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Association between cognitive impairment and risk of atrial fibrillation: The Atherosclerosis Risk in Communities study

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Abstract

Background: *Atrial fibrillation (AF) is reportedly a risk factor for cognitive impairment. Interestingly, recent studies have emphasized that impaired cognition is probably an initiating factor of cardiovascular disease. Thus, we aimed to explore the association between impaired cognition and the risk of AF, and clarify the potential mechanisms.*

Methods: *Participants of visit 2 (1991–1993) in the Atherosclerosis Risk in Communities study were included. Global cognition z-scores and factor scores were calculated using the word fluency, delayed word recall, and digit symbol substitution tests. AF incidents were diagnosed by electrocardiography and inpatient records. The association of cognitive decline with AF risk and left atrial volume index (LAVI) was explored using Cox proportional hazards and linear regression models, respectively.*

Results: *During the median follow-up of 18.2 ± 6.2 years, 2056/11,675 (17.6%) participants developed AF. Participants in the lowest quartile of global cognition z-scores and factor scores had a higher risk of AF (hazard ratio [HR]: 1.271, 95% confidence interval [CI]: 1.094–1.477, $p = 0.002$; HR: 1.305, 95% CI: 1.110–1.535, $p = 0.001$, respectively) than those in the highest quartile. Global cognition z-scores and factor scores were negatively correlated with the LAVI (B: –0.411, 95% CI: –0.749 to –0.074, $p = 0.017$; B: –0.425, 95% CI: –0.833 to –0.017, $p = 0.041$, respectively).*

Conclusions: *Cognitive decline is significantly associated with a higher risk of AF, with atrial remodeling being a potential mechanism. Our results extend previous findings of the brain-heart axis and indicate the effects of cognitive injury on cardiac function and structure.* (Cardiol J)

Registration: *URL: https://www.clinicaltrials.gov; unique identifier: NCT00005131*

Keywords: cognitive function, atrial fibrillation, atrial remodeling, stroke, Atherosclerosis Risk in Communities study

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Introduction

One of the most common supraventricular arrhythmias is atrial fibrillation (AF), and there are over 37 million prevalent cases of AF globally [1]. AF is more common in older individuals, ranging from 3.8% and 9% over the ages of 60 and 80 years, respectively [2]. AF is of particular concern because it increases risk of stroke almost fivefold [3], and it is estimated that ischemic strokes occur in 30% of patients with AF [4]. In addition, AF is also related to a higher risk of heart failure, coronary heart disease, and death [5, 6]. Although catheter ablation is a valuable therapy for AF [7], the arrhythmia-free survival rate is only 29% at 5 years [8]. Therefore, it is crucial to find novel risk factors that could aid in targeted prevention.

Cognitive decline refers to the deterioration of memory, attention, language, or executive function and is common in the older population [9, 10]. Multiple cohort studies have repeatedly confirmed that cardiovascular diseases such as AF [11, 12], heart failure [13], and coronary heart disease [14] are independent risk factors for cognitive impairment or dementia. Interestingly, according to the brain-heart axis, a brain-heart interaction exists, which implies that lesions in the brain may negatively impact the structure or function of the heart by catecholamine release, central autonomic dysregulation, inflammation, etc. [15]. For example, atrial growth and a decreased left ventricular ejection fraction can be detected after cerebral ischemic injury [16, 17]. Our previous study demonstrated that cognitive decline is related to myocardial strain and damage [18]. Atrial remodeling is crucial in the occurrence and development of AF [19]. Thus, we hypothesized that early cognitive decline reflecting brain injury might predict atrial remodeling and AF. Determining the association between these factors may provide a new theory and target for the clinical prevention and intervention of AF.

Furthermore, several previous studies have indicated that impaired cognition is related to a higher risk of stroke [20, 21]; however, the mechanism remains unclear. Considering that AF is a powerful and independent risk factor for stroke [3], we hypothesized that AF may be a mediator of cognitive decline and stroke. Thus, in the present study, we primarily aimed to investigate if cognitive function at baseline is related to the risk of AF and further explore the association between cognitive decline and atrial size. We also analyzed whether the impact of cognitive function on stroke is mediated by AF.

