Lung Function Impairment and the Risk of Incident Dementia: The Rotterdam Study

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Abstract.

Background: The etiology of dementia may partly be underpinned by impaired lung function via systemic inflammation and hypoxia.

Objective: To prospectively examine the association between chronic obstructive pulmonary disease (COPD) and subclinical impairments in lung function and the risk of dementia.

Methods: In the Rotterdam Study, we assessed the risk of incident dementia in participants with Preserved Ratio Impaired Spirometry (PRISm; FEV1/FVC ≥ 0.7, FEV1 < 80%) and in participants with COPD (FEV1/FVC < 0.7) compared to those with normal spirometry (controls; FEV1/FVC ≥ 0.7, FEV1 ≥ 80%). Hazard ratios (HRs) with 95% confidence intervals (CI) for dementia were adjusted for age, sex, education attainment, smoking status, systolic blood pressure, body mass index, triglycerides, comorbidities and Apolipoprotein E (APOE) genotype.

Results: Of 4,765 participants, 110 (2.3%) developed dementia after 3.3 years. Compared to controls, participants with PRISm, but not COPD, had an increased risk for all-type dementia (adjusted HR PRISm 2.70; 95% CI, 1.53–4.75; adjusted HR COPD 1.03; 95% CI, 0.61–1.74). These findings were primarily driven by men and smokers. Similarly, participants with FVC% predicted values in the lowest quartile compared to those in the highest quartile were at increased risk of all-type dementia (adjusted HR 2.28; 95% CI, 1.31–3.98), as well as Alzheimer’s disease (AD; adjusted HR 2.13; 95% CI, 1.13–4.02).

Conclusion: Participants with PRISm or a low FVC% predicted lung function were at increased risk of dementia, compared to those with normal spirometry or a higher FVC% predicted, respectively. Further research is needed to elucidate whether this association is causal and how PRISm might contribute to dementia pathogenesis.

Keywords: Alzheimer’s disease, chronic obstructive pulmonary disease, dementia, forced vital capacity (FVC), preserved ratio impaired spirometry

INTRODUCTION

Dementia is characterized by poor cognitive performance interfering with activities of daily living and impaired health-related quality of life at older ages [1], with an increasing prevalence worldwide [2]. In order to mitigate the burden of dementia through postponement or prevention, and to respond adequately on such a major health problem, the
identification of key modifiable risk factors is warranted and include smoking, obesity, hypertension, depression, sleep apnea, diabetes, and hyperlipidemia [3]. Chronic obstructive pulmonary disease (COPD) and decreased lung volume capacity have also been associated with a greater risk of dementia and compromised cognitive ability [4]. Possible etiological links with dementia comprise systemic inflammation and hypoxia induced oxidative stress [4–6].

More recently, preserved ratio impaired spirometry (PRISm)—with a prevalence ranging from 3% to 20% in adults [7]—has emerged as a clinically relevant entity related to premature mortality [7, 8], but thus far has been largely understudied, because of a hitherto stronger focus on COPD. The term PRISm encompasses the findings of restrictive respiratory pattern with impaired spirometry, i.e., decreased forced expiratory volume in one second (FEV1) or forced vital capacity (FVC) but preserved FEV1/FVC ratio [7]. People with PRISm suffer from lung function restriction but due to normal range of FEV1/FVC ratio would not be diagnosed as COPD according to the GOLD guidelines in clinical practice [7, 9]. Previous studies have suggested PRISm is a fluctuating state, serving as an intermediate phase between normal spirometry and COPD [8, 10]. However, very little is known about the clinical sequelae of PRISm, including risk of dementia.

Therefore, the aim of this study was to investigate the association of both COPD and subclinical reduced lung function, as evidenced by the presence of impaired lung volumes (PRISm), with the risk of dementia at follow-up within a prospective population-based cohort study.

METHODS

This study was conducted within the Rotterdam Study, a prospective cohort study that started in 1990, comprising almost 15,000 participants aged at least 45 years, with the aim of studying chronic diseases in the general population [11]. Every four to five years, participants underwent follow-up examinations, consisting of a home interview and various physical examinations at the research center. We used data collected between 2009 and 2014 as baseline for this study, when participants underwent spirometry at the research center. A total of 4,765 persons with interpretable spirometry and without asthma and without prevalent dementia were retained for analyses (Fig. 1).
lung function parameters were derived from values in this study, which is similar to quintile subgroups in a previous study [14]. For calculation of trending hazard ratio with 10% change in lung function, lung function parameters were included in cox models after being divided by 10. Airflow limitation was confirmed by the value of a post-bronchodilator FEV\textsubscript{1}/FVC below 0.7 [9].

