Long-Term Cognitive Decline After Stroke

Stroke

ORIGINAL CONTRIBUTIONS

Long-Term Cognitive Decline After Stroke: An Individual Participant Data Meta-Analysis

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BACKGROUND AND PURPOSE: Poststroke cognitive impairment is common, but the trajectory and magnitude of cognitive decline after stroke is unclear. We examined the course and determinants of cognitive change after stroke using individual participant data from the Stroke and Cognition Consortium.

METHODS: Nine longitudinal hospital-based cohorts from 7 countries were included. Neuropsychological test scores and normative data were used to calculate standardized scores for global cognition and 5 cognitive domains. One-step individual participant data meta-analysis was used to examine the rate of change in cognitive function and risk factors for cognitive decline after stroke. Stroke-free controls were included to examine rate differences. Based on the literature and our own data that showed short-term improvement in cognitive function after stroke, key analyses were restricted to the period beginning 1-year poststroke to focus on its long-term effects.

RESULTS: A total of 1488 patients (mean age, 66.3 years; SD, 11.1; 98% ischemic stroke) were followed for a median of 2.68 years (25th–75th percentile: 1.21–4.14 years). After an initial period of improvement through up to 1-year poststroke, decline was seen in global cognition and all domains except executive function after adjusting for age, sex, education, vascular risk factors, and stroke characteristics (−0.053 SD/year [95% CI, −0.073 to −0.033]; $P<0.001$ for global cognition). Recurrent stroke and older age were associated with faster decline. Decline was significantly faster in patients with stroke compared with controls (difference=−0.078 SD/year [95% CI, −0.11 to −0.045]; $P<0.001$ for global cognition in a subgroup analysis).

CONCLUSIONS: Patients with stroke experience cognitive decline that is faster than that of stroke-free controls from 1 to 3 years after onset. An increased rate of decline is associated with older age and recurrent stroke.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cognition ■ cognitive dysfunction ■ meta-analysis ■ risk factors ■ stroke

Stroke mortality rates have decreased during the last 2 decades, but a growing aging population is likely to lead to an increase in the incidence and thus the burden of stroke.[1] Poststroke cognitive impairment is common, with up to 50% of stroke survivors estimated to develop poststroke neurocognitive disorders,[2] but the natural history of poststroke cognitive function and the magnitude of domain-specific change after stroke is incompletely understood. A recent systematic review described mixed results in longitudinal studies, which may be due to variability in cognitive tests, follow-up periods, study design, and/or patient characteristics.[3] Several large population-based studies have reported significant cognitive decline in long-term follow-up,[4–6]

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Nonstandard Abbreviations and Acronyms

IPD	individual participant data
TIA	transient ischemic attack
TIS	time in study

but a number of hospital-based poststroke studies with shorter follow-up periods reported cognitive improvement in the first year after stroke.[7–9] While there is a lack of hospital-based studies that have examined the long-term cognitive outcome of patients with stroke, the studies cited above suggest that cognition may show short-term improvement and then long-term stability or decline following the first year after stroke.

The Stroke and Cognition Consortium, an international consortium of longitudinal studies of cognitive function after stroke,[10] provides an opportunity to address the inconsistencies among previous studies and systematically examine the course of poststroke cognitive function using harmonized individual participant data (IPD). We previously examined the profile of and risk factors for cognitive impairment 2 to 6 months after stroke.[11] In this article we build on that work by examining the long-term course of cognitive change and risk factors for cognitive decline after stroke. Since prior studies suggested that the course of cognitive function during the first year after stroke may vary between patients, that the mechanisms underlying cognitive change may differ between the early and later periods after stroke, and a review article suggested that cognitive assessments should begin 1 year after stroke,[12] we first examined the full course of cognitive change and the possibility that there is a "turning point" 1 year after stroke. After confirming this, we then focused on long-term outcomes beginning 1 year after stroke. Our primary hypotheses were that: 1) patients with stroke experience significant decline in global cognition and all cognitive domains beginning 1 year after stroke; 2) the rate of cognitive decline is faster in patients with stroke compared with stroke-free controls; and 3) the risk factors for cognitive impairment soon after stroke, such as diabetes, are also associated with long-term poststroke cognitive decline.

METHODS

Data Availability

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

Inclusion Criteria

The Stroke and Cognition Consortium member studies with at least one follow-up, which conducted detailed neuropsychological tests assessments, and which recruited a control group or provided data for an appropriate comparison group were included. A flow diagram showing studies that were included is given in Figure I in the Supplemental Material.

