Association of Ventricular Arrhythmias With Dementia

The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Objective

We performed a cross-sectional analysis to determine whether nonsustained ventricular tachycardia (NSVT) and premature ventricular contractions (PVCs) were associated with dementia in a population-based study.

Methods

We included 2,517 (mean age 79 years, 26% Black) participants who wore a 2-week ambulatory continuous ECG recording device in 2016 to 2017. NSVT was defined as a wide-complex tachycardia ≥4 beats with a rate >100 bpm. We calculated NSVT and PVC burden as the number of episodes per day. Dementia was adjudicated by experts. We used logistic regression to assess the associations of NSVT and PVCs with dementia.

Results

The mean recording time of the Zio XT Patch was 12.6 ± 2.6 days. There were 768 (31%) participants with NSVT; prevalence was similar in White and Black participants. There were 134 (6.5%) dementia cases (5% in White, 10% in Black participants). After multivariable adjustment, there was no overall association between NSVT and dementia; however, there was a significant race interaction ($p < 0.001$). In Black participants, NSVT was associated with a 3.67 times higher adjusted odds of dementia (95% confidence interval [CI] 1.92–7.02) compared to those without NSVT, whereas in White participants NSVT was not associated with dementia (odds ratio [95% CI] 0.64 [0.37–1.10]). In Black participants only, a higher burden of PVCs was associated with dementia.

Conclusions

Presence of NSVT and a higher burden of NSVT and PVCs are associated with dementia in elderly Black people. Further research to confirm this novel finding and to elucidate the underlying mechanisms is warranted.

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Glossary

AF = atrial fibrillation; **ARIC** = Atherosclerosis Risk in Communities; **CHD** = coronary heart disease; **CI** = confidence interval; **CVD** = cardiovascular disease; **DSM-5** = *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*; **HF** = heart failure; **ICD** = *International Classification of Diseases*; **LAVI** = left atrial volume index; **LVEF** = left ventricular ejection fraction; **MESA** = Multi-Ethnic Study of Atherosclerosis; **NSVT** = nonsustained ventricular tachycardia; **OR** = odds ratio; **PVC** = premature ventricular contraction; **WMH** = white matter hyperintensity.

Nonsustained ventricular tachycardia (NSVT) and premature ventricular contractions (PVCs) are heart rhythm conditions that affect individuals encompassing the entire health spectrum, from apparently healthy individuals to patients with severe heart disease.[1] In the presence of certain comorbid conditions, NSVT is a marker of increased risk of myocardial infarction[2] and death.[2,3] The prevalence of PVCs increases with age, and PVCs have been associated with an increased risk of stroke, particularly embolic stroke, in normotensive and nondiabetic people.[4,5] Collectively, existing data suggest that NSVT and PVCs are not benign and that their impact on health may be wide-ranging.

Dementia is a significant public health problem that will continue to be more challenging as the population ages. Many studies have documented higher prevalence and incidence of dementia, including Alzheimer disease dementia, among Black than among White participants.[6] However, currently available evidence regarding differences in dementia by race is incomplete and difficult to interpret. On one hand, some studies indicate that social, educational, and behavioral factors are the major drivers of race-based difference in dementia prevalence and incidence.[7–9] On the other hand, Black individuals have a higher prevalence of cardiovascular risk factors, including hypertension[10] and diabetes,[11] with earlier onset of risk, greater severity, and more poorly controlled conditions,[12] all of which are considered major risk factors for dementia and cognitive impairment.[13,14] Yet another conundrum is the lower prevalence and incidence of atrial fibrillation (AF)—an established risk factor for dementia—in Black than White individuals but a higher prevalence and incidence of dementia. In this regard, although the evidence for the association of AF with poorer cognitive function is compelling,[15–17] little is known about whether ventricular arrhythmias such as NSVT and PVCs are associated with dementia.

Using data from a 2-week continuous ambulatory ECG recording device, the Zio XT Patch (iRhythm Technologies, Inc, San Francisco, CA), in the setting of a community-based cohort study, the Atherosclerosis Risk in Communities (ARIC) study, we assessed the cross-sectional association of NSVT and PVCs with dementia.

Methods

Study Population

The ARIC study is a prospective cohort study of cardiovascular disease (CVD) and atherosclerosis risk factors.[18] Participants at baseline (1987–1989) included 15,792 men and women 45 to 64 years of age, mostly White or Black race, recruited from 4 communities in the United States (Washington County, Maryland [majority White participants]; the northwest suburbs of Minneapolis, MN [majority White participants]; Jackson, MS [all Black participants]; and Forsyth County, North Carolina [both Black and White participants]). Thus far, 6 study visits have been completed, with visit 6 occurring in 2016 to 2017. In addition, ARIC participants have received annual follow-up calls (semiannual since 2012), with response rates of ≥90% among survivors.

