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Family History of Stroke and Cardiovascular Health in a National Cohort

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Abstract

Objective—We investigated the association between family history of stroke and Life’s Simple 7, a public health metric defined by the American Heart Association.

Methods—REasons for Geographic And Racial Differences in Stroke is a national population-based cohort of 30,239 blacks and whites, aged 45 years, sampled from the US population in 2003 – 2007. Data were collected by telephone, mail questionnaires, and in-home exams. Family history of stroke was defined as any first degree relative with stroke. Levels of the Life’s Simple 7 components (total cholesterol, blood pressure, fasting glucose, physical activity, diet, smoking and body mass index) were each coded as poor (0 points), intermediate (1 point) or ideal (2 points) health. Ordinal logistic regression was used to model the data.

Results—Among 20,567 subjects with complete Life’s Simple 7 and family history of stroke data, there were 7702 (37 %) participants with family history of stroke. The mean age of the participants was 64 years. The mean ($\pm$ SD) overall Life’s Simple 7 score was lower for blacks (6.5 ± 2.0) than whites (7.6 ± 2.1). Family history of stroke was associated with poorer levels of physiological factors, particularly high blood pressure (OR=1.13, 95% CI = 1.07, 1.19) and inversely associated with behaviors such as smoking (OR= 0.92, 95% CI= 0.85, 0.99).

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Conclusion—Our results suggest that screening for family history of stroke can provide an opportunity for earlier detection and management of modifiable risk factors.

Keywords

Family History of Stroke; Risk factors; Life Simple 7

Effectiveness of health programs can be increased by interventions targeted at high risk individuals.¹² An important and readily accessible source of risk information in an individual is their family history. Family history represents the integration of shared genetic and environmental risk factors and could be used as a screening tool for individuals with increased disease risk including cardiovascular diseases.^{3,4–8} Family history of stroke (FHS) is a recognized risk factor for stroke events although its importance has not been conclusively confirmed by epidemiological studies.^{9,10} Familial aggregation of stroke appears to be caused by a strong association of conventional stroke risk factors such as hypertension, diabetes, and dyslipidemia between parents and offspring as previously demonstrated in the REasons for Geographic And Racial Differences in Stroke (REGARDS) population.¹¹ As yet, there is limited data on the association of FHS and health behaviors.

Many risk factors for stroke are under genetic influence and a considerable degree of heritability appears to be conferred by intermediate phenotypes. The American Heart Association and American Stroke Association (AHA/ASA) has proposed a public health metric, Life's Simple 7 (LS7), that consists of seven modifiable components, including three physiological factors (total cholesterol, blood pressure, fasting glucose) and four health behaviors (physical activity, healthy diet, smoking and body mass index (BMI)), and categorizes them into ideal, intermediate, and poor levels.¹² Recent studies have demonstrated strong association of LS7 with incident stroke.¹³ The relationship between FHS and an overall intermediate phenotype like the AHA's cardiovascular health index (LS7) has not been comprehensively evaluated. Further, there are few studies that address this issue in blacks, a group at higher stroke risk than whites in the US. In this study, we examined the association of FHS with cardiovascular physiological risk factors, health behaviors and an overall phenotype (LS7) in a large population-based, national cohort study. We hypothesized that people with a positive FHS would have a lower prevalence of ideal physiological factors and a lower prevalence of ideal health behaviors than those without FHS.

METHODS

Study Participants

The REasons for Geographic And Racial Differences in Stroke (REGARDS) study is a national, population-based cohort study investigating racial and geographic disparities in stroke and cognitive decline among black and white US adults ≥ 45 years of age.¹⁴ The study was designed to oversample blacks and to provide approximate equal representation of men and women. Residents from the Southeastern US were oversampled and represent 56% of the cohort with the remaining 44% of participants recruited from the rest of the continental United States. Potential participants were identified from commercially available

lists of US residents and recruited through an initial mailing followed by telephone contacts. Overall, 30,239 were enrolled between January 2003 and October 2007; the sample included 45% men and 55% women, 58% whites and 42% blacks. The REGARDS study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers and all participants provided informed consent.

