HHS Public Access

Author manuscript

Mayo Clin Proc. Author manuscript; available in PMC 2022 May 01.

Published in final edited form as:

Mayo Clin Proc. 2021 May ; 96(5): 1147–1156. doi:10.1016/j.mayocp.2021.01.025.

Frequent Premature Atrial Contractions are Associated With Poorer Cognitive Function in the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Objective: To evaluate the association of premature atrial contraction (PAC) frequency with cognitive test scores and prevalence of dementia or mild cognitive impairment (MCI).

Materials and Methods: We conducted a cross-sectional analysis using Atherosclerosis Risk in Communities visit 6 (January 1, 2016, through December 31, 2017) data. We included 2,163 participants without atrial fibrillation (AF) [age mean±SD 79±4 years, 59% female, 28% black] who underwent cognitive testing and wore a leadless, ambulatory ECG-monitor for 14-days. We categorized PAC frequency based on the percent of beats: <1% (minimal), 1–<5% (occasional), ≥5% (frequent). We derived cognitive domain-specific factor-scores (memory, executive function, language, global z-score). Dementia and MCI were adjudicated.

Results: During a mean analyzable time of 12.6±2.6 days, 16% had occasional PACs and 5% had frequent PACs. Individuals with frequent PACs (vs minimal) had lower executive function factor-scores by 0.30 (95% CI: −0.46,−0.14) and lower global factor-scores by 0.20 (−0.33,−0.07)

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after multivariable adjustment. Individuals with frequent PACs (vs minimal) had higher odds of prevalent dementia or MCI after multivariable adjustment [OR=1.74 (1.09, 2.79)]. These associations were unchanged with additional adjustment for stroke.

Conclusions: In community-dwelling older adults without AF, frequent PACs were cross-sectionally associated with lower executive and global cognitive function and greater prevalence of dementia or MCI, independently of stroke. Our findings lend support to the notion that atrial cardiomyopathy may be a driver of AF-related outcomes. Further research to confirm these associations prospectively and to elucidate underlying mechanisms is warranted.

Keywords

premature atrial contractions; cognitive function; dementia; aging; ECG

INTRODUCTION

Premature atrial contractions (PACs) are commonly encountered in clinical practice: In one study, 99% of Swiss participants aged ≥50 years had ≥1 PAC during 24-hour Holter monitoring.[1] Although PACs are widely regarded to be benign, recent observational studies have shown that the presence or a higher frequency of PACs is independently associated with increased risk of atrial fibrillation (AF),[2–9] stroke,[6,10,11] and all-cause mortality.[2] While it is well established that AF is associated with greater cognitive decline and risk of dementia,[12–17] independently of clinical stroke,[12,16,17] it is not known whether higher PAC frequency is associated with poorer cognitive function.

Electrocardiographic (ECG) monitoring technology has evolved in recent years, thereby permitting a longer continuous monitoring period. ECG patch monitors can now record heart rhythm continuously over 2 weeks, thus enabling a more precise measurement of PAC frequency than the traditional 24 or 48-hour Holter monitor.[18–20] We leveraged this technology in a community-based sample of older adults—the Atherosclerosis Risk in Communities (ARIC) study—to test the hypothesis that frequent PACs as determined by 2 weeks of ECG monitoring are associated with lower cognitive test scores and a higher prevalence of dementia or mild cognitive impairment (MCI).

METHODS

The ARIC study[21] is a community-based cohort study that began in 1987–89 when the 15,792 participants were middle-aged between 45 and 64 years. There are four field centers (Washington County, MD; Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN). Seven clinic visits have been completed. A total of 4,003 attended visit 6 in 2016–2017 (approximately 30 years after the initial visit). Participants have been contacted annually and since 2012 have been contacted semi-annually to identify hospitalizations. Ongoing surveillance with hospitals has also occurred.

