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Smoking and Mortality in Stroke Survivors: Can We Eliminate the Paradox?

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Abstract

Background—Many studies have suggested that smoking does not increase mortality in stroke survivors. Index event bias, a sample selection bias, potentially explains this paradoxical finding. Therefore, we compared all-cause, cardiovascular disease (CVD), and cancer mortality by cigarette smoking status among stroke survivors using methods to account for index event bias.

Methods and Results—Among 5,797 stroke survivors aged ≥45 years who responded to the National Health Interview Survey years 1997-2004, an annual, population-based survey of community-dwelling US adults, linked to the National Death Index, we estimated all-cause, CVD, and cancer mortality by smoking status using Cox proportional regression and propensity score analysis to account for demographic, socioeconomic and clinical factors. Mean follow-up was 4.5 years. From 1997 to 2004, 18.7% of stroke survivors smoked. There were 1,988 deaths in this stroke survivor cohort, with 50% of deaths due to CVD and 15% due to cancer. Current smokers had an increased risk of all-cause mortality (HR, 1.36; 95% CI, 1.14-1.63) and cancer mortality (HR, 3.83; 95% CI, 2.48-5.91) compared with never smokers, after controlling for demographic, socioeconomic and clinical factors. Current smokers had an increased risk of CVD mortality

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Conflicts of Interest and Disclosures
None

controlling for age and sex (HR, 1.29; 95% CI, 1.01-1.64) but this risk did not persist after controlling for socioeconomic and clinical factors (HR, 1.15; 95% CI, 0.88-1.50).

Conclusions—Stroke survivors who smoke have an increased risk of all-cause mortality which is largely due to cancer mortality. Socioeconomic and clinical factors explain stroke survivors' higher risk of CVD mortality associated with smoking.

Introduction

Current smoking is a known risk factor for stroke, with evidence of a strong dose-response relationship.[1-3] The proportion of stroke attributable to current smoking is nearly 20%.[4] Despite clinical practice guidelines recommending smoking cessation for survivors of stroke or transient ischemic attack for over 15 years,[5-8] 18-35% of survivors smoke.[9, 10]

While smoking increases the risk of mortality in survivors of myocardial infarction, studies conflict on whether smoking increases the risk of mortality in survivors of stroke.[1, 11-18] Many reports suggest that smoking does not increase the risk of mortality in stroke survivors.[1, 11-16] This paradoxical finding may be due to a number of methodological issues including index event bias, measurement bias, and uncontrolled confounding.

Index event bias is a type of sample selection bias. Smits and colleagues define index event bias, "As a result of selection of patients on the basis of previous disease: (1) risk factors become inversely associated when they are not in the unselected population, and (2) the crude association between the risk factor of interest and disease becomes biased toward the null."[19] A classic example is that patent foramen ovale (PFO) appears to increase the risk of cryptogenic stroke in the general population but not in stroke survivors.[20-22] However, adults with cryptogenic stroke and PFO are young and unlikely to have other stroke risk factors like hypertension, diabetes, and hypercholesterolemia.[20] Although individuals with cryptogenic stroke due to PFO are at increased risk of recurrent stroke, the fact that individuals with cryptogenic stroke without PFO are at an even higher risk of recurrent stroke (due to their greater vascular burden) makes it appear that PFO is not a risk factor for recurrent stroke.

Moreover, smoking status is often measured during stroke hospitalization. This approach can lead to measurement bias because 20-40% of acute stroke patients stop smoking.[10, 23, 24] Several studies also failed to adjust for known confounders of the smoking-mortality relationship (e.g., age, stroke disability, socioeconomic status).[25] Each of these methodological issues can bias results toward the null and potentially explains the frequent paradoxical conclusion that smoking does not increase mortality risk in stroke survivors. Also, most data on the risk of smoking in stroke survivors are from the 1990s or earlier, prior to major improvements in stroke survival, acute stroke care (e.g., thrombolysis, organized inpatient stroke care), and secondary cardiovascular disease (CVD) prevention[26] that may influence the risk and type of death from smoking.

To address these limitations, we determined whether current smoking is an independent risk factor of all-cause, CVD, and cancer mortality among contemporary stroke survivors using data from an annual, population-based survey of community-dwelling US adults that is

linked to the National Death Index. To minimize potential index event bias and uncontrolled confounding, we used Cox proportional regression with forced entry of covariates and post hoc propensity score analysis to thoroughly account for clinical, demographic, and socioeconomic factors. By assessing smoking and mortality in community-dwelling stroke survivors, we avoided misclassifying those who quit smoking during the acute stroke period.

