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Short-term Trajectories of Poststroke Cognitive Function

A STROKOG Collaboration Study

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Abstract

Background and Objectives

Past studies on poststroke cognitive function have focused on the average performance or change over time, but few have investigated patterns of cognitive trajectories after stroke. This project used latent class growth analysis (LCGA) to identify clusters of patients with similar patterns of cognition scores over the first-year poststroke and the extent to which long-term cognitive outcome is predicted by the clusters (“trajectory groups”).

Methods

Data were sought from the Stroke and Cognition consortium. LCGA was used to identify clusters of trajectories based on standardized global cognition scores at baseline (T_1) and at the 1-year follow-up (T_2). One-step individual participant data meta-analysis was used to examine risk factors for trajectory groups and association of trajectory groups with cognition at the long-term follow-up (T_3).

Results

Nine hospital-based stroke cohorts with 1,149 patients (63% male; mean age 66.4 years [SD 11.0]) were included. The median time assessed at T_1 was 3.6 months poststroke, 1.0 year at T_2 , and 3.2 years at T_3 . LCGA identified 3 trajectory groups, which were characterized by different mean levels of cognition scores at T_1 (low-performance, -3.27 SD [0.94], 17%; medium-performance, -1.23 SD [0.68], 48%; and high-performance, 0.71 SD [0.77], 35%). There was significant improvement in cognition for the high-performance group (0.22 SD per year, 95% CI 0.07–0.36), but changes for the low-performance and medium-performance groups were not significant (-0.10 SD per year, 95% CI -0.33 to 0.13; 0.11 SD per year, 95% CI -0.08 to 0.24, respectively). Factors associated with the low- (vs high-) performance group include age (relative risk ratio [RRR] 1.18, 95% CI 1.14–1.23), years of education (RRR 0.61, 95% CI 0.56–0.67), diabetes (RRR 3.78, 95% CI 2.08–6.88), large artery vs small vessel strokes (RRR 2.77, 95% CI 1.32–5.83), and moderate/severe strokes (RRR 3.17, 95% CI 1.42–7.08). Trajectory groups were predictive of global cognition at T_3 , but its predictive power was comparable with scores at T_1 .

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Coinvestigators are listed in Appendix 2 at the end of the article.

Glossary

AIC = Akaike information criterion; **ALCPP** = average latent class posterior probability; **BIC** = Bayesian information criterion; **IQR** = interquartile range; **LCGA** = latent class growth analysis; **STROKOG** = Stroke and Cognition consortium.

Discussion

The trajectory of cognitive function over the first-year poststroke is heterogeneous. Baseline cognitive function ~3.6 months poststroke is a good predictor of long-term cognitive outcome. Older age, lower levels of education, diabetes, large artery strokes, and greater stroke severity are risk factors for lower cognitive performance over the first year.

Poststroke neurocognitive disorders affect nearly 1 in 2 stroke survivors,^{1,2} but the longitudinal changes in cognitive function after stroke are incompletely understood. Various studies have differentially shown that cognitive function after stroke on average improves, declines, or remains stable, and the mixed findings may be due to the length of study, the type of cognitive instruments used, and whether the study was hospital-based or population-based.³ These variable findings motivated us to examine long-term cognitive change after stroke in the Stroke and Cognition consortium (STROKOG) in a previous publication.⁴ We identified a turning point at approximately 1 year after stroke, with patients with stroke on average demonstrating an initial short period of small improvement followed by decline beginning at 1 year, with similar rates of cognitive change observed in global cognition and in individual cognitive domains except for executive function.

In this study, we turned our attention to the period between the baseline and 1-year poststroke assessments. Past studies on poststroke cognitive function, including ours, have focused on estimating the average change in cognition over time.⁴⁻⁷ This approach assumes that change is homogenous within the stroke population, but stroke is in fact a heterogeneous condition, with variability in cognitive impairment and recovery after stroke. Identifying clusters of patients based on cognitive trajectory would benefit our understanding of the heterogeneity of poststroke cognitive outcomes.

Our project aims were to (1) use latent class growth analysis (LCGA) to identify naturally occurring clusters of patients with similar cognitive trajectories (“trajectory groups”) in the first year after the baseline assessment; (2) examine the risk factors for membership in the trajectory groups, including age, education, vascular risk factors, and stroke features; and (3) explore the extent to which the trajectory groups, cognitive performance at baseline and at 1 year, and change in performance are predictive of cognitive outcome at the long-term follow-up.

