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Apolipoprotein E Genotype Modifies the Association between Midlife Lung Function and Cognitive Function in Old Age

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Key Words
Lung function · Cognitive function · Dementia · Apolipoprotein E ε4 · Prospective cohort study

Abstract
Background/Aims: Because poor lung function may be a risk factor for cognitive decline, we aimed to test the association of respiratory function with cognitive function and dementia later in life, as well as potential effect modification by *APOE* ε4 carrier status. ***Methods:*** In a prospective population-based cohort study, forced vital capacity and forced expiratory flow were measured around 1965 in 857 men aged 45–64 years (394 from Finland, 208 from The Netherlands, and 255 from Italy). The Mini-Mental State Examination scores around 1990, 1995 and 2000 were analyzed using multilevel regression models and the Clinical Dementia Rating score around 1990 using multinomial logistic regression analyses. ***Results:*** Midlife lung function was positively associated with cognitive function in old age in *APOE* ε4 non-carriers, but not in carriers ($p < 0.05$ for interaction). In Finland and Italy, 18.6% had questionable to mild dementia and 2.8% moderate to severe dementia after 25 years of follow-up. Dementia was inversely related to midlife lung function in *APOE* ε4 non-carriers, but not in carriers ($p < 0.05$ for interaction). ***Conclusions:*** Small lung volumes were prospectively associated with an increased risk for poor cognitive function and dementia in non-carriers of the *APOE* ε4 gene.

Introduction

Cognitive impairment and dementia approximately doubles every 5 years of increasing age and is of major public health concern [1]. Carriership of the ε4 allele of the apolipoprotein E gene (*APOE* ε4) is the strongest genetic risk factor for cognitive impairment and Alzheimer's dementia [1], but also sociodemographic, lifestyle-related, and cardiovascular risk factors are of importance [2]. The concepts of 'vascular', 'arteriosclerotic', 'post-stroke' and 'multi-infarct' dementia point to a central cerebrovascular aetiology [3]. Ischemia and consequently low oxygen supply through brain hypoperfusion may therefore partly underlie cognitive impairment and dementia.

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There is some evidence that impaired respiratory function is involved in the process of cognitive dysfunction and dementia. Several studies found that acute, repeated or chronic brain hypoxia – due to the acute respiratory distress syndrome, obstructive sleep apnoea syndrome, or severe chronic obstructive pulmonary disease (COPD) – is associated with more neuropsychological dysfunction [4–7]. Poor respiratory function in spirometry tests and cognitive impairment were also found to be strongly associated in cross-sectional surveys [8–10]. Interpretation of cross-sectional studies is, however, limited by the possibility of reverse causation, as poor performance in spirometry tests may reflect cognitive difficulties and reduced motivation.

There is a growing number of prospective epidemiological studies that focused on the association between respiratory function and cognitive function later in life. In 1,778 men and women, forced expiratory flow in 1 s (FEV_1) at 43 years was inversely associated with the decline in psychomotor speed after 10 years, but not for the decline in memory [11]. Also in 222 Swedish twin pairs with a mean age of 62 years old, FEV_1 predicted for cognitive performance in some of the cognitive test results after 6 years of follow-up [12]. The latter study also gave support for an important genetic contribution to this relationship that was stronger than the environmental component [12]. Peak expiratory flow was also a predictor of cognitive decline in 1,011 men and women aged 70–79 years over a follow-up of 2.5 years [13]. Two prospective studies had longer follow-up periods. In 3,036 Japanese-American men in Hawaii, it was found that FEV_1 was strongly predictive of cognitive function after up to 23 years [14]. In 1,291 Swedish women, peak expiratory flow, FEV_1, and forced vital capacity (FVC) at midlife predicted for dementia, assessed by an extensive neuropsychiatric evaluation after up to 29 years [15]. No previous study considered the possibility that the association could be modified by *APOE* ε4 status.

We hypothesized that poor respiratory function, even in the absence of clinically significant pulmonary disease, is related to poor cognitive function in aging men. We studied whether respiratory dysfunction assessed by spirometry in midlife is a predictor of poor cognitive function up to 35 years later in life in 857 initially middle-aged men from 3 European counties, as part of the prospective Finland, Italy and the Netherlands Elderly (FINE) study, and whether the putative association was influenced by APOE ε4 carrier status.

