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# Markers of left atrial cardiopathy and cognitive function trajectories in adults aged $\geq 45$ years without atrial fibrillation: a population-based study

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## Abstract

**Introduction** The study aims to investigate associations between markers of atrial cardiopathy and cognitive function trajectories in adults without prior AF.

**Methods** The study included 4,486 participants from the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. Markers of atrial cardiopathy included atrial premature complexes and N-Terminal pro-Brain Natriuretic Peptide (NT pro-BNP). Cognitive status was measured using the Six-Item Screener (SIS). Cognitive status trajectories were identified using latent class growth models.

**Results** Three unique cognitive trajectories over the 8-year follow-up were identified: 86.7% showed a normal and stable trajectory of SIS score, 7.6% showed a progressively decreasing trajectory, and 5.7% showed a dramatic decreasing trajectory. Age, black participants, and antidepressant drugs were significantly associated with the “dramatic decrease” trajectory. Elevated NT pro-BNP was significantly associated with the “dramatic decrease” trajectory.

**Discussion** Markers of left atrial cardiopathy may have implications for early diagnosis and prevention of cognitive impairment.

**Keywords** Cognitive trajectory, Atrial cardiopathy, Biomarkers, Atrial fibrillation

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## Background

Dementia is a growing epidemic among aging adults, affecting approximately 55 million globally [1, 2]. Dementia is a leading cause of mortality and disability and has a dramatic effect on the healthcare system and resources [2–4]. Early intervention for dementia can delay functional decline and institutionalization, emphasizing the critical need for reliable predictors of dementia risk in the aging population [5]. Atrial fibrillation (AF) is the most common cardiac arrhythmia and independently increases the risk of stroke and cognitive [6–9]. If detected, the risk of AF-related stroke and dementia can be reduced significantly with anticoagulation treatment [10]. However, AF is often paroxysmal or clinically silent, potentially limiting the utility of basing risk prediction for dementia on AF [11, 12].

Clinical AF is often preceded by atrial cardiopathy, a series of structural abnormalities and electrical left atrial remodeling [13]. There is growing evidence that both AF and stroke are potential results of an underlying atrial cardiopathy, suggesting that atrial cardiopathy may be an important risk marker to identify individuals at risk of AF and stroke [14]. Several studies have shown that markers of atrial cardiopathy, including increased P-wave terminal in lead V1, left atrial enlargement, and premature complexes, increase the risk of AF and stroke [15–19]. Further, prior work from our team has also demonstrated that adding markers of atrial cardiopathy to existing stroke prediction tools (CHA<sub>2</sub>DS<sub>2</sub>-VASc) improves the predictive utility of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score for stroke risk in those without AF [20]. Emerging data have shown that atrial structure may also show associations with cognitive decline and dementia in those with AF [9, 21]; however, data on whether atrial cardiopathy are associated with cognition in those with no documented AF remains limited [22, 23]. The present study aims to investigate associations between atrial cardiopathy and cognitive function trajectories in aging adults without prior AF. Specifically, this study used data from a population-based cohort study to identify unique cognitive function trajectories in those with measures of atrial premature complexes and N-Terminal pro-Brain Natriuretic Peptide

(NT pro-BNP). Atrial premature complexes are a type of arrhythmia characterized by premature heartbeats within the atria and have been shown to be a marker of atrial cardiopathy and associated with worsened cognitive function [21]. NT pro-BNP is a serum biomarker released by the myocardium and a predictor of AF, subclinical cerebrovascular disease and stroke, and has been demonstrated strongly associated with left atrial remodeling and dysfunction [24–27]. Recent studies have reported a link between increased NT pro-BNP and cognitive decline and dementia [28].

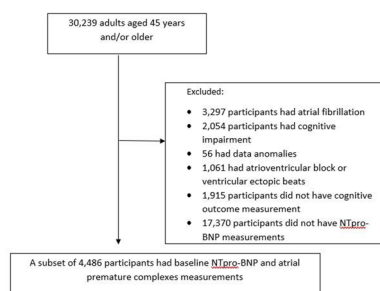
## Methods

### Cohort and study design

The study cohort was derived from the population-based prospective study (Reasons for Geographic and Racial Differences in Stroke, REGARDS). REGARDS enrolled 30,239 adults aged ≥ 45 years between January 2003 and October 2007 and followed them every 6 months by telephone or in-home visits to examine regional and racial differences in stroke mortality [29, 30]. Demographic information and medical histories were obtained via telephone interview and information regarding medications, blood samples, and a resting electrocardiogram (ECG) was collected by trained staff during the in-home visit [29, 30]. The REGARDS data set is available through a data use agreement with the University of Alabama at Birmingham. For the present study, we ascertained a cohort of adults aged ≥ 45 years with measures of atrial premature complexes and (NT pro-BNP who had no prior AF or cognitive impairment ( $N=4,486$ ), as NT pro-BNP measure is only available in this nested cohort. Exclusion criteria were a history of AF, defined as either self-report on the telephone interview or review of ECG evidence, cognitive impairment defined as a Six-Item Screener (SIS) score < 5, atherosclerosis, or ventricular ectopic beats. As our focus was on the longitudinal trajectory of cognitive function, those with < 2 cognitive outcome measurements were also excluded (Fig. 1).

### Markers of atrial cardiopathy

Markers of atrial cardiopathy included atrial premature complexes and NT pro-BNP. Baseline atrial premature complexes were detected on 12-lead ECG and defined by Minnesota code criteria (Minnesota codes 8.1.1, 8.1.3) [31]. For the present analysis, atrial premature complexes were dichotomized as present or absent. NT pro-BNP is a marker of atrial dysfunction and previous research has shown that NT pro-BNP was associated with stroke risk [32, 33]. NT pro-BNP was measured in a random nested case-cohort sample from the REGARDS cohort using an electrochemiluminescence immunoassay [34]. We treated NT pro-BNP as a continuous variable, and



**Fig. 1** A cohort diagram shows the number of participants included

defined elevated NT pro-BNP as those ranked in the top NT pro-BNP quintile ( $>235.2\text{pg/mL}$ ) [35].

