HHS Public Access

Author manuscript

Stroke. Author manuscript; available in PMC 2018 July 01.

Published in final edited form as:

Stroke. 2017 July ; 48(7): 1818–1826. doi:10.1161/STROKEAHA.117.016726.

Factors Associated with Ischemic Stroke Survival and Recovery in Older Adults

Divya Thekkethala Winovich, MPH[1,2], **W. T. Longstreth Jr., MD, MPH**[3], **Alice M. Arnold, PhD**[3], **Ravi Varadhan, PhD, PhD**[4], **Adina Zeki Al Hazzouri, PhD**[5], **Mary Cushman, MD, MSc**[6], **Anne B. Newman, MD, MPH**[7], and **Michelle C. Odden, PhD**[1]

[1]Oregon State University

[2]Oregon Health & Science University

[3]University of Washington

[4]John Hopkins University

[5]University of Miami

[6]University of Vermont

[7]University of Pittsburgh

Abstract

Background and Purpose—Little is known regarding factors that predispose older adults to poor recovery following a stroke. In the present study, we sought to evaluate pre-stroke measures of frailty and related factors as markers of vulnerability to poor outcomes after ischemic stroke.

Methods—In participants aged 65–99 years with incident ischemic strokes from the Cardiovascular Health Study, we evaluated the association of several risk factors (frailty, frailty components, C-reactive protein, interleukin-6, and cystatin C) assessed prior to stroke with stroke outcomes of survival, cognitive decline (≥5 points on Modified Mini-Mental State Examination) and activities of daily living decline (increase in limitations).

Results—Among 717 participants with incident ischemic stroke with survival data, slow walking speed, low grip strength, and cystatin C were independently associated with shorter survival. Among participants <80 years, frailty and interleukin-6 were also associated with shorter survival. Among 509 participants with recovery data, slow walking speed, and low grip strength were associated with both cognitive and ADL decline post-stroke. C-reactive protein and interleukin-6 were associated with post-stroke cognitive decline among men only. Frailty status was associated with ADL decline among women only.

Conclusions—Markers of physical function—walking speed and grip strength—were consistently associated with survival and recovery after ischemic stroke. Inflammation, kidney

Corresponding Author: Michelle Odden, 141B Milam Hall, Corvallis OR, 97331, Fax: 541-737-7001, Phone: 541-737-3184, Michelle.Odden@oregonstate.edu.

DISCLOSURES

None

function, and frailty also appeared to be determinants of survival and recovery following an ischemic stroke. These markers of vulnerability may identify targets for differing pre and post-stroke medical management and rehabilitation among older adults at risk for poor stroke outcomes.

Indexing Terms

Stroke; Recovery of Function; Mortality; Aging

Subject Terms

Biomarkers; Inflammation; Aging; Risk Factors; Mortality/Survival; Ischemic Stroke

INTRODUCTION

Stroke is the fifth most common cause of death and a leading cause of disability in the United States.[1] Among stroke victims, older adults have a higher mortality rate and increased risk of disability, [2–5] but little is known about which factors contribute to an older person's increased vulnerability to adverse outcomes following a stroke. Some studies have examined the association of clinical factors assessed at or shortly after stroke with post-stroke mortality and functional recovery.[3, 4, 6–10] However, the effect of pre-stroke characteristics on stroke outcomes has received less attention. Given that the number of incident strokes is expected to increase, with the majority of this increase occurring in persons over the age of 75 years,[2] understanding what underlying factors portend higher mortality, disability, and poor quality of life after stroke are of critical interest.

Frailty is a geriatric syndrome, characterized by decreased reserve or resilience to stressors, attributed to cumulative multisystem decline. [11–13] Given that previous research has demonstrated that age is the strongest predictor of adverse stroke outcomes, we aimed to investigate the contributing role of frailty on outcomes among older adults. A stroke event is a significant stressor; therefore, we hypothesized that frailty would be an important determinant of poor recovery after stroke. In this study, we examined frailty and the frailty-associated risk factors of chronic inflammation and renal function as predictors of survival and cognitive and physical recovery after stroke.[14–16] These measures are powerful markers of the physiologic aging process and are strongly associated with adverse outcomes.[13] For comparison, we also evaluated the importance of traditional measures of cardiovascular health. Although there is a preponderance of literature establishing the importance of frailty in older adults, this is the first study to look at the effect of frailty on recovery after stroke.

This study was conducted in the Cardiovascular Health Study, an observational cohort study. We focused exclusively on ischemic strokes because they are more common than hemorrhagic strokes among older adults. The purpose of this study was to evaluate candidate risk factors that may contribute to an older person's resilience, or ability to survive and recover, following a stroke.

METHODS

Cardiovascular Health Study

The Cardiovascular Health Study (CHS) is a community-based cohort study of 5,888 adults 65 and older intended to study risk factors of cardiovascular disease, as detailed elsewhere.[17] Participants were recruited in two waves (1989–90 and 1992–93) from Medicare eligibility lists in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. Approximately 57.3% of eligible participants were enrolled in CHS.[18] Potential disease events were identified through semi-annual phone calls, hospital discharge report review, and Centers for Medicaid & Medicare Services data. Deaths were identified by obituary review, medical records, death certificates, National Death Index and household contacts. A group of experts adjudicated all incident cardiovascular and cerebrovascular events and causes of death. CHS has achieved a 100% complete follow up of mortality status.[19] Data used for this analysis was censored on June 30, 2011. The present study was determined to be exempt by the Oregon State University Institutional Review Board.

