Impaired lung function, lung disease and risk of incident dementia

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At a Glance Commentary:

Scientific knowledge on the subject: Prior research suggests that lung disease and impaired lung function may be linked to dementia, however few studies have been prospective, evaluated different types of lung disease, or considered lung health in midlife.

What this study adds: In a community-based cohort followed for 27 years, both restrictive and, to a lesser extent, obstructive lung disease were associated with greater risk of incident dementia and mild cognitive impairment (MCI). This pattern was present for both Alzheimer's disease-related dementia and cerebrovascular disease etiologies, and persisted in analyses restricted to nonsmokers.

Online Data Supplement: This article has an online data supplement, which is accessible from this issue's table of content online at **www.atsjournals.org**

ABSTRACT

Rationale: Growing evidence suggests that compromised lung health may be linked to dementia and worsening cognitive ability.

Objectives: We tested the hypothesis that impaired lung function or lung disease in midlife would be associated with greater risk of incident dementia and mild cognitive impairment (MCI) later in life.

Methods: A total of 14,184 ARIC study participants who underwent spirometry and were asked about lung health (1987-1989) were followed. Dementia and MCI were defined by a) hospitalization diagnosis codes (1987-2013) in the whole cohort and b) with adjudication among 42% who attended a comprehensive neurocognitive exam (2011-2013).

Main Results: In analysis using adjudicated outcomes, odds of dementia or MCI were higher among participants with restrictive [multivariable-adjusted odds ratio (95% CI): 1.58 (1.15-2.19)] and obstructive lung disease [1.29 (1.05-1.59)], compared to those without disease or respiratory symptoms. Associations were similar in analyses restricted to nonsmokers, and present for both Alzheimer's disease-related dementia and cerebrovascular etiologies. Low forced expiratory volume in 1 second % predicted and forced vital capacity % predicted were also associated with increased dementia risk.

Conclusions: Midlife lung disease and reduced lung function were associated with modestly increased odds of dementia and MCI later in life. Magnitudes of association were more pronounced for restrictive impairment than for obstructive lung disease. These associations were present in both smokers and nonsmokers. If the observed associations are causal, policy

and public health efforts to reduce smoking and improve air quality may have the added benefit of preventing the development of dementia and MCI.

KEYWORDS: restrictive impairment, COPD, Alzheimer's disease dementia, dementia

INTRODUCTION

Identification of modifiable risk factors for dementia and mild cognitive impairment (MCI) is a research priority, since given the high prevalence of these conditions(1) even a modest reduction in risk factors could reduce the societal burden(2) of dementia and MCI. Lung disease and impaired lung function are preventable, and growing evidence suggests that compromised lung health may be linked to greater risk of dementia or worsening cognitive ability.(3, 4) Evidence exists for lung impairment as assessed by objective measures such as low forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and the ratio of FEV_1/FVC,(5-8) as well as clinically recognized chronic obstructive pulmonary disease (COPD), asthma, or chronic bronchitis.(9-11) Though these prior studies provide valuable information about the possible role of lung health in dementia risk, they often lacked comprehensive event adjudication or had relatively short follow-up. Importantly, for many dementia risk factors, stronger associations have been observed when the risk factors were measured at middle-age than when they were measured later in life.(12-14)

Mechanistically, impaired lung function could influence dementia and MCI risk through several pathways, largely mediated through chronic hypoxemia.(3, 15) These include systemic inflammation, oxidative stress, physiological stress (e.g. sympathetic nervous system activation), and cerebral arterial stiffness and small-vessel damage.(3, 15) Impaired lung function has also been linked to incident stroke, independent of smoking.(16, 17) Hypoxemia within the context of obstructive sleep apnea has also been associated with greater risk of dementia.(18)

Using data from the community-based Atherosclerosis Risk in Communities (ARIC) cohort, we tested the hypotheses that development of dementia and MCI over 27 years of follow-up would be more common among participants who at baseline had a) COPD or restrictive impairment or b) poorer lung function, as assessed by spirometry. Analyses were also conducted according to dementia or MCI primary etiology (i.e. Alzheimer's disease (AD) or cerebrovascular disease). Furthermore, given the importance of smoking to lung health, additional analyses were conducted restricted to nonsmokers. Lastly, we explored interactions by race.

METHODS

The ARIC study is a community-based prospective cohort of 15,792 participants who in 1987-1989 were recruited from 4 U.S. communities: suburbs of Minneapolis, Minnesota; Jackson, Mississippi; Forsyth County, North Carolina; Washington County, Maryland.(19) Participants were aged 45-64 at baseline. In the Minnesota, Maryland and North Carolina sites recruitment was representative of the racial/ethnic composition of the communities (i.e. mostly white in Minnesota and Maryland, 15% black and 85% white in North Carolina), while in Mississippi only black participants were recruited. Since cohort inception participants have been followed continuously for hospitalizations and have taken part in several follow-up clinic visits. The present manuscript uses data from baseline (visit 1: 1987-1989) and the ARIC Neurocognitive Study (NCS) visit 5 (2011-2013). The final analytic sample for the incidence analysis comprised 14,184 individuals; exclusions are shown in Figure 1. All study protocols have been approved by local Institutional Review Boards and participants provided written informed consent.

Exposure measurement

Pulmonary function was assessed by certified pulmonary technicians at baseline using a water-sealed Collins Survey II volume displacement spirometer (Collins Medical, Braintree, MA) and PULMO-SCREEN II software (PDS Healthcare Products, Louisville, CO), based on American Thoracic Society guidelines(20), as has been described previously in ARIC(21) and is detailed in the Supplemental Methods. Briefly, for each participant, at least three acceptable spirograms were sought from a minimum of five forced expirations, and a best reading was then selected. FEV1, FVC, and the FEV1/FVC ratio, as a percentage of age-, race- and sex-specific predicted values and lower limit of normal (LLN) values, were calculated.(22)

Participants also self-reported whether a doctor has ever told them they had asthma, chronic bronchitis, or emphysema. Participants were also classified into 4 mutually exclusive groups,(23) on the basis of both spirometry results and self-reported information: (24)