Methods

Sample

Nine STROKOG studies from Asia, Australia, Europe, and the United States that conducted detailed neuropsychological assessments at baseline (2, 3, or 6 months poststroke) and 1

year after stroke and recruited a control group or provided data from an appropriate comparison group contributed to this project (Table 1). All studies were hospital-based and included in our previous paper.⁴ As stated in the inclusion criteria of each study, all participants had sufficient knowledge of the language used in the assessments.

Assessment Time Points

We defined T_1 as the first detailed neuropsychological assessment (the “baseline” assessment), T_2 as the 1-year poststroke follow-up assessment, and T_3 as the third or final cognitive assessment if the patient had more than 3 assessments. Although wide ranges were set for T_1 (1.9–9 months after stroke) and T_2 (9 months–1.5 years after stroke) so that more patients could be included in the analyses, the assessment time points of many patients in certain studies did not fall within those ranges; therefore, it was necessary to exclude those patients so that we could map the cognitive trajectory between baseline and 1 year more precisely. We did not further expand the lower range for T_1 because cognition is unstable during the acute phase.⁸ By definition, T_3 must be >1.5 years poststroke. The narrower ranges of $T_1 = 2$ –6 months and $T_2 = 12$ –15 months were used in a sensitivity analysis. We compared patient characteristics between those who were included in the study vs those who were not eligible due to an assessment time point falling outside of the specified range or a lack of a qualifying follow-up assessment using χ^2 or t test as appropriate.

Cognitive Outcomes

Because the neuropsychological tests varied between the studies (eTable 1, links.lww.com/WNL/C751), they were standardized and harmonized to form z-scores for 5 domains: attention and processing speed (attention), memory, language, perceptual motor, and executive function. Global cognition, the standardized average of the 5 domains, was considered as the primary outcome; the 5 domains were considered as the secondary outcome. Global cognition at T_3 was defined as the long-term cognitive outcome.

Statistical Methods

Data Harmonization

Neuropsychological test scores from each assessment wave were harmonized by converting raw scores to standardized scores (z-scores) using an adaptation of the “category-centered” method⁹ in which raw scores were standardized as z-scores

Table 1 Included Studies and Patient Characteristics

	Bulgarian	Bundang	CASPER	COAST	EpiUSA	IDEA3	NNI	SSS	STROKDEM	All studies
Year study began	2012	2007	2013	2009	1988	2014	2011	1997	2011	—
N^a	74	71	215	211	318	23	27	96	114	1,149
Maximum no. of follow-ups	2	8	2	4	10	2	1	3	3	10
Length of follow-up, y, median (IQR)	1.0 (1.0–2.0) ^b	2.2 (1.3–4.2)	1.3 (1.3–3.3)	5.1 (1.1–6.1)	3.0 (1.3–4.1)	1.1 (1.0–2.0)	1.0 (0.9–1.2)	3.0 (1–5.6) ^b	3.2 (3.0–5.0)	2.9 (1.2–4.8)
Time of baseline assessment (T₁), months poststroke	3	3–6	3	3–6	3	6	2–6	3–6	6	—
Age (baseline), y	65.0 (5.6)	69.6 (9.2)	66.8 (12.0)	59.8 (11.6)	71.2 (7.7)	62.3 (10.8)	58.9 (12.5)	72.1 (8.7)	62.3 (12.6)	66.4 (11.0)
Male, n	59 (80)	44 (62)	141 (66)	156 (74)	150 (47)	17 (74)	21 (78)	56 (58)	78 (68)	722 (63)
Education, y	11.4 (2.0)	9.5 (5.2)	NA ^c	7.5 (4.2)	10.3 (4.9)	10.5 (2.9)	9.0 (3.2)	10.5 (3.0)	11.7 (4.1)	9.90 (4.5)
Ethnoracial group^d	White	Korean	White	Singaporean Chinese (S Chinese) ^d	45% White 42% Black ^d	White	S Chinese ^d	White	White	56% White 15% S Chinese 12% Black 6% Korean

Abbreviations: Bulgarian = Bulgarian Poststroke Study; Bundang = Bundang VCI Cohort; CASPER = Cognition and Affect After Stroke: Prospective Evaluation of Risks; COAST = Cognitive Outcome After Stroke; EpiUSA = Epidemiologic Study of the Risk of Dementia After Stroke; IDEA3 = Cerebral Amyloid Imaging Using Flortbetapir (AV-45); IQR = interquartile range; NNI = National Neuroscience Institute Study; SSS = Sydney Stroke Study; STROKDEM = Study of Factors Influencing Poststroke Dementia.