Risk Factors

Frailty was assessed according to the Fried criteria, an established measure of frailty originally developed in CHS.[13] The Fried frailty definition includes: unintentional weight loss, exhaustion, low physical activity, slow walking speed and low grip strength.[13] Participants that met 1 or 2 of the frailty components were considered “pre-frail” and participants that met 3 or more were considered “frail.” Slow walking speed was assessed as the slowest quintile at baseline, based on time to walk 15 feet, adjusted for sex and standing height.[13] Low grip strength, measured in the dominant hand, was also based on the lowest quintile, after accounting for sex and body mass index (BMI).[13] Low physical activity was defined as the lowest quintile, by gender, of kilocalories of weekly physical activity. Thresholds for slow walking speed, low grip strength, low physical activity defined at baseline were used for assessment of these measures at later assessments. Exhaustion was based off of self-report on 2 questions in the Center for Epidemiologic Studies Depression (CES-D) scale. Unintentional weight loss was defined as self-reported weight loss of >10 lbs. not due to exercise nor diet. Individual criteria of frailty we included in frailty assessment as well as separate risk factors of interest.

Stored serum samples were used to assess concentrations of biomarkers of inflammation and renal function. C reactive protein (CRP), an acute phase reactant protein, and interleukin-6 (IL-6), an inflammatory activating cytokine, were measured using high sensitivity enzyme-linked immunosorbent assays (RD systems, Minneapolis, MN; Roche Diagnostics, Indianapolis, IN). Cystatin C, a marker of kidney function, was measured by particle enhanced immunoephelometry (BNII nephelometer) (Seimens Healthcare Diagnostics, Deerfield, IL; N Latex Cystatin C).

For comparison, we included cholesterol and blood pressure as traditional cardiovascular risk factors. Total cholesterol was measured in overnight fasting blood samples. Systolic and

diastolic blood pressure was assessed in seated participants after 5 minutes of rest; 3 readings were obtained and the average of the last two readings was recorded.

Risk factor measures from baseline and years 3, 7, 16 were used in analyses (except frailty and low physical activity which were only available at baseline, and years 3, and 16). For each candidate risk factor analysis, only stroke events with candidate risk factor measurements obtained ≤ 5 years prior to incident stroke events were included, which accounts for variation in sample size across analyses. The mean time from risk factor measurement to incident stroke was 2.2 years.

Stroke Outcomes

Survival time was defined as length of time in days from stroke event until death. When available, hours from time of stroke till death were included. For 28 fatal strokes with survival time of less than 1 day and for which hours of survival were not recorded, a survival time 0.1 days was assigned.

We allowed one year for potential recovery between stroke and assessment of cognitive function and ADL score as prior research has suggested that that recovery of walking speed is minimal after the first 11 weeks and the majority of recovery for stroke patients occurs within the first 6 months.[20] The mean time from stroke to recovery assessment was 1.6 years.

Cognitive recovery was defined by examining the difference between pre and post-stroke cognitive function assessments. Cognitive function was assessed using the Modified Mini-Mental State Examination (3MSE), a 100-point scale test of global cognitive function. When possible, missing 3MSE scores were estimated using Telephone Interview for Cognitive Status. Participants who had a decrease of 5 or more points between pre and post-stroke 3MSE assessment, a clinically relevant decrease, were considered to have failed recovery in cognitive function (cognitive decline) post-stroke.

ADL recovery was defined by examining the difference between pre and post-stroke ADL limitation assessment. Rated difficulty in 6 different ADLs was assessed through questionnaires; a limitation was defined as difficulty or inability to perform one or more ADL (bathing, eating, dressing, using the toilet, getting out of bed or chair, and walking around home). Participants who had an increase of 1 or more limitations between pre and post stroke ADL assessment were considered to have failed recovery in ADLs (ADL decline) post-stroke.

Statistical Analyses

We described the characteristics of 3 groups: CHS participants with incident (first) ischemic stroke occurring during the CHS, CHS participants with incident ischemic stroke who are eligible for survival analyses, and CHS participants with incident ischemic stroke who are eligible recovery analyses. For characteristics with multiple measurements, we utilized the most recently obtained assessment that occurred prior to stroke.

We assessed the association between the potential risk factors measured prior to the stroke and survival time post-stroke using Cox proportional hazard models. Logistic models were used to assess the association of potential risk factors with both measures of recovery. In recovery analyses, the pre-frail and frail categories were combined because of sample size. Separate models were run to analyze each candidate risk factor, adjusted for time between risk factor assessment and the stroke event. Proportional hazards assumption was assessed for all the Cox models presented based on the Schoenfeld residuals [21].

