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Original Article

Mediation of Post-Stroke Function by Cognition in the Canadian Longitudinal Study on Aging

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ABSTRACT: ***Introduction:*** Cognitive and functional impairment after stroke are common, but the relation between cognitive and functional decline after stroke is not well studied. ***Methods:*** We used the comprehensive cohort in the Canadian Longitudinal Study on Aging to identify those with prior stroke, and we calculated reliable cognitive change scores from baseline to follow-up for the memory and executive domains. Functional decline was defined as an increase in the number of dependent daily activities. Using formal mediation analysis, we tested the presence and degree of mediation of the association between stroke and functional decline by cognitive decline. ***Results:*** There were 22,648 individuals with memory change scores (325 with stroke) and 17,613 individuals with executive change scores (241 with stroke). History of stroke was significantly associated with memory decline (−0.26 standard deviations, 95% CI −0.33 to −0.19), executive decline (−0.22, 95% CI −0.36 to −0.09), and new functional impairment (adjusted odds ratio 2.31, 95% CI 1.80–2.97) over a median of 3-year follow-up. Cognitive decline was a significant mediator of functional decline. Memory decline mediated only 5% of the relationship, whereas executive and overall cognitive decline mediated 13% and 22%, respectively. ***Conclusion:*** Cognitive decline is a mediator of the association between prior stroke and functional decline; consequently, strategies to delay, attenuate, or prevent cognitive decline after stroke may be important to preserving long-term functional status.

RÉSUMÉ : Médiation de l'état fonctionnel après un accident vasculaire cérébral par l'intermédiaire de l'état cognitif dans l'étude *Canadian Longitudinal Study on Aging*. *Introduction :* Les troubles cognitifs et fonctionnels sont fréquents après un accident vasculaire cérébral (AVC), mais la relation entre ces deux types de déclin après une attaque n'est pas clairement établie. ***Méthode :*** Tout d'abord, nous avons procédé au repérage des personnes qui avaient des antécédents d'AVC dans l'ensemble de la cohorte de l'étude *Canadian Longitudinal Study on Aging*, puis avons calculé des scores fiables de changement cognitif, entre le début et le suivi, dans les domaines de la mémoire et de l'exécution de tâches. Le déclin fonctionnel a été défini comme l'augmentation du nombre d'activités quotidiennes nécessitant de l'aide. La présence et le degré de médiation de l'association entre les AVC et le déclin fonctionnel par l'intermédiaire du déclin cognitif ont été évalués à l'aide d'une analyse structurée de médiation. ***Résultats :*** Dans l'ensemble, 22 648 personnes ont enregistré des scores de changement relatifs à la mémoire (325 ayant déjà subi un AVC) et 17 613 personnes, des scores de changement relatifs à l'exécution de tâches (236 ayant déjà subi un AVC). Les antécédents d'AVC étaient significativement associés aux pertes de mémoire (écart type [σ] : -0,26; IC à 95 % : -0,33 à -0,19), à la diminution de la capacité d'exécution de tâches (σ : -0,22; IC à 95 % : -0,36 à -0,09) et à l'apparition de nouveaux troubles fonctionnels (risque relatif approché rajusté : 2,31; IC à 95 % : 1,80 à 2,97) sur un suivi médian de 3 ans. Le déclin cognitif s'est révélé un médiateur significatif du déclin fonctionnel. Ainsi, les pertes de mémoire ont joué un rôle dans 5 % seulement de la relation, tandis que la diminution de la capacité d'exécution de tâches et le déclin cognitif global représentaient 13 % et 22 % de la relation, respectivement. ***Conclusion :*** Le déclin cognitif est un médiateur de l'association entre les antécédents d'AVC et le déclin fonctionnel; il se pourrait donc que des stratégies visant à retarder, à atténuer ou à prévenir le déclin cognitif après un AVC jouent un rôle important dans le maintien à long terme de l'état fonctionnel des personnes concernées.

Keywords: Stroke; Cognition; Function; Mediation; Canadian Longitudinal Study on Aging

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Introduction

The number of individuals with stroke is rising globally, along with the accompanying burden of disease and disability. Cognitive impairment and dementia after stroke are highly prevalent as shown in many hospital-based cohorts and population-based studies around the world[1–8] and are major contributors to post-stroke disability, poor quality of life, mortality, and societal costs.[3,9–11] Mortality after stroke is declining, which will increase the potential for more survivors to experience cognitive decline.[12,13]