Methods

Study design and population

Atherosclerosis Risk in Communities (ARIC) is a prospective cohort study that investigated the risk factors of atherosclerosis and other cardiovascular diseases [22]. A total of 15,792 participants aged 45 through 65 years were enrolled in the study between 1987 and 1989, and they were sampled from 4 communities: the northwest suburbs of Minneapolis, MN; Washington County, MD; Forsyth County, NC; and Jackson, MS. The participants underwent a comprehensive examination of their social, medical, and demographic data. After the baseline examination (visit 1), 4 additional examinations (visit 2–5) were performed during 1990–1992, 1993–1995, 1996–1998, and 2011–2013, respectively. The institutional review boards of all the involved institutes authorized the research program, and all participants signed consent forms.

In this study, 14,348 participants were enrolled during visit 2 (1990–1992). Individuals without cognitive tests (n = 1608), those with prevalent AF (n = 28), those without covariates (n = 755), and those who failed to undergo AF follow-up (n = 282) were excluded. After exclusions, 11,675 participants remained to analyze the relationship between cognitive impairment and risk of AF (visit 5). For 2 subsequent studies, 4865 participants were included to analyze the association between cognitive function and the size of the left atrium (LA) (visit 5), after excluding 6810 participants without an LA volume index. Moreover, to analyze the mediating effect of AF on cognitive function and stroke, we excluded patients with stroke that occurred before AF (n = 804) and those with hemorrhagic stroke (n = 15); thus, 10,865 participants were included (Fig. 1).

Cognitive assessment

Participants were given neuropsychological tests using a standardized protocol by trained examiners in a quiet room. The tests included the delayed word recall test (DWRT), digit symbol substitution test (DSST), and word fluency test (WFT) [23]. Verbal learning and memory were examined in the DWRT; participants were asked to learn 10 words, use these words to make sentences, and repeat them after 5 minutes. Participants were given scores for the number of words they could recall. In the DSST, which aimed to test processing speed and executive function, symbols were translated into numbers by partici-