### Measures of cognitive function

Cognitive function was measured using the SIS score, a global measure of cognitive function that can be measured through telephone or face-to-face interview and has previously been shown to be reliable for identifying subjects with cognitive impairment [36]. Starting in December 2003, participants' cognitive function was measured annually using the SIS (score range, 0–6) [36]. A score of 5 or 6 was defined as cognitive impairment, and a score of 0–4 was considered normal [36]. The SIS score has been widely used to identify individuals with cognitive impairment in previous published literature [37]. Using cognitive assessment and neurologic examination as the gold standard for diagnosis, previous reports have shown that the SIS demonstrated a sensitivity of 74.2% and a specificity of 80.2% in identifying cognitive impairment in the community setting, and a sensitivity of 84% and a specificity of 85.3% in the clinical setting [36, 38]. In addition, prior observational work has shown that, compared with the gold standard diagnosis recorded on the patient chart, using SIS to identify cognitive impairment resulted in a sensitivity of 86% and a specificity of 77%, and that individuals with poor SIS scores were more likely to have cognitive impairment [38]. In this study, the SIS score was used not only in the older population aged 65 years and over, but also in younger individuals [39].

### Demographic and clinical characteristics

In REGARDS, participants reported on their age, sex, race, exercise, smoking status, and alcohol use at baseline. Comorbidities included diabetes, hypertension, hyperlipidemia, left ventricular hypertrophy, and a history of myocardial infarction, stroke and heart diseases. Participants were asked about whether they were ever diagnosed with diabetes (defined as a fasting glucose  $\geq 126\text{ mg/dL}$ , a non-fasting glucose  $\geq 200\text{ mg/dL}$ , or self-reported diabetes medication use [30, 34]), hypertension (defined as systolic blood pressure of 140 mm Hg or more and diastolic blood pressure of 90 mm Hg or more or self-reported antihypertensive medication use [30, 34]), and hyperlipidemia (defined as total cholesterol of 240 mg/dL or more, low-density lipoprotein cholesterol of 160 mg/dL or more, high-density lipoprotein cholesterol of 40 mg/dL or less, or self-reported antihyperlipidemic medication use [30, 34]). Participants were also asked about whether they had used statin, antiplatelets, or antidepressant medications. Myocardial infarction and coronary artery disease were self-reported or diagnosed using ECG data. Left ventricular hypertrophy was measured using ECG data and defined by the Sokolow-Lyon

Criteria [40, 41]. A history of stroke was obtained based on clinical review of medical records by a team of stroke experts, using published guidelines [30, 41]. Data on all of these demographic and clinical characteristics were ascertained for the present study. Incident AF and stroke during the follow-up were measured through a follow-up computer-assisted telephone interview and/or in-home examination. All participants provided written informed consent, and the study was approved by the institutional review boards.

### Statistical analysis

Descriptive statistics were used to characterize the study cohort for demographic and clinical variables. Trajectories of cognitive function over an 8-year follow-up were identified using latent class growth modelling, a semi-parametric approach that identifies distinct latent subgroups of individuals following a similar pattern of an outcome over time [42]. The model used random intercepts and slopes for participants over time, and fixed effects for years of follow-up (continuous), calculated as the years since baseline. The number of trajectory groups was determined by overall model fit as assessed by the Bayesian information criterion (BIC), Akaike information criterion (AIC), and the maximum likelihood ratio in each group [42]. Trajectories were first specified for one group, and additional groups were added until the model fit worsened. We used the restricted maximum likelihood ratio to accommodate missing SIS data over time and a censored modelling approach to account for non-random attrition. Covariates were selected based on their relevance to the outcome. Multicollinearity was assessed using generalized variance inflation factors (VIF). There is no evidence of multicollinearity with all covariates' VIF lower than 2. Once the number of groups was identified, baseline exposure, demographic and clinical characteristics in each trajectory group, including age, sex, race, exercise, smoking status, alcohol use, prior history of hypertension, diabetes, coronary artery diseases, myocardial infarction, left ventricular hypertrophy, and baseline use of antiplatelet, statin, or anti-depression drugs, were compared. Mean and standard deviation (SD) were used to describe continuous variables, and proportions and percentages were used to describe categorical variables. Analysis of variance was used for continuous variables, and chi-square or Fishers' exact test was used for categorical data. A multinomial regression model was used to identify independent factors associated with each trajectory group.

To ensure incident AF and stroke during follow-up as potential mediators do not influence the observed associations, we conducted a sensitivity analysis in which participants who developed incident AF during the study follow-up ( $N=1,371$ ) were removed to estimate

the association between atrial cardiopathy and cognitive function trajectories. Similarly, participants with an incident stroke during the follow-up ( $N=5$ ) were removed to examine the association. Stratified models were also conducted to examine effect modification by sex (males and females).

All analyses were conducted using R software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Cohort characteristics

After applying exclusion criteria as described above, 4,486 participants were included for analysis. Table 1 presents a summary of baseline characteristics. On average, participants were 66.1 years old at baseline ( $SD=10.8$ ), with 50.7% females and 56.9% self-identified as white. More than half of the participants were diagnosed with hypertension (62.5%) and dyslipidemia (58.7%) at baseline. A total of 896 participants (20.0%) had elevated NT pro-BNP, and 503 (11.2%) had atrial premature complexes at baseline.

### Trajectories of cognitive function

Latent class growth modeling indicated that the data were best modeled as three subgroups of adults with

unique cognitive function trajectories (Fig. 2). Supplemental Table S1 showed the model fit indices for the tested models. The first group, labeled “stable,” was composed of 86.7% of the participants who had high SIS scores at baseline and remained relatively stable over the follow-up. The second group, “stable decrease,” was composed of 7.6% of the participants who had high SIS scores at baseline and showed a progressively decreasing trajectory. The remaining group, “dramatic decrease,” was composed of 5.7% of the participants who showed a dramatic decrease in SIS score. Table 2 summarizes the SIS scores of each trajectory at each time point. The mean difference between baseline and 8-year follow-up SIS scores was a decrease of 1.6 points (95% confidence interval [CI]: 1.4–1.9;  $p<0.01$ ) for participants in the “stable decrease” group and a decrease of 4.1 points (95% CI: 3.6–4.7;  $p<0.01$ ) for participants in the “dramatic decrease” group. There was no significant change in SIS score between baseline and 8-year follow-up for participants in the “stable” group.

### Factors associated with each trajectory

Table 3 summarizes the characteristics of each trajectory. Participants with older age, myocardial infarction, hypertension, elevated NT pro-BNP, and atrial premature complexes were more likely to have a worsening SIS trajectory.

