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Secondhand Smoke Exposure and Stroke:

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study

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Abstract

Introduction—Stroke is a major public health concern worldwide given the associated morbidity and mortality. Smoking is a risk factor for stroke, but the relationship between secondhand smoke (SHS) exposure and stroke has been inconsistent to date. The aim of the current study was to examine the association of SHS exposure and risk of stroke and its subtypes (ischemic and hemorrhagic stroke) among nonsmokers.

Methods—Demographic and clinical characteristics were compared by SHS exposure status for black and white nonsmokers aged ≥45 years in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study in 2014. Hazard ratios (HRs) and corresponding 95% CIs were calculated by Cox proportional hazards models to assess the relationship between SHS exposure and stroke risk.

Results—Of the 21,743 participants (38% African American, 45% male), SHS exposure in the past year was reported by 23%. Compared with those without SHS exposure, exposed participants were more likely to be female, white, younger, and reside with a smoker (all $p<0.001$). A total of 428 incident strokes were observed from April 2003 to March 2012 during a mean follow-up of 5.6 years. The risk of overall stroke was increased 30% among those with SHS exposure after adjustment for other stroke risk factors (95% CI=2%, 67%). This relationship appeared to be driven by ischemic strokes.

Conclusions—SHS exposure is independently associated with an increased risk of stroke. Future studies are needed to confirm these findings and examine the role of long-term effects of SHS exposure on stroke outcomes.

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Introduction

In 2010, stroke and ischemic heart disease accounted for one in four deaths globally, an increase from one in five deaths two decades prior.[1] Stroke is the fourth leading cause of death in the U.S., responsible for one of every 19 deaths.[2,3] It is also a leading cause of disability.[4] Nearly 800,000 people in the U.S. suffer a stroke each year, the large majority of whom are ischemic.[2] In addition, stroke incidence remains very high among African Americans, with risk of first stroke twice that of whites.[5]

Risk factors for stroke include smoking,[6] hypertension,[7] and atrial fibrillation.[8] Stroke risk is reduced by lowering blood pressure (BP) levels to <120/80 mm/Hg[8,9] and through physical activity.[10,11] Previous studies reported a relationship between secondhand smoke (SHS) exposure and increased risk of stroke.[12–21] However, not all studies have found an association.[14,21–23] Whincup et al.[23] evaluated the relationship between high versus low cotinine levels and stroke in male nonsmokers (hazard ratio [HR]=0.77, 95% CI=0.42, 1.41) and never smokers (HR=2.16, 95% CI=0.80, 5.80) and found no association with stroke after multivariable adjustment.

Exposure to SHS is concerning, as 18% of the U.S. adult population currently smokes.[24] Furthermore, elevated serum cotinine levels (≥0.05 ng/mL) were observed among 40% of nonsmoking adults participating in the 1999–2010 National Health and Nutrition Examination Survey, with exposure at work reported by 14% and at home by 6%.[25] Compared with individuals without environmental tobacco smoke (ETS) exposure, the risk of mortality from coronary heart disease was 25%–35% higher for those with low ETS exposure by an earlier review.[26] Development of carotid artery intimal-medial thickness, a risk factor for stroke,[27] has been associated with short- (3 years) and long-term (10 years) SHS exposure.[28,29] Proposed mechanisms for how SHS exposure increases stroke risk include increased thrombogenicity and higher fibrinogen levels, lower high-density lipoprotein (HDL) cholesterol levels, carboxyhemoglobinemia, hemodynamic and autonomic effects, acute endothelial dysfunction, oxidative stress, and progression of atherosclerosis due to 1,3-butadiene or other toxic compounds found in cigarette smoke.[6,30,31]

The aim of the current study was to examine the association between SHS exposure and risk of stroke and stroke subtypes (ischemic and hemorrhagic stroke) among nonsmokers after accounting for stroke risk factors and to evaluate potential confounding factors of any observed association. The potential relationships between SHS exposure and stroke were investigated by testing the hypotheses that: (1) higher prevalence of SHS exposure is associated with increased incidence of stroke; and (2) higher prevalence of SHS exposure is associated with increased incidence of stroke subtypes.

