SUPPLEMENTAL MATERIAL

Effect of Cognitive Reserve on Risk of Cognitive Impairment and Recovery After Stroke: The KOSCO Study

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Methods

Statistical Analysis

A multi-level model is appropriate for nested data in which observations are organized at more than one level.[1] Observations in our data, i.e., the K-MMSE scores, are nested within individuals. Because the clinical features of cognitive impairment in stroke patients are characterized by a rapid improvement at the initial stage and subsequent stable maintenance,[2] an exponential function, $\text{K–MMSE} = \beta_0 + \beta_1 \times e^{-Time} + \varepsilon$, in which *Time* is months after stroke onset, was applied first to see the natural course of recovery. We then reanalyzed the data using a linear regression function with two different slopes (piecewise regression) during the initial active stage and later stable stage to clarify the clinical meanings of the coefficients because the coefficients of the exponential function are difficult to interpret directly. This procedure was expected to improve our understanding of the course of cognitive recovery in stroke patients. In the piecewise regression model, we set the breakpoint to 3 months based on the graph derived from the exponential model. The piecewise regression function was as follows: $\text{K–MMSE} = \beta_0 + \beta_1 \times Time_1 + \beta_2 \times Time_2 + \varepsilon$, in which $Time_1$was coded as 0, 1, 3, 3, 3, 3, 3, 3, and $Time_2$ was coded as 0, 0, 0, 3, 9, 15, 21, 27. Education and occupation were coded as dummy variables, and the composite CR score was used as a continuous variable.

Table I. Number of cases followed up at each time point by educational and occupational group

	Education					Occupation				
	No formal education	Primary education	Secondary education	Higher education	Total	No occupation	Non-skilled manual	Skilled manual	Manager or professional	Total
Total N†	671 (100)	1,841 (100)	3,379 (100)	1,465 (100)	7,356 (100)	1,862 (100)	228 (100)	2,031 (100)	548 (100)	4,669 (100)
7 days	632 (94)	1,741 (95)	3,226 (95)	1,415 (97)	7,014 (95)	1,758 (94)	215 (94)	1,946 (96)	525 (96)	4,444 (95)
Discharge	648 (97)	1,769 (96)	3,272 (97)	1,431 (98)	7,120 (97)	1,790 (96)	223 (98)	1,975 (97)	537 (98)	4,525 (97)
3 months	453 (68)	1,299 (71)	2,500 (74)	1,102 (75)	5,354 (73)	1,640 (88)	209 (92)	1,849 (91)	498 (91)	4,196 (90)
6 months	399 (59)	1,212 (66)	2,360 (70)	1,043 (71)	5,014 (68)	1,568 (84)	201 (88)	1,801 (89)	472 (86)	4,042 (87)
12 months	368 (55)	1,155 (63)	2,237 (66)	1,018 (69)	4,778 (65)	1,400 (75)	189 (83)	1,668 (82)	438 (80)	3,695 (79)
18 months	373 (56)	1,098 (60)	2,164 (64)	1,007 (69)	4,642 (63)	1,344 (72)	182 (80)	1,617 (80)	432 (79)	3,575 (77)
24 months	360 (54)	1,062 (58)	2,166 (64)	997 (68)	4,585 (62)	1,339 (72)	177 (78)	1,591 (78)	432 (79)	3,539 (76)
30 months	342 (51)	1,056 (57)	2,108 (62)	972 (66)	4,478 (61)	1,280 (69)	177 (78)	1,570 (77)	416 (76)	3,443 (74)

Data are shown as n (%). † Number of participants who consented to long-term follow-up and had educational or occupational information.