For the reference paper of each study, refer to Table 1 in the work of Lo et al., 2021.⁴

Figures are n (%) or mean (SD) unless specified.

^a N = the number of those with baseline assessment (range 1.9–9 months) and follow-up at 1 year (range 9–18 months).

^b Some or all patient assessment dates were not available, and therefore, the time in study was approximate.

^c CASPER recorded years of education attained in categories.

^d The study cohort was made up predominately of the ethnoracial group shown unless otherwise specified. Ethnoracial group classification is self-identified in 3 studies (COAST, EpiUSA, and NNI), defined by the study investigators as Korean in the Bundang study based in South Korea, and defined by the study investigators as White in the European studies (Bulgarian, CASPER, IDEA3, and STROKDEM). COAST study included Singaporean Chinese (72%), Malaysians (19%), and South Asians (8%) participants; for the NNI study, the cohort consisted of Singaporean Chinese (85%) and Malaysians (11%) participants; EpiUSA included 103 Hispanics participants, 55 of whom were self-identified as White, 10 as Black, and 38 as Other.

Table 2 Properties of the 3 Trajectory Groups From the Latent Class Growth Analysis for Global Cognition

Trajectory groups	n (%)	Rate of change, SD/y (95% CI); <i>p</i> value ^a	Global cognition at T ₁ , mean (SD) ^b	Global cognition at T ₂ , mean (SD) ^b
Low-performance (group 1)	199 (17%)	-0.10 (-0.33 to 0.13); <i>p</i> = 0.38	-3.27 (0.94)	-3.32 (0.91)
Medium-performance (group 2)	551 (48%)	0.11 (-0.08 to 0.24); <i>p</i> = 0.09	-1.23 (0.68)	-1.14 (0.74)
High-performance (group 3)	399 (35%)	0.22 (0.07 to 0.36); <i>p</i> = 0.004	0.71 (0.77)	0.86 (0.83)

Total n = 1,149.

^a Rate of change is the slope obtained from the latent class growth model.

^b Mean cognition scores are average values from patients assigned to each group. T₁ were baseline assessments at approximately 3.6 months poststroke; T₂ were follow-up assessments at approximately 1-year poststroke.

using the means and SDs derived from each study's control group (or, if not recruited, a local stroke-free normative study). Predicted means and SDs were obtained using a regression model based on the control participants' raw test scores at common values of the covariates age, sex, and education. Neuropsychological tests were assigned to 1 of 5 cognitive domains based on previous work and common practice^{2,10} (eTable 1, [links.lww.com/WNL/C751](https://www.lww.com/WNL/C751)), and domain z-scores were derived as the standardized average of all tests in a domain. Global cognition was represented by the standardized average of the 5 domain z-scores. For details, refer to our previous publication.⁴

Identifying Patterns of Trajectories of Cognitive Function

LCGA was used to identify clusters of stroke patients with similar cognitive trajectories between T₁ and T₂.¹¹ The model that fits the data best was chosen based on several parameters: Bayesian information criterion (BIC) and Akaike information criterion (AIC) which evaluate model fit; entropy, which indicates how well the model defines classes; and the average latent class posterior probability (ALCPP), which assesses the quality of classification. The best model has low BIC and AIC, high entropy (>0.8), high ALCPP (≥0.9), and >50 cases for each cluster.¹² The chosen model was used to assign patients to their most likely group using the predicted probabilities of belonging to each class (i.e., trajectory group). The analysis included global cognition scores at T₁ and T₂. Only patients with qualifying baseline and follow-up assessments were included. In secondary analyses, we repeated the above using domain scores as the outcomes. The interpretation of the trajectory groups was based on their mean rate of change (the slope) in cognitive scores between T₁ and T₂ and their mean level of cognitive performance at T₁ and T₂. The Stata procedure "traj" was used.¹³

Risk Factors for Trajectory Groups

We examined the association of demographic, medical history, and stroke-related characteristics with trajectory groups using mixed-effects multinomial logistic regression.

Predictors of Long-term Cognitive Outcome

Separate linear mixed-effects models were used to examine the association of (1) trajectory groups, (2) cognitive scores at

T₁, and (3) change in cognition between T₁ and T₂ with the global cognition score at T₃. The quadratic terms of scores at T₁ and T₂ were included to account for potential nonlinearity. We compared their predictive powers by examining the approximate adjusted R², which is the proportion of variance explained after controlling for all other variables obtained from regression models with fixed effects.