Participants at all four field centers were invited to wear the Zio® XT Patch (iRhythm Technologies Inc.; San Francisco, CA) for 14 days at visit 6 (2016–2017). Exclusion criteria included history of cardiac electronic device implantation or skin allergic reaction to

adhesive tape, resulting in 3680 eligible participants. Of the 2,650 participants who agreed to participate and received a device, 17 devices were lost and 17 devices were returned with no data, resulting in a sample of 2,616 participants. The sample of 2,616 ECG patch monitoring participants tended to have a lower prevalence of cardiovascular diseases and dementia than the other 1387 participants who attended visit 6 (Supplemental Table 1). For the present analyses, we excluded participants with <48 hours of analyzable ECG patch monitoring data (N=68), who were missing cognitive function assessments (N=26), and those with either clinical or subclinical AF (N=359). Clinical AF was defined by AF on 12-lead ECG at prior examinations or hospital discharge codes before visit 6. Subclinical AF was based on any AF (>0%, intermittent or continuous) identified during the 14 days of ECG patch monitoring at visit 6 among individuals without clinical AF. This resulted in an analytic sample of 2,163 participants.

Premature Atrial Contractions

PAC frequency was calculated as the percent of heart beats recorded that were PACs. As there are no established clinical cutpoints for PAC, we categorized PAC frequency as <1% (referent; minimal), 1–<5% (occasional) and ≥5% (frequent), which are categories used by iRhythm, the manufacturer of the Zio® XT Patch. We also modeled PACs continuously per 1% higher PAC frequency.

Cognitive Function

Participants underwent a battery of cognitive tests (shown in parentheses) at visit 6 which were grouped into 3 cognitive domains:[22] **memory** [Logical Memory (immediate and delayed recall) and incidental learning from the Wechsler Memory Scale-III, and Delayed Word Recall Test], **executive functioning / processing speed** [Digit Span Backward and Digit Symbol Substitution from the Wechsler Adult Intelligence Scale-Revised (WAIS-R), and Trail Making Test (parts A and B)], **language** [Boston Naming Test, animal and letter fluency]. We used factor scores previously derived for each of the 3 domains and general cognitive performance, which leverage data from multiple cognitive tests to provide more robust measures of domain--specific function than those provided by individual tests.[23] Within the domain factor scores, individual tests were allowed to contribute information differentially by race, education, and age.[23] The interpretation of our factor scores is similar to z scores because they are scaled to have a mean of 0 and a variance of 1.

Dementia and Mild Cognitive Impairment

Dementia and mild cognitive impairment (MCI) were adjudicated at visit 6 by an expert panel of physicians and neuropsychologists based on criteria from the National Institute on Aging-Alzheimer's Association [24] and DSM-5[25] workgroups. Details on the diagnosis of dementia and MCI have been described previously.[26]

Covariates

At visit 6, participants were interviewed, underwent an examination, and provided blood samples. Participants reported their sociodemographic characteristics (birthdate, sex, race, educational attainment from visit 1) and health behaviors (smoking status). Physical activity

