	

Abbreviations: BMI: Body Mass Index: [Weight (in kgs) / Height^2 (in meters)]; M (SD): Mean (Standard Deviation); GDS: Geriatric Depression Scale; CHD Coronary Heart Disease; COPD: Chronic Obstructive Pulmonary Disease.

^{a}Sex specific quartiles.

^{b}Analysis of variance or multinomial logistic regression adjusted for sex by virtue of sex-specific quartiles of FEV_1 and age.

^{c}Measured at the time of the first spirometry;

^{d}Measured at the time of cognitive assessment;

^{e}Agatston score;

^{f}Demented and MCI subjects not included (n=416).

Table 2

Association of Cognitive Measures to Mid-life Pulmonary Function Level and Change: AGES-Reykjavik Study

Cognitive outcome	Forced Expiratory Volume in 1 second / Height^2, n=3665					
	Model 1			Model 2		
	β(SE) [a]		*P*	β(SE)[a]		*P*
Memory [b]	0.07 (0.02)		<.0001	0.05 (0.02)		0.006
Speed [b]	0.08 (0.02)		<.0001	0.04 (0.01)		0.003
Working Memory[b]	0.09 (0.02)		<.0001	0.06 (0.02)		0.0004
	OR[a]	95% CI		OR[a]	95% CI	
MCI	0.78	0.68, 0.89	0.0004	0.80	0.69, 0.93	0.003
Dementia	0.68	0.55, 0.83	0.0002	0.68	0.55, 0.84	0.0004
	Slope of FEV_1, n=1281					
	β(SE)[a]			β(SE)[a]		
Memory [c,d]	0.04 (0.03)		0.20	0.02 (0.03)		0.39
Speed [c,d]	0.02 (0.02)		0.32	0.03 (0.02)		0.25
Working Mem [c,d]	0.03 (0.03)		0.24	0.04 (0.03)		0.18
	OR[a]	(95% CI)		OR[a]	(95% CI)	
MCI[e]	1.34	1.04, 1.73	0.02	1.36	1.04, 1.77	0.03
Dementia[e]	1.15	0.83, 1.58	0.40	1.15	0.81, 1.64	0.44

Abbreviations: OR, odds ratio; CI, confidence interval.

[a] For 1 SD increase of FEV_1/ Height^2.

[b] Demented and MCI subjects excluded (N=416).

[c] Demented and MCI subjects excluded (N=130).

Model 1: linear model or multinomial logistic regression model adjusted for age and sex;
Model 2: model 1 + higher education, occupation class, mid-life BMI and physical activity; presence of depressive symptoms, COPD, coronary heart disease, hypertension, diabetes, and smoking habits.

[d] Change in score with change in PF

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[e] Likelihood of outcome with less change in PF over time.