1. 'COPD': $FEV_1/FVC < LLN$
2. 'Restrictive impairment': $FEV_1/FVC \geq LLN$ and $FVC < LLN$ (with our without self-reported respiratory symptoms)
3. 'Respiratory symptoms with normal spirometric results' (without COPD or restrictive impairment)
4. 'Normal' (without respiratory symptoms, COPD or restrictive impairment)

Covariates and potential effect modifiers

Covariate information was obtained at baseline, using standard ARIC procedures (Supplemental Methods). Briefly, questionnaire data was obtained, height, weight and sitting blood pressure were measured, a fasting blood draw was conducted, and information on participant medication bottles (which were brought to the visit) was recorded. Methods for the measurement and classification of the APOE ε4 risk allele have been described elsewhere.(5)

Dementia and MCI ascertainment

Several different approaches were used to ascertain dementia and MCI during follow-up.(25) First, 6,471 of the 6,538 ARIC participants attending visit 5 (2011-2013) underwent a detailed neurocognitive assessment, and a selected subset(25) received a neurological exam and brain magnetic resonance imaging (MRI). Second, a validated phone-based cognitive assessment, the modified telephone interview for cognitive status (TICSm), was performed in 1,461 participants who at the time of visit 5 were alive but unable or unwilling to participate in an in-person exam. Informants provided additional information in some instances, when participants were deceased or unable to complete the TICSm assessment themselves.(25) Lastly, in the full cohort, hospitalization diagnosis codes were used to identify incident dementia occurring from 1987-2013.

Outcomes of interest for the present analysis were defined according to methodology previously used in ARIC.(25) Incident dementia was defined using data from all of the potential diagnostic sources described above (i.e. visit 5 assessment, TICSm, hospitalization codes). An expert panel adjudicated syndromic dementia, MCI and etiology (AD or vascular), as detailed in the Supplemental Methods.

Statistical analysis

Participant characteristics were described according to visit 5 participation status, lung function impairment categories and quintiles of FVC% predicted**.** Figure 1 **is** a study flow chart, describing who was included in various analyses.

For the incidence analyses, Cox proportional hazards regression was used. Follow-up time began on the date of the baseline exam, and accrued until a dementia hospitalization ICD code, loss-to-follow-up, death, December 31, 2013, or the visit 5 exam date. The proportional hazards assumption was checked by plotting of log(-log) survival curves and testing the interaction between the exposures and time.

For analyses of the association between baseline lung function and risk of the neurocognitive study adjudicated outcomes we used logistic regression. Five outcomes were considered: 1) dementia or MCI, 2) dementia, 3) MCI, 4) dementia or MCI due to AD, 5) dementia or MCI due to cerebrovascular disease. For outcomes 2 through 5, we excluded from the analyses those with outcomes different from the outcome under study (e.g. for the dementia outcome, dementia was defined as 'yes' or 'no', and participants with MCI were excluded). For these analyses selection bias may have occurred as a result of differential participation and survival to visit 5. As such, we used inverse probability weighting (IPW)(26, 27) to adjust for attrition due to either death or failure to attend the follow-up neurocognitive exam (censoring) (Supplemental Methods).

A series of nested models was used for both the Cox and logistic regression analyses, with covariate information obtained from baseline. Model 1 adjusted for demographic

characteristics. Race and center were combined into a 5 level variable (i.e. whites-MN, white-MD, whites-NC, blacks-NC, blacks-MS) reflective of the race-center combinations in ARIC). Model 2 additionally adjusted for cigarette smoking and pack-years of smoking. Model 3 further adjusted for physical activity, body mass index, traditional cardiovascular risk factors, prevalent cardiovascular disease and APOE genotype. Model 4 additionally adjusted for fibrinogen, which is a marker of inflammation.

Multiplicative interactions by race were explored by including cross-product terms in the models. Additionally, because of the importance of smoking on lung health, we also conducted analyses restricted to nonsmokers. Statistical significance was defined as alpha = 0.05.

RESULTS

At baseline the 14,184 participants included in this analysis were on average 54.2 ± 5.8 years old, 55.3% were female and 25.9% African American. Supplemental Table 1 provides baseline participant characteristics according to whether the participants took part in visit 5, were alive but did not take part, or died prior to visit 5. Those who participated in visit 5 were on average slightly younger, had higher educational attainment, were less likely to smoke, and overall had a slightly better health profile than those who did not take part or died.

At baseline, mean ± standard deviation (SD) measured FEV_1 was 2.82 ± 0.77 L (percent predicted 93.5% ± 17.0), measured FVC 3.80 ± 0.99 L (% predicted 98.1% ± 14.6) and FEV_1/FVC 74.4 ± 8.1% (% predicted 94.5 ± 10.0%). Table 1 provides baseline participant characteristics according to lung disease categories; 17.6% were classified as having the COPD pattern, 5.9% restrictive impairment, 33.5% respiratory symptoms with normal spirometric results, and 43.1%

as normal. Men, those with lower educational attainment, and those who were current smokers were classified less frequently as having normal lung function. Participant characteristics according to quintiles of FVC% predicted are provided in Supplemental Table 2.

Lung disease, lung function and incident dementia

A total of 1,407 incident dementia events were identified among the full sample of 14,184 ARIC participants, over a median follow-up of 23.0 years [25th and 75th percentiles: 18.3-24.2; maximum 27.1]. As shown in Table 2, relative to participants classified as normal, risk of dementia was elevated among those with the COPD pattern [HR (95% CI): 1.23 (1.06-1.43)] and those with the restrictive impairment [1.31 (1.03-1.66)], after accounting for demographics (model 1). The associations were attenuated with additional covariate adjustment, and became nonsignificant. Participants in the lowest (versus highest) quintiles of FEV_1% predicted and FVC% predicted were at elevated risk of incident dementia after accounting for smoking (model 2), but estimates were attenuated and became nonsigificant with additional adjustment for cardiovascular risk factors (model 3). FEV_1/FVC % predicted was not associated with dementia risk.