Contributing Studies

Nine the Stroke and Cognition Consortium studies from Asia, Australia, Europe, and the United States contributed data (Table 1). All studies were hospital-based and included in our previous article[11] except for 2 studies which joined the Stroke and Cognition Consortium recently (Table I in the Supplemental Material). Since most studies did not follow their controls prospectively, we included 2 additional longitudinal population-based studies to provide controls for 2 stroke studies (Table II in the Supplemental Material). We were not able to identify appropriate control groups with longitudinal data for the other 5 studies. Two studies additionally recruited patients with transient ischemic attack (TIA), but we excluded those patients from the present article for consistency.

Standard Protocol Approvals

Procedures of the consortium have been approved by the University of New South Wales Human Research Ethics Committee (reference HC14359). All studies had ethics approval from local institutional review boards.

Statistical Methods

Data Harmonization

Consistency and completeness of data from each study were checked and data on demographics, medical history, and

Table 1. Contributing Studies

Study	Abbreviation	Country	Start date	N*
Bulgarian Poststroke Study[13]	Bulgarian	Bulgaria	2012	74
Bundang Vascular Cognitive Impairment cohort[14]	Bundang	Korea	2007	167
Cognition and Affect After Stroke: Prospective Evaluation of Risks[15]	CASPER	The Netherlands	2013	231
Cognitive Outcome After Stroke[16]	COAST	Singapore	2009	224
Epidemiologic Study of the Risk of Dementia After Stroke[17]	Epi USA	USA	1988	384
Cerebral Amyloid Imaging Using Florbetapir (AV-45)	IDEA3	France	2014	86
National Neuroscience Institute study[18]	NNI	Singapore	2011	89
Sydney Stroke Study[19]	SSS	Australia	1997	106
Study of Factors Influencing Poststroke Dementia[20]	STROKDEM	France	2011	127

*Sample size of patients with baseline neuropsychological test data and at least 1 follow-up assessment.

stroke characteristics were harmonized (Tables III through V in the Supplemental Material). 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 method[21] in which raw scores were standardized as *z*-scores 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 controls' raw test scores at common values of the covariates age, sex, and education. Neuropsychological tests were assigned to 1 of 5 cognitive domains (attention and processing speed, memory, language, perceptual motor, and executive function) based on previous work and common practice[11,22] (Table VI in the Supplemental Material), and domain *z*-scores were derived as the standardized average of all tests in a domain. Global cognitive *z*-scores were calculated as the standardized average of the 5 domain scores. See Methods I in the Supplemental Material for details about the methods of standardization.

Loss to Follow-Up

The proportion and reasons for loss to follow-up for each study were examined. The baseline characteristics of patients who had 2 or more assessments were compared with those who had only a single assessment using χ^2 tests or *t*-tests as appropriate.

Primary Statistical Model Examining Change in Cognitive Function

We used 1-step IPD meta-analysis, which analyzes data from all studies simultaneously in a 3-level linear mixed-effects model to estimate change in cognitive function.[23] The 2-step approach, which derives effect estimates from each study separately and then combines them in a traditional meta-analysis model, was used as a sensitivity analysis as described in the section "Examination of Data Heterogeneity and Other Statistical Considerations." The model included random effects for intercept and slope (for time-in-study [TIS]) to accommodate correlation of cognitive measures within studies as well as within participants over time. Cognition was censored at the time of death, loss to follow-up, or the end of follow-up. The outcomes were global cognition and the 5 cognitive domains expressed as *z*-scores. Each cognitive outcome was analyzed separately. The independent variable was TIS, which indicates the change in cognitive function per year after the index stroke.

Covariates in the Primary Model

In all adjusted models, we included demographic, medical history, and stroke-related variables, including age at baseline, sex, education (in categories), and ethno-racial group; a history of hypertension, diabetes, atrial fibrillation, and smoking (current or former); stroke subtype; and previous stroke. To address potential quadratic effects of age or TIS, age^2 and TIS^2 were included and retained if $P<0.1$. The interaction of TIS with age was included if $P<0.1$. Since some studies did not collect data on systolic blood pressure, a history of depression, body mass index, stroke severity (mild, moderate, severe), and stroke location (left, right, bilateral), these variables were included and examined in subgroups with available data based on a forward selection method and retained if $P<0.1$ for any cognitive outcome. The same set of covariates was used for all outcomes. We did not include in the model recurrent stroke, TIA, or depression during follow-up since they are often comorbid with cognitive decline and therefore on the causal pathway. A regression model that included all covariates was used to calculate the variance inflation factors, which were all <2.5, indicating no problems with multicollinearity.

Examination of Different Trajectories of Cognitive Change With 1 Year as the Turning Point

As reviewed in the Introduction section, results from several studies have suggested that there might be different patterns of change in cognition during the early and later poststroke periods. Thus, we used piecewise regression based on the mixed-effects model described above to determine if there were 2 distinct slopes before and after a range of turning points between 0.7 and 1.3 years. Guided by the existing literature and results from the above analyses, we restricted the primary model and all subsequent analyses to TIS≥1 year after stroke (the rationale for this choice is provided in the Results section).