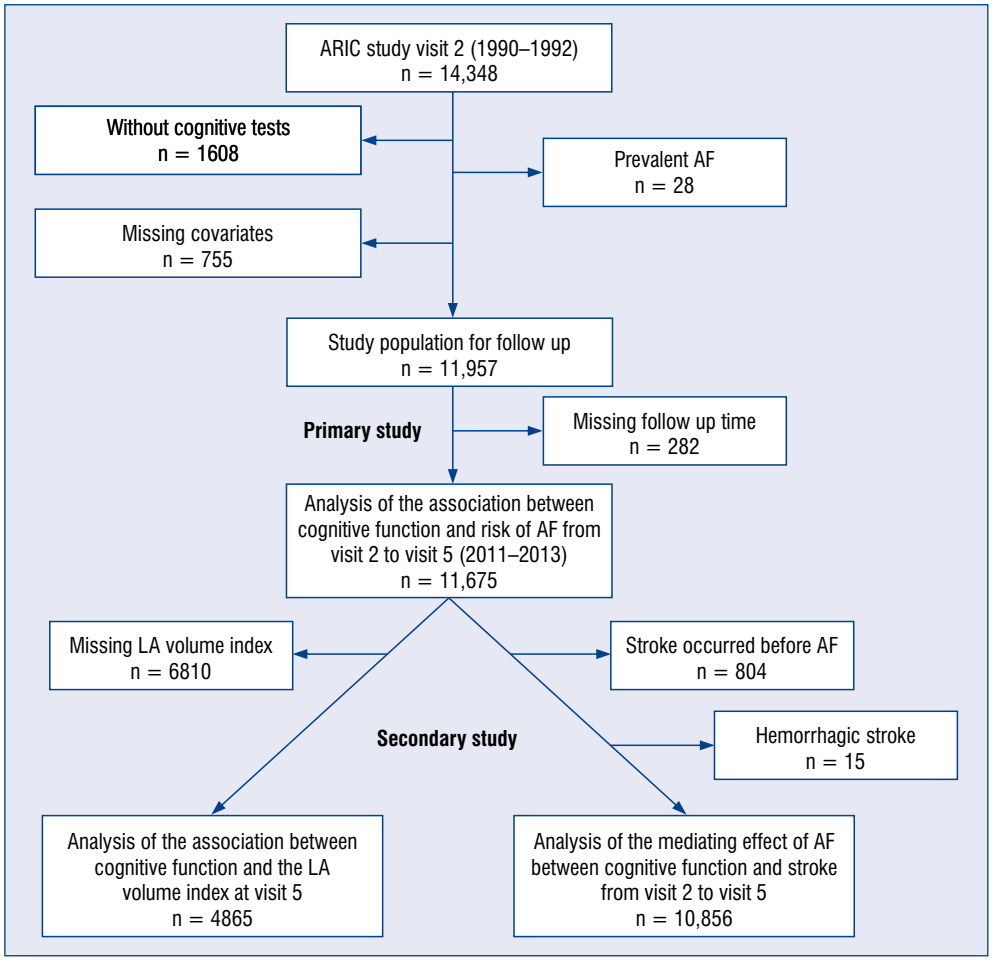

Figure 1. Study flow chart; AF — atrial fibrillation; ARIC — Atherosclerosis Risk in Communities; LA — left atrium.

pants using a keyboard, and the score represented the number of symbols translated correctly. The WFT measures expressive language and executive functioning.Participants were required to write as many words as possible starting with A, F, and S within 90 s. Their scores were the number of correct words they generated. To facilitate comparison across cognitive tests, the global cognition z-score was calculated as the mean of the 3 individual z-scores, and the mean and standard deviation (SD) were used to standardize the scores. In the factor analysis, the scores were derived for 3 domains: language, executive function, and memory. The global cognition factor score was a scaled combination of the 3 cognitive domains [12].

Ascertainment of AF

The methods to ascertain AF have been described in detail [24]. In brief, there were 3 sources to obtain AF diagnoses: electrocardiograms between visit 2 and 5, hospital discharge records, and death certificates. AF was automatically coded by the electrocardiogram recordings and confirmed by a trained cardiologist. Through annual interviewing and surveillance of local hospitals, hospitalization data of the participants were obtained. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) coded 427.31 or 427.32 represented the incidence of AF. AF was also defined if ICD-10 code I48 or ICD-9 code 427.3 were listed as one of the mortal causes in the death certificates. The date on which AF occurred was defined as the date of the first electrocardiogram diagnosis of AF, the first AF diagnosis in hospital discharge records, or death caused by AF, whichever occurred first.

Assessment of left atrial size

Two-dimensional echocardiography using apical 4- and 2-chamber views was performed to assess LA volume at the end of systole before mitral valve opening. More details regarding the design and protocols have been described previously [25]. Thereaf-

ter, the LA volume index was obtained by indexing the LA volume to body surface based on American Society of Echocardiography guidelines [26].

Ascertainment of stroke

Annual contact was performed to obtain hospitalizations and deaths of ARIC participants during the preceding year. Cardiovascular disease discharges provided by local hospitals were also examined. Possible stroke was identified if discharges had ICD-9 codes 430–438 until 1997 and ICD-9 codes 430–436 or ICD-10 codes G45.X, I60.X, I61.X, I62.X, I63.X, I65.X, I66.X, and I67.X after 1997. Patients with cerebrovascular findings revealed by computed tomography or magnetic resonance imaging scan or hospitalized in a neurological intensive care unit were eligible. All stroke events were confirmed carefully by a neurologist and adjudicated as ischemic or hemorrhagic stroke [27, 28].

Covariate assessment

Baseline medical, lifestyle, and demographic conditions were obtained at visit 2. Income was categorized as low, middle, and high, which represented < $16,000, $16,000–$35,000, and > $35,000, respectively. Level of educational attainment was separated as less than high school, high school, and college. Drinking and smoking habits were separated as never, former, and current. The calculation of body mass index was kg/m^2. A random zero sphygmomanometer was used to measure blood pressure 3 times, and the recordings were averaged. Participants with non-fasting blood glucose ≥ 200 mg/dL, fasting blood glucose ≥ 126 mg/dL, or those who previously used hypoglycemic drugs were defined as having diabetes. Participants with systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or those who previously used hypotensive drugs were defined as having hypertension. Chronic obstructive pulmonary disorder (COPD) was defined according to the results of obstructive vital capacity measurement model or doctor's diagnosis. Glucose-6-phosphate dehydrogenase or modified hexokinase method were used for the measurement of fasting blood glucose. Total cholesterol and high-density lipoprotein cholesterol were measured by an enzymatic method and precipitation method, respectively.

