



Original article

Association of secondhand tobacco smoke exposure during childhood on adult cardiovascular disease risk among never-smokers



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ABSTRACT

Purpose: Adult secondhand tobacco smoke (SHS) exposure is related to stroke and coronary heart disease (CHD) risk, but long-term effects are less clear. We evaluated whether childhood SHS exposure affects subsequent stroke or CHD risk among adult black and white never-smokers followed for stroke and CHD.

Methods: In this prospective cohort study, inverse probability weights were calculated to correct for bias due to attrition and survey nonresponse. Cox proportional hazards models were used to assess hazard ratios and 95% confidence intervals for stroke or CHD, separately, by number of childhood household smokers.

Results: Of 13,142 eligible participants, 6136 had childhood SHS exposure assessed. Baseline mean (SD) age was 63.5 (9.0), 65% were female, 30% black, 46% reported 0 childhood household smokers, 36% reported 1, and 18% reported 2+. In 60,649 person-years, 174 strokes were observed (2.9% of participants), and in 45,195 person-years, 114 CHD events were observed (2.1% of participants). The weighted and adjusted hazard ratios (95% confidence intervals) of stroke for 2+ versus 0 childhood household smokers was 1.66 (1.29–2.13) and was 1.15 (0.82–1.59) for CHD.

Conclusions: We observed a significant association between childhood SHS exposure and stroke, but not CHD, after age 45 years and adjusting for missing information.

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Introduction

Smoking is an established causal risk factor for stroke and cardiovascular disease [1–3]. In addition, numerous natural experiments (e.g., indoor smoke-free laws), case–control studies, cohort studies, and meta-analyses have shown that among nonsmokers, there is an association between secondhand tobacco smoke (SHS) exposure and stroke [4–11] and coronary heart disease (CHD) [2,12–14]. In the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, SHS was associated with a 30% increased

risk of stroke (95% confidence intervals [CIs]: 2%–67%) even adjusting for other stroke risk factors [15]. Adult smoking has decreased from 43% in 1965 to 18% in 2014 [16]; however, children have less control over exposure in their own environment [17], are more susceptible to the effects of SHS [18], and are disproportionately exposed to SHS [19]. In the National Health and Nutrition Examination Survey, the percent of children with detectable cotinine levels consistent with secondhand smoke exposure decreased from 85% of all children in 1988–1994 to 41% of children aged 3–11 years and 34% of children aged 12–19 years in 2011–2012 [20,21]. The health relevance of childhood SHS exposure is supported by previous evidence of both contemporaneous and delayed effects on respiratory health [22–25]. The Cardiovascular Risk in Young Finns Study reported that exposure to parental smoking during childhood is associated with measures of

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subclinical cardiovascular or cerebrovascular risk disease in adulthood [26–28]; however, limited data are available to assess whether childhood SHS exposure affects one's risk of stroke or CHD later in life.

The aim of the present study was to understand whether exposure to SHS as a child is associated with incident stroke and CHD risk as an adult among never-smokers in the REGARDS cohort.

Materials and methods

Study design

The REGARDS study is a nationwide prospective cohort study designed to understand racial and regional disparities in stroke mortality among blacks and whites aged 45 years or older in the 48 contiguous U.S. states. The study was approved and monitored by institutional review boards at all participating institutions, and study participants provided written informed consent. The methods [29] and a synthesis of results [30] were published previously. Briefly, participants were recruited and enrolled using mail and telephone interviews from January 2003 to October 2007. Following verbal consent, a computer-assisted telephone interview was used to collect baseline demographics and medical history, followed by an in-home examination where physical measurements, blood samples, medication inventory, and an electrocardiogram were obtained. The final cohort of 30,183 was 58% whites and 42% blacks, 55% female, and mean age at baseline of 65.3 years. Participants are followed every 6 months (on-going as of this publication) via telephone to ascertain incident medical events. In July 2012, the ancillary study Childhood and Family Life Factors was initiated to collect childhood information through a mail questionnaire to all active participants.

Measures

Smoking status of the participants was assessed at REGARDS study baseline through the question (“Have you smoked at least 100 cigarettes in your lifetime?”), and those answering affirmatively were excluded from this analysis. Current SHS was asked at baseline as well (“Does anyone living with you smoke cigarettes regularly?”). Childhood SHS was assessed through the Childhood and Family Life Factors questionnaire, which includes questions about the presence (“For most of your childhood, did you live with a regular cigarette smoker in your home?”) and number (“In your childhood, how many smokers lived in your home?”) of adult smokers in the childhood homes [31]; no specific age range was provided to define childhood.

