Cognitive Impairment Predicts Fatal Incident Stroke: Findings from a National Sample of Older Adults

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OBJECTIVES: To investigate the effect of cognitive impairment on fatal and nonfatal incident stroke in older adults.

DESIGN: A large, national, prospective, population-based study of a representative cohort of older Canadians followed over a 10-year period.

SETTING: Secondary analyses were conducted using data from the Canadian Study of Health and Aging, a population-based study of older adults followed prospectively from 1991 to 2001.

PARTICIPANTS: Nine thousand four hundred fifty-one adults aged 65 and older who had not previously been diagnosed with stroke at baseline (in 1991).

MEASUREMENTS: In addition to known risk factors, the independent contribution of cognitive function (diagnosed in a clinical examination) was examined as a risk for stroke in older adults.

RESULTS: Multinomial logistic regression analyses showed that cognitive impairment was associated with twice the odds of fatal incident stroke, controlling for well-established risk factors.

CONCLUSION: This study provides further evidence for the need to consider cognitive function in relation to stroke risk in older populations. **J Am Geriatr Soc 59:1490–1496, 2011.**

Key words: stroke; risk factors; cognitive function; Canadian Study of Health and Aging

In the United States, Canada, and much of the developed world, stroke is one of the three leading causes of death and a major cause of long-term disability.[1] The prevalence of stroke increases rapidly with age.[2,3] For older adults who survive the initial onset, a stroke can have a substantial effect on independence, quality of life, and social relationships.[4,5] Reducing the incidence of stroke in later life requires the scientific identification of risk factors in older adult populations.

Important vascular risk factors include high blood pressure, cigarette smoking, and diabetes mellitus.[6–8] Other identified risk factors include physical inactivity, excessive alcohol use, obesity, heart disease, and Parkinson's disease.[9–12] African Americans and Hispanics have higher rates of first stroke than whites, and men have higher incidence rates than women.[13] Stroke incidence and mortality are higher in people with less education, whereas social supports may reduce the risk of stroke.[14,15] Measures of physical function or frailty have also been found to be predictors of stroke in older adults,[16] perhaps because impairments in physical function develop in the preclinical phases before stroke onset, yet most of this evidence comes from geographically constrained samples (e.g., Framingham Heart Study, Atherosclerosis Risk in Communities Study (ARIC), Baltimore Longitudinal Study of Aging), not from nationally representative studies focusing exclusively on older adult populations. As a result, generalizable stroke risk factors specific to the older population may not be fully understood.

There is evidence to suggest that risk factors for stroke are not always equivalent across age groups.[17–19] Cognitive impairment, in particular, has been identified as a potentially unique risk factor in older adults.[20–24] Data from the Established Population for Epidemiologic Studies of the Elderly (EPESE) indicate that older adults with poor cognitive function had twice the risk of stroke over a 3-year period.[21] This relationship was replicated with data from the Hispanic EPESE.[20] A study using data from ARIC did not find a relationship between cognitive impairment and stroke incidence, most likely because the sample was restricted to a somewhat younger population (aged 48–67),[22] but more-recent research using the same data found cognitive function to be an independent risk factor when stroke was pooled with all other cardiovascular outcomes.[24]

Given these inconsistent findings, the purpose of this research was to investigate the effect of clinically diagnosed

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cognitive impairment as an independent risk factor for fatal and nonfatal incident stroke in a large, national, prospective, population-based study of a representative cohort of older Canadians followed over a 10-year period.

METHODS

Data

Secondary analyses were conducted with data from the Canadian Study of Health and Aging (CSHA), a population-based epidemiological study of dementia in 10,263 older adults followed prospectively over a 10-year period (1991–2001). The first wave of the study (CSHA-1) began in 1991 with a representative sample of community (n = 9,008) and institutional-dwelling (n = 1,255) Canadians aged 65 and older from 36 urban and surrounding rural areas in all 10 Canadian provinces. A second wave of the study (CSHA-2) was conducted 4 years later (1995/96) when 9,265 surviving participants from the first wave were recontacted for follow-up. A third wave in 2001/02 (CSHA-3) followed 5,456 surviving participants who were not diagnosed with dementia at CSHA-2.

