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Association of Cognitive Functioning, Incident Stroke, and Mortality in Older Adults

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Abstract

Background and Purpose—Stroke increases the risk of dementia, however, bidirectional association of incident stroke and cognitive decline below dementia threshold is not well established. Also, both cognitive decline and stroke increase mortality risk.

Methods—A longitudinal population-based cohort of 7217 older adults without a history of stroke from a biracial community was interviewed at 3-year intervals. Cognitive function was assessed using a standardized global cognitive score. Stroke was determined by linkage with Medicare claims and mortality was ascertained via the National Death Index. We used a Cox model to assess the risk of incident stroke, a joint model with a piecewise linear mixed model with incident stroke as a change point for cognitive decline process, and a time-dependent relative risk regression model for mortality risk.

Results—During follow-up, 1187 (16%) subjects had incident stroke. After adjusting for known confounders, lower baseline cognitive function was associated with a higher risk of incident stroke (HR=1.61, 95% CI, 1.46–1.77). Cognitive function declined by 0.064-unit per year prior to incident stroke occurrence, and 0.122-unit per year after stroke, a nearly 1.9-fold increase in cognitive decline (95% CI, 1.78–2.03). Both stroke (HR=1.17, 95% CI, 1.08–1.26) and cognitive decline (HR=1.90, 95% CI, 1.81–1.98) increased mortality risk.

Conclusions—Baseline cognitive function was associated with incident stroke. Cognitive decline increased significantly after stroke relative to before stroke. Cognitive decline increased

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mortality risk independent of the risk attributable to stroke, and should be followed as a marker for both stroke and mortality.

Keywords

Cognitive decline; Cerebrovascular Disease; Mortality; Epidemiology; Joint models

Alzheimer's disease and stroke have two of the largest morbidity burdens in older populations (1). Stroke is related to cognitive impairment and dementia in old age (2–5). Stroke causes cognitive impairment by lacunar infarcts, ischemic white matter disease, and cerebral hypoperfusion in old age (6–8). Previous studies that have investigated the association of stroke and cognitive function have mostly focused on post-stroke cognitive impairment, especially stroke-related vascular dementia. However, the excess risk of increased cognitive decline below the dementia threshold among those with incident stroke has not been well established (2). As the number of post-stroke survivors increase, the risk of future cognitive decline below diagnosis thresholds also seem to be on the rise.

Conversely, cognitive function in old age is an important neurological marker that can potentially increase the risk of stroke (9–11). Lower cognitive function is related to brain atrophy, white matter abnormalities, and silent cerebral infarction, all of which might serve as risk factors for future stroke events (12–14). Moreover, biological aging of the brain can also be attributed to aging of the cerebrovascular system (15). Even though most researchers have studied the impact of one mechanism on another (16–18), the bidirectional association of these two mechanisms might provide a better understanding of the underlying neurological and cerebrovascular disease mechanisms.

To further complicate matters, incident stroke increases mortality risk through cerebrovascular disease mechanism (19–22). Cognitive decline also increases mortality risk through neurodegenerative disease mechanisms even among those without a stroke event (23–26). Hence, understanding the bidirectional association of cognitive function and stroke, and their conditional association on mortality, is quite important. Another reason for jointly studying cognitive decline, stroke, and mortality is the informative censoring process that occurs during the cognitive decline process, most specifically, among those with severe cognitive decline irrespective of stroke incidence.

To perform this investigation, we used data from a longitudinal population-based cohort of 7217 older adults. We examined the association of baseline cognitive function on the risk of incident stroke, and changes in cognitive function before and after incident stroke, while also jointly studying their impact on mortality risk.

METHODS

Participants

The design of the Chicago Health and Aging Project (CHAP) has been previously described (27–28). Beginning in 1993, 78.7% of all residents over 65 years old (defined by a door-to-door census) of a geographically-defined, biracial Chicago community were enrolled in CHAP. From 2001, community residents who reached age 65 were also enrolled as

successive cohorts. The interviews were conducted in the participants' homes in approximately three-year cycles during which time cognitive function tests were administered. For the current analyses, participants were eligible if they were free of stroke at baseline.