Methods

Study Design

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is a national, population-based, longitudinal study investigating cardiovascular disease events

and mortality endpoints among white (55%) and African American (45%) adults aged ≥45 years.[32] The cohort includes participants (55% female) from the 48 contiguous U.S. states. The study received IRB approval from all participating institutions, and study participants provided written informed consent. The methods were published previously.[32]

Briefly, demographic characteristics, SES, and medical history were obtained and a risk factor evaluation carried out (including smoking status and SHS exposure) during a baseline telephone interview conducted between 2003 and 2007. In-home examinations followed and involved physical, clinical, and laboratory measurements including height, weight, BP, lipid profiles, glucose, and an electrocardiogram (ECG). Participants are called every 6 months for follow-up, with the main goals of ascertaining potential stroke events and cognitive impairment.

Measures

At baseline, current smoking was defined as active smoking among those who smoked >100 cigarettes in their lifetime. Former smoking was defined as non-current use and smoking >100 cigarettes in their lifetime. Pack years smoked was calculated for former smokers by multiplying the number of packs smoked per day by the years of smoking. The remainder of participants was classified as nonsmokers. Current smokers were excluded from the analysis. SHS exposure was assessed by duration (*Does anyone living with you smoke cigarettes regularly?*) and frequency (*During the past year, about how many hours PER WEEK, on the 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?*). The primary exposure, exposure to SHS, was defined as >1 hour per week in close contact with a smoker(s).[28,33] Thus, individuals reporting 0–1 hour of SHS exposure per week were characterized as not exposed. Continuous SHS exposure was truncated to 168 hours for 17 individuals who reported exposure exceeding the maximum number of hours in a week.

Race was self-reported as African American or white. Stroke belt region was defined as residing within a region of the country with excess stroke mortality spanning eight southeastern states of Alabama, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, and Arkansas.[34] Education was dichotomized as high school or less versus greater than high school, and annual income was categorized as <$20,000, $20,000–$35,000, $35,000–$75,000, ≥$75,000, or refused to report, and dichotomized as <$35,000 versus ≥$35,000 in the model.

Alcohol consumption was categorized as never versus ever based on self-report. Self-reported exercise was characterized as none or exercising “enough to work up a sweat” one to three times per week or four or more times per week, with further categorization for the model into none versus one or more time per week.

Baseline BMI was calculated as kg/m^2 using measured weight (kg) and height (m) and was categorized as underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), or obese (>30).[35] Waist circumference (cm) was measured, and serum chemistries, C-reactive protein (CRP) (mg/L), and white blood cell count were measured using standard methods at the University of Vermont in Burlington, Vermont.[36] Diabetes was defined as fasting glucose

≥126 mg/dL, non-fasting glucose ≥200 mg/dL, or self-reported use of diabetic medication or insulin. Left ventricular hypertrophy (LVH) was classified according to the Sokolow–Lyon LVH limb lead criteria.[37] Dyslipidemia was defined as total cholesterol ≥240 mg/dL, low-density lipoprotein ≥160 mg/dL, HDL ≤40, or self-reported use of lipid-lowering medication.

A trained technician measured systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the in-home visit using a standard protocol. Hypertension was defined as SBP ≥140, DBP ≥90, or by self-reported current use of antihypertensive medication. History of heart disease was determined by self-reported diagnoses of myocardial infarction (MI), coronary artery bypass graft, bypass, angioplasty or stenting, or by evidence of MI on ECG. Atrial fibrillation was determined by ECG evidence as recorded during the in-home visit or by self-report. Factors included in the Framingham Stroke Risk Score were age, diabetes mellitus, history of cardiovascular disease, atrial fibrillation, current antihypertensive medication use, SBP, and LVH.[38]

Fatal and non-fatal incident stroke occurring after the baseline survey was the primary outcome measure among those stroke-free at baseline. Events reported during follow-up as potential stroke, transient ischemic attack (TIA), death, hospitalization, or emergency department visit for brain aneurysm, brain hemorrhage, stroke symptoms, or unknown reason prompted a request for medical records. Those deemed potential strokes after nurse review were centrally adjudicated by physicians. For deaths without medical records, death certificates were examined and adjudicated, and interviews with surviving family members undertaken. Stroke was defined in four ways:

1. medical records confirmed focal neurological deficit for ≥24 hours;
2. medical records confirmed focal/nonfocal neurologic deficit with imaging verification;
3. stroke as underlying cause of death available from National Death Index (NDI) (ICD-10: I60–I67, I69, I672, I678–I679, G450–453 and G46) without medical record; and
4. probable stroke determination made during review of proxy interview.

