Relation of Atrial Fibrillation to Cognitive Decline (from the REasons for Geographic and Racial Differences in Stroke [REGARDS] Study)

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The association of atrial fibrillation (AF) with cognitive function remains unclear, especially among racially/geographically diverse populations. This analysis included 25,980 black and white adults, aged 48+, from the national REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort, free from cognitive impairment and stroke at baseline. Baseline AF was identified by self-reported medical history or electrocardiogram (ECG). Cognitive testing was conducted yearly with the Six Item Screener (SIS) to define impairment and at 2-year intervals to assess decline on: animal naming and letter fluency, Montreal Cognitive Assessment (MoCA), Word List Learning (WLL) and Delayed Recall tasks (WLD). Multivariable regression models estimated the relationships between AF and baseline impairment and time to cognitive impairment. Models were adjusted sequentially for age, sex, race, geographic region, and education, then cardiovascular risk factors and finally incident stroke. AF was present in 2,168 (8.3%) participants at baseline. AF was associated with poorer baseline performance on measures of: semantic fluency ($p<0.01$); global cognitive performance (MoCA, $p<0.01$); and WLD ($p<0.01$). During a mean follow-up of 8.06 years, steeper declines in list learning were observed among participants with AF ($p<0.03$) which remained significant after adjusting for cardiovascular risk factors ($p<0.04$) and incident stroke ($p<0.03$). Effect modification by race, sex and incident stroke on AF and cognitive decline were also detected. In conclusion, AF was associated with poorer baseline cognitive performance across multiple domains and incident cognitive impairment in this bi-racial cohort. Additional adjustment for cardiovascular risk factors attenuated these relations with the exception of learning. **(Am J Cardiol 2021;148:60−68)**

Atrial fibrillation (AF) is the most common form of sustained cardiac arrhythmia observed in clinical practice and can influence cognitive and physical function.[1−4] AF is associated with increased chances of stroke, [5,6] cardiovascular disease, dementia and death.[1] Growing evidence suggests that AF is also a risk factor for significant cognitive decline through pathways that may be mediated by stroke[7,8] or risk factors shared with stroke.[9] While some studies have shown that AF may affect cognitive function in the presence of stroke[1,3] others report this association independent of stroke[10]; however, these studies lack racial diversity and include limited numbers of stroke events or follow up. In this analysis, we examined the association between AF, cognitive performance and incident cognitive impairment in black and white older adults enrolled in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study, one of the largest biracial cohort studies in the United States.

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See page 67 for disclosure information.

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Methods

The REGARDS study is a longitudinal study consisting of 30,239 community-dwelling black and white adults 45 years or older enrolled between January 2003 and October 2007.[11] The study aimed to examine the causes for excess stroke mortality in the Stroke Belt of southeastern U.S. (North Carolina, South Carolina, Georgia, Tennessee, Alabama, Mississippi, Arkansas, and Louisiana) and among blacks. Initial eligibility criteria included potential participants having a name, phone number and address in the Genesys database. Exclusion criteria included race other than black or white, active treatment for cancer, medical conditions that would prevent long-term participation, inability to understand survey questions as judged by the telephone interviewer, residence in or inclusion on a waiting list for a nursing home, or inability to communicate in English. Demographic information and medical history data were collected via a computer-assisted telephone interview (CATI) system followed by an in-home physical examination 3¯4 weeks later that included blood pressure measurements, electrocardiogram (ECG) recording, and blood draw. Participants were followed every 6 months with cognitive assessments and suspected stroke events were identified. Verbal consent was obtained initially on the telephone then written informed consent was obtained during the in-home physical exam.[12] For the purpose of this analysis, we excluded participants with baseline history of stroke, missing data on AF and no follow-up cognitive assessments, resulting in a sample of 25,980 participants included in the analysis (Figure 1). The study methods and procedures were reviewed and approved by institutional review boards at all participating institutions, and by an external observational study monitoring board selected by the funding agency.