**Dementia assessment**

Dementia assessment was conducted for participants at baseline and subsequent center visits with the Mini-Mental State Examination and the Geriatric Mental Schedule [15]. Those with a Mini-Mental State Examination score <26 or Geriatric Mental Schedule score >0 underwent further investigation along with an interview with a research physician, that contained the Cambridge Examination for Mental Disorders of the Elderly. The whole population also underwent routine cognitive assessment. Moreover, the entire cohort was continuously under surveillance for dementia through electronic linkage of the study database with medical records from general practitioners and the regional institute for outpatient mental health care. If available clinical neuroimaging was used for determining dementia subtype [11]. An adjudication panel led by a consultant neurologist established the final diagnosis according to standard criteria for dementia (Diagnostic and Statistical Manual of Mental Disorder, Third Edition-Revised: DSM-III-R) and AD (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association: NINCDS–ADRDA). Follow-up until 14 December 2017 was virtually complete (95.5% of potential person-years). Within this period, participants were followed until the date of dementia and AD diagnosis, death, loss to follow-up or 14 December 2017, whichever came first.

**Covariates**

The following variables were considered as possible confounders, primarily based on previous literature and their role as shared causes between lung function and dementia. Demographic information included age, sex, education level (primary education, lower education, intermediate education, higher education), smoking status (never, former, current), systolic blood pressure (mmHg), body mass index (BMI, kg/m\textsuperscript{2}), calculated by weight [kg] divided by height [m] squared), and chronic comorbid conditions (diabetes and stroke) [11]. Blood samples were extracted for determination of levels of triglycerides and DNA at the research center. Apolipoprotein E (APOE) genotype was determined using a PCR in the original cohort (RS-I, starting between July 1989 and September 1993) and a bi-allelic TaqMan assay (rs7412 and rs429358) on labeled DNA samples in the two cohorts (RS-II-3, starting between February 2000 and December 2001; and RS-III-2, starting between February 2006 and December 2008), respectively. This study included these three sub-cohorts. APOE ε4 represented carrier of one or two ε4 alleles. Participants were categorized into three groups: high genetic risk (ε2/ε4, ε3/ε4, or ε4/ε4 genotypes), intermediate risk (ε3/ε3), or low risk (ε2/ε2 or ε2/ε3) [16]. As the strongest genetic risk factor for dementia, APOE has additionally potent cardiovascular effects, including arteriosclerosis and cardiac function. In this regard, APOE may also impact lung function. We therefore included APOE in the models as possible confounder [14, 17]. Missing values were handled by five-times imputation using chained equation [18].

**Statistical analysis**

Baseline characteristics are described among subgroups of lung function. Data are expressed as mean ± standard deviation (SD) for normally distributed variables or as median (interquartile range [IQR]) for non-normally distributed variables.

For analyses of the association between lung function at baseline and risk of incident dementia, we used Cox proportional-hazards regression analyses. Lung function was categorized as normal spirometry, PRISm, and COPD. In addition, lung volume capacity comprised subgroups of quartiles of FEV\textsubscript{1} % predicted, FVC% predicted and ratio of FEV\textsubscript{1}/FVC. Follow-up time started on the date of spirometry test at baseline and ended until diagnosis of dementia, death, lost to follow-up, or December 14, 2017. The proportional hazards assumption was checked using Schoenfeld residuals. Model 1 was adjusted for APOE category, age, sex, and education level. Model 2 was additionally adjusted for smoking status, BMI, systolic blood pressure, triglyceride, and comorbidity (history of stroke and diabetes mellitus). Covariates above were selected based on previous literature knowledge, clinical relevance and availability of the data. Given the relatively small number of incident cases of dementia, we also constructed a third model in which the covariates were accounted
Table 1
Baseline characteristics of participants, stratified by lung function category