Although the overall analysis included all four definitions of stroke, the subtype analysis did not include NDI and exit interview defined stroke, owing to unavailability of stroke subtype information.

Statistical Analysis

Demographic and clinical characteristics were summarized overall and by SHS exposure. Differences between SHS exposure groups were tested using chi-square tests, *t*-tests, and the Mann–Whitney *U* test. Crude incidence rates and corresponding 95% CIs were estimated for stroke and its subtypes by SHS exposure. Cox proportional hazards models were performed to determine whether the risk of stroke and stroke subtypes differed by SHS exposure. Survival times were censored at first stroke event (date of stroke), date of death occurring prior to stroke, or date of the last completed follow-up. Univariate models were fit, followed

by models with adjustment for demographics (age, race, sex, and the age–race interaction) and SES factors (income and educational level), then with the addition of smoking history and Framingham Stroke Risk Score factors, then with the addition of CRP, and finally with the addition of BMI and lifestyle/behavioral factors (alcohol use and exercise). An age–race interaction was identified by earlier REGARDS analyses and defined a priori. Models were fit for all participants, then separately for never smokers and former smokers to further explore the relationship between SHS exposure and risk of stroke and stroke subtypes. Overall models with adjustment beyond demographics and SES factors also adjusted for smoking history (former versus never). Models for former smokers with adjustment beyond demographics and SES factors additionally adjusted for pack years smoked. The proportional hazards assumption was examined using log–log plots and was met for any stroke event and ischemic stroke but was not met for every stratum of hemorrhagic stroke. Statistical analyses were performed in 2014 using SPSS, version 21.[39]

Results

The REGARDS parent study included a total of 30,239 individuals, of whom 21,743 were included in the overall stroke analysis and 21,717 were included in stroke subtype analyses (based on exclusion of 26 individuals missing stroke subtype information). Figure 1 shows a flow diagram for inclusion of participants.

Table 1 presents demographic and clinical characteristics stratified by SHS exposure. Of 21,743 participants, 23% (*n*=5,081) reported SHS exposure in the past year and 77% (*n*=16,662) reported no SHS exposure. Individuals reporting SHS exposure were significantly younger (62.9 [SD=8.7] vs 65.6 [SD=9.5] years) and more likely to be white (56% vs 44%), female (53% vs 47%), and with lower education levels (all $p<0.001$) than those without exposure. Certain clinical characteristics and lifestyle/behavioral factors differed among those with SHS exposure and those without SHS exposure. However, history of cardiovascular disease, atrial fibrillation, LVH, Framingham Stroke Risk Score, and region of residence (belt versus non-belt) did not differ significantly between the two groups.

Demographic and clinical characteristics of former and never smokers were further examined by SHS status (Appendix Table 1). Of the 5,081 participants reporting SHS exposure, 53% (*n*=2,668) were former smokers. Forty-four percent (*n*=7,411) of those without SHS exposure (*n*=16,662) were former smokers. Associations between SHS exposure and risk factors were similar for never and former smokers reporting SHS exposure but differed among those without SHS exposure.

This analysis included events from April 2003 to March 2012. The average follow-up time for all participants was 5.6 (SD=1.9) years (median, 6.0; range, 0–9), and 428 stroke events were observed (352 ischemic, 50 hemorrhagic, and 26 strokes of unknown subtype). Stroke incidence rates are presented by SHS exposure in Table 2.

We hypothesized that higher prevalence of SHS exposure in the past year would be associated with increased risk of stroke and its subtypes. Crude and adjusted HRs for all

nonsmoking participants and for never and formers smokers are displayed in Table 3. In unadjusted models, the risk of stroke did not differ significantly between those exposed to SHS and those without exposure. However, after adjustment for demographic and SES covariates, SHS exposure was associated with increased risk of stroke (HR=1.31, 95% CI=1.03, 1.65) among nonsmoking participants. Further adjustment did not change the HRs meaningfully, suggesting these factors were not confounders, although the association was no longer significant in the final multivariable model.

