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Environmental Tobacco Smoke and Atrial Fibrillation: The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study

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Abstract

Objective—To examine the association between environmental tobacco smoke (ETS) exposure and atrial fibrillation.

Methods—We examined the cross-sectional association between ETS exposure and atrial fibrillation in 12,021 participants (mean age: 65 ± 9.9 years; 60% women; 40% blacks) from the REasons for Geographic And Racial Differences in Stroke study who self-identified as never smokers between 2003 and 2007.

Results—A total of 2,503 (21%) participants reported ETS exposure. In a multivariate logistic regression model adjusted for socio-demographics and potential confounders, ETS exposure was significantly associated with atrial fibrillation (OR=1.27, 95%CI=1.08, 1.50).

Conclusions—Our findings suggest that the harmful effects of ETS exposure extend to sustained arrhythmias such as atrial fibrillation.

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Conflicts of Interest: None.

Keywords

environmental tobacco smoke; arrhythmia; epidemiology

Introduction

Environmental tobacco smoke (ETS) exposure has been associated with an increased risk for the development of cardiovascular disease. A positive association has been observed between ETS exposure and elevated blood pressure among non-smoking Japanese women (1). Data from INTERHEART and CARDIO2000 have implicated ETS exposure in the etiology of acute myocardial infarction (MI) (2, 3). Other reports have implicated ETS exposure with an increased risk of cardiovascular-related mortality (4). Increased levels of inflammatory markers and oxidative stress have been observed in persons exposed to ETS and potentially contribute to the increased risk of adverse cardiovascular events in this population (5).

Epidemiological studies have shown an association between ETS exposure and cardiac autonomic dysfunction as measured by reduced heart rate variability (6-8). The reduction of heart rate variability is associated with an increased susceptibility to the development of arrhythmias (9). These findings provide biological plausibility for a potential association between ETS and sustained arrhythmias, such as atrial fibrillation (AF). However, to our knowledge, this hypothesis has not been examined. Therefore, the purpose of this study was to examine the cross-sectional association between ETS exposure and AF in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study.

Methods

Study Population and Design

Details of REGARDS have been published previously (10). Briefly, this prospective cohort study was designed to identify causes of regional and racial disparities in stroke mortality. The study population over sampled blacks and residents of the stroke belt (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana). This included participants from the stroke buckle (coastal plains of North Carolina, South Carolina and Georgia) as this region experiences a stroke mortality rate considerably higher than the rest of the United States (11). Between January 2003 and October 2007, 30,239 black and white participants were recruited from a commercially available list of residents using postal mailings and telephone data. Demographic information and medical histories were obtained using a computer-assisted telephone interview (CATI) system. Additionally, a brief in-home physical examination was performed approximately 3 to 4 weeks after the telephone interview. During the in-home visit, trained staff collected information regarding medications, blood and urine samples, and a resting electrocardiogram. All participants provided written informed consent and the study was approved by the institutional review boards of all participating universities.

This analysis examined the cross-sectional association between ETS exposure and AF in REGARDS. Of the 30,239 participants in the REGARDS cohort, 56 were excluded for data anomalies. Participants also were excluded if they were missing smoking data (n=1,063), AF data (n=660), baseline covariates (n=1,912), or reported a history of smoking, either current or in the past (more than 100 cigarettes) (n=14,527).

Environmental Tobacco Smoke

ETS exposure was assessed with the following question: “During the past year, about how many hours per week, on average, were you in close contact with people when they were smoking? For example, in your home, in a car, at work, or other close quarters.” Participants who reported more than 1 hour per week of passive smoke exposure were defined as the ETS group. This classification scheme has been reported previously (12).

Atrial Fibrillation

AF was identified by the study electrocardiogram and also from self-reported history of a previous diagnosis by a physician. The electrocardiograms were read and coded at a central reading center (Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Winston-Salem, NC). Self-reported AF was defined as an affirmative response to the following question: “Has a physician or a health professional ever told you that you had atrial fibrillation?”(13).