Trained interviewers surveyed community-dwelling participants about their health, disability, and social circumstances using a standardized questionnaire (administered face-to-face in English or French). Participants were also given a screening test for cognitive impairment (the Modified Mini-Mental State Examination (3MS)[25]) and were referred (when their 3MS score was < 78) for a further clinical assessment during which trained nurses, psychometrists, neuropsychologists, and physicians performed extensive tests to ascertain the diagnosis of dementia and cognitive impairment. Participants from the institutional sample (and a random subset from the community sample who did not screen positive on the 3MS) went directly to the clinical assessment. Further details on the study methods can be found elsewhere.[26] The ethics review boards in each of the 18 study centers approved the procedures followed in CSHA, and all participating participants gave informed consent.

Measures

Outcome Variables

This study focused on two outcomes: nonfatal and fatal incident stroke. For community-dwelling participants, information on stroke incidence was collected through a self-report question: “Have you experienced a stroke or the effects of a stroke in the past year?” For participants referred to the clinical examination, a nurse or physician collected information on stroke occurrence during the clinical history. When participants had self-reported and clinical data (for community-dwelling participants referred to a clinical examination), the clinical report on stroke was used. Information on stroke mortality across the 10 years of the study was obtained from death certificates at the Office of the Registrar General in each province (underlying cause of death listed as *International Classification of Diseases, Ninth Revision* code 431 (cerebral hemorrhage), 433–434 (cerebral infarction), 436.0–437.1 or 437.9 (ill-defined cerebrovascular disease), or 438.0–438.9 (late effects of cerebrovascular disease). A stroke was considered to be an incident stroke if there was no mention of stroke in the previous waves, and the analyses are restricted to respondents without preexisting stroke at CSHA-1.

Predictor Variables

To the extent that they were available in the data, health and sociodemographic risk factors were examined as predictors of stroke. Information on heart disease, diabetes mellitus, hypertension, and Parkinson’s disease was collected at each wave (through self-report in the community sample or clinical history and examination in the clinical sample). Cognitive impairment was based on a diagnosis of dementia or cognitive impairment without dementia (CIND) at the clinical examination. Physical disability was assessed through a count of the number of activities in which respondents report difficulty; seven items ask about basic self-care activities of daily living (ADLs) (e.g., bathing, dressing), and seven items probe difficulty with more-complex activities (e.g., shopping, meal preparation). An overall disability score is created by summing the number of activities for which the respondent reported difficulty.

Information on sex, race (white vs black or other race), age (67–75, 76–85, ≥86), and educational level (< high school education, high school diploma, or ≥college degree) was also included. In addition, information on marital status, as a measure of social support, was collected at each wave (married or partnered vs separated, divorced, widowed, or never married). Information on other important risk factors, including smoking, alcohol use, diet, and obesity, were not collected for all participants.

Statistical Analyses

Multinomial logistic regression was used to determine the relationship between stroke outcomes (no stroke, incident nonfatal stroke, incident fatal stroke), time-invariant sociodemographic factors, and time-varying factors (marital status, health conditions, cognitive function, and physical disability). Models regress stroke outcomes at a given wave on risk factors at the previous wave, controlling for year of assessment. Generalized estimating equations were used to account for the correlation between observations for each participant in the repeated-measures design. Models also include a dummy variable to account for the method of stroke outcome assessment (clinic- vs self-reported stroke) as a potential confounder. Statistical significance was assessed using a two-tailed alpha of .05. All statistical analyses were performed using SAS version 9.2 for Windows (SAS Institute, Inc., Cary, NC) using weighted data to correct for the oversampling of the original CSHA-1 sample by age and region.