This analysis is based on participants who attended visit 6 and wore the Zio XT Patch, a noninvasive, single-lead ECG monitor that provides up to 2 weeks of continuous ECG data. All participants who attended visit 6 were invited to wear the Zio XT Patch, which was applied to the upper chest, over the heart, by a trained ARIC staff member. Further details have been published.[19] The longer wear time provides a more precise measurement of NSVT and PVC burden in the population compared to a 24-hour Holter monitor. Of the 4,003 participants who attended visit 6, 2,616 wore the Zio XT Patch. Of those, we excluded participants who wore the Zio XT Patch <2 days (n = 68), those missing cognitive scores (n = 26), and those missing covariates (n = 5). After exclusions, our study population included 2,517 participants (58% female, 26% Black race). We ran a secondary analysis in a subset of ARIC participants that in addition had a brain MRI performed at visit 5 (2011–2013) (n = 874) to assess the impact of cerebral vascular disease.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by institutional review boards at each participating center, and all study participants provided written informed consent.

Dementia Ascertainment

The methodology used to define dementia among ARIC participants has been described in detail elsewhere.[20] Briefly, information was obtained from a comprehensive neurocognitive battery, followed by a detailed neurologic history, interviews, and informant interviews, and that information was reviewed by a panel of neurologists and neuropsychologists. This panel classified participants as having dementia following an algorithm based on the National Institute on Aging–Alzheimer's Association working group formulations of dementia[21] and DSM-5.[22]

NSVT and PVC Ascertainment

Participants were asked to wear the Zio XT Patch for up to 14 days. At the end of the recording period, participants removed the device and mailed the heart rhythm monitor to iRhythm Technologies Inc. Data collected from the Zio XT Patch are processed with a proprietary algorithm (Zio ECG Utilization Service System) that provides information on the number of PVCs and NSVT episodes during the wearing period.[23] NSVT was defined as the presence of at least 1 wide-complex tachycardia ≥4 beats with a rate >100 bpm (yes/no). We explored the burden of NSVT by dividing the number of NSVT episodes by Zio XT Patch wear time. PVC count was calculated from the number of isolated PVCs divided by wear time to obtain a mean PVC count per day. We also determined the percentage of beats that were isolated PVCs during each participant's wear time.

Covariate Measures

Detailed procedures on covariate measure have been previously published.[18] In brief, body mass index was calculated as weight in kilograms divided by height in meters squared. Study staff measured blood pressure using a random-zero sphygmomanometer after 5 minutes of rest in the sitting position and used the average of the second and third measurements. The use of antihypertensive medications was confirmed by standardized review of medications brought to each visit by the patient. ARIC participants had *APOE* genotyping performed with the TaqMan assay (Applied Biosystems, Foster City, CA) using blood samples and were categorized into 0, 1, or 2 alleles. We defined diabetes mellitus as fasting glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, treatment for diabetes mellitus, or self-reported physician diagnosis of diabetes. Participants self-reported current cigarette smoking status. A participant was considered to have heart failure (HF) on the basis of use of HF medication in the previous 2 weeks, presence of HF according the Gothenburg criteria (baseline ARIC visit only), or presence of HF ICD codes in any hospitalization or during follow-up before their visit 6 examination.[24,25] ARIC defined coronary heart disease (CHD) as prior cardiovascular revascularization, physician-diagnosed myocardial infarction, presence of a previous myocardial infarction by ECG, or by CHD ascertained by the ARIC Morbidity and Mortality Classification Committee using data from follow-up calls and hospitalization records.[26] We ascertained AF using 3 sources in this analysis: 12-lead ECGs performed at previous study visits, hospital discharge codes during follow-up, or captured while wearing the Zio XT Patch.[27] ARIC defined stroke as a self-reported physician diagnosis of a stroke before visit 1, and after visit 1, stroke was adjudicated from diagnosis codes indicative of cerebrovascular disease using criteria adapted from the National Survey of Stroke.[28] All covariates listed above were assessed at visit 6 except for race/center, sex, and education, which were assessed at visit 1. Finally, we assessed measures of left ventricular ejection fraction (LVEF), left atrial volume index (LAVI), E/A ratio, and E/E′ lateral ratio using 2-dimensional echocardiography.[29] Echocardiography was performed at visit 5 (2011–2013), which was, on average, 5 years before Zio XT Patch application and cognitive assessments for this study. At the ARIC–Neurocognitive Study at visit 5, brain MRI scans were performed on selected individuals by using 3T brain MRI following identical protocols at each study site, as previously described.[30] Data were processed by the ARIC MRI Reading Center at the Mayo Clinic (Rochester, MN). Subclinical cerebrovascular disease, including white matter hyperintensity (WMH) volume and infarcts, was assessed on T2 fluid-attenuated inversion recovery sequences, and microbleeds were assessed on T2* gradient recalled echo sequences.

