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The Impact of Multiple Social Determinants of Health on Incident Stroke

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Abstract

Background and Purpose: Social determinants of health (SDOH) have been previously associated with incident stroke. Although SDOH often cluster within individuals, few studies have examined associations between incident stroke and multiple SDOH within the same individual. The objective was to determine the individual and cumulative effects of SDOH on incident stroke.

Methods: This study included 27,813 participants from the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study, a national, representative, prospective cohort of black and white adults aged ≥ 45 years. SDOH was the primary exposure. The main outcome was expert adjudicated incident stroke. Cox proportional hazards models examined associations between incident stroke and SDOH, individually and as a count of SDOH, adjusting for potential confounders.

Results: The mean age was 64.7 years (SD 9.4) at baseline; 55.4% were women and 40.4% were blacks. Over a median follow up of 9.5 years (IQR 6.0, 11.5), we observed 1470 incident stroke events. Of 10 candidate SDOH, seven were associated with stroke ($p < 0.10$): race, education, income, zip code poverty, health insurance, social isolation, and residence in one of the 10 lowest ranked states for public health infrastructure. A significant age interaction resulted in stratification at 75 years. In fully adjusted models, among individuals < 75 years, risk of stroke rose as the number of SDOH increased (HR for one SDOH 1.26, 95% CI 1.02–1.55; two SDOH HR 1.38, 95% CI 1.12–1.71; 3 SDOH HR 1.51, 95% CI 1.21–1.89) compared to those without any SDOH. Among those ≥ 75 years, none of the observed effects reached statistical significance.

Conclusions: Incremental increases in the number of SDOH were independently associated with higher incident stroke risk in adults aged < 75 years, with no statistically significant effects

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observed in individuals ≥ 75 years. Targeting individuals with multiple SDOH may help reduce risk of stroke among vulnerable populations.

Keywords

Stroke; Social Determinants of Health; Risk Factors

Subject Terms:

Cerebrovascular Disease/Stroke; Epidemiology; Risk Factors

Introduction

The incidence of stroke is higher in blacks than in whites in the US.^{1–5} Higher risk of stroke among blacks contributes to disparities in stroke mortality, with the greatest disparities observed in younger adults and diminishing after age 65.^{6–9} Racial disparities in incident stroke are well documented in US epidemiological cohort studies.^{1–9} However, although stroke risk factors have been identified, well-established stroke risk factors such as hypertension, diabetes, left ventricular hypertrophy, atrial fibrillation, cigarette smoking, and a history of heart disease explain only 50% of the excess stroke risk in blacks.⁸

National health disparities data for cardiovascular disease outcomes identified several social determinants of health (SDOH) that may help explain stroke disparities, including low education, low income, living in an impoverished area, residence in an area with relatively few healthcare services, Southeastern residence, living in rural areas, social isolation, and lacking health insurance.^{10–13} Studies investigating stroke risk factors beyond traditional Framingham stroke risk factors¹⁴, also reported that SDOH may explain existing stroke disparities. For example, the first National Health And Examination Survey found that living in the Southeast was significantly associated with increased stroke incidence.¹⁵ Similarly, the REasons for Geographic And Racial Differences in Stroke (REGARDS) study found that Southeastern residence over the life course was associated with higher risk for incident stroke.¹⁶ Generally, states in the Southeast have less investment in social safety nets and less healthful dietary practices.¹⁷ The Health and Retirement Study also found that low income during middle-age¹⁸ and social conditions in childhood predict incident strokes.¹⁹ Additionally, social isolation has been associated with 4-fold increased risk of stroke or transient ischemic attack in adults aged ≥ 65 years.²⁰

Despite the documented increases in stroke risk for individuals exposed to these individual SDOH, little has been reported about differences in stroke incidence conferred by the existence of multiple SDOH in the same person. Most of the existing studies either evaluated effects of a limited number of SDOH (mostly focusing on socio-economic factors), or assessed individual associations between individual SDOH and stroke, or studied the combined effect of SDOH using indices that are not easily interpretable. To address these gaps, we used data from the REGARDS study to determine the relationship between an increasing number of SDOH in the same person and incident stroke. To do so, we created a count of SDOH that has intuitive interpretation and is easy to apply in clinical practice. We

hypothesized that a greater number of SDOH would be significantly associated with a higher risk of incident stroke.

Methods

Initial contact for questions related to manuscript proposals and ancillary studies should be made through contact with REGARDSAdmin@uab.edu.

Study population and design

REGARDS is a population-based prospective cohort study of 30,239 black and white adults aged 45 years at baseline living across the 48 continental US states and the District of Columbia. REGARDS was designed to elucidate mechanisms leading to higher stroke mortality in the Southeastern US and among blacks, thus participants were recruited between 2003–2007 with oversampling in the “Stroke buckle” (coastal North Carolina (NC), South Carolina (SC) and some parts of Georgia (GA)) and the “Stroke belt” (remaining areas of NC, SC, and GA as well as Tennessee, Mississippi, Alabama, Louisiana, and Arkansas) and the other half from the rest of contiguous U.S.