Risk Factors and Modifying Factors

The effects of potential risk factors on cognitive decline for global cognition were examined by including interaction terms with TIS separately in the primary model, restricted to TIS≥1 year. The potential risk factors included age, sex, education, ethno-racial group, stroke subtype, severity of stroke, diabetes, hypertension, atrial fibrillation, smoking, prior stroke, and in a subgroup of 2 studies with data on ApoE4 status (at least one ApoE4 allele). Similarly, we examined whether cognitive decline was modified by recurrent stroke, TIA, or depression during follow-up by including interaction terms.

Comparison of Patients With Stroke With Controls

We examined whether cognitive decline in patients with stroke differed from that of stroke-free controls among 4 studies. The primary model was used, with the additional inclusion of stroke status and its interaction with TIS and the omission of stroke characteristics and a history of stroke. TIS was restricted for patients with stroke to ≥1 year but not for controls.

Examination of Data Heterogeneity and Other Statistical Considerations

Two-step IPD meta-analysis was conducted additionally to check the key results and to examine heterogeneity using forest plots and the I^2. In the first step, we constructed a 2-level linear mixed-effects model for each study; in the second step, we used standard meta-analysis with random effects to combine summary effects from each study.

Age was centered at the overall mean (66 years) to avoid multicollinearity. Marginal residuals were used to check the normality assumption with the data. Predicted global cognition *z*-scores and marginal effects based on mean values of the covariates in the final models were calculated to aid interpretation. All analyses were performed with Stata 15.1 (StataCorp, College Station, TX). The Preferred Reporting Items for a Systematic Review and Meta-Analysis IPD checklist[24] was used for reporting.

RESULTS

Summary Statistics

Nine studies (Table 1) with a total of 2295 patients with stroke were included, of whom 1488 had at least 1 follow-up cognitive assessment. Four studies provided data

on 4020 control participants. Minor issues about data inconsistency or out-of-range items were corrected after checking with data managers from the primary studies. The studies conducted between 1 and 10 follow-up assessments, and 2 studies followed their controls prospectively.

A summary of the characteristics of the patients with follow-assessments are provided in Table 2 and in Table IX in the Supplemental Material. The mean age of the overall sample was 66.3 years (SD=11.1), 62% were male, and 55% did not complete high school. Just over one-half (52%) was White (6 studies), 16% were Singaporean Chinese (2 studies), 11% were Korean (1 study), and 11% were Blacks (1 study). The median time in study was 2.68 years (25th–75th percentile: 1.21–4.14 years). Almost all patients had an ischemic stroke (98.3%), and 1.7% had a hemorrhagic stroke as the index event.

Loss to Follow-Up

Reasons for loss to follow-up included patient refusal, inability to be assessed, and death. The study from Korea and 1 study from Singapore had high proportions of loss to follow-up (75% and 52%, respectively; Table VII in the Supplemental Material), possibly because patients who were more mildly affected were not actively followed or were seen at primary care rather than study centers. Those studies led to our sample having higher proportions of Koreans and Singaporean Chinese patients not having follow-up assessments compared with whites (Table VIII in the Supplemental Material). Overall, those without a follow-up assessment had lower global cognition scores at baseline (−1.56 versus −0.99, $P<0.001$).

Examination of Different Trajectories of Cognitive Function With 1 Year as the Turning Point

Piecewise regression confirmed a change in the trajectory of cognitive function at around 1 year after stroke. We examined several turning points between 0.7 and 1.3 years and found that the slope before each turning point was large and significantly positive, while the slope after each turning point was significantly negative (Table X in the

Table 2. Characteristics of Patients With Stroke With At Least 1 Follow-Up Neuropsychological Assessment