Baseline AF was determined by the presence of AF or atrial flutter on ECG or self-reported physician diagnosis.[13] Self-reported AF was defined as a positive response to the question, "Has a physician or a health professional ever told you that you had atrial fibrillation?"[12]. REGARDS ECG tracings were read and coded at a central reading center by analysts who were masked to other REGARDS data (Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Winston-Salem, NC, USA). AF was identified from ECG tracings using the Standard Minnesota ECG Classification[14], then verified by a physician.[13]

To characterize cognitive function and cognitive decline, cognitive assessments were performed at baseline and repeated over time. The six-item screener (SIS) was added to the baseline assessment in December 2003 and was

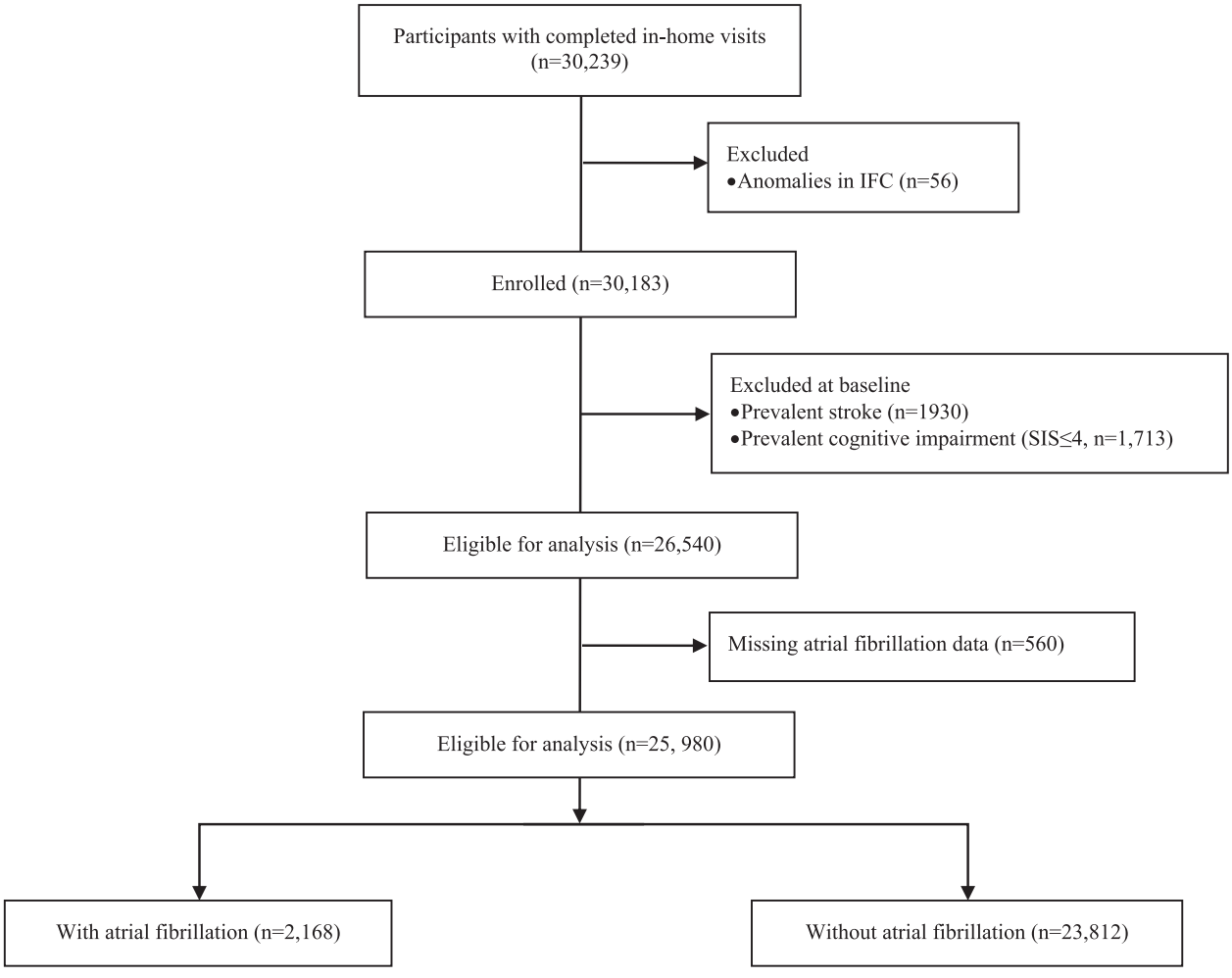

Figure 1. Consort diagram of REGARDS participants.

