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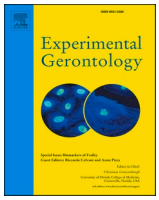

Pulmonary function and trajectories of cognitive decline in aging population

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ABSTRACT

Background: The number of older people with cognitive impairment is increasing worldwide. Impaired lung function might be associated with cognitive decline in older age; however, results from large longitudinal studies are lacking. In this study, we examined the longitudinal associations between pulmonary function and the trajectories of cognitive decline using prospective population-based SHARE data from 14 countries.
Methods: The analytic sample included $N = 32{,}049$ older adults (Mean age at baseline = 64.76 years). The dependent variable was cognitive performance, measured repeatedly across six waves in three domains: verbal fluency, memory, and numeracy. The main predictor of interest was peak expiratory flow (PEF). The data were analyzed in a multilevel accelerated longitudinal design, with models adjusted for a variety of covariates.
Results: A lower PEF score was associated with lower cognitive performance for each domain as well as a lower global cognitive score. These associations remained statistically significant after adjusting for all covariates Q4 vs Q1 verbal fluency: unstandardized coefficient B = -3.15; numeracy: B = -0.52; memory: B = -0.64; global cognitive score $B = -2.65$, all $p < .001$). However, the PEF score was not found to be associated with the rate of decline for either of the cognitive outcomes.
Conclusions: In this large multi-national longitudinal study, the PEF score was independently associated with lower levels of cognitive functions, but it did not predict a future decline. The results suggest that pre-existing differences in lung functions are responsible for variability in cognitive functions and that these differences remained stable across aging.

1. Introduction

Demographic projections of the World Health Organization (WHO) indicate that the proportion of the world's population over 60 years will nearly double, from 12 % to 22 % (2 billion people), by 2050 (World Health Organization, 2015). Demographic transition is explained mainly by declining fertility rates and increasing life expectancy at birth (Vaupel, 2010). Thus, in 2020, a 60-year-old woman living in a high-income country could expect to live another 23 years on average (The World Bank - DataBank, 2020). However, determining whether people live longer and healthier lives or whether the additional years are spent mainly in poor health is crucial. In the recently published World Report on Aging and Health, WHO defines healthy aging as "*the process of developing and maintaining the functional ability that enables well-being in older age.*" It has been emphasized that functional ability tends to decline over time but with different individual rates depending on various environmental factors (World Health Organization, 2015; Wu et al., 2021). Therefore, a growing body of evidence underlines the need to understand biological functioning across the lifespan.

Functional changes related to aging have been observed in a variety of biological markers, including cognitive performance (Lara et al., 2015). Cognitive health is among the major factors relevant to preserving the quality of life as it allows older people to maintain a sense of purpose and the ability to live independently (Clare et al., 2017; Dekhuijzen et al., 2020). However, the proportion of people with cognitive impairment is estimated to triple by 2050 (Kukull and Ganguli, 2012a; Przedborski et al., 2003), posing a high socioeconomic burden worldwide (Campbell and Unverzagt, 2013; Russ et al., 2020). Cognitive functioning is known to differ in its rate of decline due to a number of factors, including age, education, race/ethnicity, anthropometric measures, social activity, healthy diet, environmental exposures, genetics, depression, and chronic health issues (Clare et al., 2017; Fabbri et al.,

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2016; Wu et al., 2020; Zaninotto et al., 2018).

A number of previous research suggested that impaired lung function may be associated with worse cognition as well as faster decline (Finkel et al., 2013; Hüls et al., 2018; Qiao et al., 2020; Singh-Manoux et al., 2011; Wang et al., 2022). The possible mechanisms underlying this association include chronic hypoxemia and reduced brain oxygenation, leading to vascular endothelial dysfunction that impacts neurotransmission and results in subsequent neuronal death (Gorelick et al., 2011; Shibata, 2018). In addition, in line with other risk factors, including cardiovascular and metabolic, impaired lung function may cause systemic inflammation and oxidative stress that impact neurotransmission and accelerate cognitive decline (Gorelick et al., 2011; Saleem et al., 2019; Vinkers et al., 2005). The indirect effect of impaired lung function on cognitive function might also be considered via increasing risk of cardiovascular events (Gorelick et al., 2011; Richards et al., 2005; Saleem et al., 2019; Vinkers et al., 2005).

There is a paucity of studies that assessed the possible relationship between lung function and cognitive decline in a longitudinal design (Wu et al., 2020; Zaninotto et al., 2018). A recent meta-analysis included data from the US and various European populations suggested weak longitudinal associations between spirometry and cognitive decline (Duggan et al., 2019). However, the study's results may be affected by heterogeneity in the study population and variations in spirometry indices and cognitive domains used across selected studies (Aiken-Morgan et al., 2018; Qiao et al., 2020; Richards et al., 2005). As mentioned, most of the previous epidemiological studies relied on a cross-sectional design that does not allow for observing longitudinal change, which is essential for studies of aging. Longitudinal studies with data collected from at least three time points enable us to determine the 'trajectories' or 'patterns' of cognitive functioning that emphasize the dynamic nature of cognitive aging. Furthermore, this approach takes into account both intra-individual and inter-individual differences, which more comprehensively describes the natural and risk-related process of cognitive aging (Duggan et al., 2020; Finkel et al., 2013). Finally, most studies are representative of a particular national-based population and not generalizable to other populations (M. D. A. Carlson and Morrison, 2009). A large sample size, including different populations, will increase the external validity and enhance the precision of results (Duggan et al., 2019; Kukull and Ganguli, 2012b).