Covariates

Age, sex, race, income, and education were self-reported. Annual household income was dichotomized at <\$20,000 or ≥\$20,000. Education was categorized into “high school or less,” or “some college or more.” Fasting blood samples were obtained and assayed for total cholesterol, high-density lipoprotein (HDL) cholesterol, C-reactive protein, and glucose. Diabetes was defined as a fasting glucose level ≥126 mg/dL (or a non-fasting glucose ≥200 mg/dL among those failing to fast) or self-reported diabetes medication use. Aspirin, antihypertensive, and lipid-lowering medication use were defined by the self-reported current use of these medications. Body mass index was computed as the weight in kilograms divided by the square of the height in meters. Weight and height were measured during the in-home examination. After the participant rested for 5 minutes in a seated position, blood pressure was measured using a sphygmomanometer. Two values were obtained following a standardized protocol and averaged. Using baseline electrocardiogram data, left ventricular hypertrophy was defined by the Sokolow-Lyon Criteria (14). Cardiovascular disease was defined as a history of coronary heart disease or stroke. Coronary heart disease was confirmed by self-report of prior MI, coronary artery bypass grafting, coronary angioplasty or stenting, or if evidence of prior MI was present on the baseline electrocardiogram. Electrocardiographic evidence of MI was defined by Minnesota code classification as major Q waves (Minnesota codes 1.1 and 1.2) or minor Q waves (Minnesota code 1.3) plus major ST/T wave abnormalities (Minnesota codes 4.1, 4.2, 5.1, 5.2). Prior stroke also was ascertained by participant self-report.

Statistical Analyses

Categorical variables were reported as frequency and percentage while continuous variables were reported as mean $\pm$ standard deviation. Statistical significance of differences for categorical variables was tested using the chi-square method and the Wilcoxon rank sum procedure for continuous variables. Logistic regression was used to compute odds ratios (OR) and 95% confidence intervals (CI) for the association between ETS and AF. Multivariate models were adjusted as follows: Model 1 adjusted for age, sex, race, education, income, and geographic region; Model 2 included covariates in Model 1 with the addition of systolic blood pressure, HDL cholesterol, total cholesterol, body mass index, diabetes, antihypertensive medications, lipid-lowering therapies, left ventricular hypertrophy, and cardiovascular disease. Subgroup analyses were performed by age (dichotomized at 65 years), sex (male vs. female), race (black vs. white), and cardiovascular disease (yes vs. no) using a stratification technique and by comparing models with and without interaction terms. As an additional analysis we included ever smokers (n=14,527), defined as current or past smoker, regardless of ETS exposure to examine the magnitude of the association between ETS exposure and AF compared with ever smokers. A sensitivity analysis also was performed with further adjustment for C-reactive protein due to the known association between inflammation and AF (15). Statistical significance for all comparisons including interactions was defined as $p < 0.05$. SAS[®] Version 9.3 (Cary, NC) was used for all analyses.

Results

A total of 12,021 study participants (mean age: 65 ± 9.9 years; 60% women; 40% blacks) were included in the primary analysis. There were 2,503 (21%) participants who reported ETS exposure. The prevalence of AF was higher for those with ETS exposure (8.5%) compared with those without (7.6%). Figure 1 shows the prevalence of AF by ETS exposure in all participants and in subgroups stratified by age, sex, race, and cardiovascular disease.

Table 1 shows the baseline characteristics of participants by ETS exposure. Participants exposed to ETS were more likely to be younger, black, to have diabetes, to reside in the stroke belt, and to have lower educational attainment and income compared with those without ETS exposure. Participants with ETS exposure also were more likely to have higher values for body mass index, systolic blood pressure, and total cholesterol than those without ETS exposure.

In a model adjusted for age, sex, race, income, and education, ETS exposure was associated with AF (OR=1.30, 95%CI=1.10, 1.53) (Table 2). After further adjustment for cardiovascular risk factors and potential confounders, the association between ETS exposure and AF remained statistically significant (OR=1.27, 95%CI=1.08, 1.50) (Table 2). In a sensitivity analysis adjusted for C-reactive protein, the association between ETS exposure and AF remained statistically significant (OR=1.26, 95%CI=1.06, 1.49).

In a subgroup analysis by race, a stronger association was observed between ETS exposure and AF for black (OR=1.63, 95%CI=1.27, 2.08) compared with white (OR=1.03, 95%CI=0.82, 1.30) participants (p -interaction=0.0007) (Table 3). When we included ever

smokers in the analysis, the associations of ETS exposure (OR=1.27, 95% CI=1.08, 1.50) and past smoking (OR=1.18, 95% CI=1.07, 1.30) with AF were statistically significant.

