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## The association of sleep apnea - diagnosed by self-reported physician diagnosis or hospital discharge codes - with atrial fibrillation and ectopy using ambulatory electrocardiogram in the Atherosclerosis Risk in Communities (ARIC) Study:

Gellert, Sleep apnea and cardiac arrhythmias

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### Keywords

Arrhythmia; Atrial Fibrillation; Sleep Apnea

Sleep apnea is associated with cardiac arrhythmias<sup>1</sup> such as atrial fibrillation (AF), premature ventricular contractions (PVC), and premature atrial contractions (PAC). Mechanisms that may explain this association include autonomic imbalance, hypertension, intermittent hypoxia, and atrial remodeling<sup>1,2</sup>. However, prior studies of sleep apnea and cardiac arrhythmias relied on a single ten second, 12-lead electrocardiogram, and/or hospital medical records, which would miss paroxysmal, asymptomatic, and intermittent arrhythmias.<sup>3</sup> The Reveal XT-SA study reported that using a medically implanted device for cardiac monitoring in patients with severe obstructive SA may help to identify newly detected AF, however application of this study's findings to our work was limited as the Reveal XT-SA study used a small sample size in a clinical population.<sup>4</sup> Our study overcomes these limitations by adding standardized 48-hour continuous ambulatory ECG

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Disclosures

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(aECG) monitoring to the population-based Atherosclerosis Risk in Communities (ARIC) study to examine the association between sleep apnea and AF, PACs, and PVCs.

Availability of data and detailed policies for accessing ARIC Study data can be found online, <https://www2.csc.unc.edu/aric/>. The ARIC Study data are made available through the National Heart, Lung, and Blood Institute BioLINCC repository, <https://biolincc.nhlbi.nih.gov/home/>.

Selected ARIC participants from 2 study sites - Forsyth county, N.C. and Jackson, M.S. (enriched for AF risk factors and African American race) - were invited to participate in a brief clinic visit (2015-2016) followed by 48-hour aECG. There were 716 African American and 438 White participants, after excluding 52 participants from our analysis for poor quality measures, and paced rhythm. Participants provided written informed consent, and the study was approved by the Institutional Review Boards at the field centers, the Collaborative Studies Coordinating Center, and the Epidemiology Cardiology Research Center (EPICARE).

Sleep apnea was defined as hospital discharge International Classification of Diseases, Ninth Revision, Clinical Modification codes 327.23 (obstructive sleep apnea) or 780.57 (unspecified sleep apnea) or self-reported physician diagnosis on a standardized questionnaire at the time of the clinic visit. The standardized questionnaire included the following questions: 1) Have you ever been told by a doctor that you have sleep apnea?; 2) Have you had any treatment for sleep apnea?; 3) Have you ever used a CPAP or BIPAP machine for sleep apnea, which are breathing machines you wear when sleeping?; 4) Have you ever used a mouth piece for sleep apnea that you wear when sleeping?; and 5) Have you ever had surgery for sleep apnea, called UPPP which is to remove extra tissue in your throat so the airway is wider?. If participants answered yes to the first question, they were considered to have sleep apnea and asked the rest of the questions.

Atrial fibrillation was defined as AF on: 1) study visit ECGs, or hospital discharge code (427.3) since study visit 1 in 1987-1989, or 2) 48-hour aECG. We defined presence of ectopy-PACs and PVCs measured by 48-hour aECG-as 1-5% (occasional) and >5% (frequent) of the recording time as compared to <1% of the recording time (referent). These thresholds are based on the percentile of our population that might represent abnormal since there are no clinical thresholds. Anthropometric, blood pressure measurements, serum cholesterol and glucose measures were completed at ARIC study visit 5 (2011-2013) using standardized methodology. Hypertension and diabetes were defined based on self-reported medication use, prior history of either condition, and relevant measures from Visit 5. Medication use was defined with self-report and medication bottles. Prevalent coronary heart disease and stroke prior to this study visit were defined using standardized methodology for events classification.

Logistic regression with inverse variance weighting to account for sampling and non-response was used to examine the association between sleep apnea and each of the study outcomes (Table). Binary logistic regression was used for atrial fibrillation and ordinal logistic regression was used for PACs and PVCs. Model 1 included only age, gender, and

race-center and Model 2 includes the covariates of Model 1 along with the confounders identified in the literature<sup>2,3</sup> examining the association between sleep apnea and cardiac arrhythmias including education, body mass index, current smoking, diabetes, total cholesterol, hypertension, and use of antiarrhythmic/ vasoactive medication.