	Bulgarian	Bundang	CASPER	COAST	Epi USA	IDEA3	NNI	SSS	STROKDEM	All studies
N	74	167	231	224	384	86	89	106	127	1488
Maximum number of follow-ups	2	8	3	4	10	2	1	3	3	10
Length of follow-up, y, median (range)	1 (1–2)*	2.18 (0.26–7.4)	1.32 (0.65–3.9)	5.14 (0.91–6.6)	2.98 (0.86–10.2)	3.03 (0.5–7.1)	1.34 (0.68–2.4)	3.00 (1–7.4)*	3.18 (0.9–5.9)	2.68 (0.26–10.2)
Age (baseline), y	65.0 (5.6)	68.9 (9.9)	67.0 (11.7)	59.6 (11.6)	71.1 (7.8)	62.8 (10.8)	59.6 (11.2)	71.8 (8.8)	62.6 (12.6)	66.3 (11.1)
Male, n	59 (80%)	99 (59%)	149 (65%)	168 (75%)	176 (46%)	59 (69%)	62 (70%)	64 (60%)	81 (64%)	917 (62%)
Education, y	11.4 (2.0)	9.5 (5.2)	NA†	7.6 (4.3)	10.3 (4.8)	10.5 (2.8)	9.0 (3.2)	10.6 (3.0)	11.5 (4.1)	9.82 (4.4)
Ethno-racial group‡	White	Korean	White	Singaporean Chinese (S Chinese)	44% White; 43% Black (AA)‡	White	S Chinese	White	White	52% White; 16% S Chinese; 11% Korean; 11% AA; 6% Other Asian
Medical history										
Hypertension	64/74 (86%)	126/167 (75%)	168/231 (73%)	159/224 (71%)	288/384 (75%)	53/86 (62%)	71/89 (80%)	66/101 (65%)	68/127 (54%)	1063/1483 (72%)
Diabetes	22/74 (30%)	52/167 (31%)	33/231 (14%)	101/224 (45%)	134/384 (35%)	18/86 (21%)	31/89 (35%)	17/100 (17%)	15/127 (12%)	423/1482 (29%)
Atrial fibrillation	13/74 (18%)	22/166 (13%)	22/231 (9.5%)	23/224 (10%)	51/382 (13%)	16/86 (19%)	16/89 (18%)	24/99 (24%)	10/127 (7.9%)	197/1478 (13%)
History of previous stroke	0	16/167 (9.6%)	15/231 (6.5%)	37/224 (17%)	96/384 (25%)	2/77 (2.6%)	13/89 (15%)	14/99 (14%)	13/127 (10%)	206/1472 (14%)
Smoking (ever)	19/74 (26%)	53/136 (39%)	173/231 (75%)	98/223 (44%)	225/381 (59%)	32/86 (37%)	35/89 (39%)	65/102 (64%)	26/127 (20%)	726/1449 (50%)
Index event (at baseline)										
Ischemic stroke	74 (100%)	167 (100%)	214 (93%)§	224 (100%)	384 (100%)	77 (90%)	89 (100%)	106 (100%)	126 (99%)	1461 (98%)

Figures are mean (SD) or number (percent) unless specified. Bulgarian indicates Bulgarian Poststroke Study; Bundang, Bundang Vascular Cognitive Impairment cohort; CASPER, Cognition and Affect After Stroke: Prospective Evaluation of Risks; COAST, Cognitive Outcome After Stroke; EpiUSA, Epidemiological Study of the Risk of Dementia After Stroke; IDEA3, Cerebral Amyloid Imaging Using Florbetapir (AV-45); NNI, National Neuroscience Institute; SSS, Sydney Stroke Study; and STROKDEM, Study of Factors Influencing Post-Stroke Dementia.

*Assessment dates were not available, thus the length of follow-up is approximate only.

†CASPER recorded years of education attained in categories; see Table IX in the Supplemental Material.

‡The study cohort was made up entirely or predominately of the ethno-racial group(s) shown. EpiUSA included 127 Hispanics, 65 of whom were self-identified as White, 15 as Black, and 47 as other.

§Contains missing data or unknown lesion location.

Supplemental Material). We chose to use 1 year as the turning point based on results that show a tighter confidence interval, a recommendation from a review article,[12] and the simplicity of the number. Our cohort significantly improved in global cognition and all domains except language and executive function from baseline to 1 year after stroke (0.14 SD/year [95% CI, 0.076–0.21]; $P<0.001$ for global cognition; Table 3). Since results for the language and executive function domains were not consistent with results for global cognition and the other domains, we explored study heterogeneity using 2-step IPD meta-analysis. Results showed that for the language domain, 1 study appeared to be an outlier (Figure II in the Supplemental Material); with this study excluded the results became significant and consistent (Table 3). Heterogeneity for executive function was moderate (I^2=55%; Figure II in the Supplemental Material).

Course of Cognitive Function Beginning 1 Year After Stroke

Our primary analysis showed that there was a significant decline in global cognition and all domains except executive function beginning 1 year after stroke, after covariate adjustment (Table 4). Global cognition declined on average by 0.053 SD per year ([95% CI, 0.033–0.073]; $P<0.001$). The effect size for executive function was near 0 (95% CI, −0.042 to 0.039]; P=0.74). Unadjusted analyses produced similar results (Table XI in the Supplemental Material).

The largest rate of decline was observed in the memory domain, with a 0.065 SD/year reduction ([95% CI, 0.042–0.088]; $P<0.001$), while the domains other than executive function had rates of decline ranging from −0.035 to −0.039 SD/year. One study had to be omitted to include stroke subtype and stroke severity as covariates, which were both significant in the model.