Physician diagnosis of history of stroke and heart disease (myocardial infarction or coronary revascularization, coronary artery bypass grafting, bypass, angioplasty, or stenting) before baseline were assessed by self-report, and additionally myocardial infarction by evidence on the baseline electrocardiogram. These data were used to exclude participants who were no longer at risk for incident stroke, or CHD, for the corresponding analyses.

Outcome variables

Suspected incident stroke and CHD were ascertained by telephone follow-up every 6 months with living participants or their proxies, and medical records were retrieved for reported hospitalizations and deaths. Deaths were detected by report of family members, proxies, or sources such as the Social Security Death Index or the National Death Index, and death certificate and associated medical records were collected in addition to interviews with proxies or next of kin. Committees of stroke or CHD experts

adjudicated all suspected events. Fatal versus nonfatal outcomes were not differentiated in this analysis. Follow-up and adjudication for stroke events were complete through March 2016, and follow-up and adjudication for CHD events were complete through December 2013 [32,33]. Participants who did not experience a stroke event were censored at the end of March 2016; those who did not have a CHD event were censored at the end of March 2013.

Statistical analysis

From the parent study, 12,630 participants who reported smoking 100 cigarettes or more were compared with those who did not to check for an association between childhood SHS exposure and adult smoking, but all subsequent analyses were among never-smokers only. Baseline characteristics were compared by number of childhood household smokers (0, 1, or 2+) using χ^2 tests for categorical variables or analysis of variance for continuous variables.

Childhood SHS exposure was not assessed until 10 years after the initiation of the study, which was 5 years after the termination of new participant enrollment; thus, there is the potential for bias due to selective attrition of participants at higher risk of stroke or CHD. In addition, survey nonresponse among those who were contacted might differ by many of the same characteristics associated with stroke or CHD. To account for these potentially problematic patterns of missing data, we developed inverse probability weights (IPW) for attrition [34] and nonresponse [35] using baseline sociodemographic and clinical characteristics. In addition to missing data on childhood SHS, data were missing on sociodemographic characteristics and risk factors used in the IPW (and/or main analysis) models. Few observations of any single characteristic were missing in substantial numbers of participants (at most 6.1%), but 16.3% of participants had at least one characteristic missing; therefore a single imputation using fully conditional specification [36] was performed to avoid listwise deletion during the estimation of the weights. Logistic regression was used to estimate the probability of a participant having been censored in REGARDS as of January 2013 when the childhood questionnaire results were being received (probability of attrition), or in a separate model, of not returning the survey, given that they were active in January 2013 (probability of nonresponse). Weights were calculated as $1/(1-P)$, where P is the respective probability and multiplied together to obtain final weights.

Cox proportional hazards models were used to assess hazard ratios (HRs) and 95% CI for stroke or CHD by number of childhood household smokers using model-based estimate of variance. Stroke and CHD were considered in separate models. Age (years), race (black or white), sex (male or female), region (stroke buckle [153-county coastal region of North Carolina, South Carolina, and Georgia], stroke belt [the rest of those states plus Tennessee, Alabama, Mississippi, Louisiana, and Arkansas], other), and the interaction between age and race were adjusted for in all stroke models as in Howard et al [30]. Age, race, sex, and region were adjusted for in all CHD models as in Safford et al. [32]. Fully adjusted models included socioeconomic factors, adult SHS exposure (yes/no), annual income, highest education, and greatest parental education (all categorized), and Framingham Risk Score factors. Different Framingham Risk Score factors were selected for the stroke models (self-reported diabetes, history of heart disease, atrial fibrillation, current antihypertensive medication use, systolic blood pressure, and Sokolow-Lyon Left Ventricular Hypertrophy Limb lead criteria) and CHD models (self-reported diabetes, systolic blood pressure, total cholesterol, current antihypertensive medication use, and high-density lipoprotein cholesterol). Some covariate data were missing in the fully adjusted models, so we created 10 imputed

datasets using fully conditional specification [36] and calculated HRs using multiple imputation. Everything other than outcomes and childhood variables was collected at study baseline. All statistical analyses were performed with SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Results

Among participants from the parent study who answered both the baseline smoking question and the survey childhood SHS exposure question, fewer number of regular smokers in the participant's childhood home was associated with never smoking; 2825 (55%) of 5093 with 0 childhood household smokers reported never smoking, compared with 2237/4868 (46%) with 1, and 1134/2669 (42%) with 2+ ($P < .001$). All subsequent analyses exclude participants who reported ever smoking.