Methods

Subjects

The present study cohorts started as contributions to the Seven Countries Study (SCS) [16]. Respiratory function was assessed around 1965, when participating men were aged between 45 and 64 years old. In Finland, there were 2 cohorts that consisted of all men born in 1900–1919 from 2 geographically defined areas: Ilomantsi in eastern Finland and Pöytyä and Mellilä in southwestern Finland. In The Netherlands, there was 1 cohort that consisted of men born between 1900 and 1920 from the town of Zutphen, in the eastern part of the country. In Italy, there were 2 cohorts that consisted of men born in 1901–1920 from 2 villages: Crevalcore in the north and Montegiorgio in the centre of Italy.

Follow-up visits with the MMSE took place from 1990 onwards, when participating men were aged between 70 and 89 years old, as part of the subsequent FINE study [17]. In Finland, 469 (89.7%) of 523 men who were still alive were examined in 1989, 274 (87.5%) in 1994, and 131 (82.9%) in 1999. In The Netherlands, 252 (83.4%) of 302 alive were examined in 1990, 152 (77.6%) in 1995, and 77 (74.8%) in 2000. In Italy, 391 men (79.3%) of 493 alive were examined in 1991, 269 (73.5%) in 1995, and 201 (91.4%) in 2000. Of the 1,112 participants, 857 (77.1%) were eligible for the present analyses because they had at least 1 valid MMSE assessment at follow-up, had complete data on all other variables of interest, and were free of cancer in 1970. Appropriate institutional review boards approved the SCS project with informed – but unwritten – consent, as was the custom in the 1960s before the era of the Helsinki Declaration. The study was fully explained to all participants. The subsequent FINE study was approved by local medical ethics committees in Finland, The Netherlands, and Italy, and informed consent was obtained from all participants around 1985.

Respiratory Function

In Finland, the FVC (i.e. maximal volume of air that can be forcefully expelled from the lungs after maximal inhalation) and FEV in 0.75 s ($FEV_{0.75}$; i.e. a flow rate measurement of the volume of air that can be forcibly exhaled from the lungs in the first 0.75 s of a forced expiratory maneuver) were measured with a McKerrow spirometer [16, 17] with subjects in a sitting position wearing a noseclip. The highest values produced in 3 attempts were used in the analyses. In The Netherlands, the FVC and FEV_1 were measured with a Godart Pulmotest with subjects sitting in an upright position [16, 17]. In The Netherlands, FEV was measured during 1 s, and these levels were transformed from 1 to 0.75 s by applying an estimated coefficient of 0.93. The mean of the 2 highest values established in 3 attempts was used. In Italy, the FVC and $FEV_{0.75}$ were measured with a Pulmonor Jones spirometer with the subjects standing and wearing a noseclip [16, 17]. The highest values produced in 2 or 3 attempts were used in the analyses.

The FVC and $FEV_{0.75}$ correlated strongly (Pearson's $r = 0.76$; $p < 0.001$). Forced expiratory flow measured during 0.75 s ($FEV_{0.75}$) was transformed by dividing by 0.93 to calculate the predicted FEV_1 and FEV_1/FVC ratio, an indicator of airflow obstruction. FEV_1 as the percentage of predicted was calculated using the following formula: $FEV_{predicted} = 1.010 \times height^2$ (in m) $- 0.028 \times$ age (in years) + 1.861 [18].

Cognitive Function

The Mini-Mental State Examination (MMSE) assesses multiple cognitive domains and was used in 1990, 1995, and 2000 to assess global cognitive functioning, except for Finland in 1995 [19]. If a subject did not answer ≥4 individual items (of a total of 20), the total MMSE score was considered missing. If <4 items were missing, these items were rated as errors and a total MMSE score was calculated. In 1990, valid MMSE data from 853 Finnish, Italian and Dutch men was obtained. In 1995, 286 Italian and Dutch men participated in the survey, and in 2000, 266 Finnish, Italian and Dutch men participated.

For men who did not reach a score of 27 on the MMSE, a brief neuropsychological evaluation was performed. This information was collected around 1990 for 646 participants: in Finland (n = 392) and Italy (n = 254), but not in The Netherlands. The Clinical Dementia Rating form was filled in by the physician, following the criteria reported in the questionnaire [20, 21]. It includes items on memory, orientation, judgment and problem solving, community affairs, life at home and hobbies, and personal care. A score of 0 indicates no dementia, a score of 0.5–1 indicates questionable to mild dementia and a score of 2–3 indicates moderate to severe dementia.