Sociodemographic information, medical history, and stroke risk factors were collected during a 45-minute computer assisted telephone interview (CATI) at baseline. Participants also underwent in-home physical examinations, where physical measurements and electrocardiograms were obtained and biologic samples were collected. After the baseline survey, participants were contacted by phone every 6 months to assess their vital status and determine if they experienced a hospitalization. This process has been previously described in detail.⁵ This study was approved by the participating institutions’ Institutional Review Boards. All participants provided written informed consent.

Primary outcome: clinically adjudicated incident strokes

Incident stroke was based on expert adjudication after medical record review.⁹ A stroke event was defined as: 1) focal neurological deficit consistent with ischemia lasting for >24 hours and confirmed with medical records; 2) clinical strokes (focal or non-focal neurological deficit with diagnostic brain imaging regardless of symptom duration); and 3) expert adjudicated stroke deaths.

Primary exposure

Our selection of the 10 candidate SDOH was guided by the Healthy People 2020 framework,²¹ which consists of five major domains related to influences from economic, educational, social context, health and healthcare, and neighborhood and community factors.²¹ We selected SDOH to represent each of domain (Figure 1): economic domain (annual household income <\$35,000 vs. \$35,000); education (<high school vs. high school graduate or more); social context (black vs. white race; seeing no friend or family member at least once a month vs. 1 or more; having nobody to care for you if you become seriously ill or disabled vs. having someone); healthcare (rural urban commuting area codes 9 and 10 vs all others, or residence in a county with poor availability of primary care physicians, defined as Health Professional Shortage Area [HPSA] vs. partial HPSA or not

HPSA); neighborhood and community characteristics (living in a zip code with >25% of residents living below Federal poverty line, living in the worst ranked states for public health infrastructure, bottom 20% vs. all others).

We created the public health infrastructure metric based on data from America's Health Ranking (AHR)²² (Supplemental Table I). We examined state rankings from 1993–2002 (ten-year period prior to the beginning of REGARDS enrollment in 2003). For this analysis, nine states that fell into the bottom 20% of US states for public health infrastructure for at least 8 years (80% of the 10 year period) were considered to have poor public health infrastructure (Supplemental Table II).

Covariates Collected at Baseline

Demographic factors included the participant's age at baseline, sex, and region. Medical conditions included self-reported history of heart disease; high blood pressure (antihypertensive medication use or blood pressure 140/90 mm Hg); dyslipidemia (self-report of a diagnosis, use of lipid-lowering medications, total cholesterol 200 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, or low-density lipoprotein cholesterol >100 mg/dL); diabetes (use of hypoglycemic medications or fasting blood glucose 126 mg/dL or non-fasting glucose 200 mg/dL); atrial fibrillation (self-report or present on baseline ECG); and left ventricular hypertrophy (LVH) based on the baseline ECG using the Sokolow criteria.²³ Use of medications included antihypertensives, statins, and insulin. Functional status was defined by the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores from the Short Form-12.²⁴ Health behaviors include cigarette smoking (current smoker vs. former or never), alcohol use (heavy drinking based on sex-specific National Institute of Alcohol Abuse And Alcoholism cut points vs. moderate or no consumption)²⁵, physical activity (enough activity to work up a sweat on most days of the week vs. no physical activity), and Mediterranean diet adherence score (highest quartile vs. others).²⁶ Physiological variables included body mass index (BMI), high sensitivity c-reactive protein (hsCRP), urinary albumin-to-creatinine ratio (ACR), and estimated glomerular filtration rate (eGFR) using the CKD-Epi equation.²⁷

Statistical analyses

We examined bivariate associations between 10 dichotomized candidate SDOH and incident stroke in separate Cox proportional hazards models²⁸, controlling for age at baseline and sex. SDOH that were significantly associated with stroke at the $p < 0.10$ level and were retained for further analyses. We evaluated collinearity among SDOH using a variance inflation factor (VIF) threshold of 5.0.²⁹ Using seven SDOH ($p < 0.10$), we created a SDOH count variable: 0, 1, 2, and 3.

Since previous studies suggested age differences in the relationship between SDOH and stroke,³⁰ we examined interactions between SDOH count and age.

We described baseline characteristics across groups defined by SDOH counts for each age stratum. We then estimated Kaplan Meier survival functions for groups defined by SDOH counts separately by age groups, and calculated incidence rates of stroke per 1,000 person-years with 95% CIs.