Among 30,183 participants in REGARDS, 13,142 (44%) reported no prior history of both stroke and heart disease, had follow-up information, and reported never having smoked 100 cigarettes or more (Fig. 1). Of the 12,648 participants who reported no stroke before study entry, 3583 (28%) were lost to attrition before the childhood SHS survey. Of those who were still active when the questionnaire was mailed, 6003 (66%) returned the survey with nonmissing responses for childhood SHS exposure. Of the 11,287 participants with follow-up for CHD and who reported no CHD before study entry, 3137 (28%) were lost to attrition before the childhood survey, and of those who were still active when the questionnaire was mailed, 5377 (66%) returned the survey with nonmissing responses for childhood SHS exposure.

Table 1 shows the outcomes and baseline characteristics of participants by their attrition and survey response status. Stroke and CHD both occurred more often in participants who were lost to attrition before the survey than participants who did not answer or who did answer (6.1%, 4.1%, and 3.0% for stroke, $P < .001$, 9.9%, 3.9%, 2.6% for CHD, $P < .001$, respectively). Attrition was more common in older participants (mean 67.2 [SD 10.9]), but age was similar in

survey nonresponders (63.7 [9.7]) and responders (63.5 [9.0]), $P < .001$ overall. Blacks were disproportionately less represented among survey responders (30% vs. 70% white) because they were lost to attrition (49% vs. 51% white) and to survey nonresponse (54% vs. 46% white), $P < .001$ overall. However, there was no difference in any of the groups by sex (65%–66% female in all three groups, $P = .76$). The area under the curve (AUC) represents the ability of the model to distinguish between the outcomes on a scale from 0.5 to 1.0. The AUC (standard error) for each weight's prediction of its respective outcome was 0.679 (0.005) for the attrition weights, 0.680 (0.005) for the nonresponse weights among those active in January 2013, and 0.695 (0.005) for the combination of attrition and nonresponse. Median (25% percentile, 75% percentile) weights in the analysis sample were 1.31 (1.21–1.47) for attrition, 1.39 (1.28–1.67) for nonresponse, and 1.86 (1.58–2.39) for their product.

Among the 6136 participants eligible for either the stroke (6003) or the CHD (5377) analysis, 46% reported 0 childhood household smokers, 36% reported 1 (which included 0.7% who reported “yes” but did not specify the number of smokers in their household), and 18% reported 2+ (which was exactly 2 for 89%, but a maximum of 7). In 60,649 person-years through March 2016 (median 10.5 years), 174 strokes were observed (2.9% of participants), and in 45,195 person-years through December 2013 (median 8.6 years), 114 CHD events were observed (2.1% of participants). Table 2 shows the baseline characteristics of participants by their childhood SHS exposure. Their mean (SD) age was 63.5 (9.0), they were 65% female, and 30% black.

Table 3 shows the results from the Cox proportional hazards models for stroke and CHD, all adjusted by age, sex, race, with the interaction between age and race in the stroke models. The HR (95% CI) of stroke for 2+ versus 0 childhood household smokers exposed was 1.36 (0.89–2.07), and for 1 versus 0 was 1.00 (0.71–1.39), $P = .31$ for an overall difference. After applying the IPW, which brought the weighted sample size from 6003 to 12,835.2, the HR of stroke for 2+ versus 0 was 1.69 (1.32–2.17), and for 1 versus 0 was 0.89 (0.72–1.11), $P < .001$. After IPW and adjusting for all other