Statistical Analysis

To describe NSVT burden and to assess the association with dementia, we initially explored associations using restricted cubic splines and found the median burden value to be a natural split. Therefore, we stratified those with NSVT by the number of NSVT episodes per week on the median (0.59 episode per week) into low and high burden. We explored the relationship between PVC burden and dementia using a restricted cubic spline and found it to be linear. Because there are no established clinical cut points for PVC burden, we present results by tertiles and per 1-SD increase in the number of PVCs per day. As a secondary analysis, we grouped the percentage of beats that were isolated PVCs into 3 categories (<0.1%, 0.1%–4.99%, ≥5%) to look at associations in those with a high burden of PVCs (≥5%).

We used multivariable logistic regression to estimate the cross-sectional associations of NSVT and PVCs with dementia. For all analyses, we further tested for effect modification by race and sex using a multiplicative term in the models. Models were adjusted for the baseline variables of age (continuous), sex, race/center (5 levels), *APOE* genotype (0, 1 or 2 alleles), education (high school graduate vs not), cigarette smoking (current vs not current), body mass index (continuous), systolic and diastolic blood pressures (continuous), antihypertensive medication use (yes/no), diabetes (yes/no), CHD (yes/no), HF (yes/no), AF (yes/no), stroke (yes/no), and antiarrhythmic medication use. We performed a secondary analysis limited to participants with echocardiographic measures at visit 5 (89% of participants in our study had echocardiography measures). In those participants, a second model adjusts for LVEF, LAVI, E/A ratio, and E/E′ lateral ratio, all as continuous measures. We performed a sensitivity analysis excluding those with prevalent CVD, which consisted of CHD, HF, and stroke. We performed an additional secondary analysis to assess cerebral vascular disease, and this analysis was limited to participants who in addition underwent brain MRI measures at visit 5. We used multivariable logistic regression models adjusted for the covariates listed above plus cerebral infarcts, microbleeds, and WMH volume. All statistical analyses were performed with SAS version 9.4 (SAS Inc, Cary, NC) and Stata 14.0 (StataCorp LP, College Station, TX).

Data Availability

ARIC data are available through the NIH National Heart, Lung, and Blood Institute–sponsored Biologic Specimen and Data Repository Information Coordinating Center at biolincc.nhlbi.nih.gov/

Results

Of the 2,517 participants (mean age 79 ± 5 years, 58% female, 26% Black race) who wore the Zio XT Patch, the mean recording time was 12.6 ± 2.5 days. There were 768 (31%) participants with at least 1 episode of NSVT recorded, ranging from 0.5 to 526 episodes per week (median 0.58, 25th–75th percentile 0.51–1.51). Baseline characteristics of ARIC participants by both the presence and burden of NSVT are shown in table 1. Participants with NSVT detected were slightly older, were more likely to be male, and had a higher prevalence of CHD, HF, AF, and stroke compared to those without NSVT. Those with a higher burden of NSVT were more likely to be male and had a higher prevalence of CHD, HF, AF, and stroke compared to those with a lower burden of NSVT. The prevalence of NSVT was similar in White (31%) and Black (30%) participants, and burden was the same in White and Black individuals.

NSVT and NSVT Burden

A total of 134 (6.5%) dementia cases were identified at visit 6, and the prevalence of dementia was 5.2% in White and 9.9% in Black participants. The multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of dementia by NSVT status and burden are given in table 2. Overall, there was no significant association between dementia and NSVT status (OR [95% CI] 1.28 [0.86–1.91]). However, there was a significant interaction by race (p = 0.0004); therefore, we stratified the dementia results by Black and White race. In White participants, there was no association between dementia by NSVT status (OR [95% CI] 0.64 [0.37–1.10]). In Black participants, NSVT was associated with a 3.67 times higher adjusted odds of dementia (95% CI 1.92–7.02) compared to those without NSVT. Furthermore, this association was stronger in Black participants with a higher burden (OR [95% CI] 4.79 [2.16–10.66]) than it was in Black participants with a lower burden (OR [95% CI] 2.89 [1.31–6.39]) compared to Black participants without NSVT. There were no significant associations in White participants by NSVT status and dementia. Interaction by sex was not significant. In a sensitivity analysis limited to those without prevalent CVD, the estimates were similar.