Table 4 summarizes the results of multinomial models and reports adjusted odds ratios (OR) and 95% CI of belonging to each group trajectory relative to the stable group. Older age (OR: 1.08; 95% CI: 1.07–1.07,11), black participants (white vs. black, OR: 0.36; 95% CI: 0.25–0.52), and use of antidepressant drugs at baseline (OR: 2.00; 95% CI: 1.22–3.29) were significantly associated with the “dramatic decrease” trajectory. Age (OR: 1.08; 95% CI: 1.06–1.10), black participants (white vs. black, OR: 0.37; 95% CI: 0.27–0.52), and male participants (OR: 1.80; 95% CI: 1.30–2.49) were significantly associated with the “stable decrease” trajectory. Elevated NT pro-BNP was significantly associated with the “dramatic decrease” trajectory (OR: 2.14; 95% CI: 1.02–4.49). Supplemental Figure S1 and S2 show the forest plots of odds ratios for all covariates.

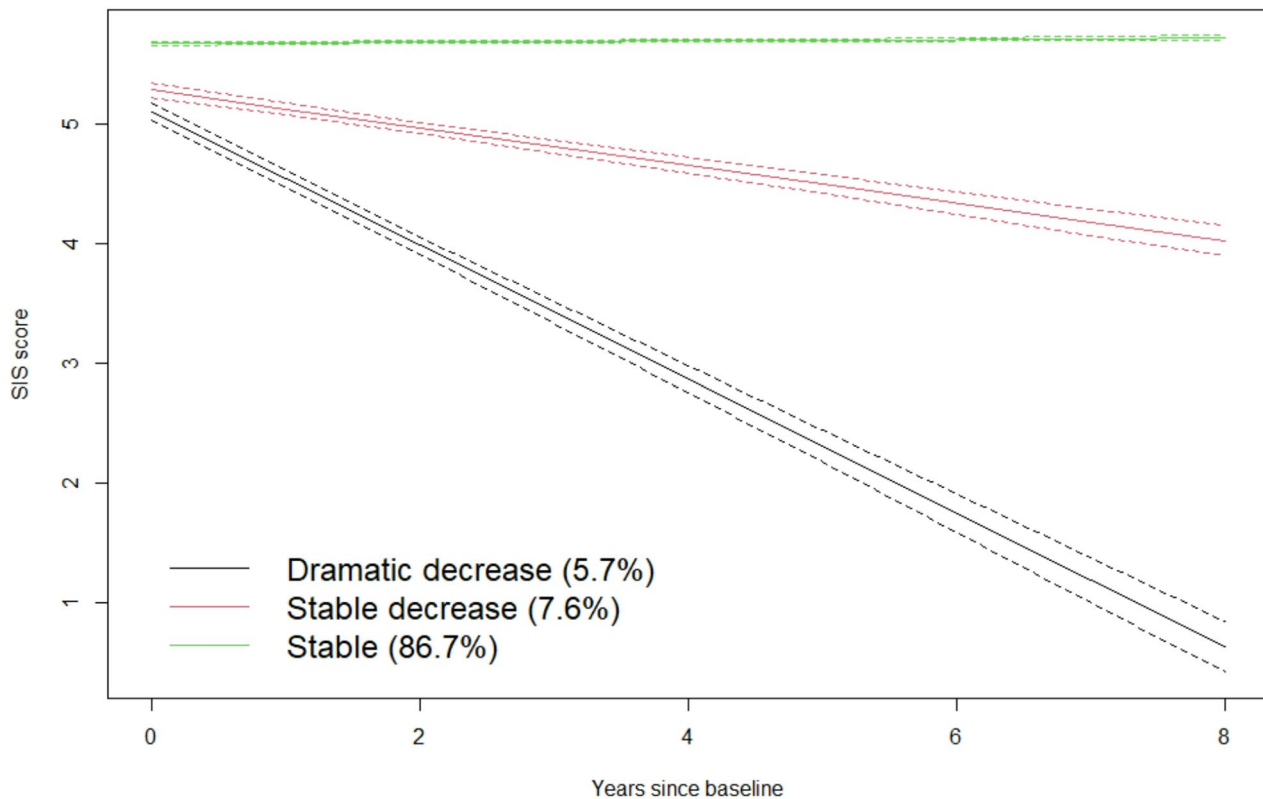
Table 5 presents the results of the sensitivity and effect modification analyses. After removing participants who had an incident AF during the follow-up, elevated NT pro-BNP was significantly associated with the “stable decrease” and “dramatic decrease” groups. Removing those who had an incident stroke during the follow-up resulted in insignificant associations between atrial cardiopathy and worse cognitive trajectory. Both elevated NT pro-BNP and atrial premature complexes were significantly associated with the “dramatic decrease” trajectory only in males.

**Table 1** Baseline characteristics of the cohort ( $N=4486$ )

Baseline characteristics	Mean (SD), or N (proportion)
Age, mean	66.1 (10.8)
Gender, female	2274 (50.7%)
Race, white	2554 (56.9%)
Exercise	
1–3 times per week	1571 (35.0%)
4 or more time per week	1319 (29.4%)
Smoke, current	695 (15.5%)
Smoke, past	1739 (38.8%)
Alcohol, current	2220 (49.5%)
Alcohol, past	865 (19.3%)
Myocardial infarction	551 (12.3%)
Coronary artery disease	781 (17.4%)
Diabetes	1093 (24.4%)
Hypertension	2802 (62.5%)
Dyslipidemia	2633 (58.7%)
Stroke	149 (3.3%)
Medication use, statin	1408 (31.4%)
Medication use, antiplatelets	240 (5.3%)
Medication use, antidepressant	532 (11.9%)
Medication use, diabetes	921 (20.5%)
Left ventricular hypertrophy	152 (3.4%)
Elevated NT pro-BNP (top quintile)	896 (20.0%)
NT pro-BNP, pg/mL	261.1 ± 899.4
Atrial premature complexes	503 (11.2%)

*N* number of participants, *SD* standard deviation, *NT pro-BNP* N-Terminal pro-Brain Natriuretic Peptide

### Cognitive Function Trajectories in Adults Aged 45 Years or Older



**Fig. 2** Cognitive trajectories in adults aged 45 years or older. The band around each trajectory represents the 95% confidence interval

**Table 2** SIS score of each trajectory at each time point

SIS score at baseline and during follow-up	Group 1 Stable	Group 2 Stable decrease	Group 3 Dramatic decrease
Baseline	5.8 (0.4)	5.5 (0.5)	5.5 (0.5)
1 year	5.5 (0.7)	4.7 (1.0)	4.1 (1.4)
2 years	5.7 (0.6)	4.9 (1.0)	3.8 (1.5)
5 years	5.7 (0.6)	4.5 (1.0)	2.3 (1.5)
8 years	5.8 (0.5)	3.9 (1.4)	1.2 (1.1)
Change in SIS score (95% CI)	0.0 (-0.02, 0.03), <i>p</i> =0.94	-1.6 (-1.9, -1.4), <i>p</i> <0.01	-4.1 (-4.7, -3.6), <i>p</i> <0.01

