ONLINE SUPPLEMENT

Factors Associated with Ischemic Stroke Survival and Recovery in Older Adults

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

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

SUPPLEMENTAL METHODS:

Cardiovascular Health Study Visits:

The Cardiovascular Health Study (CHS) is a community-based cohort study of 5888 adults age 65 and older intended to study risk factors of cardiovascular disease, as detailed elsewhere.[1] For the first 10 years of CHS, annual in-person visits alternated with 6-month phone calls. Annual visits included physical exams, health questionnaires, interviews and laboratory specimen collection. After 1999, participants were contacted by phone semi-annually and at year 16 participants were offered an in-person visit. Semi-annual follow-up via telephone correspondence is ongoing.

Stroke Event Assessment:

All incident stroke and transient ischemic attacks were reviewed and confirmed by a Cerebrovascular Adjudication Committee, composed of a neurologist from each study site, a neuroradiologist from the CHS MRI Reading Center, and an internist or neurologist from the CHS Coordinating Center.[2] The Cerebrovascular Adjudication Committee determined whether suspect events were considered a TIA, fatal stroke or nonfatal stroke as well as whether the stroke was ischemic, hemorrhagic or other based on pre-specified criteria. Ischemic stroke type was classified as atherosclerotic, lacunar, cardio-embolic, other, or unknown. Reliability for determining stroke type and ischemic stroke subtype were high, with kappa scores of 1.0 and 0.77, respectively.[2] Location of the stroke was also assessed.

Study Populations:

During 22 years of follow up, 893 incident ischemic strokes occurred (Supplemental Figure). Stroke events eligible for survival and recovery analyses were restricted to incident ischemic stroke events that occurred within 5 years after a study visit and had assessment of stroke events. Additionally, stroke events eligible for recovery analyses were restricted to those with assessment of recovery measures (described below) . Statistical models of each risk factor included only strokes that within 5 years after an assessment of the risk factor. To ensure comparability between potential risk factors, we only used risk factor measures that were gathered at baseline, and 3, 7, or 16 years later. As such, participants eligible for the survival analysis were participants who suffered an incident ischemic stroke between baseline and the 12^{th} annual follow-up or between the 16^{th} and 21^{th} follow-up years in CHS (n=717). Participants eligible for the recovery analysis included those who suffered an incident ischemic stroke between baseline and the 8^{th} annual follow-up or between of the 16^{th} and 20^{th} follow-up years (n=509).

Stroke Outcomes Assessment:

For pre-stroke ADL and 3MSE assessment we utilized the most recently obtained assessment that occurred prior to stroke. For post-stroke ADL and 3MSE assessment we utilized the earliest available post-stroke assessment that occurred at least 1 year after stroke. Participants who survived less than 1 year following stroke were assumed to have failed recovery cognitive function and ADLs. Participants lacking pre-stroke assessments within 3 years before stroke or post-stroke assessments within 5 years after stroke were excluded from these analyses. In sensitivity analyses, participants who did not return for study participation were imputed as "not recovered," under the assumption that loss of study participants to follow up is related to worse health status.[3] As an alternative analysis, participants who did not return were imputed as "recovered."

SUPPLEMENTAL REFERENCES:

1. 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
2. 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
3. Engels JM, Diehr P. Imputation of missing longitudinal data: A comparison of methods. *J Clin Epidemiol*. 2003;56:968-976

SUPPLEMENTAL TABLES:

Table I. Sensitivity analysis of risk factors for cognitive decline after stroke, assuming all participants with missing post-stroke cognitive function measures had cognitive decline

	Unadjusted*				Fully Adjusted†			
	OR	95% CI	p-value	Int. ‡	OR	95% CI	p-value	Int. ‡
Frail or Pre-Frail	2.18	1.35, 3.53	0.001		1.71	0.97, 3.01	0.062	
CRP§								
Males	1.35	1.10, 1.66	0.005	0.005	1.43	1.13, 1.84	0.004	0.03
Females	0.93	0.80, 1.09	0.39		1.02	0.84, 1.24	0.82	
IL-6§	1.69	1.33, 2.15	<0.001		1.46	1.09, 1.96	0.01	
Cystatin C§	1.79	1.08, 2.97	0.02		1.30	0.73, 2.33	0.38	
Systolic Blood Pressure| |	1.02	0.94, 1.11	0.59		1.04	0.95, 1.14	0.42	
Diastolic Blood Pressure| |	0.98	0.84, 1.15	0.81		1.06	0.88, 1.28	0.53	
Total Cholesterol#	0.96	0.91, 1.00	0.07		0.98	0.92, 1.04	0.43	