Data Collection

Socio-demographic and clinical data were collected at baseline through a telephone interview, self-administered questionnaires and an in-home examination. Trained interviewers conducted computer-assisted telephone interviews to obtain information on participant's demographics, socioeconomic factors, and medical history including the use of antihypertensive, diabetes, and cholesterol lowering medications. After the telephone interview, trained health professionals conducted an in-home study visit that included a physical examination, electrocardiogram and the collection of blood and urine samples. Self-administered questionnaires were left with the participant to complete and return by mail. These included the Block 98 Food Frequency Questionnaire (FFQ)^{15,16} and a family history questionnaire asking whether first-degree relatives (biological parents and siblings) ever had a stroke. FHS was considered positive if at least one parent or one sibling had a stroke. Ischemic and hemorrhagic stroke were not identified separately. Using the FFQ, each participant recorded food intake for one year prior to their in-home visit. Nutrient analysis was conducted by NutritionQuest.

Life's Simple Seven

Components of LS7 include cigarette smoking, physical activity, diet, BMI, blood pressure, total cholesterol and fasting glucose. These components are categorized as being poor, intermediate or ideal as per AHA guidelines.¹⁷ (Table 1) Current and former smoking and time since smoking cessation for former smokers was determined by participant questions. Physical activity was assessed through a single question "How many times per week do you engage in intense physical activity, enough to work up a sweat?" Height and weight were measured using calibrated equipment and BMI was calculated. The diet score for the LS7 was based on fish, fruit and vegetable consumption and sodium, sugar, and fiber/carbohydrate ratio intake. An ideal diet was defined by the following 5 factors: fish consumption 2 servings/week, fruit/vegetables 4.5 cups/day, sodium intake < 1500 mg/day, sugar < 450 kcal/week, and fiber/carbohydrate ratio > 0.1 as per recommendations of the new metric. Systolic and diastolic blood pressure was measured two times using aneroid sphygmomanometers following a standardized protocol. The two BP measurements were averaged for the current analyses. Total cholesterol was measured using an enzymatic reaction. Glucose was measured in serum using colorimetric reflectance spectrophotometry. In addition to using all seven components for a composite LS7 score, the components were grouped into two domains: physiological factors (total cholesterol, blood pressure, and fasting glucose) and health behaviors (physical activity, diet, smoking and BMI). We classified each LS7 component equally into a sum score assigning 2, 1 and 0 points respectively to ideal, intermediate or poor status. A total LS7 score pooled the individual component scores and was categorized as: optimum (10–14), adequate (5–9) and inadequate

(0–4) cardiovascular health. Those with the highest number of points are therefore in better cardiovascular health.

Other Measurements and Definitions

Age, race, sex, use of medications (for hypertension, diabetes and cholesterol), alcohol use, annual family income, and education level were defined from self-report. Alcohol use was categorized as current versus past and never use. Income was categorized as low < \$20,000 vs high > \$20,000. Education was dichotomized as less than high school vs. high school graduate or above. Participants were asked whether they had ever experienced the sudden onset of each of six stroke symptoms using the Questionnaire for Verifying Stroke-Free Status (QVSS).¹⁸ Prevalent stroke symptoms was defined as answering “yes” to 1 or more symptoms vs. “no” to all symptoms. History of stroke was defined by self-reported physician diagnosis. Peripheral arterial disease was defined as self-reported procedures or surgeries to repair arteries in the legs. History of coronary artery disease was defined as self-reported physician diagnosis of myocardial infarction, self-reported coronary revascularization, or evidence of myocardial infarction on the electrocardiogram.

We included participants who had data on LS7 components and FHS, all ascertained at the time of study enrollment). Participants were excluded if they had stroke symptoms (n=1930), coronary artery disease (n=5314), peripheral arterial disease (n=602) or if they lacked any family history data (n=3785). We excluded participants who had coronary artery disease, peripheral arterial disease or stroke as they may have already changed their behavior or may be on medications that affect LS7 components (cholesterol, BP, glucose). To preserve an adequate sample size for the present analyses, we imputed information on diet (20%) for these participants. Diet scores were imputed using imputation by chained equations.¹⁹ Our final sample size was 20,567 for all analyses.