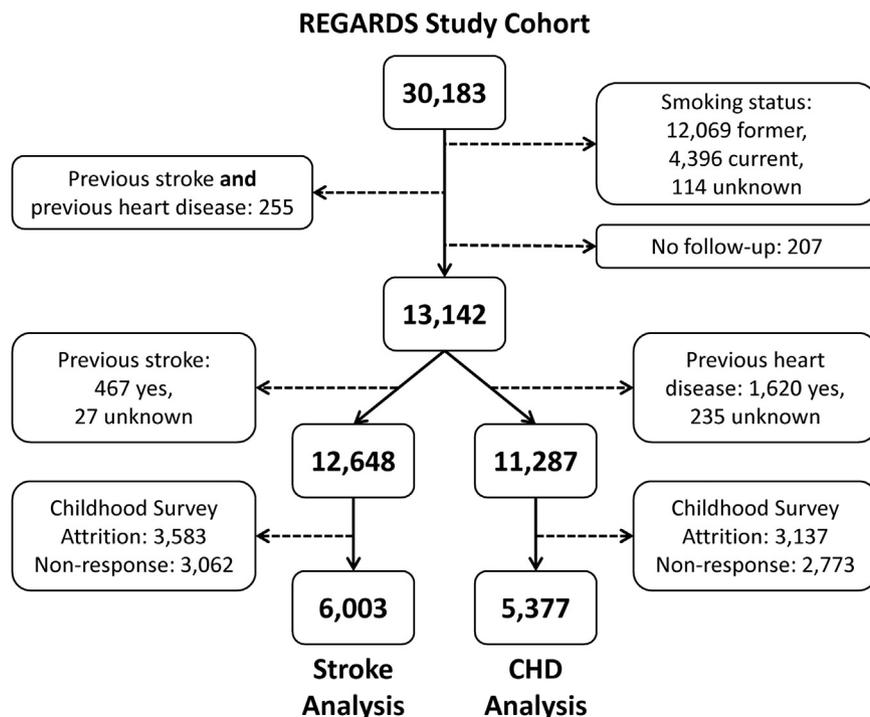


Fig. 1. Flowchart describing the study participants. There are 6136 unique participants in the stroke and CHD analyses combined. CHD = coronary heart disease.

Table 1
Outcomes and baseline characteristics of participants by attrition and survey response

Characteristic	Total, n = 13,142	Attrition before survey, n = 3811 (29%)	Survey unanswered, n = 3195 (24%)	Survey answered, n = 6136 (47%)	P
Stroke	545 (4.1%)	231 (6.1%)	132 (4.1%)	182 (3.0%)	<.001
CHD	662 (5.0%)	377 (9.9%)	125 (3.9%)	160 (2.6%)	<.001
Age (y)					
Mean (SD)	64.7 (9.9)	67.2 (10.9)	63.7 (9.7)	63.5 (9.0)	<.001
45–54	1913 (15%)	441 (12%)	553 (17%)	919 (15%)	<.001
55–64	4914 (37%)	1182 (31%)	1217 (38%)	2515 (41%)	
65–74	3937 (30%)	1091 (29%)	935 (29%)	1911 (31%)	
75+	2378 (18%)	1097 (29%)	490 (15%)	791 (13%)	
Gender (female)	8570 (65%)	2487 (65%)	2099 (66%)	3984 (65%)	.76
Race (black)	5409 (41%)	1864 (49%)	1721 (54%)	1824 (30%)	<.001
Region*					
Nonstroke belt	5693 (43%)	1680 (44%)	1333 (42%)	2680 (44%)	.001
Stroke belt	4609 (35%)	1374 (36%)	1172 (37%)	2063 (34%)	
Stroke buckle	2840 (22%)	757 (20%)	690 (22%)	1393 (23%)	
Adult SHS exposure					
No	10,437 (79%)	2962 (78%)	2451 (77%)	5024 (82%)	<.001
Yes	1748 (13%)	535 (14%)	464 (15%)	749 (12%)	
Unknown/missing/refused	957 (7%)	314 (8%)	280 (9%)	363 (6%)	
Income					
<\$20K	2158 (16%)	901 (24%)	573 (18%)	684 (11%)	<.001
\$20K–\$34K	3058 (23%)	1011 (27%)	740 (23%)	1307 (21%)	
\$35K–\$74K	3877 (30%)	928 (24%)	911 (29%)	2038 (33%)	
\$75K and above	2333 (18%)	409 (11%)	502 (16%)	1422 (23%)	
Refused	1716 (13%)	562 (15%)	469 (15%)	685 (11%)	
Highest education (missing = 10)					
Less than high school	1360 (10%)	633 (17%)	407 (13%)	320 (5%)	<.001
High school graduate	3288 (25%)	1101 (29%)	823 (26%)	1364 (22%)	
Some college	3287 (25%)	965 (25%)	840 (26%)	1482 (24%)	
College graduate and above	5197 (40%)	1105 (29%)	1123 (35%)	2969 (48%)	
Systolic blood pressure, mean (SD) (missing = 42)	126.8 (16.4)	129.6 (17.5)	127.6 (16.6)	124.5 (15.3)	<.001
Use of antihypertensive medication (missing = 510)	6597 (52%)	2115 (58%)	1712 (56%)	2770 (47%)	<.001
Diabetes (missing = 497)	2564 (20%)	971 (27%)	711 (23%)	882 (15%)	<.001
History of stroke (missing = 27)	467 (4%)	222 (6%)	127 (4%)	118 (2%)	<.001
History of heart disease (missing = 235)	1620 (13%)	600 (16%)	361 (12%)	659 (11%)	<.001
Atrial fibrillation (self-report or ECG evidence) (missing = 268)	1004 (8%)	364 (10%)	251 (8%)	389 (6%)	<.001
Sokolow-Lyon LVH Limb lead criteria (missing = 218)	1433 (11%)	543 (14%)	410 (13%)	480 (8%)	<.001
Total cholesterol (mg/dL), mean (SD) (missing = 562)	194.2 (39.1)	194.2 (40.8)	194.3 (38.9)	194.2 (38.2)	1.00
HDL cholesterol (mg/dL), mean (SD) (missing = 622)	53.5 (16.2)	53.0 (16.4)	53.2 (16.0)	54.1 (16.2)	.003

ECG = electrocardiogram; HDL = high-density lipoprotein; LVH = left ventricular hypertrophy.