Sensitivity Analyses

A sensitivity analysis excluding stroke subtype and stroke severity but including all studies showed similar results (Table XII in the Supplemental Material). In another sensitivity analysis in which we excluded 2 studies with large proportions of patients who were lost to follow-up, results were also similar (Table XIII in the Supplemental Material).

Additional Analyses and 2-Step IPD Meta-Analysis

We performed several tests to explore the lack of decline in executive function. We found that patients' mean *z*-scores for all domains at baseline were similar, ranging from −0.78 to −0.88 SD. We also examined decline in the most commonly administered executive function tests, Trail Making Test B (4 studies) and verbal fluency for letters (2 studies), and the results were not significant (Trail Making Test B [95% CI, −0.039 to 0.11]; P=0.34; verbal fluency [95% CI, −0.036 to 0.0003]; P=0.054).

Results from the 2-step IPD meta-analyses matched those from the 1-step. The I^2 statistic, which describes the percentage of variation across studies that is due to heterogeneity, was between 0% and 61% (Table XIV and Figure IIIA in the Supplemental Material). Since 3 studies had only one follow-up assessment, we removed those studies in a sensitivity analysis. The new I^2 was between 0% and 21% for global cognition and all domains except executive function (I2=61%; Table XIV and Figure IIIB in the Supplemental Material).

Risk Factors and Modifying Factors

Age was a significant risk factor for poststroke decline in global cognition (−0.003 SD/year [95% CI, −0.005 to −0.001]; $P<0.001$), but the rate of decline was not modified by sex, education, ethno-racial group, vascular risk factors, stroke severity, or stroke subtype (Table 5). We further explored the nonsignificant results by examining the association with baseline global cognition scores in a mixed model and found that patients with more severe strokes, and with large artery, cardioembolic and hemorrhagic strokes, in comparison to patients with small vessel strokes, had worse cognitive function at baseline (Table XV in the Supplemental Material).

Patients with stroke who had a recurrent stroke during follow-up (n=181, 12%) had a faster decline in global cognition (−0.14 SD/year) compared with those who did

Table 3. Rate of Cognitive Change Before and Beginning 1 Year After Stroke

	TIS<1			TIS≥1*		
	Effect size (TIS-1)	95% CI	*P* value	Effect size (TIS-2)	95% CI	*P* value
Global cognition	0.14	0.076 to 0.21	<0.001	−0.056	−0.074 to −0.038	<0.001
Attention and processing speed	0.11	0.031 to 0.19	0.006	−0.032	−0.049 to −0.014	<0.001
Memory	0.25	0.16 to 0.34	<0.001	−0.061	−0.083 to −0.040	<0.001
Language	−0.002	−0.17 to 0.17	0.98	−0.097	−0.26 to 0.063	0.23
Language (1 study excluded)†	0.10	0.027 to 0.18	0.008	−0.046	−0.067 to −0.024	<0.001
Perceptual motor	0.17	0.046 to 0.29	0.007	−0.051	−0.082 to −0.020	0.001
Executive function	0.051	−0.027 to 0.13	0.20	−0.013	−0.032 to 0.006	0.18

All models were adjusted for sex, age, age^2, age×TIS-2, education, ethno-racial group, stroke subtype, severity of stroke, hypertension, diabetes, atrial fibrillation, prior stroke, and smoking (ever). Effect size describes the change in cognitive function (*z*-scores) per year. TIS indicates time in study.

*These estimates are constrained by the node at 1 y; for the nonconstrained estimates, refer to Table 4.

†One study was excluded in a sensitivity analysis since it appeared to be an outlier (see Figure II in the Supplemental Material).

Table 4. Rate of Cognitive Decline Beginning 1 Year After Stroke

Cognitive function*	Effect size (TIS)†	95% CI	*P* value	I^2‡
Global cognition (8; 1004)	−0.053	−0.073 to −0.033	<0.001	61%
Attention and processing speed (8; 940)	−0.035	−0.057 to −0.013	0.002	0%
Memory (6; 816)	−0.065	−0.088 to −0.042	<0.001	25%
Language (8; 1001)	−0.039	−0.061 to −0.017	0.001	49%
Perceptual motor (6; 773)	−0.039	−0.068 to −0.011	0.007	0%
Executive function (7; 928)	−0.006	−0.042 to 0.039	0.74	60%

All models were adjusted for sex, age, age^2, age×TIS, education, ethno-racial group, stroke subtype, severity of stroke, hypertension, diabetes, atrial fibrillation, prior stroke, and smoking (ever). Analyses were restricted to TIS ≥1 y. IPD indicates individual participant data; and TIS, time in study.