APOE *and Other Variables*

The *APOE* genotype was determined by isoelectric focusing of delipidated plasma samples followed by immunoblotting in the laboratory TNO-Institute of Preventive Health Research PG-TNO, Leiden, The Netherlands for the Dutch and Italian samples, and in the laboratory of the National Public Health Institute (Helsinki, Finland) using a largely similar method [22]. The Hardy-Weinberg assumption was tested using χ^2 tests for the triallelic *APOE*.

Age was calculated from the year and month of birth. A questionnaire of the reported profession was used to construct the categorical variables socioeconomic status (SES) and job-related physical activity [16]. For Finland and The Netherlands, the reported profession from 1960 was used, but for Italy this information was available only in 1965. SES was categorized over 3 levels (i.e. higher: professionals, managers, businessmen, and landowners/middle: foremen, clerical workers, skilled workers, farmers and fishermen/lower: firemen, policemen, guards, transporters, railroad workers, unskilled workers, unemployed and disabled). Job-related physical activity was derived from matching the reported physical engagement with the professional profile, and categorized over 3 levels (i.e. lower: sedentary or bedridden/middle: moderately active/higher: hard physical work). Detailed standardized questionnaires were used to assess cigarette smoking status (i.e. never or long-term ex-smoker ≥10 years ago/recent ex-smoker <10 years ago/current smoker, <10 cigarettes per day/current smoker, ≥10 cigarettes per day), cigar or pipe smoking status (i.e. non-smoker/current smoker) [23], and marital status (i.e. currently married/unmarried: never married, widowed or divorced).

Clinical disease at baseline in 1965 was assessed by physical examination and history. Cardiovascular disease was defined as angina pectoris, myocardial infarction, chronic heart disease of possible coronary origin, intermittent claudication, or stroke. In the field examination of 1970, but not in 1965, prevalent cancer and chronic lung disease (i.e. bronchial asthma, pulmonary emphysema, chronic bronchitis, and/or pulmonary tuberculosis) was recorded. Weight and height were measured, and used to calculate the body mass index (BMI). Blood pressure was recorded with a calibrated mercury sphygmomanometer [16]. For the time-dependent dichotomous variable of prevalent disease the following clinical diagnoses were considered in 1990: COPD, myocardial infarction, heart failure, stroke, diabetes mellitus and cancer. In 1995 and 2000, only myocardial infarction, stroke, diabetes mellitus and cancer were considered. Prevalent disease in Finland was available up to 1998.

Statistical Analysis

Data presented are numbers (with percentages) or means (± standard deviation). In table 2, multilevel analysis was used to analyze associations between respiratory function variables and the MMSE score, using an unstructured covariance model. Stratified analyses were done in *APOE* ε4 non-carriers and in *APOE* ε4 carriers. Quartiles for FVC and $FEV_{0.75}$ were calculated for *APOE* ε4 non-carriers (n = 665), whereas a median split was used for the smaller group of *APOE* ε4 carriers (n = 192). Subjects were categorized within each country. As the distribution of MMSE scores was negatively skewed (due to the ceiling effect of the maximum score of 30), 32 minus the score was log-transformed to normalize the distribution. Appropriate back-transformed means are presented. Because of important differences between countries, standard scores (i.e. z-values [i.e. $(\chi - \mu)/\sigma$] adjusted for country) were used for $FEV_{0.75}$, FVC, BMI, body height and systolic blood pressure. A two-level structure consisted of the observations (i.e. lower level) and the subjects (i.e. higher level). The outcome transformed MMSE variable was used as a continuous variable, and estimated marginal means (with 95% confidence intervals (CIs)) were given. Model 1 started with country and age as covariates. In model 2, we additionally adjusted for chronic disease at baseline in 1965, SES, job-related physical activity, smoking status, BMI, body height and systolic blood pressure. Prevalent chronic disease at follow-up in 1990, 1995, and 2000 was a time-dependent covariate. In the combined group, appropriate interaction terms were added to the multivariable model.