However, whether cognitive decline promotes functional decline after stroke has not been well elucidated. Cognitive decline is hypothesized to mediate functional decline in the general population and in those with minor cognitive impairment or dementia.[14–16] While studies have shown an acute decline in cognitive and functional ability after stroke, recent evidence has pointed to an ongoing accelerated decline in the years following a stroke compared to the pre-stroke rate.[17] These studies have shown both functional decline and cognitive decline occurring simultaneously after stroke,[6] but whether cognitive decline mediates the relationship with functional decline in the pre-dementia phase has not been well characterized among stroke survivors. It is plausible that cognitive decline is a significant mediator of the relationship between stroke and functional decline, given the importance of cognition function in activities of daily living,[14] but the presence and degree of mediation by cognition decline is unknown. Given the evidence of such mediation in non-stroke survivors and the prominence of cognitive impairment after stroke, we hypothesize that cognitive decline is a mediator of functional decline among community-dwelling stroke survivors. A better understanding of these factors would aid in targeting cognitive decline as a key component of functional loss after stroke.

We sought to determine if, and to what degree, cognitive decline was a mediator of stroke-related functional decline in a population-based sample of community dwellers in Canada.

Methods

Participants

The Canadian Longitudinal Study on Aging (CLSA) is a study of approximately 50,000 individuals who were between the age of 45 and 85 years at entry with plans to follow them for over 20 years.[18] The CLSA consists of a Tracking Cohort ($N = 21,241$), in which questions are administered over telephone, and a Comprehensive cohort ($N = 30,097$), in which participants are assessed in person at one of eleven data collection sites across Canada. We used data from the Comprehensive cohort due to the more detailed cognitive assessments. The CLSA collects a wide range of data including detailed information on sociodemographics, health and functional status, and social supports, as well as physical measurements in the Comprehensive cohort such as blood pressure, body mass index, and motor function (see https://www.clsa-elcv.ca/researchers/data-collection for the description of the data collection overview and tools). Data are available from the CLSA (www.clsa-elcv.ca) for researchers who meet the criteria for access to de-identified CLSA data. For the current study, participants were included if they had baseline (2011–2015) and follow-up (2015–2018) assessments complete including neuropsychological testing at both time points (Figure 1).

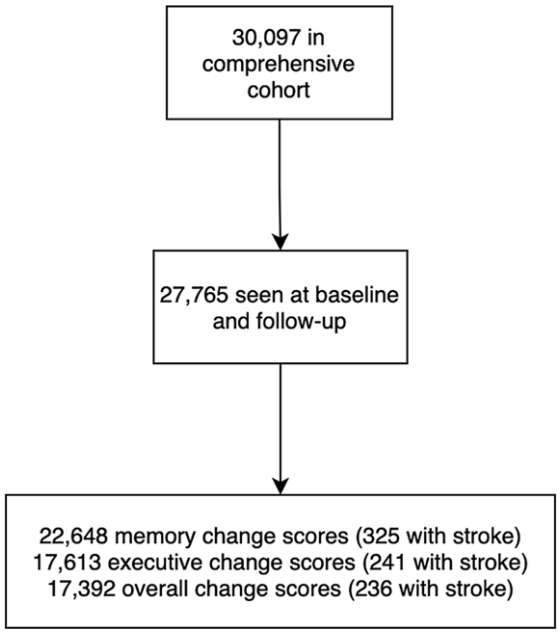

Figure 1: Participant flowchart.

Neuropsychological Testing and Normative Scores

Cognitive tests include a modified Rey Auditory Verbal Learning Test immediate recall after one learning trial (REY I) and 5-minute delayed recall (REY II), the Mental Alternation Test (MAT), Animal Fluency (AF), the Controlled Oral Word Association Test (COWAT; total score of the letters F, A, and S), and the Victoria Stroop Test with the Interference ratio (defined as the performance on the "color" task divided by performance on the "dot" task). Scores for the Stroop test were reversed to be compatible with the other tests. The neuropsychological tests are described in more detail elsewhere.[19,20]

We generated normed neuropsychological scores in multiple steps. First, for each neuropsychological test, each participant's raw score was transformed into standardized scores (mean 0 and SD 1) based on comparisons with the healthy normative subsample. Normative comparisons require correction because measurement of cognitive function can be biased; for example, few years of education can make someone who is cognitively intact appear impaired because the cognitive tests capture educational status in addition to cognitive status. Full regression models did not reduce measurement bias (e.g., due to education), instead stratification and regression models for demographic corrections were the only method that reduced measurement bias.[21] In other words, any analysis that includes demographic variables as covariates in regression models will not remove measurement bias in the cognitive tests. The standardized normed scores in CLSA were adjusted for language of administration (French/English), age, sex, and years of formal education using stratification and regression models (hybrid regression models).[21] Second, scores were normed for baseline and follow-up separately, and then, third, reliable change scores were calculated. Reliable change scores account for error in measurement, regression to the mean, aging, and expected practice effects based on the performance of the subsample of participants who were healthy at baseline and first follow-up

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(O'Connell et al., in preparation). For this paper, reliable change scores were calculated for the composite memory (REYI and REYII), composite executive function (AF, MAT, COWAT, Stroop), and overall cognitive composite for participants with complete data for tests included in the respective composite scores.