Table II. Cerebrovascular risk factors of the patients included in the analysis

Variables	Educational groups					Occupational groups				
	No information	No formal education	Primary education	Secondary education	Higher education	No information	No occupation	Non-skilled manual	Skilled manual	Manager or professional
Cross-sectional analysis: Patients with at least one K-MMSE score available at any time point (N=7,459)										
n	103 (100)	671 (100)	1,841 (100)	3,379 (100)	1,445 (100)	2,790 (100)	1,862 (100)	228 (100)	2,031 (100)	548 (100)
Risk factors										
Hypertension	57 (55)	445 (66)	1,124 (61)	1,799 (53)	720 (49)	1601 (57)	1,157 (62)	119 (52)	992 (49)	276 (50)
Diabetes mellitus	21 (20)	168 (25)	455 (25)	764 (23)	310 (21)	651 (23)	477 (26)	48 (21)	431 (21)	111 (20)
Coronary heart disease	5 (5)	50 (8)	114 (6)	224 (7)	106 (7)	189 (7)	157 (8)	18 (8)	102 (5)	33 (6)
Atrial fibrillation	3 (3)	79 (12)	226 (12)	303 (9)	117 (8)	322 (12)	204 (11)	13 (6)	138 (7)	51 (9)
Left ventricular hypertrophy	1 (1)	12 (2)	19 (1)	28 (1)	14 (1)	28 (1)	18 (1)	1 (0)	21 (1)	6 (1)
Peripheral artery disease	1 (1)	7 (1)	14 (1)	26 (1)	2 (0)	21 (1)	16 (1)	1 (0)	9 (0)	3 (1)
Hyperlipidemia	18 (18)	86 (13)	230 (13)	477 (14)	228 (16)	365 (13)	287 (15)	22 (10)	282 (14)	83 (15)
Low cholesterol	1 (1)	14 (2)	91 (5)	102 (3)	33 (2)	102 (4)	78 (4)	6 (3)	47 (2)	8 (2)
Unruptured intracranial aneurysm	2 (2)	10 (2)	23 (1)	45 (1)	17 (1)	31 (1)	23 (1)	2 (1)	32 (2)	9 (2)
Arteriovenous malformation	0 (0)	3 (0)	6 (0)	13 (0)	5 (0)	10 (0)	9 (0)	0 (0)	6 (0)	2 (0)
Moyamoya disease	0 (0)	1 (0)	5 (0)	25 (1)	12 (1)	11 (0)	6 (0)	0 (0)	23 (1)	3 (1)
Obesity	13 (13)	72 (11)	183 (10)	410 (12)	207 (14)	293 (11)	215 (12)	31 (14)	252 (12)	94 (17)
Smoking	33 (32)	115 (17)	508 (28)	1,549 (46)	656 (45)	1,017 (37)	503 (27)	99 (43)	1,012 (50)	230 (42)
Alcohol consumption	37 (36)	121 (18)	476 (26)	1,490 (44)	760 (52)	965 (35)	501 (27)	115 (50)	1,042 (51)	261 (48)
Longitudinal analysis: Patients classified as having cognitive impairment at baseline assessment (N=3,109)										
n	0 (100)	251 (100)	1,015 (100)	1,453 (100)	390 (100)	1,410 (100)	758 (100)	95 (100)	702 (100)	144 (100)
Risk factors										
Hypertension	NA	159 (63)	613 (60)	777 (54)	204 (52)	827 (59)	458 (60)	50 (53)	342 (49)	76 (53)
Diabetes mellitus	NA	62 (25)	246 (24)	307 (21)	80 (20)	323 (23)	186 (25)	14 (15)	143 (20)	29 (20)
Coronary heart disease	NA	20 (8)	57 (6)	94 (7)	30 (8)	100 (7)	57 (8)	7 (7)	32 (5)	5 (4)
Atrial fibrillation	NA	34 (14)	131 (13)	150 (10)	35 (9)	192 (14)	92 (12)	5 (5)	51 (7)	8 (6)
Left ventricular hypertrophy	NA	8 (3)	10 (1)	12 (1)	3 (1)	16 (1)	10 (1)	1 (1)	6 (1)	0 (0)
Peripheral artery disease	NA	3 (1)	8 (1)	12 (1)	1 (0)	11 (1)	8 (1)	1 (1)	4 (1)	0 (0)
Hyperlipidemia	NA	32 (13)	107 (11)	169 (12)	47 (12)	170 (12)	86 (11)	5 (5)	76 (11)	18 (13)
Low cholesterol	NA	6 (2)	52 (5)	39 (3)	6 (2)	53 (4)	29 (4)	2 (2)	18 (3)	1 (1)
Unruptured intracranial aneurysm	NA	4 (2)	12 (1)	24 (2)	8 (2)	17 (1)	13 (2)	1 (1)	12 (2)	5 (4)
Arteriovenous malformation	NA	1 (0)	3 (0)	8 (1)	2 (1)	5 (0)	5 (1)	0 (0)	4 (1)	0 (0)
Moyamoya disease	NA	1 (0)	3 (0)	14 (1)	3 (1)	8 (0)	3 (0)	0 (0)	9 (1)	1 (1)
Obesity	NA	26 (10)	86 (9)	145 (10)	46 (12)	128 (9)	71 (9)	12 (13)	69 (10)	23 (16)
Smoking	NA	36 (14)	261 (27)	607 (42)	160 (41)	444 (32)	188 (25)	40 (42)	336 (48)	56 (39)
Alcohol consumption	NA	40 (16)	246 (24)	557 (38)	181 (46)	411 (29)	187 (25)	49 (52)	315 (45)	62 (43)

Data are shown as n (%) or the mean (SD). K-MMSE: Korean version of the Mini-Mental Status Examination; NIHSS: National Institute of Health Stroke Scale; NA: not available.

Table III. Score on the Korean version of the Mini-Mental Status Examination by the four education groups and four occupation groups at eight time points