(sports index) was based on the validated Baecke questionnaire with scores ranging from 1 (low) to 5 (high).[27] Participants were asked to bring all medication bottles to the clinic visits; medications were transcribed and coded. Participants also underwent anthropomorphic and blood pressure measurements. Height and weight were used to calculate body mass index (BMI, kg/m^2). After sitting at rest for 5 minutes, systolic and diastolic blood pressure was measured three times. An average of the second and third measurement was used for this analysis. Diabetes was defined by fasting blood glucose ≥126 mg/dL, non-fasting blood glucose ≥200 mg/dL, use of diabetic medications or self-report physician diagnosis. The APOE ε4 genotype was assessed using the TaqMan assay (Applied Biosystems, Foster City, CA). Estimated glomerular filtration rate (eGFR) was calculated based on creatinine and cystatin-C using the CKD-EPI equation.[28] N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured in EDTA plasma using an electrochemiluminescent immunoassay (Roche Diagnostics) on a Roche Cobas e411 analyzer (Roche Diagnostics, Indianapolis, IN). Left atrial volume index (in mL/m^2), as described previously,[29] was derived based on left atrial volume divided by body surface area using echocardiography (performed at visit 5, 2011–2013). Peripheral arterial disease was defined based on hospital discharge codes prior to visit 6 or an ankle-branchial index ≤0.90 (performed at visit 5, 2011–2013). Coronary heart disease,[30] heart failure,[31] and ischemic stroke[32] were adjudicated based on previously published criteria. Briefly, possible hospitalized coronary heart disease and stroke events were abstracted by trained staff onto standardized forms and classified by physicians using computer-assisted classification algorithms. Heart failure was defined by a prior hospital discharge code in any position or classified based on outpatient heart failure using previously published criteria.[33] Brain MRI scans were performed at visit 5 in a selected subset of individuals using 3T brain MRI as previously described.[34] Microbleeds were measured using T2*GRE sequences, and cerebral infarcts and white matter hyperintensity volume using T2 FLAIR sequences.

Statistical Analysis

We report participant characteristics stratified by frequency of PACs. Multiple linear regression was used to assess the association between PACs with cognitive domain z-scores. In Model 1, we adjusted for age, race-center and sex. In Model 2, we further adjusted for educational attainment, APOE ε4 genotype, current smoking status, physical activity, BMI, diabetes, hypertension medication use, systolic blood pressure, diastolic blood pressure, estimated glomerular filtration rate, NT-proBNP, left atrial volume index, peripheral arterial disease, coronary heart disease, and heart failure. In Model 3, we additionally adjusted for ischemic stroke. We explored the association between PAC frequency with probability of dementia or MCI using restricted cubic splines with 4 knots (located at PAC frequency 1%, 2.5%, 5%, 10%). Logistic regression was used to evaluate the association between PAC frequency and dementia or MCI prevalence (composite and individually). The logistic regression models used the same series of model adjustments as used for cognitive domain z-scores. In a sensitivity analysis, we excluded participants with a history of stroke n=69, coronary heart disease n=127, or heart failure n=92. We tested for multiplicative interactions by age, race, and sex. To account for cerebrovascular abnormalities, we conducted another sensitivity analysis restricted to the 757 participants who had brain MRI measures (based on a selected subset) from visit 5, where we adjusted Model 3 further for cerebral infarcts,

microbleeds, and white matter hyperintensity volume. SAS version 9.4 (SAS Institute Inc.; Cary, NC) was used for analyses. Two-sided p-values of 0.05 were used for tests of statistical significance.

RESULTS

The 2,163 ARIC study participants were aged 79 ± 4 years (mean ± SD), 59% were female and 28% were black. During a mean analyzable time of 12.6 ± 2.6 days, 79% had minimal PACs, while 16% had occasional PACs and 5% had frequent PACs. As shown in Table 1, individuals with frequent PACs tended to be male, had higher left atrial volume index, higher prevalence of heart failure, and greater white matter hyperintensity volume than those with minimal PACs.

Compared to those with minimal PACs, those with frequent PACs had lower executive function z-scores by 0.34 (95% CI: −0.50, −0.18) and lower global factor z-scores by 0.23 (−0.37, −0.09) with adjustment for demographics (Table 2). To provide context to these estimates, each additional year in age has been associated with an approximately 0.04–0.05 SD lower typical cross-sectional cognitive score.[35–37] As such, the lower executive function (−0.34) and global (−0.23) cognitive test factor scores found in individuals with frequent PACs would correspond to a score of someone roughly 5–7 years older. Occasional PACs were not associated with any cognitive domain factor score. These associations remained largely unchanged for both executive function and global factor scores after multivariable adjustment and with additional adjustment for ischemic stroke [Executive Function: −0.30 (−0.46, −0.14); Global: −0.20 (−0.33,−0.07)]. PAC frequency was not associated with memory or language factor scores. When we modeled PAC frequency continuously, each 1% higher PAC frequency was associated with a lower executive function and global factor score by 0.02 (0.04, 0.01). There were no differences by age, sex, or race in the association between PAC burden and any of the cognitive domain z-scores.