Cognitive Function

Cognitive function was evaluated using a battery of four tests including two tests of episodic memory (immediate and delayed recall story) derived from the East Boston Test (29,30); a test of perceptual speed (the Symbol Digits Modalities Test) (31) and a test of general orientation and global cognition (the Mini-Mental State Examination: MMSE) (32). Because tests loaded on a single factor that accounted for about 75% of the variance in a factor analysis (33), we constructed a composite measure of global cognitive function based on standardized scores from the four tests.

Stroke Hospitalizations

All CHAP participants were aged 65 years or older, and therefore qualified for reimbursement for medical services by the Center for Medicare and Medicaid Services (CMS). Participants were excluded from analysis for incident stroke any time during follow-up when they were actively involved in a health maintenance organization (HMO), since they would not simultaneously be enrolled in Medicare during those periods. In CHAP, 83% of time participants were enrolled in Medicare and 17% of time in HMO. Stroke hospitalization was ascertained by linkage to Medicare enrollment and claims data and was complete through 12/31/2009. Prevalent stroke cases were ascertained using stroke hospitalization data as well as the self-reported question "Have you ever been told by a doctor, nurse or therapist that you had a stroke or brain hemorrhage?" with "Yes" and "Suspect or possible" as a positive response, and excluded from our analysis. For this study, we coded two types of strokes, ischemic strokes identified by ICD-9 codes 433.01, 433.1, 433.2, 433.21, 433.3, 433.31, 433.81, 434.01, 434.1, 434.11, 434.91, 435.2, 435.3, 435.8, 435.9, 436.0, 437.1, 437.7, 437.9, and 438.0, and hemorrhagic strokes identified by ICD-9 codes 430, 431, 432.1, and 432.9. These codes were validated by a co-author (NTA), who is a board-certified neurologist and CHAP investigator, and published previously (34).

Mortality

Information on vital status was obtained at each follow-up interview through field reports of interviewers, during which time participants were linked with the Social Security Administration Death Master File. Personal identifiers from the Death Master File were then linked to the National Death Index (NDI). Ascertainment and verification of mortality using NDI was complete from the beginning of the study through 12/31/2010. Of the 4082 subjects who had deceased, NDI reports were confirmed for 3458 (85%) subjects, and 489 (12%) subjects had deceased between 1/1/2011 to 9/12/2012, but waiting to be confirmed following the release of upcoming NDI database. The remaining 135 (3%) unconfirmed deaths were reported either during in-home visits or in Medicare records but could not be confirmed from NDI due to lack of personal identifiers.

Covariates

Our analysis adjusted for two sets of variables: demographic variables, including age (measured in years and centered at 75), sex (males or females), race (blacks or whites), and education (measured in number of years of schooling completed centered at 12) were included in all models; analyses of mortality further included health and lifestyle measures, including body mass index (kg/m^2), heart disease, diabetes, systolic blood pressure, diastolic blood pressure, smoking status (former smoker and current smokers vs. never smoker), physical activities (total minutes of walking, jogging, yard work, dancing, calisthenics or general exercise) and daily alcohol consumption (grams of alcohol per day). All covariates were selected based on prior evidence of association and were measured at baseline.

Statistical Analysis

Descriptive statistics were computed using means and standard deviations for continuous variables and percentages for categorical variables and compared between subjects without and with incident stroke using two-sample independent t-tests and chi-square likelihood ratio tests. We used a Cox proportional hazards regression model with baseline cognitive function and demographic, health, and lifestyle measures predicting incident stroke risk (35). In a separate model, we included race and sex interactions with baseline cognitive function to predict incident stroke. We modeled the cognitive decline process and mortality using a joint model with a longitudinal model for cognitive decline and the time-to-event model for mortality (36). For the longitudinal model, we used a piecewise linear mixed-effects regression model with time of incident stroke as a change point to study cognitive decline before and after incident stroke (37). Using this approach, we compartmentalized time into two components, time before stroke and time after stroke. Random effects were included for the intercept and slopes. Each model also included fixed effects for main effects of time before and after stroke and time after stroke and their interactions with demographic variables. For the mortality model, we used a time-dependent Cox proportional hazards model. We also performed a case-only analysis by removing subjects who did not have an incident stroke to capture cognitive decline trajectory before and after stroke and contrast those with all at-risk subjects. All models were fitted using JM package in R software (38).