To determine if the SDOH count had an independent effect on incident stroke, we fitted minimally adjusted Cox proportional hazards models adjusting for age and sex for each age stratum. We then fitted fully adjusted Cox models that included potential confounders captured at baseline.

We conducted additional sensitivity analyses: a) exploring alternative National Heart, Lung, and Blood Institute (NHLBI) definitions of the Stroke Belt³¹, b) adding exposure to tobacco smoke to multivariable models, c) adding Dietary Approaches to Stop Hypertension (DASH) diet scores to the healthy diet variable (Supplemental Table III).

To minimize bias due to missing data, we performed multiple imputations by chained equations.³² Analyses were conducted in SAS version 9.4 and R 3.4.1.

Results

The analytic sample included 27,813 adults (Supplemental Figure I).

Seven SDOH were associated with stroke ($p < 0.10$) and retained for further analysis (Table 1). VIF values were < 1.3 , confirming no collinearity among retained SDOH.

The mean age of the sample was 64.7 years (SD 9.4) at baseline; 55.4% were women and 40.4% were black (Table 2).

We observed statistically significant age interactions at age 75 years ($p = 0.41$, $p = 0.06$, and $p = 0.01$ for 1, 2, and 3 SDOH, respectively), and stratified subsequent analyses by age < 75 and ≥ 75 years. From the clinical perspective, age ≥ 75 years is a potent risk factor for stroke, as stroke rates are highest among adults ≥ 75 .^{33,34}

The younger cohort (< 75 years) included 83.4% of participants. Of these, 55.9% were women and 41.6% were blacks. The older cohort (≥ 75 years) included 52.6% women and 34.7% blacks. In both age strata, individuals with a greater number of SDOH were more likely to be black women, have low annual income, live in an impoverished neighborhood, and reside in the states with poor public health infrastructure. Individuals with a greater number of SDOH were more likely to have a history of hypertension or diabetes, taking antihypertensive medications and insulin. Compared to the younger cohort, the older cohort had a smaller percentage of Stroke Belt or Buckle residents, and a greater proportion with a history of heart disease, atrial fibrillation, LVH, antihypertensive medication use, and statin use.

Over a median follow up of 9.5 years, we observed 1,470 incident strokes. Stroke incidence was lower in the younger cohort (< 75 years), compared to the older cohort (≥ 75 years) (Figure 2). In the younger cohort, the incidence of stroke increased with each additional SDOH. Stroke incidence was 2 times larger for individuals with 3 SDOH compared to those without SDOH. In the older cohort, the incidence of stroke was 1.3 times higher for individuals with 3 SDOH compared with those with no SDOH. The absolute difference in stroke incidence between individuals without SDOH vs. those with 3 SDOH was 3.42 per 1000 person-years for the younger group and 3.72 for the older group.

Kaplan Meier curves are shown in Figure 3. In the younger cohort, participants with a greater number of SDOH had a greater probability of incident stroke. The log-rank test did not show statistically significant differences among survival functions in the older cohort ($p=0.19$).

In minimally adjusted Cox proportional hazards models, for the younger cohort, the risk of incident stroke gradually rose as the number of SDOH increased (Table 3). Compared to adults without any SDOH, the HR for incident stroke was 1.44 (95% CI 1.07–1.78) for individuals with 1 SDOH, 1.82 (95% CI 1.48–2.24) for those with 2 SDOH, and 2.38 (95% CI 1.94–2.92) for those with 3 SDOH, respectively. The upward trend of incident stroke risk was significant in the older cohort, but only the HR for 3 SDOH reached statistical significance (HR 1.40, 95% CI 1.02–1.92).

In fully adjusted Cox models, observed effects from the minimally adjusted models were attenuated across both age groups, but the upward risk trend persisted among those <75 years of age (p for trend <0.001). Compared to having no SDOH, having 1 SDOH was associated with an adjusted HR of 1.26 (95% CI 1.02–1.55), 2 SDOH were associated with a HR of 1.38 (95% CI 1.12–1.71), and 3 SDOH were associated with a HR of 1.51 (95% CI 1.21–1.89). In the older cohort, none of the observed effects reached statistical significance.

Sensitivity analyses show that in fully adjusted models, results for the <75 year old cohort remained unchanged. For the 75 year old cohort, results remained insignificant for all levels of the exposure (Supplemental Table IV).

Discussion

We observed statistically significant associations between seven SDOH and increased risk of incident stroke. Importantly, consistent with existing stroke literature³⁰, we observed statistically significant interactions between age and stroke risk factors. That is, when selected SDOH were operationalized as a count reflecting the combined burden of SDOH within the same individual, we found that each incremental increase in SDOH was significantly associated with an increased risk of stroke for individuals younger than 75, with stroke incidence nearly two and a half times higher for those with three or more SDOH compared with those without SDOH; these excess risks remained significant after adjusting for a host of individual characteristics including well known stroke risk factors. Consistent with the existing literature, the effect did not reach statistical significance in older individuals,³⁰ and selective survival may be one of the most likely explanation of this important finding.