Statistical Methods

The goal of our study was to examine the contribution of FHS to cardiovascular health status in adults. Our primary predictor variable was FHS measured as a dichotomous variable using the family history questionnaire. Ordinal groupings of the total LS7 score (optimum, adequate and inadequate) were used as the dependent variable in the analyses. Individual components of the LS7 categories were treated as a 3-point ordinal scale (0,1,2), as defined by AHA (see Table 1) for testing in ordinal logistic regression. The seven metrics were then summed to obtain a score that ranged between 0 and 14. Baseline characteristics were calculated and compared for REGARDS participants by LS7 categories using t-tests or chi square tests. Next, for FHS, odds ratios for LS7 physiological factors and behaviors were calculated (ideal and intermediate compared with the reference group of poor). The odds ratios were adjusted for demographic and other confounders. The analyses of LS7 components (physiological factors and health behaviors) were further stratified by specific FHS (paternal history, maternal history and sibling history). We also did a sensitivity analyses defining family history of early onset stroke with either father, mother having had a stroke before the age of 65 years.

To further evaluate the association between FHS and total LS7, we used multivariable ordinal logistic regression, a method that allows the outcome variable to have more than 2 categories. Ordinal logistic regression calculates a single odds ratio (OR) for the association between the predictor variable (FHS) and levels of higher (better) versus lower (poorer) cardiovascular health categories. Additionally, we also examined the relationship of FHS and LS7 as a continuous score and as a summary measure of behavioral and physiological factors separately. The proportional odds assumption of ordinal logistic regression, using the score test, was verified for our models. Results are reported as ORs with 95% CI. Statistical analysis was performed with SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

The mean age of the 20,567 participants was 64 years; 59 % were women, 39 % blacks, and 37 % had any FHS. Among the included participants, 19% had maternal history of stroke, 15% had paternal history of stroke, and 11% had a sibling history of stroke.

Overall, 15% of participants had optimum, 74% had adequate, and 11% had inadequate cardiovascular health. Older age, male sex, black race, lower income, less than < 12 years of education, geographic region of stroke belt and current alcohol consumption were significantly associated with LS7 categories (Table 2). Examining by individual LS7 factors, blood pressure was associated with FHS and all its subtypes after adjusting for demographic factors and other physiological and behavioral factors (Table 3). Participants with a positive FHS had 13% (OR=1.13, 95% CI = 1.07, 1.19) higher odds to have poorer blood pressure levels versus ideal or intermediate levels (p-value <0.01). Participants with maternal or sibling history of stroke also had higher odds of poor levels of blood pressure. Similarly, participants with a positive FHS had 8% (OR=1.08, 95% CI= 1.03, 1.15) higher odds to have poorer total cholesterol levels versus ideal or intermediate (p-value =0.002). Participants with family history of stroke were more likely to have poorer levels of glucose control although the association was not significant (OR 1.06, 95% CI = 0.99, 1.13). A composite score which included the sum of the three LS7 physiological factors (poor levels of total cholesterol, blood pressure, and fasting glucose) was significantly associated with FHS (OR=1.04, 95% CI =1.02, 1.07). Individual LS7 healthy behaviors, particularly diet, were inversely associated with FHS and any of its subtypes (Table 3). For example, participants with a positive FHS had 11% (OR=0.89, 95% CI = 0.82, 0.96) lower odds to have poorer diet score than ideal or intermediate (p-value <0.006). Similarly, participants with FHS had 8% (OR=0.92, 95% CI= 0.85, 0.99) lower odds to have poorer levels of smoking versus ideal or intermediate (p-value=0.03). Other health behaviors like physical activity and BMI were not significantly associated with family history. A composite score that included the sum of all four LS7 behaviors (healthy diet, smoking, BMI, physical activity) was, however, not significantly associated with FHS (OR=0.98, 95% CI= 0.97, 1.00).