Methods

Study Population

The National Health Interview Survey (NHIS) is a continuing, in-person household survey of the civilian, non-institutionalized US population that is nationally representative and conducted annually by the National Center for Health Statistics (NCHS) using face-to-face interviews.[27] Data from NHIS survey years 1997 to 2004, which use similar survey designs and data collection methods, were combined for this report.[27] The final response rates for the sample adult survey years 1997 to 2004 ranged from 70% to 80%.[27]

We identified stroke survivors aged 45 and older by respondents who answered yes to the question, “Have you ever been told by a doctor or other health professional that you had a stroke?” The NHIS over-samples Black and Hispanic persons at approximate rates of 1.5:1 for Blacks and 2:1 for Hispanics.[28] Place of residence was identified by geographic region. The US Census Bureau groups the 50 states and the District of Columbia for statistical purposes into 4 geographic regions—Northeast (ME, VT, NH, MA, CT, RI, NY, NJ, PA), Midwest (OH, IL, IN, MI, WI, MN, IA, MO, ND, SD, KS, NE), South (DE, MD, DC, WV, VA, KY, TN, NC, SC, GA, FL, AL, MS, LA, OK, AR, TX) and West (WA, OR, CA, NV, NM, AZ, ID, UT, CO, MT, WY, AK, HI).[27] The NHIS was designed to produce population-based estimates for the entire US and for each of the 4 census regions.[28]

We combined self-reports of cigarette smoking (ever was defined as smoking at least 100 cigarettes in lifetime) to create 3 mutually exclusive categories: smoked never, in the past, or currently.

Outcome Measures

All-cause mortality was the primary outcome measure. Mortality of NHIS respondents through December 31, 2006 was ascertained using the public-use NHIS Linked Mortality Files that have matched National Death Index (NDI) data for >95% of NHIS respondents for years 1986-2004.[27, 29, 30] The NDI has death certificate information for all US deaths since 1986. The 1986–2004 NHIS Linked Mortality Files provide a unique data source for examining the associations between demographic, socioeconomic, and health factors and subsequent mortality in a large heterogeneous sample that is representative of the US population.[31] Time to death (months) was calculated from mid-quarter date of interview to mid-quarter date of death because dates of interview and death were only given by quarter and year. Mortality of each NHIS cohort ascertained by the linked NDI data correspond closely to that of the US population.[31]

The two secondary outcome measures were cardiovascular disease (CVD)-related death and cancer-related death. The NDI obtains cause of death from death certificates and classifies

cause of death using 113 selected causes defined by ICD-10 codes.[29] The proportion of survivors who died of CVD-related causes was calculated by dividing the number of deaths of a cardiovascular cause (ICD-10 I00-I78) by the number of adults who did not die or who died from a non-cardiovascular cause. The proportion of survivors who died of cancer-related causes was calculated by dividing the number of deaths of a cancer cause (ICD-10 C00-C97) by the number of adults who did not die or who died from a non-cancer cause.

Covariates

Covariates were selected based on literature review. Demographic factors were self-reported sex, race (white, black, other), Hispanic ethnicity, marital status, and region (Northeast, Midwest, South, West). Socioeconomic factors were self-reported annual household income (<$20,000, ≥$20,000, missing/unreported), education (<high school, ≥high school), and insurance status (Private, Medicare and Medicaid, Medicare only, other, uninsured). Clinical factors were self-reported and included health status, body mass index (BMI), serious mental illness, histories of hypertension, coronary artery disease, diabetes mellitus, emphysema, heart disease and cancer, and functional disability attributable to stroke. Low self-reported health status was defined as poor or fair on a 5-point Likert scale. Body mass index (BMI, kg/m^2) was calculated from self-reported height and weight and BMI categories defined according to US guidelines[32] (Underweight <18.5, Normal 18.5-24.9, Overweight 25-29.9,Obese ≥30). Serious mental illness was determined using the K6 scale of nonspecific psychological distress developed for use in the NHIS core sample adult survey.[33] The K6 scale asks respondents to report how frequently they experienced six symptoms of psychological distress in the past 30 days. A cut-point of <13 and ≥13 on the K6 scale has total classification accuracy of 92% in predicting serious mental illness in the general population.[33]

Functional disability attributable to stroke was defined by the adult respondent's report of having difficulty, without using special equipment, with 1 or more specific named functional activities (walk a quarter mile, walk up 10 steps, stand for 2 hours, sit for 2 hours, stoop/bend/kneel, reach over head, grasp objects, lift/carry 10 pounds, push large object, go out to events, social activities, or acts to relax) and that stroke caused his/her functional disability. The NHIS only asks adult respondents who have functional disability attributable to stroke to report the timing of the stroke.

Statistical Analysis

The outcome measure and covariates were compared using ANOVA or χ^2 test as indicated and US population-based estimates were calculated. We calculated age-standardized rates of death using the year 2000 Census population as the standard and compared death rates by smoking status (never, former, and current).[34] With Cox proportional hazard regression and forced entry of all covariates, we compared hazards of death by smoking status, after adjusting for all demographic, socioeconomic, and clinical factors.

We assessed for heterogeneity of the smoking-mortality association by examining interactions of smoking with age, sex, BMI, diabetes, stroke duration, or history of cancer. All analyses used SAS-callable SUDAAN software, version 9.0.1 (Research Triangle Inst)

to obtain proper variance estimations that accounted for the complex NHIS sampling design and results that were weighted to reflect national population estimates. We used the NHIS survey weights that were adjusted to account for participants who were ineligible for linkage to the NDI.