All Analyses

One-stage individual participant data meta-analysis based on mixed models with study as the random effect was used in all analyses unless otherwise specified. We conducted the unadjusted analyses first and then the fully adjusted analyses, which included sex, age, education in years, ethnorracial groups, prior stroke, severe/moderate stroke, stroke subtype, a history of atrial fibrillation, diabetes, hypertension, and smoking as covariates in the models. *APOE* status was available in only 2 studies and was examined in a subgroup. We did not include recurrent stroke as a covariate in the risk factor analysis because it could be on the causal pathway, but in a sensitivity analysis, we examined recurrent stroke (a second stroke up until T₁) as a potential risk factor by including it as a covariate in the model. Education in 4 categories (eTable 2, [links.lww.com/WNL/C751](https://www.lww.com/WNL/C751)) was used in place of education in years in the risk factor model in an additional analysis. Time in study for T₁, T₂, and T₃ was included as a covariate as appropriate to account for differences in assessment times. The significance level was assessed at the 0.05 level (2-sided). All analyses were performed using Stata 15.1 (StataCorp, College Station, TX). The Strengthening the Reporting of Observational Studies in Epidemiology Statement was used for reporting.¹⁴

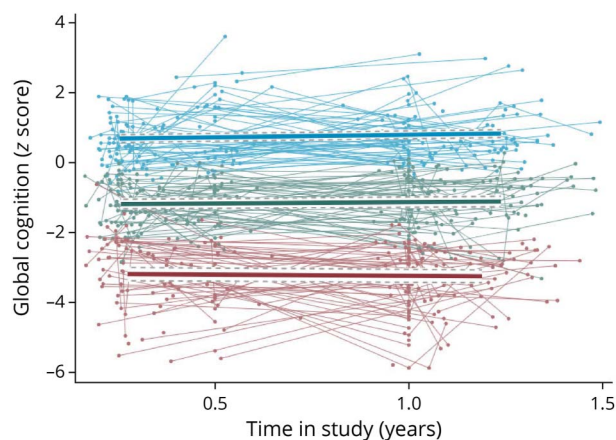
Standard Protocol Approvals, Registrations, and Patient Consents

Approval from the University of New South Wales Human Research Ethics Committee to conduct this project was received (reference HC210709). The ethics board had determined that participant consent was waived for all included studies.

Data Availability

Anonymized data will be shared on request from any qualified investigator.

Figure 1 Individual Changes in Global Cognition and the 3 Trajectory Groups Obtained From the Latent Class Growth Model



Blue = high-performance; green = medium-performance; red = low-performance. A random sample of 735 observations were used to plot the individual trajectories.

Results

Nine studies contributed 2,280 patients with stroke, of whom 61% were followed up at T_2 . Seventeen percent ($n = 239$) of those patients were assessed outside of the ranges we specified for T_1 and T_2 , so a total of 1,149 patients were included in our main analyses (see eFigure 1, links.lww.com/WNL/C751 for a flow diagram). Regarding significant differences between those who were included and excluded, there were higher proportions of smokers and patients with severe/moderate stroke excluded, and those excluded had significantly worse baseline global cognitive function than those included (-1.09 vs -0.96 ; $p = 0.028$; eTable 3). There were also a higher proportion of patients with small vessel strokes and a lower proportion of patients with cardioembolic strokes excluded from the analyses. Two studies had $>50\%$ loss to follow-up possibly because patients who were more mildly affected were not actively followed or were seen at primary care rather than study centers (eTable 4). We excluded the 2 studies with high proportions of loss to follow-up in a sensitivity analysis.

Of the 1,149 patients included, 63% were male, the mean age was 66.4 years (range: 23–94 years), and 54% did not complete high school (eTable 2, links.lww.com/WNL/C751). The median time between T_1 and T_2 was 9.0 months (interquartile range [IQR] 7.0–11.6). Of the 8 studies which conducted more than 1 follow-up assessments, 65% had at least 3 assessments and the median for the long-term follow-up (T_3) was 3.2 years poststroke (IQR 2.1–4.7 years). Thirteen percent had a recurrent stroke before T_3 . Patient characteristics by study are summarized in Table 1 and eTable 2.

Trajectory Groups From T_1 to T_2

Based on our model selection criteria, the 3-class and 4-class models were in the acceptable range for good class delineation

(eTable 5, links.lww.com/WNL/C751). We chose the 3-class model for parsimony, ease of interpretation, and greater power in the next set of analyses. Sensitivity analyses using stricter ranges for T_1 and T_2 and, secondly, excluding 2 studies with high percentage of loss to follow-up ($n = 98$) showed a similar pattern of results (eTable 6A).