To address these gaps, we used data from the Survey of Health, Aging and Retirement in Europe (SHARE), which provides an opportunity to examine the association between baseline pulmonary function and six repeated cognitive measures in 14 countries. We conducted an accelerated longitudinal design analysis to evaluate the effect of baseline pulmonary function and other potential risk factors on cognitive functions and their trajectory over time in different populations.

2. Methods

2.1. Study design and participants

This study used SHARE data, a cross-national, longitudinal study of health, socioeconomic conditions, and family and social networks of adults aged 50 and over across 28 European countries and Israel (Börsch-Supan et al., 2013). The first data collection started in 2004 and included data on age, sex, health status, medical examination, lifestyle, and socioeconomic and psychosocial factors collected using a questionnaire, computer-assisted interview combined with physical examination with follow-up updates every two years (Börsch-Supan et al., 2013). The latest data collection (Wave 8) was in 2020. The SHARE study was approved by the Ethics Committee at the University of Mannheim (Waves 1–4) and by the Ethics Council of the Max-Planck-Society (Waves 5–8). Additionally, country-specific ethics committees or institutional review boards approved implementations of SHARE in the participating countries. All study participants provided informed consent.

The measure of lung function was peak expiratory flow (PEF), which was assessed at Wave 2 for the first time, and thus Wave 2 served as our baseline. Participants with at least one available measurement of cognitive function from Wave 2 up to Wave 8 were included. Wave 3 was not included, as it only assessed the retrospective life histories of participants. All the covariates except for age were assessed at baseline (Wave 2). The total number of participants was $N = 37{,}152$. There were 15 countries that were included in Wave 2: Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Ireland, Israel, Italy, the Netherlands, Poland, Spain, Sweden, and Switzerland. Follow-up data on Waves 4 to 7 were not available for Ireland; therefore, this country was excluded from the analyses. Greece, the Netherlands, Poland, and Israel were included, but they missed data on Wave 4 and Wave 5 (Greece), Wave 6 and Wave 7 (the Netherlands), Wave 4 (Israel), and Wave 5 (Poland), making the total number of countries involved 14. To control for the pre-existing diseases, we removed participants who indicated that they were diagnosed with chronic lung disease, asthma, cancer in the larynx or lungs, Parkinson's disease, or Alzheimer's disease/dementia/senility at the baseline, resulting in a sample of $N = 32{,}111$. The age at Wave 2 (baseline) varied from 15 to 105. The resulting age span for the accelerated longitudinal design (see Statistical analysis) was reduced to 43–97 years due to a low number of individuals at the tails of the age distribution, making the final analytic sample $N = 32{,}049$ (Mean baseline age = 64.8 years). Fig. S1 presents a flowchart of the sample selection.

2.2. Measures

2.2.1. Peak expiratory flow (PEF)

The PEF is the maximal flow achieved during a forced expiratory vital capacity maneuver starting from the level of full inspiration (Quanjer et al., 1993). The PEF was assessed using a mini-Wright peak flow meter under standardized condition (de Hamel, 1982; Wright, 1978). Each respondent was measured twice, and the higher value of the PEF was selected for further analysis. The predicted PEF regression equation using a "normal" lung function population was used to calculate the respondent's predicted PEF value standardized for sex, age, and height (Quanjer et al., 1993). Subsequently, the percentage of the predicted PEF was obtained by dividing the actual and predicted values. This was recoded into quartile groups (1 = worst to 4 = best) to identify potential thresholds in the association between lung function and cognition.

2.2.2. Cognitive functions

Cognitive functions were assessed in three domains.

2.2.2.1. Verbal fluency. This was measured by asking the participants to list as many animals as they could think of within a minute, with the score representing the number of unique animals the participants reported (scores ranging from 0 to 100).

2.2.2.2. Numeracy. This was measured in two ways. At Wave 2, the participants were asked to answer four multiple-choice items, which asked them to calculate the correct percentage from a certain number (Example: "If the chance of getting a disease is 10 percent, how many people out of 1,000 (one thousand) would be expected to get the disease? 1. 100; 2. 10; 3. 90; 4. 900"). From Wave 4, another task was added – participants were asked to subtract the number 7, starting from 100 (i.e., 93, 86, 79, etc.), for a total of 5 subtractions. Because there was little overlap from Wave 2 to Wave 4 in terms of repeated measures for the first numeracy task, we decided to only use numeracy task 2, starting from Wave 4. The number of correct answers (ranging from 0 to 5) was used to measure numeracy.