Potential confounders, selected *a priori,* included in adjusted analyses were age at time of stroke, ischemic stroke subtype, stroke location, race, sex, and education. The most recent but prior to stroke assessments of smoking status, alcohol consumption, living arrangement, atrial fibrillation, coronary heart disease, heart failure, diabetes, depressive symptoms (CES-D>12), low cognitive function (3MSE<80), BMI, anticoagulant use and antihypertensive medication use were also included in adjusted models. Effect modification of risk factors by age at time stroke, sex, race, and time between risk factor measurement and stroke was also assessed. Stratum specific estimates were presented if the p-value for interaction was <0.05 in unadjusted or adjusted analyses.

Additional details regarding the CHS, stroke event assessment, study populations, and recovery measures are included in the Supplemental Methods (see http://stroke.ahajournals.org).

RESULTS

Among 5,639 participants without stroke at baseline, 894 incident ischemic strokes occurred during 22 years of follow up. To accommodate the timing of the risk factor measures, our sample included 717 participants eligible for the survival analysis and 509 eligible for the recovery analysis. (Supplemental Figure, see http://stroke.ahajournals.org) The median survival time after stroke was 3.3 years for the stroke survival population and 3.8 years for the stroke recovery population. Of the 717 participants eligible for the survival analysis, 645 died and 72 were censored; of the 509 eligible for the recovery analysis, 206 had post-stroke cognitive decline and 256 had ADL decline. Table 1 details characteristics of all participants with ischemic stroke as well as of the stroke survival and stroke recovery eligible study populations.

In separate models, cystatin C was associated with shorter survival after stroke in unadjusted and adjusted models (Table 2). Among participants younger than 80 years, frailty and IL-6 were associated with shorter survival after stroke, although these associations were not observed among older participants: adjusted p-values for interaction were 0.05 for pre-frail, 0.06 for frail and 0.03 for IL-6. Among participants 80 and older only, higher total cholesterol was associated with longer survival after stroke before adjustment for potential confounders (unadjusted p-value for interaction = 0.02). Sex, race, and time since risk factor measurement did not modify the effect of any of the candidate risk factors on post-stroke survival time: all p-values for interaction > 0.05.

In unadjusted models, frailty status and cystatin C were significantly associated with cognitive decline after stroke, although these associations were modestly attenuated and no longer reached statistical significance in an adjusted model. (Table 3) Among men only, inflammatory markers CRP and IL-6 were independently associated with cognitive decline: adjusted p-values for interaction were 0.01 for CRP and 0.04 for IL-6). Age, race, and time since risk factor measurement did not modify the effect of any of the candidate risk factors on cognitive decline after adjustment and accounting for the sex interaction. Results were similar in sensitivity analyses that assumed participants with missing cognitive measures had cognitive decline or no cognitive decline (Supplemental Tables I & II, respectively, see http://stroke.ahajournals.org), although cystatin C emerged as a statistically significant risk factor in analyses imputing missing cognitive measures as no cognitive decline

In unadjusted models, IL-6 and cystatin C were significantly associated with post-stroke ADL decline, although these associations were modestly attenuated and not statistically significant after adjustment. (Table 4) In women, pre-frail or frail status were associated with post-stroke ADL decline before and after adjustment. Age, race, and time-since risk factor measurement did not modify the effect of any of the candidate risk factors on ADL decline after adjustment and accounting for effect modification by sex. Results were similar in sensitivity analyses that imputed missing ADL measures as ADL decline or no ADL decline (Supplemental Tables III and IV, respectively, see http://stroke.ahajournals.org), although higher CRP and IL-6 emerged as statistically significant risk factors analyses imputing missing ADL measures as ADL decline.

Among the frailty components, slow walking speed and grip strength were consistently associated with the outcomes of shorter survival, cognitive decline, and increased ADL limitation. (Table 5) Low physical activity was associated with shorter survival only among participants <80 years (adjusted p-value for age interaction = 0.009) and with ADL decline only among women (unadjusted p-value for sex interaction = 0.04). Unintentional weight loss was borderline statistically significantly associated with shorter survival, and exhaustion was modestly associated with ADL decline.

DISCUSSION

This the first study to evaluate the association of frailty and related clinical characteristics with the clinically relevant adverse outcomes of shorter survival and poor recovery post-stroke. Pre-stroke frailty, inflammation, and renal function were associated with ischemic stroke outcomes of survival and recovery. The low physical function components of frailty, measured by walking speed and grip strength, were the most consistent determinant of shorter survival and lack of post-stroke recovery in cognition and ADL. The associations of inflammation, renal function, and frailty with recovery after stroke varied by the outcome measured and by sex and age. Established cardiovascular risk factors —elevated systolic and diastolic blood pressure and total cholesterol—were not independently associated with survival or recovery in cognition or ADL. Because of the long follow up and large sample size of incident ischemic strokes, we were able to assess a number of relevant risk factors while simultaneously adjusting for previously established predictors of adverse stroke outcomes. Taken together, our findings support our hypothesis that frailty factors, including

the frailty syndrome and physical function, as well as the related pathways of chronic inflammation and renal function may indicate vulnerability to poor recovery after ischemic stroke. These factors could help identify those individuals at the greatest risk for poor stroke outcomes, or be evaluated as potential clinical targets for intervention.