Statistical analysis

Participants were classified into quartiles (Q1, Q2, Q3, and Q4) according to their global cognition z- and global cognition factor score. Nonparametric and parametric variables are presented as medians (25^{th} and 75^{th} percentiles) and mean ± SD, respectively; the Mann–Whitney U-test, Kruskal–Wallis H test, and analysis of variance were used to compare them. Categorical variables are presented as frequencies and percentages and compared by the chi-square test.

A Cox proportional hazards model was performed for analysis of the relationship between cognitive function and occurrence of AF; hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained. For further determination of independent risk factors, the model was adjusted for demographic variables (sex, income, education, race, age), lifestyle (drinking, smoking), physical and lab variables (body mass index, total cholesterol, heart rate, high-density lipoprotein, triglycerides, systolic blood pressure), and chronic medical conditions (COPD, diabetes, hypertension). After adjusting for confounding factors, different subgroups were stratified by sex, race, age, diabetes, and hypertension, and the Cox proportional hazards model was used to analyze the association between cognitive function and AF in these subgroups.

A linear regression model was used to evaluate the association between cognitive function and LA size. The model covariates were the same as those used to investigate the association between cognitive function and AF.

The degree to which AF mediates the association between cognitive decline and stroke was analyzed by path analysis using structural equation modeling [29]. The proportion of the mediating effect was calculated as the estimated indirect effect size divided by the estimated total effect size. The results are shown by HR and mediated proportions.

A 2-tailed p value of < 0.05 was considered significant for all tests. All statistical analyses were performed using SPSS version 26.0 (IBM Corp, Armonk, NY, United States) and R software 3.5.0 (Vienna, Austria).

Results

Baseline characteristics

A total of 11,675 participants were included in our study. The average age of the participants was 57.1 ± 5.7 years; 6378 (54.6%) were male, and 9223 (79%) were Caucasian. During the 18.2 ± 6.2 years of follow-up, 2056 (17.6%) participants developed AF. Baseline characteristics (1990–1992) were described and compared based on the occurrence of AF (Table 1). Compared to participants without AF, participants with AF were more likely to be older,

Table 1. Baseline (1990–1992) participant characteristics by the occurrence of atrial fibrillation (AF).

	Total (n = 11,675)	Non-AF (n = 9619)	AF (n = 2056)	P
Demographic variables				
Age [years]	57.1 ± 5.71	56.6 ± 5.66	59.4 ± 5.4	< 0.001
Male sex	6378 (54.6)	5422 (56.4)	956 (46.5)	< 0.001
Caucasian	9223 (79.0)	7467 (77.6)	1756 (85.4)	< 0.001
Education:				< 0.001
Less than high school	2367 (20.3)	1874 (19.5)	493 (24.0)	
High school	3690 (31.6)	3030 (31.5)	660 (32.1)	
College	5618 (48.1)	4715 (49.0)	903 (43.9)	
Income, US$:				0.003
< 16,000	2252 (19.3)	1845 (19.2)	407 (19.8)	
16,000–35,000	3927 (33.6)	3179 (33.0)	748 (36.4)	
> 35,000	5496 (47.1)	4595 (47.8)	901 (43.8)	
Smoking:				< 0.001
Never	4630 (39.7)	3917 (40.7)	713 (34.7)	
Former	4450 (38.1)	3593 (37.4)	857 (41.7)	
Current	2595 (22.2)	2109 (21.9)	486 (23.6)	
Drinking:				0.015
Never	2534 (21.7)	2125 (22.1)	409 (19.9)	
Former	2348 (20.1)	1895 (19.7)	453 (22.0)	
Current	6793 (58.2)	5599 (58.2)	1194 (58.1)	
Physiological and lab variables				
Body mass index [kg/m^2]	27.9 ± 5.31	27.6 ± 5.18	29.0 ± 5.78	< 0.001
SBP [mmHg]	118 (108, 131)	117 (108, 130)	123 (112, 136)	< 0.001
DBP [mmHg]	71.0 (65.0, 78.0)	71.0 (65.0, 78.0)	72.0 (65.0, 78.0)	0.655
Heart rate [/min]	65.0 (59.0, 72.0)	65.0 (59.0, 72.0)	64.0 (58.0, 71.0)	0.032
Total cholesterol [mmol/L]	5.41 ± 1.00	5.42 ± 1.01	5.38 ± 0.97	0.079
HDL [mmol/L]	1.28 ± 0.43	1.30 ± 0.43	1.21 ± 0.40	< 0.001
LDL [mmol/L]	3.46 ± 0.95	3.46 ± 0.96	3.45 ± 0.90	0.745
Triglycerides [mmol/L]	1.47 ± 0.74	1.45 ± 0.73	1.57 ± 0.78	< 0.001
Creatinine [mg/dL]	1.15 ± 0.31	1.14 ± 0.31	1.17 ± 0.30	< 0.001
Blood glucose [mmol/L]	5.72 (5.33, 6.22)	5.66 (5.33, 6.16)	5.83 (5.44, 6.49)	< 0.001
Chronic medical conditions				
Hypertension	3323 (28.5)	2538 (26.4)	785 (38.2)	< 0.001
Diabetes mellitus	1631 (14.0)	1238 (12.9)	393 (19.1)	< 0.001
COPD	2652 (22.7)	2033 (21.1)	619 (30.1)	< 0.001
Cognition score				
Global cognition z-score	0.10 (-0.58, 0.71)	0.12 (–0.56, 0.74)	-0.02 (-0.69, 0.56)	< 0.001
DWRT score	7 (6, 8)	7 (6, 8)	7 (6, 7)	< 0.001
DSST score	46 (37, 55)	47 (37, 55)	44 (36, 53)	< 0.001
WFT score	33 (25, 42)	33 (25, 42)	32 (24, 40)	0.001
Global cognition factor score	0.11 (–0.51, 0.65)	0.13 (–0.50, 0.66)	–0.03 (–0.60, 0.53)	< 0.001
Language domain factor score	0.07 (–0.51, 0.38)	0.07 (–0.51, 0.38)	0.07 (–0.51, 0.38)	0.003
Memory domain factor score	0.12 (–0.24, 0.47)	0.12 (–0.24, 0.47)	0.11 (–0.24, 0.12)	< 0.001
Executive domain factor score	0.01 (–0.27, 0.36)	0.03 (–0.25, 0.37)	–0.02 (–0.32, 0.22)	< 0.001