To further control for potential index event bias affecting the analyses of CVD mortality in this population with CVD (stroke), we performed a post hoc propensity score analysis of CVD mortality by smoking status matching current smokers and never smokers by age, gender, BMI category, annual household income, health status, neurological disability attributable to stroke, and histories of coronary artery disease, diabetes, and emphysema, and accounting for the complex survey design. Methods and sample data are available in the **Online Supplement**. We then performed Cox proportional hazard regression comparing hazards of CVD mortality by smoking status before and after full multivariable adjustment excluding the variables used for matching. We repeated this analysis matching former smokers and never smokers.

Sensitivity Analysis

To assess the robustness of our results, we repeated the entire analysis after excluding those with BMI <18.5 kg/m^2 or after excluding those with a history of cancer.

Standard Protocol Approvals, Registrations, and Patient Consents

The University of Michigan institutional review board ruled the project exempt.

Results

We identified 5,797 stroke survivors aged 45 or older, representing an estimated 4.03 million stroke survivors, responding to the NHIS years 1997 to 2004 and eligible for mortality follow-up in the linked NDI years 1997 to 2006. There were 1,988 deaths in this stroke survivor cohort over a mean follow-up time of 4.5 (0.04) years, representing an estimated 1,406,000 US deaths. Of the deaths, 357 (28.4%) were among current smokers, 838 (35.0%) among former smokers, and 793 (33.1%) among never smokers.

Subject characteristics by smoking status are shown in **Table 1**. During the period 1997 to 2004, 18.7% of stroke survivors, approximately 800,000 individuals, reported current smoking. Current smokers were younger with a mean age of 61.6 years compared with 71.8 years for never smokers. Compared with never smokers, a higher percentage of current smokers were male, described fair or poor health status, lacked health insurance, reported a history of emphysema or coronary artery disease, and met criteria for serious mental illness. Never smokers were more likely to be married, Hispanic, and report a history of hypertension, diabetes, heart disease, or cancer.

Subject characteristics by mortality status are shown in **Table 2**. Compared with survivors, those who died during follow-up were disproportionately male, disabled from their stroke, less educated, and reported more medical co-morbidities including coronary artery disease, chronic kidney disease, and cancer.

All-Cause Mortality Rates by Smoking Status

Age-standardized rates (standard errors) for all-cause mortality for never vs. current smokers were 46.2 (2.5) vs. 69.2 (5.4) per 1000 person-years (**Table 3**). Current smokers had higher age-standardized all-cause mortality rates across all age strata.

Current smokers had an increased risk of all-cause mortality (hazard ratio, HR, 1.36; 95% CI, 1.14-1.63) compared with never smokers after controlling for demographic, socioeconomic, and clinical factors. There was no heterogeneity in the smoking-mortality association by age, sex, BMI, stroke duration, diabetes, and history of cancer (**data not shown**). Former smokers had greater risk of all-cause mortality compared to never smokers (HR, 1.15; 95% CI, 1.02-1.29) but lower risk when compared to current smokers (HR, 0.84; 95% CI, 0.71-1.01; P=0.058).

Sensitivity Analysis

Results were similar in analyses that excluded underweight stroke survivors (BMI <18.5 kg/m^2) or stroke survivors with a history of cancer. After controlling for demographic, socioeconomic, and clinical factors, current smokers had an increased risk of all-cause mortality compared with never smokers among stroke survivors with a BMI ≥18.5 kg/m^2 (hazard ratio, 1.35; 95% CI, 1.11-1.64) and among stroke survivors without a history of cancer (hazard ratio, 1.36; 95% CI, 1.13-1.64).

Cause-Specific Mortality Rates by Smoking Status

Of 1,988 deaths, 980 (50.0%) were due to CVD, representing an estimated 704,000 deaths, and 294 (14.5%) were due to cancer, representing an estimated 204,000 deaths. Current smokers had an increased risk of cancer mortality (hazard ratio, 3.83; 95% CI, 2.48-5.91) compared with never smokers after controlling for demographic, socioeconomic, and clinical factors. Former smokers had higher risk of cancer mortality than never smokers (HR, 2.35; 95% CI, 1.62-3.40) but lower risk of cancer mortality than current smokers (HR, 0.61; 0.42-0.89).

Current smokers had an increased risk of CVD mortality compared to never smokers (HR, 1.29; 95% CI, 1.01-1.64) after adjustment for age and sex but not after full multivariable adjustment (HR, 1.15; 95% CI, 0.88-1.50). Former smokers did not have higher risk of CVD mortality when compared to never smokers (HR, 0.96; 95% CI, 0.81-1.14) or current smokers (HR, 0.84; 95% CI, 0.64-1.09). In a post hoc propensity score analysis (N=1,448; 724 matched pairs), current smokers had similar risk of CVD mortality compared to never smokers before (HR, 1.21; 95% CI, 0.87-1.69) and after multivariable adjustment (HR, 1.14; 95% CI, 0.82-1.60). In a post hoc propensity score analysis (N=2,778; 1389 matched pairs), former smokers had similar risk of CVD mortality compared to never smokers before (HR, 0.92; 95% CI, 0.75-1.13) and after multivariable adjustment (HR, 0.90; 95% CI, 0.74-1.11).