|                          | Normal   | PRISm    | COPD     | p       |
|--------------------------|----------|----------|----------|---------|
| n (%)                    | 3683 (77.3) | 319 (6.7) | 763 (16.0) | -       |
| Age, y                   | 67.8 (12.5) | 68.6 (14.4) | 70.6 (13.4) | < 0.001 |
| Female, (%)              | 2120 (57.6) | 171 (53.6) | 324 (42.5) | < 0.001 |
| Education level          |          |          |          |         |
| Primary education        | 246 (6.8) | 31 (9.9)  | 81 (10.7) | < 0.001 |
| lower education          | 1445 (39.7) | 117 (37.1) | 279 (36.9) |         |
| Intermediate education   | 1089 (29.8) | 93 (29.5)  | 249 (32.9) |         |
| Higher education         | 864 (23.7) | 74 (23.5)  | 148 (19.6) |         |
| Smoking status, (%)      |          |          |          |         |
| Never                    | 1383 (37.6) | 97 (30.4)  | 135 (17.7) | < 0.001 |
| Former                   | 1960 (53.2) | 177 (55.5) | 415 (54.4) |         |
| Current                  | 340 (9.2)  | 45 (14.1)  | 213 (27.9) |         |
| Systolic pressure        | 141 (29)   | 142 (29)   | 142 (26)   | 0.369   |
| Body mass index, kg/m2   | 27.0 (5.0) | 28.4 (5.9) | 26.1 (5.0) | < 0.001 |
| Triglycerides, mg/dl     | 1.3 (0.7)  | 1.4 (0.9)  | 1.2 (0.7)  | < 0.001 |
| History of stroke        | 34 (0.9)   | 7 (2.2)    | 12 (1.6)   | 0.040*  |
| History of diabetes mellitus | 292 (8.0) | 31 (10.0)  | 73 (9.7)   | 0.200   |
| Apolipoprotein E genotype, (%) |          |          |          |         |
| e4-allele positive       | 937 (27.3) | 66 (22.8)  | 196 (27.8) | 0.142   |
| e4-allele negative       | 2496 (72.7) | 224 (77.2) | 509 (72.2) |         |
| FEV1/FVC                 | 78.7 (6.4) | 76.1 (7.1) | 65.6 (7.6) | < 0.001 |
| FEV1% predicted          | 103.2 (18.7) | 73.8 (10.6) | 79.1 (24.7) | < 0.001 |
| FVC% predicted           | 101.2 (17.9) | 72.2 (11.7) | 94.0 (24.9) | < 0.001 |

COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; PRISm, preserved ratio impaired spirometry. Data represent original data without imputed values. Missing values were present for education attainment (1.0%), systolic blood pressure (2.8%), triglyceride (1.7%), and history of diabetes (7.1%). *Fisher’s exact test.

In addition, we conducted stratified analyses in women, men, non-smoking participants, smokers and participants without APOE e4 allele and history of stroke and diabetes. These were selected as possible effect modifiers based on previous literature and biological plausibility [3, 23–27].

RESULTS

Clinical and lung functional characteristics of participants

Among 4,765 participants (mean age 68.2 ± 12.9 years, 54.9% women), 16.0% (n = 763) had COPD, 6.7% (n = 319) had PRISm, and 77.3% (n = 3683) had normal spirometry. More than twenty percent (23.0%) of the participants received higher education, and two thirds (66.1%) were current or former smokers. The participants had a median BMI of 27.0 ± 5.1 Kg/m², systolic blood pressure of 141 ± 29.0 mmHg, and triglyceride level of 1.3 ± 0.8 mg/dl. While 8.4% (n = 396) had a history of diabetes mellitus, 11.1% of them experienced stroke before (n = 53). 1,199 (27.1%) participants carried APOE e4 allele (Table 1).
During a median of 3.3 years of follow-up, 110 participants (2.3%) developed incident dementia, of whom 89 (1.9%) developed AD. Moreover, among all participants, 292 (6.1%) died due to non-dementia related causes within the follow-up period (Table 2).

First, we evaluated the association between lung function impairment at baseline and risk of incident dementia. As shown in Table 2, higher proportion of participants with PRISm developed dementia compared to participants with normal spirometry, while COPD patients did not. Compared with participants with normal spirometry, participants with PRISm exhibited a higher risk of all-type dementia (Model 2 hazard ratio [HR], 2.70; 95% confidence interval [CI], 1.53–4.75), while subjects with COPD did not (HR, 1.03; 95% CI, 0.61–1.74), after accounting for all covariates. After being adjusted for propensity score, age and sex, results of model 3 were similar to model 2 (Table 2). Hazard ratios of association of PRISm and COPD with all-type dementia were 2.47 (95% CI, 1.40–4.35) and 1.08 (95% CI, 0.63–1.83), respectively.