In analyses restricted to never smokers (N = 6,018, Supplemental Table 3), results were generally similar to those of the full analyses, though CIs were less precise. In model 3, the HRs for COPD and restrictive impairment, versus being classified as normal, were 1.31 (0.99-1.72) and 1.12 (0.78-1.62), respectively. Although interactions by race were not statistically significant at p=0.05, associations were generally stronger in blacks than in whites (Supplemental Table 4). Among blacks the model 3 HR's for having COPD and restrictive

impairment patterns (versus normal) were 1.31 (0.98-1.76) and 1.23 (0.76-1.98) respectively, while in whites the HRs were 0.99 (0.82-1.21) and 0.93 (0.70-1.23). Also, for FEV_1% predicted and FVC% predicted there was some evidence that the proportional hazards assumption was violated, whereby associations were stronger earlier in follow-up than later in follow-up (Supplemental Table 5).

Lung disease, lung function and neurocognitive study-adjudicated dementia

Among the 5,889 participants who had lung function data and cognitive assessments as part of the neurocognitive exam, we also evaluated the association between baseline lung disease category and risk of dementia or MCI, dementia, MCI, and MCI or dementia due to AD, or due to cerebrovascular disease (Table 3). After Model 3 adjustments, odds ratios (ORs) of associations between participants with restrictive impairment versus those who were normal were 1.58 (1.14-2.19) for dementia or MCI, 1.16 (0.56-2.40) for dementia, 1.71 (1.23-2.38) for MCI, 1.79 (1.24-2.58) for dementia or MCI due to AD, and 1.60 (0.78-3.31) for dementia or MCI due to cerebrovascular disease. Presence of the COPD pattern, versus normal, was after model 3 adjustments associated with ORs of 1.33 (1.07-1.64) for dementia or MCI, 1.16 (0.74-1.82) for dementia, 1.40 (1.12-1.76) for MCI, 1.24 (0.97-1.60) for AD-type dementia or MCI, and 1.33 (0.79-2.23) for dementia or MCI due to cerebrovascular disease. Magnitudes of association were smaller for comparisons of participants categorized as having respiratory symptoms with normal spirometric results to those classified as normal. The above results were similar in analyses restricted to nonsmokers (Supplemental Table 6). For instance, after model 3

adjustments, the restrictive impairment and COPD patterns were associated with ORs for dementia or MCI of 1.69 (1.04-2.76) and 1.72 (1.23-2.40), respectively.

There was some evidence of effect modification by race, as shown in Supplemental Table 7. Among blacks, the COPD pattern was most associated with elevated odds of the outcomes [e.g. Model 3 OR (95%CI) of dementia/MCI for COPD pattern versus normal: 2.13 (1.34-3.40)] whereas in whites there was no association. Among whites, the restrictive impairment pattern was most strongly associated with increased odds [e.g. Model 3 OR of dementia/MCI versus normal: 1.79 (1.27-2.54)], while in blacks there was no association.

ORs for the associations of FEV_1% predicted and odds of outcomes are shown in Table 4. The lowest (versus highest) quartile of FEV_1% predicted was associated with an OR of 1.27 (1.05-1.54) for dementia or MCI, after model 3 adjustments. The ORs were 1.23 (0.98-1.54) for dementia or MCI due to AD, and 1.43 (0.91-2.24) for dementia or MCI due to cerebrovascular disease. The associations between FEV_1% predicted and the dementia outcomes did not differ significantly by race, however in general, the magnitudes of association were larger in blacks than in whites (Supplemental Table 7).

Associations between FVC% predicted and dementia are presented in Table 5. The Model 3 OR for the lowest versus highest quartile of FVC% predicted was 1.25 (1.04-1.51) for dementia or MCI, 1.30 (1.04-1.62) for dementia or MCI due to AD, and 1.51 (0.95-2.39) for dementia or MCI due to cerebrovascular disease. No statistical interaction by race was present, though magnitudes of effect tended to be larger in blacks than in whites (Supplemental Table 7).

FEV_1/FVC % predicted was not associated with risk of any of the outcomes, regardless of degree of adjustment (Supplemental Table 8).

For the main results of analyses of adjudicated dementia outcomes we also conducted sensitivity analyses without IPW. Results of these sensitivity analyses are presented in Supplemental Tables 9 (exposure lung disease category), 10 (exposure FEV_1) and 11 (exposure FVC), respectively. Effect estimates were similar to those of the primary IPW-weighted analysis.

DISCUSSION

Lung disease and impaired lung function were associated with greater risk of dementia and MCI in this community-based sample of more than 14,000 individuals followed for over 23 years. Several important patterns emerged, particularly in analyses employing adjudicated neurocognitive outcomes, though associations were at most of moderate strength and results were not always statistically significant after multivariable adjustment for a broad array of dementia risk factors. First, though both the COPD and restrictive impairment patterns tended to be associated with greater dementia and MCI risk, the magnitude of association was generally stronger for the restrictive impairment pattern. Second, there was evidence that suboptimal lung health may be related to dementia or MCI risk through both AD and cerebrovascular etiologies. Third, patterns were similar among nonsmokers, as in the overall population. Fourth, when evaluating spirometric measures and dementia risk, inverse associations were present for FEV_1% predicted and FVC% predicted, but not for the ratio FEV_1/FVC % predicted. These results provide novel information about the potential influence of lung disease and impaired lung function on future risk of dementia and MCI due to both AD and cerebrovascular disease. An important strength of this study is the prospective evaluation of midlife lung health and dementia risk more than 20 years later, since for many dementia risk

factors, stronger associations have been observed when the risk factors were measured at middle-age than when they were measured later in life.(12-14)