Functional Status

The Older Americans Resources and Services (OARS) Multidimensional Assessment scale[22,23] was used to assess functional decline between baseline and follow-up. The OARS questionnaire obtains information about seven activities of daily living (dressing, feeding, taking care of appearance, walking, getting out of bed, bathing, trouble getting to the bathroom in time) and seven instrumental activities of daily living (using the telephone, ability to travel, shopping/groceries, housework, taking medicine, handling money, and meal preparation).[24] We calculated the total number of times the respondent indicated that they need help with an activity or are completely unable to do an activity. Our primary outcome was the numerical change in the number of dependent activities from baseline to follow-up. We also assessed the outcome as any increase in dependence versus no increase in dependence.

Stroke and Other Covariates

Prior history of stroke was the primary exposure. This variable was obtained from self-report. For stroke and other co-morbidities, participants were asked to respond yes/no to the question: "Has a doctor ever told you that you have (the chronic condition)?"

Covariates included age, sex, education, self-reported co-morbidities of heart disease, peripheral vascular disease, high blood pressure, diabetes, smoking, rural residence, ethnicity, income, marital status, physical activity, fruit and vegetable consumption, and calculated body mass index. Categorization of variables is shown in Table 1. Physical activity was measured with the Physical Activity Scale for the Elderly (PASE).[25] PASE evaluates physical activity over the last 1 week and includes leisure, occupational, and household activities, ranging from 0 to 793 where a higher score indicates more activity. The PASE score was the only variable not collected at baseline, as it was collected as part of a maintaining contact questionnaire 18 months after the baseline assessment.

Statistical Analysis

Presence of stroke was the independent variable, standardized cognitive decline was the mediator, and functional decline was the dependent variable. Figure 2 shows the hypothetical model where stroke is related to functional decline directly, as well as indirectly through cognitive decline. We first tested the three components of the pathway independently using linear regression – the association between stroke and cognitive decline (path a; first component of the indirect effect), the association between cognitive decline and functional decline (path b; second component of the indirect effect), and the association between stroke and functional decline (path c'; the direct effect). The simple association between stroke and functional decline is measured by path c, which is contrasted with path c' where cognitive decline is modeled as a mediator removing some of the variance in the association between stroke and functional decline. Mediation was completed using the "medsem" package in Stata, which provides two approaches to the statistical analysis of mediation. The first approach to mediation was first developed by Baron & Kenny.[26] Structural equation modeling is used to simultaneously estimate regression coefficients for the three pathways. If all three pathways are statistically significant (steps 1–3), and c' is reduced to zero after controlling for the mediation (step 4), then there is "full mediation." If steps 1–3 are met but step 4 is not, there is "partial mediation." The statistical significance of the reduction in path c' after controlling for the mediator is determined using the Sobel test.[27] Medsem employs the modified approach of the above steps for use with structural equation modeling.[28]

The second approach is based on Zhao et al.,[29] in which mediation can be determined solely with a bootstrap test of the indirect effect (pathways a and b), and is thought to be a better option than the Sobel test. If the confidence intervals do not include the value of zero, the indirect effect is significant. If the bootstrap test of the indirect effect is significant but path c' remains significant after controlling for the mediator, there is partial mediation. If the bootstrap test of the indirect effect is significant and path c' no longer significant after controlling for the mediator, there is full mediation. Medsem uses the Monte Carlo approach, an alternative to bootstrapping which is less computationally intensive.[30–33]

We used both the Baron & Kenny and the Zhao approaches and compared for compatibility. We computed the presence and degree of mediation for each cognitive domain and for both functional outcomes separately. We estimated the proportion mediated by cognitive decline by calculating the proportion of the bootstrapped indirect effect (a * b) divided by the total effect (a * b + c').