RESULTS

Population Characteristics

Demographic and health characteristics for all subjects categorized by incident stroke during follow-up are shown in Supplemental Table I. Subjects were mostly African American females, with an average age of 72.5 years and education of 12.4 years. Mean MMSE was 26.7. The average cognitive function at baseline was 0.271 ($\text{SD}=0.712$). During follow-up, 1187 (16%) subjects had incident stroke. Among subjects still alive at end of study, the mean follow-up time among those without stroke was 8.1 years, and among those with stroke was 9.7 years. Among participants who had died, the mean follow-up time among those with incident stroke was 5.6 years and that without stroke was 5.0 years. The mean follow-up time after incident stroke was 4.2 ($\text{SD}=3.9$) years. Subjects with incident stroke also had lower baseline scores on all four cognitive function tests, and a large proportion (78%) had died during follow-up.

Baseline Cognitive Function & Incident Stroke

The relative risk of incident stroke predicted by baseline cognitive function, after adjusting for demographic and other known risk factors, is shown in Supplemental Table II. Baseline cognitive function was associated with increased risk of incident stroke (HR=1.62, 95% CI, 1.54–1.70). Higher age at baseline, male sex, heart disease, diabetes, higher systolic blood pressure, and current and former smoking behavior also increased the risk of incident stroke. On the other hand, the risk of stroke was lower among blacks and among subjects with higher levels of physical activity; however these associations were conditioned on holding baseline cognitive function at the same level.

In a separate analysis, we tested if the association of baseline cognitive function and incident stroke differed by race and sex. Lower cognitive function increased incidence of stroke by 30% among whites (HR=1.30, 95% CI, 1.19–1.42), and by 63% among blacks (HR=1.63, 95% CI 1.52–1.74). The increase in risk of incident stroke was significantly different between blacks and whites (p-for-interaction=0.008). The association of baseline cognitive function with the risk of incident stroke was not significantly different between males (HR=1.66, 95% CI, 1.59–1.72) and females (HR=1.54, 95% CI, 1.47–1.61) (p-for-interaction=0.32).

Cognitive Decline & Incident Stroke

Supplemental Table III shows the average levels of baseline cognitive function and decline in cognitive function before and after incident stroke from the joint model. This analysis was based on subjects who were stroke-free at baseline and subjects without stroke only contributing to before stroke decline. Increasing age, males, and blacks had greater stroke risk, whereas education was positively associated with baseline cognitive function.

Cognitive function declined by 0.064-units/year prior to an incident stroke event. This decline in cognitive function increased by an additional 0.050-units for 10 years of age ($p<0.0001$), 0.006-units/year among females ($p=0.024$), and 0.006-units/year among blacks ($p=0.035$). After incident stroke, cognitive decline increased by 0.058-units/year, resulting in a total cognitive decline of 0.122-units/year (adding 0.064 and 0.058). Thus, cognitive decline was roughly 1.9-fold higher after stroke relative to before stroke. Age, sex, race, and education did not significantly modify cognitive decline after incident stroke compared to before stroke.

In a case-only analysis, cognitive function declined by 0.054-units/year prior to stroke and 0.114-units/year (adding 0.054 and 0.060) after incident stroke. This was roughly a 2.1-fold increase in cognitive decline after incident stroke compared to before stroke. Interestingly, cognitive decline increased by an additional 0.030-units/year among blacks compared to whites ($p=0.004$), roughly 5 times higher than cognitive decline before incident stroke in our primary analysis.

Relative Risk of Mortality

The relative risk of mortality was associated with demographic and health variables, incident stroke, and cognitive decline (Supplemental Table IV). For one unit change in cognitive

function, mortality risk increased by 90% (HR=1.90, 95% CI, 1.81–1.98). Incident stroke also significantly increased mortality risk by 17% (HR=1.17, 95% CI, 1.08–1.26). Older age, male sex, education, systolic BP, heart disease, and smoking status were all positively associated with mortality, whereas black race, and higher diastolic BP and physical activities were negatively associated with mortality. Even though the findings with regard to race may seem as an anomaly, it shows that if we compare blacks and whites with similar cognitive functioning, blacks have a lower risk of mortality compared to whites.