To account for potential confounding by cardiac structure and function, a secondary analysis was performed limited to participants with echocardiographic measures performed at visit 5, ≈5 years before the baseline for this study. The results are presented in table 3. Further adjustment for the variables of LVEF, LAVI, E to A ratio, and E/E′ lateral ratio slightly strengthened the associations of NSVT and NSVT burden with dementia in Black individuals, although estimates in this table are less precise due to a smaller sample size. In contrast, effect estimates were largely unchanged in White participants after adjustment for echocardiographic measures.

To account for cerebral vascular disease, a secondary analysis was performed that was limited to subset of participants who had a brain MRI at visit 5. These results are presented in table 4. Further adjustment for the variables of cerebral infarcts, microbleeds, and WMH volume had little effect on the estimates of association between NSVT and dementia; however, power was very limited in this subset analysis.

Premature Ventricular Contractions

In this elderly cohort, 98.9% of the participants had PVCs detected by the Zio XT Patch. The mean (SD) number per day was 716 (2,194) and the median (25th-75th percentile) was 64 (9.99–406). The mean (SD) in Black participants was 648 (2,183) and in White participants was 740 (2,197). In Black participants, for every 1% increase in the number of beats that were PVCs, the odds of dementia was 2 times higher (OR [95% CI] 2.03 [1.14–3.60]). There was no association in White participants. Results by PVC tertiles are presented in table 5. Overall, there was no significant association between PVCs and dementia. However, there was a significant interaction by race (p = 0.04). Black participants in the highest tertile burden of PVCs had a 2.34 higher odds (95% CI 1.08–5.08) of dementia compared to those in the lowest tertile burden. Interaction by sex was not significant. In a sensitivity analysis limited to those without prevalent CVD, the estimates were similar.

The association of PVCs with dementia limited to those with echocardiographic variable measures is presented in table 6. Associations were similar to the main analysis with further adjustment for echocardiographic variables.

The results for a secondary analysis limited to subset of participants who had a brain MRI at visit 5 are presented in table 7. Further adjustment for the variables of cerebral infarcts, microbleeds, and WMH volume had little effect on the estimates of association between PVCs and dementia; however, power was very limited in this subset analysis.

Discussion

In this population-based cross-sectional study of Black and White individuals, we observed the following principal findings: (1) the prevalence of NSVT in an elderly population (mean age 79 years) was high (31%), with a similar prevalence in White and Black participants; and (2) the association of NSVT and PVCs with dementia was modified by race. Presence of NSVT and higher burden of NSVT and PVCs were independently associated with dementia in elderly Black but not White individuals.

Table 1 Participant Characteristics Stratified by Race and NSVT, ARIC Study, Visit 6 (2016–2017)[a]

	White Race (n = 1859)		Black Race (n = 658)	
	No NSVT (n = 1,290)	NSVT (n = 569)	No NSVT (n = 459)	NSVT (n = 199)
Age, mean (SD), y	79 (5)	80 (5)	79 (5)	79 (5)
Female sex, %	60	40	74	54
Education less than high school, %	9	9	22	24
***APOE* ε4, 2 alleles, %**	0.85	1.93	2.61	3.52
***APOE* ε4, 1 allele, %**	23	22	35	30
Current smoker, %	5.4	5.3	11	12
Body mass index, kg/m^2	28 (5)	28 (5)	30 (6)	30 (6)
Diabetes mellitus, %	19	20	33	37
Hypertensive medication use, %	71	77	88	92
Systolic BP, mm Hg	135 (19)	134 (19)	138 (19)	137 (20)
Diastolic BP, mm Hg	67 (10)	68 (10)	67 (10)	67 (10)
Total cholesterol, mg/dL	176 (40)	167 (39)	184 (39)	182 (38)
LDL cholesterol, mg/dL	98 (33)	94 (31)	108 (33)	109 (33)
Coronary heart disease, %	5.6	11	4.8	12
Heart failure, %	4.2	7.7	5.7	16
Atrial fibrillation, %	13	23	6.5	13
Stroke, %	3.1	5.3	3.7	9.6
Antiarrhythmic medication use, %	1.9	1.8	1.5	2.0
Left ventricular ejection fraction, %[b]	66 (5)	65 (6)	66 (5)	67 (10)
Left atrial volume index, mL/m^{2b}	25 (7)	27 (11)	25 (7)	27 (8)
E to A ratio[b]	0.9 (0.3)	0.8 (0.3)	0.8 (3)	0.8 (0.3)
E/E′ lateral ratio, cm/s[b]	9.8 (3)	9.9 (4)	9.8 (3)	9.8 (5.7)
Cerebral infarction, %[c]	18	28	22	28
Microbleed, %[c]	21	19	22	28
White matter hyperintensity volume, cm^{3c}	13.6 (13.7)	15.9 (13.7)	14.8 (15.7)	19.5 (18.3)