Values are expressed as number (%), mean ± standard deviation, and median (25th, 75th). Global cognition z-score was calculated by computing the mean from the z score versions of the DSST, WFT, and DWRT administered during the visit 2; SBP — systolic blood pressure; DBP — diastolic blood pressure; HDL — high-density lipoprotein; LDL — low-density lipoprotein; COPD — chronic obstructive pulmonary disease; DSST — digit symbol substitution test; WFT — word fluency test; DWRT — delayed word recall test

Table 2. Unadjusted and adjusted hazard ratios (HR) (95% confidence interval [CI]) for the association of baseline (1990–1992) cognition function with presence of atrial fibrillation.

Variable	Quartile	Unadjusted		Adjusted	
		HR (95% CI)	P	HR (95% CI)	P
Global cognition z-score:			< 0.001		0.015
	Q1	1.853 (1.634–2.102)	< 0.001	1.271 (1.094–1.477)	0.002
	Q2	1.496 (1.317–1.699)	< 0.001	1.154 (1.010–1.319)	0.036
	Q3	1.284 (1.127–1.463)	< 0.001	1.082 (0.947–1.235)	0.245
	Q4	Reference	–	Reference	–
Global cognition factor score:			< 0.001		0.014
	Q1	1.859 (1.633–2.116)	< 0.001	1.305 (1.110–1.535)	0.001
	Q2	1.675 (1.473–1.904)	< 0.001	1.185 (1.033–1.360)	0.015
	Q3	1.423 (1.249–1.622)	< 0.001	1.148 (1.005–1.311)	0.043
	Q4	Reference	–	Reference	–

Univariate and multivariate Cox regression analysis between cognition function and presence of atrial fibrillation. Multivariate Cox regression was adjusted by age (< 57, ≥ 57), sex, center-race, education (< high school, high school, or > high school), annual household income (< $16,000, %16,000 to $35,000, or > $35,000), smoking (never, former, current), drinking (never, former, current), body mass index, systolic blood pressure, heart rate, total cholesterol, triglycerides, high-density lipoprotein, hypertension, diabetes, and chronic obstructive pulmonary disease

female, African American, and have lower education and income, while also having smoking habits, hypertension, diabetes, and COPD ($p < 0.05$). In addition, participants with AF had significantly lower global cognition z- and global cognition factor scores ($p < 0.001$). Baseline participant characteristics by quartiles of global cognition z-scores were also compared (**Suppl. Table 1**).

