Impaired Lung Function, Lung Disease, and Risk of Incident Dementia

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Abstract

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

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

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

Measurements and Main Results: In analysis using adjudicated outcomes, odds of dementia or MCI were higher among participants with restrictive (multivariable-adjusted odds ratio, 1.58; 95% confidence interval, 1.14–2.19) and obstructive lung disease

(multivariable-adjusted odds ratio, 1.33; 95% confidence interval, 1.07–1.64), compared with 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 FEV_1% predicted and FVC% 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 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; chronic obstructive pulmonary disease; Alzheimer's disease dementia; dementia

Identification of modifiable risk factors for dementia and mild cognitive impairment (MCI) is a research priority, because 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 FEV_1, FVC, and the ratio of FEV_1/FVC (5–8), and clinically

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 to the Field: 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. This pattern was present for both Alzheimer's disease–related dementia and cerebrovascular disease etiologies, and persisted in analyses restricted to nonsmokers.

recognized chronic obstructive pulmonary disease (COPD), asthma, or chronic bronchitis (9–11). Although 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, physiologic 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 ARIC (Atherosclerosis Risk in Communities) 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 COPD or restrictive impairment or 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 four U.S. communities: *1*) suburbs of Minneapolis, Minnesota; *2*) Jackson, Mississippi; *3*) Forsyth County, North Carolina; and *4*) 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), whereas 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 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.
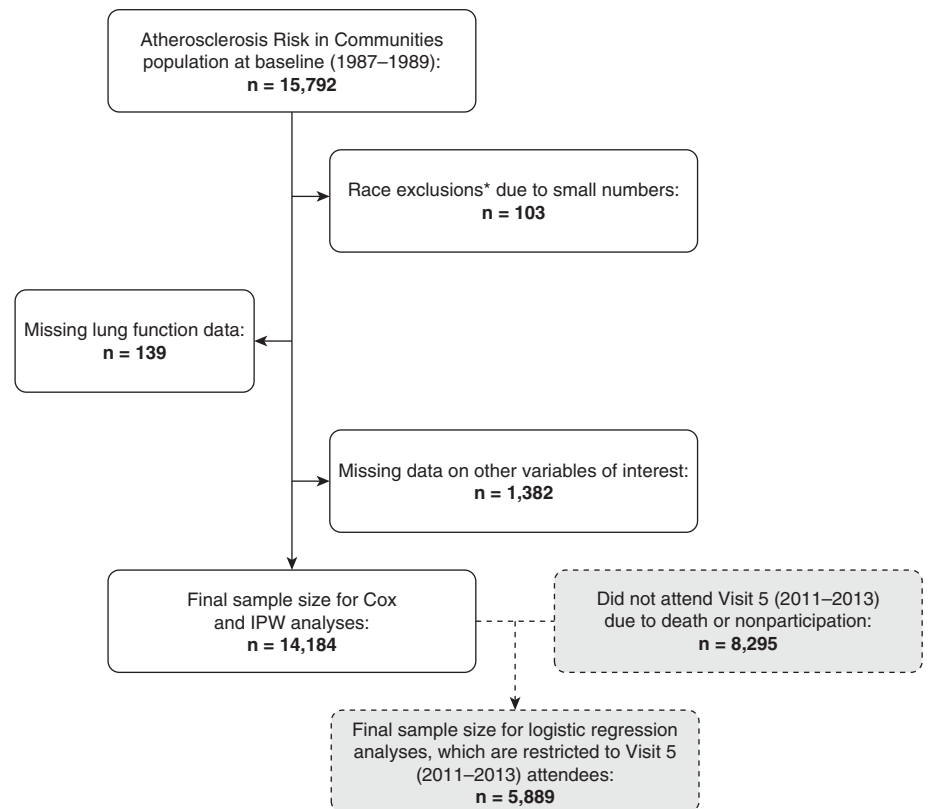
Exposure Measurement
Pulmonary function was assessed by certified pulmonary technicians at baseline using a water-sealed Collins Survey II

Figure 1. Participant flow chart for incidence and probability-weighted analyses. IPW = inverse probability weighting. *Not black or white, and black individuals from the Minnesota and Maryland centers.

volume displacement spirometer (Collins Medical) and PULMO-SCREEN II software (PDS Healthcare Products), based on American Thoracic Society guidelines (20), as has been described previously in ARIC (21) and is detailed in the METHODS section of the online supplement. 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. FEV_1, FVC, and the FEV_1/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 four 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 $\geqslant$ LLN and FVC < LLN (with or 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 (see METHODS section of the online supplement). Briefly, questionnaire data were 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 (apolipoprotein E) 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 neurologic examination and brain magnetic resonance imaging. Second, a validated telephone-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 examination. 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 to 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 previously (i.e., visit 5 assessment, TICSm, and hospitalization codes). An expert panel adjudicated syndromic dementia, MCI, and etiology (AD or vascular), as detailed in the METHODS section of the online supplement.