Stroke belt refers to the rest of those states plus Tennessee, Alabama, Mississippi, Louisiana, and Arkansas.

* Stroke buckle includes a 153-county coastal region of North Carolina, South Carolina, and Georgia.

covariates, the HR of stroke for 2+ versus 0 was 1.66 (1.29–2.13), and for 1 versus 0 was 0.91 (0.73–1.13), $P < .001$.

The HR of CHD for 2+ versus 0 childhood household smokers exposed was 0.91 (0.52–1.61), and for 1 versus 0 was 1.01 (0.68–1.51), $P = .85$. With IPW, the HR for 2+ versus 0 was 1.36 (0.99–1.88), and for 1 versus 0 was 0.97 (0.75–1.26), $P = .01$, and with IPW and full adjustment, the HR for 2+ versus 0 was 1.15 (0.82–1.59), and for 1 versus 0 was 1.00 (0.77–1.30), $P = .16$.

A sensitivity analysis involving partial adjustment and weighting only for attrition was also performed, which resulted in an HR of 1.53 (1.10–2.14) for stroke among 2+ versus 0 SHS exposed, and 0.97 (0.61–1.54) for CHD among 2+ versus 0 SHS exposed. Models for the attrition weighting and all fully adjusted models are presented in [Supplementary Table 1](#).

Adult SHS was also considered as a possible mediator of the childhood SHS association with stroke and CHD, so a sensitivity analysis was performed using the fully adjusted and weighted models but without adjusting for adult SHS and separately stratified by adult SHS. The HRs for 2+ versus 0 childhood SHS exposed without adjustment were 1.68 (1.30–2.15) for stroke, and 1.16 (0.84–1.61) for CHD, which were very similar to the adjusted values, indicating no direct mediation. For stroke, the HR for 2+ versus 0 childhood SHS exposed was 2.09 (1.06–4.09) among adult SHS exposed (12% of participants) and 1.40 (1.03–1.90) among adult SHS nonexposed (82% of participants); 6% of participants had unknown adult SHS exposure. No participants with adult SHS

exposure experienced CHD during study follow-up, and full results from these models are available in [Supplementary Table 2](#).

Discussion

The main findings of this study are that among never-smokers, aged older than 45 years, exposure during childhood to SHS from two or more household smokers was associated with a 1.66 times increased hazard of stroke, but no significant increased hazard of CHD. The association with stroke was independent of adult SHS exposure as well as demographic, socioeconomic, and Framingham risk factors. There is a growing body of evidence linking exposures across the life course to chronic diseases in adulthood [37], and despite indications that harm from SHS could be reversible in healthy young adults [38], our study is the first we are aware of to report on these particular associations in a well-characterized older adult cohort. It is important to note that these results were observed only among the IPW data, but not when examining the unweighted data, and thus, the results should be interpreted with caution.

A limitation of this study was its reliance on a primary exposure that was retrospectively assessed with respect to both the time of exposure and the time of study entry. Several studies have looked at consequences of childhood SHS exposure that are present into early adulthood [26–28], but it is inherently difficult to study the relationship between an exposure and an outcome that occur at least 27 and possibly 60 or more years apart [39]. However, there are few

Table 2
Baseline characteristics of participants by number of smokers in childhood home