Next, the relationship between SHS exposure and stroke subtype was assessed. Upon adjustment for demographic and SES covariates, the HR for ischemic stroke was 1.29 (95% CI=1.00, 1.68). The risk of ischemic stroke with SHS exposure remained non-significantly elevated for all nonsmokers, never smokers, and former smokers for the remaining models. There was no association between SHS exposure and hemorrhagic stroke.

Additional models were performed including SHS exposure as a continuous variable. Trends for any stroke were similar to those observed when dichotomizing SHS exposure, although an association was observed for hemorrhagic stroke only when including SHS exposure continuously (Appendix Table 2).

Discussion

The main findings of this study were that the risk of stroke was 30% higher among those reporting SHS exposure than those not reporting such exposure, and appeared to be driven by ischemic strokes. This finding existed independent of demographics, SES factors, smoking history, Framingham Stroke Risk factors, and CRP concentration, and although there was no confounding by lifestyle factors, statistical significance was lost after adjustment for these.

These findings are consistent with prior studies, meta-analyses, and government reports demonstrating increased stroke risk among nonsmokers exposed to SHS.[14–16,18,20,21,40] One meta-analysis observed a non-linear dose–response relationship between SHS and stroke.[18] Specifically, the risk of stroke was highest for those exposed to 40 cigarettes per day compared with those without exposure (HR=1.56, 95% CI=1.25, 1.96), although an association was also present for five cigarettes per day.[18] A U.S. study of never smokers found an association between 20 hours or more of SHS exposure per week at home and stroke overall (relative risk [RR]=1.42, 95% CI=1.08, 1.88) and among women.[14] An increased risk of stroke was observed for never smokers (HR=1.42, 95% CI=1.05, 1.93), former smokers (HR=1.72, 95% CI=1.33, 2.22), and men and (cigarette-smoking) women with spouses who smoke.[12,40] Therefore, several studies have reported associations between SHS exposure and stroke.

However, not all studies have replicated the association between SHS exposure and stroke.[14,21–23] A 2004 British study comparing high (2.8–14 ng/mL) versus low (<0.7 ng/mL) serum cotinine levels among male nonsmokers observed a non-significantly decreased risk of stroke after covariate adjustment (HR=0.77, 95% CI=0.42, 1.41) and a non-significantly increased risk for never smokers (HR=2.16, 95% CI=0.80, 5.80).[23] SHS

exposure, assessed by cotinine levels (0.71–15 ng/mL vs ≤0.05 ng/mL cotinine levels), was not associated with stroke among nonsmokers or when excluding former smokers in another British study.[41] Considering subtypes, a meta-analysis found no association for SHS exposure and hemorrhagic stroke (RR=0.97, 95% CI=0.68, 1.37).[21] SHS exposure was also not associated with hemorrhagic stroke among nonsmokers (OR=0.9, 95% CI=0.6, 1.5) or past smokers (OR=1.2, 95% CI=0.8, 2.0) in a 2004 Australian study.[22] No associations were observed between SHS and ischemic stroke for exposure to 1–19 hours per week at home (RR=0.95, 95% CI=0.73, 1.22), among men exposed to 20 hours or more per week at home, or for exposure outside of the home.[14]

To summarize, previous studies suffer from limitations in that few were prospective, adjustment for potential confounders has varied, stroke and SHS exposure have not been consistently defined, measurement and sources of SHS exposure have differed, stroke subtypes have not always been assessed, and some studies have been underpowered by inadequate sample size. Four prospective studies reported an overall direct association[12,14,23,40] and three reported a null association,[14,41] although one only included men.[23]

Exposure to SHS is causally associated with coronary heart disease morbidity and mortality among nonsmokers,[42] and the CDC states that the evidence for stroke is only suggestive of a relationship.[43] SHS exposure has been linked to subclinical vascular disease, as determined by coronary flow velocity reserve, coronary artery dilation, systemic atherosclerosis, aortic pressure diameter relation, and damage to the brachial artery.[28,29,44–48]

An association was found between SHS exposure and stroke following adjustment for covariates. This negative confounding effect may indicate the potential for confounding of SHS exposure with stroke risk factors. When comparing the factors individually in Model 2, an increased risk of stroke was found after adjustment for age (HR=1.44, 95% CI=1.16, 1.80). Exercise and alcohol were included separately in Model 5 and the risk of stroke was increased only following adjustment for exercise (HR=1.30, 95% CI=1.01, 1.68).