Abbreviations: ARIC = Atherosclerosis Risk in Communities; BP = blood pressure; LDL = low-density lipoprotein; NSVT = nonsustained ventricular tachycardia.
[a] Data are presented as mean (SD) when appropriate.
[b] Echocardiographic measures are from visit 5 (2011–2013) and not available in all participants; 2,239 of the 2,517 participants have these 4 measures.
[c] Brain MRI was performed on a subset of ARIC participants at visit 5. In this study, 874 (35%) of the 2,517 participants had these measures.

Limited information is available from general population studies about the prevalence of ventricular arrhythmias with extended recording, both overall and by race. The prevalence rates of NSVT and PVCs in our study in ARIC are comparable to those in a similar study that was conducted in Multi-Ethnic Study of Atherosclerosis (MESA), a community-based study with a selected sample of older individuals (mean age 75 years in MESA) who wore the Zio XT Patch. We report an overall prevalence of 31% with NSVT and 98.9% with PVCs, whereas MESA reported a prevalence of 34.6% with NSVT and 99.5% with PVCs.[31] In our study, the prevalence of NSVT was similar in White and Black participants (31% and 30%, respectively) on the basis of up to 2 weeks of continuous ECG recording. Previous studies, including those at prior ARIC visits,[6,8] have indicated that PVCs are more prevalent in Black individuals compared to White individuals[4,32,33]; however, we did not find that to be the case in our study because White participants had, on average, ≈90 more PVCs per day. One reason for the discrepancy could be that in previous ARIC studies, the prevalence was reported in middle-aged populations with a 2-minute rhythm ECG, whereas this study consists of an elderly population and uses 2-week ambulatory monitoring.

Table 2 ORs (95% CIs) for the Cross-Sectional Association of NSVT With Dementia in the ARIC Study, 2016 to 2017

	Presence of NSVT		Burden of NSVT (Reference Is No NSVT)	
	No NSVT	NSVT	Lower Burden (<0.59 NSVT Episodes/wk)	Higher Burden (≥0.59 NSVT Episodes/wk)
Total population, N	1,749	768	384	384
Dementia, n (%)	82 (5)	52 (7)	23 (6)	29 (8)
OR (95% CI)[a]	Ref	1.28 (0.86–1.91)	1.06 (0.64–1.76)	1.38 (0.85–2.24)
Black race, n	459	199	100	99
Dementia, n (%)	25 (5)	30 (15)	13 (13)	17 (17)
OR (95% CI)[a]	Ref	3.67 (1.92–7.02)	2.89 (1.31–6.39)	4.79 (2.16–10.66)
White race, n	1,290	569	284	285
Dementia, n (%)	57 (4)	22 (4)	10 (4)	12 (4)
OR (95% CI)[a]	Ref	0.64 (0.37–1.10)	0.62 (0.30–1.28)	0.65 (0.32–1.30)

Abbreviations: ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; NSVT = nonsustained ventricular tachycardia; OR = odds ratio; Ref = referent.
[a] Model adjusted for age, sex, race/center, education, *APOE* ε4 genotype, current smoking, body mass index, diabetes, antihypertensive medication, systolic blood pressure, diastolic blood pressure, coronary heart disease, heart failure, atrial fibrillation, stroke, and antiarrhythmic medication use.

Our study advances the field on several fronts. We evaluated the relationship of ventricular arrhythmias to dementia in a community-based cohort who used continuous ECG monitoring. We observed a race-based difference in the association: in elderly Black but not in White participants, presence of NSVT and higher burden of NSVT and PVCs were associated with higher odds of dementia. These associations were independent of concomitant cardiovascular conditions and cardiac structure and function. This consideration is critical because cardiovascular conditions such as CHD, HF, AF, valvular disorder, aortic stiffening, left ventricular hypertrophy, and left ventricular systolic/diastolic dysfunction[34–39] are

Table 3 ORs (95% CIs) of NSVT With Dementia, Limited to Those With Echocardiograph Measures in 2011 to 2013 in the ARIC Study