RESULTS

Table 1 summarizes the sociodemographic and health characteristics of the study sample. On average, respondents were aged 73.6 ± 6.8; 58% were female. At baseline, 812 participants (7.9% of the study sample) had already experienced a stroke and were dropped from subsequent analyses, leaving 9,451 eligible participants. During the 10-year follow-up period, 873 incident strokes occurred (701 nonfatal, 172 fatal), with an overall incidence of 9.3 per 1,000 person-years (consistent with incidence rates re-

Table 1. Baseline Characteristics for Study Sample (N = 9,451) According to Stroke Outcome: Canadian Study of Health and Aging

Characteristic	No Stroke (n = 8,578)	Nonfatal Incident Stroke (n = 701)	Fatal Incident Stroke (n = 172)
Age, %			
65–75	65.7	68.5	33.3*
76–85	27.7	27.7	43.5*
≥86	6.6	3.8	23.2*
Sex, %			
Male	41.5	42.7	37.6
Female	58.5	57.3	62.4
Race, %			
White	96.8	96.8	97.7
Nonwhite	3.2	3.2	2.3
Education, %			
<High school	63.1	65.2	71.2*
High school diploma	27.1	26.2	23.8
College degree	9.8	8.6	5.0*
Marital status, %			
Married	54.5	55.3	41.8*
Not married	45.5	44.7	58.2*
Health conditions, %			
Heart disease	26.1	31.2*	26.3
Hypertension	32.0	43.4*	39.3
Diabetes mellitus	9.2	15.1*	9.2
Parkinson's disease	0.9	1.4	2.7*
Cognitive impairment, %			
Yes	18.0	12.8	39.5*
No	82.0	87.2	60.5*
Physical disability			
Number of activity of daily living disabilities, mean ± standard deviation	0.95 ± 1.93	0.89 ± 1.84*	1.69 ± 1.90*

* Statistically different from nonstroke group ($P < .05$).

ported elsewhere[23,27]). The majority (66%) of the nonfatal incident strokes were documented in the clinical examination, whereas self-report was the most common method for determining that a stroke had not occurred. Health conditions, including hypertension, heart disease, and diabetes mellitus, were more prevalent in those with nonfatal incident stroke than in those with no stroke or fatal incident stroke, whereas Parkinson's disease was more common in those with a fatal incident stroke than in those with no stroke or nonfatal incident stroke. Approximately 4.6% of all study deaths were due to stroke.

Table 2 reports the results from the multinomial logistic regression analyses for the two stroke outcomes (no stroke is the reference group). Model 1 presents the logistic regression coefficients and corresponding odds ratios (ORs) for the time-invariant sociodemographic characteristics as they relate to nonfatal incident stroke and fatal incident stroke. Older age is a strong risk factor for fatal stroke, with the OR for fatal incident stroke almost seven times as high in those aged 86 and older at baseline as in those aged 65 to 75. As a result of this high mortality risk, adults aged 75 and older were less likely to have a nonfatal incident stroke (Model 1, Table 2). Individuals referred to a clinical examination were significantly more likely than those providing self-reported data to have had a nonfatal incident stroke than no stroke (probably because lower poststroke cognitive dysfunction was the trigger for referral to a clinical examination), but the method of stroke assessment did not modify the effects of age or any of the other important predictor variables in the analyses. Lower education conveys a greater risk for fatal stroke, with 95% higher odds in those with less than a high school education than in those with a college degree. No significant differences were found according to sex or race, but a strong period effect indicates that the risk of nonfatal and especially fatal incident stroke decreased dramatically over time, net of the effects of age.