Our study contributes to the literature on SDOH and incident stroke in several ways. To date, many previous studies focused on either individual-level^{30,35,36} or area-level SDOH.^{36–39} We defined SDOH as a combination of individual-level as well as neighborhood-level factors, and evaluated their combined effect on incident stroke. Moreover, many prior studies explored relationships between SDOH and incident stroke, limiting definitions of SDOH to only SES factors.^{8,18,30,37} We expanded the list of SDOH to represent five major domains

of SDOH including economic stability, education, social and community context, healthcare, neighborhood and the built environment.²¹

Although some studies have assessed associations between multiple SDOH within individuals and incidence of stroke, the SDOH in these studies were combined in composite indices,^{37,40–42} such as the Social Deprivation Index (SDI).⁴⁰ The SDI used similar variables to the SDOH count in our study. Butler, et al,⁴⁰ found that the SDI was positively associated with poor health outcomes, and this finding persisted after adjustment for other measures of healthcare access. The SDI was more strongly associated with health outcomes than poverty alone.⁴⁰ However, the SDI may not be as interpretable as a count of SDOH, which was used in our study. Furthermore, operationalizing SDOH as a count is easier to calculate and interpret, which is appealing in clinical settings.

Our finding of a graded effect of multiple SDOH on the risk of incident stroke especially in younger individuals is concordant with a recent REGARDS study on a treatment disparity in cardiovascular disease prevention. Schroff, et al⁴³, observed that among individuals with an indication for statins, only 45% of those with 4+ SDOH were taking statins compared to 65% of individuals without any SDOH.⁴³ These findings support the value of examining multiple SDOH to identify particularly high-risk individuals for effective population health management.

Although eradicating SDOH may be beyond the scope of individual physicians or health systems, our study adds to understanding the crucial role of SDOH in impacting health outcomes. Durable policy solutions are needed to eliminate the deleterious influences of SDOH on health outcomes, especially for adults younger than 75 years. Ample evidence shows that there is need for continued improvement in the prevention of and control of stroke risk factors such as behavioral interventions to help people to quit smoking, eat a healthy diet, and be physically active.³³ While prevention and better control of stroke risk factors cannot entirely overcome the influence of the cumulative burden of SDOH, considering these factors may substantially reduce overall risks. In our study, adults with 3 SDOH had minimally adjusted HR 2.38 that reduced to 1.51 after accounting for physiologic risk factors. While most physicians likely already recognize that certain demographic groups face poor health outcomes, our study elucidates the magnitude of this residual risk, which has not yet been reported.

Our study's strengths include the large, national biracial sample, rich baseline data, and rigorously adjudicated stroke outcomes. Limitations include the use of some self-reported variables, which may introduce a risk of recall bias. Tobacco exposure information was limited to cigarette smoking at baseline. Additional SDOH such as perceived discrimination or environmental factors were not available in our dataset. The reliance of REGARDS procedures on reaching participants may have missed some stroke events, but we have shown that the magnitude of this limitation is similar to that in other epidemiology studies.^{42,44,45}

Conclusions

We found that among adults <75 years, as the number of SDOH within the same individual increased, the incidence of stroke increased and was nearly two and a half times higher in those with 3 SDOH compared to those with no SDOH. After controlling for potential confounders, stroke risk remained 50% higher among those with 3 SDOH compared to those without any SDOH. Individuals with multiple SDOH such as black women living in impoverished neighborhoods in the Southeast may be excellent targets for focused interventions to reduce incidence of strokes. Healthcare professionals should consider heightening their vigilance to prevent the development of risk factors and achieve improved physiologic risk factor control in persons with multiple SDOH. Elimination of disparities in the incidence of stroke may require societal interventions targeted at SDOH, especially in younger individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures

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Non-standard Abbreviations and Acronyms:

REGARDS	REasons for Geographic And Racial Differences in Stroke
SDOH	Social Determinants Of Health
DASH	Dietary Approaches to Stop Hypertension