Comparison to prior studies

Relatively little is known about the relationship between restrictive impairment and risk of dementia and MCI. In the present analysis, after extensive covariate adjustment, participants with the restrictive impairment pattern were at 58% greater risk of developing dementia or MCI over 27 years of follow-up. There was evidence this pattern was present for dementia and MCI of both Alzheimer's disease etiology (78% increased risk) and cerebrovascular disease etiology (68% increased risk). The association for dementia of cerebrovascular etiology was not significant in the fully-adjusted model, but notably precision was poor. A prior ARIC publication reported that the restrictive pattern was associated with 60% (0-160%) increased risk of hospitalized dementia after adjusting for demographics [HR (95% CI): 1.6 (1.0-2.6) though association was attenuated with additional adjustment [1.4 (0.9-2.3)].(5) Diseases which result in restrictive impairment are characterized by reduced lung volumes, consequent to alteration in lung parenchyma or due to a disease of the pleura, chest wall, or neuromuscular apparatus.(28) Although symptoms of restrictive impairment are specific to the underlying condition, in addition to reduced lung volumes, patients tend to have ventilation-perfusion mismatch and hypoxemia. Overnight polysomnography data from the Study of Osteoporotic Fractures demonstrated that two indicators of hypoxemia – elevated oxygen desaturation and a high percentage of sleep time in apnea or hypopnea – were associated with elevated risk of

developing MCI or dementia over a mean follow-up of 4.7 years.(18) In a recent ARIC publication based on a smaller sample than the present analysis, there was modest evidence that obstructive sleep apnea was associated with greater dementia and MCI risk.[29] Extensive work in experimental rodent models of sleep apnea has suggested that intermittent hypoxia and asphyxia lead to neuronal damage and adverse behavioral consequences.(30, 31) Less research has evaluated the impact of a constant state of hypoxemia, as may be expected in the context of restrictive impairment, on neurologic structure and function.

Our finding that COPD was linked to greater risk of dementia and MCI when using the adjudicated outcome definition is consistent with prior literature. Two studies have reported that diagnosis with COPD is associated with an approximately 80% higher risk of developing MCI over 5 years,(9) and MCI or dementia over 25 years,(10) respectively. Furthermore, in the shorter study a dose-response relationship was observed according to COPD duration and risk of MCI.(9) Clinical history of COPD has also been associated with decreasing cognitive performance over time.(11) Notably, in a prior analysis of the ARIC data, which followed participants through 2005, presence of an obstructive ventilator function pattern was not associated with greater risk of dementia hosptialization.(5) Unique aspects of the present analysis include the objective ascertainment of COPD in a community-based sample (as opposed to COPD diagnosed via clinical diagnosis codes) and evaluation of the association in analyses restricted to nonsmokers. Patients with COPD suffer from systemic manifestations of the disease,(32) and growing evidence suggests that these comorbidities are independent of smoking and traditional risk factors.(33-35)

In the present analysis spirometry-assessed impaired lung function, as quantified by being in the lowest versus highest quartile of % predicted FEV_1 and FVC, was associated with greater risk of MCI and dementia overall and due to both AD and cerebrovascular disease etiologies. Several other studies,(6-8) though not all,(3) have also shown impaired lung function to be associated with worsening cognitive ability. Some of the most important previous work exploring the relation between objectively measured impaired lung function and cognitive status comes from a prior ARIC analysis. In this publication, impaired lung function was associated cross-sectionally with poorer performance in baseline cognitive assessments, and with increased risk of dementia hospitalization.(5) However, no association was found between lung function and cognitive decline over approximately 6 years of follow-up (between ARIC visits 2 and 4). Limitations of this previous analysis include short intervals between cognitive assessments in the cohort and insensitivity of the dementia definition used.

In the present analysis associations between lung disease and function persisted even in analyses restricted to nonsmokers. This enhances etiological understanding – as it suggests that impaired lung function is linked to dementia and MCI risk independent of smoking and smoking-related confounders.

An unexpected finding from the present analysis was the suggestive (but nonsignificant) difference in associations by race, whereby among blacks the COPD pattern was most strongly associated with dementia and MCI risk, whereas in whites the restrictive impairment pattern was most strongly associated. Importantly, both restrictive impairment and COPD are heterogeneous classifications, and the prevalence of specific pathologies is known to vary by race.(36-39) If these varied underlying pathologies are associated with dementia and MCI risk,

then the differences observed in the present study are not unexpected. It is possible that these underlying pathologies differ in their association with dementia and MCI risk, which could explain the observed race differences. Other possible explanations for the interaction are poor precision (e.g. there were only 11 blacks with restrictive impairment and MCI), selection bias that is differential by race, or chance. Future studies should aim to replicate these observations.

Strengths and limitations

The 23-year time-span between assessment of lung health and the neurocognitive exam is an important strength of our study, since both all-cause and AD-type dementia have a long natural history. However, this timespan also complicates the interpretation of our results, since we undoubtedly missed numerous cases of dementia that occurred among individuals who did not attend the neurocognitive exam as they had died (36.7%) or did not participate for other reasons (21.8%). Although for these participants we do not have information from the full neurocognitive battery, we do have some information about their cognitive status via dementia hospitalization ICD codes and in some instances TICSm and informant interviews. Sensitivity of dementia hospitalization ICD codes is, however, poor.(25, 40) A prior ARIC Neurocognitive Study publication reported that hospital and death diagnostic codes for dementia had a sensitivity of 25% and a specificity of 99%.(25) This may explain why in the present analysis, as in a prior ARIC analysis,(29) associations were stronger when adjudicated outcomes were employed than when hospitalization ICD codes were also used to define dementia. In the present analysis we used IPW to attempt to correct for selection bias resulting from differential outcome ascertainment between participants and nonparticipants of the neurocognitive exam.

The true cognitive status of non-attenders is, however, unknown and it is possible that some bias remained. Nonattendess were also more likely to be smokers, have greater pack years, and more respiratory impairment by both spirometry and self-report. Though we attempted to correct for this selection bias through IPW, the fact that participation at visit 5 was differential by smoking and lung function status is noteworthy.

Additional limitations are the single assessment of lung function, lack of biomarkers to verify AD-type dementia, residual confounding and poor precision for some comparisons despite the relatively large sample size. Additionally, bronchodilation was not used when assessing baseline lung function, and total lung capacity was not quantified. Furthermore, also absent are details about symptoms, such as the nature of dyspnea, chronic cough, chronic sputum production or history of recurrent lower respiratory tract infections. Despite these limitations our study had important strengths, including the large community-based sample, objective ascertainment of lung function in using standardized protocols, comprehensive neurocognitive assessment, and representation of men and women and blacks and whites.