conducted annually thereafter. The SIS is a brief screening measure that assesses global cognitive function with 3-item temporal orientation and 3-item delayed recall.[15] The SIS score ranges from 0 to6; a score ≤4 suggests cognitive impairment.[16] We assessed incident impairment based on time to first SIS score ≤4. As a sensitivity analysis, we also examined incident impairment based on the time until 2 consecutive assessments with SIS score ≤4. A three-test battery which consists of the Consortium to Establish a Registry for Alzheimer Disease (CERAD) Word List Learning (WLL) (range, 0−30), Word List Delayed Recall (WLD) (range, 0−10) and animal naming test, was introduced in 2006 and conducted at 2-year intervals.[16] The WLL score is the total number of words immediately recalled on a 10-item, three-trial word list learning task. The WLD task involves recalling the number of words recalled after a filled 5-minute delay.[16] The animal naming score is the total number of spontaneously named animals in 60 seconds. The Letter F Fluency test was introduced into follow-up telephone assessments in 2008 and administered at 2-year intervals along with WLL, WLD, animal naming, and the rest of the short battery. This fluency measure required participants to name as many words as they could that begin with the letter 'F' in 60 seconds. The NINDS/CSN 5-minute protocol was recommended by the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards for use in studies calling for very brief assessments, epidemiological studies, and/or telephone administration.[17] This protocol includes subsets of the Montreal Cognitive Assessment (MoCA) consisting of a 5-word memory registration, 5-word delayed memory recall (5 points), 6-item temporal orientation (6 points), and 1-letter F phonemic fluency (1 point if >10 words that begin with the letter "F" generated in 60 seconds), was implemented into the follow-up telephone assessment at 2-year intervals.[17,18] During telephone administration, the spatial orientation items (place and city) were modified such that the participant was asked his or her street address and city (confirmed by the interviewer via a pre-populated field in the computer script). Higher scores on cognitive assessments reflect better performance.

Methods of determination of incident stroke have previously been reported.[12] During telephone follow-up, participants or their proxies were asked about events that required hospitalization, as well as physician evaluations for stroke-like symptoms. For potential strokes, medical records were requested and adjudicated by a team of stroke experts. Stroke events were defined by the 1989 World Health Organization (WHO) classification or classified as clinical strokes if imaging was consistent with a stroke and categorized as hemorrhagic or ischemic.[12]

Baseline age was calculated from the day the baseline telephone interview was conducted and self-reported birth date. Sex, race (black or white), education (<high school, high school graduate, some college, college graduate and above) and region (stroke belt, stroke buckle or non-stroke belt) were also self-reported. Urban and or rural status was defined by residence based on percentage of the census track residing inside of urban areas/clusters; the status was rural if ≤25% urban, mixed between 25 and 75% urban, and urban if ≥75% urban. Behaviors included in this analysis were current cigarette smoking (pack-years) and exercise habits (none, 1−3 days per week and 4 days per week). Coronary artery disease was defined as self-reported physician diagnosis of myocardial infarction (MI), self-reported coronary revascularization, or evidence of MI on ECG. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on average of two measurements or self-reported use of hypertension medication. Dyslipidemia was defined as total cholesterol ≥240 mg/dL, LDL ≥160, HDL ≤40 or self-reported lipid-lowering drug use. Left ventricular hypertrophy (LVH) assessed by ECG was defined using Sokolow-Lyon criteria. Diabetes was determined by fasting glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL or self-reported use of diabetes medications. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI and MDRD equations. C-reactive protein (CRP) was measured in plasma samples collected at baseline using a validated, high sensitivity, particle enhanced immunonephelometric assay. Waist circumference was measured over skin or lightweight clothing at the midpoint between the lowest rib on the right side and the top of the iliac crest using a cloth tape measure at the end of expiration. Sex-specific waist circumference criteria was assigned to participants in three categories: low (<80 cm for women, <94 cm for men), moderate (80−88 cm for women, 94 −102 cm for men) or high (>88 cm for women, >102 cm for men) based on the National Institutes of Health and international guidelines. Body mass index (BMI) was calculated from height and weight measurements and categorized participants as underweight <18.5 kg/m^2, normal 18.5 to 24.5 kg/m^2, overweight 25 to 29.9 kg/m^2, or obese ≥30 kg/m^2. The Center for Epidemiologic Studies Depression (CESD) 4-item version was used to evaluate depressive symptoms.[19]

Baseline characteristics and cardiovascular risk factors were compared between participants with and without AF using student t-tests for continuous variables and chi-square tests of association for categorical variables. The relationships between AF and baseline cognitive performance were assessed in multivariable general linear regression models. The relationships between baseline AF and longitudinal cognitive performance was examined using multivariable linear mixed models, including the interaction between AF and time to assess the association of AF and cognition over time. We report these results as least squares mean and standard errors, adjusted as above, as well as adjusted for incident stroke. Survival analyses using Cox proportional hazards models were also employed to estimate the association between AF and time to first assessment of incident impairment (as defined above). All models relating AF with cognitive performance and impairment were assessed in incremental models, as follows: model 1 was adjusted for age, sex, race, region and education; model 2 was further adjusted for hypertension, dyslipidemia, history of heart disease, LVH, diabetes, obesity, current smoking and depressive symptoms; and model 3 (longitudinal analyses) was further adjusted for incident stroke in longitudinal models only. Effect modification by sex, race and incident stroke were considered. Statistical significance for all

analyses was set at $p<0.05$. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