Next, we examined interaction of LS7 with age, race and sex. Interaction with age was significant ($P_{\text{interaction}} < 0.001$) but not with race ($P_{\text{interaction}} = 0.90$) and sex ($P_{\text{interaction}} = 0.89$). In our final model, after adjustment for appropriate confounders (age, sex, race, income, education, alcohol use, geographic region), there was no significant association between

LS7 and FHS (OR=1.00, 95% CI=0.94, 1.07) (Table 4). When we examined by FHS subtypes, the subtype of sibling history of stroke was significantly associated with LS7 (OR=1.06, 95% CI=1.01, 1.18, p-value =0.01). When we stratified by age (age interaction significant), among older individuals, people with FHS had a 12% lower odds (OR=0.88, 95% CI 0.79, 0.97) to have inadequate cardiovascular health versus optimum and adequate. Younger participants with FHS had higher odds to have inadequate cardiovascular health versus optimum and inadequate, but the association was not significant (Table 4). Our results were unchanged when we kept cardiovascular health (LS7) as a continuous variable. Finally, in sensitivity analyses assessing the relationship with early onset of stroke in family, blood pressure was the only LS7 component significantly associated with family history of stroke (OR= 1.2, 95% CI 1.09, 1.28). Results were also similar when participants with imputed diet scores were excluded, or were all assumed to have a poor diet or an intermediate diet

Discussion

Although a modest association of positive FHS and stroke is well recognized, the role of cardiovascular risk factors, particularly health behaviors, is not as clear.^{20,21} In our study, FHS was not associated with the total LS7 score- a comprehensive metric of physiological factors and health behaviors. Many of the components of LS7 including blood pressure and total cholesterol are intermediate phenotypes in the pathway to stroke and have a substantial genetic component themselves. When we considered physiological factors and health behaviors components of LS7 metric separately, our study yielded important observations. The physiological factors, particularly high blood pressure was significantly associated with a positive FHS and all its subtypes. Conversely, among health behaviors, healthy diet and not smoking were inversely associated with a positive FHS. Finally, we also found a modest association of LS7 and sibling history of stroke, suggesting the importance of environmental factors in a shared household.

In our study, participants with a positive FHS including paternal, maternal or sibling history of stroke had a poor levels of blood pressure. These data suggest that people with positive FHS are more likely to have hypertension. Hypertension is the single most powerful risk factor for stroke and may thus account for an important component of the heritability of stroke.²² Our results are consistent with previous studies demonstrating that heritability of stroke is mediated through the heritability of risk factors, particularly hypertension.^{23,24} A positive FHS was also associated with poorer levels of other LS7 physiological factors such as total cholesterol. The link between FHS and health behaviors however was inversed. FHS may motivate individuals for improvement in health behaviors and our data suggest that there is an association of positive FHS with healthier diet and former or never smoking. This is possible as few studies have shown that people with family history of a major disease or illness are likely to practice risk-reducing behaviors.^{25,26,27,28} We extend this finding to family history of stroke data.

We also examined the relationship between LS7 and FHS subtypes- maternal history, paternal history and sibling history of stroke. Sibling history of stroke was the only FHS subtype that was related to LS7. Previous studies have shown that a positive sibling history

of stroke is indeed strongly correlated with incidence of stroke.^{29–31} Meschia et al showed that the severity of stroke was also more closely correlated with a history of stroke in the siblings than in the parents.³⁰ Cardiovascular risk factors are more closely correlated with sibling-sibling relations than with parental-sibling relations and this may explain our finding.³² This suggests that environmental factors in a shared household among siblings may be an important determinant in the familial aggregation of cardiovascular risk factors.

Family history of stroke has been associated with a young age at onset, with the highest rates in persons aged 60 years or younger.²³ In our study, the association of FHS and LS7 appeared to be modified by age. Younger individuals with FHS had higher odds of inadequate LS7 but the opposite was true in older individuals. A possible explanation is that the relative importance of family history and genetic factors may diminish with increasing age as other acquired factors become more dominant. Alternatively, we defined family history as a stroke event at any age. It is possible that a family history of stroke occurring at an advanced age is protective of both cardiovascular risk factors and incident stroke events in the proband. For example, if a parent of proband has a stroke event at age 100, that would indicate both: 1) a general good health of the parent to live to such an age, and 2) a low risk of stroke for the parent, as he/she lived 99 years stroke-free. We generally observed that a FHS at young age was associated with a poorer health profile. However, younger people in the cohort have parents that have not yet reached this “oldest-old” category, so a larger proportion of strokes in these younger parents would represent “premature” stroke that is likely to impart greater risk for poor health profiles. Conversely, the family members of the older cohort members have reached the oldest-old ages and so a larger proportion of stroke events could represent the “protective” family strokes occurring at older ages. The finding of age-interaction needs further exploration.