Previous studies have shown that age,[22] sex,[4, 23] smoking status,[24] living arrangement,[6, 10] history of heart failure,[3, 10] coronary heart disease,[24] depression, dementia,[3, 10] diabetes,[4, 7, 24] BMI,[6] atrial fibrillation,[3, 10, 25] and stroke subtype[22] are associated with stroke severity, fatality, functional status or some combination of these outcomes. The majority of these studies assessed risk factors at the time of stroke. [3, 4, 6–10] In a previous study of the CHS cohort, stroke subtype, older age and slow walking speed were associated with stroke fatality among incident strokes.[22] A subsequent CHS study of exclusively ischemic stroke demonstrated that age, sex and stroke subtype were associated with death after stroke and participation in CHS study visits after stroke.[24] In the same study, diabetes, smoking status and total cholesterol were associated with post-stroke outcomes of recurrent stroke and coronary heart disease.

We found a differential association of some pre-stroke risk factors and outcomes by age and sex; associations of frailty and IL-6 with post-stroke survival were significantly attenuated at older age. This might be attributable to increasing heterogeneity among the oldest old, a difference in phenotype of resilience to ischemic stroke among very old individuals, or chance. For post-stroke recovery, we observed effect modification by sex, consistent with previous studies that have reported that impairment and institutionalization after stroke differ by sex.[23, 26] Inflammatory biomarkers, CRP and IL-6 were only associated with post-stroke cognitive decline in men. Additionally, frailty was only associated with post-stroke cognitive decline, and ADL decline in women. Our findings suggest that not only do rates of recovery differ by sex, but that the profile of underlying factors that influence stroke recovery may differ between men and women.

Well-established cardiovascular risk factors of high blood pressure and elevated total cholesterol were not associated with an increased risk of death, cognitive decline, or ADL decline post-stroke. Although high blood pressure and high cholesterol may increase the risk of ischemic stroke, these factors do not appear to increase the risk of adverse outcomes after stroke. Interestingly, we found that total cholesterol appeared modestly protective for post-stroke survival among participants aged 80 years and older in unadjusted analyses. Similar findings between total cholesterol and function outcomes post-stroke have been observed previously,[8] and other research suggests that a low cholesterol may be a marker of frailty and poor nutritional status in older age.[27]

The associations of frailty, physical function, chronic inflammation and renal function with poor stroke outcomes suggest that these factors may indicate decreased physiologic resilience to ischemic stroke events. These associations may also relate to stroke severity and medical and rehabilitation therapy following stroke. Multiple previous studies demonstrated that stroke severity, commonly assessed by National Institute of Health stroke scale, is significantly associated with adverse stroke outcomes.[3, 7] Without scores on this scale, we were not able to address the effect of stroke severity as a potential confounder, effect

modifier or mediator on the relationship between pre-stroke risk factors and post-stroke outcomes. We attempted to address potential confounding by stroke severity by adjusting for variables that were previously demonstrated to be associated with stroke severity in our adjusted analyses, including atrial fibrillation, previous heart failure, and low cognitive function prior to stroke.[10] We were also unable to adjust for aggressiveness of care after stroke, but attempted to address this issue by adjusting for living arrangement prior to stroke, as well as sex and age, which are known to contribute to treatment after stroke.[23, 24]

Another limitation to our study is missing data in both the risk factors presented and in stroke recovery outcomes. Missing data on the risk factors may have limited our sample size and power to detect associations. Missing data on stroke recovery were substantial as some participants did not return to follow up after stroke and may have introduced selection bias into our study design. To address this issue, we ran a sensitivity analyses on the participants who survived beyond 1 year but did not return for study follow up.[28] Findings from these analyses were largely consistent with our primary analysis. Missing data on recovery may have also hindered our power to detect significant associations after adjustment.

Although a number of studies previously addressed risk factors for stroke incidence, few have considered what factors may predispose stroke victims to adverse outcomes. This study represents the largest study we are aware of on the association between inflammatory, renal, cardiovascular, physical–functioning, and frailty measures assessed prior to stroke with clinically relevant stroke outcomes of duration of survival, cognitive decline, and ADL decline. Pre-stroke physical function and renal function were strong predictors of ischemic stroke outcomes in older adults and may serve as markers of resilience or vulnerability to ischemic stroke. Markers of frailty and inflammation were associated with shorter survival, but performed differently between men and women as markers of post-stroke recovery. We did not attempt to address the underlying mechanism for associations of these risk factors with stroke outcomes, namely whether risk factors influenced the severity of the stroke, ability to recovery after stroke or assignment of treatment post-stroke. Regardless of whether identified risk factors affect stroke severity or ability to recover, modifying these risk factors has the possibility to improve stroke outcomes if the associations demonstrated in this study are proven causal. Further understanding of the factors that lead to increased vulnerability to poor cerebrovascular outcomes may help address how to improve resilience to potentially fatal and debilitating stroke events and optimize prevention and post-stroke care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

SOURCES OF FUNDING

This research was supported by contracts HHSN268201200036C, N01HC85239, N01 HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grant HL080295 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by R01AG023629, R01AG027002, K01AG039387, and R01AG46206 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/PI.htm.