Sleep apnea was identified in 217 participants of which 32 were identified by ICD-9 CM codes, 108 were self-reported and 24 were both self-reported and had a prior ICD-9 CM code. Of note, of the 32 that self-reported, 27 also reported prior treatment for SA including CPAP, BiPAP, prior surgery or mouth piece. The following characteristics were significantly different ( $p<0.05$ ) in those with SA compared to those without SA: female (55% vs. 66%), White race (52% vs. 45%), current smoker (57% vs. 49%), diabetes mellitus (44% vs. 30%), and prevalent coronary heart disease (14% vs. 9%). The following characteristics were not significantly different ( $p<0.05$ ) in those with SA compared to those without SA: high school education or beyond (88% vs. 82%), hypertension (82% vs. 78%), obesity (57% vs. 36%), and prevalent stroke (3.2% vs. 4%).

Atrial fibrillation (N=152) was identified in 6%. The frequencies of occasional and frequent PVCs were 10% and 5%, respectively, and 13% and 5% for occasional and frequent PACs. The multivariable adjusted odds ratios comparing those with sleep apnea to those without for the outcome of AF was 7.3 (95% CI: 3.7-14.5), and for the outcomes of occasional PACs and frequent PACs were 1.2 (0.7, 1.9) and 1.5 (0.7, 3.2). The findings for PVCs were non-significant for both frequent and occasional PVCs, and not in the expected direction for frequent PVCs.

To our knowledge, this is the first study to use 48-hour continuous aECG to examine the association between sleep apnea and AF, PVCs, and PACs in a community-based population. Although self-report and under diagnosis of sleep apnea may be a study limitation,<sup>5</sup> we used a standardized approach to include cases recognized clinically and those identified using a standardized questionnaire. We observed that sleep apnea was strongly associated with AF, which is similar to the findings of previous studies.<sup>2</sup> In addition, we found a positive although non-significant association for PACs. The association of sleep apnea with PACs and AF is interesting and implies that sleep apnea may result in atrial remodeling.<sup>2</sup> Evidence suggests that sleep apnea treatment may improve or reverse arrhythmias by modifying physiologic pro-arrhythmic factors<sup>2</sup>. The positive association between sleep apnea and AF emphasizes the importance of sleep apnea in addressing the burden of cardiac arrhythmias.

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## Non-standard Abbreviations and Acronyms:

<b>AF</b>	Atrial Fibrillation
<b>PVC</b>	Premature Ventricular Contractions
<b>PAC</b>	Premature Atrial Contractions
<b>aECG</b>	Ambulatory Electrocardiogram
<b>ARIC</b>	Atherosclerosis Risk in Communities study
<b>CPAP</b>	Continuous Positive Airway Pressure
<b>BIPAP</b>	Bilevel Positive Airway Pressure
<b>UPPP</b>	Uvulopalatopharyngoplasty
<b>EPICARE</b>	Epidemiology Cardiology Research Center

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The association between sleep apnea and atrial fibrillation, PAC, and PVC as measured by 48-hour aECG

**Table.**

Measure of association	N (weighted)	Model 1* OR (95% CI)	Model 2† OR (95% CI)
<b>Atrial fibrillation prevalence</b>	152	9.3 (5.2, 16.8)	7.3 (3.7, 14.5)
<b>Premature atrial contractions (PAC)</b>			
>5% (Frequent)	107	1.7 (0.9, 3.6)	1.5 (0.7, 3.2)
1-5% (Occasional)	316	1.3 (0.8, 2.0)	1.2 (0.7, 1.9)
<1% (Referent)	1936	Referent	Referent
<b>Premature ventricular contractions (PVC)</b>			
>5% (Frequent)	119	0.9 (0.4, 2.0)	0.8 (0.4, 1.9)
1-5% (Occasional)	246	1.2 (0.7, 1.9)	1.1 (0.6, 1.8)
<1% (Referent)	1994	Referent	Referent

Ambulatory electrocardiography ECG), odds ratio (OR)

\* Adjusted for age, gender and race-center

† Adjusted for age, gender, race-center, education, body mass index, current smoking, diabetes, hypertension, total cholesterol, and use of antiarrhythmic/ vasoactive medication