2.2.2.3. Memory. Memory was measured by giving participants a list of 10 words, which they were instructed to memorize and then recall (scores ranging from 0 to 10). Immediate recall and delayed recall scores were reported. Given the high correlations ($r \sim 0.75$) between immediate and delayed recall, these were combined into a single variable by averaging them within each wave.

2.2.2.4. Global cognitive score. This was estimated as a multilevel latent factor, which used the three measures of cognitive functions as observed indicators at different levels (repeated measures of the same person at level 1 and aggregated levels for each person at level 2).

2.2.3. Covariates

Data on covariates were obtained from questionnaires at Wave 2.

2.2.3.1. Age. Used in the analyses twice: first, as a time-varying covariate, predicting the within-person change per year, and second, as a time-invarying covariate, assessing the effect of age at baseline on cognitive functions, to capture the cohort effects.

2.2.3.2. Sex. Self-reported, coded as 1 = female, 0 = male.

2.2.3.3. Education level. Assessed using the International Standard Classification of Education (ISCED) 1997, ranging from 0 = no education or pre-primary education to 6 = second stage of tertiary education (advanced research qualification). These seven education stages were recoded into three categories: primary education (categories 0–2), reflecting preprimary, primary, and lower secondary education; secondary education (categories 3–4), reflecting upper secondary and post-secondary non-tertiary education; and tertiary education (categories 5–6), reflecting the first and second stages of tertiary education.

2.2.3.4. BMI. Based on self-reported weight and height. This was categorized into four categories = underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), and obese (BMI 30+), with normal weight serving as the reference group.

2.2.3.5. Smoking quantity. For individuals who indicated that they were current smokers, we computed their smoking quantity by summing items asking about the average number of cigarettes, pipes, or cigars they smoked per day. For non-smokers, this was coded as 0.

2.2.3.6. Alcohol consumption. Assessed as a number of days a week individuals consumed alcohol in the past month, ranging from 0 to 7.

2.2.3.7. Cardiovascular disease. Participants who indicated they suffered from any of the following: heart attack, hypertension, or stroke were coded as 1, and the rest were coded as 0.

2.2.3.8. Depression. Depressive symptoms were measured by the Euro-D scale and consisted of 12 items, yielding a potential range of 0 to 12 for this scale. The scale was dichotomized based on the original protocol, where a score of 4 and higher is considered "a case of depression," while a score less than 4 is "not depressed" (Prince et al., 1999).

2.3. Statistical analysis

Descriptive statistics were computed for the variables used in the analyses. Then, we compared proportions and means of covariates based on PEF quartiles. In the main part of our analysis, we estimated an accelerated longitudinal model based on individual ages and not waves. This is a specific type of research design analyzing multiple birth cohorts with varying baseline age as a single cohort. In this way, it is able to cover a wide range of ages that would take too long if a single (birth) cohort was followed.

Multilevel modeling (MLM) with repeated measures of cognitive function at level 1 (nested within person), individual differences in cognitive function at level 2 (between person), and adjusting standard errors for nesting within countries using TWOLEVEL COMPLEX model was carried out. Missing data were imputed using the full information maximum likelihood with robust standard errors (MLR). All analyses were computed in Mplus 8.6.

A total of four outcomes were used: verbal fluency, numeracy, memory, and a latent factor of global cognitive score.

First, we assessed descriptive statistics of the study covariates and their proportions in different tertiles of cognitive functions. Then, we estimated the multilevel models. At the within-person level (level 1), age, age^{2,} and age^{3} were used as predictors to describe the shape of the trajectory. The age terms that were found statistically significant were included in the subsequent analyses. Second, the focal variable of our study, PEF, was used to predict the intercept and the slope of each cognition variable and to evaluate unadjusted associations, with statistically significant age terms included as predictors at level 1. Quartiles of PEF were entered into the model accounting for the level of lung function impairment, with the highest quartile (no impairment) set as a reference. Finally, to assess how the effect of PEF on cognition changed when adjusted for covariates, the intercept was regressed on all the between-person covariates in addition to PEF. Furthermore, the linear slope and quadratic slope of age, where applicable, were defined as random and then regressed on between-level covariates to test whether the covariates affected the development (slope) beyond the effect on the intercept. At the within-level, age was group-mean centered, while grand-mean centering was used for between-level covariates, including age at baseline. The reported *B* values are unstandardized regression coefficients, referring to a change in the outcome variable per one unit

Table 1
Descriptive statistics of study variables at the baseline.