SIS Six-Item Screener, CI confidence interval

### Discussion

This study identified longitudinal trajectories of cognitive status in adults aged ≥ 45 years and with no prior AF. The longitudinal cohort followed three unique trajectories of cognitive function measured by SIS score over time, with 5.7% of adults showing a dramatic decrease in cognitive status. Results of this study suggested that old age and race (black) were significantly associated with a worse trajectory of cognitive function, and elevated NT pro-BNP, a marker of atrial dysfunction [32, 33], was

associated with a decreasing trajectory of cognitive function among those without known AF or incident AF during follow-up. Sensitivity analyses in which incident AF and stroke during the follow-up were removed showed that among male participants, both elevated NT pro-BNP and atrial premature complexes were significantly associated with increased odds of having a worse cognitive trajectory.

Findings of this study adds to prior evidence on associations between markers of left atrial cardiopathy and cognitive decline independent of AF [21, 43, 44]. Previous cross-sectional analyses of data from the Atherosclerosis Risk in Communities (ARIC) study [21, 45] have demonstrated that a burden of atrial premature complexes is associated with cognitive decline or dementia in community-dwelling older adults without AF, with atrial premature complexes associated with 74% higher odds of prevalent dementia [21]. Further to this, a retrospective analysis of data from the ARIC study showed that several ECG measures of lower left atrial function (i.e., left atrial reservoir strain, conduit strain, contractile strain, and emptying fraction) were significantly associated with an increased risk of incident dementia in 4,096 older adults without AF or stroke, suggesting that impaired

**Table 3** Characteristics of three cognitive trajectories

Age, mean	Group 1, Stable (N=3891)	Group 2, Stable decrease (N=341)	Group 3, Dramatic decrease (N=254)	p-value
	<b>65.0±10.6</b>	<b>72.4±9.5</b>	<b>74.7±9.7</b>	<b>&lt;0.01</b>
Gender, female	2004 (51.5)	135 (39.6)	135 (53.1)	<0.01
Race, white	2312 (59.4)	139 (40.7)	103 (40.6)	<0.01
Exercise				
1–3 times per week	1385 (35.6)	118 (34.6)	68 (26.8)	0.02
4 or more times per week	1154 (29.7)	90 (26.4)	75 (29.5)	0.45
Smoke, current	626 (16.1)	38 (11.1)	31 (12.2)	0.02
Smoke, past	1502 (38.6)	145 (42.5)	92 (36.2)	0.25
Alcohol, current	1974 (50.7)	146 (42.8)	100 (39.4)	<0.01
Alcohol, past	736 (18.9)	79 (23.2)	50 (19.7)	0.16
Myocardial infarction	453 (11.6)	55 (16.1)	43 (16.9)	<0.01
Coronary artery disease	647 (16.6)	80 (23.5)	54 (21.3)	<0.01
Diabetes	925 (23.8)	95 (27.9)	73 (28.7)	0.06
Hypertension	2385 (61.3)	237 (69.5)	180 (70.9)	<0.01
Dyslipidemia	2295 (59.0)	185 (54.3)	153 (60.2)	0.21
Stroke	12 (0.003)	114 (33.4)	23 (9.1)	<0.01
Medication use, statin	1212 (31.1)	110 (32.3)	86 (33.9)	0.62
Medication use, antiplatelets	193 (4.9)	28 (8.2)	19 (7.5)	0.01
Medication use, antidepression	459 (11.8)	36 (10.6)	37 (14.6)	0.31
Medication use, diabetes	781 (20.0)	85 (24.9)	55 (21.7)	0.09
Left ventricular hypertrophy	125 (3.2)	16 (4.7)	11 (4.3)	0.24
NT pro-BNP quintile, 1st	834 (21.4)	45 (13.2)	20 (7.9)	<0.01
NT pro-BNP quintile, 2nd	797 (20.5)	62 (18.2)	39 (15.4)	0.10
NT pro-BNP quintile, 3rd	784 (20.1)	70 (20.5)	45 (17.7)	0.63
NT pro-BNP quintile, 4th	754 (19.4)	76 (22.3)	64 (25.2)	0.04
NT pro-BNP quintile, 5th	722 (18.6)	88 (25.8)	86 (33.9)	<0.01
NT pro-BNP, pg/mL	164.7±678.0	183.5±415.9	264.8±408.7	<0.01
Atrial premature complexes	403 (10.4)	51 (15.0)	49 (19.3)	<0.01

NT pro-BNP quintile, 1st : ≤32.1 pg/mL  
 NT pro-BNP quintile, 2nd : >32.1 pg/mL and ≤60.1 pg/mL  
 NT pro-BNP quintile, 3rd : >60.1 pg/mL and ≤109.8 pg/mL  
 NT pro-BNP quintile, 4th : >109.8 pg/mL and ≤235.2 pg/mL  
 NT pro-BNP top quintile, 5th : >235.2 pg/mL

N number of participants, NT pro-BNP N-Terminal pro-Brain Natriuretic Peptide

**Table 4** Adjusted odds ratios and 95% confidence intervals of belonging to each group trajectory relative to the stable group

Baseline characteristics	Class 2: Stable decrease	Class 3: Dramatic decrease
Age	1.08 (1.06–1.10)	1.08 (1.07–1.11)
Race – white vs. black	0.37 (0.27–0.52)	0.36 (0.25–0.52)
Males	1.80 (1.30–2.49)	0.87 (0.59–1.28)
Exercise		
1–3 times/week	1.22 (0.85–1.74)	1.08 (0.71–1.65)
4 + times/week	1.05 (0.71–1.54)	1.34 (0.88–2.07)
Smoke, current	0.71 (0.42–1.20)	0.99 (0.56–1.77)
Smoke, past	0.84 (0.60–1.19)	0.88 (0.59–1.32)
Alcohol, current	0.86 (0.59–1.23)	0.87 (0.58–1.30)
Alcohol, past	1.13 (0.74–1.73)	0.70 (0.41–1.19)
Myocardial infarction	0.75 (0.39–1.45)	1.73 (0.68–4.42)
Coronary artery disease	1.65 (0.90–3.00)	0.74 (0.30–1.81)
Diabetes	0.91 (0.48–1.71)	1.46 (0.75–2.83)
Hypertension	0.93 (0.67–1.29)	0.97 (0.65–1.44)
Dyslipidemia	0.76 (0.54–1.07)	1.20 (0.81–1.78)
Stroke	1.05 (0.38–2.87)	1.54 (0.50–4.79)
Baseline use of medications		
Statin	0.82 (0.56–1.19)	0.80 (0.52–1.22)
Diabetes	1.26 (0.65–2.44)	0.73 (0.36–1.49)
Antiplatelets	1.39 (0.79–2.47)	0.95 (0.46–1.97)
Antidepression	1.41 (0.88–2.26)	2.00 (1.22–3.29)
Left ventricular hypertrophy	1.36 (0.76–2.46)	1.02 (0.52–2.03)
Elevated NT pro BNP (top quintile)	1.03 (0.58–1.83)	2.14 (1.02–4.49)
NT pro-BNP, pg/mL	1.00 (0.99–1.14)	1.00 (0.19–1.11)
Atrial premature complexes	1.01 (0.66–1.55)	1.18 (0.73–1.89)