Our study has several strengths including the large national sample, with over-sampling of blacks and use of standardized questionnaires and measured risk factor levels. REGARDS is the largest study of FHS among blacks— a subgroup of the US population with the highest mortality and incidence of stroke. In our study, a positive FHS does not appear to confer increased risk of a poorer cardiovascular health profile among the black population any differently than whites. We excluded participants with history of stroke or heart disease and thus there is limited potential for reverse causation—i.e., people changing behaviors or treating risk factors due to a clinical event. There are a few important limitations. Misclassification is possible for a few reasons. Firstly, FHS was assessed by informant interview and not by examination or medical record review of family members. Secondly, we have no details on the classification of stroke (ischemic or hemorrhagic) and the diagnosis of stroke itself may have been inaccurate due to poorer diagnostic tools used in the past. Thirdly, our study uses family history as a dichotomous variable and this may also cause misclassification or otherwise limit information, as shown in recent studies which have used a continuous measure.^{11,33} Recall bias is also possible due to use of self-reported data, although previous studies have found self-reported history to be reliable for stroke data.³⁴ Due to early case fatality, sicker individuals could have been excluded because they died before reaching age of inclusion eligibility of REGARDS and thus survivorship bias could also have diluted our study findings.

In conclusion, a positive FHS is associated with poorer levels of LS7 physiological factors, particularly hypertension but more improved levels of LS7 behaviors like healthy diet.³⁵ In the presence of FHS, earlier detection and treatment of modifiable risk factors, may be valuable in further reducing the burden of stroke. Our data support the potential public health benefits of using family history of stroke information to identify and improve cardiovascular health in diverse patient groups.

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Table 1

Life's Simple Seven as a measure of Cardiovascular Health

Health Metric	Levels	Score	Definition
Total cholesterol	Ideal	2	<200 mg/dl, without lipid lowering medication
	Intermediate	1	200–239 mg/dl or treated to <200 mg/dl
	Poor	0	≥240 mg/dl
Blood pressure	Ideal	2	<120/<80 mm Hg, without antihypertensive medication
	Intermediate	1	SBP 120–139 or DBP 80–89 mm Hg or treated with antihypertensive to <120/<80 mm Hg
	Poor	0	SBP ≥140 or DBP ≥90 mm Hg
Fasting glucose	Ideal	2	<100 mg/dl, without antidiabetes medication
	Intermediate	1	100–125 mg/dl or treated with antidiabetes to <100 mg/dl
	Poor	0	≥126 mg/dl
Physical activity*	Ideal	2	4 or more times per week of intense physical activity
	Intermediate	1	1–3 times per week of intense physical activity
	Poor	0	No physical activity
Healthy diet score†	Ideal	2	4–5 components
	Intermediate	1	2–3 components
	Poor	0	0–1 components
Smoking	Ideal	2	Never or quit >12 months
	Intermediate	1	Former, quit ≤12 months
	Poor	0	Current
Body mass index	Ideal	2	<25 kg/m ²
	Intermediate	1	25–29.99 kg/m ²
	Poor	0	≥30 kg/m ²

* modified for REGARDS. Participants in REGARDS were asked “How many times per week do you engage in intense physical activity, enough to work up a sweat?” We defined ideal physical activity as a frequency of 4 or more times per week, intermediate as 1–3 times per week, and poor as none.

† modified for REGARDS. Responses to the Block FFQ were used for the ‘healthy diet score’ that is based on how many components of the 5 diet goals are met. Fruits and vegetables ≥4.5 cups/day; Fish ≥3.5 ounces = 2 servings/week; Sodium <1500 mg/day; Sweets/sugar-sweetened beverages <450 kcal/week; Whole grains (1.1g of fiber in 10 gms of carbohydrates), 1-oz equivalent servings ≥3 servings/day.