In a sensitivity analysis, the PAC burden-executive function association was attenuated but followed a similar direction after excluding the 245 participants with prevalent stroke, coronary heart disease, or heart failure (Supplemental Table 2). In the MRI subset, frequent PAC (vs minimal PAC) were associated with lower z-scores for executive function, language, and global domains. Results were unchanged with further adjustment for cerebral infarcts, microbleeds, and white matter hyperintensity volume (Supplemental Table 3)

As shown in Figure 1, higher PAC frequency was associated with a greater probability of the composite MCI or dementia outcome. Compared to those with minimal PACs, individuals with frequent PACs had higher odds of prevalent dementia or MCI [OR=1.64 (95% CI: 1.07–2.51)], and prevalent MCI [OR=1.63 (95% CI: 1.02–2.62)] alone after adjustment for demographics (Table 3). The demographic adjusted OR for prevalent dementia alone was not statistically significant [OR=1.80 (0.85–3.81)] but precision was poor and the estimate was similar in magnitude to those for prevalent dementia or MCI and prevalent MCI alone. The associations were similar after multivariable adjustment and with additional adjustment for ischemic stroke. Occasional PACs were not associated with MCI or dementia (either as a composite or the individual outcomes). The associations between PAC frequency with MCI

or dementia did not different according to age, sex, or race. When we modeled PAC frequency continuously, each additional 1% of heart beats that were PACs was associated with slightly elevated odds of MCI or dementia [$OR_{per\ 1\%}$ = 1.04 (1.00–1.08)].

In a sensitivity analysis, the frequent PACs-dementia/MCI association remained even after excluding those with ischemic stroke, coronary heart disease, or heart failure (Supplemental Table 4). In the subset of 757 individuals with brain MRI measures at visit 5, our effect estimates for PAC frequency and MCI or dementia were similar to the main results, even after further adjustment for cerebrovascular disease (Supplemental Table 5).

DISCUSSION

In this community-based cohort of elderly individuals without AF, we observed two principal findings: first, frequent PACs were cross-sectionally associated with lower executive and global cognitive function; and second, frequent PACs were associated with a higher prevalence of dementia or MCI. These associations were independent of ischemic stroke. Our findings lend support to the notion that atrial cardiomyopathy may be a driver of AF-related outcomes.

In recent years, there has been increasing interest in the relationship of arrhythmias to cognitive function.[38] Much of the work in this area has focused on the association between AF and greater cognitive decline and risk of dementia. To our knowledge, no prior studies have examined PAC frequency in relation to cognitive status (including cognitive tests scores and prevalence of dementia or MCI). To date, most research on arrhythmias and cognitive function has not included >24 hours monitoring. Particularly for arrhythmias that are often subclinical (e.g., PACs), short term monitoring may not adequately characterize the spectrum of burden of these arrhythmias as they are intermittent and exhibit diurnal variability. Thus, our study advances current knowledge by using 2 weeks of continuous heart rhythm monitoring to accurately quantify PAC frequency and to demonstrate an independent association with poorer cognitive function and higher odds of dementia or MCI.

Several potential mechanisms may explain our observations. PACs are a manifestation of atrial electrical remodeling and are considered an intermediate phenotype of AF.[1] Potential pathophysiologic pathways connecting frequent PACs and poorer cognitive function are likely similar to traditional risk factors linking AF to poorer cognition, such as ischemic stroke. The association between PAC frequency and executive function is congruent with associations reported for AF and cognition.[12,39] However, in our study, the association between frequent PACs with lower executive function and higher dementia or MCI prevalence occurred independently of clinically recognized stroke and existed even in participants without a history of clinical stroke. Other mechanisms linking AF to cognitive impairment may include reduced cerebral perfusion, microbleeds, a pro-inflammatory state, or small vessel disease, manifested as white matter hyperintensities in brain MRI.[13,40] Notably, many of these brain abnormalities have been associated with poorer executive functioning,[41–43] which is suggestive of a vascular relationship. Whether a higher PAC frequency itself is related to these brain abnormalities and whether there is a

pathophysiologic pathway linking PAC frequency to brain abnormalities independently of AF has yet to be characterized.