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics—2016 update a report from the american heart association. Circulation. 2015; 133:e38–e60. [PubMed: 26673558]
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics—2015 update a report from the american heart association. Circulation. 2015; 131:e29–e322. [PubMed: 25520374]
3. 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]
4. Weimar C, Ziegler A, König IR, Diener H-C. Predicting functional outcome and survival after acute ischemic stroke. J Neurol. 2002; 249:888–895. [PubMed: 12140674]
5. Casper, M., Croft, JB., Nilasena, DS., Nwaise, IA. Centers for Medicare & Medicaid Services. Atlas of stroke hospitalizations among medicare beneficiaries. US Department of Health and Human Services, Centers for Disease Control and Prevention; 2008.
6. Doehner W, Schenkel J, Anker SD, Springer J, Audebert HJ. Overweight and obesity are associated with improved survival, functional outcome, and stroke recurrence after acute stroke or transient ischaemic attack: Observations from the tempis trial. Eur Heart J. 2013; 34:268–277. [PubMed: 23076781]
7. Johnston K, Connors A, Wagner D, Knaus W, Wang X-Q, Haley EC. A predictive risk model for outcomes of ischemic stroke. Stroke. 2000; 31:448–455. [PubMed: 10657421]
8. Pan S-L, Lien I-N, Chen TH-H. Is higher serum total cholesterol level associated with better long-term functional outcomes after noncardioembolic ischemic stroke? Arch Phys Med Rehabil. 2010; 91:913–918. [PubMed: 20510983]
9. Weir CJ, Muir SW, Walters MR, Lees KR. Serum urate as an independent predictor of poor outcome and future vascular events after acute stroke. Stroke. 2003; 34:1951–1956. [PubMed: 12843346]
10. Appelros P, Nydevik I, Seiger Å, Terént A. Predictors of severe stroke influence of preexisting dementia and cardiac disorders. Stroke. 2002; 33:2357–2362. [PubMed: 12364721]
11. Brown PJ, Roose SP, Zhang J, Wall M, Rutherford BR, Ayonayon HN, et al. Inflammation, depression, and slow gait: A high mortality phenotype in later life. J Gerontol A Biol Sci Med Sci. 2016; 71:221–227. [PubMed: 26392405]
12. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci. 2014; 69(Suppl 1):S4–9. [PubMed: 24833586]
13. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56:M146–M157. [PubMed: 11253156]
14. Soysal P, Stubbs B, Lucato P, Luchini C, Solmi M, Peluso R, et al. Inflammation and frailty in the elderly: A systematic review and meta-analysis. Ageing Res Rev. 2016; 31:1–8. [PubMed: 27592340]
15. Wilhelm-Leen ER, Hall YN, MKT, Chertow GM. Frailty and chronic kidney disease: The third national health and nutrition evaluation survey. Am J Med. 2009; 122:664–671. e662. [PubMed: 19559169]
16. Dalrymple LS, Katz R, Rifkin DE, Siscovick D, Newman AB, Fried LF, et al. Kidney function and prevalent and incident frailty. Clin J Am Soc Nephrol. 2013; 8:2091–2099. [PubMed: 24178972]
17. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, et al. The cardiovascular health study: Design and rationale. Ann Epidemiol. 1991; 1:263–276. [PubMed: 1669507]
18. Tell GS, Fried LP, Hermanson B, Manolio TA, Newman AB, Borhani NO. Recruitment of adults 65 years and older as participants in the cardiovascular health study. Ann Epidemiol. 1993; 3:358–366. [PubMed: 8275211]
19. Ives DG, Fitzpatrick AL, Bild DE, Psaty BM, Kuller LH, Crowley PM, et al. Surveillance and ascertainment of cardiovascular events: The cardiovascular health study. Ann Epidemiol. 1995; 5:278–285. [PubMed: 8520709]

20. Hankey G, Spiesser J, Hakimi Z, Bego G, Carita P, Gabriel S. Rate, degree, and predictors of recovery from disability following ischemic stroke. Neurology. 2007; 68:1583–1587. [PubMed: 17485645]

21. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994; 81:515–526.

22. Longstreth W, Bernick C, Fitzpatrick A, Cushman M, Knepper L, Lima J, et al. Frequency and predictors of stroke death in 5,888 participants in the cardiovascular health study. Neurology. 2001; 56:368–375. [PubMed: 11171903]

23. Glader E-L, Stegmayr B, Norrving B, Terént A, Hulter-Åsberg K, Wester P-O, et al. Sex differences in management and outcome after stroke a swedish national perspective. Stroke. 2003; 34:1970–1975. [PubMed: 12855818]

24. Kaplan R, Tirschwell D, Longstreth W, Manolio T, Heckbert S, Lefkowitz D, et al. Vascular events, mortality, and preventive therapy following ischemic stroke in the elderly. Neurology. 2005; 65:835–842. [PubMed: 16186519]

25. Marini C, De Santis F, Sacco S, Russo T, Olivieri L, Totaro R, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke results from a population-based study. Stroke. 2005; 36:1115–1119. [PubMed: 15879330]

26. Gargano JW, Reeves MJ. Sex differences in stroke recovery and stroke-specific quality of life results from a statewide stroke registry. Stroke. 2007; 38:2541–2548. [PubMed: 17673706]