*The numbers in the brackets show the number of studies and the number of patients included in each analysis.

†Effect size describes the change in cognitive function (*z*-scores) per year.

‡I^2 are from the 2-step IPD meta-analysis.

not have a recurrent stroke (−0.033 SD/year; difference in rate [95% CI, −0.15 to −0.054]; $P \leq 0.001$; Figure IVA in the Supplemental Material). Interaction of recurrent stroke status with TIS^2 was not significant, indicating no evidence of a quadratic trend for those with recurrent stroke. There was no significant difference between those who had an incident TIA and those who did not ($P=0.94$); however, only 28 patients had an incident TIA without stroke. The interactions of vascular risk factors and TIS were not significant. There was no evidence that

Table 5. Subgroup Differences and Potential Risk Factors for Decline in Global Cognition Beginning 1 Year After Stroke

	Effect size (factor×TIS)	95% CI	*P* value
Patient characteristics			
Male sex	−0.003	−0.038 to 0.045	0.88
Education, y	−0.002	−0.007 to 0.002	0.33
Age (at stroke onset; y)	−0.003	−0.005 to −0.001	0.001
Ethno-racial group			Overall 0.25
Singaporean Chinese vs White	0.057	−0.17 to 0.28	0.62
Korean vs White	0.048	−0.20 to 0.29	0.71
Black vs White	−0.030	−0.10 to 0.036	0.37
Risk factors at baseline (medical history)			
Diabetes	−0.018	−0.060 to 0.024	0.40
Hypertension	−0.029	−0.072 to 0.013	0.17
History of previous stroke	−0.027	−0.077 to 0.023	0.29
Smoking (ever)	0.001	−0.038 to 0.040	0.95
Atrial fibrillation	−0.004	−0.056 to 0.057	0.91
ApoE4 (at least 1 apoE4 allele; 2 studies; n=83)	−0.089	−0.22 to 0.044	0.19
Index event			
Severity of stroke (moderate or severe versus mild)	0.016	−0.063 to 0.032	0.51
Stroke subtype			Overall 0.087
Small vessel versus large artery	−0.042	−0.094 to 0.009	0.11
Cardioembolic versus large artery	0.017	−0.044 to 0.079	0.58
Other (ischemic) versus large artery	−0.11	−0.29 to 0.067	0.23
Events during follow-up			
Recurrent stroke (at any time during follow-up)	−0.10	−0.15 to −0.054	<0.001
Incident TIA (at any time during follow-up, without having a recurrent stroke)	−0.004	−0.12 to 0.11	0.94
Incident depression (at any time during follow-up)	−0.009	−0.049 to 0.031	0.66

Effect size is the interaction of a variable of interest and TIS, which describes the difference in rate of change in global cognition (*z*-scores). All models were adjusted for sex, age, age^2, TIS, age×TIS, education, ethno-racial group, stroke subtype, severity of stroke, hypertension, diabetes, atrial fibrillation, prior stroke, smoking (ever). Analyses were restricted to TIS ≥1 y. TIA indicates transient ischemic attack; and TIS, time in study.

having depressive symptoms during follow-up modified the course of cognitive function (*P*=0.66).

Comparison of Patients With Stroke With Controls

The baseline characteristics of each control group and its corresponding patient group are presented in Table XVI in the Supplemental Material. The mean age of the controls was 69.1 years, 45% were male, and 58% did not complete high school. Mixed models demonstrated that the rate of cognitive decline in patients with stroke was significantly faster than in controls in global cognition and all domains after covariate adjustment (Table 6; Figure IVB in the Supplemental Material). The size of the difference was −0.078 SD/year ([95% CI, −0.11 to −0.045]; *P*<0.001) for global cognition, and for the 5 cognitive domains it ranged from −0.028 to −0.067 SD/year. The result for perceptual motor function was borderline significant (*P*=0.047). We also confirmed in this subgroup of studies that patients with stroke who had a recurrent stroke had a faster decline (−0.13 SD/year) compared with those who did not have a recurrent stroke (−0.039 SD/year; difference in rate: −0.15 to −0.034; *P*=0.002 for global cognition).

Two-Step IPD Meta-Analysis

For global cognition and all cognitive domains other than perceptual motor function, the results from the 2-step IPD meta-analysis matched those of the 1-step; for perceptual motor function, the 2-step IPD meta-analysis did not produce a significant finding (Table XVII and Figure V in the Supplemental Material). I^2 was 31% for global cognition, 69% for 1 cognitive domain, and 0% for the other 4. While these meta-analyses included only 3 or 4 studies, the forest plots showed that patients with stroke generally declined faster than controls across all studies.