Model 2 added time-varying marital status, which had little effect on stroke incidence. Model 3 added the important health risk factors. With the exception of hypertension, health conditions were not significantly associated with the risk of fatal incident stroke (Model 3, Table 2), but all four health conditions were positively associated with greater risk of nonfatal stroke at a subsequent survey wave. Individuals with hypertension and diabetes mellitus had roughly 50% greater odds of incident stroke at follow-up, whereas heart disease was associated with 39% higher

Table 2. Multinomial Logistic Regression: Canadian Study of Health and Aging 1991–2001 (N = 9,451)

Variable	Coefficient, Odds Ratio (95% Confidence Interval)				
	Model 1: Time-Invariant Sociodemographics	Model 2: + Time-Varying Marital Status	Model 3: +Time-Varying Health Conditions	Model 4: + Time-Varying Cognitive Function	Model 5: +Time-Varying Physical Disability
Nonfatal incident stroke†					
Intercept	−3.19***	−3.11***	−3.35***	−3.32***	−3.29***
Age (reference 65–75)					
76–85	−0.31**, 0.73 (0.60–0.91)	−0.26*, 0.77 (0.62–0.96)	−0.25*, 0.77 (0.63–0.96)	−0.18, 0.83 (0.67–1.04)	−0.23*, 0.79 (0.63–0.99)
≥86	−0.79***, 0.45 (0.31–0.65)	−0.69***, 0.51 (0.35–0.73)	−0.64***, 0.53 (0.36–0.76)	−0.45*, 0.64 (0.43–0.94)	−0.70***, 0.49 (0.33–0.74)
Female (reference male)	0.04, 1.04 (0.84–1.3)	0.01, 1.01 (0.80–1.3)	−0.03, 0.97 (0.77–1.23)	−0.05, 0.95 (0.75–1.20)	−0.05, 0.95 (0.76–1.20)
White (reference other)‖	−0.07, 0.93 (0.53–1.63)	−0.09, 0.91 (0.52–1.60)	−0.08, 0.92 (0.53–1.61)	−0.10, 0.91 (0.51–1.59)	−0.11, 0.89 (0.50–1.59)
Education (reference ≥college degree)					
<High school education	0.01, 1.00 (0.69–1.5)	0.03, 1.03 (0.71–1.5)	−0.02, 0.98 (0.67–1.42)	0.06, 1.06 (0.73–1.55)	0.08, 1.08 (0.74–1.58)
High school education	0.09, 1.10 (0.73–1.7)	0.11, 1.12 (0.74–1.7)	0.08, 1.08 (0.72–1.62)	0.09, 1.09 (0.73–1.64)	0.10, 1.11 (0.74–1.66)
Wave 3 (2001) (reference Wave 2, 1995)	−0.70***, 0.49 (0.44–0.55)	0.55***, 0.58 (0.52–0.65)	−0.56***, 0.57 (0.51–0.65)	−0.50***, 0.61 (0.53–0.69)	−0.39***, 0.68 (0.60–0.77)
Clinic-reported stroke (reference self-reported stroke)	1.82***, 6.19 (4.9–7.8)	1.70***, 5.47 (4.4–6.9)	1.73***, 5.62 (4.5–7.1)	1.79***, 5.96 (4.75–7.5)	1.65***, 5.22 (4.12–6.6)
Married (reference unmarried)		−0.02, 0.98 (0.79–1.22)	−0.02, 0.98 (0.79,1.23)	−0.04, 0.96 (0.76–1.20)	−0.03, 0.96 (0.77–1.21)
Heart disease			0.33**, 1.39 (1.13–1.7)	0.30**, 1.35 (1.09–1.7)	0.27**, 1.31 (1.1–1.61)
Hypertension			0.38***, 1.46 (1.19–1.8)	0.38***, 1.46 (1.18–1.8)	0.37***, 1.45 (1.18–1.8)
Diabetes mellitus			0.38**, 1.47 (1.08–2.0)	0.39**, 1.48 (1.08–2.01)	0.37* 1.45 (1.1–1.96)
Parkinson's disease			0.31, 1.37 (0.69–2.7)	0.35, 1.41 (0.72–2.78)	0.35, 1.42 (0.71–2.82)
Cognitive impairment				−0.55***, 0.58 (0.44–0.76)	−0.85***, 0.42 (0.31–0.57)
Physical disability					0.01, 1.01 (0.96–1.1)
Fatal incident stroke†					
Intercept	−5.32***	−5.26***	−5.44***	−5.52***	−5.58***
Age (reference 65–75)					
76–85	1.15***, 3.16 (2.1–4.7)	1.17***, 3.22 (2.2–4.7)	1.17***, 3.22 (2.21–4.7)	1.03***, 2.80 (1.9–4.1)	1.01***, 2.74 (1.9–4.1)
≥86	1.92***, 6.86 (4.5–10.5)	1.95***, 7.00 (4.6–10.5)	1.96***, 7.09 (4.7–10.7)	1.61***, 5.00 (3.1–7.9)	1.63***, 5.08 (3.1–8.2)
Female (reference male)	0.05, 1.05 (0.77–1.45)	0.01, 1.01 (0.70–1.46)	−0.01, 0.99 (0.68–1.46)	0.02, 1.02 (0.69–1.5)	0.02, 1.02 (0.69–1.5)
White (reference other)‖	0.22, 1.25 (0.54–2.87)	0.21, 1.23 (0.53–2.84)	0.33, 1.39 (0.57–3.39)	0.37, 1.45 (0.6–3.53)	0.38, 1.46 (0.59–3.6)
Education (reference ≥college degree)					
<High school education	0.67*, 1.95 (1.05–3.6)	0.68*, 1.97 (1.05–3.68)	0.65*, 1.92 (1.03–3.6)	0.52, 1.67 (0.89–3.1)	0.49, 1.63 (0.87–3.1)
High school education	0.49, 1.63 (0.82–3.20)	0.50, 1.65 (0.83–3.27)	0.49, 1.63 (0.82–3.20)	0.46, 1.58 (0.79–3.1)	0.45, 1.56 (0.79–3.10)
Wave 3 (2001) (reference Wave 2, 1995)	−2.86***, 0.06 (0.03–0.11)	−2.24***, 0.11 (0.05–0.20)	−2.24***, 0.11 (0.06–0.20)	−2.26***, 0.10 (0.05–0.19)	−2.42***, 0.09 (0.05–0.17)
Clinic-reported stroke (reference self-reported stroke)	−0.43*, 0.65 (0.43–0.99)	−0.49*, 0.61 (0.41–0.91)	−0.49*, 0.61 (0.41–0.92)	−0.52*, 0.60 (0.40–0.89)	−0.14, 0.87 (0.60–1.25)
Married (reference unmarried)		−0.06, 0.94 (0.66–1.35)	−0.06, 0.94 (0.66–1.36)	−0.02, 0.98 (0.68–1.41)	−0.02, 0.98 (0.68–1.42)