Discussion

In this nationally representative sample of stroke survivors, 18.7% of stroke survivors smoked between 1997 and 2004, representing approximately 800,000 individuals. Current

smoking increased the risk of all-cause mortality by more than 35%, after adjusting for demographic, socioeconomic, and clinical factors including neurological disability due to stroke. Smoking increased the risk of mortality largely by increasing the risk of cancer mortality. We did not find a smoking paradox, possibly because shared risk factors were thoroughly accounted for by forcing covariates into the logistic regression analysis.

Our results suggest that index event bias, unmeasured confounding, and measurement bias likely explain the paradoxical finding of many studies showing that smoking does not increase the risk of mortality in stroke survivors.[1, 11-16] Many studies allowed the model to select covariates using stepwise regression; we forced all covariates into the model. Our findings are consistent with other reports showing that adequate accounting for risk factors can minimize index event bias[20] and unmeasured confounding[21] and eliminate some, but not all, paradoxical findings in recurrent risk research.[35, 36] For example, socioeconomic status is associated with smoking status and mortality after stroke.[25] Despite this, socioeconomic status was often absent from analyses of post-stroke mortality.[11, 13, 14] Also, we assessed smoking in community-dwelling stroke survivors and avoided misclassifying survivors who quit smoking in the acute stroke period as current smokers and potentially biasing results toward the null. Our estimated effect of current smoking on all-cause mortality is comparable to reports from stroke registries in Europe and Asia.[18, 37, 38] Moreover, our findings of increased risk of death attributable to smoking were consistent across strata of age, sex, BMI, stroke duration, diabetes, and history of cancer, and robust to sensitivity analyses that excluded underweight stroke survivors or those with a history of cancer.

Current smokers had increased CVD mortality after adjusting for age and sex, however, socioeconomic and clinical factors appeared to explain this risk. There are several potential explanations for this finding. First, smoking may not have additional prognostic value in predicting death in stroke survivors after controlling for vascular factors (that are potentially on the causal pathway) and functional disability due to stroke (a marker for stroke severity), consistent with a recent report that diabetes did not predict CVD events after accounting for disease severity in survivors of CVD.[39] Smokers, particularly those with CVD, may also receive more aggressive CVD treatments and secondary prevention to reduce their risk of CVD mortality. Smokers may have “more favorable” atherosclerosis (severity or type) and have greater clinical improvement to treatments than non-smokers.[40-42] Unfortunately, we could not explore any of these factors in our study. There may be residual index event bias. Statistical methods such as multivariable regression or propensity score analysis may address most, but not all, of the index event bias operating in recurrent risk analyses. For example, stratification and propensity score analysis eliminated the paradox that obesity is associated with lower mortality in heart failure patients with diabetes but not in those without diabetes.[35] Our estimated confidence interval for the fully adjusted hazard of CVD mortality does not rule out a potentially meaningful effect of smoking on CVD mortality.

This study has limitations. Although all variables including tobacco use and history of stroke were self-reported and thus prone to recall bias and reporting error, recent data suggests high accuracy of self-reported stroke, with sensitivity rates ranging from 86-95%,[43, 44] and of self-reported smoking status, with strong correlation to biological measures of tobacco use (e.g., cotinine levels).[45] We lacked detailed information on smoking intensity, duration, or

quit date. A single measurement of smoking status was available at study baseline. Although some stroke survivors may have quit during follow-up, any over-estimation of their mortality risk would be small over 4.5 years of follow-up.[30] We may underestimate mortality in some former smokers who quit recently and have risk closer to current smokers.[30] Our findings are generalizable only to community-dwelling stroke survivors. Misclassification of cause of death by death certificates may affect estimated hazards of cause-specific mortality but not estimated hazards of all-cause mortality.[30] The NHIS data does not include physiologic measurements or severity of co-morbidities; our findings may underestimate the effect of increased severity of the co-morbidities on mortality. Although we were able to adjust for important clinical factors, other factors associated with mortality in survivors of acute stroke including heavy alcohol use, atrial fibrillation,[11, 13, 37] heart failure,[14] dementia,[11] peripheral vascular disease,[15] physical activity, hyperlipidemia, stroke severity or type, and history of prior stroke[17] could not be assessed adequately.

In summary, smoking after stroke significantly increases the risk of all-cause mortality largely by increasing cancer mortality. These data suggest that smoking is a modifiable risk factor for post-stroke mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Wolf PA, D'Agostino RB, Kannel WB, et al. Cigarette smoking as a risk factor for stroke. The Framingham study. JAMA. 1988; 259:1025–1029. [PubMed: 3339799]
2. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. BMJ. 1989; 298:789–794. [PubMed: 2496858]
3. Bhat VM, Cole JW, Sorkin JD, et al. Dose-response relationship between cigarette smoking and risk of ischemic stroke in young women. Stroke. 2008; 39:2439–2443. [PubMed: 18703815]
4. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the Interstroke study): A case-control study. Lancet. 2010; 376:112–123. [PubMed: 20561675]
5. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke: A statement for healthcare professionals from the American Heart Association. American Heart Association task force on risk reduction. Circulation. 1997; 96:3243–3247. [PubMed: 9386200]
6. Albers GW, Hart RG, Lutsep HL, et al. AHA scientific statement. Supplement to the guidelines for the management of transient ischemic attacks: A statement from the ad hoc committee on guidelines for the management of transient ischemic attacks, stroke council, American Heart Association. Stroke. 1999; 30:2502–2511. [PubMed: 10548693]

7. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011; 42:227–276. [PubMed: 20966421]
8. Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: A statement for healthcare professionals from the American Heart Association/American Stroke Association council on stroke: Co-sponsored by the council on cardiovascular radiology and intervention: The American Academy of Neurology affirms the value of this guideline. Stroke. 2006; 37:577–617. [PubMed: 16432246]
9. Brenner DA, Zweifler RM, Gomez CR, et al. Awareness, treatment, and control of vascular risk factors among stroke survivors. J Stroke Cerebrovasc Dis. 2010; 19:311–320. [PubMed: 20472464]
10. Bak S, Sindrup SH, Alslev T, et al. Cessation of smoking after first-ever stroke: A follow-up study. Stroke. 2002; 33:2263–2269. [PubMed: 12215597]
11. Appelros P, Nydevik I, Viitanen M. Poor outcome after first-ever stroke: Predictors for death, dependency, and recurrent stroke within the first year. Stroke. 2003; 34:122–126. [PubMed: 12511762]
12. Elneihoum AM, Goransson M, Falke P, et al. Three-year survival and recurrence after stroke in Malmo, Sweden: An analysis of stroke registry data. Stroke. 1998; 29:2114–2117. [PubMed: 9756591]
13. Petty GW, Brown RD Jr. Whisnant JP, et al. Survival and recurrence after first cerebral infarction: A population-based study in Rochester, Minnesota, 1975 through 1989. Neurology. 1998; 50:208–216. [PubMed: 9443482]
14. Sacco RL, Shi T, Zamanillo MC, et al. Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: The Northern Manhattan Stroke study. Neurology. 1994; 44:626–634. [PubMed: 8164815]
15. Hankey GJ, Jamrozik K, Broadhurst RJ, et al. Five-year survival after first-ever stroke and related prognostic factors in the Perth Community Stroke study. Stroke. 2000; 31:2080–2086. [PubMed: 10978033]
16. Kimura K, Minematsu K, Kazui S, et al. Mortality and cause of death after hospital discharge in 10,981 patients with ischemic stroke and transient ischemic attack. Cerebrovasc Dis. 2005; 19:171–178. [PubMed: 15644630]
17. Kim J, Gall SL, Dewey HM, et al. Baseline smoking status and the long-term risk of death or nonfatal vascular event in people with stroke: A 10-year survival analysis. Stroke. 2012; 43:3173–3178. [PubMed: 23103491]
18. Liu X, Xu G, Wu W, et al. Subtypes and one-year survival of first-ever stroke in chinese patients: The Nanjing Stroke Registry. Cerebrovasc Dis. 2006; 22:130–136. [PubMed: 16691021]
19. Smits LJ, van Kuijk SM, Leffers P, et al. Index event bias-a numerical example. J Clin Epidemiol. 2013; 66:192–196. [PubMed: 23257150]
20. Dahabreh IJ, Kent DM. Index event bias as an explanation for the paradoxes of recurrence risk research. JAMA. 2011; 305:822–823. [PubMed: 21343582]
21. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. Epidemiology. 2004; 15:615–625. [PubMed: 15308962]
22. VanderWeele TJ, Hernan MA, Robins JM. Causal directed acyclic graphs and the direction of unmeasured confounding bias. Epidemiology. 2008; 19:720–728. [PubMed: 18633331]
23. Suner-Soler R, Grau A, Gras ME, et al. Smoking cessation 1 year poststroke and damage to the insular cortex. Stroke. 2012; 43:131–136. [PubMed: 22052507]
24. Ives SP, Heuschmann PU, Wolfe CD, et al. Patterns of smoking cessation in the first 3 years after stroke: The South London Stroke Register. Eur J Cardiovasc Prev Rehabil. 2008; 15:329–335. [PubMed: 18525389]
25. Arrich J, Lalouschek W, Mullner M. Influence of socioeconomic status on mortality after stroke: Retrospective cohort study. Stroke. 2005; 36:310–314. [PubMed: 15625296]
26. Fonarow GC, Reeves MJ, Smith EE, et al. Characteristics, performance measures, and in hospital outcomes of the first one million stroke and transient ischemic attack admissions in Get With The Guidelines-Stroke. Circ Cardiovasc Qual Outcomes. 2010; 3:291–302. [PubMed: 20177051]
27. National Health Interview Survey. http://www.cdc.gov/nchs/nhis.htm. [January 9, 2013]