Table 2
Baseline characteristics of 20, 567 REGARDS study participants and LS7 health categories

Characteristic	Overall (%)	Cardiovascular Health Categories (n= 20,567)			P-value*
		Optimum n=3,064	Adequate n=15,273	Inadequate n=2,230	
Age >65 years %	45.3	14.3	75.8	9.9	<0.001
Female %	59.2	14.4	73.5	12.5	<0.001
Black race %	39.2	7.3	76.6	16.2	<0.001
Income < \$20,000k %	15.6	7.7	73.6	18.7	<0.001
Education <12 years %	9.9	5.8	75.0	19.3	<0.001
Geographic Region Stroke Belt %	21.5	15.0	75.4	9.6	0.01
Alcohol consumption Current %	54.1	17.4	72.8	9.7	<0.001

* comparing the two strata of demographic characteristics

Table 3

Family History of stroke for LS7 components among REGARDS participants

Physiological factors (Poor vs Intermediate and Ideal)	Family History of Stroke (7,702 positive)		Paternal History of Stroke (3,141 positive)		Maternal History of Stroke (3,983 positive)		Sibling History of Stroke (2,180 positive)	
	OR* (95% CI)	P-Value	OR* (95% CI)	P-value	OR* (95% CI)	P-value	OR* (95% CI)	P-value
Total cholesterol (n=19,848)	1.08 (1.03, 1.15)	0.002	1.02 (0.95, 1.1)	0.55	1.10 (1.03, 1.20)	<0.01	1.07 (0.98, 1.17)	0.09
Blood pressure (n=20,504)	1.13 (1.07, 1.19)	<0.01	1.08 (1.0, 1.16)	0.04	1.10 (1.01, 1.16)	0.01	1.17 (1.07, 1.28)	<0.01
Fasting Glucose (n=17,387)	1.06 (0.99, 1.13)	0.07	1.01 (0.93, 1.10)	0.69	1.05 (0.97, 1.14)	0.16	1.11 (1.0, 1.20)	0.04
Health Behaviors (Poor vs Intermediate and Ideal)	Family History of Stroke (7,702 positive)		Paternal History of Stroke (3,141 positive)		Maternal History of Stroke (3,983 positive)		Sibling History of Stroke (2,180 positive)	
	OR* (95% CI)	P-value	OR* (95% CI)	P-value	OR* (95% CI)	P-value	OR* (95% CI)	P-value
Physical activity (n=15,355)	0.95 (0.91, 1.07)	0.08	0.97 (0.90, 1.04)	0.50	0.94 (0.88, 1.01)	0.06	0.94 (0.86, 1.02)	0.16
Healthy diet score (n=16,451)	0.89 (0.82, 0.96)	0.006	0.98 (0.88, 1.09)	0.79	0.85 (0.77, 0.93)	<0.01	0.97 (0.85, 1.10)	0.66
Smoking (n=20,557)	0.92 (0.85, 0.99)	0.03	0.87 (0.78, 0.97)	0.01	0.98 (0.88, 1.08)	0.69	0.95 (0.84, 1.08)	0.49
Body mass index (n= 20,426)	1.01 (0.94, 1.05)	0.90	0.98 (0.91, 1.05)	0.65	0.96 (0.9, 1.03)	0.28	1.09 (1.0, 1.19)	0.03

* adjusted for age, race, sex, income, education, alcohol use, geographic region (and other physiological and behavioral factors)

Table 4
Odds Ratio (95% CI) for Family History of Stroke and LS7 overall categories by Age-group

	Overall* (n=20, 567)		Age < 65 years (n=11, 255)		Age ≥ 65 years (n=9, 312)	
	Inadequate vs Optimum and Adequate Cardiovascular health	p-value	Inadequate vs Optimum and Adequate Cardiovascular Health		Inadequate vs Optimum and Adequate Cardiovascular Health	P-value
Family History of Stroke (n=7,702)	1.00 (0.94, 1.07)	0.85	1.05 (0.95, 1.17)	0.28	0.88 (0.79, 0.97)	0.009
Paternal History of Stroke (n=3,141)	0.99 (0.91, 1.08)	0.84	1.01 (0.90, 1.13)	0.79	0.94 (0.82, 1.08)	0.41
Maternal History of Stroke (n=3,983)	0.96 (0.89, 1.04)	0.42	1.09 (0.98, 1.21)	0.09	1.09 (0.98, 1.21)	0.09
Sibling History of Stroke (n=2,180)	1.06 (1.01, 1.18)	0.01	1.18 (1.02, 1.38)	0.02	0.95 (0.83, 1.10)	0.55

* adjusted for age, sex, socioeconomic status, alcohol use, education and geographic region