Baseline characteristic	Number of smokers in childhood home				P
	Total, n = 6136	0, n = 2792 (46%)	1, n = 2221 (36%)	2+, n = 1123 (18%)	
Age					
Mean (SD)	63.5 (9.0)	64.5 (9.3)	63.7 (8.9)	60.8 (8.1)	<.001
45–54	919 (15%)	369 (13%)	313 (14%)	237 (21%)	<.001
55–64	2515 (41%)	1062 (38%)	915 (41%)	538 (48%)	
65–74	1911 (31%)	916 (33%)	712 (32%)	283 (25%)	
75+	791 (13%)	445 (16%)	281 (13%)	65 (6%)	
Gender (female)	3984 (65%)	1810 (65%)	1455 (66%)	719 (64%)	.69
Race (black)	1824 (30%)	976 (35%)	596 (27%)	252 (22%)	<.001
Region*					
Nonstroke belt	2680 (44%)	1215 (44%)	948 (43%)	517 (46%)	.07
Stroke belt	2063 (34%)	974 (35%)	739 (33%)	350 (31%)	
Stroke buckle	1393 (23%)	603 (22%)	534 (24%)	256 (23%)	
Adult SHS exposure					
No	5024 (82%)	2329 (83%)	1800 (81%)	895 (80%)	.005
Yes	749 (12%)	295 (11%)	289 (13%)	165 (15%)	
Unknown/missing/refused	363 (6%)	168 (6%)	132 (6%)	63 (6%)	
Income					
<\$20K	684 (11%)	335 (12%)	236 (11%)	113 (10%)	<.001
\$20K–\$34K	1307 (21%)	619 (22%)	493 (22%)	195 (17%)	
\$35K–\$74K	2038 (33%)	937 (34%)	721 (32%)	380 (34%)	
\$75K and above	1422 (23%)	603 (22%)	496 (22%)	323 (29%)	
Refused	685 (11%)	298 (11%)	275 (12%)	112 (10%)	
Highest education (missing = 1)					
Less than high school	320 (5%)	162 (6%)	110 (5%)	48 (4%)	.002
High school graduate	1364 (22%)	610 (22%)	541 (24%)	213 (19%)	
Some college	1482 (24%)	676 (24%)	541 (24%)	265 (24%)	
College graduate and above	2969 (48%)	1344 (48%)	1029 (46%)	596 (53%)	
Highest education of parents (missing = 76)					
Less than high school	2666 (44%)	1207 (44%)	1050 (48%)	409 (37%)	<.001
High school graduate	1409 (23%)	597 (22%)	522 (24%)	290 (26%)	
At least some college	1523 (25%)	714 (26%)	474 (22%)	335 (30%)	
Unknown	462 (8%)	243 (9%)	145 (7%)	74 (7%)	
Systolic blood pressure, mean (SD) (missing = 20)	124.5 (15.3)	125.1 (15.4)	124.2 (15.0)	123.8 (15.4)	.03
Use of antihypertensive medication (missing = 215)	2770 (47%)	1292 (48%)	1022 (47%)	456 (42%)	.004
Diabetes (missing = 209)	882 (15%)	409 (15%)	305 (14%)	168 (15%)	.56
History of stroke (missing = 15)	118 (2%)	62 (2%)	38 (2%)	18 (2%)	.30
History of heart disease (missing = 100)	659 (11%)	307 (11%)	238 (11%)	114 (10%)	.69
Atrial fibrillation (self-report or ECG evidence; missing = 105)	389 (6%)	172 (6%)	151 (7%)	66 (6%)	.52
Sokolow-Lyon LVH limb lead criteria (missing = 99)	480 (8%)	219 (8%)	183 (8%)	78 (7%)	.41
Total cholesterol (mg/dL), mean (SD) (missing = 209)	194.2 (38.2)	193.9 (37.8)	194.4 (38.5)	194.6 (38.5)	.83
HDL cholesterol (mg/dL), mean (SD) (missing = 240)	54.1 (16.2)	54.1 (16.1)	53.8 (15.9)	54.5 (17.3)	.55

ECG = electrocardiogram; HDL = high-density lipoprotein; LVH = left ventricular hypertrophy.

Stroke belt refers to the rest of those states plus Tennessee, Alabama, Mississippi, Louisiana, and Arkansas.

* Stroke buckle includes a 153-county coastal region of North Carolina, South Carolina, and Georgia.

existing studies any better suited than REGARDS to evaluate these relationships. Self-reported retrospective assessments of childhood circumstances are widely used and have been repeatedly shown to predict adult CVD outcomes [40,41]. We acknowledge the limitations of self-reported and retrospective data; however, we used questions

similar to what other studies have used and validated [31,42,43]. Exposure assessment years after the study baseline, on the other hand, posed a challenge specific to this analysis, particularly because loss to follow-up before the assessment is associated with both risk factors and outcome [44]. In addition, childhood SHS exposure was

Table 3
Cox proportional hazards of stroke and CHD by number of smokers in childhood home

Outcome	Number of smokers in childhood home	Outcome, n (%) [‡]	Unweighted		Weighted		Fully adjusted [†]	
			Partially adjusted*		HR (95% CI)	P	HR (95% CI)	P
			HR (95% CI)	P				
Stroke	0	83 (3.0)	Reference	.31	Reference	<.001	Reference	<.001
	1	60 (2.8)	1.00 (0.71–1.39)		0.89 (0.72–1.11)		0.91 (0.73–1.13)	
	2+	31 (2.8)	1.36 (0.89–2.07)		1.69 (1.32–2.17)		1.66 (1.29–2.13)	
CHD	0	55 (2.3)	Reference	.85	Reference	.01	Reference	.16
	1	43 (2.2)	1.01 (0.68–1.51)		0.97 (0.75–1.26)		1.00 (0.77–1.30)	
	2+	16 (1.6)	0.91 (0.52–1.61)		1.36 (0.99–1.88)		1.15 (0.82–1.59)	

LVH = left ventricular hypertrophy; SBP = systolic blood pressure.