CONCLUSIONS

In this large prospective community-based cohort both lung disease and impaired lung function were associated with greater risk of dementia and MCI over 23 years of follow-up, with evidence that this occurred for dementia due to both AD and vascular etiologies. Although both COPD and restrictive impairment were associated with increased risk of the dementia phenotypes, magnitudes of association were most pronounced for restrictive impairment. These associations were present in both smokers and nonsmokers. If the observed associations

are causal, policy and public health efforts to reduce smoking and improve air quality may have the added benefit of preventing the development of dementia and MCI.

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Table 1 Baseline characteristics according to lung function categories: The Atherosclerosis Risk in Communities (ARIC) study, 1987-1989

	Lung Function Category				
	Normal	Respiratory symptoms with normal spirometric results	Restrictive impairment pattern	COPD pattern	
N	6,108 (43%)	4,754 (34%)	832 (6%)	2,490 (18%)	p-value
Demographics					
Age, years	53.9 (5.7)	53.9 (5.7)	54.5 (5.6)	55.1 (5.8)	<0.001
Female, %	57.1	56.0	52.4	50.5	<0.001
African American, %	27.1	27.4	20.3	22.1	<0.001
Education level, %					<0.001
<High school	17.9	26.0	31.3	29.5	
High school graduate	40.8	41.8	39.5	40.2	
College/Graduate school	41.3	32.2	29.2	30.3	
Behaviors					
Smoking status, %					<0.001
Current	12.3	29.2	35.1	49.7	
Former	33.7	30.4	29.6	30.1	
Never	54.0	40.4	35.3	20.2	
Pack-years†	12.5 (6.5, 30.0)	18.1 (11.2, 37.0)	22.0 (16.0, 43.0)	28.9 (21.0, 48.0)	<0.001
Physical activity*	2.5 (0.8)	2.4 (0.8)	2.3 (0.8)	2.4 (0.8)	<0.001
Respiratory Indicators					
FEV_1%, predicted	101.0 (12.1)	97.2 (12.0)	72.6 (8.3)	74.8 (18.4)	<0.001
FVC%, predicted	102.3 (11.7)	99.2 (11.4)	72.6 (7.3)	94.1 (18.0)	<0.001
FEV_1/FVC %, predicted	98.2 (5.7)	97.4 (5.6)	99.5 (7.5)	78.4 (9.5)	<0.001
FEV_1, Liter	3.03 (0.71)	2.91 (0.71)	2.23 (0.54)	2.31 (0.74)	<0.001
FVC, Liter	3.93 (0.95)	3.81 (0.95)	2.87 (0.72)	3.74 (1.06)	<0.001
FEV_1/FVC	77.3 (4.7)	76.7 (4.7)	78.0 (6.2)	61.4 (7.8)	<0.001
Self-reported symptoms					
Cough, %	0.0	20.0	17.9	26.4	<0.001
Phlegm, %	0.0	15.0	13.2	21.8	<0.001
Dyspnea, %	0.0	13.2	16.0	14.1	<0.001
Self-reported MD diagnosis					
Bronchitis, %	2.5	11.4	10.9	15.9	<0.001
Emphysema, %	0.3	1.2	1.4	6.2	<0.001
Asthma, %	2.1	7.1	4.9	13.3	<0.001
Other Physiologic Characteristics					
Body mass index, kg/m^2	27.3 (4.8)	28.5 (5.7)	30.3 (6.5)	26.0 (4.9)	<0.001
Systolic blood pressure, mmHg	120.4 (17.8)	121.2 (18.7)	124.8 (20.1)	120.7 (19.2)	<0.001
Antihypertensive medications, %	22.4	27.3	36.2	22.2	<0.001

Prevalent diabetes, %	9.4	13.0	22.4	9.1	<0.001
HDL cholesterol, mg/dL	53.3 (17.0)	50.8 (16.6)	46.1(15.0)	52.3 (17.7)	<0.001
LDL cholesterol, mg/dL	137.3 (38.7)	139.1 (39.6)	140.3 (40.0)	134.5 (39.4)	<0.001
Lipid lowering medication, %	2.7	2.7	4.9	2.5	0.002
Prevalent CHD, %	3.3	4.4	10.3	6.3	<0.001
Prevalent heart failure, %	0.8	7.3	5.9	17.6	<0.001
Prevalent stroke, %	3.2	5.9	8.1	4.7	<0.001
APOE, %					0.27
e4/e4	2.7	2.6	3.5	2.3	
e2/e4 or e3/e4	27.4	28.0	27.9	29.5	
Other	69.9	69.5	68.6	68.3	
Weights					
Unstabilized weights (all)	3.1	3.8	5.7	5.8	
Unstabilized weights (V5)	2.0	2.3	3.2	2.9	
Stabilized weights (V5)	0.9	1.0	1.2	1.1	

Data shown as mean (SD) or percentage except for *geometric mean (25th percentile, 75th percentile)

†Among ever smokers

*Score on the sport index of the Baecke physical activity questionnaire(41)

FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; CHD = coronary heart disease

Table 2 Lung disease categories, objective indices of lung function, and risk of incident dementia: The Atherosclerosis Risk in Communities (ARIC) study, 1996-2013

	Lung Disease Category			
	Normal	Respiratory symptoms with normal spirometric results	Restrictive impairment pattern	COPD pattern
N	6,108	4,754	832	2,490
Dementia cases, *n*	616	483	79	229
Person-years	130,103	96,713	15,485	46,012
Incident Rate*	4.7	5.0	5.1	5.0
Hazard ratio (95% CI)				
Model 1	1	1.10 (0.97, 1.24)	1.31 (1.03, 1.66)	1.23 (1.06, 1.43)
Model 2	1	1.06 (0.94, 1.20)	1.24 (0.97, 1.57)	1.11 (0.94, 1.31)
Model 3	1	0.99 (0.88, 1.12)	0.99 (0.78, 1.27)	1.08 (0.92, 1.28)
Model 4	1	0.99 (0.87, 1.12)	0.99 (0.78, 1.27)	1.08 (0.92, 1.27)