NT pro-BNP N-Terminal pro-Brain Natriuretic Peptide

left atrial function is an important risk factor associated with cognitive decline [22]. NT pro-BNP is an indicator of left atrial dysfunction and has been demonstrated to significantly increase the risk of atrial fibrillation and the odds of dementia independent of vascular risk factors in case-control studies [32, 33, 46, 47]. The present study is unique in several ways. In this study, the cognitive function was measured using the SIS score annually. With a long follow-up duration, this study allows for examining how markers of atrial cardiopathy are associated with cognitive function over several years. Moreover, this study identified three trajectories of cognitive function in aging adults without documented AF and showed that atrial cardiopathy markers were associated with a dramatic decline in cognitive status, and the associations remained significant in males after controlling for AF and stroke during the follow-up suggesting that atrial cardiopathy, structural abnormalities and electrical left atrial remodeling preceding clinically AF, may be important determinants of a worse cognitive trajectory in selected populations.

**Table 5** Adjusted odds ratio and 95% confidence intervals from sensitivity and effect modification analyses

Participant without incident AF	Class 2: Stable decrease	Class 3: Dramatic decrease
Elevated NT pro-BNP (top quintile)	2.50 (1.22–5.11)	11.2 (1.12–112.10)
Atrial premature complexes	1.49 (0.85–2.61)	1.15 (0.31–4.28)
Participant without incident stroke		
Elevated NT pro-BNP (top quintile)	0.72 (0.02–28.45)	0.23 (0.10–8.77)
Atrial premature complexes	1.20 (0.10–14.58.10.58)	0.87 (0.07–10.06)
Females		
Elevated NT pro-BNP (top quintile)	0.84 (0.62–1.13)	0.95 (0.68–1.32)
Atrial premature complexes	1.05 (0.83–1.35)	1.19 (0.93–1.52)
Males		
Elevated NT pro-BNP (top quintile)	1.43 (0.99–2.04)	3.88 (1.95–7.72)
Atrial premature complexes	1.02 (0.80–1.31)	1.74 (1.23–2.48)

All models were adjusted for covariates age, race, sex, exercise, smoking, alcohol, myocardial infarction, coronary artery disease, diabetes, hypertension, dyslipidemia, stroke, medications, and left ventricular hypertrophy

AF atrial fibrillation, NT pro-BNP N-Terminal pro-Brain Natriuretic Peptide

The observed associations between atrial cardiopathy markers and a worse cognitive trajectory in adults without AF are consistent with existing evidence for a new mechanistic model of atrial cardiopathy, AF and related cognitive outcomes [48, 49]. There has been strong evidence from prospective and retrospective studies that the major pathophysiologic pathway leading from left atrial cardiopathy to the onset of cognitive decline and dementia may not be fully through elevations in thromboembolic risk via the development of clinical AF or ischemic stroke. Instead, atrial cardiopathy, a state of structural abnormality and left atrial remodelling, may be an important impetus for thrombi and subsequent embolism without the development of AF [50]. Under this new mechanistic model, AF is no longer a necessary step in the pathogenesis of ischemic stroke or cognitive impairment [48, 51], and potential mechanisms linking left atrial cardiopathy and a worse cognitive trajectory may be microembolism, hypoperfusion, inflammation, breakdown of the blood-brain barrier, and subsequent clinical stroke, similar to mechanisms linking AF and related cognitive outcomes [49]. Although several cardiac comorbidities were adjusted for at baseline, including myocardial infarction, coronary artery disease, diabetes, hypertension, dyslipidemia, stroke, and left ventricular hypertrophy, given that additional comorbidities during follow-up may moderate the observed association between these markers and cognitive decline and residual

confounding may be present. Future studies could control for follow-up cardiovascular comorbidities to mitigate potential residual confounding for the observed association.

The results of this study have implications for the identification of target candidates for preventative interventions to promote cognitive function in ageing population. Although cognitive change is a normal process of ageing, some older adults are more likely to experience more cognitive decline. Analyses of data from the English Longitudinal Study of Ageing showed that gender and age predicted faster decline in all cognitive function domains, including memory, executive function, processing speed and global cognitive function [52]. Using data from the ASPREE (Aspirin in Reducing Events in the Elderly), another study identified four trajectories of global cognitive function measured using the Mini-Mental State Examination, and the study also found that participants in the lower-functioning trajectory were more likely to be older, male, and with a lower education level [53]. The present study demonstrated that in addition to demographic factors, markers of left atrial cardiopathy were also associated with a worse cognitive decline, suggesting that ageing adults with evidence of left atrial cardiopathy (i.e., atrial premature complexes and elevated NT pro-BNP) may be a potential therapeutic target for interventions, such as screening services and early treatment of anticoagulation. Notably, the ongoing ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke) trial has been testing the efficacy of anticoagulation treatment for stroke prevention in participants with evidence of atrial cardiopathy who did not have AF [54]. Further studies may examine the efficacy of early preventative services among ageing adults with left atrial cardiopathy.

The results of stratified analyses demonstrated that sex modified the effect of atrial cardiopathy on cognitive function trajectories. For instance, elevated NT pro-BNP and atrial premature complexes were significantly associated with a worse cognitive decline only in males. The findings suggest that different markers may have different relevance for different populations. Further studies may need to explore how other markers of left atrial cardiopathy (i.e., left atrial enlargement, P-wave terminal force in lead V1) affect cognitive trajectories across different populations.