28. Design and estimation for the National Health Interview Survey, 1995-2004. Vital Health Stat 2. 2000:1–31.
29. Lochner K, Hummer RA, Bartee S, et al. The public-use National Health Interview Survey linked mortality files: Methods of reidentification risk avoidance and comparative analysis. Am J Epidemiol. 2008; 168:336–344. [PubMed: 18503037]
30. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med. 2013; 368:341–350. [PubMed: 23343063]
31. Ingram DD, Lochner KA, Cox CS. Mortality experience of the 1986-2000 National Health Interview Survey linked mortality files participants. Vital Health Stat 2. 2008:1–37.
32. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults--the evidence report. National Institutes of Health. Obes Res. 1998; 6(Suppl 2):51S–209S.
33. Kessler RC, Barker PR, Colpe LJ, et al. Screening for serious mental illness in the general population. Arch Gen Psychiatry. 2003; 60:184–189. [PubMed: 12578436]
34. Klein RJ, Schoenborn CA. Age adjustment using the 2000 projected u.S. Population. Healthy People 2000 Stat Notes. 2001:1–9.
35. Adamopoulos C, Meyer P, Desai RV, et al. Absence of obesity paradox in patients with chronic heart failure and diabetes mellitus: A propensity-matched study. Eur J Heart Fail. 2011; 13:200–206. [PubMed: 20930001]
36. Frankenstein L, Zugck C, Nelles M, et al. The obesity paradox in stable chronic heart failure does not persist after matching for indicators of disease severity and confounders. Eur J Heart Fail. 2009; 11:1189–1194. [PubMed: 19887494]
37. Kammersgaard LP, Olsen TS. Cardiovascular risk factors and 5-year mortality in the copenhagen stroke study. Cerebrovasc Dis. 2006; 21:187–193. [PubMed: 16388194]
38. Wolfe CD, Smeeton NC, Coshall C, et al. Survival differences after stroke in a multiethnic population: Follow-up study with the South London Stroke Register. BMJ. 2005; 331:431. [PubMed: 16055452]
39. Rizza S, Copetti M, Cardellini M, et al. Atherosclerosis severity but not undiagnosed diabetes predicts new cardiovascular events of subjects in secondary cardiovascular prevention. Atherosclerosis. 2012; 223:448–453. [PubMed: 22695529]
40. Ovbiagele B, Saver JL. The smoking-thrombolysis paradox and acute ischemic stroke. Neurology. 2005; 65:293–295. [PubMed: 16043802]
41. Barbash GI, Reiner J, White HD, et al. Evaluation of paradoxic beneficial effects of smoking in patients receiving thrombolytic therapy for acute myocardial infarction: Mechanism of the “smoker's paradox” from the gusto-i trial, with angiographic insights. Global utilization of streptokinase and tissue-plasminogen activator for occluded coronary arteries. J Am Coll Cardiol. 1995; 26:1222–1229. [PubMed: 7594035]
42. Levine SR. Smoke without fire: The complex effects of cigarette smoking on thrombolytic therapy for acute ischemic stroke. Neurology. 2005; 65:183. [PubMed: 16047406]
43. Horner RD, Cohen HJ, Blazer DG. Accuracy of self-reported stroke among elderly veterans. Aging Ment Health. 2001; 5:275–281. [PubMed: 11575067]
44. O'Mahony PG, Dobson R, Rodgers H, et al. Validation of a population screening questionnaire to assess prevalence of stroke. Stroke. 1995; 26:1334–1337. [PubMed: 7631332]
45. Patrick DL, Cheadle A, Thompson DC, et al. The validity of self-reported smoking: A review and meta-analysis. Am J Public Health. 1994; 84:1086–1093. [PubMed: 8017530]

Table 1

Characteristics of US Stroke Survivors by Smoking Status: National Health Interview Survey 1997-2004, National Death Index, 1997-2006[*†‡]

Characteristic	Current Smoking	Former Smoking	Never Smoking	P-value
N	1,155	2,282	2360	
Population estimate	800,100	1,779,847	1,679,161	
Mean age (SE), years	61.6 (0.4)	70.1 (0.3)	71.8 (0.3)	
Age 45-54	311 (28.4)	187 (9.3)	208 (10.2)	<0.0001
Age 55-64	395 (34.4)	426 (19.2)	334 (15.0)	
Age 65-74	298 (24.6)	736 (32.3)	611 (25.7)	
Age 75+	151 (12.6)	933 (39.2)	1,207 (49.1)	
Male sex	569 (51.7)	1,299 (62.0)	665 (32.4)	<0.0001
Functional disability due to stroke	366 (31.8)	745 (33.4)	765 (32.6)	0.73
Race				0.0002
White	851 (79.0)	1,893 (86.0)	1,886 (82.7)	
Black	251 (16.7)	312 (10.7)	393 (13.4)	
Other	53 (4.3)	77 (3.3)	81 (4.0)	
Hispanic ethnicity	101 (6.0)	189 (5.3)	265 (7.9)	0.004
<High school education	476 (40.0)	859 (35.6)	919 (36.5)	0.09
Insurance				<0.0001
Private	441 (45.3)	1,293 (60.0)	1,301 (59.7)	
Medicare and Medicaid	139 (9.2)	231 (8.1)	280 (9.3)	
Medicare only	237 (18.4)	475 (19.6)	485 (19.9)	
Other	231 (18.0)	219 (9.4)	204 (7.8)	
Uninsured	103 (9.0)	59 (3.0)	81 (3.4)	
Income				<0.0001
<$20,000	696 (48.6)	1,013 (35.0)	1,189 (40.2)	
>/=$20,000	413 (47.3)	1,112 (58.1)	977 (51.4)	
Missing/unreported	46 (4.1)	157 (6.9)	194 (8.5)	
Region				0.02
Northeast	183 (16.2)	423 (19.7)	374 (17.2)	
Midwest	286 (26.5)	533 (23.8)	561 (23.9)	
South	478 (42.7)	872 (38.8)	943 (39.9)	
West	208 (14.7)	454 (17.7)	482 (19.0)	
BMI				<0.0001
<18.5	53 (4.6)	60 (2.5)	74 (3.2)	
18.5-24.9	479 (42.5)	719 (31.1)	816 (35.1)	
25-29.9	370 (33.2)	858 (39.9)	785 (35.4)	
>/=30	223 (19.7)	595 (26.6)	604 (26.3)	