Lastly, to verify the unique role of cognition in mediation versus other control variables we replaced cognitive decline with the following potential mediators in different domains: change in depression status using the Center for Epidemiologic Studies Depression scale (CES-D-10), change in systolic blood pressure, change in Timed Get Up and Go Test, and change in Social Support Scale from baseline to follow-up. The CES-D-10 is a 10-item Likert scale questionnaire assessing depressive symptoms in the past week.[34] It includes three items on depressed affect, five items on somatic symptoms, and two on positive affect. Options for each item range from "rarely or none of the time" (score of 0) to "all of the time" (score of 3). Total scores can range from 0 to 30. Higher scores suggest greater severity of symptoms. The Social Support Scale was adapted from the Medical Outcomes Study Social Support Survey[35] and has 19 items which address tangible social support, affection, positive social interaction, and emotional or informational support. An overall social support score is obtained by averaging the responses over all 19 items and transforming the score into a 0–100 scale, where higher score indicates better social support. The Timed Get Up and Go Test measures the time taken to stand up and walk a distance of 3 m, turn around, walk back to the chair, and sit down again.

In a separate sensitivity analysis, the associations with functional decline were assessed with logistic regression using a dichotomous outcome of any increase in dependence. In the main models, we adjusted for age, sex, education, heart disease, peripheral vascular disease, high blood pressure, diabetes, smoking, body mass index, rural residence, and ethnicity. Although cognitive scores were normed by age, sex, and education, these variables were included to ensure that the direct causal relationship between stroke and functional decline was appropriately adjusted for confounders. In a sensitivity analysis, we excluded age, sex, and education. In the full model, additional adjustment was made for

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Table 1: Baseline characteristics of those with memory scores comparing people with and without stroke

	Total ($N = 22,648$)	No stroke ($N = 22,323$)	Stroke ($N = 325$)	*p*-value
Age	62.3 (10.1)	62.3 (10.1)	67.9 (9.3)	<0.001
Female sex	11,346 (50.1%)	11,207 (50.2%)	139 (42.8%)	0.008
Education				0.002
<high school	1057 (4.7%)	1031 (4.6%)	26 (8.0%)	
High school graduate	2010 (8.9%)	1973 (8.8%)	37 (11.4%)	
Some post-secondary	1645 (7.3%)	1615 (7.2%)	30 (9.2%)	
Post-secondary degree/diploma	17,936 (79.2%)	17,704 (79.3%)	232 (71.4%)	
Heart disease	2400 (10.6%)	2303 (10.4%)	97 (29.8%)	<0.001
Peripheral vascular disease	1110 (4.9%)	1060 (4.8%)	50 (15.6%)	<0.001
High blood pressure	9379 (41.4%)	9152 (41.0%)	227 (69.8%)	<0.001
Diabetes	3987 (17.6%)	3881 (17.4%)	106 (32.6%)	<0.001
Smoking				0.25
Never smoker	20,788 (91.8%)	20,492 (91.8%)	296 (91.1%)	
Former smoker	371 (1.6%)	368 (1.6%)	3 (0.9%)	
Current smoker	1404 (6.2%)	1378 (6.2%)	26 (8.0%)	
Missing	85 (0.4%)	85 (0.4%)	0 (0.0%)	
Body mass index				0.004
Underweight/normal (<25.0 kg/m^2)	6936 (30.6%)	6858 (30.7%)	78 (24.0%)	
Overweight (25.0–29.9 kg/m^2)	9116 (40.3%)	8992 (40.3%)	124 (38.2%)	
Obese (>30.0 kg/m^2)	6516 (28.8%)	6399 (28.7%)	117 (36.0%)	
Missing	80 (0.4%)	74 (0.3%)	6 (1.8%)	
Rural residence	1727 (7.6%)	1711 (7.7%)	16 (4.9%)	0.064
Non-Caucasian	4104 (18.3%)	4043 (18.3%)	61 (18.8%)	0.79
Total household income				<0.001
$<20k	1005 (4.4%)	975 (4.4%)	30 (9.2%)	
$20k to <50k	4460 (19.7%)	4366 (19.6%)	94 (28.9%)	
$50k to <100k	7543 (33.3%)	7440 (33.3%)	103 (31.7%)	
$100k to <150k	8375 (37.0%)	8299 (37.2%)	76 (23.4%)	
Missing	1265 (5.6%)	1243 (5.6%)	22 (6.8%)	
Marital status				0.003
Married/Common Law	15,403 (68.0%)	15,211 (68.1%)	192 (59.1%)	
Single, never married	1800 (7.9%)	1768 (7.9%)	32 (9.8%)	
Widowed/divorced/separated	4820 (21.3%)	4730 (21.2%)	90 (27.7%)	
Missing	625 (2.8%)	614 (2.8%)	11 (3.4%)	
PASE score	143.6 (73.7)	143.9 (73.7)	121.7 (70.8)	<0.001
Fruit and vegetable consumption				0.010
2 or less	5041 (22.3%)	4950 (22.2%)	91 (28.0%)	
3–6/day	14,420 (63.7%)	14,217 (63.7%)	203 (62.5%)	
7+/day	2711 (12.0%)	2685 (12.0%)	26 (8.0%)	
Missing	476 (2.1%)	471 (2.1%)	5 (1.5%)	
Center for Epidemiologic Studies Depression Scale −10, mean (SD)	5.1 (4.6)	5.1 (4.6)	6.2 (5.2)	<0.001
Systolic blood pressure, mean (SD)	120.5 (16.3)	120.4 (16.3)	121.8 (17.8)	0.13
Timed Get Up and Go test (seconds), mean (SD)	9.4 (2.5)	9.4 (2.4)	11.5 (4.5)	<0.001
Social Support Scale, mean (SD)	81.9 (16.8)	81.9 (16.8)	78.6 (18.6)	<0.001
Baseline standardized memory score, mean (SD)	100.1 (15.1)	100.1 (15.1)	98.1 (16.2)	0.017