In figure 1, multilevel analysis was also used to analyze associations between respiratory function and the MMSE score, using an unstructured covariance model, while adjusting for country and age. In table 3, multinomial logistic regression analysis was used to yield odds ratios for dementia groups according to baseline standard scores of $FEV_{0.75}$ and FVC. In *APOE* ε4 carriers, the questionable to mild dementia (n = 34) and moderate to severe dementia (n = 7) categories were collapsed into 1 category because of small numbers. We tested for linear trends over the 3 dementia groups for the mean values of $FEV_{0.75}$ and FVC using polynomial contrast in multivariate analysis of variance. All tests were 2-sided, and a $p < 0.05$ was considered statistically significant. The software used was SPSS for Windows version 16.0.

Results

Baseline characteristics in 1965 are shown in table 1. There were no statistically significant deviations for *APOE* from Hardy-Weinberg equilibrium in the Finnish, Dutch, Italian and combined study populations (all $p > 0.05$). *APOE* ε4 carriership varied between countries, be-

Table 1. Baseline characteristics of the study cohort of 857 men aged 45–64 according to *APOE* ε4 carrier status from the 3 European countries in 1965

	APOE ε4 non-carriers	*APOE* ε4 carriers
Number of men	665	192
Age, years	50.9 ± 4.4	51.4 ± 4.6
Country		
Finland	284 (42.7%)	110 (57.3%)
The Netherlands	163 (24.5%)	45 (23.4%)
Italy	218 (32.8%)	37 (19.3%)
Socioeconomic status		
Higher	74 (11.1%)	8 (4.2%)
Middle	418 (62.9%)	136 (70.8%)
Lower	173 (26.0%)	48 (25.0%)
Job-related physical activity		
Sedentary or bedridden	77 (11.6%)	14 (7.3%)
Moderately active	205 (30.8%)	57 (29.7%)
Hard physical work	383 (57.6%)	121 (63.0%)
Marital status		
Married	622 (93.5%)	173 (90.1%)
Never married, widowed or divorced	43 (6.5%)	19 (9.9%)
Cigarette smoking status		
Never and long-term ex-smoker	193 (29.0%)	73 (38.0%)
Recent ex-smoker	119 (17.9%)	44 (22.9%)
Current smoker, <10 per day	114 (17.1%)	20 (10.4%)
Current smoker, ≥10 per day	239 (35.9%)	55 (28.6%)
Cigars or pipe smoking status		
Non-smoker	562 (84.5%)	161 (83.9%)
Current smoker	103 (15.5%)	31 (16.1%)
Chronic disease		
CVD and/or diabetes mellitus	26 (3.9%)	7 (3.6%)
Chronic lung disease	170 (25.6%)	34 (17.7%)
Any chronic disease	189 (28.4%)	41 (21.4%)
BMI[1]	25.0 (24.7–25.2)	25.0 (24.5–25.4)
Body height[1], cm	170.2 (169.7–170.7)	170.5 (169.6–171.4)
Systolic blood pressure[1], mm Hg	135.8 (134.6–137)	136.2 (134.0–138.5)
Diastolic blood pressure[1], mm Hg	83.1 (82.4–83.8)	82.8 (81.4–84.1)
$FEV_{0.75}$ [1], l	3.1 (3.1–3.2)	3.1 (3.0–3.1)
FVC[1], l	4.6 (4.6–4.7)	4.5 (4.4–4.7)

Chronic lung disease was defined as chronic obstructive pulmonary disease (COPD) and/or pulmonary tuberculosis. Data are numbers, (percentages), means ± SD or 95% CIs (in parentheses). The $FEV_{0.75}$ needs to be multiplied by 1.08 to estimate the FEV_1.

CVD = Cardiovascular disease. [1] Data are estimated marginal means (with 95% CI) adjusted for age and country.

ing 27.9% in Finland, 21.6% in The Netherlands, and 14.5% in Italy. The mean age of the participating men was 51 years (range 45–64), and was 50.9 (SD 4.4) for *APOE* ε4 non-carriers and 51.4 (SD 4.6) for carriers. Pulmonary disease was most prevalent in Italy, especially due to higher prevalence rates of chronic bronchitis.

The men were followed for up to 35 years (mean follow-up ± SD: 29.1 ± 4.5 years). The *APOE* ε4 carriership predicted for lower MMSE scores (back-transformed mean 24.6 [95% CI: 24.1–25.1] vs. 25.3 [95% CI: 25.0–25.5]: p = 0.02; fig. 1), and a higher multivariable-adjusted odds ratio of (moderate to severe) dementia of 1.57, though not statistically significant (95% CI: 0.58–4.22). The *APOE* ε4 carriers did not differ from non-carriers for $FEV_{0.75}$, FVC, the FEV_1/FVC ratio, nor FEV_1 as the percentage of predicted (all $p > 0.2$).