Estimated Rate of Decline in Controls

Decline among controls was estimated to be near 0 for global cognition and the attention and processing speed, language, and perceptual motor domains (Table XVIII in the Supplemental Material), and small but not significant in memory (−0.010 SD/year [95% CI, −0.027 to 0.006]; *P*=0.22). For the executive function domain, controls demonstrated a small but significant improvement over time (0.019 SD/year [95% CI, 0.009–0.029]; *P*<0.001).

DISCUSSION

In this international collaboration that included 9 stroke cohorts from 7 countries, we found that patients exhibited significant improvement in cognitive function from baseline to 1 year after stroke followed by a significant decline in global cognition and all cognitive domains except executive function from 1 to 3 years after stroke, after adjusting for demographic variables, stroke characteristics, and vascular risk factors. The initial period of improvement was likely to have been the result of a combination of genuine recovery as well as practice effects, but we did not perform additional analyses due to the short timeframe and lack of multiple data points.

It is likely that the cause of long-term cognitive decline after stroke is multifactorial. First, we recognized that clinically evident recurrent stroke is an important risk factor, but it is possible that a subset of patients also experienced a clinically "silent" progression of cerebrovascular disease, or the initial burden of cerebrovascular disease may be a factor, given the known association of significant cerebrovascular disease markers with incident stroke and dementia.[25] Second, certain comorbid medical conditions that we were unable to explore may have played a role, such as those that might be associated with cerebral hypoxia or ischemia.[26] Third, it is likely that Alzheimer's disease contributed to cognitive decline in some of our patients with stroke, as suggested by the greater rate of decline

Table 6. Comparison of Cognitive Decline in Patients With Stroke Versus Controls

Cognitive function*	Effect size† (stroke status×TIS)	95% CI	*P* value	I^2‡
Global cognition (3)	−0.078	−0.11 to −0.045	<0.001	31%
Attention and processing speed (4)§	−0.061	−0.081 to −0.041	<0.001	69%
Memory (3)	−0.053	−0.081 to −0.025	<0.001	0%
Language (4)§	−0.062	−0.082 to −0.041	<0.001	0%
Perceptual motor (3)	−0.028	−0.055 to −0.0003	0.047	0%
Executive function (3)	−0.039	−0.059 to −0.020	<0.001	0%

All models are adjusted for sex, age, age^2, age×TIS, education, ethno-racial group, hypertension, diabetes, and atrial fibrillation. Smoking was not included because it was not available in one external control group. Analyses were restricted to TIS ≥1 for patients with stroke. IPD indicates individual participant data; and TIS, time in study.

*The number in the brackets shows the number of stroke studies included in each model.

†Effect size is the interaction between stroke status and TIS; it denotes the difference in rate of change in cognitive function (*z*-scores) between stroke patients and controls.

‡I^2 are from the 2-step IPD meta-analysis.

§Atrial fibrillation was not included because it was not available in one external control group.

in memory, but the contribution of cortical Lewy bodies and other pathologies must also be considered as a possibility. We had very limited data on ApoE and were not able to explore the potential contribution of this genotype, which has generally been associated with Alzheimer's disease. We compared the course of our stroke sample to that of our control sample in part to account for the effects of such conditions, but it should be noted that any tendency of our control sample to have been healthier or higher functioning than the general population would have contributed to an increased divergence of the trajectory of cognitive decline of those 2 groups.

In global cognition, the rate of decline was on average 0.053 SD per year, which translates to an estimated 0.10 SD decline in global cognition between 1 and 3 years after stroke. Projecting a linear trend, the estimated decline would be 0.53 SD over a decade, with a decline of ≥0.5 SD considered to be clinically meaningful.[4,27] In addition, compared with an estimated 0.006 SD decline in our stroke-free controls over 2 years, and given that the stroke cohort started off with poorer cognitive function at baseline (an average of −1.00 SD), the faster rate of cognitive decline in these initially more cognitively impaired patients is striking and should be considered clinically relevant.

In addition to global cognition, we found that patients with stroke experienced faster cognitive decline compared with stroke-free controls in all domains, although the result for perceptual motor function should be interpreted with caution due to the borderline significant result from the 1-step analysis and the nonsignificant result from the 2-step approach. We also found that the magnitude of decline in patients with stroke was dependent on their age at stroke onset, although the effect was small.

A recent systematic review that included 14 studies found results similar to our own about the course of cognitive function after stroke, with hospital-based cohorts with shorter follow-up (3 weeks to 13 months) demonstrating cognitive improvement and population-based studies with longer follow-up (3–6 years) demonstrating cognitive decline.[3] Our results add to the evidence that patients with stroke from hospital-based cohorts also demonstrate cognitive decline beginning 1 year after stroke. The population-based studies, such as 2 large American studies and a recent English study with 6 to 12 years of follow-up, compared pre- and poststroke memory function[5] and performance in global cognition and several cognitive domains.[4,6] Our primary results about a decline in global cognition agree with those of these studies. Most of those studies did not report standardized scores, however, which makes it difficult for results to be directly compared.