Our study has important biological and public health implications. Our findings add an important piece to the evolving story of atrial cardiomyopathy as an important driver of AF-related outcomes.[44,45] Atrial cardiomyopathy has many facets, one of which is electrical remodeling manifesting as increased atrial ectopic activity. Just as left atrial enlargement has been shown to be independently associated with higher risk of ischemic stroke and poorer cognitive function,[46,47] we now provide evidence to show that increased atrial ectopic activity is associated with poorer cognitive function in the absence of AF and other cardiovascular diseases. Our data in combination with existing literature indicate that in tackling AF-related dementia, rather than treating AF once it has become established, we may need to focus on preventing AF from developing in the first place.

The strengths of our study include the comprehensive in-person assessments of cognitive status, adjudicated dementia status. Additionally, the greater than 30 years of follow-up with the now elderly ARIC participants results in a well-characterized population at the time of visit 6. There are also limitations to note. First, this is a cross-sectional analysis of supraventricular arrhythmias and cognitive function; therefore, the temporality of the association is not clear and causal interpretations should not be drawn. Second, despite adjustment for numerous confounding characteristics, residual confounding may still explain the association, in part, between higher PAC frequency and poorer cognition. Third, there are no established clinical cut-points for defining PAC frequency, but we used cut-points as reported to participants by the manufacturer. Fourth, there were few individuals with prevalent cognitive impairment, which resulted in imprecise estimates (particularly when dementia/MCI were examined as outcomes individually). Last, despite the longer monitoring period used in our study, two weeks of ECG monitoring may still underestimate burden of subclinical arrhythmias.[48] While we excluded individuals with AF (clinically ascertained or subclinically identified on the 2-week patch monitor), it is possible that an even longer ECG monitoring duration could capture additional subclinical AF cases, particularly among individuals with higher PAC frequency.

Conclusion

In this community-based sample of older adults without AF, frequent PACs as measured over 2 weeks of continuous ECG monitoring was cross-sectionally associated with lower executive function scores and higher prevalence of dementia or MCI as compared to those with no or minimal PACs. Of note, stroke did not explain these novel findings. Further research to confirm these associations prospectively and to elucidate the underlying mechanisms is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

The authors thank the staff and participants of the ARIC study for their important contributions.

Funding:

The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract nos. (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I). Neurocognitive data is collected by U01 2U01HL096812, 2U01HL096814, 2U01HL096899, 2U01HL096902, 2U01HL096917 from the NIH (NHLBI, NINDS, NIA and NIDCD), and with previous brain MRI examinations funded by R01HL70825 from the NHLBI. Funding for biospecimen collection and laboratory testing at ARIC Visit 6 was supported by grant R01DK089174 from the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH. This work was also supported by grants from the NHLBI [R01HL126637–01A1 (LYC), R01HL141288 (LYC), T32HL007779 (MRR), K24HL148521 (AA)], and the American Heart Association [16EIA26410001 (AA)]. Reagents for the NT-proBNP assay were donated by the Roche Diagnostics Corporation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or AHA.