This study has several limitations. First, the study only included residents who self-identified as non-Hispanic black or white in the stroke belt region, defined as the 8 southern states (North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas) [30], and the stroke mortality rate in this stroke belt region was substantially greater than the national average in the United States [55]. Thus, the

study participants may not be representative of the general population, leading to selection bias. Second, trajectories of cognitive function were modeled based on baseline characteristics. Several important time-varying covariates, such as medication status and comorbidities, were not available for analysis. In addition, both markers were only measured at baseline in REGARDS. Lack of repeated measurements cannot provide insights into whether changes in these markers over time are associated with cognitive trajectory. Third, due to the limited data, this study only considered two markers of atrial cardiopathy (atrial premature complexes and NT pro-BNP). Other markers of atrial cardiopathy, including left atrial volume index, P-wave terminal force at V1, and excessive atrial ectopy, may also be important determinants of cognitive function trajectories [56–58]. Moreover, atrial premature complexes were measured as a dichotomous (absence versus presence), and thus we were unable to test the continuous scale of the markers and cognitive trajectories over time. Fourth, the cohort was a nested sample from REGARDS, and, compared to those excluded from the analysis due to lack of NT pro-BNP measures, the participants included in the analysis were older and more likely to be male and Black. These participants were more likely to have cardiovascular comorbidities, including myocardial infarction, coronary artery disease, diabetes, hypertension, and dyslipidemia, and were less likely to have a history of stroke (Supplemental Table S3). Fifth, this study focused on demographic, behavioural, and cardiac history covariates. Although we have conducted sensitivity analysis by adjusting for participants' education level and income to confirm the robustness of the observed association, future studies may consider including more socioeconomic status (region, marital status, employment status) to explore how these factors modify the effect of these markers on cognitive trajectories. Finally, due to the limited data availability, this study only used the SIS score, a brief cognitive function test, to assess cognitive impairment. Although a brief cognitive test can help determine the degree of cognitive status, a diagnosis of cognitive impairment should also be based on other clinical tests such as neurological exams and brain imaging.

In conclusion, atrial premature complexes and elevated NT pro-BNP, both markers of left atrial cardiopathy, are found to be significantly associated with a worse cognitive trajectory in this observed cohort of adults aged  $\geq 45$  years without documented atrial fibrillation. These findings may have implications for the early identification of phenotypes at high-risk of cognitive decline and the development of prevention strategies to promote cognitive health in ageing populations. However, future studies are required using more comprehensive data, including cognitive assessments, to confirm these

association and methods explore causal mechanisms of these associations.

#### Abbreviations

AF	Atrial fibrillation
APCs	Atrial premature complexes
NT-proBNP	N-Terminal pro-Brain Natriuretic Peptide
SIS	Six-Item Screener
REGARDS	REasons for Geographical and Racial Differences in Stroke
HR	Hazard ratio
CI	Confidence interval

#### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12883-026-04856-y>.

Supplementary Material 1.

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#### Authors' contributions

Z.L., D.M., E.S., D.G., H.K., D.B., D.M., and J.D. conceptualized the research design. Z.L., J.B., V.H., F.U., and J.E. developed a data creation plan and an analytic plan. Z.L. conducted the analysis. Z.L. drafted the manuscript. All authors reviewed the manuscript.

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#### Data availability

In order to abide by its obligations with NIH/NINDS and the Institutional Review Board of the University of Alabama at Birmingham, REGARDS facilitates data sharing through formal data use agreements. Any investigator is welcome to access the REGARDS data through this process. Requests for data access may be sent to [regardsadmin@uab.edu](mailto:regardsadmin@uab.edu).

#### Declarations

##### Ethics approval and consent to participate

All participants provided written informed consent, and the REGARDS review boards approved the study. The study was in compliance with the Helsinki Declaration.

##### Consent for publication

All necessary parties agree to the publication of this study.

##### Competing interests

The authors declare no competing interests.