	n	*Mean/ %*	*SD*
PEF predicted values	28,158	0.85	0.33
Cognitive functions			
Verbal fluency (number of words per minute)	31,360	19.01	7.47
Numeracy (number of correct subtraction tasks)[a]	16,870	3.99	1.55
Memory (number of words remembered)	31,543	4.30	1.77
Sex			
Males	14,113	44 %	
Females	17,936	56 %	
Age group			
43–55 years	6,468	21 %	
56–60 years	6,286	20 %	
61–65 years	5,482	17 %	
66–70 years	4,625	14 %	
71–75 years	3,704	12 %	
76–80 years	2,782	9 %	
80+ years	2,630	8 %	
Smoking			
Non-smoker	25,235	80 %	
Smoker	6,379	20 %	
Education			
Primary	14,891	47 %	
Secondary	10,521	33 %	
Tertiary	6,049	19 %	
BMI			
Underweight	357	1 %	
Normal weight	11,606	37 %	
Overweight	13,343	43 %	
Obese	5,761	19 %	
CV disease			
No CV disease	18,899	59 %	
CV disease	13,150	41 %	
Depression			
Not depressed	24,078	77 %	
Depressed	7,260	23 %	
Alc. Drinks per week	31,786	4.61	2.23

[a] The baseline for Numeracy was during SHARE Wave 4, not Wave 2 as for the rest of the variables (See Methods).

change in the predictor. The units are described in Table 1.

3. Results

Table 1 shows descriptive statistics of the analytic sample. The average age at the baseline was 64.80 years. The proportion of women was slightly larger (56 %). A total of 19 % of participants reported having tertiary education, 33 % reported secondary, and 47 % reported primary as their highest attained education level. The mean of PEF predicted was equal to 85 %. Around 62 % of participants reported being overweight or obese, and 20 % were active smokers. Around 41 % of participants reported having some cardiovascular disease. About 23 % of participants would meet the criteria for depression defined by the EURO-D scale. Then, we compared the proportions and means of covariates by the tertiles of cognitive functions at the baseline. This is shown in Table 2. The results showed the proportion of females was the highest in the lowest tertiles of verbal fluency and numeracy, but it was the highest in the highest tertile of memory. Individuals with normal weight based on BMI were more likely to be represented in higher tertiles, yet individuals with overweight and obesity were more represented in lower tertiles. Actively smoking individuals were more likely to be represented in the highest tertiles of numeracy and memory. The representation of individuals with higher education increased with an increase in tertiles of all cognitive functions. Individuals with cardiovascular disease or with depression were less likely to be represented in higher tertiles of cognitive functions. In addition, the frequency of alcohol drinking was negatively associated with cognitive functions.

In the next step, the unconditional multilevel models were fitted. The results showed a decline with age for verbal fluency ($B = -0.115$ per year, $p < .001$), numeracy ($B = -0.032$ per year, $p < .001$), while for memory, a quadratic term was also significant, suggesting that the decrease accelerated in later age, B linear $= -0.057$ per year, $p < .001$, B squared $= -0.002$ per year, $p < .001$. The quadratic term was also confirmed for the global cognitive score, B linear $= -0.142$ per year, $p < .001$, and B quadratic $= -0.011$ per year, $p = .002$. The predicted values of the three cognitive functions across age are shown in Fig. 1, showing that the levels of cognitive functions remained stable from the forties until about the age of 60, when the decline started.

Then, we estimated the unadjusted associations between PEF quartiles and each cognitive function with regard to their mean levels (intercept) and development (slope of decline), in the multilevel model. The results with unstandardized coefficients (change in cognitive function score per one unit change in the covariate) are shown in Table 3. They showed an inverse association between the PEF quartiles and mean levels of cognitive functions (intercept), with a gradual decrease in average levels of cognitive functions at each quartile (as compared to Q4), verbal fluency: Q1 vs Q4 $B = -5.73$, $p < .001$, numeracy: $B = -0.96$, p $< .001$, memory: B $= -1.34$, $p < .001$.

However, there was no effect on the slope for verbal fluency, while there was a significantly lower decline for Q2 ($B = -0.02$, $p < .001$) and Q1 for numeracy ($B = -0.04$, $p < .001$) and for Q1 in memory ($B = -0.02$, $p = .034$; no effect on the quadratic slope). In the next step, we included all the baseline covariates in these models. With the exception of Q3 and numeracy, all the effects of PEF quartiles on intercepts remained statistically significant. The significant effect of PEF on linear decline in numeracy for Q2 and Q1 persisted but no statistically significant effects of PEF quartiles were found on the verbal fluency or memory slope.

The findings were similar when cognitive function was tested as a single global latent variable: for intercept, there were strong gradients in cognition by PEF quartile (Q4 vs Q1 B $= -2.65$, $p < .001$). In the unadjusted model, the lower two quartiles (Q2 and Q1) of PEF were associated with a higher decline in global cognitive score (both linear and quadratic slopes). However, only the effect on quadratic slope remained statistically significant (Q4 vs Q1 B $= -0.01$, $p = .015$) in the model with all covariates (Table 4). Full results, including estimates for all covariates, are shown in Supplementary File (Tables S1-S3).

3.1. Sensitivity analyses

We carried out sensitivity analyses to make sure that the results were not affected by the wide age range at the baseline. For this, we selected only those scores that were provided by participants who were 60 years and older. Compared to the main analyses, the results remained unchanged (See Tables S4-S6).