ABBREVIATIONS

AF	atrial fibrillation
APOE	apolipoprotein E
ARIC	Atherosclerosis Risk in Communities
BMI	body mass index
CHD	coronary heart disease
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
MCI	mild cognitive impairment
PAC	premature atrial contraction

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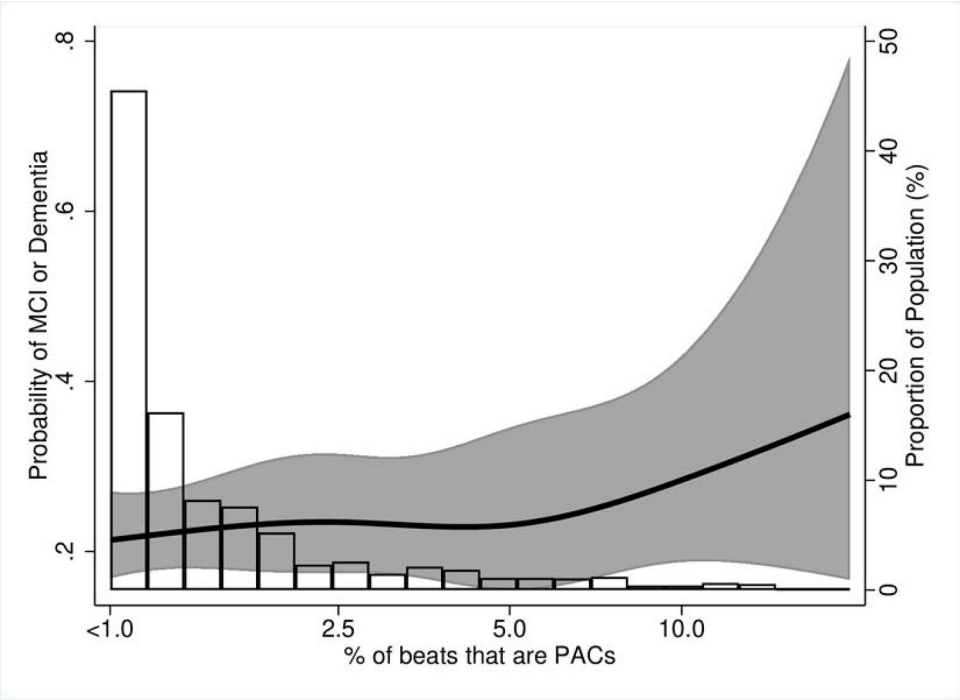

Figure 1.

Association of PAC frequency with the prevalence of MCI or dementia composite: ARIC study, 2016–2017. Predicted probabilities of MCI or dementia composite calculated from logistic regression modeling PAC frequency (% of beats that are PACs) using restricted cubic splines with adjustment for age, sex, and race. There were four knots, which were located at PAC frequency values of 1%, 2.5%, 5%, and 10%. Values above the 99th percentile (>13%) removed from figure for ease of display. For every 1% unit increment in PAC frequency, the odds of MCI or dementia was slightly higher OR: 1.04 (95% CI: 1.00–1.08).

Table 1.

Participant Characteristics Stratified by Categories of Premature Atrial Contraction Frequency, the ARIC Study, 2016–2017