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#### References

1. World Health Organization, Dementia. <https://www.who.int/news-room/fact-sheets/detail/dementia>.

2. Fitzpatrick AL, Kuller ALH, Ives DG et al. Incidence and prevalence of dementia in the cardiovascular health study. *J Am Geriatr Soc*. Published online 2004;195–204.
3. Agüero-Torres H, Fratiglioni L, Guo Z, Viitanen M, Winblad B. Mortality from dementia in advanced age: a 5-year follow-up study of incident dementia cases. *J Clin Epidemiol*. 1999;52(8):737–43. [https://doi.org/10.1016/S0895-4356\(99\)00067-0](https://doi.org/10.1016/S0895-4356(99)00067-0).
4. Villarejo A, Benito-León J, Trincado R, et al. Dementia-associated mortality at thirteen years in the NEDICES cohort study. *J Alzheimers Dis*. 2011;26(3):543–51. <https://doi.org/10.3233/JAD-2011-110443>.
5. Geldmacher DS, Kirson NY, Birnbaum HG, et al. Implications of early treatment among Medicaid patients with Alzheimer's disease. *Alzheimers Dement*. 2014;10(2):214–24. <https://doi.org/10.1016/J.JALZ.2013.01.015>.
6. Bailey MJ, Soliman EZ, McClure LA, et al. Relation of atrial fibrillation to cognitive decline (from the REasons for Geographic and Racial Differences in Stroke [REGARDS] Study). *Am J Cardiol*. 2021;148:60–8. <https://doi.org/10.1016/j.amjcard.2021.02.036>.
7. Thacker EL, McKnight B, Psaty BM, et al. Atrial fibrillation and cognitive decline. *Neurology*. 2013;81(2):119–25. <https://doi.org/10.1212/WNL.0B013E31829A33D1>.
8. Chen LY, Norby FL, Gottesman RF, et al. Association of atrial fibrillation with cognitive decline and dementia over 20 years: the ARIC-NCS (atherosclerosis risk in communities neurocognitive study). *J Am Heart Assoc*. 2018;7:e007301. <https://doi.org/10.1161/JAHA.117.007301>.
9. Zhang MJ, Norby FL, Lutsey PL, et al. Association of left atrial enlargement and atrial fibrillation with cognitive function and decline: the ARIC-NCS. *J Am Heart Assoc*. 2019;8:e013197. <https://doi.org/10.1161/JAHA.119.013197>.
10. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146(12):857–67. <https://doi.org/10.7326/0003-4819-146-12-200706190-00007>.
11. Reiffel JA, Verma A, Kowey PR, et al. Incidence of Previously Undiagnosed Atrial Fibrillation Using Insertable Cardiac Monitors in a High-Risk Population: The REVEAL AF Study. *JAMA Cardiol*. 2017;2(10):1120. <https://doi.org/10.1001/JAMACARDIO.2017.3180>.
12. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med*. 2014;370(26):2467–77. [https://doi.org/10.1056/NEJM0A1311376/SUPPL\\_FILE/NEJM0A1311376\\_DISCLOSURES.PDF](https://doi.org/10.1056/NEJM0A1311376/SUPPL_FILE/NEJM0A1311376_DISCLOSURES.PDF).
13. Goldberger JJ, Arora R, Green D, et al. Evaluating the atrial myopathy underlying atrial fibrillation. *Circulation*. 2015;132(4):278–91. <https://doi.org/10.1161/CIRCULATIONAHA.115.016795>.
14. Kamel H, Okin PM, Longstreth WT, Elkind MSV, Soliman EZ. Atrial cardiopathy: a broadened concept of left atrial thromboembolism beyond atrial fibrillation HHS public access. *Futur Cardiol*. 2015;11(3):323–31. <https://doi.org/10.2217/fca.15.22>.
15. Rangel MO, O'Neal WT, Soliman EZ. Usefulness of the electrocardiographic p-wave axis as a predictor of atrial fibrillation. *Am J Cardiol*. 2016;117(1):100–4. <https://doi.org/10.1016/J.AMJCARD.2015.10.013>.
16. Gupta DK, Shah AM, Giugliano RP, et al. Left atrial structure and function in atrial fibrillation: ENGAGE AF-TIMI 48. *Eur Heart J*. 2014;35:1457–65. <https://doi.org/10.1093/eurheartj/ehu500>.
17. Acharya T, Tringali S, Bhullar M, et al. Frequent atrial premature complexes and their association with risk of atrial fibrillation. *Am J Cardiol*. 2015;116(12):1852–7. <https://doi.org/10.1016/J.AMJCARD.2015.09.025>.
18. Binici Z, Intzilakis T, Nielsen OW, Køber L, Sajadieh A. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. *Circulation*. 2010;121(17):1904–11. <https://doi.org/10.1161/CIRCULATIONAHA.109.874982>.
19. Kamel H, Elkind MSV, Bhavne PD, et al. Paroxysmal supraventricular tachycardia and the risk of ischemic stroke. *Stroke*. 2013;44:1550–4. <https://doi.org/10.1161/STROKEAHA.113.001118>.
20. Edwards JD, Healey JS, Fang J, Yip K, Gladstone DJ. Atrial cardiopathy in the absence of atrial fibrillation increases risk of ischemic stroke, incident atrial fibrillation, and mortality and improves stroke risk prediction. *J Am Heart Assoc*. 2020;9(11):13227. <https://doi.org/10.1161/JAHA.119.013227>.
21. Rooney MR, Norby FL, Maheshwari A, et al. Frequent Premature Atrial Contractions Are Associated With Poorer Cognitive Function in the Atherosclerosis Risk in Communities (ARIC) Study. *Mayo Clin Proc*. 2021;96(5):1147–56. <https://doi.org/10.1016/J.MAYOCP.2021.01.025>.
22. Wang W, Zhang MJ, Inciardi RM, et al. Association of Echocardiographic Measures of Left Atrial Function and Size With Incident Dementia. *JAMA*. 2022;327(12):1138–48. <https://doi.org/10.1001/JAMA.2022.2518>.
23. Johansen MC, Wang W, Zhang M, et al. Risk of Dementia Associated With Atrial Cardiopathy: The ARIC Study. *J Am Heart Assoc*. 2022. <https://doi.org/10.1161/JAHA.121.025646>.
24. Daniels LB, Laughlin GA, Clopton P, Maisel AS, Barrett-Connor E. Minimally elevated cardiac troponin T and elevated N-terminal pro-B-type natriuretic peptide predict mortality in older adults: results from the Rancho Bernardo Study. *J Am Coll Cardiol*. 2008;52(6):450–9. <https://doi.org/10.1016/J.JACC.2008.04.033>.
25. Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA*. 2005;293(13):1609–16. <https://doi.org/10.1001/JAMA.293.13.1609>.
26. Dadu RT, Fornage M, Virani SS, et al. Cardiovascular biomarkers and subclinical brain disease in the atherosclerosis risk in communities study. *Stroke*. 2013;44(7):1803–8. <https://doi.org/10.1161/STROKEAHA.113.001128>.
27. Berntsson J, Zia E, Borné Y, Melander O, Hedblad B, Engström G. Plasma natriuretic peptides and incidence of subtypes of ischemic stroke. *Cerebrovasc Dis*. 2014;37(6):444–50. <https://doi.org/10.1159/000363279>.
28. Gallo G, Bianchi F, Cotugno M, Volpe M, Rubattu S. Natriuretic Peptides, Cognitive Impairment and Dementia: An Intriguing Pathogenic Link with Implications in Hypertension. *J Clin Med*. 2020;9(7):1–11. <https://doi.org/10.3390/JCM9072265>.
29. Howard G. The Reasons for Geographic and Racial Differences in Stroke Study: Objectives and Design. *Neuroepidemiology*. 2005;25:135–43. <https://doi.org/10.1159/000086678>.
30. Howard VJ, Kleindorfer DO, Judd SE, et al. Disparities in stroke incidence contributing to disparities in stroke mortality. *Ann Neurol*. 2011;69(4):619–27. <https://doi.org/10.1002/ANA.22385>.
31. Prineas RJ, Crow RS, Zhang Z-M. The Minnesota Code Manual of Electrocardiographic Findings. Minnesota Code Man Electrocardiogr Find. Published online 2010. <https://doi.org/10.1007/978-1-84882-778-3>.
32. Di Castelnuovo A, Veronesi G, Costanzo S, et al. NT-proBNP (N-Terminal Pro-B-Type Natriuretic Peptide) and the risk of stroke: results from the biomarcare consortium. *Stroke*. 2019;50(3):610–7. <https://doi.org/10.1161/STROKEAHA.118.023218>.
33. Werhahn SM, Becker C, Mende M, et al. NT-proBNP as a marker for atrial fibrillation and heart failure in four observational outpatient trials. *ESC Heart Fail*. 2022;9(1):100–9. <https://doi.org/10.1002/EHF2.13703>.
34. Bajaj NS, Gutierrez OM, Arora G, et al. Racial differences in plasma levels of N-terminal pro-B-type natriuretic peptide and outcomes: the reasons for geographic and racial differences in stroke (REGARDS) study. *JAMA Cardiol*. 2018;3(1):11. <https://doi.org/10.1001/JAMACARDIO.2017.4207>.
35. Yaghi S, Kamel H, Elkind MSV. Atrial cardiopathy: a mechanism of cryptogenic stroke. *Expert Rev Cardiovasc Ther*. 2017;15(8):591. <https://doi.org/10.1080/14779072.2017.1355238>.
36. Callahan CM, Unverzagt FW, Hui SL, Perkins AJHH. Six-item screener to identify cognitive impairment among potential subjects for clinical research. *Med Care*. 2002;40:771–81.
37. Bailey MJ, Soliman EZ, McClure LA et al. Relation of Atrial Fibrillation to Cognitive Decline (from the REasons for Geographic and Racial Differences in Stroke [REGARDS] Study). *Am J Cardiol* Published online 2022:60–8. <https://doi.org/10.1016/j.amjcard.2021.02.036.Relation>.
38. Bissig D, Decarli CS. Global & community health: brief in-hospital cognitive screening anticipates complex admissions and may detect dementia. *Neurology*. 2019;92(13):631. <https://doi.org/10.1212/WNL.0000000000001716>.
39. Chen M, Guo Q, Cao X, Hong Z, Liu X. A preliminary study of the Six-Item Screener in detecting cognitive impairment. *Neurosci Bull*. 2010;26(4):317–21. <https://doi.org/10.1007/s12264-010-0106-1>.
40. O'Neal WT, Kamel H, Judd SE, et al. Usefulness of atrial premature complexes on routine electrocardiogram to determine the risk of atrial fibrillation (from the REGARDS study). *Am J Cardiol*. 2017;120(5):782–5. <https://doi.org/10.1016/j.amjcard.2017.06.007>.
41. Halanych JH, Shuaib F, Parmar G, et al. Agreement on cause of death between proxies, death certificates, and clinician adjudicators in the reasons for geographic and racial differences in stroke (REGARDS) study. *Am J Epidemiol*. 2011;173(11):1319–26. <https://doi.org/10.1093/AJE/KWR033>.
42. Jung T, Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. *Soc Personal Psychol Compass*. 2008;2(1):302–17. <https://doi.org/10.1111/J.1751-9004.2007.00054.X>.
43. Gyanwali B, Liu B, Lai MK, Richards AM, Chen C, Hilal S. Blood-based cardiac biomarkers and the risk of cognitive decline, vascular events and mortality.