	FEV1%, predicted					
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Trend (per 1 SD decrease)
N	2,836	2,838	2,837	2,837	2,836	
Dementia cases, *n*	275	282	246	290	314	
Person-years	50,632	57,102	59,400	60,115	61,066	
Incident Rate*	5.4	4.9	4.1	4.8	5.1	
Hazard ratio (95% CI)						
Model 1	1.36 (1.15, 1.60)	1.12 (0.95, 1.32)	0.92 (0.77, 1.08)	1.08 (0.92, 1.26)	1	1.13 (1.07, 1.19)
Model 2	1.23 (1.04, 1.47)	1.07 (0.91, 1.26)	0.89 (0.75, 1.06)	1.07 (0.91, 1.25)	1	1.09 (1.03, 1.15)
Model 3	1.10 (0.93, 1.32)	0.98 (0.83, 1.16)	0.83 (0.70, 0.99)	1.02 (0.86, 1.19)	1	1.05 (0.98, 1.11)
Model 4	1.11 (0.93, 1.32)	0.99 (0.83, 1.16)	0.84 (0.71, 0.99)	1.02 (0.87, 1.20)	1	1.05 (0.98, 1.11)

FVC%, predicted

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Trend (per 1 SD decrease)
N	2,836	2,838	2,835	2,839	2,836	
Dementia cases, *n*	283	292	257	297	278	
Person-years	52,072	56,824	58,743	59,860	60,815	
Incident Rate*	5.4	5.1	4.4	5.0	4.6	
Hazard ratio (95% CI)						
Model 1	1.44 (1.22, 1.70)	1.29 (1.09, 1.52)	1.10 (0.93, 1.30)	1.24 (1.06, 1.47)	1	1.12 (1.08, 1.19)
Model 2	1.36 (1.14, 1.61)	1.25 (1.06, 1.47)	1.08 (0.91, 1.28)	1.24 (1.05, 1.46)	1	1.11 (1.04, 1.17)
Model 3	1.14 (0.96, 1.36)	1.19 (1.00, 1.40)	0.99 (0.83, 1.17)	1.17 (0.99, 1.38)	1	1.06 (1.00, 1.11)
Model 4	1.15 (0.96, 1.37)	1.20 (1.01, 1.42)	1.00 (0.84, 1.19)	1.18 (1.00, 1.39)	1	1.06 (1.00, 1.11)

	FEV1/FVC%, predicted					
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Trend (per 1 SD decrease)
N	2,836	2,838	2,837	2,835	2,838	
Dementia cases, *n*	257	247	266	287	350	
Person-years	52,834	58,333	59,125	59,380	58,652	
Incident Rate*	4.9	4.2	4.5	4.8	6.0	
Hazard ratio (95% CI)						
Model 1	0.97 (0.83, 1.15)	0.83 (0.70, 0.98)	0.84 (0.72, 0.99)	0.91 (0.78, 1.06)	1	1.03 (0.97, 1.08)
Model 2	0.87 (0.73, 1.03)	0.79 (0.67, 0.93)	0.82 (0.70, 0.97)	0.90 (0.77, 1.05)	1	0.99 (0.92, 1.05)
Model 3	0.93 (0.78, 1.10)	0.85 (0.72, 1.00)	0.87 (0.74, 1.03)	0.94 (0.80, 1.10)	1	1.00 (0.94, 1.06)
Model 4	0.93 (0.78, 1.10)	0.85 (0.72, 1.00)	0.88 (0.75, 1.04)	0.94 (0.80, 1.10)	1	1.00 (0.94, 1.06)

*Per 1,000 person-years

Model 1: Cox regression adjusted for age, sex, center, education level, and race-center (5-level variable)

Model 2: Model 1 + additional adjustment for cigarette smoking and pack-years of smoking

Model 3: Model 2 + additional adjustment for physical activity, body mass index, systolic blood pressure, blood pressure medication use, diabetes, HDL cholesterol, LDL cholesterol, lipid lowering medications, prevalent coronary heart disease, heart failure, stroke and APOE genotype

Model 4: Model 3 + fibrinogen

Table 3 Weighted* odds ratios (ORs) and 95% confidence intervals (CI) of lung disease categories with dementia, mild cognitive impairment (MCI), AD-type dementia or MCI, and dementia or MCI due to cerebrovascular disease: The Atherosclerosis Risk in Communities (ARIC) study, 1987-2013

	Lung Disease Category			
	Normal	Respiratory symptoms with normal spirometric results	Restrictive impairment pattern	COPD pattern
N	2,953	1,967	239	730
Dementia or MCI, n	721	518	87	212
Model 1	1	1.15 (1.00, 1.33)	1.92 (1.40, 2.63)	1.30 (1.07, 1.60)
Model 2	1	1.15 (0.99, 1.33)	1.89 (1.37, 2.59)	1.28 (1.03, 1.58)
Model 3	1	1.10 (0.95, 1.28)	1.58 (1.14, 2.19)	1.33 (1.07, 1.64)
Model 4	1	1.09 (0.94, 1.27)	1.56 (1.12, 2.16)	1.31 (1.06, 1.62)
Dementia, n	147	94	15	42
Model 1	1	1.00 (0.74, 1.37)	1.67 (0.86, 3.26)	1.20 (0.79, 1.82)
Model 2	1	0.98 (0.71, 1.34)	1.56 (0.78, 3.12)	1.10 (0.71, 1.69)
Model 3	1	0.94 (0.68, 1.32)	1.16 (0.56, 2.40)	1.16 (0.74, 1.82)
MCI, n	574	424	72	170
Model 1	1	1.21 (1.04, 1.40)	1.97 (1.42, 2.74)	1.35 (1.10, 1.68)
Model 2	1	1.21 (1.04, 1.42)	1.98 (1.42, 2.76)	1.36 (1.08, 1.71)
Model 3	1	1.15 (0.99, 1.35)	1.71 (1.23, 2.38)	1.40 (1.12, 1.76)
AD dementia or MCI, n	474	344	59	127
Model 1	1	1.18 (1.00, 1.40)	1.97 (1.38, 2.82)	1.14 (0.90, 1.45)
Model 2	1	1.20 (1.02, 1.43)	2.02 (1.41, 2.90)	1.18 (0.92, 1.52)
Model 3	1	1.16 (0.98, 1.38)	1.79 (1.24, 2.58)	1.24 (0.97, 1.60)
Cerebrovascular dementia or MCI, n	88	62	12	26
Model 1	1	1.04 (0.72, 1.51)	2.39 (1.15, 4.97)	1.46 (0.89, 2.39)
Model 2	1	0.98 (0.67, 1.44)	2.10 (1.00, 4.38)	1.19 (0.71, 2.00)
Model 3	1	0.92 (0.62, 1.36)	1.60 (0.78, 3.31)	1.33 (0.79, 2.23)