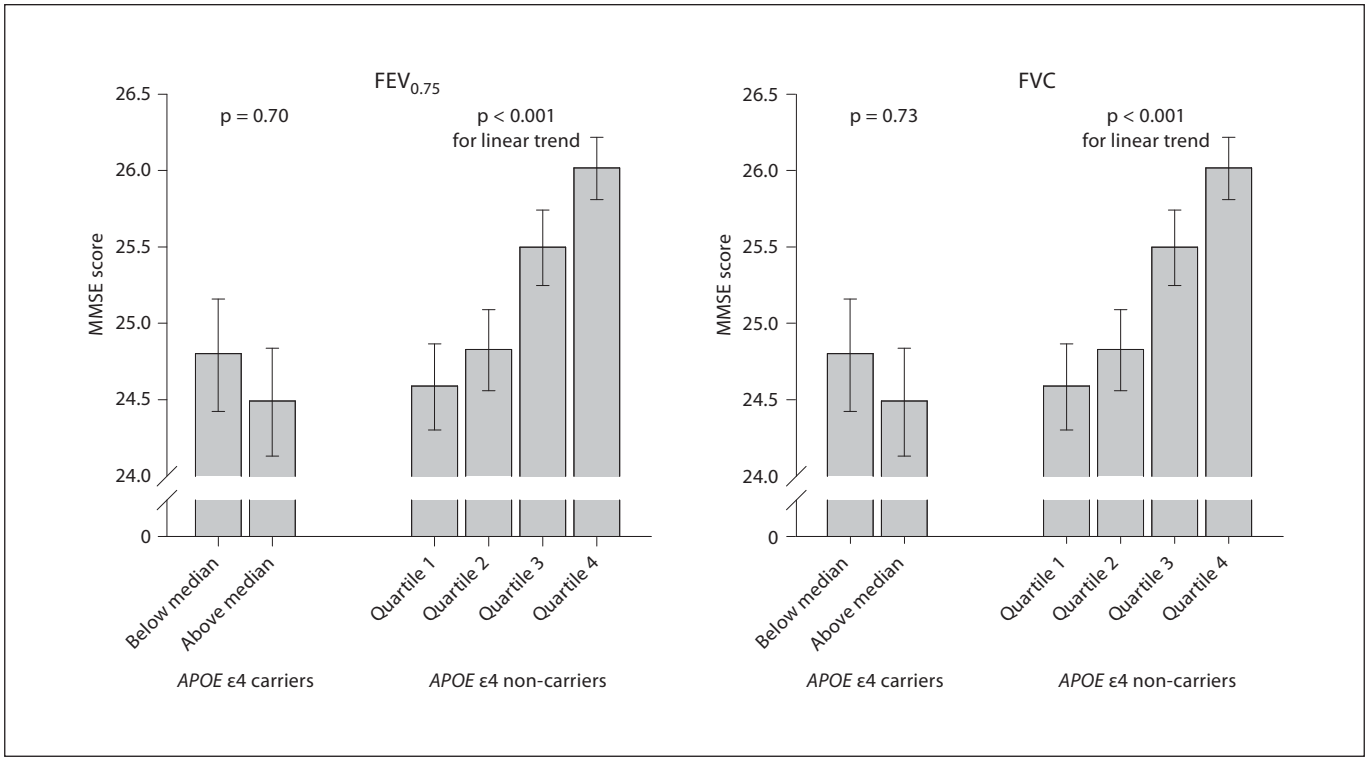

Fig. 1. Cognitive functioning assessed by the MMSE during follow-up (from 1990 until 2000) according to baseline $FEV_{0.75}$ and FVC in 1965, from 857 men in Finland, The Netherlands and Italy. The 192 (22.4%) *APOE* ε4 carriers were categorized according to a median split of respiratory function, and the 665 *APOE* ε4 non-carriers were categorized into quartiles. Data are estimated means (with error bars indicating SEM) by multilevel regression analysis, adjusted for country and age. Respiratory function was associated with MMSE scores in *APOE* ε4 non-carriers, but not in *APOE* ε4 carriers ($p < 0.05$ for both interaction terms). The *APOE* ε4 carriers had MMSE scores that were similar in comparison to *APOE* ε4 non-carriers in quartiles 1 and 2 (i.e. those men with relatively poor respiratory function; $p > 0.5$).