Furthermore, we also carried out the analyses within each country separately. Figs. S2-S5 show forest plots for the adjusted effects of PEF Q1 (lowest quartile) as compared to Q4 on the intercept for all cognitive functions. These results mirror the findings from the main analyses; the effects of higher PEF quartiles (Q2 and Q3) are less pronounced, which might be due to inadequate power or specific country idiosyncrasies. The full results are shown in Tables S7 and S9. The results for the effects of covariates on the slope of cognitive functions also resemble the main results in that most of the effects of covariates were not significantly associated with the decline (see Tables S8 and S10).

4. Discussion

In this large multi-national longitudinal study, PEF as a measure of pulmonary function was identified as an important predictor of baseline cognitive functions among older European men and women. Compared with individuals with normal or greater than normal lung function, those with reduced PEF achieved significantly lower scores in verbal fluency, numeracy, and memory tasks, as well as in global cognitive score. The effect size gradually increased from the highest to the lowest quartile of PEF, and the associations remained significant after

Table 2
Proportions and means of study covariates by tertiles of baseline cognitive functions.

		Verbal Fluency Tertiles			Numeracy Tertiles			Memory Tertiles		
		1	2	3 (highest)	1	2	3 (highest)	1	2	3 (highest)
Female		58.6 %	54.8 %	54.6 %	62.0 %	55.3 %	52.2 %	52.4 %	53.5 %	61.9 %
Smoker		18.6 %	21.2 %	20.8 %	16.6 %	18.1 %	21.4 %	17.0 %	21.7 %	21.8 %
Education	Primary	67.8 %	46.1 %	27.7 %	62.5 %	34.6 %	39.8 %	67.0 %	44.7 %	30.0 %
	Secondary	23.5 %	36.8 %	40.2 %	26.6 %	41.5 %	34.4 %	23.9 %	36.9 %	39.7 %
	Tertiary	8.7 %	17.1 %	32.0 %	10.9 %	24.0 %	25.8 %	9.0 %	18.4 %	30.3 %
BMI	Underweight	1.4 %	1.0 %	1.0 %	1.4 %	0.9 %	0.8 %	1.5 %	0.9 %	0.9 %
	Normal weight	33.7 %	36.4 %	41.7 %	35.1 %	37.8 %	40.7 %	34.1 %	35.9 %	41.9 %
	Overweight	44.3 %	43.9 %	41.0 %	42.7 %	42.4 %	42.5 %	44.3 %	44.1 %	40.8 %
	Obese	20.6 %	18.8 %	16.3 %	20.8 %	18.9 %	16.1 %	20.1 %	19.1 %	16.3 %
CV disease		48.3 %	40.6 %	33.9 %	44.7 %	39.0 %	36.0 %	49.3 %	40.5 %	33.2 %
Depressed		31.4 %	21.3 %	16.4 %	29.6 %	19.0 %	19.2 %	31.9 %	21.0 %	16.5 %
Alc. drinks per week		5.15	4.52	4.10	4.70	4.18	4.06	4.91	4.54	4.34

Note. All the differences among tertiles statistically significant at $p < .01$ or lower except for normal weight and numeracy tertiles ($p = .943$).