Table 2 summarizes the properties of the 3 trajectory groups regarding global cognition. Figure 1 indicates that there were large differences between the groups in the level of global cognition at T_1 and T_2 . Group 1 (17%) was characterized by low levels of global cognition (on average -3.27 SD at T_1) and declining cognitive function (-0.10 SD per year; 95% CI -0.33 to 0.13), although the slope was not significantly different from 0 ($p = 0.38$). Group 2 (48%) had medium levels of global cognition (-1.23 SD at T_1) and showed a trend for small improvement (0.11 SD per year; 95% CI -0.08 to 0.24 ; $p = 0.09$). Group 3 (35%) had high levels of global cognition (0.71 at T_1) and showed significantly improving cognitive function (0.22 SD per year; 95% CI 0.07 – 0.36). Since the overall level of global cognition at T_1 and T_2 rather than slope was the strongest distinguishing feature between the 3 trajectory groups, we labeled them low-performance, medium-performance, and high-performance groups. The rate of change for the low-performance group was significantly different from that of the high-performance group ($t = 2.31$; $p = 0.021$), but other pairwise comparisons for change were not significant. The 2 sensitivity analyses showed similar percentages and intercept values as the main results (eTable 6B, links.lww.com/WNL/C751).

LCGA also identified 3-class models for all cognitive domains except for the perceptual motor, where a model with good separation of the latent classes could not be found (entropy values were <0.6). Similar to global cognition, the trajectory groups identified in each domain were distinguished by the level of cognitive performance at T_1 and T_2 (eFigure 2 and eTable 7, links.lww.com/WNL/C751). However, all of the trajectory groups for each domain showed stable or a trend for improving cognition except for the language domain, where patients with the poorest performance at T_1 showed significant and large decline (-0.37 SD per year; 95% CI -0.68 to -0.05). Patients with medium and high memory scores at T_1 or medium attention scores at T_1 showed significant improvement. For the executive function domain, all patients regardless of performance at T_1 showed stable cognition, with rates of change that were near 0.

Risk Factors for Trajectory Groups

Patient characteristics of the trajectory groups are presented in eTable 8 (links.lww.com/WNL/C751). We examined the risk factors of belonging in the low-performance group using mixed-effects multinomial logistic regression. Results from the unadjusted analysis are given in eTable 9. *APOE* status was not significant ($p = 0.36$) and due to small numbers ($n = 91$), and it was not included in the multivariable model. The fully adjusted model, which adjusted for all factors simultaneously,

Table 3 Risk Factors for Low-Performance Group vs High-Performance Group

	Relative risk ratio (95% CI)	p Value
Age	1.18 (1.14–1.23)	<0.001
Male sex	1.20 (0.65–2.23)	0.55
Education, y	0.61 (0.56–0.67)	<0.001
Ethnoracial groups^a		
Asian vs White patients	0.46 (0.09–2.42)	0.36
Black vs White patients	0.90 (0.29–2.82)	0.86
Stroke subtype^b		
Large artery vs small vessel	2.77 (1.32–5.83)	0.007
Cardioembolic vs small vessel	1.23 (0.55–2.75)	0.62
Unknown (ischemic) vs small vessel	1.87 (0.67–5.19)	0.23
Prior stroke	0.71 (0.33–1.51)	0.38
Hypertension	1.36 (0.73–2.52)	0.33
Diabetes	3.78 (2.08–6.88)	<0.001
Smoking (ever)	0.39 (0.22–0.71)	0.002
Severe/moderate stroke (index event)	3.17 (1.42–7.08)	0.005
Recurrent stroke ^c	0.49 (0.07–3.56)	0.48

Mixed multinomial logistic analysis included 813 patients from 7 studies and all factors (except recurrent stroke) were included in a single model. High performance was the reference group. Atrial fibrillation was not included because it did not allow the model to converge (it was not significant in the unadjusted analysis). Bold p-values indicate significance at $p < 0.05$.

^a Korean and Singaporean Chinese participants were combined to form the Asian group due to small numbers of Korean patients.

^b Hemorrhagic strokes and other ischemic strokes were not included because of small numbers in the trajectory groups.

^c Recurrent stroke (up until baseline assessment at T₁) was added into the model additionally and separately.

showed that older age, a lower level of education, diabetes, large artery vs small vessel strokes, severe/moderate stroke, and, surprisingly, an absence of a history of smoking were associated with higher relative risk of membership in the low-performance group compared with high-performance over the first year after stroke (Table 3). The same factors except for large artery strokes were associated with the low-performance group compared with the medium-performance group (eTable 10). In the sensitivity analysis with 2 studies excluded, the results were nearly identical. Recurrent stroke was not significant when included as a covariate (unadjusted: $p = 0.27$; adjusted: $p = 0.48$); however, the number of patients with recurrent strokes before T₁ is small ($n = 6$).