(Continued)

Table 2. (Contd.)

Variable	Coefficient, Odds Ratio (95% Confidence Interval)				
	Model 1: Time-Invariant Sociodemographics	Model 2: + Time-Varying Marital Status	Model 3: + Time-Varying Health Conditions	Model 4: + Time-Varying Cognitive Function	Model 5: + Time-Varying Physical Disability
Heart disease			−0.19, 0.83 (0.60–1.15)	−0.15, 0.86 (0.61–1.20)	−0.14, 0.87 (0.62–1.22)
Hypertension			0.35*, 1.42 (1.02–1.9)	0.37*, 1.45 (1.0–2.0)	0.38*, 1.46 (1.05–2.0)
Diabetes mellitus			−0.03, 0.97 (0.58–1.62)	−0.05, 0.95 (0.57–1.61)	−0.03, 0.97 (0.58–1.62)
Parkinson's disease			0.87, 2.40 (0.74–7.78)	0.81, 2.24 (0.7–7.48)	0.79, 2.20 (0.7–7.20)
Cognitive impairment				0.68***, 1.98 (1.4–2.8)	0.72***, 2.06 (1.4–3.10)
Physical disability					0.01, 1.01 (0.94,1.07)

* $P < .05$, ** .01, *** .001 (two-tailed tests).
† No stroke is the reference group.

odds. Consistent with the literature,[12] Parkinson's disease was positively associated with greater risk of stroke, but the rarity of this condition leads to wide confidence intervals around this estimate.