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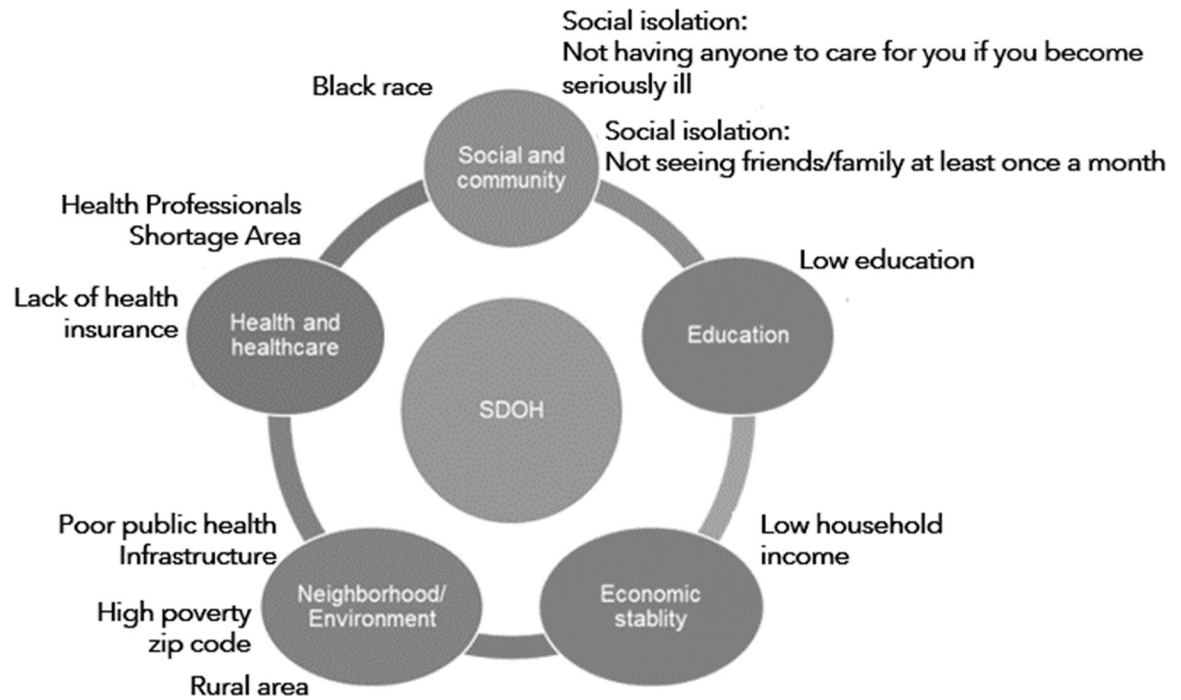


Figure 1: SDOH Guided by the Healthy People 2020 Conceptual Framework
Black race, social isolation; low education, low annual household income, living in a rural area; living in a zip code with high poverty, living in a Health Professional Shortage Area, lack of health insurance, and living in a state with poor public infrastructure.