Cognitive function and AF

In the adjusted Cox proportional hazards model, participants in the lowest quartile (Q1) of global cognition z- and global cognition factor scores had a higher risk of AF (HR: 1.271, 95% CI: 1.094–1.477, $p = 0.002$; HR: 1.305, 95% CI: 1.110––1.535, $p = 0.001$, respectively) than those in Q4 (Table 2). Associations of lower DSST, language, memory, and executive functioning domain factor scores with a higher risk of AF were significant in unadjusted and adjusted Cox proportional hazards models (**Suppl. Table 2**).

Subgroup analysis

A significant association between cognitive scores and the risk of AF was observed in the subgroups stratified by sex, age, race, hypertension, and diabetes. Furthermore, the association between cognition decline and an increased risk of AF was stronger in participants with diabetes or hypertension than in those without it (Fig. 2).

Cognitive function and left atrial size

Participants with lower global cognition z- or factor scores had significantly higher LA volume indices. In the adjusted linear regression model, global cognition z- and factor scores were negatively correlated with the LA volume index (B: –0.411, 95% CI: –0.749 to –0.074, $p = 0.017$; B: –0.425, 95% CI: –0.833 to –0.017, $p = 0.041$, respectively; Table 3).

Mediation analysis

A significant mediating effect of AF on the relationship between cognitive function and stroke was observed (Table 4). In the structural equation modeling, the indirect effects of global cognition z-scores (Q1 vs. Q4) and factor scores (Q1 vs. Q4) on stroke mediated by AF were 23.4% (HR: 1.236) and 29.3% (HR: 1.472), respectively.

Discussion

In the prospective cohort of the ARIC study with a large number of participants over a long follow-up period, we found a significant association between cognitive impairment and AF. Participants with the lowest quartile of cognition score had a > 25% higher risk of AF even after adjusting for other risk factors such as smoking, drinking, hypertension, and diabetes. Moreover, we found that impairment of language and executive functioning