The risk of mortality in the case-only analysis is also shown in Supplemental Table IV. Cognitive decline increased the risk of mortality among those with stroke by a relative risk of 1.74 (95% CI, 1.60–1.90). Age and male sex were positively associated with mortality among those who developed incident stroke. Blacks had a lower risk of mortality compared to whites with a comparable cognitive decline process. Heart disease, diabetes, and smoking status were all associated with an increased risk of mortality. Physical activity was also associated with a lower risk of mortality among those with stroke.

DISCUSSION

In this longitudinal population-based study of older adults, we found a bidirectional association between cognitive function and stroke. Baseline cognitive function was associated with an increased risk of incident stroke. Cognitive decline increased by about 1.9-fold after incident stroke. Cognitive function was a strong predictor of mortality even after adjusting for stroke, demographic, and health-related risk factors suggesting the necessity to monitor cognitive decline as a marker of both stroke and mortality in older adults. From a care standpoint, cognitive decline is not only a strong marker of neurological deterioration and physical health in older adults, but also serves as a marker for stroke in old age.

Baseline cognitive function increased the risk of incident stroke in African Americans more than European Americans. In the stroke-incident case only analysis, cognitive decline before stroke was 5-fold higher among African Americans compared to European Americans. A separate analysis of time-dependent cognitive function predicting mortality also suggested a larger association of cognitive function with mortality in blacks than in whites. Hence, the burden of poor cognitive function and increased cognitive decline is higher in African Americans leading to increased risk of stroke and mortality.

Cognitive impairment after stroke has been extensively investigated in population and clinical studies. However, to the best of our knowledge, no longitudinal study has investigated the bidirectional association of cognitive function and incident stroke, and cognitive decline before and after stroke among subjects at risk for or with incident stroke. Previous longitudinal studies have investigated mortality risk in terms of cognitive function and history of stroke using a Cox proportional hazards regression model. However, we used a joint modeling framework to simultaneously study cognitive decline and risk of mortality while using incident stroke as a change point.

The main strength of this study is the study design and analytical methods. Participants were drawn from a large geographically-defined biracial population, making it likely that a broad spectrum of subjects and paths of cognitive changes were represented. Cognitive function was assessed using four well-known scales and measured on 3 to 6 occasions among those at risk of stroke. Almost 57% of older adults died during the follow-up period leading to informative censoring as well as providing sufficient power to detect robust relative risk findings. Accounting for the mortality also made it possible to precisely estimate person-specific change in cognitive function related to incident stroke. The unique contributions of cognitive decline and stroke are important information given that they have both independent and overlapping etiologies in the mortality process. Selective survivorship forms a source of potential bias in all longitudinal studies of older populations. Rather than using a simple ad-hoc procedure, such as a term for survivorship in a regression model, our joint modeling approach used a time-dependent model to simultaneously study cognitive decline and mortality in terms of stroke.

One of the limitations is the length of time between cognitive evaluations. The 3-year interval between cognitive evaluations limited our ability to track short-term changes in cognition around the time of incident stroke. However, such an approach is usually cost-prohibitive in the context of a large, longitudinal study, and prohibitive due to participant burden, especially in the end-of-life period. Another limitation is the assessment of incident stroke using Medicare data. Even though Medicare data covered about 83% of study period; subjects could have had an incident stroke event in the remaining 17% of time in an HMO plan. Also, Medicare could have misclassified non-stroke events as stroke-related events. Since no proper validation of incident stroke is available, we may have missed milder stroke events, and in some cases categorized events incorrectly as stroke. These misclassification errors could result in bias in our estimates. In the first scenario of missing milder stroke events, our cognitive decline estimates after incident stroke may have been overestimated. In the second scenario of incorrectly classifying non-stroke as stroke events, our estimates may have been underestimated. Moreover, in CHAP, over 90.7% of incident strokes were ischemic and the remaining 9.3% were hemorrhagic. We conducted a sensitivity analysis limiting our models to ischemic stroke events, and our parameter estimates from these models were slightly larger and our standard errors were smaller. Our analysis included 624 (15%) subjects with unconfirmed deaths. A baseline comparison of demographic and health characteristics between those with confirmed and unconfirmed deaths yielded no significant differences in demographic variables or cognitive function; hence, these subjects were not removed from our analysis. In this population, 8% of subjects did not participate in an interview before stroke and 7% did not participate after stroke. Also, 45% of those with incident stroke died before an interview resulting in truncation of observations. Since subjects who did not provide data are expected to have worse cognitive function, it is most likely that our cognitive decline after stroke was underestimated.