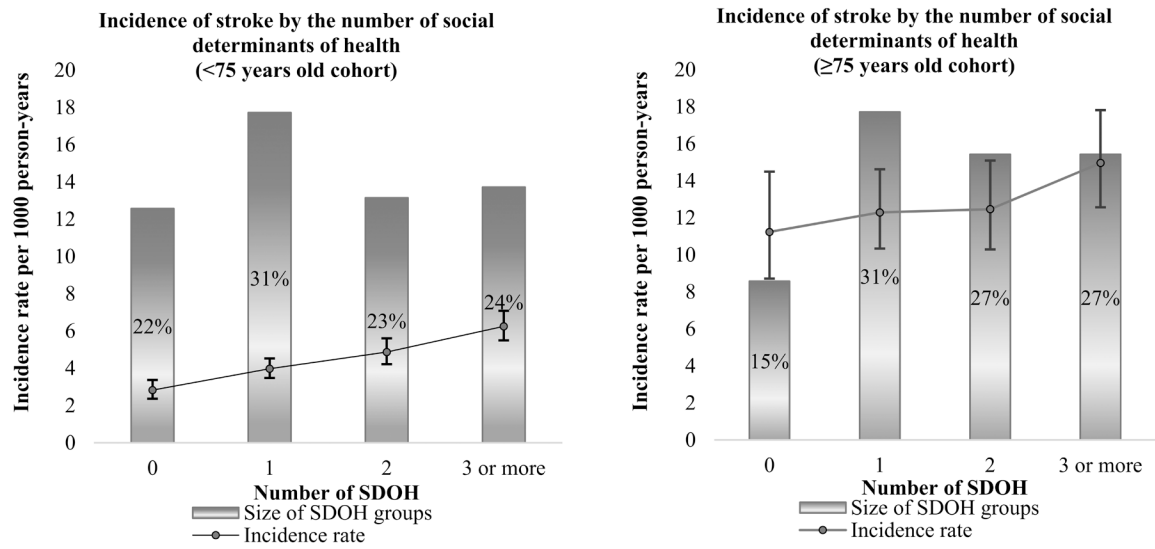


Figure 2.
Age Adjusted Incidence of Stroke per 1,000 Person-years

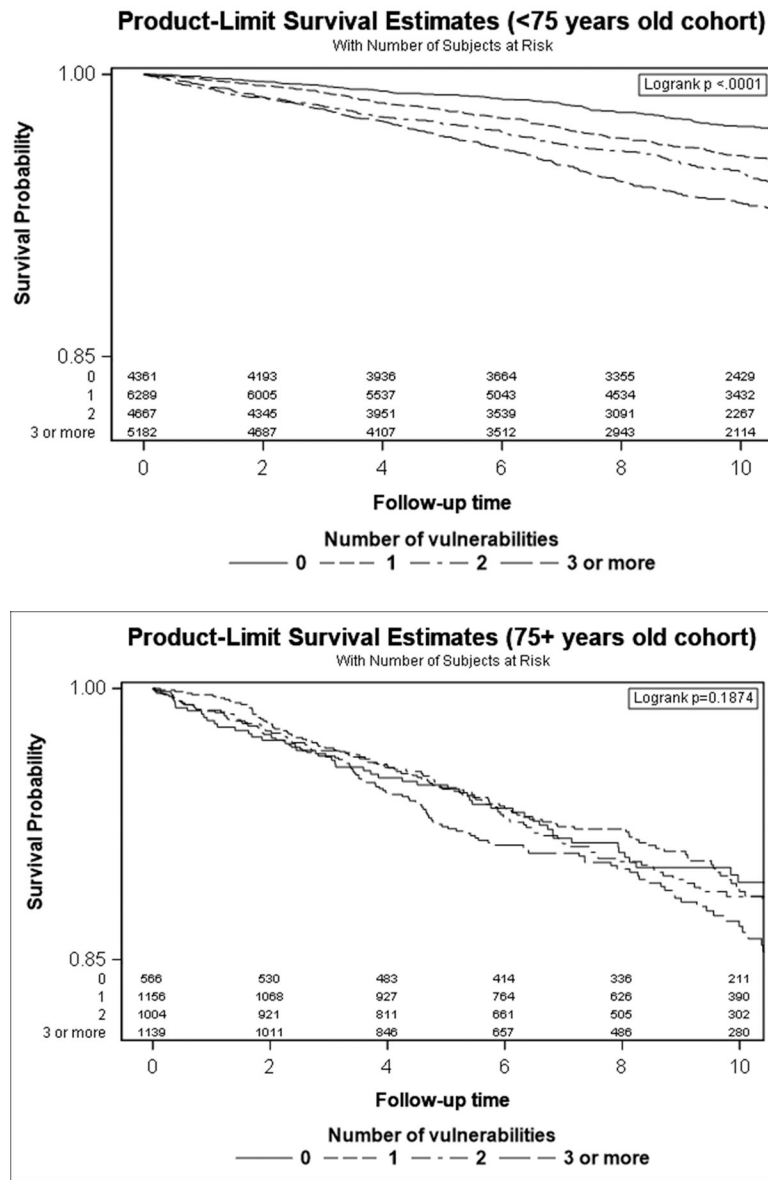


Figure 3. Kaplan-Meier Curves by Age Strata and Number of SDOH and Incident Stroke

Table 1.

Minimally Adjusted Associations of Each SDOH with Stroke Outcomes

SDOH	HR (95% CI) [†]	<i>P</i>
Black race	1.34 (1.20, 1.48) [*]	<.0001
Low education	1.32 (1.14, 1.52) [*]	0.001
Low annual household income	1.59 (1.41, 1.79) [*]	<.0001
Zip code poverty	1.25 (1.10, 1.42) [*]	0.001
Residence in Health Professional Shortage Areas	1.01 (0.91, 1.12)	0.921
Residence in the worst ranked states for public health infrastructure	1.17 (1.05, 1.30) [*]	0.003
Lack of health insurance	1.46 (1.16, 1.84) [*]	0.002
Rural residence	1.02 (0.74, 1.42)	0.902
Social isolation (Not seeing friends or family members at least once a month)	1.25 (1.00, 1.60) [*]	0.054
Social isolation (Not having anyone to care for you if become seriously ill or disabled)	1.02 (0.88, 1.19)	0.775

*
p<0.10

[†]Adjusted for age and gender

Table 2. Participants' Characteristics by Age Strata and Number of Social Determinants of Health (SDOH)