	PAC Frequency			p-value[a]
	Minimal <1%	**Occasional 1–<5%**	**Frequent ≥5%**	
N	1717	339	107	
ECG patch analyzable time, days[b]	13 ± 3	13 ± 2	13 ± 3	0.33
PAC count/day				
Minimum	0	806	4637	
25th percentile	50	1372	6397	
Median	128	1964	8960	
75th percentile	650	3168	12949	
Maximum	4752	8181	43781	
Average heart rate, bpm/day	73 ± 9	71 ±9	71 ± 8	<0.001
Age, years	79 ± 4	80 ± 5	80 ± 4	<0.001
Male	670 (39.0)	160 (47.2)	60 (56.1)	<0.001
Black race	467 (27.2)	102 (30.1)	35 (32.7)	0.29
Educational attainment				
<High school	203 (11.9)	45 (13.3)	19 (17.8)	0.45
High school or GED	711 (41.5)	140 (41.3)	43 (40.2)	
>High school	799 (46.6)	154 (45.4)	45 (42.1)	
Current smoker	119 (6.9)	25 (7.4)	9 (8.4)	0.82
Physical activity (sports index)	2.6 ± 0.8	2.5 ± 0.8	2.6 ± 0.8	0.59
BMI, kg/m^2	28 ± 5	28 ± 5	29 ± 6	0.44
Apolipoprotein ε4 alleles				
1	439 (25.6)	88 (26.0)	26 (24.3)	0.83
2	31 (1.8)	3 (0.9)	2 (1.9)	
Diabetes	393 (22.9)	89 (26.3)	25 (23.4)	0.41
Hypertension medication use	1290 (75.1)	254 (74.9)	85 (79.4)	0.60
Systolic blood pressure, mmHg	136 ± 19	137 ± 19	134 ± 19	0.26
Diastolic blood pressure, mmHg	67 ± 10	68 ± 12	67 ± 11	0.18
eGFR, mL/min per 1.73 m^2	64 ± 18	62 ± 18	60 ± 19	0.01
≥90	120 (7.2)	15 (4.6)	6 (6.1)	0.22
60–<90	923 (55.6)	171 (52.6)	52 (53.1)	
15–<60	616 (37.1)	139 (42.3)	40 (40.8)	
NT-proBNP, pg/mL	273.9 ± 1684.1	331.4 ± 887.3	347.0 ± 607.7	0.76
Left atrial volume index, mL/m^2	24 ± 7	26 ± 7	27 ± 8	<0.001
≥34 mL/m^2	130 (8.1)	33 (10.5)	15 (15.2)	0.03
Peripheral arterial disease	104 (6.1)	30 (8.9)	5 (4.7)	0.12
Coronary heart disease	105 (6.1)	17 (5.0)	5 (4.7)	0.63
Heart failure	66 (3.8)	19 (5.6)	7 (6.5)	0.17

	PAC Frequency			p-value[a]
	Minimal <1%	**Occasional 1–<5%**	**Frequent ≥5%**	
Ischemic Stroke	54 (3.2)	12 (3.5)	3 (2.8)	0.91
Cerebral infarct[c]	123 (20.3)	35 (29.2)	7 (21.9)	0.10
Microbleed[c]	114 (18.8)	34 (28.3)	8 (25.0)	0.05
White matter hyperintensity volume[c], cm^3	14 ± 14	18 ± 17	22 ± 19	<0.001

Abbreviations: Atherosclerosis Risk in Communities, ARIC; premature atrial contraction, PAC; general educational development, GED; body mass index, BMI; estimated glomerular filtration rate, eGFR; N-terminal pro-B-type natriuretic peptide, NT-proBNP

[a] p-value from ANOVA for continuous characteristics or chi-squared test for categorical characteristics

[b] Mean ± standard deviation or n (%) unless indicated otherwise

[c] Brain MRI was performed on a subset of ARIC participants at visit 5. Of the 2163 in this study, 757 (35%) participants had these measures.

Table 2.

Association of Premature Atrial Contraction Frequency with Cognitive Domain Z-Scores (95% CI), the ARIC Study, 2016–2017