A total of 25,980 (mean age = 64±9.3 years; 56% women; 39% black) participants had baseline assessments of AF and cognitive data. Of these, 2,168 (8.3%) had AF at baseline of which 1784 (6.9%) were identified by self-reported physician diagnosis and 129 (0.5%) by ECG. Table 1 shows the demographic characteristics, comorbidities and socio-demographic factors among those with and without AF. Those with AF were significantly older, more likely to be white, and displayed more symptoms of depression compared to those without AF. Participants with AF at baseline were more likely to have a greater prevalence of cardiovascular risk factors and educational attainment <high school completion.

Table 2 shows the results from the cross-sectional analysis of baseline AF and cognitive function assessed by animal naming, letter F, SIS, MoCA, WLL and WLD. In models adjusted for age, sex, race, region and education, baseline AF was significantly associated with poorer baseline performance on animal naming, MoCA, and WLD. After further adjustment for cardiovascular risk factors, these relationships were no longer significant.

We assessed the associations between AF and cognitive change over a mean of 8.06 years; results are shown in Table 3. Statistically significant differences in decline in learning were detected between those with and without AF

Table 1
Baseline characteristics stratified by Atrial Fibrillation (AF) status

Variables	All (n = 25980)	Atrial Fibrillation		p-Value[a]
		Yes (n = 2168)	No (n = 23812)	
Age, years, mean (SD)	64.38 ± 9.32	67.19 ± 9.68	64.12 ± 9.23	<0.0001
Black	10473 (39.46%)	758 (34.96%)	9458 (39.72%)	<0.0001
Women	14729 (55.50%)	1164 (53.69%)	13216 (55.50%)	0.1043
4-Item CES-D score, mean (SD)[b]	1.09 ± 1.98	1.51 ± 2.38	1.04 ± 1.93	<0.0001
Hypertension	13154 (51.59%)	1325 (63.79%)	11522 (50.35%)	<0.0001
Left ventricular hypertrophy	2439 (9.33%)	207 (9.75%)	2197 (9.26%)	0.4646
Diabetes mellitus	5237 (20.48%)	524 (25.17%)	4580 (19.95%)	<0.0001
History of heart disease[c]	4328 (16.59%)	737 (34.80%)	3458 (14.62%)	<0.0001
Dyslipidemia	14968 (58.54%)	1365 (65.19%)	13289 (57.90%)	<0.0001
eGFR (CKD-EPI), mean (SD)[d]	85.70 ± 19.76	80.79 ± 21.58	86.14 ± 19.49	<0.0001
eGFR (MDRD), mean (SD)	85.86 ± 23.33	81.62 ± 25.04	86.23 ± 23.12	<0.0001
C-reactive protein, mean (SD) (mg/L)	4.53 ± 8.56	5.47 ± 9.65	4.43 ± 8.43	<0.0001
Waist circumference, mean (SD) (cm)	95.95 ± 15.69	97.66 ± 16.09	95.80 ± 15.65	<0.0001
Body mass index				
<18.5	260 (0.99%)	22 (1.03%)	234 (0.99%)	.
18.5 −24.9	6251 (23.72%)	517 (24.10%)	5611 (23.71%)	.
25 −29.9	9722 (36.88%)	7591 (35.38%)	8766 (37.04%)	.
≥30	10125 (38.41%)	847 (39.49%)	9054 (38.26%)	0.4952
Exercise				
None	8646 (34.04%)	864 (40.54%)	7574 (32.23%)	<0.0001
1−3 d/week	9678 (36.98%)	699 (32.80%)	8791 (37.41%)	.
4 d/week	7847 (29.89%)	568 (26.65%)	7135 (30.36%)	.
Current smoking	3787 (14.33%)	284 (13.15%)	3427 (14.45%)	0.0996
Education				
<High school	2930 (11.05%)	270 (12.47%)	2575 (10.82%)	.
High school graduate	6746 (25.43%)	586 (27.07%)	6016 (25.28%)	.
Some college	7204 (27.16%)	586 (27.07%)	6461 (27.14%)	0.0035
≥College graduate	9646 (36.36%)	723 (33.39%)	8750 (36.76%)	.
Region of residence				
Outside Stroke belt	11811 (44.50%)	924 (42.62%)	10655 (44.75%)	0.1153
Stroke buckle[e]	5585 (21.04%)	486 (22.42%)	4986 (20.94%)	.
Stroke belt[f]	9144 (34.45%)	758 (34.96%)	8171 (34.31%)	.
Urban/rural residence				
Mixed	2653 (11.06%)	231 (11.86%)	2368 (11.00%)	.
Rural	2635 (10.99%)	222 (11.40%)	2358 (10.95%)	.
Urban	18699 (77.95%)	1494 (76.73%)	16805 (78.05%)	0.3796