- Alzheimers Dement. 2020;16(S4):e041689. <https://doi.org/10.1002/ALZ.041689>.
44. Li Z, Marion D, Blair J, et al. Association between markers of atrial cardiopathy and cognitive impairment risk among adults with no suggestive history of atrial fibrillation. *CJC Open*. 2025. <https://doi.org/10.1016/j.cjco.2025.07.010>.
  45. Norby FL, Alonso A, Rooney MR, et al. Association of ventricular arrhythmias with dementia. *Neurology*. 2021;96(6):e926–36. <https://doi.org/10.1212/WNL.00000000000011122>.
  46. Sieweke JT, Pfeffer TJ, Biber S, et al. miR-21 and NT-proBNP correlate with echocardiographic parameters of atrial dysfunction and predict atrial fibrillation. *J Clin Med*. 2020;9(4):1118. <https://doi.org/10.3390/JCM9041118>.
  47. Hilal S, Ling Chai Y, Kamran Ikram M, et al. Markers of cardiac dysfunction in cognitive impairment and dementia. *Medicine (Baltimore)*. 2015;94(1):e297. <https://doi.org/10.1097/MD.0000000000000297>.
  48. Nattel S, Harada M. Atrial Remodeling and Atrial Fibrillation Recent Advances and Translational Perspectives. *J Am Coll Cardiol*. 2014. <https://doi.org/10.1016/j.jacc.2014.02.555>.
  49. Diener HC, Hart RG, Koudstaal PJ, Lane DA, Lip GYH. Atrial fibrillation and cognitive function: JACC review topic of the week. *J Am Coll Cardiol*. 2019;73(5):612–9. <https://doi.org/10.1016/J.JACC.2018.10.077>.
  50. Johansen MC, Mosley TH, Knopman DS, et al. Associations between atrial cardiopathy and cerebral amyloid: The aric-pet study. *J Am Heart Assoc*. 2020;9(24):18399. <https://doi.org/10.1161/JAHA.120.018399/FORMAT/EPUB>.
  51. Brambatti M, Connolly SJ, Gold MR, et al. Temporal relationship between sub-clinical atrial fibrillation and embolic events. *Circulation*. 2014;129(21):2094–9. <https://doi.org/10.1161/CIRCULATIONAHA.113.007825>.
  52. Zaninotto P, Batty GD, Allerhand M, Deary IJ. Cognitive function trajectories and their determinants in older people: 8 years of follow-up in the English Longitudinal Study of Ageing. *J Epidemiol Community Heal*. 2018;72(8):685–94. <https://doi.org/10.1136/JECH-2017-210116>.
  53. Wu Z, Woods RL, Wolfe R, et al. Trajectories of cognitive function in community-dwelling older adults: a longitudinal study of population heterogeneity. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2021;13(1):e12180. <https://doi.org/10.1002/dad2.12180>.
  54. Kamel H, Longstreth WT, Tirschwell DL, et al. The Atrial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke (ARCADIA) randomized trial: Rationale and Methods. *Int J Stroke*. 2019;14(2):207. <https://doi.org/10.1177/1747493018799981>.
  55. Howard G, Anderson R, Johnson NJ, Sorlie P, Russell G, Howard VJ. Evaluation of social status as a contributing factor to the stroke belt region of the United States. *Stroke*. 1997;28(5):936–40. <https://doi.org/10.1161/01.STR.28.5.936>.
  56. Gladstone DJ, Dorian P, Spring M, et al. Atrial Premature Beats Predict Atrial Fibrillation in Cryptogenic Stroke: Results from the EMBRACE Trial. *Stroke*. 2015;46(4):936–41. <https://doi.org/10.1161/STROKEAHA.115.008714>.
  57. He J, Tse G, Korantzopoulos P, et al. P-wave indices and risk of ischemic stroke: a systematic review and meta-analysis. *Stroke*. 2017;48(8):2066–72. <https://doi.org/10.1161/STROKEAHA.117.017293>.
  58. Vieira MJ, Teixeira R, Gonçalves L, Gersh BJ. Left atrial mechanics: echocardiographic assessment and clinical implications. *J Am Soc Echocardiogr*. 2014;27(5):463–78. <https://doi.org/10.1016/J.ECHO.2014.01.021>.

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