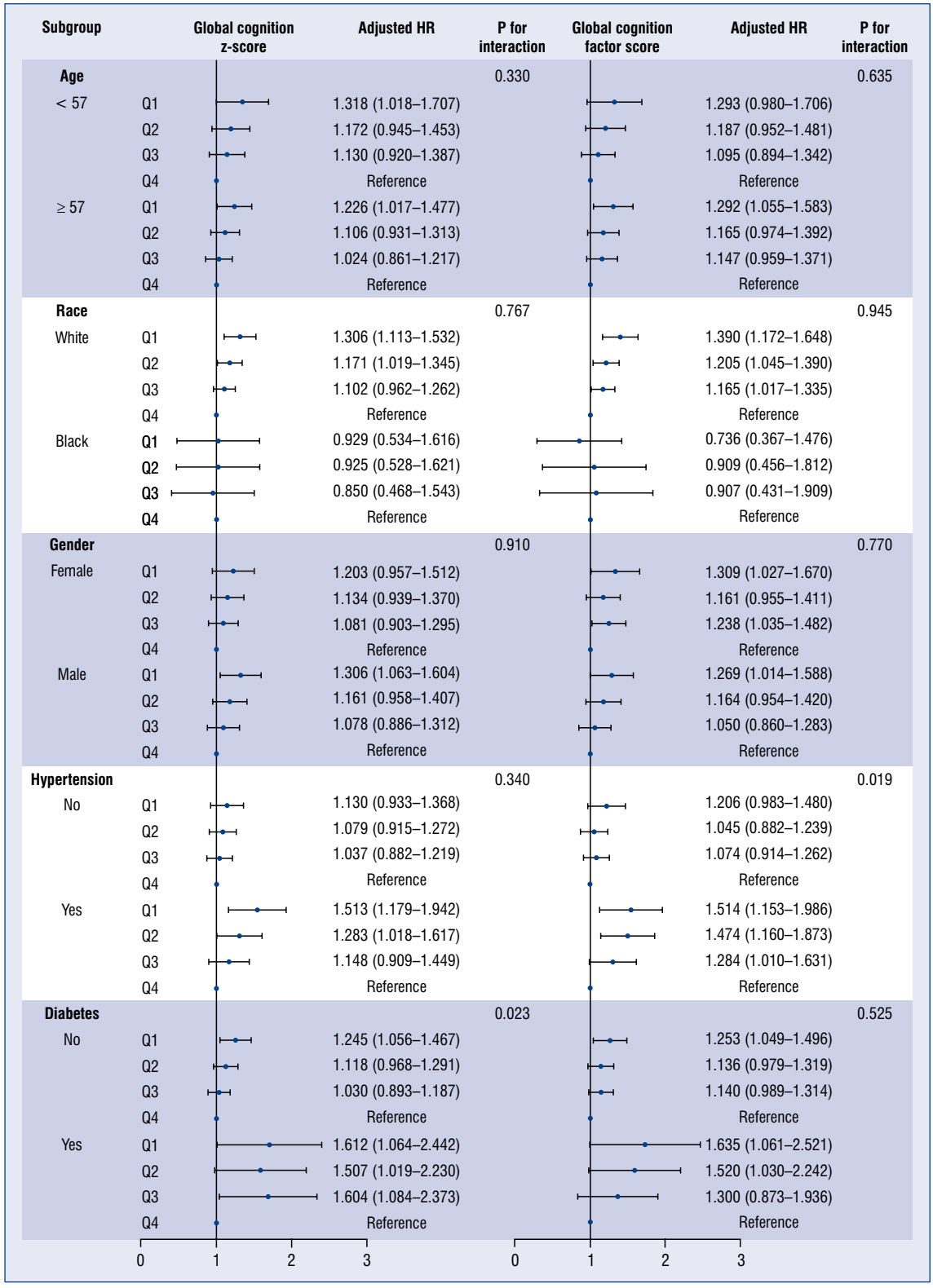

Figure 2. Adjusted hazard ratios (HR) (95% confidence intervals) for the association of baseline (1990–1992) cognition function with the occurrence of atrial fibrillation in different subgroups. Multivariate Cox regression analysis between cognition function and occurrence of atrial fibrillation adjusted by age (< 57, ≥ 57 years), sex, center-race, education (< high school, high school, or > high school), annual household income (< $16,000, $16,000 to $35,000, or > $35,000), smoking (never, former, current), drinking (never, former, current), body mass index, systolic blood pressure, heart rate, total cholesterol, triglycerides, high density lipoprotein, hypertension, diabetes, and chronic obstructive pulmonary disease.

Table 3. Univariate and multivariate liner regression analysis between cognition function and left atrial volume index.

	B (95% CI)	SE	β	t	P
Unadjusted					
Global cognition z-score	–0.948 (–1.227 to –0.668)	0.142	–0.095	–6.653	< 0.001
Global cognition factor score	–1.067 (–1.385 to –0.750)	0.162	–0.094	–6.593	< 0.001
Adjusted					
Global cognition z-score	–0.411 (–0.749 to –0.074)	0.172	–0.041	–2.391	0.017
Global cognition factor score	–0.425 (–0.833 to –0.017)	0.208	–0.037	–2.044	0.041

Multivariate liner regression was adjusted by age (< 57, ≥ 57), sex, center-race, education (< high school, high school, or > high school), annual household income (< $16,000, $16,000 to $35,000, or > $35,000), total cholesterol, triglycerides, high-density lipoprotein, hypertension, diabetes, and chronic obstructive pulmonary disease; CI — confidence interval; SE — standard error

domains were independent impact factors of AF. Declined cognition is associated with a larger LA volume, which may explain the potential relationship between impaired cognition and AF. Finally, we demonstrated that > 20% of the effects of cognitive impairment on stroke were mediated by AF.

Considering that age, race, comorbidities, and other covariates significantly impact cognition [30–33], we performed a subgroup analysis suggesting a consistent relationship between cognitive impairment and AF in the subgroups stratified by sex, age, race, hypertension, and diabetes. Notably, the association was stronger in participants with hypertension or diabetes than in those without (p for interaction < 0.05), which indicates that declined cognition in combination with hypertension or diabetes increases the risk of AF; thus, preventive measures should be considered for such a population to prevent the occurrence of AF.