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 examination, and accrued until a dementia hospitalization International Classification of Diseases (ICD) code; loss to follow-up; death; December 31, 2013; or the visit 5 examination 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 caused by AD, and 5) dementia or MCI caused by 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 caused by either death or failure to attend the follow-up neurocognitive examination (censoring) (see the METHODS section of the online supplement).

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 five-level variable (i.e., white individuals/Minnesota, white individuals/Maryland, white individuals/North Carolina, black individuals/North Carolina, and black individuals/Mississippi) 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 apolipoprotein E 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 α of 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% were African American. Table E1 in the online supplement provides baseline participant characteristics according to whether the participants took part in visit 5, were alive but did not take part, or died before 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 ± SD measured FEV_1 was 2.82 ± 0.77 L (% 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

Table 1. Baseline Characteristics according to Lung Function Categories: ARIC Study, 1987–1989

	Lung Function Category				
	Normal	**Respiratory Symptoms with Normal Spirometric Results**	**Restrictive Impairment Pattern**	**COPD Pattern**	**P Value**
n (%)	6,108 (43)	4,754 (34)	832 (6)	2,490 (18)	
Demographics					
Age, yr	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, L	3.03 (0.71)	2.91 (0.71)	2.23 (0.54)	2.31 (0.74)	<0.001
FVC, L	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 medical 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, mm Hg	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
ε4/ε4	2.7	2.6	3.5	2.3	
ε2/ε4 or ε3/ε4	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 (visit 5)	2.0	2.3	3.2	2.9	
Stabilized weights (visit 5)	0.9	1.0	1.2	1.1	

Definition of abbreviations: APOE = apolipoprotein E; ARIC = Atherosclerosis Risk in Communities; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
Data are shown as mean (SD) or percentage unless otherwise indicated.
*Among ever-smokers. Data are shown as geometric mean (25th percentile–75th percentile).
[†]Score on the sport index of the Baecke physical activity questionnaire (41).

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 Table E2.

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 (hazard ratio [HR], 1.23; 95% confidence interval [CI], 1.06–1.43) and those with the restrictive impairment (HR, 1.31; 95% CI, 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 (vs. 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 nonsignificant 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 ($n = 6,018$; see Table E3), results were generally similar to those of the full analyses, although 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 black individuals than in white individuals (see Table E4). Among black individuals, the model 3 HRs for having COPD and restrictive impairment patterns (vs. normal) were 1.31 (95% CI, 0.98–1.76) and 1.23 (95% CI, 0.76–1.98), respectively, whereas in white individuals the HRs were 0.99 (95% CI, 0.82–1.21) and 0.93 (95% CI, 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 (see Table E5).

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 examination, we also evaluated the association between baseline lung disease category and risk of dementia or MCI, dementia, MCI, and MCI or dementia caused by AD, or caused by cerebrovascular disease (Table 3). After model 3 adjustments, odds ratios (ORs) of associations between participants with restrictive impairment and those who were normal were 1.58 (95% CI, 1.14–2.19) for dementia or MCI, 1.16 (95% CI, 0.56–2.40) for dementia, 1.71 (95% CI, 1.23–2.38) for MCI, 1.79 (95% CI, 1.24–2.58) for dementia or MCI caused by AD, and 1.60 (95% CI, 0.78–3.31) for dementia or MCI caused by cerebrovascular disease. Presence of the COPD pattern, versus normal, was after model 3 adjustments associated with ORs of 1.33 (95% CI, 1.07–1.64) for dementia or MCI, 1.16 (95% CI, 0.74–1.82) for dementia, 1.40 (95% CI, 1.12–1.76) for MCI, 1.24 (95% CI, 0.97–1.60) for AD-type dementia or MCI, and 1.33 (95% CI, 0.79–2.23) for dementia or MCI caused by 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 previously mentioned results were similar in analyses restricted to nonsmokers (see Table E6). For instance, after model 3 adjustments, the restrictive impairment and COPD patterns were associated with ORs for dementia or MCI of 1.69 (95% CI, 1.04–2.76) and 1.72 (95% CI, 1.23–2.40), respectively.

There was some evidence of effect modification by race, as shown in Table E7. Among black individuals, 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 vs. normal: 2.13 [95% CI, 1.34–3.40]), whereas in white individuals, there was no association. Among white individuals, the restrictive impairment pattern was most strongly associated with increased odds (e.g., model 3 OR of dementia/MCI vs.

normal: 1.79 [95% CI, 1.27–2.54]), whereas in black individuals, there was no association.

ORs for the associations of FEV_1% predicted and odds of outcomes are shown in Table 4. The lowest (vs. highest) quartile of FEV_1% predicted was associated with an OR of 1.27 (95% CI, 1.05–1.54) for dementia or MCI, after model 3 adjustments. The ORs were 1.23 (95% CI, 0.98–1.54) for dementia or MCI caused by AD, and 1.43 (95% CI, 0.91–2.24) for dementia or MCI caused by 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 black individuals than in white individuals (see Table E7).

