

Reduced Lung Function and Cognitive Decline in Ageing: A Longitudinal Cohort Study

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Author Contributions: Conceived and designed the study: W. Xie and L. Xie. Statistical analysis: W. Xie and F. Zheng. Wrote the manuscript: W. Xie and F. Zheng. Discussed the results and implications and commented on the manuscript at all stages: all co-authors.

Support Statement: This work was funded by the National Natural Science Foundation of China (project no. 81974490), the Beijing Natural Science Foundation (project no. 7182108), the Newton International Fellowship from the Academy of Medical Sciences (project no. NIF001-1005-P56804), and 2019 Irma and Paul Milstein Program for Senior Health Research Project Award.

Conflict of Interest: We declare no competing interests.

Running Title: Reduced lung function and cognitive decline.

Word Count: 1000

To the Editor:

Emerging evidence from cross-sectional studies suggested that lung function might be a risk factor of dementia (1-4), although the longitudinal associations of lung function with subsequent cognitive decline remain inconsistent (2, 5-8). The English Longitudinal Study of Ageing (ELSA), with its lung function measurements at baseline (forced expiratory volume in one second [FEV₁] and forced vital capacity [FVC] and biennial cognitive assessments over 12 years based on a large, national-representative cohort, provides us with the opportunity to explore the longitudinal association of lung function with the temporal pattern of subsequent cognitive decline.

Methods

The ELSA is an ongoing and longitudinal cohort study conducted in a representative sample of the English population aged 50 and over living in England (9, 10). The ELSA cohort was established in 2002/2003 (wave 1), and has been followed up every two years until 2016/2017 (wave 8). Lung function was firstly measured at wave 2 (2004/2005) and therefore it was regarded as the baseline of the present study and follow-up of cognitive function was from waves 3 to 8 (2006/2007 to 2016/2017). Flow chart of the study population is presented in Figure 1. Finally, 6107 individuals were included in this study. The London Multicentre Research Ethics Committee approved the ELSA study (MREC/01/2/91), and all participants provided informed consent at each wave.

Cognitive assessment was conducted in all waves and included three aspects: memory, executive function and orientation (11, 12). The Z score for global cognitive function was calculated by averaging the Z scores of three tests and re-standardizing to baseline according to the mean and SD of the baseline global cognitive Z scores (13, 14). Pre-bronchodilation measures of FEV₁ and FVC were conducted by trained nurses using spirometer (Escort, Vitalograph, Bucks, UK) in the participant's house at wave 2. The percentage of the FEV₁ predicted (FEV₁% pred) and the percentage of the FVC predicted (FVC% pred) were calculated based on published equations for Caucasian (15).

Covariates at baseline that might be related to both lung function and cognitive decline were selected *a priori* for this analysis. Linear mixed models were used to evaluate the longitudinal associations between baseline lung function and cognitive decline over time. All analyses in this study were divided by sex, as both lung function and cognitive function are significantly different between sexes (16).

Results

The mean \pm SD of age at baseline (2004/2005) for men and women was 65.5 ± 9.1 and 65.8 ± 9.4 years, respectively. The median follow-up period was 12 years (interquartile range: 8 to 12 years). The scores of memory, executive function, and orientation increased linearly with increasing quartiles of FEV₁ in both men and women.

In women, for each of the lung function indicator, a lower baseline level was significantly

associated with a faster decline of global cognitive Z scores after multivariable adjustment (Table 1). However, in men, only FEV₁ and FVC were significantly associated with global cognitive decline (Table 1). In both men and women, we observed that FEV₁ and FVC were significantly associated with a faster decline of memory, executive function, and orientation Z scores.

Cognitive Z scores declined faster with decreasing quartiles of FEV₁ at baseline, with the trend being statistically significant (Table 2). Compared with the highest quartile of FEV₁, the rate of decline of global Z scores associated with the lowest quartile was faster by -0.069 SD/year (95% CI: -0.082 to -0.056 SD) and -0.049 SD/year (95% CI: -0.063 to -0.034 SD) in women and men, respectively.

Discussion

As far as we know, this is one of the largest cohort studies which simultaneously employed multiple pulmonary measurements to explore the association of lung function and cognitive decline. Previous studies focusing on this association only used one or two pulmonary measurements and therefore yielded conflicting results. Few cohort studies have investigated the relationship between baseline lung function and consequent decline of cognitive function in general populations (17). Recently, Atherosclerosis Risk in Communities (ARIC) study reported that baseline lung function was associated with incident dementia and mild cognitive impairment (18). In this study, we found that global Z scores in the lowest quartile of FEV₁

declined faster by -0.069 SD/year and -0.049 SD/year compared with that in the highest quartile in women and men, respectively. Previous studies have defined that a change of 0.5 SD in a health-related indicator is a clinically significant change (19, 20). According to this definition, accelerated cognitive decline in participants with the lowest quartile would achieve a clinically significant change in approximately 7 to 10 years, therefore our results support the findings from ARIC study.

Interestingly, significant longitudinal associations were only detected between the FEV_1 and FVC, but not the calculated indicators ($FEV_1\%$ pred, $FVC\%$ pred, and FEV_1/FVC ratio) and global cognitive performance. We consider that the results are reasonable, because both the numerator and the denominator of a calculated indicator of lung function were significantly associated with cognitive function, which would dilute the relationship of the calculated indicator with cognitive function.