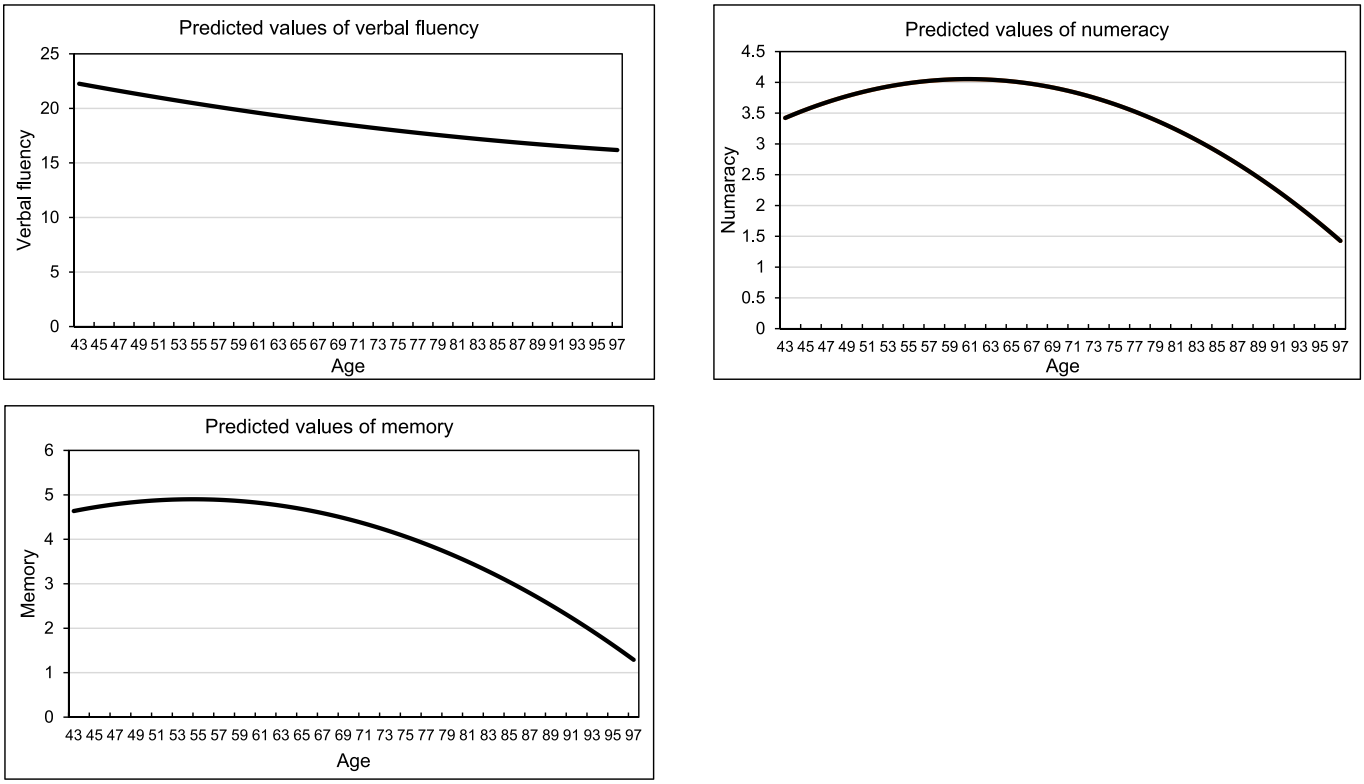

Fig. 1. The predicted values of cognitive functions by age.

controlling for age, socioeconomic indicators, lifestyle factors, and current health status. However, with the exception of numeracy, we did not find a significant association between PEF and subsequent decline in other cognitive functions during follow-up.

The significant effect of poor lung function on levels of cognitive function has been described in previous studies in the middle-aged and older population (Duggan et al., 2020). For instance, the results of English Longitudinal Study of Aging (ELSA), consisting of 6,080 older participants, suggested that poor lung function was associated with lower scores in memory tasks, numeracy, and verbal fluency (Qiao et al., 2020). Similarly, findings from a community-based Normative Aging Study (NAS) showed that men with average pulmonary function were more likely to achieve better general cognition compared to those with impaired lung function (Weuve et al., 2011).

Interestingly, we did not observe a consistent positive effect of PEF on the cognitive decline (slope) for any of the cognitive measures. Similar to our findings, the authors using data from NAS reported no significant association between pulmonary function and decline in any of the tested cognitive domains using generalized estimating equation regression models (Weuve et al., 2011). By contrast, several previous studies reported a significant effect on cognitive decline. For instance, using data from the Victoria Longitudinal Study, the results showed that pulmonary function decline was significantly associated with the decline in performance on computation span, fact recall, and vocabulary, while no effect on the slope was observed in word recall and numeracy (MacDonald et al., 2011). Furthermore, the study using data from the Swedish Adoption/Twin Study of Aging indicated that pulmonary function led to a subsequent modest decline in verbal ability (Emery et al., 2012). Lastly, a meta-analysis consisting of eight longitudinal studies showed that aggregated longitudinal slope correlations were different from zero, suggesting a significant association between pulmonary functions and cognitive decline (Duggan et al., 2019). The inconsistency with previously reported longitudinal changes might be explained by numerous factors, including sample, analytical methods, various measures for pulmonary and cognitive functions, and inclusion of key covariates.

The results of our study showed the negative effects of age on decline in all three cognitive domains. However, compared to verbal fluency and numeracy, a decrease in memory accelerated in later age. This finding is consistent with the previous research of the Women's Health and Aging Study II, showing that the decrease in memory accelerated later after the other studied cognitive domains, including executive functions (M. C. Carlson et al., 2009).

In our study, the majority of baseline covariates (with the exception of negative effects on the slope by age and smoking status) that were found to be significant predictors of the intercept were not found to predict the slope, as seen in Tables S1-S3. This suggests that there was substantial rank-order stability in this sample regarding the development of cognitive functions in older age, meaning that individuals tended to keep their initial rank order throughout development and that cognitive functions decline at a similar rate regardless of the factors affecting the initial status, at least for the covariates considered in this study, resembling the effect of normal cognitive aging (Harada et al., 2013).

The lack of covariate effects on the slope in this data may be linked to the inclusion criteria of the analytic sample, which did not include participants with major conditions affecting pulmonary functions or cognitive abilities. As such, our results reflect cognitive development in an older population free of severe chronic conditions. In addition, impaired pulmonary function is linked with increased mortality risk for respiratory and cardiovascular causes. Therefore, we were unable to examine whether people who were censored due to death during follow-up would have experienced faster cognitive decline. The underestimation of the effect of pulmonary function on cognitive decline needs to be considered as a possible explanation. In addition, the inconsistency of the current findings with previously reported longitudinal effects might be explained by numerous factors, including sample characteristics, differences in measures of pulmonary and cognitive functions, and inclusion of key covariates. It is also possible that the main damage to the biological system was done before participants entered the study (aged

Table 3
Unadjusted and adjusted estimates of PEF impairment for each cognitive measure.