Strengths of the current study include the population-based sample of a large, prospectively followed, well-characterized cohort that includes a large proportion of African Americans and physician-adjudicated incident strokes. Furthermore, the 23% prevalence of SHS exposure found by our study is similar to that of U.S. nonsmokers in 2011–2012 (25.3%).[49]

Limitations

Limitations must also be considered, which include lack of cotinine measures to validate SHS exposure and use of self-reports to classify prevalent stroke and TIA. Statistical power to examine the risk of SHS exposure by stroke subtype may have been limited. Although no association was observed between SHS exposure and hemorrhagic stroke, the proportional hazards assumption was not met for every stratum, which may have increased the probability of type II error. The null finding may be due to the small number of hemorrhagic strokes in our cohort. Lifetime SHS exposure was also unavailable.

Conclusions

Exposure to SHS is associated with increased risk of stroke. Our findings suggest the possibility for adverse health outcomes such as stroke among nonsmokers exposed to SHS, and add to the body of evidence supporting stricter smoking regulations. Future research will need to investigate the role of cardiovascular disease risk factors in the association and explore potential exposure to additional environmental variables, such as ambient air pollutants, in relation to stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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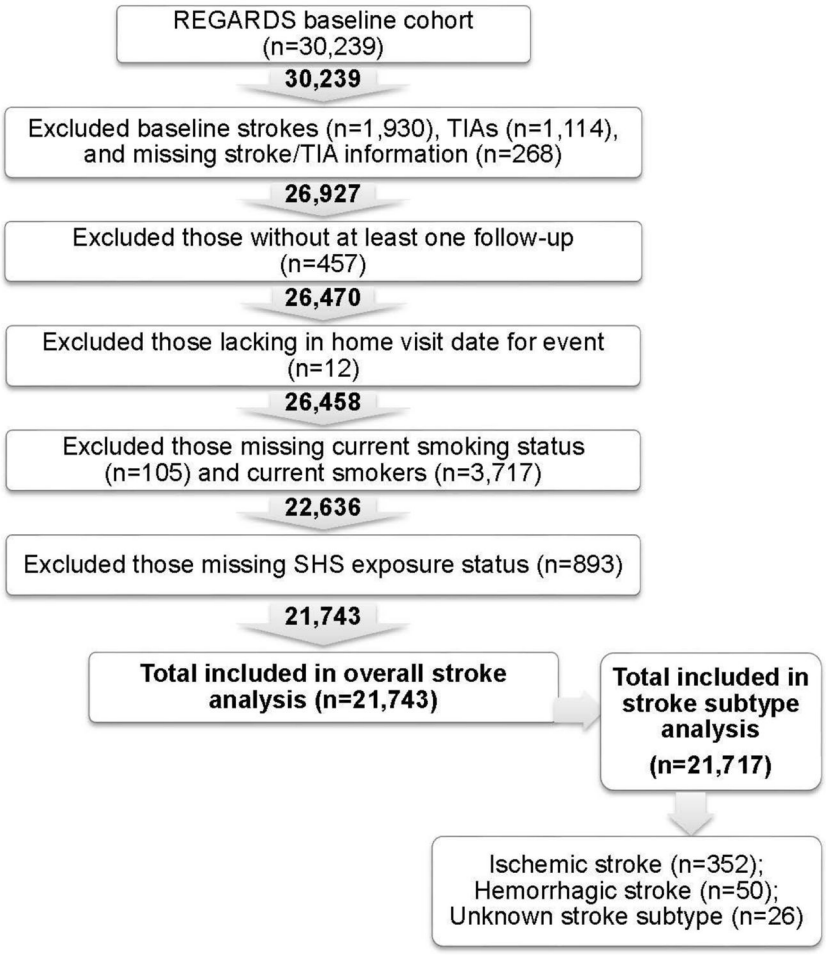

Figure 1.
Participant selection criteria.