Characteristic	Current Smoking	Former Smoking	Never Smoking	P-value
Married	396 (49.7)	1,103 (63.3)	863 (50.6)	<0.0001
Serious mental illness	170 (14.6)	179 (7.3)	174 (7.9)	<0.0001
History of cancer	163 (13.6)	395 (17.4)	357 (15.5)	0.04
Medical History				
Hypertension	802 (69.0)	1,680 (73.3)	1,746 (74.1)	0.02
Coronary artery disease	396 (35.1)	887 (40.4)	771 (33.8)	0.0002
Chronic kidney disease	106 (8.5)	208 (9.1)	214 (9.3)	0.8
Diabetes mellitus	215 (19.2)	673 (30.2)	635 (26.9)	<0.0001
Heart disease	273 (24.1)	680 (29.9)	621 (27.3)	0.007
Chronic obstructive pulmonary disease	189 (16.9)	284 (12.8)	97 (3.7)	<0.0001
2 or more comorbidities	574 (50.2)	1,377 (60.7)	1,238 (52.6)	<0.0001
Fair or poor health status	686 (58.6)	1,238 (54.5)	1,254 (52.4)	0.01

§Low self-reported health status defined as poor or fair on 5-point Likert scale.

*Data Source: National Center for Health Statistics (1997–2004) and National Death Index (1997-2006).

†All percentages are weighted according to sampling fractions used by the National Health Interview Survey.

‡Population estimates were calculated using SAS-callable SUDAAN software, version 9.00.1 (Research Triangle Inst) to obtain proper variance estimations that accounted for the complex sampling design of the National Health Interview Survey and results that were weighted to reflect national population estimates.

Table 2

Characteristics of US Stroke Survivors by Mortality Status: National Health Interview Survey 1997-2004, National Death Index, 1997-2006[*†‡]

Characteristic	Alive	Dead	P-value
N	3,809	1,988	
Population estimate	2,852,903	1,406,204	
Mean age (SE), years	66.7 (0.2)	74.3 (0.3)	
Age 45-54	610 (17.3)	96 (5.0)	<0.0001
Age 55-64	927 (24.8)	228 (11.5)	
Age 65-74	1,125 (29.4)	520 (25.9)	
Age 75+	1,147 (28.5)	1,144 (57.6)	
Male sex	1,590 (46.6)	943 (52.1)	0.0003
Functional disability due to stroke	1,120 (29.3)	756 (39.8)	<0.0001
Race			0.0004
White	3,017 (82.9)	1,613 (84.5)	
Black	630 (12.6)	326 (13.4)	
Other	162 (4.6)	49 (2.1)	
Hispanic ethnicity	414 (7.6)	141 (4.2)	<0.0001
<High school education	1,378 (33.7)	876 (42.9)	<0.0001
Insurance			<0.0001
Private	2,004 (57.6)	1,031 (56.2)	
Medicare and Medicaid	397 (7.9)	253 (10.4)	
Medicare only	730 (18.0)	467 (22.5)	
Other	470 (11.2)	184 (8.6)	
Uninsured	195 (5.3)	48 (2.2)	
Income			<0.0001
<$20,000	1,810 (37.5)	1,088 (44.0)	
>/=$20,000	1,749 (55.9)	753 (48.5)	
Missing/unreported	250 (6.7)	147 (7.6)	
Region			0.027
Northeast	672 (19.1)	308 (15.9)	
Midwest	896 (24.4)	484 (24.2)	
South	1,480 (38.7)	813 (42.6)	
West	761 (17.9)	383 (17.2)	
BMI			<0.0001
<18.5	63 (1.6)	124 (6.2)	
18.5-24.9	1,179 (30.6)	835 (43.3)	
25-29.9	1,424 (39.7)	589 (31.1)	
>/=30	1,036 (28.1)	386 (19.4)	

Characteristic	Alive	Dead	P-value
Married	1,650 (58.7)	712 (49.6)	<0.0001
Serious mental illness	328 (8.5)	195 (9.7)	0.2
History of cancer	520 (14.1)	395 (19.7)	<0.0001
Medical History			
Hypertension	2,770 (72.3)	1,458 (73.9)	0.23
Coronary artery disease	1,198 (32.2)	856 (46.0)	<0.0001
Chronic kidney disease	277 (7.4)	251 (12.5)	<0.0001
Diabetes mellitus	912 (24.2)	611 (32.0)	<0.0001
Heart disease	948 (25.0)	626 (33.3)	<0.0001
Chronic obstructive pulmonary disease	321 (8.7)	249 (12.5)	0.0002
2 or more comorbidities	1,937 (51.1)	1,252 (64.5)	<0.0001
Fair or poor health status	1,955 (50.8)	1,223 (61.8)	<0.0001
Smoking status[§]			0.002
Current	798 (20.1)	357 (16.2)	
Former	1,444 (40.6)	838 (44.3)	
Never	1,567 (39.4)	793 (39.6)	

[*] Data Source: National Center for Health Statistics (1997–2004) and National Death Index (1997-2006).