	Presence of NSVT		Burden of NSVT	
	No NSVT	NSVT	Lower Burden (<0.59 NSVT Episodes/wk)	Higher Burden (≥0.59 NSVT Episodes/wk)
Total population, N	1,573	666	342	324
Dementia, n	66	45	20	25
Model 1, OR (95% CI)[a]	Ref	1.34 (0.87–2.05)	1.18 (0.68–2.05)	1.51 (0.89–2.55)
Model 2, OR (95% CI)[b]	Ref	1.33 (0.86–2.04)	1.19 (0.69–2.07)	1.48 (0.86–2.52)
Black race, n	382	167	86	81
Dementia, n	17	25	11	14
Model 1, OR (95% CI)[a]	Ref	5.42 (2.48–11.87)	4.34 (1.71–11.02)	7.02 (2.70–18.22)
Model 2, OR (95% CI)[b]	Ref	5.76 (2.59–12.84)	4.71 (1.82–12.20)	7.26 (2.74–19.22)
White race, n	1,191	499	256	243
Dementia, n	49	20	9	11
Model 1, OR (95% CI)[a]	Ref	0.69 (0.39–1.24)	0.67 (0.31–1.44)	0.71 (0.34–1.50)
Model 2, OR (95% CI)[b]	Ref	0.67 (0.37–1.20)	0.66 (0.31–1.42)	0.67 (0.31–1.43)

Abbreviations: ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; NSVT = nonsustained ventricular tachycardia; OR = odds ratio; Ref = referent.
[a] Model adjusted for age, sex, race/center, education, *APOE* ε4 genotype, current smoking, body mass index, diabetes, antihypertensive medication, systolic blood pressure, diastolic blood pressure, coronary heart disease, heart failure, atrial fibrillation, stroke, and antiarrhythmic medication use.
[b] Model 2 is adjusted for model 1 plus left ventricular ejection fraction, left atrial volume index, E to A ratio, and E/E′ lateral ratio.

Table 4 ORs (95% CI) for the Cross-Sectional Association of NSVT With Dementia in the ARIC Study, Limited to Those With Brain MRI Measures at Visit 5 (2011–2013)

	Presence of NSVT	
	No NSVT	**NSVT**
Total population, N	605	269
Dementia, n (%)	37 (6)	22 (8)
Model 1, OR (95% CI)	Ref	1.27 (0.69–2.35)
Model 2, OR (95% CI)	Ref	1.23 (0.66–2.29)
Black race, n	196	82
Dementia, n (%)	10 (5)	14 (17)
Model 1, OR (95% CI)	Ref	5.63 (1.76–18.05)
Model 2, OR (95% CI)	Ref	5.73 (1.74–18.85)
White race, n	409	187
Dementia, n (%)	27 (7)	8 (4)
Model 1, OR (95% CI)	Ref	0.47 (0.19–1.17)
Model 2, OR (95% CI)	Ref	0.47 (0.19–1.19)

Abbreviations: ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; NSVT = nonsustained ventricular tachycardia; OR = odds ratio; Ref = referent.
Model 1 adjusted for age, sex, race/center, education, *APOE* ε4 genotype, current smoking, body mass index, diabetes, antihypertensive medication, systolic blood pressure, diastolic blood pressure, coronary heart disease, heart failure, atrial fibrillation, stroke, and antiarrhythmic medication use. Model 2 adjusted for model 1 plus cerebral infarct, microbleeds, and white matter hyperintensity volume measured at visit 5 (2011–2013).

associated with brain hypoperfusion and cognitive impairment. These conditions can lower cardiac output and with time will reduce regional cerebral blood flow.[40–42] It has been shown that even a subtle but persistent drop in cardiac output can affect cerebral perfusion homeostasis and increase the risk of cognitive decline in the elderly.[41,42]

Several mechanisms may explain the relationship of ventricular arrhythmias to dementia. First, subclinical cerebrovascular disease could potentially explain the relationship of ventricular arrhythmias to dementia. To explore this possibility, we evaluated a subset of participants who wore the Zio XT Patch at visit 6 and who had brain MRI measures at visit 5.