(*Continued*)

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Table 1: (*Continued*)

	Total ($N = 22,648$)	No stroke ($N = 22,323$)	Stroke ($N = 325$)	*p*-value
Baseline standardized executive score, mean (SD)	99.9 (15.1)	99.9 (15.1)	94.3 (16.4)	<0.001
Baseline standardized overall score, mean (SD)	100.0 (15.1)	100.1 (15.1)	95.0 (16.4)	<0.001
Number of dependent activities at baseline, mean (SD)	0.1 (0.6)	0.1 (0.6)	0.5 (1.2)	<0.001
Average change in dependent activities from baseline to follow-up, mean (SD)	0.1 (0.7)	0.1 (0.6)	0.2 (1.2)	<0.001
Any increase in dependence from baseline to follow-up, *N* (%)	1876 (8.3%)	1812 (8.1%)	64 (19.7%)	<0.001
Change in standardized memory score, mean (SD)	−0.07 (1.0)	−0.07 (1.0)	−0.43 (1.0)	<0.001
Change in standardized executive score, mean (SD)	−0.04 (1.0)	−0.02 (1.0)	−0.28 (1.0)	<0.001
Change in overall cognitive score, mean (SD)	−0.04 (1.0)	−0.03 (1.0)	−0.46 (1.0)	<0.001

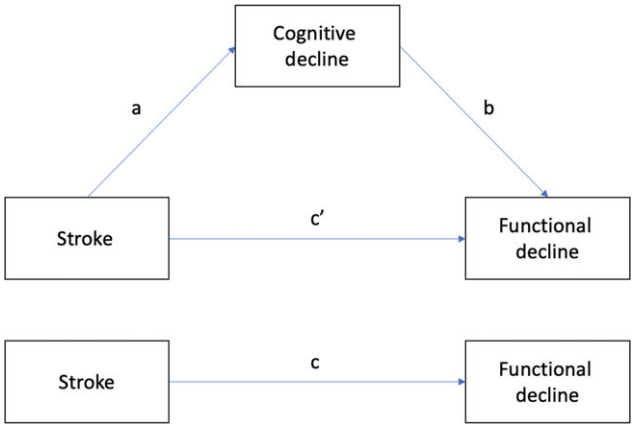

Figure 2: Theoretical causal model for mediation of the relationship between stroke and function decline by cognitive decline. a: association between stroke and cognitive decline; b: association between cognitive decline and functional decline; c': association between stroke and functional decline in presence of mediator; c: association between stroke and functional decline without mediator present; a * b = indirect effect; a * b + c' = total effect.

income, marital status, physical activity, and fruit and vegetable consumption. In additional sensitivity analyses we (1) reversed the order of cognitive and functional impairment, to test whether functional change is a mediator of cognitive change, (2) assessed whether baseline cognition mediates functional change, and (3) changed the independent variable to Parkinson's disease or myocardial infarction.

Analyses were conducted in Stata 17.0 (College Station, TX).

Results

In the analytic sample, there were 22,648 individuals for which memory change scores could be derived from baseline to follow-up (325 with stroke) and 17,613 individuals with executive functioning change scores (241 with stroke; See flowchart in Figure 1). The number of people who died between baseline and follow-up was 390 (1.4%) for the non-stroke group and 19 (4.4%) for the stroke group. Median follow-up time was 2.9 years (interquartile range 2.8–3.1). Median reported time between stroke and participation in the CLSA was 6 years (IQR 2–14). Baseline characteristics for those with and without stroke in the memory sample are shown in Table 1. Those with stroke were older, less likely to be female, and more likely to have co-morbidities, lower income, and lower physical activity. Those with stroke were also more likely to have any increase in activity dependence at follow-up compared to baseline (19.7% vs. 8.1%, $p < 0.001$). Histograms for standardized cognitive change scores are shown in Figure 3, with a shift to greater cognitive decline in those with stroke.