*Inverse-probability weighting was used.
Model 1: Logistic regression adjusted for age, sex, education level, and race-center (5-level variable)
Model 2: Model 1 + additional adjustment for cigarette smoking and pack-years of smoking
Model 3: Model 2 + additional adjustment for physical activity, body mass index, systolic blood pressure, blood pressure medication use, diabetes, HDL cholesterol, LDL cholesterol, lipid lowering medications, prevalent coronary heart disease, heart failure, stroke and APOE genotype
Model 4: Model 3 + fibrinogen

Table 4 Weighted* odds ratios (ORs) and 95% confidence intervals (CI) of FEV1 percent predicted quartile with dementia, mild cognitive impairment (MCI), AD-type dementia or MCI, and dementia or MCI due to cerebrovascular disease: The Atherosclerosis Risk in Communities (ARIC) study, 1987-2013

	FEV1%, predicted				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Trend (per 1 SD decrease)
N	1,473	1,471	1,472	1,473	
Dementia or MCI, n	450	364	346	378	
Model 1	1.38 (1.15, 1.65)	1.02 (0.85, 1.23)	0.92 (0.77, 1.11)	1	1.14 (1.07, 1.22)
Model 2	1.35 (1.12, 1.63)	1.01 (0.84, 1.22)	0.92 (0.77, 1.11)	1	1.13 (1.06, 1.21)
Model 3	1.27 (1.05, 1.54)	0.97 (0.80, 1.17)	0.89 (0.73, 1.07)	1	1.11 (1.04, 1.20)
Model 4	1.26 (1.04, 1.53)	0.96 (0.79, 1.16)	0.88 (0.73, 1.06)	1	1.11 (1.03, 1.19)
Dementia, n	87	59	69	83	
Model 1	1.33 (0.91, 1.93)	0.88 (0.59, 1.30)	0.95 (0.65, 1.40)	1	1.10 (0.97, 1.26)
Model 2	1.23 (0.83, 1.81)	0.85 (0.57, 1.27)	0.95 (0.65, 1.39)	1	1.06 (0.93, 1.22)
Model 3	1.09 (0.73, 1.65)	0.77 (0.50, 1.18)	0.90 (0.61, 1.33)	1	1.03 (0.89, 1.20)
MCI, n	363	305	277	295	
Model 1	1.41 (1.16, 1.71)	1.08 (0.89, 1.31)	0.93 (0.77, 1.14)	1	1.16 (1.08, 1.24)
Model 2	1.41 (1.16, 1.72)	1.08 (0.89, 1.32)	0.94 (0.77, 1.14)	1	1.16 (1.08, 1.25)
Model 3	1.34 (1.10, 1.64)	1.04 (0.85, 1.27)	0.90 (0.74, 1.10)	1	1.14 (1.06, 1.23)
AD dementia or MCI, n	284	223	237	260	
Model 1	1.23 (1.00, 1.52)	0.91 (0.73, 1.13)	0.91 (0.74, 1.13)	1	1.09 (1.01, 1.18)
Model 2	1.26 (1.01, 1.56)	0.92 (0.74, 1.15)	0.92 (0.74, 1.13)	1	1.10 (1.01, 1.19)
Model 3	1.23 (0.98, 1.54)	0.90 (0.72, 1.13)	0.89 (0.72, 1.10)	1	1.10 (1.01, 1.19)
Cerebrovascular dementia or MCI, n	57	53	35	43	
Model 1	1.84 (1.18, 2.88)	1.33 (0.85, 2.07)	0.97 (0.58, 1.60)	1	1.33 (1.14, 1.55)
Model 2	1.58 (1.02, 2.46)	1.26 (0.80, 1.97)	0.95 (0.57, 1.57)	1	1.25 (1.08, 1.44)
Model 3	1.43 (0.91, 2.24)	1.15 (0.72, 1.83)	0.90 (0.54, 1.49)	1	1.23 (1.05, 1.43)

*Inverse-probability weighting was used.

Model 1: Logistic regression adjusted for age, sex, center, education level, and race-center (5-level variable)

Model 2: Model 1 + additional adjustment for cigarette smoking and pack-years of smoking

Model 3: Model 2 + additional adjustment for physical activity, body mass index, systolic blood pressure, blood pressure medication use, diabetes, HDL cholesterol, LDL cholesterol, lipid lowering medications, prevalent coronary heart disease, heart failure, stroke and APOE genotype

Model 4: Model 3 + fibrinogen

Table 5 Weighted* odds ratios (ORs) and 95% confidence intervals (CI) of FVC percent predicted quartile with dementia, mild cognitive impairment (MCI), AD-type dementia or MCI, and dementia or MCI due to cerebrovascular disease: The Atherosclerosis Risk in Communities (ARIC) study, 1987-2013