27. Renzo, Ranieri, Simone, Rozzini, Piera, Franzoni, Marco, Barbisoni, Trabucchi, P. Serum cholesterol levels as a measure of frailty in elderly patients. Exp Aging Res. 1998; 24:169–179. [PubMed: 9555569]

28. Engels JM, Diehr P. Imputation of missing longitudinal data: A comparison of methods. J Clin Epidemiol. 2003; 56:968–976. [PubMed: 14568628]

Table 1

Descriptive characteristics of all CHS participants with incident ischemic stroke and populations eligible for survival analysis and recovery analysis

	All CHS participants with incident ischemic stroke (N=893)	Eligible Survival Analysis Study Population (N=717)	Eligible Recovery Analysis Study Populations (N=509)
Characteristics*	**N (%) or Mean (SD) or Median [IQR]**		
Age at time of stroke(years)	81.8 (6.4)	81.0 (6.4)	80.2 (6.6)
Sex			
Female	545 (61.0%)	434 (60.5%)	289 (56.8%)
Race			
White	766 (85.7%)	623 (86.9%)	448 (88.0%)
Black or Other	128 (14.3%)	94 (13.1%)	61 (12.0%)
Education			
No high school completion	273 (30.5%)	214 (29.9%)	160 (31.4%)
Completed High School	270 (30.2%)	215 (30.0%)	148 (29.1%)
Any higher education	351 (39.3%)	288 (40.2%)	201 (39.5%)
Smoking			
Never	442 (49.4%)	362 (50.5%)	269 (52.9%)
Former	386 (43.2%)	304 (42.4%)	209 (41.1%)
Current	66 (7.4%)	51 (7.1%)	31 (6.1%)
Alcohol Consumption			
None	561 (62.8%)	437 (61.0%)	298 (58.3%)
≤ 5 drinks per week	236 (26.4%)	196 (27.3%)	152 (29.9%)
> 5 drinks per week	97 (10.9%)	84 (11.7%)	59 (11.6%)
Living Arrangements			
Lives alone	252 (28.2%)	195 (27.2%)	119 (23.4%)
Lives with others	518 (57.9%)	420 (58.6%)	318 (64.5%)
Unknown	124 (13.9%)	102 (14.2%)	72 (14.2%)
Prior history of CHD	260 (29.1%)	228 (31.8%)	163 (32.0%)
Prior history of heart failure	83 (9.3%)	77 (10.7%)	56 (11.0%)
Atrial Fibrillation			
Diagnosed prior to stroke	207 (23.2%)	152 (21.2%)	100 (19.7%)
Diagnosed at stroke	68 (7.6%)	49 (6.8%)	34 (6.7%)
Depressive symptoms (CES-D≥12)	169 (18.9%)	140 (19.5%)	100 (19.7%)
Low Cognitive Function (3MSE<80)	130 (14.7%)	112 (15.8%)	83 (16.5%)
Diabetes	287 (32.3%)	233 (32.6%)	178 (35%)
BMI (kg/m^2)	26.8 (4.7)	26.7 (4.6)	26.7 (4.6)
Fatal Stroke	73 (8.2%)	60 (8.4%)	36 (7.1%)
Stroke location			
Left hemisphere	383 (42.8%)	296 (41.3%)	216 (42.5%)
Right hemisphere	337 (37.7%)	271 (37.8%)	187 (36.7%)

	All CHS participants with incident ischemic stroke (N=893)	Eligible Survival Analysis Study Population (N=717)	Eligible Recovery Analysis Study Populations (N=509)
Characteristics*	**N (%) or Mean (SD) or Median [IQR]**		
Basilar	108 (12.1%)	93 (13.0%)	61 (12.0%)
Other or Unknown	66 (7.4%)	57 (8.0%)	45 (8.8%)
Ischemic Stroke Subtype			
Lacunar	116 (13.0%)	102 (14.2%)	75 (14.7%)
Atherosclerotic	43 (4.8%)	35 (4.9%)	25 (4.9%)
Cardio-embolic	249 (27.9%)	187 (26.1%)	125 (24.6%)
Other and unknown	486 (54.4%)	393 (54.8%)	284 (55.8%)
Anti-hypertensive med. Use	579 (64.8%)	469 (65.4%)	331 (65.0%)
Anticoagulant med. Use	48 (5.4%)	41 (5.7%)	27 (5.3%)
Frailty Status†			
Not Frail	148 (27.8%)	160 (30.1%)	111 (28.8%)
Pre-Frail	292 (54.9%)	294 (55.3%)	217 (56.2%)
Frail	92 (17.3%)	78 (14.7%)	58 (15.0%)
Slow Walking Speed†	279 (44.8%)	280 (44.9%)	212 (46.1%)
Low Grip Strength†	192 (32.7%)	192 (32.7%)	149 (34.5%)
C Reactive Protein (mg/dL)†	3.0 [1.5–6.5]	3.0 [1.5–6.5]	2.9 [1.5–6.7]
Interleukin-6 (pg/mL)†	2.9 [1.9–4.3]	2.9 [1.9–4.3]	2.7 [1.7–4.2]
Cystatin C (mg/dL)†	1.1 [1.0–1.3]	1.1 [1.0–1.3]	1.1 [1.0–1.4]
Systolic Blood Pressure (mmHg)†	144 (24)	144 (24)	144 (25)
Diastolic Blood Pressure (mmHg)†	72 (12)	72 (12)	72 (13)
Total Cholesterol (mg/dL)†	208 (41)	208 (41)	209 (41)

*Most recently obtained measurements that occurred prior to stroke.