The relationship between cognitive decline and AF incidents may be multipath. First, we considered atrial remodeling as the most crucial impact factor of AF. According to the brain-heart axis, most common causes of cognitive decline, such as Alzheimer's disease, vascular dementia, psychological stress, and covert stroke [34, 35], may lead to cardiac remodeling through hyperactivation of the sympathetic nerve, catecholamine release, inflammation, etc. [15]. We analyzed the association between cognitive function and LA volume and found a significant negative correlation. Thus, atrial remodeling is probably a key mechanism for the association between cognitive decline and AF. Second, cognitive decline and AF share similar cardiovascular disease risk factors, such as aging, smoking, obesity, hypertension, and diabetes [36, 37]. Thus, cardiovascular disease risk factors may indirectly mediate the association between cognitive decline and AF.

Atrial fibrillation is recognized as a crucial risk factor for stroke, which brings a huge social and economic burden; thus, it has been receiving increasing attention. Several studies have demonstrated that populations with cognitive decline have a higher risk of stroke. The authors of these studies proposed some potential mechanisms, such as unrecognized cerebrovascular injury [38] or higher polygenic risk [39]. Notably, we used a structural equation to investigate whether AF mediates the association between cognitive function and stroke. Therefore, these results provide a strong clinical implication that the cognitive function-AF-stroke axis is an important intervention pathway, and early cognitive assessment and intervention may help to reduce the prevalence of AF and related complications

Limitations of the study

Our study has some limitations. First, we did not distinguish between paroxysmal AF and persistent AF, in which cognitive decline may have different effects. Second, AF was identified primarily from hospitalization discharges and study electrocardiograms; therefore, asymptomatic AF and AF treated only in the outpatient setting may not have been included in our study. Third, several other validated assessment tools for cognitive function [9, 40] were unavailable for the ARIC study. Fourth, we adjusted our model using several risk factors; however, we could have missed some potential factors, such as psychological factors. Fifth, the participants we investigated were chiefly middle--aged or older people in the community; therefore, whether the results are consistent in young people remains unclear. Sixth, echocardiography was performed at visit 5 (2011–2013), and over 80% of AF occurred before the echocardiography examination. Therefore, the study lacks direct evidence

Table 4. Estimated direct and indirect effect sizes of impaired cognitive function on stroke mediated by atrial fibrillation.

Cognitive function	Case/Total (%)	HR (95% CI)			Mediated b
		Total effect	Direct effect	Indirect effect	
Global cognition z-score:					
Q1	70/2714 (2.6%)	1.956 (1.423–2.689)	1.603 (1.312–2.037)	**1.236 (1.082–1.542)**	**23.4%**
Q2	63/2714 (2.3%)	1.768 (1.258–2.398)	1.529 (1.164–1.895)	**1.165 (1.010–1.463)**	**18.7%**
Q3	43/2714 (1.6%)	1.256 (0.896–1.787)	1.205 (0.873–1.719)	1.021 (0.738–1.359)	8.2%
Q4	27/2714 (1.0%)	Reference	Reference	Reference	–
Global cognition factor score:					
Q1	75/2715 (2.8%)	2.501 (1.976–3.269)	1.920 (1.511–2.590)	**1.472 (1.132–1.825)**	**29.3%**
Q2	51/2725 (1.9%)	1.723 (1.251–2.306)	1.521 (1.172–2.001)	1.123 (0.998–1.271)	16.1%
Q3	53/2708 (2.0%)	1.729 (1.259–2.287)	1.538 (1.159–1.928)	**1.163 (1.009–1.442)**	**20.5%**
Q4	24/2708 (0.9%)	Reference	Reference	Reference	–

Hazard ratio was calculated by Cox proportional hazards model. A total of 1000 iterations were performed for bootstrapping to estimate 95% bias-corrected confidence interval. The percentage mediated was calculated by log (estimated indirect effect)/ log (estimated total effect). Bold value indicates $p < 0.05$; CI — confidence interval; HR— hazard ratio

that atrial remodeling mediates the relationship between cognitive function and AF.

Conclusions

Our study provides evidence that cognitive decline is associated with a high risk of AF. Declined cognition is associated with a larger left atrial volume, which may explain the potential relationship between impaired cognition and AF. Moreover, AF is a mediator of cognitive decline and stroke. Therefore, cognitive decline is not only the outcome of cardiovascular disease but also the original risk factor of atrial remodeling, AF, and stroke.

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