	FVC%, predicted				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Trend (per 1 SD decrease)
N	1,472	1,473	1,471	1,473	
Dementia or MCI, n	434	381	361	362	
Model 1	1.40 (1.16, 1.68)	1.15 (0.96, 1.38)	1.08 (0.89, 1.29)	1	1.17 (1.10, 1.25)
Model 2	1.37 (1.14, 1.64)	1.14 (0.95, 1.37)	1.07 (0.89, 1.29)	1	1.16 (1.09, 1.24)
Model 3	1.25 (1.04, 1.51)	1.06 (0.88, 1.28)	1.04 (0.86, 1.25)	1	1.12 (1.05, 1.20)
Model 4	1.25 (1.04, 1.51)	1.06 (0.88, 1.28)	1.04 (0.86, 1.25)	1	1.12 (1.05, 1.20)
Dementia, n	80	69	71	78	
Model 1	1.29 (0.88, 1.89)	1.07 (0.73, 1.57)	1.19 (0.82, 1.74)	1	1.17 (1.02, 1.33)
Model 2	1.20 (0.82, 1.77)	1.03 (0.70, 1.52)	1.18 (0.81, 1.72)	1	1.14 (0.99, 1.30)
Model 3	1.06 (0.71, 1.59)	0.92 (0.62, 1.37)	1.15 (0.78, 1.70)	1	1.08 (0.93, 1.25)
MCI, n	354	312	290	284	
Model 1	1.43 (1.17, 1.73)	1.17 (0.96, 1.42)	1.04 (0.86, 1.27)	1	1.18 (1.09, 1.27)
Model 2	1.41 (1.16, 1.72)	1.17 (0.96, 1.42)	1.04 (0.85, 1.26)	1	1.17 (1.09, 1.27)
Model 3	1.32 (1.08, 1.60)	1.11 (0.91, 1.35)	1.02 (0.84, 1.24)	1	1.14 (1.06, 1.23)
AD dementia or MCI, n	284	237	238	245	
Model 1	1.34 (1.09, 1.66)	1.02 (0.82, 1.26)	1.07 (0.86, 1.32)	1	1.15 (1.06, 1.24)
Model 2	1.35 (1.09, 1.68)	1.01 (0.82, 1.26)	1.07 (0.86, 1.32)	1	1.15 (1.06, 1.25)
Model 3	1.30 (1.04, 1.62)	0.99 (0.79, 1.23)	1.04 (0.84, 1.29)	1	1.13 (1.04, 1.23)
Cerebrovascular dementia or MCI, n	57	52	43	36	
Model 1	2.02 (1.26, 3.23)	1.68 (1.05, 2.68)	1.31 (0.80, 2.14)	1	1.37 (1.16, 1.61)
Model 2	1.80 (1.14, 2.84)	1.61 (1.00, 2.58)	1.29 (0.79, 2.12)	1	1.31 (1.11, 1.53)
Model 3	1.51 (0.95, 2.39)	1.40 (0.87, 2.26)	1.27 (0.78, 2.08)	1	1.22 (1.04, 1.43)

*Inverse-probability weighting was used.

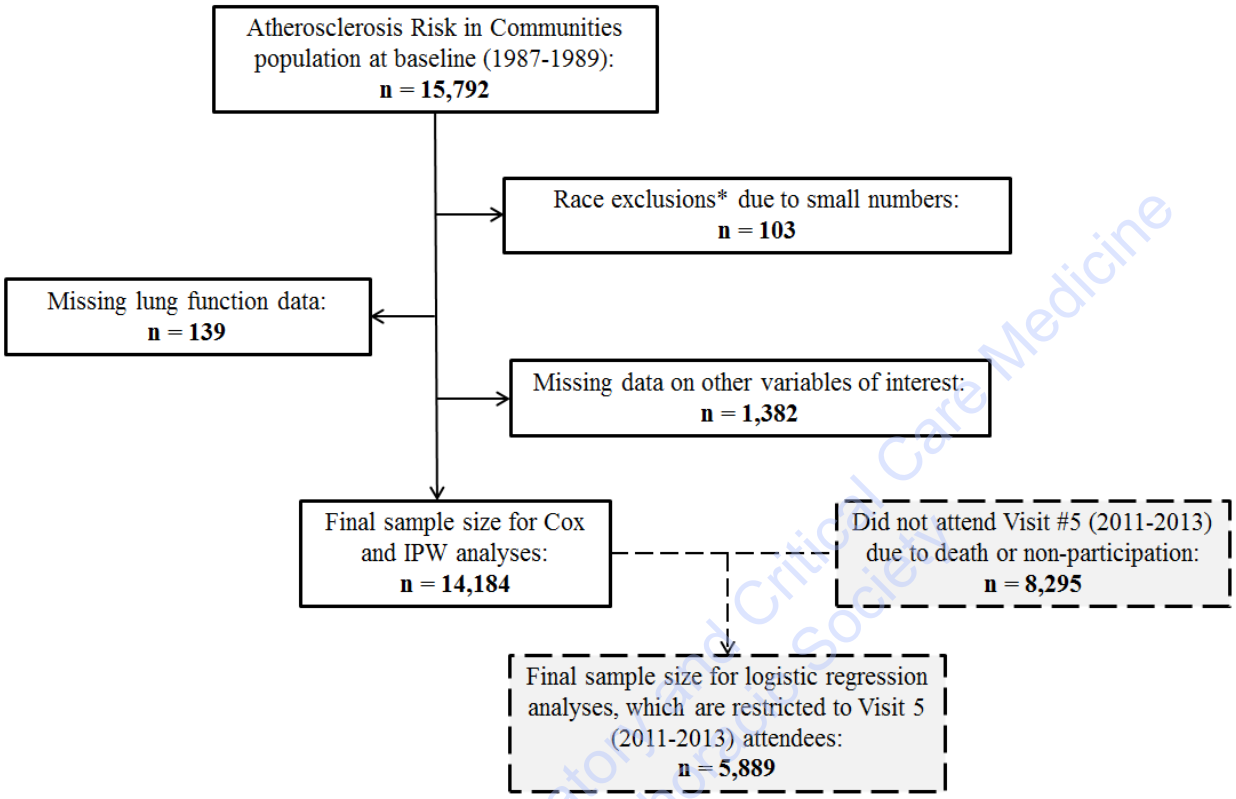
Model 1: Logistic regression adjusted for age, sex, center, education level, and race-center (5-level variable)

Model 2: Model 1 + additional adjustment for cigarette smoking and pack-years of smoking

Model 3: Model 2 + additional adjustment for physical activity, body mass index, systolic blood pressure, blood pressure medication use, diabetes, HDL cholesterol, LDL cholesterol, lipid lowering medications, prevalent coronary heart disease, heart failure, stroke and APOE genotype

Model 4: Model 3 + fibrinogen

Figure 1 Participant flow chart for incidence and inverse probability-weighted analyses



IPW = inverse probability weighting
*Not black or white, and blacks from the MN and MD centers