* Partially adjusted models are adjusted for: Stroke: age, race, sex, region, and the interaction between age and race. CHD: age, race, sex, and region.

† Fully adjusted models are adjusted for the above plus: Stroke: income, education, parent education, adult SHS exposure, and Framingham Stroke Risk Score factors (diabetes, cardiovascular disease history, atrial fibrillation, current antihypertensive medication use, SBP, and LVH). CHD: income, education, parent education, adult SHS exposure, diabetes, current antihypertensive medication use, SBP, total cholesterol, and high-density lipoprotein cholesterol.

‡ Sample sizes: 6003 (stroke) and 5377 (CHD); weighted sample sizes in analyses: 12,835.2 (stroke) and 11,498.0 (CHD).

part of a mailed survey and therefore subject to nonresponse bias, although likely less so than many mailed surveys due to the participants' ongoing commitment to the REGARDS study, evidenced by a response rate of 66%. To address selection bias resulting from these latter two issues, we used IPW to reclaim our baseline cohort using a pseudo-population based on the participants for whom we could obtain childhood SHS. The AUC for the prediction of attrition (0.679) and nonresponse (0.680) were not especially high, indicating that the weighted pseudo-population may not accurately represent the baseline cohort, leaving the potential for introduced bias. However, all the characteristics used to predict likelihood of attrition or survey nonresponse were measured during the thorough telephone and in-home visits at study baseline, and they represent our best chance at recovering these data.

Based on our IPW analyses we found that our initial unweighted analyses had substantially underestimated the risk of 2+ versus 0 childhood household smokers, both for stroke (HR 1.36 vs. 1.69) and CHD (0.91 vs. 1.36), and we attribute this to survivorship selection bias. For CHD, much of this risk was confounded by other factors such as cholesterol; thus, the nonsignificant weighted and fully adjusted final estimate of 1.15, so we expect that even if we had SHS exposure assessed in our entire cohort, there would be no detectable causal association with CHD. However, fully adjusting our stroke model resulted in almost no change in the magnitude of the association (HR 1.66); therefore, we propose that the same mechanisms responsible for the established shorter term relationships between SHS and subclinical vascular disease [45–49] and stroke [15] and may be responsible for an increased long-term risk of stroke. Data from the Cardiovascular Risk in Young Finns Study have shown that exposure to parental smoking during childhood is associated with increased risk of carotid atherosclerotic plaque in adulthood [28] and increased carotid intima-media thickness [26], up to 25 years later. Other research has shown impaired endothelial function measured by flow-mediated dilation in young adults after having been exposed to SHS during childhood [27]. Increased sensitivity of the brain during development may account for the magnitude of the association we found, as well as for the difference between stroke and CHD risk. The precise mechanisms await further research, specifically life course research in which childhood exposure is more directly assessed, and temporal changes over time that mediate stroke outcomes are measured.

Strengths of this study include it is being a large, population-based, prospective cohort. Extensive information was obtained in person at study baseline, and careful follow-up was maintained with respect to stroke and CHD outcomes. Furthermore, the novel REGARDS approach to in-home data collection resulted in a cohort that included people who live far from academic medical centers, likely enhancing generalizability. In addition, because we used IPW in our analyses, it is likely that we not only increased our functional sample size, but that we did so in a way that allowed less bias in our estimation, as we accounted for differential loss to follow-up. Limitations beyond those discussed previously include the potential lack of reliability in quantifying SHS exposure during childhood or adulthood, lack of precision in the estimation of attrition due to different possible causes, and potential confounding by unmeasured and possibly correlated childhood risk factors. Finally, although our hope is that we diminished the bias by use of IPW, it is alternatively possible that we induced additional bias through our weighting, and thus, the results should be viewed with this caveat.

Conclusion

Exposure during childhood to SHS is associated with increased risk of stroke much later in life in our sample weighted to reduce the effects of potential selection bias. Our findings extend the time

that stroke risk lingers farther than any of the previous literature and are particularly relevant to considerations of protecting children, who have far less ability to avoid SHS. In contrast, our findings indicate little or no increased risk from CHD. Future research will hopefully be able to assess exposures and cardiovascular outcomes across the life course to better assess temporal mediators and avoid long-term recall bias.