Discussion

In this analysis from REGARDS, ETS exposure was significantly associated with prevalent AF. A differential association was observed by race with black participants having a stronger association between ETS exposure and AF compared with whites. The magnitude of the association was higher than that observed among ever smokers.

Several reports have implicated ETS as an independent risk factor for the development of cardiovascular disease (1-4, 16). To our knowledge, our findings are the first to suggest that the harmful effects of ETS exposure extend to arrhythmias such as AF. Our findings also show that the association between ETS and AF is stronger for blacks compared with whites. Interestingly, a higher prevalence of AF has been reported in whites than blacks (17). However, racial differences in susceptibility to tobacco smoke among patients with chronic obstructive pulmonary disease have been reported with blacks losing more lung function per pack-year compared with whites (18). Therefore, it is possible that similar differences exist regarding susceptibility to ETS exposure which results in blacks having a higher risk of AF compared with whites.

ETS exposure has been associated with increased levels of inflammatory biomarkers and decreased heart rate variability, a measure of cardiac autonomic dysfunction (5-8). Alterations in the inflammatory response have been linked to AF development (15). Higher levels of inflammation associated with ETS exposure possibly predispose to AF through the activation of atrial ectopic foci near the pulmonary vein ostia. However, the association between ETS and AF remained significant with further adjustment for C-reactive protein. Additionally, data from animal models support an association between decreased heart rate variability and arrhythmogenesis (9). In aggregate, the aforementioned findings provide biological plausibility that passive tobacco smoke increases the risk for AF development.

The association between active smoking and AF development remains controversial. Data from the Framingham Heart Study have shown that smoking is an independent risk factor for AF in women but not men (19). Similarly, data from the Rotterdam Study, Atherosclerosis Risk in Communities Study, and Manitoba Follow-up Study have shown an increased risk for AF in men and women among current and past smokers (20, 21). In contrast, data from the Danish Diet, Cancer, and Health Study failed to show an association between smoking and AF (22). Our results support that ever smokers are more likely to have prevalent AF and this association extends to ETS exposure.

Recently, public health policies have attempted to limit ETS exposure through the implementation of smoking bans in public areas and reductions in cardiovascular outcomes have been reported. In New York State, an 8% reduction in admissions for acute MIs was observed after the implementation of a state-wide law prohibiting indoor smoking in workplaces, restaurants, and bars (23). A similar law in Arizona was associated with nearly 13% fewer admissions for MI, 33% fewer admissions for unstable angina, and 14% fewer

admissions for stroke (24). Increased levels of inflammatory markers and oxidative stress have been observed in persons with ETS exposure and these abnormalities possibly lead to an increased risk for cardiovascular disease development (5). These data provide additional evidence of the harmful effects of ETS exposure and the substantial health benefits from comprehensive bans on smoking. Given that reductions in hospital admissions for several cardiovascular outcomes have been reported, these policies possibly improve outcomes related to arrhythmias such as AF. However, to our knowledge no studies have explored this hypothesis. AF represents a substantial burden to the healthcare system with incremental costs projected between \$6 billion for AF-related care and \$26 billion for AF-related care plus other cardiovascular and non-cardiovascular care (25). As we strive for more cost-effective options within our healthcare system, smoking bans possibly have a role to reduce the burden of AF, including cost.

Our results should be interpreted in the context of certain limitations. Exposure to ETS was self-reported and subjected our analysis to recall bias and subsequent misclassification bias. Non-permanent AF cases possibly were missed due to the time-dependent nature of various AF events (e.g., paroxysmal). The intensity of ETS exposure was not quantified and the relationship between ETS and AF potentially varies by exposure duration. Additionally, we were unable to establish the temporal relationship between ETS exposure and AF due to the cross-sectional design of the current study. However, it is unlikely that AF would lead to ETS exposure, but the opposite is more plausible (e.g., ETS exposure leads to AF). Furthermore, we adjusted for several potential confounders but acknowledge that residual confounding remains a possibility similar to other epidemiologic studies. For example, we were unable to account for left atrial diameter and it is possible that ETS exposure is associated with left atrial enlargement which predisposes to AF development.

In conclusion, we have shown that ETS exposure is associated with prevalent AF in REGARDS and the magnitude of this association is stronger in blacks compared with whites. Further research is needed to confirm our findings and to determine the temporal relationship between ETS exposure and AF development.

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Figure 1. Prevalence of Atrial Fibrillation (N=12,021)

*Denotes statistically significant difference ($p < 0.05$).