We found that those who had a recurrent stroke during follow-up had a 4-fold increase in their rate of decline compared with those who did not have a recurrent stroke. While previous large population-based studies did not consider recurrent strokes, our result is consistent with that of a previous community-based study.[28] We have estimated an overall linear trend although it is likely that there was a step change with cognition deteriorating more rapidly shortly after a stroke event. However, we are limited by the data on the timing and characteristics of recurrent stroke to examine further. In contrast, we did not find any differences in the rate of decline between those who had an incident TIA and those who did not. While we might be underpowered to detect a significant difference due to the small number of TIAs that occurred during follow-up, our results suggest that a recurrent stroke has a far greater impact on cognitive function than a TIA. Furthermore, the cognitive decline of patients without a recurrent stroke did not reach clinically meaningful change even at 10 years if a linear trend was assumed (−0.03 SD/10 years); this suggests that secondary stroke prevention is critical to reduce the risk of stroke-related cognitive decline and dementia.

We found that vascular risk factors as well as stroke subtype and the severity of stroke did not increase the risk of cognitive decline 1 year after stroke. However, in the present study and in our previous work, we found that diabetes, hypertension, atrial fibrillation, stroke subtype, and the severity of stroke were associated with poorer cognitive function at baseline.[11] Therefore, the impact of these risk factors on cognitive function might actually be the greatest at or before stroke onset. A population-based study that compared pre- and poststroke cognitive function similarly reported that changes in global cognition were not influenced by hypertension, diabetes, or smoking status at baseline.[29]

We did not find evidence of decline in executive function, and patients with stroke were comparably impaired in that domain relative to other domains at baseline. It is possible that we failed to recognize a decline in executive function for methodologic reasons. Our results showed some heterogeneity between studies for this domain, suggesting potential differences in the way the tests were administered or in the sensitivity of the different tests included in that domain. In addition, improvement in executive function was demonstrated by controls, which may point to practice effects and suggest that stability of scores among patients with stroke may actually represent a poorer long-term course.

Our results comparing patients and controls showed low to medium heterogeneity; however, the number of studies that provided suitable control groups was small. We sought several external longitudinal population-based studies to serve as control groups for the Stroke and Cognition Consortium studies from the same regions, but most were deemed inappropriate because baseline characteristics did not match or there were few overlaps in terms of neuropsychological tests. In addition, participants from general population-based studies, such as those who were recruited from their primary physicians,

tended to have more health problems, and they may have been more cognitively impaired than a more representative sample. This has implications for the design of future studies, which will not only need to address sample size and length of follow-up but also the recruitment of an appropriate control group that will need to be followed for the same length of time as the patient group.

Two studies had high proportions of loss to follow-up and their samples might have been biased toward patients with poorer cognitive function. We excluded these studies in a sensitivity analysis that showed that our results remained robust. In addition, in our overall sample, while patients who did not undergo a follow-up evaluation had significantly poorer cognitive function at baseline compared with those who underwent multiple assessments, demographic variables other than ethno-racial group, vascular risk factors, and the proportions of patients with dementia and moderate/severe strokes at baseline were similar by follow-up status, suggesting that our findings were unlikely to have been influenced by differential attrition.

The strengths of our study include the use of detailed neuropsychological test batteries administered by psychologists or trained research assistants for the assessment of cognitive function in 5 domains; the examination of cognitive function on a continuum based on standardized scores; the diversity of our stroke cohort, which was drawn from different ethno-racial groups and countries; and our ability to adjust for a number of potential contributing and confounding factors, including stroke characteristics, vascular risk factors, and demographic variables.

The limitations of our work include the small number of studies with comparable control samples, the relatively short follow-up period in some studies that limited our estimation of the course of cognitive function to 3 years, selective attrition due to individuals with poorer baseline cognitive function dropping out of the study, and data harmonization methods (eg, applying cut-offs), which generally resulted in loss of information and increased heterogeneity. The exclusion of studies which did not conduct extensive neuropsychological tests may also bias our sample toward patients with less severe strokes and better cognitive function. Despite these limitations, our study provides a comprehensive profile of the course of cognitive function in a diverse hospital-based patient group after stroke. It has implications for the design of clinical trials of therapies to prevent or slow poststroke cognitive decline, which should take into consideration the trajectory of initial improvement and subsequent decline in cognition after stroke. Our results could also help clinicians better understand and plan for the long-term needs of patients with stroke.

ARTICLE INFORMATION

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Supplemental Materials

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