[a] p-value: unadjusted model.
[b] CES-D-4: 4-item Center for Epidemiologic Studies − Depression scale.
[c] History of heart disease was defined as coronary artery disease.
[d] eGFR: estimated glomerular filtration rate.
[e] Stroke buckle: coastal plains of North Carolina, South Carolina, and Georgia.
[f] Stroke belt: North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas.

Table 2
Baseline association between atrial fibrillation and baseline cognitive performance

Assessment	Model	Total Observations	Atrial Fibrillation			p-Value[c]	AF*Sex Interaction p-Value	AF*Race Interaction p-Value
			Yes (n = 2168)		No (n = 23812)			
			Estimate	Standard Error				
MoCA								
	Model 1[a]	19351	-0.13	0.04	Referent	0.0015	0.2556	0.5542
	Model 2[b]	17289	-0.07	0.04	Referent	0.1248		
Animal Naming								
	Model 1	20172	-0.43	0.13	Referent	0.0008	0.1867	0.1051
	Model 2	17992	-0.24	0.14	Referent	0.0815		
Letter Fluency								
	Model 1	17832	-0.13	0.12	Referent	0.2973	0.7303	0.7728
	Model 2	15944	0.07	0.13	Referent	0.6140		
Six-item Screener								
	Model 1	25489	0.02	0.01	Referent	0.1842	0.4441	0.0902
	Model 2	22658	0.02	0.01	Referent	0.1803		
Word List Learning								
	Model 1	18469	-0.24	0.13	Referent	0.0605	0.2480	0.2257
	Model 2	16497	0.03	0.13	Referent	0.8100		
Word List Delayed Recall								
	Model 1	17935	-0.14	0.06	Referent	0.0098	0.1509	0.4433
	Model 2	16021	-0.06	0.06	Referent	0.3234		

[a] Model 1 adjusted for age, sex, race, region and education.
[b] Model 2 further adjusted for hypertension, dyslipidemia, coronary artery disease, left ventricular hypertrophy, diabetes mellitus, obesity, current smoking and CESD.
[c] Statistical significance for categorical variables tested using the chi-squared method and for continuous variables the t test was used Montreal Cognitive Assessment (MoCA), Six-Item Screener (SIS), Word List Learning (WLL), Word List Delayed Recall (WLD).

(WLL ($p = 0.0007$)), adjusted for age, sex, race, region and education and these associations remained significant even after further adjustment for cardiovascular risk factors ($p<0.04$) and incident stroke ($p = 0.03$). There were no statistically significant associations between cognitive decline and AF for animal naming, letter fluency, MoCA and WLD. Effect modification by race, sex and incident stroke on AF and cognitive decline were also analyzed. We observed a significant interaction between race and AF on declines in animal naming (p-interaction = 0.04), such that black participants with AF experienced a steeper decline in semantic fluency. We also detected a significant interaction between sex and AF on decline in cognition in WLD (p-interaction = 0.006), suggesting that women with AF (p-interaction<0.05) experience greater decline in memory compared to women without AF. Incident stroke modified the association between AF and cognitive decline in MoCA (p-interaction<0.0001), WLL (p-interaction = 0.0003), and WLD (p-interaction = 0.0005) tests, suggesting that individuals with AF and incident stroke decreased in global cognitive function, learning and memory, respectively.

Table 4 presents the association between AF and time to first occurrence of cognitive impairment in which the participant scored 4 or lower on the SIS, and secondary event of incident impairment based on the time until two consecutive instances where the participant scored 4 or less as a sensitivity analysis. AF was significantly associated with an 30% increased risk of time to incident cognitive impairment on the SIS, and this association remained after further adjustment for cardiovascular risk factors (HR, 1.21; 95% CI, 1.05−1.38) and incident stroke (HR, 1.20; 95% CI, 1.05−1.38). In addition, the Kaplan-Meier curve displays the association of AF with a slightly greater incidence of global cognitive impairment over time (Figure 2). In sensitivity analyses, when impairment was defined based on two consecutive occurrences of SIS≤4, the associations were supportive but less pronounced (HR, 1.17; 95% CI, 0.94−1.46) in this sample.