Number of SDOH	<75 years					75 years						
	0	1	2	3 +	0	1	2	3 +	0	1	2	3 +
N	4,361	6,289	4,667	5,182	566	1,156	1,004	1,139	N (%) or Mean (SD) or Median [IQR]			
Social Determinants of Health:												
Black race	0 (0.0)	1968 (31.3)	2496 (53.5)	4341 (83.8)	0 (0.0)	146 (12.6)	382 (38.0)	898 (78.8)	0 (0.0)	18 (1.6)	119 (11.9)	614 (53.9)
Low education	0 (0.0)	79 (1.3)	370 (7.9)	1754 (33.8)	0 (0.0)	657 (56.8)	821 (81.8)	972 (85.3)	0 (0.0)	25 (2.2)	150 (14.9)	673 (59.1)
Low annual household income	0 (0.0)	1609 (25.6)	2890 (61.9)	4279 (82.6)	0 (0.0)	2 (0.2)	10 (1.0)	44 (3.9)	0 (0.0)	2 (0.2)	10 (1.0)	44 (3.9)
Zip code poverty	0 (0.0)	238 (3.8)	923 (19.8)	2976 (57.4)	0 (0.0)	274 (23.7)	456 (45.4)	630 (55.3)	0 (0.0)	34 (2.9)	70 (7.0)	113 (9.9)
Lack of health insurance	0 (0.0)	80 (1.3)	308 (6.6)	1270 (24.5)	0 (0.0)	477 (9.2)	556 (55.4)	688 (60.4)	0 (0.0)	543 (47.0)	556 (55.4)	688 (60.4)
Residence in the states with poor public health infrastructure	0 (0.0)	2145 (34.1)	2061 (44.2)	3148 (60.7)	0 (0.0)	79.3 (3.7)	79.3 (3.8)	79.6 (4.0)*	0 (0.0)	173 (30.6)	173 (30.6)	173 (30.6)
Not seeing friends or family members at least once a month	0 (0.0)	170 (2.7)	286 (6.1)	477 (9.2)	0 (0.0)	516 (44.6)	546 (54.4)	650 (57.1)	0 (0.0)	3311 (63.9)	3311 (63.9)	3311 (63.9)
Demographic Factors:												
Female	1951 (44.7)	3257 (51.8)	2779 (59.5)	3311 (63.9)	173 (30.6)	543 (47.0)	556 (55.4)	688 (60.4)	1951 (44.7)	3257 (51.8)	2779 (59.5)	3311 (63.9)
Age	60.8 (7.1)	61.7 (7.1)	62.1 (7.2)	61.8 (7.2)	79.3 (3.9)	79.3 (3.7)	79.3 (3.8)	79.6 (4.0)*	60.8 (7.1)	61.7 (7.1)	62.1 (7.2)	61.8 (7.2)
Southeast region residence	1750 (40.1)	3533 (56.2)	2860 (61.3)	3494 (67.4)	190 (33.6)	516 (44.6)	546 (54.4)	650 (57.1)	1750 (40.1)	3533 (56.2)	2860 (61.3)	3494 (67.4)
Medical Conditions:												
History of heart disease	548 (12.6)	907 (14.4)	718 (15.4)	809 (15.6)	179 (31.6)	340 (29.4)	266 (26.5)	252 (22.1)	548 (12.6)	907 (14.4)	718 (15.4)	809 (15.6)
Hypertension	1828 (41.9)	3365 (53.5)	2810 (60.2)	3579 (69.1)	332 (58.7)	733 (63.4)	694 (69.1)	838 (73.6)	1828 (41.9)	3365 (53.5)	2810 (60.2)	3579 (69.1)
Dyslipidemia	2497 (57.3)	3602 (57.3)	2616 (56.1)	2822 (54.5)*	347 (61.3)	687 (59.4)	579 (57.7)	626 (55.0)*	2497 (57.3)	3602 (57.3)	2616 (56.1)	2822 (54.5)*
Diabetes	468 (10.7)	1090 (17.3)	1088 (23.3)	1585 (30.6)	71 (12.5)	172 (14.9)	213 (21.2)	319 (28.0)	468 (10.7)	1090 (17.3)	1088 (23.3)	1585 (30.6)
Atrial fibrillation	252 (5.8)	441 (7.0)	371 (7.9)	428 (8.3)	92 (16.3)	159 (13.8)	118 (11.8)	115 (10.1)	252 (5.8)	441 (7.0)	371 (7.9)	428 (8.3)
Left ventricular hypertrophy	52 (1.2)	141 (2.2)	141 (3.0)	265 (5.1)	27 (4.8)	38 (3.3)	57 (5.7)	66 (5.8)	52 (1.2)	141 (2.2)	141 (3.0)	265 (5.1)
Use of Medications:												
Antihypertensives	1866 (42.8)	3321 (52.8)	2805 (60.1)	3399 (65.6)	389 (68.7)	818 (70.8)	728 (72.5)	877 (77.0)	1866 (42.8)	3321 (52.8)	2805 (60.1)	3399 (65.6)
Statins	1337 (30.7)	1883 (29.9)	1359 (29.1)	1412 (27.2)	238 (42.0)	443 (38.3)	330 (32.9)	369 (32.4)	1337 (30.7)	1883 (29.9)	1359 (29.1)	1412 (27.2)
Insulin	86 (2.0)	245 (3.9)	277 (5.9)	481 (9.3)	16 (2.8)	29 (2.5)	46 (4.6)	94 (8.3)	86 (2.0)	245 (3.9)	277 (5.9)	481 (9.3)