History of stroke was significantly associated with functional decline (adjusted odds ratio [aOR] 2.31, 95% CI 1.80–2.97; Table 2). Change in cognitive performance was also significantly associated with functional decline (memory aOR 1.24 per 1 SD decline, 95% CI 1.18–1.30; executive aOR 1.25, 95% CI 1.19–1.32; and overall aOR 1.27, 95% CI 1.20–1.34). Results from the full model were similar (Table 2). History of stroke was also associated with significantly lower cognitive scores at baseline and follow-up, as well as greater decline in cognitive scores between baseline and follow-up (Table 3).

There was significant mediation of the relationship of stroke with functional decline by memory, executive, and overall cognitive decline (Table 4). The relation between stroke and functional decline was partially mediated by declines in memory, but this was small (at 5% in the fully adjusted model). Declines in executive function mediated 13% of the relation between stroke and functional decline and overall cognition mediated 22% of the relation between stroke and functional decline. Results remained similar in the full model and when removing age, sex, and education from the model (as these variables were adjusted for in the use of normed cognitive scores). In the sensitivity analysis, substituting the cognitive mediator for other control variables, or reversing the order of cognitive and functional change resulted in no significant mediation. Lastly, there was no mediation when substituting stroke for Parkinson's disease or myocardial infarction. The results for both mediation methods (Baron & Kenny and Zhao) were compatible for all analyses.

Discussion

In this cohort study, we found that history of stroke was associated with both cognitive decline and functional decline over a median of 3 years of follow-up among community dwellers. Furthermore, cognitive performance was a significant mediator of the relation between stroke and functional decline. The greatest mediation proportion of 22% was observed for overall cognitive change, which is a composite of the tests measuring memory and executive functioning. Our results suggest that recognizing and preventing cognitive decline in stroke survivors may help preserve function.

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Table 2: Associations between stroke and cognitive change with functional loss

Variable	Main model	*p*-value	Full model	*p*-value
Continuous variable (mean change in number of dependent activities) – linear regression				
Stroke	0.10 (0.03–0.17)	0.003	0.09 (0.02–0.16)	0.01
Change in memory (per 1 SD reduction)	0.032 (0.024–0.041)	<0.001	0.025 (0.016–0.033)	<0.001
Change in executive (per 1 SD reduction)	0.026 (0.018–0.034)	<0.001	0.027 (0.018–0.035)	<0.001
Overall change (per 1 SD reduction)	0.026 (0.018–0.034)	<0.001	0.024 (0.015–0.032)	<0.001
Dichotomous outcome (any increase in dependence) – logistic regression				
Stroke	2.31 (1.80–2.97)	<0.001	2.11 (1.60–2.78)	<0.001
Change in memory (per 1 SD reduction)	1.24 (1.18–1.30)	<0.001	1.16 (1.10–1.22)	<0.001
Change in executive (per 1 SD reduction)	1.25 (1.19–1.32)	<0.001	1.24 (1.17–1.32)	<0.001
Overall change (per 1 SD reduction)	1.27 (1.20–1.34)	<0.001	1.22 (1.15–1.30)	<0.001

Changes in cognitive scores are continuous variables (standardized change scores), and odds ratios are per 1 SD lower change score.
Main model adjusted for age, sex, education, heart disease, peripheral vascular disease, high blood pressure, diabetes, smoking, body mass index, rural residence, and ethnicity, and full model additionally adjusted for income, marital status, physical activity, and fruit and vegetable consumption.

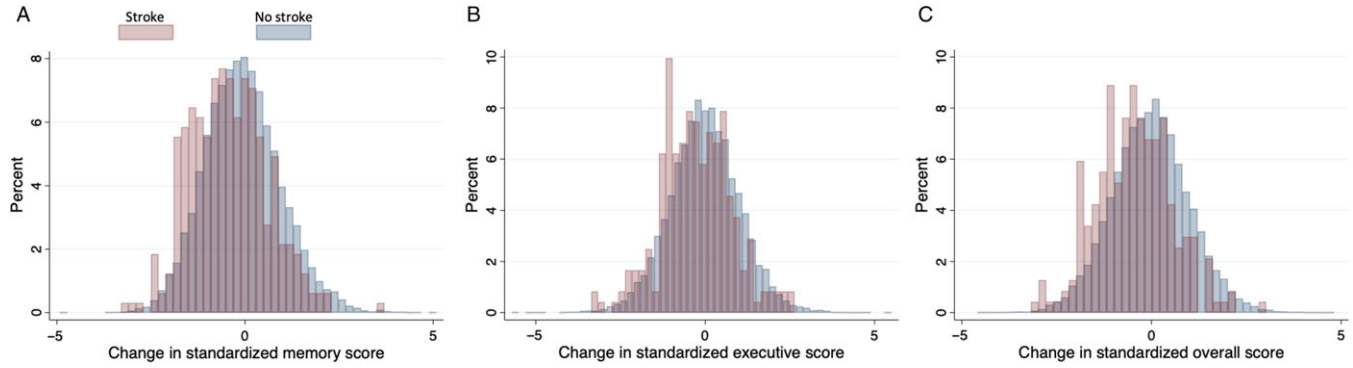

Figure 3: Cognitive change scores among those with and without stroke for memory (A), executive function (B), and combining both (C).