Discussion

In this analysis of the REGARDS study, a national cohort of White and Black older adults, we observed cross-sectional associations between prevalent AF and baseline performance on global cognitive function, animal naming, learning and memory. AF was also associated with decline in word list learning over time. After adjustment for cardiovascular risk factors and incident stroke, only the association between AF and poorer word list learning over time remained significant. Effect modification by race, sex and incident stroke of the association between AF and decline in cognitive performance was generally not indicated, suggesting that relationships between AF and cognitive performance and decline were similar among the races and sexes. AF was also associated with time to incident impairment on SIS in fully adjusted models. Taken together, we observed associations between baseline AF and cognitive performance at baseline and longitudinal decline that may be attributable to other cardiovascular risk factors. The

Table 3
Longitudinal cognitive decline and atrial fibrillation

Cognitive Assessment	Month	Participants Included	Atrial Fibrillation Yes (n = 2168) LSMean (SE)	Atrial Fibrillation No (n = 23812) LSMean (SE)	Model 1[a]	Model 2[b] p-value AF*Time	Model 3[c]
Animal Naming					0.6649	0.5266	0.5307
	24	2737 (4.62%)	16.34 (0.31)	16.47 (0.09)			
	48	6217 (10.49%)	15.65 (0.20)	16.01 (0.06)			
	72	13765 (23.21%)	15.04 (0.15)	15.37 (0.05)			
	96	14484 (24.43%)	14.59 (0.15)	15.05 (0.05)			
	120	11022 (18.59%)	14.04 (0.17)	14.62 (0.05)			
	144	298 (0.50%)	13.84 (0.81)	13.54 (0.24)			
Letter Fluency					0.9451	0.9991	0.9992
	24	2539 (6.84%)	10.33 (0.28)	10.43 (0.09)			
	48	5770 (15.55%)	10.13 (0.18)	10.23 (0.06)			
	72	13476 (36.33%)	9.82 (0.13)	9.96 (0.04)			
	96	14151 (38.15%)	9.72 (0.13)	9.89 (0.04)			
	120	1159 (3.12%)	9.84 (0.43)	9.67 (0.11)			
MoCA					0.3719	0.4677	0.5521
	24	1724 (2.84%)	9.35 (0.14)	9.36 (0.04)			
	48	5078 (8.38%)	9.51 (0.08)	9.56 (0.02)			
	72	18109 (29.87%)	9.55 (0.04)	9.65 (0.01)			
	96	16687 (27.52%)	9.42 (0.05)	9.56 (0.01)			
	120	12496 (20.61%)	9.34 (0.05)	9.39 (0.02)			
	144	6531 (10.77%)	9.17 (0.07)	9.34 (0.02)			
Word List Learning					0.0007	0.0367	0.0328
	24	9651 (16.92%)	16.31 (0.15)	16.29 (0.05)			
	48	11142 (19.53%)	16.07 (0.15)	16.43 (0.05)			
	72	11936 (20.92%)	16.07 (0.15)	16.47 (0.04)			
	96	11355 (19.90%)	16.02 (0.15)	16.76 (0.05)			
	120	8653 (15.17%)	16.08 (0.17)	16.73 (0.05)			
	144	4310 (7.56%)	16.01 (0.23)	16.88 (0.06)			
Word Learning Delayed Recall					0.0829	0.1272	0.1176
	24	9435 (51.54%)	6.09 (0.07)	6.14 (0.02)			
	48	6597 (36.04%)	5.92 (0.07)	6.13 (0.02)			
	72	1823 (9.96%)	5.98 (0.06)	6.22 (0.02)			
	96	394 (2.15%)	6.08 (0.07)	6.29 (0.02)			
	120	51 (0.28%)	5.99 (0.08)	6.29 (0.02)			
	144	5 (0.03%)	5.99 (0.11)	6.40 (0.03)			

[a] Model 1 adjusted for age, sex, race, region and education
[b] Model 2 further adjusted for hypertension, dyslipidemia, coronary artery disease, left ventricular hypertrophy, diabetes mellitus, obesity, current smoking and CESD
[c] Further adjusted for incident stroke (longitudinal models only)

exception to this was that AF predicted decline in word list learning and cognitive impairment, which remained significant in fully adjusted models.