†Measurements obtained from baseline or years 3, 7, 16 were eligible for this study

Table 2

Risk factors for shorter survival among participants with incident ischemic stroke

	Unadjusted*					Fully Adjusted†				
	n‡	HR	95% CI	p-value	Int. §	n‡	HR	95% CI	p-value	Int. §
Pre-Frail										
<80 years	300	1.48	1.13, 1.94	0.003	0.20	294	1.64	1.23, 2.18	0.001	0.04
≥80 years	232	1.11	0.78, 1.57	0.57		221	0.99	0.68, 1.46	0.96	
Frail										
<80 years	300	2.08	1.38, 3.13	<0.001	0.05	294	2.03	1.31, 3.16	0.002	0.06
≥80 years	232	1.18	0.79, 1.76	0.43		221	1.13	0.71, 1.80	0.61	
CRP //	616	1.05	0.99, 1.10	0.11		606	1.05	0.99, 1.12	0.08	
IL-6 //										
<80 years	294	1.47	1.30, 1.67	<0.001	0.007	292	1.41	1.23, 1.62	<0.001	0.03
≥80 years	291	1.13	0.97, 1.30	0.12		285	1.12	0.95, 1.31	0.17	
Cystatin C //	578	2.24	1.81, 2.77	<0.001		568	1.97	1.55, 2.50	<0.001	
Systolic Blood Pressure#	637	1.01	0.97, 1.04	0.62		622	1.02	0.98, 1.05	0.39	
Diastolic Blood Pressure#	637	0.96	0.90, 1.03	0.23		622	0.99	0.92, 1.06	0.79	
Total Cholesterol¶										
<80 years	312	0.99	0.96, 1.03	0.70	0.02	309	1.02	0.98, 1.05	0.36	0.10
≥80 years	307	0.94	0.92, 0.97	<0.001		300	0.98	0.95, 1.00	0.16	

*Adjusted for time between risk factor assessment and stroke

†Adjusted for time between risk factor assessment and stroke, ischemic stroke subtype, stroke location, race, sex, education attainment, smoking status, alcohol consumption, living alone status, atrial fibrillation, coronary heart disease, congestive heart failure, diabetes, depression (CES-D>12), low cognitive function (3MSE<80), BMI, anti-coagulant use, and anti-hypertensive medication use

‡n in each analysis

§p-value for interactions

//per doubling in concentration

#per 10 mm Hg

¶per 10 mg/dL

Table 3

Risk factors for cognitive decline after incident ischemic stroke

	Unadjusted*					Fully Adjusted†				
	n‡	OR	95% CI	p-value	Int. §	n‡	OR	95% CI	p-value	Int. §
Frail or Pre-Frail	305	2.28	1.35, 3.86	0.002		291	1.71	0.91, 3.22	0.10	
CRP//										
Males	157	1.40	1.12, 1.74	0.003	0.003	156	1.48	1.14, 1.92	0.004	0.01
Females	188	0.92	0.87, 1.08	0.30		185	0.98	0.80, 1.19	0.81	
IL-6//										
Males	154	1.94	1.32, 2.85	0.001	0.27	153	2.02	1.28, 3.20	0.003	0.04
Females	181	1.46	1.05, 2.03	0.03		178	1.06	0.70, 1.61	0.78	
Cystatin C//	317	2.13	1.23, 3.68	0.007		313	1.53	0.80, 2.92	0.20	
Systolic Blood Pressure#	354	1.02	0.93, 1.11	0.65		348	1.04	0.94, 1.16	0.45	
Diastolic Blood Pressure#	355	0.97	0.82, 1.15	0.73		347	1.04	0.84, 1.29	0.70	
Total Cholesterol¶	346	0.97	0.91, 1.02	0.20		342	0.99	0.93, 1.06	0.79	

*Adjusted for time between risk factor assessment and stroke

†Adjusted for time between risk factor assessment and stroke, ischemic stroke subtype, stroke location, race, sex, education attainment, smoking status, alcohol consumption, living alone status, atrial fibrillation, coronary heart disease, congestive heart failure, diabetes, depression (CES-D>12), low cognitive function (3MSE<80), BMI, anti-coagulant use, and anti-hypertensive medication use