Table 5 ORs (95% CIs) of PVCs With Dementia in the ARIC Study, 2016-2017

	PVC Tertiles, No. Isolated PVCs/d			
	0–20	**21–215**	**216–29,470**	**Per 1-SD Increase (2,194 PVCs/d)**
Total population, N	839	839	839	
Dementia, n (%)	32 (4)	47 (6)	55 (7)	
OR (95% CI)[a]	Ref	1.28 (0.79–2.09)	1.45 (0.89–2.36)	1.04 (0.89–1.22)
Black race, n	229	216	213	
Dementia, n (%)	12 (5)	16 (7)	27 (13)	
OR (95% CI)[a]	Ref	1.11 (0.48–2.56)	2.34 (1.08–5.08)	1.23 (1.01–1.50)
White race, n	610	623	626	
Dementia, n (%)	20 (3)	31 (5)	28 (4)	
OR (95% CI)[a]	Ref	1.41 (0.77–2.57)	1.02 (0.53–1.94)	0.83 (0.60–1.14)

Abbreviations: ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; OR = odds ratio; PVC = premature ventricular contraction; Ref = referent.
[a] Model adjusted for age, sex, race/center, education, *APOE* ε4 genotype, current smoking, body mass index, diabetes, antihypertensive medication, systolic blood pressure, diastolic blood pressure, coronary heart disease, heart failure, atrial fibrillation, stroke, and antiarrhythmic medication use.

Table 6 ORs (95% CI) of PVCs with Dementia, Limited to Those With Echocardiographic Measures in 2011–2013 in the ARIC Study

	PVC Tertiles, No. Isolated PVCs/d			
	0–20	21–215	216–29,470	Per 1-SD Increase (2,194 PVCs/d)
Total population, N	762	747	728	
Dementia, n	25	39	47	
Model 1, OR (95% CI)[a]	Ref	1.33 (0.77–2.30)	1.62 (0.94–2.80)	1.06 (0.86–1.24)
Model 2, OR (95% CI)[b]	Ref	1.34 (0.78–2.32)	1.65 (0.95–2.87)	1.06 (0.86–1.24)
Black race, n	227	218	213	
Dementia, n	12	16	27	
Model 1, OR (95% CI)[a]	Ref	1.51 (0.57–4.01)	3.01 (1.16–7.82)	1.24 (0.96–1.60)
Model 2, OR (95% CI)[b]	Ref	1.55 (0.58–4.18)	3.26 (1.24–8.59)	1.25 (0.95–1.62)
White race, n	612	621	626	
Dementia, n	20	31	28	
Model 1, OR (95% CI)[a]	Ref	1.28 (0.66–2.49)	1.08 (0.54–2.17)	0.80 (0.55–1.15)
Model 2, OR (95% CI)[b]	Ref	1.27 (0.65–2.47)	1.10 (0.54–2.23)	0.82 (0.56–1.16)

Abbreviations: ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; OR = odds ratio; PVC = premature ventricular contraction; Ref = referent.
[a] Model adjusted for age, sex, race/center, education, *APOE* ε4 genotype, current smoking, body mass index, diabetes, antihypertensive medication, systolic blood pressure, diastolic blood pressure, coronary heart disease, heart failure, atrial fibrillation, stroke, and antiarrhythmic medication use.
[b] Model 2 is adjusted for model 1 plus left ventricular ejection fraction, left atrial volume index, E to A ratio, and E/E′ lateral ratio.

Those with NSVT had a higher prevalence of cerebral infarcts and higher volumes of WMH compared to those without NSVT. Our findings in this limited subset were similar to findings in the broader sample: ventricular arrhythmias were associated with higher odds of dementia in Black people. In addition, the effect estimates were minimally affected after adjustment for markers of subclinical cerebrovascular disease. Thus, these findings suggest that subclinical cerebrovascular disease does not completely explain the relationship of ventricular arrhythmias to dementia. Second, NSVT causes ventricular dyssynchrony and may contribute to mechanical abnormalities in the left atrial appendage, which might explain the potential for enhanced stroke/thromboembolic events and cognitive impairment. Furthermore, ventricular dyssynchrony asymmetrically increases wall thickness and alters blood flow in the myocardium,[43] which could lead to cerebral hypoperfusion and cognitive decline.[44,45] Although we controlled for echocardiogram measures in a sensitivity analysis, it is possible that we are not capturing all functional measures of the heart. Third, changes in heart rate, blood pressure, and stroke volume during and after PVCs—a consequence of changes in ventricular filling, ventricular contractility, and baroreflex activity—are well described, and reductions in blood flow to the brain may contribute to dementia and cognitive impairment.[44,45] Moreover, frequent PVCs are associated with impaired ventricular relaxation and have the potential to remodel the heart.[46–48] Finally, ventricular arrhythmias could be related to many reported noncardiac systemic diseases, including metabolic, liver disease, and electrolyte imbalance,[1] which could affect cognitive function, although we adjusted for many of these contributing factors in our analysis.