Number of SDOH	<75 years				75 years			
	0	1	2	3+	0	1	2	3+
Functional Status:								
SF-12 physical component score	53.1 [47.3, 55.9]	51.7 [44.2, 55.5]	49.7 [39.7, 54.7]	46.9 [36.3, 53.2]	51.4 [44.1, 55.3]	48.7 [39.4, 54.2]	46.5 [37.9, 53.0]	45.6 [35.9, 52.4]
SF-12 mental component score	56.9 [53.3, 58.8]	56.9 [52.9, 59.3]	56.6 [50.9, 59.4]	55.3 [47.2, 58.9]	57.9 [55.2, 60.0]	57.8 [54.0, 60.2]	57.2 [52.7, 59.9]	55.9 [49.5, 59.9]
Health Behaviors								
Current cigarette smoking	438 (10.0)	830 (13.2)	809 (17.3)	1219 (23.5)	17 (3.0)	60 (5.2)	82 (8.2)	79 (6.9)
Risky alcohol consumption	265 (6.1)	288 (4.6)	167 (3.6)	150 (2.9)	35 (6.2)	34 (2.9)	21 (2.1)	16 (1.4)
Physical activity	3176 (72.8)	4374 (69.6)	3043 (65.2)	3206 (61.9)	371 (65.5)	701 (60.6)	561 (55.9)	600 (52.7)
High adherence to Mediterranean diet	987 (22.6)	1390 (22.1)	807 (17.3)	660 (12.7)	156 (27.6)	275 (23.8)	185 (18.4)	132 (11.6)
Physiological Factors:								
Body mass index	28.4 (5.3)	29.3 (5.9)	30.3 (6.6)	31.2 (7.1)	26.5 (4.1)	27.0 (4.6)	27.4 (5.2)	28.5 (5.7)
Systolic blood pressure	122.8 (14.7)	125.6 (15.5)	127.2 (16.23)	130.5 (17.3)	128.9 (14.9)	130.3 (17.8)	131.9 (16.8)	133.2 (18.4)
Diastolic blood pressure	75.6 (8.9)	76.6 (9.4)	77.1 (9.4)	78.8 (10.3)	73.0 (9.3)	74.0 (9.8)	74.5 (9.6)	75.0 (10.1)
Total cholesterol	192.7 (37.5)	193.0 (39.3)	194.5 (40.7)	194.1 (42.2)*	178.5 (35.2)	183.7 (37.7)	187.1 (38.6)	189.9 (41.5)
High density lipoprotein cholesterol	48.0 [39.0, 60.0]	49.0 [40.0, 61.0]	49.0 [40.0, 61.0]	50.0 [41.0, 61.0]	48.0 [39.0, 59.0]	49.0 [39.0, 60.0]	50.0 [40.0, 62.0]	51.0 [42.0, 63.0]
C-reactive protein 3	1207 (27.7)	2241 (35.6)	1963 (42.1)	2484 (47.9)	173 (30.6)	389 (33.7)	356 (35.5)	440 (38.6)
Urinary Albumin/ Creatinine ratio 30 (mg/g)	357 (8.2)	632 (10.1)	631 (13.5)	934 (18.0)	95 (16.8)	207 (17.9)	215 (21.4)	281 (24.7)
Estimated GFR	90.1 [78.6, 97.3]	90.2 [77.5, 99.1]	90.9 [76.4, 102.1]	93.8 [78.4, 107.6]	72.7 [60.4, 82.9]	72.3 [59.9, 83.4]	72.9 [57.0, 84.5]	72.6* [56.4, 85.3]

* p>0.05, no asterisk denotes statistical significance

Note. *p*-values correspond to ANOVA, Kruskal-Wallis test, Pearson's chi-squared or Fisher's exact test, depending on variable's distribution

Table 3.

Number of SDOH and Associations with Stroke by Age Strata

Number of SDOH	<75 years		75 years	
	Minimally adjusted [†]	Fully adjusted [‡]	Minimally adjusted [†]	Fully adjusted [‡]
	HR (95% CI)			
None	<i>(reference)</i>		<i>(reference)</i>	
1	1.44 (1.07, 1.78) [*]	1.26 (1.02, 1.55) [*]	1.13 (0.82, 1.55)	0.92 (0.66, 1.26)
2	1.82 (1.48, 2.24) [*]	1.38 (1.12, 1.71) [*]	1.15 (0.83, 1.60)	0.94 (0.66, 1.33)
3+	2.38 (1.94, 2.92) [*]	1.51 (1.21, 1.89) [*]	1.40 (1.02, 1.92) [*]	0.97 (0.69, 1.35)
<i>p</i> for trend	<.0001	0.0002	0.03	0.97

*
p<0.05[†]Adjusted for age and gender[‡]Adjusted for all covariates in Table 2