CVD=cardiovascular disease; ETS=environmental tobacco smoke.

Table 1
Baseline Characteristics (N=12,021)

Characteristic	No ETS Exposure (n=9,518)	ETS Exposure (n=2,503)	P-value*
Age, mean (SD), years	65 (10)	62 (9.1)	<0.0001
Male (%)	3,455 (36)	870 (35)	0.15
Black (%)	3,616 (38)	1,172 (47)	<0.0001
Region			
Stroke buckle (%)	2,054 (22)	562 (22)	
Stroke belt (%)	3,250 (34)	905 (36)	
Non-belt (%)	4,214 (44)	1,036 (41)	0.034
Education, high school or less (%)	3,177 (33)	985 (39)	<0.0001
Annual income, <\$20,000 (%)	1,429 (15)	476 (19)	<0.0001
Body mass index, mean (SD) kg/m ²	29 (6.4)	30 (6.2)	<0.0001
Diabetes (%)	1,753 (18)	532 (21)	0.0013
Systolic blood pressure, mean (SD), mm Hg	126 (16)	127 (17)	0.032
Total cholesterol, mean (SD), mg/dL	193 (39)	197 (40)	<0.0001
HDL cholesterol, mean (SD), mg/dL	53 (16)	53 (16)	0.29
Aspirin use (%)	3,867 (41)	960 (38)	0.039
Antihypertensive medication use (%)	4,684 (49)	1,333 (53)	0.0003
Lipid-lowering medication use (%)	2,875 (30)	720 (29)	0.16
Left ventricular hypertrophy (%)	1,027 (11)	303 (12)	0.062
Cardiovascular disease (%)	1,645 (17)	401 (16)	0.13

* Statistical significance for categorical variables was tested using the chi-square method and for continuous variables the Wilcoxon rank sum procedure was used.

ETS=environmental tobacco smoke; HDL=high-density lipoprotein; SD=standard deviation.

Table 2
Association between Environmental Tobacco Smoke Exposure and Atrial Fibrillation (N=12,021)

	AF Cases	Model 1* OR (95%CI)	P-value	Model 2† OR (95%CI)	P-value
No ETS Exposure	720/9,518	1.0	-	1.0	-
ETS Exposure	213/2,503	1.30 (1.10, 1.53)	0.0018	1.27 (1.08, 1.50)	0.0049

* Adjusted for age, sex, race, education, income, and geographic region.

† Adjusted for Model 1 covariates with the addition of systolic blood pressure, HDL cholesterol, total cholesterol, body mass index, diabetes, antihypertensive medications, lipid-lowering therapies, left ventricular hypertrophy, and cardiovascular disease.

CI=confidence interval; ETS=environmental tobacco smoke; HDL=high-density lipoprotein; OR=odds ratio.

Table 3
Subgroup Analyses by Age, Sex, Race, and Cardiovascular Disease (N=12,021)

	Model 1* OR (95%CI)	P-value	Model 2† OR (95%CI)	P-value	Interaction‡ P-value
Age					
<65 years	1.29 (1.02, 1.62)	0.031	1.26 (1.00, 1.59)	0.050	0.30
65 years	1.15 (0.91, 1.46)	0.23	1.15 (0.91, 1.46)	0.23	
Sex					
Female	1.32 (1.08, 1.61)	0.0077	1.28 (1.05, 1.58)	0.017	0.25
Male	1.26 (0.95, 1.66)	0.11	1.21 (0.91, 1.61)	0.19	
Race					
Black	1.65 (1.30, 2.10)	<0.0001	1.63 (1.27, 2.08)	0.0001	0.0007
White	1.06 (0.85, 1.34)	0.59	1.03 (0.82, 1.30)	0.80	
Cardiovascular disease					
No	1.25 (1.02, 1.54)	0.029	1.24 (1.01, 1.52)	0.041	0.42
Yes	1.35 (1.02, 1.80)	0.038	1.37 (1.03, 1.82)	0.033	

* Adjusted for age, sex, race, education, income, and geographic region.

† Adjusted for Model 1 covariates with the addition of systolic blood pressure, HDL cholesterol, total cholesterol, body mass index, diabetes, antihypertensive medications, lipid-lowering therapies, left ventricular hypertrophy, and cardiovascular disease.

‡ Interactions tested using Model 2 covariates.

CI=confidence interval; HDL=high-density lipoprotein; OR=odds ratio.