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Appendix

Supplementary Table 1

Cox proportional hazards of stroke and CHD by number of smokers in childhood home, all models

Outcome	Model	Weighted sample size	Number of smokers in childhood home	Outcome, n (%)	Partially adjusted [*]		Fully adjusted [†]	
					HR (95% CI)	P	HR (95% CI)	P
Stroke	Unweighted	6003	0	3.0%	Reference	.31	Reference	.45
			1	2.8%	1.00 (0.71–1.39)		1.01 (0.72–1.42)	
			2+	2.8%	1.36 (0.89–2.07)		1.30 (0.85–1.99)	
	Attrition weighted	8225.9	0	3.4%	Reference	.02	Reference	.04
			1	2.9%	0.96 (0.73–1.27)		0.98 (0.74–1.29)	
			2+	3.5%	1.53 (1.10–2.14)		1.48 (1.06–2.06)	
Attrition and nonresponse weighted	12,835.2	0	3.7%	Reference	<.001	Reference	<.001	
		1	2.9%	0.89 (0.72–1.11)		0.91 (0.73–1.13)		
		2+	4.2%	1.69 (1.32–2.17)		1.66 (1.29–2.13)		
CHD	Unweighted	5377	0	2.3%	Reference	.94	Reference	.91
			1	2.2%	1.01 (0.68–1.51)		1.00 (0.67–1.50)	
			2+	1.6%	0.91 (0.52–1.61)		0.88 (0.50–1.57)	
	Attrition weighted	7311.2	0	2.5%	Reference	.99	Reference	.95
			1	2.4%	1.00 (0.72–1.39)		1.01 (0.72–1.41)	
			2+	1.8%	0.97 (0.61–1.54)		0.94 (0.59–1.50)	
Attrition and nonresponse weighted	11,498	0	2.7%	Reference	.11	Reference	.69	
		1	2.4%	0.97 (0.75–1.26)		1.00 (0.77–1.30)		
		2+	2.7%	1.36 (0.99–1.88)		1.15 (0.82–1.59)		

LVH = left ventricular hypertrophy; SBP = systolic blood pressure.

^{*} Partially adjusted models are adjusted for: Stroke: age, race, sex, region, and the interaction between age and race. CHD: age, race, sex, and region.[†] Fully adjusted models are adjusted for the above plus: Stroke: income, education, parent education, adult SHS exposure, and Framingham Stroke Risk Score factors (diabetes, cardiovascular disease history, atrial fibrillation, current antihypertensive medication use, SBP, and LVH). CHD: income, education, parent education, adult SHS exposure, diabetes, current antihypertensive medication use, SBP, total cholesterol, and high-density lipoprotein cholesterol.

Supplementary Table 2

Attrition and nonresponse weighted models, sensitivity with respect to adult smoke exposure

Outcome	Model [*]	Weighted sample size	Number of smokers in childhood home	Outcome (%)	Fully adjusted [*]	
					HR (95% CI)	P
Stroke	Not adjusted for adult SHS exposure	12,835.2	0	3.7%	Reference	<.001
			1	2.9%	0.91 (0.73–1.14)	
			2+	4.2%	1.68 (1.30–2.15)	
	Among adult SHS exposed	1695.2	0	3.5%	Reference	.08
			1	3.7%	1.55 (0.84–2.87)	
			2+	6.5%	2.09 (1.06–4.09)	
Among adult SHS nonexposed	10,267.4	0	3.7%	Reference	.004	
		1	2.6%	0.80 (0.62–1.03)		
		2+	3.5%	1.40 (1.03–1.90)		
CHD	Not adjusted for adult SHS exposure	11,498	0	2.7%	Reference	.64
			1	2.4%	1.00 (0.77–1.30)	
			2+	2.7%	1.16 (0.84–1.61)	
	Among adult SHS exposed	1573.4	0	3.9%		
			1	2.1%	N/A	
			2+	0%		
Among adult SHS nonexposed	9136.6	0	2.8%	Reference	.73	
		1	2.3%	0.89 (0.66–1.19)		
		2+	2.1%	0.93 (0.62–1.40)		

LVH = left ventricular hypertrophy; N/A = not available; SBP = systolic blood pressure.

^{*} Stroke models are adjusted by age, race, sex, region, the interaction between age and race, income, education, parent education, diabetes, and Framingham Stroke Risk Score factors (cardiovascular disease history, atrial fibrillation, current antihypertensive medication use, SBP, and LVH). CHD models are adjusted by age, race, sex, region, income, education, parent education, diabetes, current antihypertensive medication use, SBP, total cholesterol, and high-density lipoprotein cholesterol.