‡n in each analysis

§p-value for interactions

//per doubling in concentration

#per 10 mm Hg

¶per 10 mg/dL

Table 4

Risk factors for increased ADL limitation after incident ischemic stroke

	Unadjusted*					Fully Adjusted†				
	n‡	OR	95% CI	p-value	Int.§	n‡	OR	95% CI	p-value	Int. §
Frail or Pre-Frail										
Males	152	1.40	0.70, 2.77	0.34	0.02	147	1.15	0.52, 2.56	0.73	0.10
Females	180	5.22	2.33, 11.70	<0.001		174	3.21	1.27, 8.13	0.01	
CRP//	391	1.11	0.98, 1.25	0.11		384	1.13	0.97, 1.32	0.12	
IL-6//	375	1.49	1.18, 1.88	0.001		369	1.28	0.96, 1.72	0.09	
Cystatin C//	361	2.33	1.38, 3.95	0.002		354	1.85	0.99, 3.47	0.05	
Systolic Blood Pressure#	402	0.99	0.91, 1.07	0.80		391	1.00	0.91, 1.10	0.95	
Diastolic Blood Pressure#	403	0.89	0.76, 1.05	0.16		392	0.91	0.75, 1.10	0.33	
Total Cholesterol¶	392	0.96	0.91, 1.01	0.08		385	0.98	0.92, 1.04	0.50	

*Adjusted for time between risk factor assessment and stroke

†Adjusted for time between risk factor assessment and stroke, ischemic stroke subtype, stroke location, race, sex, education attainment, smoking status, alcohol consumption, living alone status, atrial fibrillation, coronary heart disease, congestive heart failure, diabetes, depression (CES-D>12), low cognitive function (3MSE<80), BMI, anti-coagulant use, and anti-hypertensive medication use

‡n in each analysis

§p-value for interactions

//per doubling in concentration

#per 10 mm Hg

¶per 10 mg/dL

Stroke. Author manuscript; available in PMC 2018 July 01.

Table 5

Associations of Frailty Components with Survival Time, Cognitive Decline, and Increased ADL limitations after Ischemic Stroke

	Unadjusted Hazard of Death after Stroke				Adjusted Hazard of Death After Stroke			
	n‡	**HR* (95% CI)**	**p-value**	**Int.§**	**n‡**	**HR† (95% CI)**	**p-value**	**Int.§**
Slow Walking Speed	623	1.57 (1.33, 1.86)	<0.001		610	1.47 (1.22, 1.77)	<0.001	
Low Grip Strength	587	1.53 (1.27, 1.84)	<0.001		580	1.33 (1.09, 1.63)	0.006	
Low Physical Activity	329	<80 years: 1.58 (1.23, 2.03)	<0.001	0.04	319	<80 years: 1.65 (1.26, 2.15)	<0.001	0.009
	272	≥80 years: 1.09 (0.86, 1.39)	0.48		257	≥80 years: 1.00 (0.77, 1.31)	0.98	
Exhaustion	651	1.03 (0.86, 1.23)	0.74		626	1.11 (0.89, 1.39)	0.34	
Unintentional Weight Loss	662	1.35 (1.03, 1.77)	0.03		635	1.32 (0.99, 1.75)	0.06	
	Unadjusted Odds of Cognitive Decline After Stroke				Adjusted Odds of Cognitive Decline After Stroke			
	n‡	OR *(95% CI)	p-value	Int.§	n‡	OR†(95% CI)	p-value	Int.§
Slow Walking Speed	348	2.57 (1.65, 4.00)	<0.001		341	2.00 (1.18, 3.39)	0.01	
Low Grip Strength	329	2.20 (1.35, 3.56)	0.001		327	1.86 (1.05, 3.32)	0.03	
Low Physical Activity	329	1.75 (1.10, 2.78)	0.02		321	1.52 (0.85, 2.70)	0.16	
Exhaustion	357	1.19 (0.76, 1.85)	0.45		347	1.24 (0.68, 2.27)	0.49	
Unintentional Weight Loss	346	1.64 (0.75, 3.59)	0.22		337	1.25 (0.50, 3.16)	0.63	
	Unadjusted Odds of Increased ADL limitations				Adjusted Odds of Increased ADL limitations			
	n‡	OR *(95% CI)	p-value	Int.§	n‡	OR†(95% CI)	p-value	Int§
Slow Walking Speed	394	2.70 (1.78, 4.10)	<0.001		384	2.19 (1.33, 3.62)	0.002	
Low Grip Strength	371	2.30 (1.45, 3.64)	<0.001		366	1.74 (1.01, 3.02)	0.05	
Low Physical Activity	167	males: 1.21 (0.60, 2.45)	0.59	0.038	160	males: 1.05 (0.44, 2.50)	0.91	0.138
	197	females: 3.24 (1.77, 5.91)	<0.001		189	females: 2.42 (1.21, 4.86)	0.01	
Exhaustion	407	1.66 (1.08, 2.55)	0.02		391	1.82 (1.02, 3.24)	0.04	
Unintentional Weight Loss	411	1.49 (0.72, 3.06)	0.28		397	1.20 (0.52, 2.76)	0.67	

*Adjusted for time between risk factor assessment and stroke

†Adjusted for time between risk factor assessment and stroke, ischemic stroke subtype, stroke location, race, sex, education attainment, smoking status, alcohol consumption, living alone status, atrial fibrillation, coronary heart disease, congestive heart failure, diabetes, depression (CES-D>12), low cognitive function (3MSE<80), BMI, anti-coagulant use, and anti-hypertensive medication use

‡ n in each analysis

§ p-value for interactions