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 (95% CI, 1.04–1.51) for dementia or MCI, 1.30 (95% CI, 1.04–1.62) for dementia or MCI caused by AD, and 1.51 (95% CI, 0.95–2.39) for dementia or MCI caused by cerebrovascular disease. No statistical interaction by race was present, although magnitudes of effect tended to be larger in black individuals than in white individuals (see Table E7).

FEV_1/FVC% predicted was not associated with risk of any of the outcomes, regardless of degree of adjustment (see Table E8).

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 Tables E9 (exposure lung disease category), E10 (exposure FEV_1), and E11 (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 more than 23 years. Several important patterns emerged, particularly in analyses using adjudicated neurocognitive outcomes, although associations were at most of moderate strength and results were not always statistically significant after

Table 2. Lung Disease Categories, Objective Indices of Lung Function, and Risk of Incident Dementia: 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
Incidence 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)

	FEV$_1$% 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	
Incidence 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	
Incidence 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)

(Continued)

Table 2. (Continued)

	FEV$_1$/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	
Incidence 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)

Definition of abbreviations: ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; COPD = chronic obstructive pulmonary disease.
Model 1: Cox regression adjusted for age, sex, center, education level, and race–center (five-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, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, lipid-lowering medications, prevalent coronary heart disease, heart failure, stroke, and apolipoprotein E genotype. Model 4: model 3 + fibrinogen.
*Per 1,000 person-years.

Table 3. Weighted* Odds Ratios and 95% Confidence Intervals of Lung Disease Categories with Dementia, MCI, Alzheimer's Disease–Type Dementia or MCI, and Dementia or MCI Caused by Cerebrovascular Disease: 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-type 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)

Definition of abbreviations: AD = Alzheimer's disease; ARIC = Atherosclerosis Risk in Communities; COPD = chronic obstructive pulmonary disease; MCI = mild cognitive impairment.
Model 1: Logistic regression adjusted for age, sex, education level, and race–center (five-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, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, lipid-lowering medications, prevalent coronary heart disease, heart failure, stroke, and apolipoprotein E genotype. Model 4: model 3 + fibrinogen.
*Inverse-probability weighting was used.

multivariable adjustment for a broad array of dementia risk factors. First, although 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 caused by 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, because 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 with 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 AD etiology (79% increased risk) and cerebrovascular disease etiology (60% 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, 1.6; 95% CI, 1.0–2.6), although the association was attenuated with additional adjustment (HR, 1.4; 95% CI, 0.9–2.3) (5). Diseases that result in restrictive impairment are characterized by reduced lung volumes, consequent to alteration in lung parenchyma or caused by 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

Table 4. Weighted* Odds Ratios and 95% Confidence Intervals of FEV$_1$% Predicted Quartile with Dementia, MCI, Alzheimer's Disease–Type Dementia or MCI, and Dementia or MCI Caused by Cerebrovascular Disease: ARIC Study, 1987–2013

| | FEV$_1$% 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-type 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)

Definition of abbreviations: AD = Alzheimer's disease; ARIC = Atherosclerosis Risk in Communities; MCI = mild cognitive impairment.
Model 1: Logistic regression adjusted for age, sex, center, education level, and race–center (five-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, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, lipid-lowering medications, prevalent coronary heart disease, heart failure, stroke, and apolipoprotein E genotype. Model 4: model 3 + fibrinogen.
*Inverse-probability weighting was used.

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 hospitalization (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 caused by AD and cerebrovascular disease. Several

other studies (6–8), although 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 relationship 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 etiologic understanding because it suggests that impaired lung function is linked to dementia and MCI risk

Table 5. Weighted* Odds Ratios and 95% Confidence Intervals of FVC% Predicted Quartile with Dementia, MCI, Alzheimer's Disease–Type Dementia or MCI, and Dementia or MCI Caused by Cerebrovascular Disease: 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-type 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)

For definition of abbreviations, *see* Table 4.
Model 1: Logistic regression adjusted for age, sex, center, education level, and race–center (five-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, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, lipid-lowering medications, prevalent coronary heart disease, heart failure, stroke, and apolipoprotein E genotype. Model 4: model 3 + fibrinogen.
*Inverse-probability weighting was used.

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 black individuals the COPD pattern was most strongly associated with dementia and MCI risk, whereas in white individuals 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). 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 black individuals 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 examination is an important strength of our study, because all-cause and AD-type dementia have a long natural history. However, this timespan also complicates the interpretation of our results, because we undoubtedly missed numerous cases of dementia that occurred among individuals who did not attend the neurocognitive examination because 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 used 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 examination. The true cognitive status of nonattenders is, however, unknown and it is possible that some bias remained. Nonattendees were also more likely to be smokers, have greater pack-years, and more respiratory impairment by both spirometry and self-report. Although 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 black and white individuals.

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 increased risk of dementia was due to both AD and vascular etiologies. Although 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 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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