The results of the analysis with education treated as a 4-category variable showed that for each increasing level of education, there was a decrease in the magnitude of the effect sizes, that is, having completed high school compared with not having completed high school had the greatest increase in benefit, but there was no significant additional protective

effect of having completed a bachelor's degree compared with technical/college diploma (eTable 11, [links.lww.com/WNL/C751](https://www.lww.com/WNL/C751)).

In a complementary analysis, we examined the risk factors of cognitive function at T₁ and T₂. The fully adjusted models revealed the same set of factors except for smoking (eTables 12 and 13, [links.lww.com/WNL/C751](https://www.lww.com/WNL/C751)).

To make sense of the result relating to smokers having higher odds of belonging in the high-performance group, we examined the unadjusted association of smoking and cognition at T₁, T₂, and T₃ and found that smokers had significantly higher global cognition scores at all 3 time points, indicating that our results were not due to chance multicollinearity.

Trajectory Groups as Predictors of Long-term Cognitive Outcome

The trajectory groups significantly predicted global cognition at the long-term follow-up in the unadjusted and adjusted analyses (Table 4, eTable 14, [links.lww.com/WNL/C751](https://www.lww.com/WNL/C751)). The trajectory groups identified for each domain were also significantly associated with global cognition at T₃ (eTable 15).

Cognition at T₁ and T₂ and Rate of Change Between T₁ and T₂, as Predictors of Long-term Cognitive Outcome

Linear mixed models showed strong prediction of global cognition at T₃ by cognition scores at both T₁ and T₂, with the effect of cognition at T₂ being only slightly stronger than that at T₁ (1.1% higher; Table 4). The rate of change in cognition from T₁ to T₂ was also significant, but its level of prediction was much lower.

Post Hoc Analyses

We examined the extent to which the prediction of global cognition at T₃ by trajectory groups can be accounted for by baseline scores at T₁. Adding trajectory groups to the model with global cognition at T₁ resulted in an increase in R² of only 0.037 (eTable 16, [links.lww.com/WNL/C751](https://www.lww.com/WNL/C751)). Thus, controlling for global cognition at T₁ reduced the variance explained by trajectory groups from an R² of 0.718 to only 0.037, indicating that the prediction by trajectory groups of global cognition at T₃ is largely explained by variation in performance at T₁.

Discussion

In this collaborative study that included 9 international hospital-based stroke cohorts, we identified 3 groups in relation to cognitive trajectories between baseline and 1 year after stroke. Patients with high cognitive function at baseline, on average 3.6 months poststroke, experienced significant cognitive improvement, while those with medium and low cognitive function at baseline did not show a significant change in cognitive function. The predictive powers of global cognition scores at baseline and 1 year were very

Table 4 Predictors of Global Cognition at the Long-term Follow-up

Predictors	Global cognition at the long-term follow-up (T ₃)	Model diagnostics	
	Effect size (95% CI); p value	AIC	Approximate adjusted R ^{2a}
Trajectory groups			
Medium vs low	1.99 (1.71–2.27); <0.001	1,505	0.672
High vs low	3.50 (3.17–3.83); <0.001		
High vs medium ^b	1.51 (1.29–1.74); <0.001		
Baseline scores (at T ₁)	0.90 (0.79–1.01); <0.001	1,277	0.785
Follow-up scores at 1 year (at T ₂)	0.95 (0.89–1.00); <0.001	1,224	0.806
Rate of change (between T ₁ and T ₂)	0.30 (0.12–0.48); 0.001	1,801	0.378

Abbreviation: AIC = Akaike information criterion.

N = 520. Low = low-performance group; medium = medium-performance group; high = high-performance group (Table 2). T₁ refers to baseline assessment conducted at approximately 3.6 months poststroke and T₂ at approximately 1-year poststroke. The 4 models examined the association between each predictor and global cognition at the long-term follow-up. Cognitive scores were harmonized global cognition z-scores (SD). One patient was omitted from this analysis because the T₃ assessment occurred before 1 year. All models adjusted for age, sex, education, ethnorracial groups, stroke severity, stroke subtype, hypertension, atrial fibrillation, diabetes, smoking, and previous stroke.

^a Approximate adjusted R² were obtained from an equivalent regression model with study as a fixed effect.