*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

‡p-value for interactions

§per doubling in concentration

\| \|per 10 mm Hg

#per 10 mg/dL

Table II. Sensitivity analysis of risk factors for cognitive decline after stroke, assuming all participants with missing post-stroke cognitive function measures had no cognitive decline

	Unadjusted*				Fully Adjusted†			
	OR	95% CI	p-value	Int. ‡	OR	95% CI	p-value	Int. ‡
Frail or Pre-Frail	1.78	1.10, 2.88	0.02		1.31	0.75, 2.26	0.34	
CRP§								
Males	1.33	1.10, 1.62	0.004	0.005	1.35	1.08, 1.69	0.007	0.02
Females	0.94	0.81, 1.09	0.39		0.97	0.82, 1.15	0.75	
IL-6§	1.40	1.12, 1.76	0.003		1.33	1.02, 1.74	0.04	
Cystatin C§	2.11	1.31, 3.40	0.002		1.96	1.14, 3.37	0.02	
Systolic Blood Pressure| |	1.02	0.95, 1.10	0.59		1.03	0.95, 1.12	0.50	
Diastolic Blood Pressure| |	0.97	0.84, 1.12	0.69		1.00	0.84, 1.19	0.99	
Total Cholesterol#	0.99	0.95, 1.04	0.78		1.02	0.97, 1.08	0.40	

*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

‡p-value for interactions

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Table III. Sensitivity analysis of risk factors for ADL limitation after stroke assuming all participants with missing post-stroke ADL limitation measures had increased ADL limitation

	Unadjusted*				Fully Adjusted†			
	OR	95% CI	p-value	Int. ‡	OR	95% CI	p-value	Int. ‡
Frail or Pre-Frail								
Male	1.48	0.77, 2.83	0.24	0.03	1.39	0.65, 2.95	0.39	0.33
Female	4.28	2.10, 8.73	<0.001		2.41	1.07, 5.43	0.03	
CRP§	1.13	1.00, 1.27	0.05		1.18	1.01, 1.36	0.03	
IL-6§	1.57	1.25, 1.97	<0.001		1.37	1.04, 1.81	0.03	
Cystatin C§	2.35	1.42, 3.90	0.001		1.95	1.08, 3.49	0.03	
Systolic Blood Pressure| |	1.00	0.92, 1.08	0.96		1.01	0.93, 1.11	0.78	
Diastolic Blood Pressure| |	0.91	0.78, 1.05	0.20		0.93	0.78, 1.12	0.47	
Total Cholesterol#	0.96	0.92, 1.01	0.12		0.99	0.93, 1.04	0.63	

*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

‡p-value for interactions

§per doubling in concentration

\| \|per 10 mm Hg

#per 10 mg/dL

Table IV. Sensitivity analysis of risk factors for ADL limitation after stroke assuming all participants with missing post-stroke ADL limitation measures had no increases in ADL limitations

	Unadjusted*				Fully Adjusted†			
	OR	95% CI	p-value	Int. ‡	OR	95% CI	p-value	Int. ‡
Frail or Pre-Frail								
Male	1.07	0.56, 2.05	0.84	0.006	0.90	0.43, 1.88	0.77	0.03
Female	4.48	2.06, 9.72	<0.001		3.25	1.36, 7.77	0.008	
CRP§	1.08	0.96, 1.21	0.18		1.07	1.93, 1.23	0.33	
IL-6§	1.35	1.08, 1.68	0.008		1.17	0.90, 1.53	0.25	
Cystatin C§	2.11	1.32, 3.39	0.002		1.98	1.14, 3.45	0.02	
Systolic Blood Pressure| |	0.98	0.91, 1.05	0.54		0.99	0.91, 1.08	0.80	
Diastolic Blood Pressure| |	0.91	0.79, 1.05	0.20		0.93	0.78, 1.10	0.39	
Total Cholesterol#	0.96	0.92, 1.01	0.11		0.98	0.93, 1.03	0.46	

*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

‡p-value for interactions

§per doubling in concentration

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#per 10 mg/dL

SUPPLEMENTAL FIGURE: Inclusion criteria for stroke survival time, cognitive recovery, and ADL recovery after stroke analyses