Our study has several strengths including large sample size, national-representation, longitudinal design, long-term follow-up, seven repeated measurements of cognitive function, multiple indicators of lung function, three measurements of lung function, and multiple domains of cognitive function. However, several potential limitations should be considered before performing causal inference. First, its observational design had inherent limitations in concluding the causal relationship. Second, 746 participants with complete baseline data were excluded from our analyses owing to lost to follow-up, which might lead to selection bias. Third, the present study had adjusted for a number of covariates, however, unmeasured covariates,

like APOE status, might still cause confounding bias. Last, the present study focused on English adults aged over 50 and 98% of them were white, thus the findings might not be completely generalized to young people or other populations.

In conclusion, this prospective cohort study demonstrated that baseline FEV₁ and FVC were significantly associated with cognitive decline over 12 years. Our results suggest that physicians should carefully and prospectively monitor cognitive function of the elderly patients with reduced lung function in clinical practice.

Acknowledgements

We thank the original data creators, depositors, copyright holders, the funders of the Data Collections, and the UK Data Archive for the use of data from English Longitudinal Study of Ageing: Waves 0-8, 1998-2017. The original data creators, depositors, or copyright holders bear no responsibility for the current analysis or interpretation.

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Figure Legends

Figure. 1 Flow chart of participant selection for the present study population.

Table 1. Longitudinal associations between baseline indicators of lung function and the rate of change in global cognitive Z scores (standard deviation/year): using linear mixed models

Indicators of lung function	Women (n=3343)		Men (n=2764)	
	β (95% confidence interval)*	<i>P</i> value*	β (95% confidence interval)*	<i>P</i> value*
	for the interaction		for the interaction	
FEV ₁ (per 100 ml decrease)	−0.004 (−0.005, −0.003)	<0.001	−0.002 (−0.003, −0.001)	<0.001
FEV ₁ % pred (per 20% decrease)**	−0.006 (−0.010, −0.002)	0.005	−0.001 (−0.006, 0.003)	0.527
FVC (per 100 ml decrease)	−0.003 (−0.004, −0.002)	<0.001	−0.002 (−0.002, −0.001)	<0.001
FVC% pred (per 20% decrease)**	−0.004 (−0.009, −0.000)	0.032	−0.004 (−0.009, 0.001)	0.120
FEV ₁ /FVC ratio (per 0.20 decrease)	−0.009 (−0.016, −0.002)	0.008	−0.003 (−0.009, 0.004)	0.461

*Models including each indicator, time, indicator×time interaction, age, ethnicity, education, height, body mass index, current smoking, cigarettes per day, alcohol consumption, chronic lung disease, asthma, stroke, and cancer.

**Age, ethnicity, and height were not included in these models as these covariates have been already adjusted for when generating a % predicted value; a 20% decrease of the absolute percent predicted values.

FEV₁, forced expiratory volume in 1 second; FEV₁% pred, percentage of the FEV₁ predicted; FVC, forced vital capacity; FVC% pred, percentage of the FVC predicted.

Table 2. Longitudinal associations between baseline quartiles of forced expiratory volume in 1 second (FEV₁) and the rate of change in cognitive Z scores (standard deviation/year): using linear mixed models

		Mean difference in the rate of change in cognitive Z scores (95% CI)* across sex-specific quartiles of FEV ₁					
		Quartile 1 (<2.27 L)	Quartile 2 (2.27 to 2.84 L)	Quartile 3 (2.85 to 3.37 L)	Quartile 4 ≥3.37 L	P for trend*	
Women (n=3343)							
Global cognitive scores	Z	-0.069 (-0.082, -0.056)	-0.052 (-0.065, -0.039)	-0.023 (-0.036, -0.009)	Reference	<0.001	
Memory Z scores		-0.046 (-0.056, -0.037)	-0.026 (-0.035, -0.016)	-0.010 (-0.020, -0.001)	Reference	<0.001	
Executive function scores	Z	-0.038 (-0.048, -0.028)	-0.030 (-0.040, -0.020)	-0.011 (-0.021, -0.001)	Reference	<0.001	
Orientation Z scores		-0.054 (-0.070, -0.038)	-0.045 (-0.061, -0.029)	-0.022 (-0.038, -0.006)	Reference	<0.001	
Men (n=2764)							
Global cognitive scores	Z	-0.049 (-0.063, -0.034)	-0.033 (-0.047, -0.018)	-0.013 (-0.028, 0.002)	Reference	<0.001	
Memory Z scores		-0.031 (-0.041, -0.021)	-0.019 (-0.029, -0.009)	-0.001 (-0.011, 0.010)	Reference	<0.001	
Executive function scores	Z	-0.032 (-0.043, -0.021)	-0.025 (-0.037, -0.014)	-0.012 (-0.024, 0.001)	Reference	<0.001	
Orientation Z scores		-0.039 (-0.056, -0.022)	-0.026 (-0.043, -0.008)	-0.012 (-0.030, 0.006)	Reference	<0.001	

*Models including quartile, time, quartile×time interaction, age, ethnicity, education, height, body mass index, current smoking, cigarettes per day, alcohol consumption, chronic lung disease, asthma, stroke, and cancer.

FEV₁, forced expiratory volume in 1 second; CI, confidence interval.