Table 2 shows the results for multivariable analyses, when subjects were classified according to baseline respiratory function. There was a positive association between respiratory function and MMSE scores in *APOE* ε4 non-carriers but not in carriers (fig. 1), which remained significant in the final multivariable model 2. Associations in *APOE* ε4 non-carriers were largely consistent over 3 different European countries, and interaction terms (for country × lung function) were not statistically significant (all $p > 0.2$). Body height and respiratory function were significantly intercorrelated, with partial correlation coefficients adjusted for country being 0.41 ($p < 0.001$) for the $FEV_{0.75}$ and 0.55 ($p < 0.001$) for FVC. Therefore, it is of importance that after adjustment for body height, the association between $FEV_{0.75}$ and FVC with MMSE scores remained statistically significant in *APOE* ε4 non-carriers. The FEV_1 as the percentage of predicted, but not the FEV_1/FVC ratio, was statistically significantly associated with MMSE scores in the final multivariable-adjusted model (data not shown). In all participants combined, *APOE* genotype modulated the association with the MMSE score. The formal tests for interaction were statistically significant, both for *APOE* ε4 carrier status × $FEV_{0.75}$ ($t = -2.62$; $p = 0.009$) and *APOE* ε4 carrier status × FVC ($t = -2.14$; $p = 0.03$) in multilevel analyses.

Table 3 shows the association between baseline respiratory function in Finland and Italy and the prevalence of dementia according to the Clinical Dementia Rating score. There were 463 subjects without dementia, 159 men with questionable to mild dementia (18.6%), and 24 men with moderate to severe dementia (2.8%) at 25 years of follow-up. In *APOE* ε4 non-carriers, a 1-SD increase in $FEV_{0.75}$ was associated with a lower odds ratio of 0.41 (95% CI: 0.25–0.68) of dementia as compared to no dementia, adjusted for age and country. FVC was also associated with a lower odds ratio for dementia of 0.56 (95%

Table 2. Association between quartiles of baseline respiratory function around 1965 and cognitive functioning at follow-up (between 1990 and 2000) in 857 men from Finland, The Netherlands, and Italy

APOE ε4 non-carriers	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p
$FEV_{0.75}$					
Number of men	165	172	150	178	
$FEV_{0.75}$ – mean ± SD, l	2.3 ± 0.4	3.0 ± 0.2	3.3 ± 0.1	3.9 ± 0.3	
MMSE					
Model 1	24.7 (24.1–25.2)	24.9 (24.4–25.4)	25.6 (25.1–26.0)	26.1 (25.6–26.4)	<0.001
Model 2	25.6 (24.9–26.3)	25.7 (24.9–26.3)	26.2 (25.5–26.8)	26.4 (25.8–27.0)	0.005
FVC					
Number of men	166	165	168	166	
FVC – mean ± SD, l	3.7 ± 0.4	4.4 ± 0.2	4.9 ± 0.2	5.5 ± 0.4	
MMSE					
Model 1	24.8 (24.3–25.4)	24.9 (24.4–25.4)	25.5 (25.0–25.9)	26.1 (25.7–26.5)	<0.001
Model 2	25.8 (25.0–26.5)	25.7 (24.9–26.3)	26.0 (25.4–26.6)	26.5 (25.9–27.1)	0.02

APOE ε4 carriers	Below median	Above median	p
$FEV_{0.75}$			
Number of men	91	101	
$FEV_{0.75}$ – mean ± SD, l	2.6 ± 0.4	3.5 ± 0.4	
MMSE			
Model 1	24.3 (23.4–25.1)	24.1 (23.3–24.9)	0.70
Model 2	23.8 (21.9–25.3)	23.5 (21.6–25.0)	0.65
FVC			
Number of men	94	98	
FVC – mean ± SD, l	4.0 ± 0.5	5.1 ± 0.6	
MMSE			
Model 1	24.3 (23.4–25.1)	24.1 (23.3–24.9)	0.73
Model 2	23.9 (22.0–25.4)	23.5 (21.6–25.0)	0.57

p values for linear trend over the quartiles by linear mixed models.