Table 3: Association between stroke and cognitive performance

	Main model		Full model	
Variable	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value
Baseline				
Memory	−1.47 (−3.0 to 0.07)	0.06	−0.65 (−2.26 to 0.96)	0.4
Executive	−4.32 (−5.95 to −2.68)	<0.001	−3.6 (−5.3 to −1.90)	<0.001
Overall	−3.82 (−5.45 to −2.18)	<0.001	−2.87 (−4.57 to −1.17)	0.001
Follow-up				
Memory	−4.24 (−6.08 to −2.40)	<0.001	−3.25 (−5.19 to −1.32)	0.001
Executive	−3.8 (−5.54 to −2.07)	<0.001	−3.49 (−5.29 to −1.69)	<0.001
Overall	−4.75 (−6.61 to −2.89)	<0.001	−4.26 (−6.19 to −2.33)	<0.001
Change score				
Memory	−0.26 (−0.37 to −0.14)	<0.001	−0.21 (−0.33 to −0.09)	<0.001
Executive	−0.22 (−0.36 to −0.09)	0.001	−0.20 (−0.35 to −0.06)	0.005
Overall	−0.33 (−0.47 to −0.20)	<0.001	−0.31 (−0.45 to −0.17)	<0.001

Estimates represent change in SD for cognitive performance in presence of stroke.
Main model adjusted for age, sex, education, heart disease, peripheral vascular disease, high blood pressure, diabetes, smoking, body mass index, rural residence, and ethnicity, and full model additionally adjusted for income, marital status, physical activity, and fruit and vegetable consumption.

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Table 4: Mediation of stroke-functional decline relationship by cognitive decline

Domain	Indirect effect* and 95% CI	Total effect	Amount of mediation (%)	Type of mediation
Main model				
Memory	0.005 (0.002–0.008)	0.095	4.8	Partial
Executive	0.005 (0.002–0.009)	0.038	13.1	Full
Overall	0.006 (0.003–0.010)	0.029	21.5	Full
Full model				
Memory	0.004 (0.001–0.007)	0.094	3.9	Partial
Executive	0.005 (0.001–0.010)	0.039	13.1	Full
Overall	0.006 (0.002–0.010)	0.027	21.8	Full
Main model (no age, sex, or education)				
Memory	0.008 (0.004–0.012)	0.111	6.8	Partial
Executive	0.006 (0.002–0.010	0.046	12.7	Full
Overall	0.009 (0.005–0.014)	0.037	23.4	Full
Full model (no age, sex, or education)				
Memory	0.005 (0.002–0.009)	0.103	5.1	Partial
Executive	0.006 (0.002–0.010)	0.043	13.1	Full
Overall	0.007 (0.003–0.012)	0.031	23.9	Full
Sensitivity analyses				
Different mediator				
Change in depression score	−0.001 (−0.004 to 0.001)	0.061	2	None
Change in systolic blood pressure	0 (−0.001 to 0.001	0.049	0	None
Change in timed get up and go score	0.001 (−0.007 to 0.009)	0.064	1	None
Change in social support	0 (−0.001 to 0.001)	0.041	0	None
Change in functional dependence (cognition as dependent variable)	−0.002 (−0.008, 0.003)	0.29	1	None
Baseline global cognition rather than change	0.004 (0.002–0.008)	0.087	5	Partial mediation
Different independent variable				
Parkinson's disease ($N = 84$)	0.004 (−0.001, 0.01)	0.672	1	None
Myocardial infarction ($N = 966$)	0 (−0.002, 0.002)	0.037	1	None

The estimate of indirect effect represents the product of the coefficients of path a (association between stroke and cognitive decline) and path b (association between cognitive decline and functional decline). The total effect represents the estimate of indirect effect + the estimate for path c' (association between stroke and functional decline). The amount of mediation is the indirect effect divided by the total effect.