Concurrently, participants with PRISm were also at increased risk of AD, albeit this did not reach statistical significance (HR, 1.87; 95% CI, 0.92–3.81). COPD was not significantly associated with AD (HR, 0.87; 95% CI, 0.48–1.59) (Table 2).

We also investigated the risk of developing dementia associated with lower lung function by using continuous parameters (FEV1%, FVC%, FEV1/FVC%) and their categorized quartiles (Fig. 2). A lower value in FEV1% predicted was associated with an elevated risk of all-type dementia (HR2, 1.12; 95% CI, 1.02–1.23). Relative to participants with the highest FVC% predicted values (Quartile 4), those with the lowest FVC% predicted values (Quartile 1) were at increased risk of both all-type dementia (Model 2 hazard ratio [HR], 2.28; 95% confidence interval [CI], 1.31–3.98) and AD (HR, 2.13; 95% CI, 1.13–4.02), after accounting for demographics and APOE genotypes. A lower value in FVC% predicted was significantly associated with an increased risk of both all-type dementia and AD in all models. FEV1/FVC was not associated with dementia risk in any model (Fig. 2).

Moreover, a competing risk model was used to measure the competing risk of mortality during the follow-up period on the observation of dementia events. Although participants with PRISm suffered from higher cumulative incidence of all-cause mortality than participants with normal spirometry, participants with PRISm still exhibited significantly higher cumulative incidence of all-type dementia (p = 0.018), but not of AD (p > 0.05) (Supplementary Figure 1).

### Stratified analysis

Methods and figures on the stratified analyses are presented in the Supplementary Material. Regarding the association between COPD or PRISm and the risk of incident dementia, stratified analyses were performed in women, men, smokers, non-smokers...
participants, participants without history of stroke and diabetes, and APOE e4 non-carriers. Significant associations were found between PRISm and all-type dementia in men (adjusted HR = 5.29, 95% CI, 2.40–11.65), but not in women (adjusted HR = 1.65, 95% CI, 0.71–3.87); current or former smokers (adjusted HR = 3.36, 95% CI, 1.71–6.60), but not in never-smoking participants (adjusted HR = 1.95, 95% CI, 0.68–5.57); participants without a history of stroke (adjusted HR = 2.58, 95% CI, 1.45–4.59) and diabetes (adjusted HR = 2.56, 95% CI, 1.38–4.78); and participants without APOE e4 allele (HR = 1.56, 95% CI, 0.71–3.45). Significant association between PRISm and AD risk were only observed among men (Supplementary Figure 2).

We have tested the effect of interaction of lung function and sex, and interaction of lung function and smoking status in cox models, respectively, which
tests for multiplicative interaction. These tests of
interaction did not reach statistical significance (data
not shown).

In addition, Supplementary Figure 3 shows the
association between continuous spirometry param-
eters with the risk of newly diagnosed dementia
(Supplementary Figure 3A) or newly diagnosed
AD (Supplementary Figure 3B), stratified by sex,
smoking status and absence of stroke, diabetes,
and APOE e4 non-carriers. A lower FEV1% pre-
dicted was associated with a greater risk of all-type
dementia only among women, never-smoking partic-
ipants, and those without prior stroke, but not among
men, current or former smoking participants, and
participants without prior diabetes and APOE e4 non-
carriers. A lower FVC% predicted was associated
with an increased risk of all-type dementia among
all subgroups except APOE e4 non-carriers. Statis-
tical significance was not found between decreased
FEV1/FVC and risk of all-type dementia. Regarding
elevated risk of AD, reduced FVC% predicted and
FEV1/FVC elevated were associated with AD among
women, nonsmokers and those without prior stroke,
while FEV1% predicted did not show an increased
risk of AD among those without prior stroke.

DISCUSSION

In this population-based cohort study, individu-
als with PRISm were at increased risk of all-type
dementia, while those with COPD were not. Espe-
cially, predicted FVC% was strongly associated with
a higher risk of dementia among the whole study
population.

The main finding of this study is that PRISm
was associated with an increased risk of dementia.
Comorbidities, such as diabetes and stroke, are more
common among participants of this restrictive lung-
function pattern [28], and may confound the link with
impaired cognition and the increased risk for demen-
tia. However, while we found a higher prevalence of
prior stroke in participants with PRISm, the associ-
ation between PRISm and dementia persisted after
adjusting for these comorbidities. There are several
possible mechanisms linking PRISm with dementia.
Firstly, ambient pollution and inhalational exposures
are associated with higher risk of PRISm [29], which
could also contribute to the development of dementia
[30, 31]. For example, fine particulate matter in air
could not only lead to impaired lung function through
disturbing alveolarization process and altering lung
elastance at an earlier life stage [32], but also be linked
to higher dementia risk via accumulation of Aβ42
and alteration on neuroinflammation and brain immune
response, as exposure to certain level of air pollu-
tion could upregulate expression of mRNA COX2
and IL-1β in olfactory bulb, disrupt tight junctions in
frontal blood-brain barrier and activate nuclear NFκB
in brain endothelial cells [31, 33].