	PAC Frequency		
	Minimal <1%	**Occasional 1–<5%**	**Frequent ≥5%**
N	1717	339	107
Memory			
Mean score ± SD	0.07 ± 0.84	−0.04 ± 0.83	−0.11 ± 0.74
Model 1[a,b]	0 (Ref)	−0.01 (−0.10, 0.09)	−0.05 (−0.20, 0.10)
Model 2	0 (Ref)	−0.02 (−0.12, 0.07)	−0.07 (−0.22, 0.09)
Model 3	0 (Ref)	−0.02 (−0.12, 0.07)	−0.07 (−0.22, 0.09)
Executive function			
Mean score ± SD	−0.08 ± 0.99	−0.22 ± 1.02	−0.55 ± 1.00
Model 1	0 (Ref)	−0.01 (−0.10, 0.09)	−0.34 (−0.50, −0.18)
Model 2	0 (Ref)	0.01 (−0.08, 0.10)	−0.30 (−0.46, −0.14)
Model 3	0 (Ref)	0.01 (−0.09, 0.10)	−0.30 (−0.46, −0.14)
Language			
Mean score ± SD	−0.02 ± 0.93	−0.14 ± 0.94	−0.23 ± 1.03
Model 1	0 (Ref)	−0.02 (−0.11, 0.08)	−0.10 (−0.27, 0.06)
Model 2	0 (Ref)	−0.00 (−0.10, 0.09)	−0.07 (−0.23, 0.10)
Model 3	0 (Ref)	−0.01 (−0.10, 0.09)	−0.07 (−0.23, 0.09)
Global			
Mean score ± SD	0.01 ± 0.90	−0.12 ± 0.91	−0.38 ± 0.93
Model 1	0 (Ref)	−0.00 (−0.09, 0.08)	−0.23 (−0.37, −0.09)
Model 2	0 (Ref)	0.00 (−0.08, 0.08)	−0.20 (−0.33, −0.07)
Model 3	0 (Ref)	0.00 (−0.08, 0.08)	−0.20 (−0.33, −0.07)

Abbreviations: Atherosclerosis Risk in Communities, ARIC; premature atrial contraction, PAC; standard deviation, SD

[a]Model 1: adjusted for age, race-center, and sex

Model 2: Model 1 + educational attainment, APOE ε4 genotype, current smoking status, physical activity, body mass index, diabetes, hypertension medication use, systolic blood pressure, diastolic blood pressure, estimated glomerular filtration rate, NT-proBNP, left atrial volume index, peripheral arterial disease, coronary heart disease, and heart failure

Model 3: Model 2 + ischemic stroke

[b]To provide context for the difference in cognitive scores, each additional year in age has previously been associated with an approximately 0.04–0.05 SD lower typical cross-sectional cognitive score.[35–37] As such, the lower executive function (−0.34) and global (−0.23) cognitive test z-scores found in individuals with frequent PACs would correspond to a score of someone roughly 5 to 7 years older.

Table 3.

Odds Ratios and 95% Confidence Intervals for the Association of Premature Atrial Contraction Frequency with Prevalence of Dementia and Mild Cognitive Impairment, the ARIC Study, 2016–2017

	PAC Frequency		
	Minimal <1%	**Occasional 1–<5%**	**Frequent ≥5%**
N	1717	339	107
Dementia or MCI, N	371	78	35
Model 1[a]	1 (Ref)	0.96 (0.72–1.27)	1.64 (1.07–2.51)
Model 2	1 (Ref)	1.00 (0.73–1.37)	1.74 (1.09–2.79)
Model 3	1 (Ref)	1.00 (0.73–1.37)	1.76 (1.10–2.82)
Dementia only, N	80	19	9
Model 1	1 (Ref)	0.98 (0.57–1.67)	1.80 (0.85–3.81)
Model 2	1 (Ref)	1.09 (0.59–2.05)	1.82 (0.73–4.49)
Model 3	1 (Ref)	1.11 (0.59–2.09)	1.94 (0.78–4.81)
MCI only, N	291	59	26
Model 1	1 (Ref)	0.96 (0.70–1.31)	1.63 (1.02–2.62)
Model 2	1 (Ref)	0.99 (0.70–1.40)	1.85 (1.11–3.08)
Model 3	1 (Ref)	0.99 (0.70–1.40)	1.83 (1.10–3.06)

Abbreviations: Atherosclerosis Risk in Communities, ARIC; premature atrial contraction, PAC; mild cognitive impairment, MCI

[a]Model 1: adjusted for age, race-center, and sex

Model 2: Model 1 + educational attainment, APOE ε4 genotype, current smoking status, physical activity, body mass index, diabetes, hypertension medication use, systolic blood pressure, diastolic blood pressure, estimated glomerular filtration rate, NT-proBNP, left atrial volume index, peripheral arterial disease, coronary heart disease, and heart failure

Model 3: Model 2 + ischemic stroke