In conclusion, we found that baseline cognitive function was a strong predictor of stroke. In turn, stroke incidence was associated with a significant increase in cognitive decline. The trajectories of cognitive decline before and after stroke showed significant differences in older persons. The cognitive decline process was strongly associated with a higher risk of mortality even after controlling for stroke and other health and behavior risk factors. The

findings of this research suggest that cognitive function is an important marker of health that impacts the future risk of stroke and mortality in older persons. Therefore, minimizing the risk of cognitive decline may also minimize the risk of stroke and mortality in older age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*. 2006; 367:1747–1757. [PubMed: 16731270]
2. Savva GM, Stephan BCM. the Alzheimer's Society Vascular Dementia Systematic Review Group. Epidemiological Studies of the Effect of Stroke on Incident Dementia: A Systematic Review. *Stroke*. 2010; 41:e41–e46. [PubMed: 19910553]
3. Vinters HV, Ellis WG, Zarow C, Zaias BW, Jagust WJ, Mack WJ, et al. Neuropathologic substrates of ischemic vascular dementia. *J Neuropathol Exp Neurol*. 2000; 59:931–945. [PubMed: 11089571]
4. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189–198. [PubMed: 1202204]
5. Tomlinson BE, Blessed G, Roth M. Observations on the brains of demented old people. *J Neurol Sci*. 1970; 11:205–242. [PubMed: 5505685]
6. Rockwood K, Bowler J, Erkinjuntti T. Subtypes of vascular dementia. *Alzheimer Dis Assoc Disord*. 1999; 13:S59–S65. [PubMed: 10609683]
7. Yao H, Sadoshima S, Ibayashi S. Leukoaraiosis and dementia in hypertensive patients. *Stroke*. 1992; 23:1673–1677. [PubMed: 1440720]
8. Hénon H, Durieu I, Guerouaou D, Lebert F, Pasquier F, Leys D. Poststroke dementia: incidence and association to prestroke cognitive decline. *Neurology*. 2001; 57:1216–1222. [PubMed: 11591838]
9. Rist PM, Chalmers J, Arima H, Anderson C, Macmahon S, Woodward M, et al. Baseline Cognitive Function, Recurrent Stroke, and Risk of Dementia in Patients With Stroke. *Stroke*. 2013; 44:1790–1795. [PubMed: 23686974]
10. DeCarli C, Miller BL, Swan GE, Reed T, Wolf PA, Garner J, et al. Predictors of brain morphology for the men of the NHLBI twin study. *Stroke*. 1999; 30:529–536. [PubMed: 10066847]
11. Desmond DW. Cognition and white matter lesions. *Cerebrovascular diseases*. 2002; 13:53–57. [PubMed: 11901244]
12. Seshadri S, Wolf PA, Beiser A, Elias MF, Au R, Kase CS, et al. Stroke risk profile, brain volume, and cognitive function: the Framingham Offspring Study. *Neurology*. 2004; 63:1591–1599. [PubMed: 15534241]
13. Seshadri S. Methodology for measuring cerebrovascular disease burden. *International review of psychiatry*. 2006; 18:409–422. [PubMed: 17085360]
14. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol*. 2009; 8:1006–1018. [PubMed: 19782001]