Data are numbers, means ± SD for $FEV_{0.75}$, and the back-transformed estimated marginal means with 95% CI for the MMSE score.

Model 1: adjusted for country and age.

Model 2: additionally adjusted baseline time-independent variables (i.e., chronic disease including COPD, socioeconomic status, job-related physical activity, marital status, smoking status, BMI, body height, and systolic blood pressure), and for prevalent chronic disease at follow-up (as a time-dependent variable).

CI: 0.34–0.93; table 3). The strength of these associations did not change when several potential confounders were added to the multivariable model.

In *APOE* ε4 carriers, however, a 1-SD increase in $FEV_{0.75}$ and FVC were associated with increased odds ratios for (questionable to severe) dementia of 1.57 (95% CI: 1.00–2.45) and 1.59 (95% CI: 1.06–2.39), respectively. Again, there was effect modification by *APOE* ε4 carriership. The tests for interaction were statistically significant for both the interaction terms: *APOE* ε4 carrier status × $FEV_{0.75}$ (χ^2 (d.f. 2) = 9.0; p = 0.01) and *APOE* ε4 carrier status × FVC (χ^2 (d.f. 2) = 6.8; p = 0.03) in likelihood ratio tests.

Discussion

We found a temporal inverse relationship between respiratory function measured through spirometry and subsequent cognitive function and dementia rating scores, indicating that poor respiratory function is a risk factor for poor cognitive functioning in *APOE* ε4 non-carriers. Restrictive impairment was associated with cognitive function, rather than airways obstruction. There was effect modification by *APOE* ε4 status, as in *APOE* ε4 carriers larger indices of respiratory function were not associated with a lower risk for dementia.

Our data extends previous prospective epidemiological studies, suggesting that poor respiratory function is

Table 3. Odds ratios for dementia at 25 years of follow-up according to baseline respiratory function in 652 men from Finland and Italy

APOE ε4 non-carriers	No dementia	Questionable to mild dementia	Moderate to severe dementia	p for trend*
Number of men	358	125	17	
$FEV_{0.75}$				
Model 1	1.00	0.84 (0.67–1.06)	0.41 (0.25–0.68)	<0.001
Model 2	1.00	0.86 (0.66–1.12)	0.43 (0.24–0.76)	0.002
FVC				
Model 1	1.00	0.96 (0.76–1.21)	0.56 (0.34–0.93)	0.03
Model 2	1.00	1.02 (0.76–1.36)	0.59 (0.32–1.08)	0.07
APOE ε4 carriers	No dementia	Questionable to severe dementia		p
Number of men	105	41		
$FEV_{0.75}$				
Model 1	1.00	1.57 (1.00–2.45)		0.048
Model 2	1.00	1.57 (0.87–2.85)		0.14
FVC				
Model 1	1.00	1.59 (1.06–2.39)		0.03
Model 2	1.00	1.59 (0.91–2.77)		0.10

Odds ratios are calculated per 1-SD increase in baseline respiratory function (z-scores of $FEV_{0.75}$ and FVC) using multinomial logistic regression analysis. No dementia was defined as having a MMSE ≥27 or a Clinical Dementia Rating score of 0, questionable to mild dementia as a score of 0.5–1, and moderate to severe dementia as a score of 2–3 [20, 21].

Model 1: adjusted for country and age.

Model 2: adjusted for country, age, chronic disease including COPD, SES, job-related physical activity, marital status, smoking status, BMI, body height, and systolic blood pressure.

* p for linear trend over the 3 groups for the mean values of respiratory function using polynomial contrast in multivariate analysis of variance.

an independent risk factor for poor cognitive function [11–14] and dementia in elderly subjects [15]. It has been shown that poor respiratory function is associated with cardiovascular disease [24, 25], higher BMI, and higher blood pressure [26]. It is therefore of importance that associations between lower respiratory function and cognitive dysfunction remained significant after adjusting for these factors.