Table 1

Demographic and Clinical Characteristics of REGARDS Participants by Exposure to Secondhand Smoke (n=21,743)

Characteristic	SHS Exposure [a] (*n* =5,081) *n* (%), mean + SD, median (range)	No SHS Exposure [b] (*n*=16,662) *n* (%), mean + SD, median (range)	*p*-value
Age (years)	62.9 + 8.7	65.6 + 9.5	**<0.001**
45–64	3,023 (60)	7,874 (47)	**<0.001**
>65	2,058 (41)	8,788 (53)	
African-American	2,231 (44)	6,106 (37)	**<0.001**
Female	2,675 (53)	9,283 (56)	**<0.001**
Region			
Belt	2,861 (56)	9,187 (55)	0.14
Non-belt	2,220 (44)	7,475 (45)	
Education			
<High school	577 (11)	1,629 (10)	**<0.001**
High school graduate	1,472 (29)	3,893 (23)	
Some college	1,434 (28)	4,348 (26)	
>College graduate	1,598 (31)	6,783 (41)	
Income, $			
<20,000	865 (17)	2,430 (15)	**<0.001**
20,000–34,000	1,258 (25)	3,804 (23)	
35,000–74,000	1,695 (33)	5,231 (31)	
>75,000	769 (15)	3,173 (19)	
Refused	494 (10)	2,024 (12)	
Alcohol consumption			
None	2,890 (57)	10,511 (63)	**<0.001**
Moderate	1,850 (36)	5,408 (32)	
Heavy	244 (5)	496 (3)	
Smoking history			
Never	2,413 (48)	9,251 (56)	**<0.001**
Former	2,668 (53)	7,441 (45)	
Reside with regular smoker	1,216 (24)	938 (6)	**<0.001**
Exercise			
None	1,533 (30)	5,277 (32)	**0.01**
1–3 times/wk	1,973 (39)	6,065 (36)	
>4 times/wk	1,507 (30)	5,113 (31)	
Atrial fibrillation	403 (8)	1302 (8)	0.80
BMI (kg/m^2)	30.1 + 6.1	29.3 + 6.1	**<0.001**
Underweight	27 (1)	126 (1)	**<0.001**
Normal	923 (18)	3,930 (24)	

Characteristic	SHS Exposure [a] (*n* =5,081) *n* (%), mean + SD, median (range)	No SHS Exposure [b] (*n*=16,662) *n* (%), mean + SD, median (range)	*p*-value
Overweight	1,873 (37)	6,266 (38)	
Obese	2,212 (44)	6,246 (37)	
Waist circumference (cm)	98.1 + 15.8	95.6 + 15.5	**<0.001**
Cardiovascular disease history	772 (15)	2,628 (16)	0.33
Diabetes	1,115 (22)	3,142 (19)	**<0.001**
C-reactive protein (mg/L), (IQR)	2.3 (4.1)	2.0 (3.7)	**<0.001**
White blood cell count	5.9 + 5.0	5.7 + 2.1	**0.048**
Systolic blood pressure (mmHg)	128 + 17	127 + 16	**<0.001**
Hypertension	3,021 (59)	9,279 (56)	**<0.001**
Hypertension, SR	2,987 (59)	9,107 (55)	**<0.001**
Dyslipidemia	2,919 (57)	9,223 (55)	**0.01**
Antihypertensive medication			
Ever	2,809 (55)	8,587 (52)	**<0.001**
Current	2,634 (52)	8,079 (48)	**<0.001**
Framingham Stroke Risk Score	5.6 (0.5 – 82.9)	6.2 (0.5 – 93.9)	0.70
Left ventricular hypertrophy	517 (10.3)	1,621 (9.9)	0.38

Note: Boldface indicates statistical significance ($p<0.05$).

SHS, secondhand smoke; $, U.S. dollar; wk, week; IQR, interquartile range; SBP, systolic blood pressure; DPB, diastolic blood pressure; SR, self-reported; med, medication; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

[a] Secondhand smoke exposure was defined as >1 hour per week in close contact with a smoker(s) in the past year.

[b] No secondhand smoke exposure was defined as 0 to 1 hour per week in close contact with a smoker(s) in the past year.