15. Reitz C, Bos MJ, Hofman A, Koudstaal PJ, Breteler MM. Prestroke cognitive performance, incident stroke, and risk of dementia: the Rotterdam Study. *Stroke*. 2008; 39:36–41. [PubMed: 18006863]
16. Wang Q, Capistrant BD, Ehntholt A, Glymour MM. Long-term rate of change in memory functioning before and after stroke onset. *Stroke*. 2012; 43:2561–2566. [PubMed: 22935399]
17. Brønnum-Hansen H, Davidsen M, Thorvaldsen P. Long-term survival and causes of death after stroke. *Stroke*. 2001; 32:2131–2136. [PubMed: 11546907]
18. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, 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]
19. Dennis MS, Burn JP, Sandercock PA, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke*. 1993; 24:796–800. [PubMed: 8506550]
20. Loor HI, Groenier KH, Limburg M, Schuling J, Meyboom-de Jong B. Risks and causes of death in a community-based stroke population: 1 month and 3 years after stroke. *Neuroepidemiology*. 1999; 18:75–84. [PubMed: 10023130]
21. Batty GD, Deary IJ, Gottfredson LS. Premorbid (early life) IQ and later mortality risk: systematic review. *Ann Epidemiol*. 2007; 17:278–288. [PubMed: 17174570]
22. Bennett DA, Wilson RS, Schneider JA, Evans DA, Beckett LA, Aggarwal NT, et al. Natural history of mild cognitive impairment in older persons. *Neurology*. 2002; 59:198–205. [PubMed: 12136057]
23. Dewey ME, Saz P. Dementia, cognitive impairment and mortality in persons aged 65 and over living in the community: a systematic review of the literature. *Int J Geriatr Psychiatry*. 2001; 16:751–761. [PubMed: 11536341]
24. Gale CR, Martyn CN, Cooper C. Cognitive impairment and mortality in a cohort of elderly people. *BMJ*. 1996; 312:608–611. [PubMed: 8595334]
25. Neale R, Brayne C, Johnson AL. Cognition and survival: an exploration in a large multicentre study of the population aged 65 years and over. *Int J Epidemiol*. 2001; 30:1383–1388. [PubMed: 11821351]
26. Sabia S, Guéguen A, Marmot MG, Shipley MJ, Ankri J, Singh-Manoux A. Does cognition predict mortality in midlife? Results from the Whitehall II cohort study. *Neurobiol Aging*. 2010; 31:688–695. [PubMed: 18541343]
27. Bienias JL, Beckett LA, Bennett DA, Wilson RS, Evans DA. Design of the Chicago Health and Aging Project. *J Alz Dis*. 2003; 5:349–355.
28. Evans DA, Bennett DA, Wilson RS, Bienias JL, Morris MC, Scherr PA, et al. Incidence of Alzheimer disease in a biracial urban community. *Arch Neurol*. 2003; 60:185–189. [PubMed: 12580702]
29. Albert M, Smith LA, Scherr PA, Taylor JO, Evans DA, Funkenstein HH. Use of brief cognitive tests to identify individuals in the community with clinically diagnosed Alzheimer's disease. *Int J of Neurosci*. 1991; 57:167–78. [PubMed: 1938160]
30. Wilson RS, Bennette DA, Bienias JL, Aggarwal NT, Mendes De Leon CF, Morris MC, et al. Cognitive activity and incident AD in a population-based sample of older adults. *Neurology*. 2002; 59:1910–4. [PubMed: 12499482]
31. Smith, A. Symbol Digits Modalities Test. Western Psychological Services; Los Angeles: 1982.
32. Folstein MF, Folstein SE, McHugh TR. "Mini-Mental State". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189–98. [PubMed: 1202204]
33. Wilson RS, Benette DA, Beckett LA, Morris MC, Gilley DW, Bienias JL, et al. Cognitive activity in older persons from a geographically defined population. *J Gerontol B Psychol Sci Soc Sci*. 1999; 54:155–60.
34. Henderson KM, Clark CJ, Lewis TT, Aggarwal NT, Beck T, Guo H, et al. Psychosocial distress and stroke risk in older adults. *Stroke*. 2013; 44:367–72. [PubMed: 23238864]
35. Hosmer, DW.; Lemeshow, S.; May, S. *Applied Survival Analysis*. 2. Wiley & Sons; 2008.
36. Rizopoulos, D. *Joint models for longitudinal and time-to-event data*. CRC Press; Boca Raton, FL: 2012.

37. Diggle, P.J.; Heagerty, P.; Liang, K.Y. Analysis of longitudinal data. 2. New York, NY: Oxford University Press Inc; 2004.
38. R: A language and environment for statistical computing. Version 2.15.2. Vienna, Austria: R Foundation for Statistical Computing; 2010.