Cognitive decline and dementia after stroke are well recognized. The OXVASC study demonstrated an incidence for post-event dementia of 34.4% among survivors of major stroke and 8.2% in those with minor stroke at 1 year, with risk increasing into 5-year follow-up.[5] The population-based REGARDS study in the US showed that participants with stroke had accelerated and persistent cognitive decline over 6 years.[17] Cognitive deficits are even present in long-term follow-up among younger individuals with stroke,[36] and among those with TIA.[37,38] The relationship between cognition and function is less clear. Functional decline is also known to occur progressively after stroke, as the proportion of patients with functional independence after stroke declines yearly.[39] Furthermore, a number of studies have shown both functional decline and cognitive decline simultaneously after stroke.[17] A clinical trial on nitric oxide in stroke showed cognition was associated with functional impairment in cross-sectional associations.[10] Observational studies have shown that cognitive impairment is independently associated with dependent living after adjustment for age, physical impairment, and other factors.[3] This is compatible with the fact that baseline cognitive impairment predicts rate of functional decline in people with dementia.[40] However, whether longitudinal decline in cognition is related to decline in functional impairment is not well understood. Furthermore, it is unknown whether cognitive decline mediates the greater functional decline seen in people with stroke compared to those without stroke.

Our study found that cognitive decline was a mediator of functional decline attributable to prior stroke. The degree of mediation from executive function decline was greater than for memory decline, in keeping with evidence that executive control and is more important than episodic memory for activities of daily living.[41,42] Although there was "full mediation" in the mediation model by overall cognitive decline, the degree of mediation overall was only 22%. There are multiple potential explanations for the moderate amount of mediation. Firstly, cognitive testing under structured conditions likely incompletely captures cognitive function required for daily tasks. The challenges of neuropsychological

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tests predicting daily function are well known (i.e., the evidence for ecological validity is lacking[43]). Second, only memory and executive function were tested; other domains such as social cognition, visuospatial function, and praxis were not specifically tested and are important for activities of daily living. Third, other factors may be important mediators of functional decline, including frailty and sarcopenia, impact of recurrent stroke and other co-morbidities, inflammation and post-stroke neurodegeneration.[8,44–47] Changes in psychological health, motor function, and loss of social supports may also have importance, although we found no mediation by surrogate measures of these items. While the mechanisms of post-stroke cognitive decline in the chronic phase of stroke are unknown, possible pathways include accelerated brain atrophy,[48] induction of accelerated amyloid deposition possibly through interference with amyloid clearance pathways,[49] as well as inflammatory changes.[50] These alterations may impact on cognitive test performance and daily function in overlapping but also independent ways. Nevertheless, in our analysis there was no reciprocity between functional and cognitive decline. Our results support the directionality of the hypothesized model that cognitive changes are one of the causal mechanisms by which functional decline occurs after chronic stroke. In contrast, cognitive decline was not mediated functional decline within the median 3 years of follow-up of our study. This further emphasizes the potential of cognitive vulnerability and impairment as a primary target to prevent functional decline after stroke.

Our results confirm that stroke survivors, even in the chronic phase after stroke, have greater cognitive and functional decline compared to control counterparts. Therefore, individuals with prior stroke warrant monitoring for cognitive decline years after the event. Preventing or slowing cognitive impairment may also be an avenue toward preserving long-term function. Vascular risk factor management is associated with long-term reduced risk of cognitive impairment, including, or combination of antihypertensives, anti-thrombotics, and lipid-lowering medications.[51] Lifestyle factors such as physical activity have also been associated with post-stroke cognition.[52] Further well designed prospective studies and clinical trials are needed to identify targets and treatments vascular cognitive impairment after stroke.[53]

Our study had limitations. Results were generalizable only to community-dwelling stroke or survivors in the chronic phase, without aphasia or dementia. Participants had a median time from stroke to CLSA participation of 6 years, with a wide IQR of 2–14. Rates of cognitive and functional decline and strength of mediation may vary depending on time since stroke, but our sample size was not large enough to analyze by time subgroup and this should be considered for future studies. We were unable to control for stroke features, such as stroke type, severity, location, or laterality. Selective attrition may lead to underestimation of cognitive decline as participants with the worst cognition may have dropped out or died. We did not capture the immediate post-stroke period where significant cognitive decline could occur, and participants may have already experienced a substantial amount of cognitive decline by baseline assessment, as evidenced by the lower scores at baseline among those with stroke. We could not account for recurrent stroke, which may be an important mediator of cognitive decline.[8] Our study also relied on self-reported stroke, which has moderate agreement with hospital-recorded stroke.[54,55]

In conclusion, cognitive performance decline, particularly in the executive domain, is a mediator of functional decline in a cohort of community-dwelling chronic stroke survivors. Strategies to prevent cognitive decline after stroke to preserve function should be further studied.

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