Our findings are generally consistent with previous cross-sectional studies in the literature showing associations between AF and cognitive performance. In a previous community-based study, individuals with a history of AF performed more poorly on a range of cognitive measures compared to those without AF.[20] Findings with working memory were similar to the present study despite differences in the underlying cognitive assessments used to evaluate working memory. In a cross-sectional study, an association

Table 4
The relationship between baseline atrial fibrillation, prevalent and incident cognitive impairment on the six-item screener (SIS≤4)

Baseline Impairment			Time to Initial Impairment (SIS≤4)		
Logistic Model[a]			Survival Analysis[a]		
Cases/ total	OR (95%CI)	Race interaction p-value	Cases/ total	HR (95%CI)	Race interaction p-value
598/ 25489	0.74 (0.54, 1.02)	0.07	2657/ 24886	1.29 (1.14, 1.47)	0.27

CI - confidence interval, *HR* - hazard ratio, *OR*- odds ratio.
[a] Model 1 adjusted for age, sex, race, region and education.

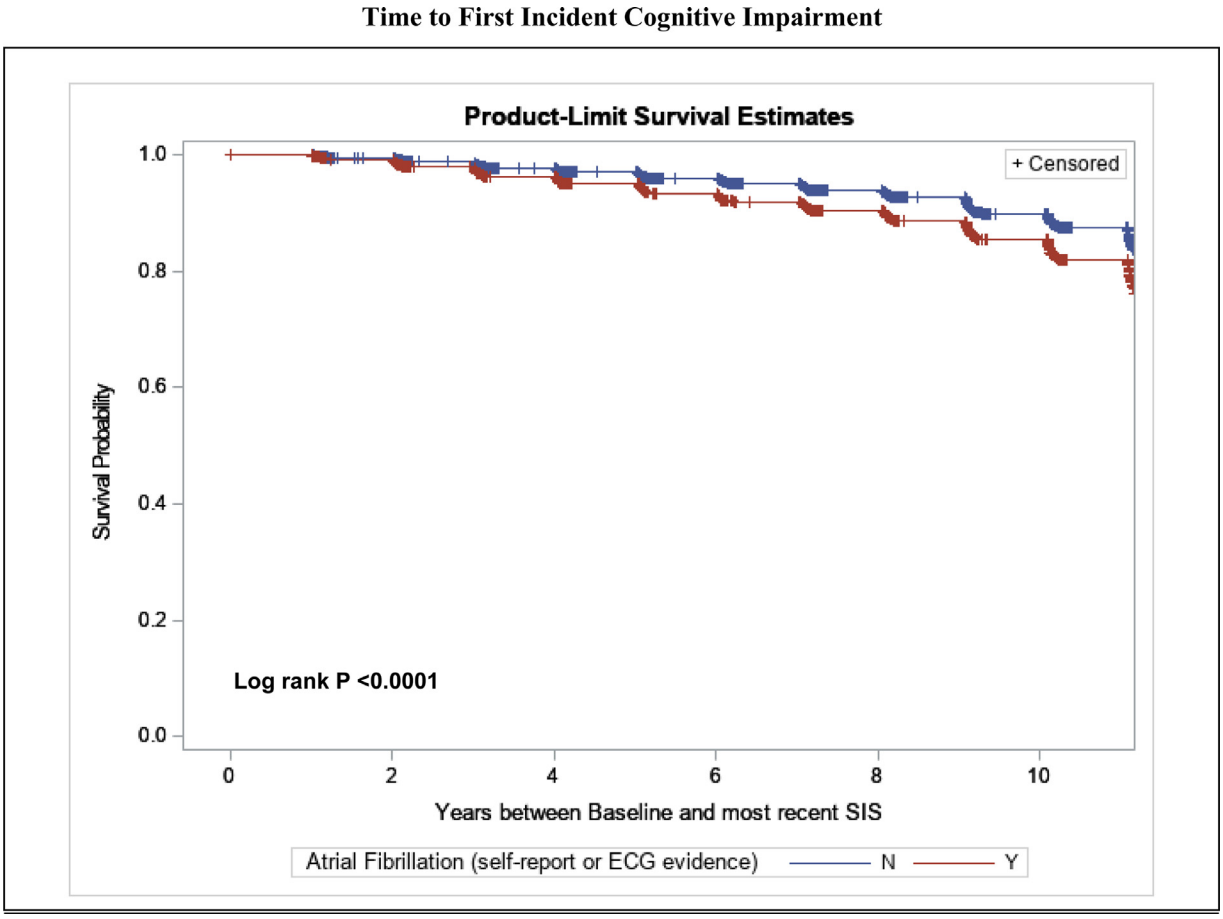

Figure 2. Kaplan Meier curve of global cognitive function over time by atrial fibrillation status. The horizontal axis shows follow up time in days for the interval between the most recent assessment and the baseline assessment. The vertical axis shows the survival rate of the sample with incident cognitive decline for those without (blue line) and with (red line) AF.

between AF and low cognitive function independent of stroke was observed,[21] consistent with our results.