Table 2

Stroke Incidence by Exposure to Secondhand Smoke

	No. of Events	Cumulative Person-Years	Event Rate/1,000 Person- Years (95% CI)
Any stroke [a]	428	121,231	3.53 (3.20, 3.87)
SHS exposure	111	28,359	3.91 (3.22, 4.68)
No SHS exposure	317	92,872	3.41 (3.05, 3.80)
Ischemic stroke	352	121,231	2.90 (2.61, 3.21)
SHS exposure	90	28,359	3.17 (2.55, 3.86)
No SHS exposure	262	92,872	2.82 (2.49, 3.17)
Hemorrhagic stroke	50	121,231	0.41 (0.31, 0.53)
SHS exposure	12	28,359	0.42 (0.29, 0.55)
No SHS exposure	38	92,872	0.41 (0.29, 0.55)

SHS, secondhand smoke

[a]Twenty-six strokes were of unknown subtype.

Table 3

Association of Secondhand Smoke Exposure and Stroke among All Participants and Never and Former Smokers

Any Stroke		Secondhand smoke exposure (>1 hour/week over past year)				
	No. of Events	Model 1 Unadjusted	Model 2 [a]	Model 3 [b]	Model 4 [c]	Model 5 [d]
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Overall [e]	428	1.16 (0.93, 1.44)	1.31 (1.03, 1.65)	1.30 (1.02, 1.67)	1.31 (1.02, 1.69)	1.27 (0.98, 1.64)
Never smokers	217	1.07 (0.77, 1.48)	1.32 (0.94, 1.87)	1.28 (0.84, 1.84)	1.28 (0.89, 1.86)	1.17 (0.80, 1.72)
Former smokers [f]	211	1.22 (0.91, 1.63)	1.30 (0.94, 1.80)	1.33 (0.95, 1.87)	1.36 (0.96, 1.93)	1.37 (0.97, 1.95)

Ischemic Stroke		Secondhand smoke exposure (>1 hour/week over past year)				
	No. of Events	Model 1 Unadjusted	Model 2 [a]	Model 3 [b]	Model 4 [c]	Model 5 [d]
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Overall [e]	352	1.13 (0.89, 1.44)	1.29 (1.00, 1.68)	1.29 (0.98, 1.69)	1.28 (0.97, 1.69)	1.21 (0.91, 1.61)
Never smokers	184	1.11 (0.78, 1.57)	1.63 (0.94, 1.98)	1.32 (0.89, 1.96)	1.31 (0.87, 1.95)	1.17 (0.77, 1.78)
Former smokers [f]	168	1.15 (0.82, 1.60)	1.25 (0.87, 1.79)	1.27 (0.87, 1.86)	1.26 (0.85, 1.87)	1.26 (0.85, 1.87)

Hemorrhagic Stroke		Secondhand smoke exposure (>1 hour/week over past year)				
	No. of Events	Model 1 Unadjusted	Model 2 [a]	Model 3 [b]	Model 4 [c]	Model 5 [d]
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Overall [e]	50	1.04 (0.55, 2.00)	0.84 (0.38, 1.85)	0.86 (0.39, 1.91)	0.94 (0.42, 2.09)	0.95 (0.42, 2.12)
Never smokers	23	0.81 (0.28, 2.39)	0.89 (0.29, 2.72)	0.94 (0.31, 2.89)	1.04 (0.34, 3.24)	1.03 (0.33, 3.22)
Former smokers [f]	27	1.18 (0.52, 2.69)	0.80 (0.26, 2.45)	0.77 (0.25, 2.37)	0.84 (0.27, 2.61)	0.89 (0.28, 2.76)

HR, hazard ratio

[a] Model 2: Adjusted for demographics (age, race, sex, age*race), SES factors (education [<high school vs. >high school] and income [<$35,000 vs. >$35,000]).

[b] Model 3: Adjusted for demographics, SES factors, and Framingham Stroke Risk Score factors (diabetes, cardiovascular disease history, atrial fibrillation, current antihypertensive medication use, systolic blood pressure [SBP] and left ventricular hypertrophy).

[c] Model 4: Adjusted for demographics, SES factors, Framingham Stroke Risk Score factors, and C-reactive protein (CRP).

[d] Model 5: Adjusted for demographics, SES factors, Framingham Stroke Risk Score factors, BMI and lifestyle/behavioral factors (physical activity [none vs. >1 time per week], and weekly alcohol consumption [ever vs. never]).

[e] Overall models 3–5 also adjusted for smoking history (former vs. never).

[f] Models 3–5 for former smokers adjusted for pack years smoked.