^b The reference group was changed in the model to obtain the effect size.

similar, while the rate of change was a significant but poorer predictor. Therefore, a stroke patient's prognosis relating to long-term cognitive outcome can be based on their cognitive assessment at around 3 months alone, with further assessment within the 1-year period adding little to the accuracy of the prediction.

A recent cohort study examined the different trajectories of cognitive function after strokes and similarly identified 3 trajectory groups differentiated by their levels of cognitive function over 3 time points.¹⁵ However, they did not find significant improvement from 3 to 12 months in any of the trajectory groups, which may be because only the Montreal Cognitive Assessment was used, which is not as sensitive as the tests used in our studies. Being a 1-year study, they were not able to examine long-term cognitive outcomes.

The importance of baseline cognitive function in predicting the cognitive trajectory and outcome was a noteworthy finding of our study. Some differences were also seen in the patterns related to the individual domain scores. The trajectory groups based on different domain scores were distinguished by their level of cognitive function across the 2 time points, but the rate of change was near zero in several trajectory groups. Although patients with the poorest performance in language at T₁ showed significant decline, patients with the highest performance in memory at T₁ showed

significant improvement, and all patients showed a trend for small improvement, regardless of baseline scores in the attention domain. The reasons for these differences are not clear, and it is likely that the language domain differentially influenced the course of the group with initially low and then declining global cognitive function. We speculate that the differences may be related to the differential recovery patterns of brain regions and networks subserving these cognitive functions.

For a large proportion of the patients who experienced cognitive improvement over the first year after stroke, this may have been the result of a combination of genuine recovery and practice effects. The effects of drugs such as statins may have played a part, but we do not have sufficient data at present to examine this. For those with the poorest performance at baseline and declining cognition, baseline cognitive impairment at or before the time of stroke may reflect a reduction in neurologic reserve and neuroplastic potential, which may in turn reduce the potential for cognitive recovery.¹⁶ An acute stroke is followed by a period of enhanced plasticity in neural circuits during the period of recovery. This period has been divided into 4 phases: hyperacute, acute, subacute, and chronic.¹⁷ The hyperacute phase is characterized by extensive cell death, while in the acute phase, which lasts for about a week, there is delayed apoptosis, a prominent inflammatory response, and enhanced neuronal excitability. The inflammation is reduced in the subacute phase, and there is enhanced plasticity, with maximal recovery that continues until about 3 months. This is followed by the chronic phase, which is the period being investigated in this paper. Recovery is possible in this period, but previous research suggests that this is greatly dependent on neurorehabilitative therapy.¹⁸ However, this model of recovery has largely been developed using motor recovery in animal models of stroke,¹⁷ and its application to cognitive recovery in humans has not been demonstrated. Our study shows that improvement does occur in this period up to about a year, but not in all cases, and this is dependent on the baseline from which individuals begin the process following the subacute phase. We do not have data to explore whether neurorehabilitation played a role in our study, but most studies did not report any systematic cognitive rehabilitation in their patients.

We were unable to examine the cognitive function of patients with stroke before stroke onset because participants were recruited after being admitted to hospital for stroke. A recent population-based study from the Netherlands found that participants who had had a stroke compared with stroke-free participants had had steeper declines in cognitive function up to 10 years before stroke onset and that there was an acute decline in cognition at the time of stroke.¹⁹ One of the major limitations of that study and other population-based studies is that it did not examine stroke features. Although the Dutch study stratified results by sex, education, and APOE genotype, they presented average trajectories and did not examine the potentially heterogeneous course of cognition before stroke.

Our results call for more in-depth assessment of longitudinal change in cognitive function beginning before stroke and then during long-term follow-up that includes the examination of individual features such as stroke characteristics.

Our analyses of the risk factors for the trajectory groups and cognitive function at baseline and at 1 year revealed that those with poorer global cognition during the first-year poststroke had less education and they were older and more likely to have diabetes, large artery strokes rather than small vessel strokes, and a severe or moderately severe stroke.

Our results suggest a potential threshold effect of education, which has been reported in general population studies on the effect of education and cognitive decline. These studies found that after a certain level of educational attainment, additional schooling does not contribute to further reductions in risk of cognitive impairment.^{20,21} However, a recent systematic review²² and 2 stroke studies^{23,24} which examined the association of cognitive reserve and poststroke cognitive function did not report such an effect; further investigation is therefore warranted. The idea that cognitive reserve, operationalized as level of education, could delay the expression of the clinical manifestation of brain pathology has been discussed in the context of Alzheimer disease and could be extended to patients with stroke.^{16,24,25}

Furthermore, our studies comprise older people recruited at different periods. Research data show that there has been a continuous increase in average years of schooling in the past century.²⁶ The mean education level in our combined sample is low (9.9 years) compared with that in the current population. Although it is in keeping with the age of our cohorts (Table 1), it could bias our results for application to younger contemporary cohorts because education is a strong predictor of cognitive performance.