APOE ε4 carriership increases the risk of Alzheimer's disease [1], and we confirm the association with poor cognitive function. We also found the expected variation in *APOE* ε4 carriership between countries, with a European north-south gradient [27]. Our study compared *APOE* ε4 carriers and non-carriers, to identify whether there was effect modification by this important genetic risk factor for dementia. We found that only in *APOE* ε4-negative men positive associations between lung volumes and cognitive function were found, but not in *APOE* ε4 carriers. Quite contrarily, *APOE* ε4 carriers with other common physical limitations – atherosclerosis, peripheral vascular disease, or diabetes mellitus – were found to be at a markedly increased risk of cognitive decline [28, 29]. A remarkable finding in the present study was that larger lung volumes were associated with a higher risk of dementia in *APOE* ε4 carriers. No previous studies examined potential modifying effects of *APOE* ε4 carriership on the association between respiratory function and cognition, but a twin study found evidence for important genetic effects [12]. Our findings may partly be due to negative influences of *APOE* ε4 on cognitive function that may have overshadowed any potential beneficial effect of greater lung volumes. Alternatively, there might be biological factors affected by *APOE* that modified the relationship between respiratory and cognitive function. The mechanism of this effect modification has to be elucidated in future studies.

There are several potential explanations for the relationship between respiratory and cognitive function in *APOE* ε4 non-carriers. First, poor respiratory function is associated with a reduced surface available for gas exchange and may therefore increase the chance to hypoven-

tilation and chronic hypoxia and hypercapnia, which may subsequently affect neurocognitive performance [30]. Chronic hypoxia and hypercapnia may induce changes in neurotransmitter metabolism, glucose metabolism, ATP production, oxidative stress, inflammatory responses, and blood-brain barrier function [31]. Moreover, neural cells, especially in the hippocampus, are vulnerable to hypoxia [32], due to an energy crisis [3]. It has already been shown that poor respiratory function is associated with more subcortical brain atrophy [10], white matter lesions, and lacunar infarcts [33]. Positron-emission tomographic scans of hippocampi of dementia patients have shown widespread diminished glucose uptake and metabolism in the brain [34], but it is unclear whether this is a causal factor or attributable to brain atrophy [35]. Second, the association may be due to impaired fetal and postnatal development. Children exposed to undernourishment, sickness and prenatal stressors (e.g. poor diet, active and passive smoking, or misuse of alcohol) are shorter and may have underdeveloped lungs [36] as well as a higher vulnerability to cognitive dysfunction. This is in line with a study that found that respiratory function was already associated with cognitive development in children [37]. Third, there might be an indirect relationship as both declines in respiratory and cognitive function, caused by nonspecific aging processes or by overlapping vulnerabilities to unmeasured genetic or environmental risk factors.

Principal strengths of this study are the prospective design with long follow-up, sequential measurement of cognitive function at old age, and a range of potential modulators/confounders including *APOE* ε4 status. Our study also has limitations. We studied the MMSE and the Clinical Dementia Rating scale, but did not include other more elaborate neuropsychological tests. The Clinical Dementia Rating is a screening instrument of dementia that overlaps with, but is not similar to, the use of more elaborate NINCDS-ADRDA criteria [38]. Moreover, data of the Clinical Dementia Rating scale were missing in The Netherlands. We could not adjust for the baseline level of education, but we adjusted for SES that is correlated with education. We did not adjust at baseline for cognitive function or dementia. However, it is considered improbable that a substantial part of the participating men had dementia at baseline, because of the mean age of 51 years at baseline and because all men also participated at least 20 years later. Since we were studying men, extrapolation of our findings to women must be done with caution. In longitudinal studies, there is important attrition due to a reduction of the available sample from the original cohort, because of drop-out and death. Although loss to follow-up may have biased our results, we would expect the result to be attenuation towards the null hypothesis. It should also be noted that genotype assessment through the protein isoforms is valid [22], but is not considered as good as actual DNA-based typing. *APOE* genotyping with this method in 200 serum samples stored at –20°C for 1 to 4 years gave similar results as obtained with the conventional method (at that time) based on isoelectric focusing of delipidated very low-density lipoprotein isolated from fresh serum followed by protein staining; no incorrect results were obtained [22].

The results of this and other studies [11–15] indicate that poor respiratory function may increase cognitive impairment during aging, especially in elderly who are negative for the *APOE* ε4 allele. These findings may increase our understanding in the pathophysiology of cognitive decline. A possible explanation is that a chronic lowering of oxygen supply to the brain may increase the vulnerability to nongenetic dementia. As respiratory function can be objectively, reliably and easily assessed by spirometry, it may be utilized as a predictor of cognitive decline, decades before the onset of cognitive decline. Further research is needed into the risk of dementia that may be modified by gene-environment interaction between the *APOE* genotype and respiratory function.

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