Secondly, some studies reported that FVC decline
in subjects with PRISm was accompanied with sys-
temic inflammation [34–36]. Systemic inflammation
in turn may be linked with cognitive impairment and/
or occurrence of dementia [37]. Serum inflammatory
cytokines, like (IL)-18, IL-1 receptor antagonist
and IL-6, have been linked with AD [38], and high lev-
ers of serum IL-6 were associated with a greater risk
of non-AD dementia as well [39]. Unfortunately, we
did not have inflammatory markers available in this
population to test this hypothesis.

Thirdly, reduced lung function could limit peak
oxygen uptake and oxygen saturation, resulting in
potential hypoxia [6, 40, 41]. In turn, hypoxia has
been reported to induce cognitive deficiency and
dementia in both human and animal studies [42,
43]. Mice with hypoxia exhibited tau hyperphos-
phorylation, Aβ upregulation, and dysfunction of
neurotransmitter system [43].

In stratified analyses, we found that the association
between PRISm and dementia was present in men,
current and past smokers, and participants without
history of stroke and diabetes.

Though speculative, sex differences can poten-
tially be explained by unmeasured confounding by
sex hormones [44, 45]. Indeed, estrogen has protec-
tive effects on systemic and cerebrovascular athero-
sclerosis, which in turn impact both lung function
dand dementia risk [24, 44]. In this population-based
study, we could not corroborate this speculation and
future research is therefore needed to explore these
hypotheses further.

The effect modification by smoking status indi-
cates that the effect of poor lung function on risk of
dementia is further aggravated in presence of smok-
ing. This may be related to direct toxic effects of
smoking in the brain, for instance increased levels of
oxidants and free radical species, which promotes for-
mation of senile plaque and neurofilibrillary tangles.
In turn, these pathological processes may interact with
cerebral hypoxia and hypoperfusion due to poor lung
function [46, 47].

With respect to stroke, APOE e4 carriehship and
diabetes, we only had sufficient power to show the
largest stratum and found that associations among persons without stroke, APOE ε4 non-carriers, and non-diabetics remained largely similar to the overall population.

Among continuous lung function parameters, FVC% predicted, but not FEV1/FVC ratio or FEV1% predicted, was significantly associated with both all-type dementia and AD risk. Previous studies have variably reported on FEV1, FEV1/FVR ratio, or FVC% predicted to be associated with dementia. Heterogeneity across study population, including differences in age-range, sampling strategy and comorbid conditions may explain differences in the strength of associations of the various parameters with dementia.

We did not demonstrate an association between COPD and the risk of dementia, in contrast to the prior study [14]. Previously, we found participants with PRISm and COPD to suffer from increased all-cause and cardiovascular mortality [7], and similarly the present competing risk model suggested the highest figure of all-cause mortality in COPD group. Therefore, mortality may hinder the occurrence of incident dementia during the follow-up period.

**Strengths and limitations**

An important strength of this study is the relatively large number of elderly participants included for assessment of the lung function through standardized protocols and dementia data based on continuous follow-up. Competing risks is a limitation when using traditional cox proportion-hazard regression analyses. However, we used competing risk model to calculate cumulative risk of dementia to correct effect of variable of interest. The small number of incident dementia cases limited our study power, but we applied propensity scores to avoid potential overfitting problem with adjustment for extensive covariates.

**CONCLUSIONS**

As a conclusion, among this community-dwelling population, participants with PRISm or participants with a low FVC% predicted lung function were at increased risk of dementia, compared to those with normal spirometry or a higher FVC% predicted, respectively. Further research is needed to elucidate whether this association is causal and how PRISm might contribute to dementia pathogenesis. Therefore, it is necessary to recognize PRISm and evaluate status of FVC% predicted when conducting spirometry tests in clinical settings.

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**SUPPLEMENTARY MATERIAL**

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-210162.

**DATA AVAILABILITY**

Data may be shared on request through contacting with Dr. Arfan.

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