The higher proportion of men in our studies (63% overall) reflects the higher stroke risk in men compared with women during midlife.²⁷ In addition, women are on average older at the time of stroke and have greater stroke severity and disability, which may affect their participation rates.²⁸ However, we found no evidence that sex is associated with cognitive performance.

Several recent studies have linked diabetes mellitus with an increased risk of cognitive impairment, decline, and dementia.²⁹⁻³¹ Our results further confirm diabetes as an important modifiable risk factor for poststroke cognitive impairment.

Several population-based studies have shown that the risk of dementia is elevated in patients with more severe stroke.^{32,33} However, the literature examining the longitudinal association of stroke severity and cognitive decline is limited. We found that moderate or severe stroke was associated with cognitive decline over the first year. It is likely that the brain lesions associated with severe strokes have direct effects on cognition

and that the volume, location, and/or number of such lesions in these patients may hamper cognitive recovery.³³

We found that large artery vs small vessel strokes were predictive of poorer cognitive performance over the first year. Research examining cognitive outcome by stroke subtype is sparse, and it is unclear whether cognitive impairment risk varies by stroke subtype. A recent stroke study found no significant difference in the severity of impairment between subtypes,³⁴ while a population-based study found a higher prevalence of cognitive impairment with large artery strokes and a lower prevalence of impairment with small vessel strokes.³⁵ Although large artery strokes tend to affect a larger area of the brain and thus increase the risk of cognitive impairment, smaller lacunar strokes are part of the spectrum of cerebral small vessel disease that can be a cause of vascular cognitive impairment in certain patients.³⁶ More research is needed to examine short-term and long-term cognitive outcomes by stroke subtype.

Research has shown that smoking is a risk factor for cognitive decline and dementia.³⁷ Surprisingly, we found that smoking was significantly associated with membership in the high-performance group over the first year after stroke, but the associations between smoking and cognitive scores at baseline and at the 1-year follow-up were not significant after covariate adjustment. We postulate that there is something inherently different about smokers that our cohort studies did not fully capture. Regardless, smoking is a well-established risk factor for stroke, cardiovascular diseases, and dementia and must be avoided.

The strengths of our work include the participation of 9 international studies which provided us with a diverse stroke cohort, the use of detailed neuropsychological tests for the assessment of global cognition and 5 cognitive domains, and our ability to adjust for several potential contributing and confounding factors, including stroke characteristics, vascular risk factors, and demographic variables. The sensitivity analyses produced consistent results suggesting that our conclusions are robust and not affected by slight variations in assessment schedule or by 2 studies with large proportion of loss to follow-up. Limitations include selective attrition due to patients with poorer baseline cognitive function or more severe stroke dropping out of the study or dying, and possible limited generalizability of findings to current stroke populations due to a lower mean education level in the sample. Our study is also limited by unmeasured or unknown confounding variables including medication use and stroke treatment, which could bias our results. Despite these limitations, our study provides a detailed examination of cognitive trajectory over the first year after stroke. Our results may help clinicians provide earlier guidance on prognosis to patients and their families and better determine early treatment and preventive strategies. An important future direction will be to study the effect of cognitive rehabilitation on cognitive outcomes through the first year after stroke.

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Disclosure

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John D. Crawford, PhD	UNSW, Sydney, Australia	Design and conceptualized study and methods; interpreted the data; and revised the manuscript for intellectual content
David W. Desmond, PhD		Major role in the acquisition of data; substantially revised the manuscript for intellectual content
Hee-Joon Bae, MD	Seoul National University School of Medicine, South Korea	Major role in the acquisition of data
Jae-Sung Lim, MD, PhD	University of Ulsan College of Medicine, Seoul, South Korea	Major role in the acquisition of data
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Julie Staals, MD, PhD	Maastricht University Medical Center, the Netherlands	Major role in the acquisition of data; contributed to revising manuscript for intellectual content
Frans Verhey, MD, PhD	Maastricht University, the Netherlands	Major role in the acquisition of data
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Appendix 1 (continued)

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Appendix 2 Coinvestigators

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Continued

Appendix 2 (continued)

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Vincent Mok MD, FRCP	Chinese University of Hong Kong	Research Scientific Committee member	Reviewed, approved project proposal and contributed data from cohort
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Appendix 2 (continued)

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