Model 4 added the time-varying indicator of cognitive status; individuals with cognitive impairment had almost twice the odds of fatal incident stroke by a subsequent wave, controlling for other health conditions and sociodemographic risk factors (Table 2). Cognitive impairment accounted for 22% of the education effect ((0.67–0.52)/0.67 = 0.25, Model 1 to Model 4, Table 2) and explained 17% of the health-adjusted age effect ((1.96–1.61)/1.96 = 0.17, Model 3 to Model 4, Table 2) between those aged 86 and older and those aged 65 to 75. As a result of this strong stroke mortality risk, cognitive impairment was negatively associated with nonfatal stroke. Physical disability had no effect on the odds of stroke at a subsequent wave (Model 5, Table 2).

DISCUSSION

With a nationally representative cohort of older Canadians, the CSHA provides a unique opportunity to examine the risk factors for incident stroke in later life. Although several longitudinal studies have examined risk factors for stroke,[21,23] there has not been an attempt to examine the different risk factors for fatal and nonfatal incident stroke in a national population-based sample that includes community-dwelling and institutionalized older adults. This study provided the opportunity to assess the effect of risk factors, including clinically diagnosed cognitive impairment, that are more common in older than younger adults.

Consistent with declining stroke rates in developed countries,[28] results from this representative cohort indicate that the risks for fatal and nonfatal incident stroke in older adults have been declining since the study began in 1991. The protective period effect is particularly strong for fatal incident stroke, probably because of the introduction of thrombolytic agents to treat acute stroke over this period.[29]

Stroke risk factors identified in this prospective cohort of older Canadians, including older age, hypertension, heart disease, and diabetes mellitus, are similar to those reported in other studies.[6,8] In addition, cognitive impairment was a significant independent risk factor for fatal incident stroke in these older adults. Consistent with results from other elderly samples,[20,21,23] cognitive impairment may be associated with incident stroke because it captures a preclinical phase of "silent" or lacunar strokes (associated with vascular-related cognitive deficits) that predict more-serious subsequent strokes that are more likely to be fatal.[3] Significant educational disparities in incident fatal stroke exist in this population-based cohort, and consistent with observed associations in the literature between lower education and dementia,[30] lower cognitive function in the less-educated participants partly explained the educational disparities in stroke in this study.

In contrast to other results,[16] no relationship was found between physical disability and stroke incidence, perhaps because a measure of difficulty with ADLs was relied on, rather than difficulty with functional performance (e.g., climbing stairs), which was used in other work.[16] This is a potentially important subject that could be investigated further with secondary data from other national surveys.

Limitations

Although the comprehensive clinical assessments of cognitive function and the nationally representative older sample are major strengths of this analysis, a lack of data on other stroke risk factors, including smoking, alcohol use, obesity, and depression, limited this study.[8] To some extent, the dummy variable for clinically reported stroke captured the effects of these unmeasured confounders (because less-healthy people tended to be referred to the clinical examination), but they could potentially attenuate the results. In addition, information on stroke incidence in the community-dwelling sample was self-reported based on experiencing a stroke, or the effects of stroke, in the past year. Although self-reports of stroke have been found to be valid in other population-based surveys,[27] more-mild strokes (without any residual sequelae) might be missed using this method. Information on stroke subtype (hemorrhage or infarct) was not available in the survey data, and information from death certificates is not always accurate. To ascertain causal direction and minimize recall bias, the analyses were restricted to time-varying risk factors documented at the survey wave before stroke onset. As a result, the effects of risk factors that progress or emerge between waves might have been underestimated.

In spite of these limitations, this study highlights the importance of cognitive impairment as an important risk factor for fatal stroke in older adults. This finding provides further evidence of the need for targeted screening for cognitive impairment in older adults, even those without preexisting clinical conditions. Early intervention in older adults with cognitive deficits may decrease the incidence of fatal stroke in later life.

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Author Contribution: Philippa Clarke and Vanessa Blount prepared the manuscript and analyzed and interpreted the data. Angela Colantonio assisted with the preparation of the manuscript and with the analysis and interpretation of the data.

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