The race-based difference in association warrants further explanation. There are several potential considerations: (1) differences in severity of ventricular arrhythmias, (2) variability at the brain tissue level in response to ventricular arrhythmias, and (3) differences in genetic susceptibility to the effect of ventricular arrhythmias. In regard to the first consideration, we evaluated NSVT and PVC burden to account for severity of ventricular arrhythmias. However, we could not account for the duration of exposure to NSVT and high PVC burden because we do not have data on the onset of ventricular arrhythmias. Whether the onset of ventricular arrhythmias (hence, longer duration of exposure) is earlier in Black than White individuals is unknown. With respect to the last 2 considerations, previous ARIC studies have shown that certain risk factors such as diabetes may differentially affect the brain in Black vs White individuals.[14] Whether ventricular arrhythmias have greater effect on cardiac hemodynamics and brain perfusion in Black than White people is unknown and deserves further attention. Due to the cross-sectional nature of this study, we cannot rule out a bidirectional relationship whereby cognitive or autonomic dysfunction results in a higher risk of cardiac arrhythmias.

Strengths of this study include the large number of Black and White men and women from a community-based sample of

Table 7 ORs (95% CI) of PVCs With Dementia in the ARIC Study, Limited to Those With Brain MRI Measures at Visit 5

	PVC Tertiles, No. Isolated PVCs/d			
	0–20	21–215	216–29,470	Per 1-SD Increase (2,194 PVCs/d)
Total population, N	286	301	287	
Dementia, n (%)	16 (6)	19 (6)	24 (8)	
Model 1, OR (95% CI)	Ref	1.12 (0.53–2.34)	1.22 (0.58–2.55)	0.99 (0.76–1.29)
Model 2, OR (95% CI)	Ref	1.09 (0.52–2.30)	1.20 (0.57–2.55)	0.97 (0.75–1.27)
Black race, n	101	91	86	
Dementia, n (%)	6 (6)	7 (8)	11 (13)	
Model 1, OR (95% CI)	Ref	1.54 (0.41–5.80)	2.01 (0.55–7.32)	0.95 (0.60–1.51)
Model 2, OR (95% CI)	Ref	1.42 (0.37–5.44)	2.01 (0.54–7.54)	0.95 (0.59–1.53)
White race, n	185	210	201	
Dementia, n (%)	10 (5)	12 (6)	13 (6)	
Model 1, OR (95% CI)	Ref	1.05 (0.31–2.66)	0.82 (0.30–2.23)	0.95 (0.64–1.42)
Model 2, OR (95% CI)	Ref	1.07 (0.41–2.72)	0.83 (0.30–2.26)	0.94 (0.63–1.40)

Abbreviations: ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; OR = odds ratio; PVC = premature ventricular contraction; Ref = referent. Model 1 adjusted for age, sex, race/center, education, *APOE* ε4 genotype, current smoking, body mass index, diabetes, antihypertensive medication, systolic blood pressure, diastolic blood pressure, coronary heart disease, heart failure, atrial fibrillation, stroke, and antiarrhythmic medication use. Model 2 adjusted for model 1 plus cerebral infarct, microbleeds, and white matter hyperintensity volume measured at visit 5 (2011–2013).

elderly participants, the excellent analyzable time achieved with the monitoring device, and the rigorous adjudication of dementia in ARIC. Our analysis is not without limitations. First, our analysis is cross-sectional; therefore, temporality of conditions cannot be established. Next, we do not have echocardiographic measures of atrial and ventricular function at the time of the Zio XT Patch and cognitive assessment. However, we adjusted for echocardiographic measures at visit 5, which was only ≈4 years before visit 6, and associations remained significant. Third, Black participants in this study are located mainly in Jackson, MS (91%), which has a high rate of CHD, stroke, and vascular risk factors. Although we are underpowered to detect a site-based difference, the estimates of association in Black participants at the Jackson site appeared similar to that in Black participants at the Forsyth County, North Carolina, site, where both White and Black individuals have been included. Finally, although we adjusted extensively for potential confounders such as cardiovascular risk factors and conditions, we cannot completely exclude residual confounding as an explanation for our observations.

In this population-based cross-sectional study of elderly Black and White men and women, both the presence of NSVT and a higher burden of NSVT and PVCs were independently associated with dementia in elderly Black participants. These associations remained significant after adjustment for many cardiovascular risk factors, including echocardiographic variables of left atrial and left ventricular function. The mechanisms of this novel association are unclear and warrant further investigation. Further research with a larger sample size and a prospective design is warranted.

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