Unadjusted estimates									
PEF quartile	Verbal fluency Intercept			Numeracy Intercept			Memory Intercept		
	B	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Q4 (best)	Ref.								
Q3	−1.29	0.22	<0.001	−0.12	0.02	<0.001	−0.22	0.03	<0.001
Q2	−3.31	0.31	<0.001	−0.37	0.04	<0.001	−0.66	0.04	<0.001
Q1 (worst)	−5.73	0.50	<0.001	−0.96	0.18	<0.001	−1.34	0.08	<0.001
	Linear slope			Linear slope			Linear slope		
	B	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Q4 (best)	Ref.								
Q3	−0.01	0.02	0.718	−0.01	0.01	0.162	−0.01	0.01	0.286
Q2	−0.02	0.02	0.232	−0.02	0.01	<0.001	−0.01	0.01	0.059
Q1 (worst)	−0.03	0.03	0.356	−0.04	0.01	<0.001	−0.02	0.01	0.034
							Quadratic slope		
							B	*SE*	*p*
Q4 (best)							Ref.		
Q3							<−0.01	<0.01	0.864
Q2							<−0.01	<0.01	0.477
Q1 (worst)							<−0.01	<0.01	0.639
Adjusted estimates									
	Verbal fluency Intercept			Numeracy Intercept			Memory Intercept		
	B	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Q4 (best)	Ref.								
Q3	−0.87	0.24	<0.001	−0.04	0.03	0.266	−0.15	0.03	<0.001
Q2	−2.03	0.35	<0.001	−0.15	0.05	0.002	−0.35	0.04	<0.001
Q1 (worst)	−3.15	0.44	<0.001	−0.52	0.11	<0.001	−0.64	0.05	<0.001
	Linear slope			Linear slope			Linear slope		
	B	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Q4 (best)	Ref.								
Q3	0.01	0.02	0.495	−0.01	0.01	0.351	<0.01	<0.01	0.721
Q2	0.01	0.02	0.851	−0.02	0.01	0.018	<0.01	0.01	0.811
Q1 (worst)	0.04	0.03	0.047	−0.03	0.01	0.001	0.01	0.01	0.199
							Quadratic slope		
							B	*SE*	*p*
Q4 (best)							Ref.		
Q3							<0.01	<0.01	0.929
Q2							<−0.01	<0.01	0.377
Q1 (worst)							<−0.01	<0.01	0.183

Note. Unstandardized values. Adjusted models included the following covariates: age, sex, smoking status, education level, BMI, cardiovascular disease, depression, and alcohol drinks per week.

50 or more), and the association in later years was weaker and therefore not detected. The results from sensitivity analyses showed that the lack of covariate effects on the decline was unlikely due to the inclusion of younger participants, as the results remained identical when the sample was limited to people aged 60 and older.

4.1. Implications of the current study

One of the biggest strengths of this study is its large longitudinal sample, comprising 13 European countries and Israel, collected over a 16-year period in six waves. This is one of the largest and most extensive studies to date evaluating the associations between lung functions and cognitive development in a sample from both high and middle-income countries. Employing the accelerated longitudinal design enabled us to take advantage of the varying age at baseline by structuring the analyses based on age and not wave, thereby extending the analyzed age range to cover >50 years instead of 16 years, as would be the case for wave-based analyses. Another great benefit of the accelerated longitudinal design is that by its nature, it adjusts for the effects of repeated exposure, enabling to disentangle the true effect of age (maturation) from the effects due to practice (McCormick, 2021). In this way, we were able to model a prototypical development of cognitive functions among older adults, maximizing the age range as well as available data. Furthermore, modeling the global cognitive score using a multilevel latent variable with the three cognitive dimensions as indicators provides a psychometrically robust way of modeling general cognition or what the different cognitive dimensions have in common.

The current study suggests that standardized PEF can be used as a valid index of pulmonary health, especially as it relates to cognitive functions, at least cross-sectionally. Although forced expiratory volume measured in one second (FEV1) and forced vital capacity (FVC) are well-established measures of lung function recommended by the American Thoracic Society (ATS)/European Respiratory Society (ERS), the comparable ability of PEF in lung function assessment was reported in the healthy population (Agarwal and Gupta, 2007). Moreover, due to its wide availability and simplicity to use, PEF might be a more beneficial measurement to use among older people (Cook et al., 1991; Roberts and Mapel, 2012). It has been demonstrated that PEF might be an independent predictor of cardiovascular events and mortality and better predict survival in the COPD population (Hansen et al., 2001). This measure showed a good correlation with several risk factors and was associated with cognitive performance in fully adjusted models (Cook et al., 1989, 1991; Hansen et al., 2001). However, studies validating the PEF diagnostic ability in the measurement of lung function are limited, and there are some previous studies that found that compared to FEV1 and FVC, PEF is a less valid approach in the assessment of lung function

Table 4
Unadjusted and adjusted estimates of PEF impairment for the global cognitive score model.