[†] All percentages are weighted according to sampling fractions used by the National Health Interview Survey.

[‡] Population estimates were calculated using SAS-callable SUDAAN software, version 9.00.1 (Research Triangle Inst) to obtain proper variance estimations that accounted for the complex sampling design of the National Health Interview Survey and results that were weighted to reflect national population estimates.

[§] P-value for current vs. never smokers P=0.0009 and P-value for former vs. never smokers, P=0.018

Table 3

Age-Standardized Rates and Adjusted Hazard Ratios (95%CIs) for All-Cause Mortality, Cancer Mortality, and Cardiovascular Disease Mortality by Smoking Status among US Stroke Survivors: National Health Interview Survey 1997-2004, National Death Index, 1997-2006 [*†‡]

All-Cause Mortality	**Current Smoker**	**Former Smoker**	**Never Smoker**
No. of events	357	838	793
No. of participants	1,155	2,282	2,360
Weighted % dead	28.4%	35.0%	33.1%
Age-standardized mortality rates per 1000 person-years, overall	69.2 (5.4)	58.7 (2.8)	46.2 (2.5)
Age-standardized mortality rates per 1000 person-years, 45-64 years	38.7 (3.6)	31.0 (3.7)	24.2 (3.3)
Age-standardized mortality rates per 1000 person-years, 65-74 years	81.3 (8.5)	68.1 (4.6)	50.3 (4.7)
Age-standardized mortality rates per 1000 person-years, 75-84 years	132.8 (19.6)	126.2 (7.2)	94.7 (5.5)
Age-standardized mortality rates per 1000 person-years, 85+ years	269.7 (85.4)	219.4 (21.4)	203.9 (15.0)
Cox proportional hazards models results: adjusted hazard ratios (95% CIs)			
Model [†]			
Age and sex-adjusted hazard ratios (n=5,787)	1.54 (1.31-1.82)	1.16 (1.03-1.30)	Referent
Fully adjusted hazard ratios (n=5,308)	1.36 (1.14-1.63)	1.15 (1.02-1.29)	Referent
Cancer Mortality			
No. of events	85	140	69
No. of participants	1,155	2,282	2,360
Weighted % dead	6.9%	5.8%	2.7%
Age-standardized rates per 1000 person years (SE)	15.2 (2.2)	9.5 (1.1)	4.4 (0.8)
Age and sex-adjusted hazard ratios (n=5,787)	3.88 (2.61-5.77)	2.17 (1.53-3.06)	Referent
Fully adjusted hazard ratios (n=5,308)	3.83 (2.48-5.91)	2.35 (1.62-3.40)	Referent
Cardiovascular Disease Mortality			
No. of events	157	390	433
No. of participants	1,155	2,282	2,360
Weighted % dead	12.5%	16.6%	18.3%
Age-standardized rates per 1000 person years (SE)	297.8 (15.7)	310.9 (28.4)	304.4 (22.1)
Age and sex-adjusted hazard ratios (n=5,787)	1.29 (1.01-1.64)	0.96 (0.82-1.13)	Referent

All-Cause Mortality	Current Smoker	Former Smoker	Never Smoker
Fully adjusted hazard ratios (n=5,308)	1.15 (0.88-1.50)	0.96 (0.81-1.14)	Referent

Of 1988 deaths, 294 were due to cancer (14.5%; 95%CI, 12.9-16.3%) representing a population estimate of 203,935 deaths.

Of 1988 deaths, 980 were due to CVD (50.0%; 95%CI, 47.5-52.6%) representing a population estimate of 703,632 deaths.

[*] Data Source: National Center for Health Statistics (1997–2004) and National Death Index (1997-2006).

[†] All percentages are weighted according to sampling fractions used by the National Health Interview Survey. Population estimates were calculated using SAS-callable SUDAAN software, version 9.00.1 (Research Triangle Inst) to obtain proper variance estimations that accounted for the complex sampling design of the National Health Interview Survey and results that were weighted to reflect national population estimates.

[‡] Fully adjusted model includes age, sex, race, Hispanic ethnicity, annual household income, region, marital status, insurance status, self-reported health status, body mass index, and histories of hypertension, coronary artery disease, diabetes mellitus, emphysema, heart disease, and cancer. chronic kidney disease, tobacco use, diabetes mellitus, coronary heart disease, hypertension, emphysema, serious mental illness, and functional disability due to stroke.