Results from longitudinal studies are somewhat inconsistent. Several longitudinal studies have shown that individuals with AF experience higher rates of cognitive decline.[1,4,10,22] However, other reports suggest that AF does not increase the risk of cognitive decline.[23,24] Further, findings from the population-based Kungsholmen Project suggest that AF was not significantly associated with dementia or AD.[23] Our data in REGARDS suggest that AF may be associated with baseline decrements in global cognition, verbal learning, and recall and accelerated decline in executive function and learning over time; yet, there is evidence that these relationships may be explained by the presence of shared cardiovascular risk factors. Interestingly, longitudinal associations between AF, declines in verbal learning, and cognitive impairment were independent of shared cardiovascular risk factors.

Most studies examining the association of AF with cognitive trajectories have been performed in predominantly white populations with the exception of the Atherosclerosis Risk in Communities (ARIC) Study and Cardiovascular Health Study (CHS), and less is known about AF risk factors in nonwhite populations. Data from REGARDS and these other cohorts suggest that the association of AF with cognitive performance and decline are indeed similar for blacks and whites. Interestingly, the prevalence of AF appears to be less in blacks compared to whites despite blacks having an increased prevalence of modifiable risk factors associated with AF such as obesity, hypertension, and diabetes, termed the "AF race paradox".[6,25,26] Some cohorts have assessed the impact of AF-associated risk factors between blacks and whites.[25,27] Studies examining the racial differences in AF determined the impact of AF on the rates of stroke and mortality was considerably larger in black individuals than white individuals.[3,13] Data from CHS provided evidence that BMI and hypertension are predictive of incident AF after adjustment for age and sex in both blacks and whites, but diabetes was associated with AF in whites but not blacks.[27] There is some evidence that blacks are less likely to be aware of their diagnosis than whites,[28] thus suggesting an under reporting of AF in blacks. In contrast, the ECG monitoring is objective and does not require the participant to be aware of this diagnosis.

Our study had limitations that warrant attention. Inclusion of only black and white adults limits the generalizability of these findings to other races and ethnicities. Despite this, generalizability was increased compared to other studies since the cohort was composed of a large sample from the contiguous United States. Furthermore, self-reported AF was not verified by medical record review; however, a previous study demonstrated that self-reported AF is a

predictor of stroke and could be used interchangeably with ECG detected AF in stroke risk prediction models.[13] Additional reports from CHS displayed that self-reported AF has similar associations with risk factors as AF detected by ECG.[29] These two well-defined large biracial cohorts validate self-reported AF as validation approaches however; future studies including objective measures may provide additional insight into these relationships. Lastly, we were not able to evaluate the effect of incident AF. REGARDS only collected AF at the first two visits; therefore, this paper focused on the baseline AF. Despite these noted limitations, our study was able to answer a number of questions related to AF and its association with longitudinal cognitive decline in a well-defined, large, racially diverse cohort.

This analysis of the role of AF in cognitive performance and longitudinal cognitive decline has several strengths. REGARDS is one of the largest national samples assessing stroke risk among black and white participants. An additional strength of this longitudinal study design is that it allowed us to evaluate the relationship between AF and cognitive decline and account for the contribution of incident stroke. The longitudinal cognitive assessments in this population permitted estimates of whether stroke modified the relationship between AF and cognitive decline across cognitive domains, including learning, memory, global cognition and executive function. Finally, this cohort did not limit its AF measurement to self-reported AF alone, but also included ECG confirmed AF.

In summary, we have demonstrated that AF was associated with poorer baseline cognitive performance on measures across multiple domains when adjusting for demographic factors and declines in learning and global cognitive function over time. Additional adjustment for cardiovascular risk factors attenuated these relations with the exception of learning. These data suggest that the observed declines in cognition associated with AF may be explained by cardiovascular risk factors including stroke in this racially diverse cohort.

Authorship Statement

Each author contributed to the design, analysis, production and revision on the manuscript.

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Disclosures

The authors have no conflicts of interest.

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