Unadjusted estimates						
PEF quartile	Intercept			Linear slope		
	B	*SE*	*p*	*B*	*SE*	*p*
Q4 (best)	Ref.					
Q3	−0.99	0.17	<0.001	−0.02	0.01	0.300
Q2	−2.79	0.25	<0.001	−0.05	0.02	0.018
Q1 (worst)	−5.47	0.45	<0.001	−0.08	0.03	0.002
				Quadratic slope		
				B	*SE*	*p*
Q4 (best)						
Q3				<−0.01	<0.01	0.165
Q2				−0.01	<0.01	0.047
Q1 (worst)				−0.01	<0.01	0.002
Adjusted estimates						
	Intercept			Linear slope		
	B	*SE*	*p*	*B*	*SE*	*p*
Q4 (best)	Ref.					
Q3	−0.59	0.17	<0.001	<0.01	0.01	0.802
Q2	−1.46	0.21	<0.001	<−0.01	0.01	0.671
Q1 (worst)	−2.65	0.29	<0.001	<0.01	0.02	0.665
				Quadratic slope		
				B	*SE*	*p*
Q4 (best)				Ref.		
Q3				<−0.01	<0.01	0.307
Q2				−0.01	<0.01	0.158
Q1 (worst)				−0.01	<0.01	0.015

Note. Unstandardized values. Adjusted models included the following covariates: age, sex, smoking status, education level, BMI, cardiovascular disease, depression, and alcohol drinks per week.

impairment by prediction equations (PEF % predicted value; Aggarwal et al., 2006; Llewellin et al., 2002). It might lead to underestimation and overestimation of our results in the group of people with mild and severe lung function impairment, respectively.

4.2. Limitations

Although the accelerated longitudinal design was the optimal choice for a longitudinal study with a large variance in age at the baseline, there are some limitations to this approach. First, we treated data from different countries as a single sample. Although the analytic approach directly modeled the clustering of individuals within countries, this approach did not estimate country-specific development of cognitive functions. We did not propose any specific hypotheses regarding the effects of countries in this study but future studies might focus on specific country-level variables that might affect the outcome or modify the hypothesized association. Relatedly, the limitation of the accelerated longitudinal design is that the modeled development across time does not follow a cohort of individuals but rather provides a "cross-sectional" overview of cognitive scores at different ages. In this way, the captured development is prototypical to the sample and is not necessarily sensitive to specific birth cohort effects (Galbraith et al., 2017). Furthermore, given the complexity of the data, we opted for age polynomials for estimating the developmental trajectory. However, researchers interested in more precisely approximating the trajectory might employ more data-driven methods, such as generalized additive mixed models (GAMMs; Sørensen et al., 2021).

There were also some limitations regarding the selection of the analytic sample and the measures used. As the form of the numeracy task changed from Wave 2, we could not use the Wave 2 scores. However, thanks to the accelerated longitudinal design, the missing Wave 2 did not translate to a limited age range, yet the analytic sample for numeracy was lower compared to the other cognitive tasks. Similarly, there were several countries that missed one or two waves of data collection. Again, this limitation would predominantly manifest as decreased statistical power and a lesser impact from these countries on the overall pattern, particularly if their trajectories were unusually distinct.

The cognitive tests used in our study were found to have good validity in differentiating healthy aging people and individuals with cognitive impairment (Yagi et al., 2016). These tests are included in the National Institute of Aging's Consortium to Establish a Registry for Alzheimer's Disease's (CERAD) neuropsychological battery (Morris et al., 1989). That said, the cognitive tests were likely to capture cases that transition from healthy aging to cognitive impairment, which is in the scope of the aim of our study. In addition to screening cognitive tasks, the criteria for diagnosing mild cognitive impairment (MCI) and dementia include biomarkers, structural and molecular neuroimaging, and cerebrospinal fluid (CSF) analysis of amyloid-β or tau proteins (Jagust, 2021). These measures were not available in SHARE data; therefore, it is possible that some individuals with cognitive impairment were not detected in our sample. People with a previous history of cognitive impairment were excluded from our analysis, although dementia diagnoses were self-reported, leading to the possibility of selection bias. However, the large sample size and standardized cognitive measures across all populations likely minimized these limitations.

5. Conclusion

The current study estimated the effect of lung function, indexed by PEF, on cognitive performance using a large, multi-national sample of older adults. The results confirmed that verbal fluency, memory, numeracy, and global cognitive functions decreased with age. Individuals with a reduced level of PEF showed significantly lower levels of all cognitive outcomes. These associations remained significant even when controlling for a variety of covariates.

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CRediT authorship contribution statement

Albert J. Ksinan: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Andrea Dalecká:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Tatyana Court:** Writing – review & editing, Writing – original draft, Conceptualization. **Hynek Pikhart:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Martin Bobák:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

None.

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