	Educational groups								Occupational groups							
Timepoints	N	No formal education[a]	Primary education[b]	Secondary education[c]	Higher education[d]	F	Partial η^2	Post hoc analysis† (P<0.05)	N	No occupation[a]	Non-skilled manual[b]	Skilled manual[c]	Manager or professional[d]	F	Partial η^2	Post hoc analysis† (P<0.05)
7 days	7,014	15.3 (8.6)	18.3 (9.2)	22.3 (8.4)	25.0 (7.5)	76.7***	0.03	a<b<c<d	4,444	21.9 (7.5)	23.5 (6.7)	23.8 (7.0)	25.6 (6.3)	7.4***	0.01	a=c<d, a=b=c, b=d
Discharge	7,120	16.1 (8.5)	19.1 (9.0)	23.6 (7.6)	26.2 (6.2)	108.8***	0.04	a<b<c<d	4,525	22.9 (6.8)	25.0 (5.5)	25.1 (5.7)	26.8 (4.8)	8.2***	0.01	a=c<d, a=b=c, b=d
3 months	5,354	17.9 (8.9)	21.4 (7.4)	25.4 (6.1)	27.7 (4.9)	104.8***	0.06	a<b<c<d	4,196	24.1 (5.6)	26.5 (3.7)	26.5 (4.1)	28.1 (3.2)	14.7***	0.01	a<c<d, a=b, b=c, b=d
6 months	5,014	18.8 (7.8)	21.9 (7.3)	25.9 (5.9)	28.0 (4.6)	92.8***	0.05	a<b<c<d	4,042	24.5 (5.7)	26.7 (4.5)	27.0 (3.8)	28.5 (2.8)	12.9***	0.01	a<c<d, a=b, b=c, b=d
12 months	4,778	18.7 (8.1)	22.1 (7.3)	26.3 (5.5)	28.1 (4.7)	106.3***	0.06	a<b<c<d	3,695	24.8 (5.6)	26.6 (4.1)	27.1 (3.8)	28.6 (2.8)	9.3***	0.01	a<d, a=b=c, b=d, c<d
18 months	4,642	18.2 (8.6)	22.1 (7.4)	26.5 (5.4)	28.2 (4.7)	122.9***	0.07	a<b<c<d	3,575	24.8 (5.7)	27.0 (3.8)	27.2 (4.0)	28.8 (2.4)	13.6***	0.01	a<c<d, a=b, b=c, b=d
24 months	4,585	18.8 (8.0)	22.0 (7.7)	26.5 (5.4)	28.1 (4.6)	111.6***	0.07	a<b<c<d	3,539	25.1 (5.6)	27.1 (3.9)	27.1 (4.2)	28.7 (2.8)	9.3***	0.01	a<d, a=b=c, b=d, c<d
30 months	4,478	18.1(8.4)	22.2 (7.6)	26.3 (5.6)	28.2 (4.6)	112.0***	0.07	a<b<c<d	3,443	24.9 (5.9)	27.0 (4.0)	27.0 (4.3)	29.0 (2.7)	10.8***	0.01	a<d, a=b=c, b=d, c<d

Data are the mean (SD). †Multiple comparisons were adjusted with the Bonferroni correction. *P<0.05, **P<0.01, *** P<0.001.

Table IV. Frequency of cognitive impairment in each education and occupation group at eight time points

	Educational groups						Occupational groups					
Time points after onset	N	No formal education	Primary education	Secondary education	Higher education	Total	N	No occupation	Non-skilled manual	Skilled manual	Manager or professional	Total
MMSE<16th percentile												
7 days	7,014	41.3%	59.2%	46.0%	28.2.%	45.3%	4,444	43.1%	44.2%	36.1%	27.4%	38.3%
Discharge	7,120	36.1%	55.6%	39.1%	21.2%	39.4%	4,525	38.2%	33.6%	29.5%	19.7%	32.0%
3 months	5,354	29.6%	47.8%	28.2%	11.7%	29.7%	4,196	31.3%	21.1%	19.8%	11.0%	23.4%
6 months	5,014	27.3%	45.4%	24.2%	8.4%	26.3%	4,042	27.7%	18.9%	16.9%	8.1%	20.2%
12 months	4,778	27.2%	42.5%	21.0%	8.0%	23.9%	3,695	25.9%	22.8%	14.7%	6.4%	18.3%
18 months	4,642	32.7%	41.4%	20.5%	7.4%	23.6%	3,575	26.1%	17.6%	14.4%	3.9%	17.7%
24 months	4,585	25.3%	41.9%	19.9%	7.9%	22.8%	3,539	24.4%	16.4%	14.1%	4.9%	17.0%
30 months	4,478	28.1%	40.8%	21.3%	7.2%	23.3%	3,443	25.3%	17.5%	15.2%	4.6%	17.8%
MMSE<2nd percentile												
7 days	7,014	27.1%	41.7%	30.0%	17.0%	30.0%	4,444	26.5%	22.3%	21.6%	14.7%	22.7%
Discharge	7,120	24.7%	37.5%	24.3%	11.8%	25.1%	4,525	21.8%	18.8%	15.3%	9.1%	17.3%
3 months	5,354	19.2%	27.6%	15.3%	5.8%	16.7%	4,196	15.8%	8.6%	7.4%	5.2%	10.5%
6 months	,5014	17.0%	25.2%	13.4%	5.4%	14.9%	4,042	14.5%	9.0%	5.8%	3.4%	9.0%
12 months	4,778	18.8%	22.1%	11.3%	4.8%	13.1%	3,695	12.2%	7.4%	5.3%	3.9%	7.8%
18 months	4,642	20.9%	23.9%	10.5%	4.5%	13.2%	3,575	12.8%	7.1%	4.7%	2.3%	7.6%
24 months	4,585	17.2%	24.3%	10.5%	5.3%	13.1%	3,539	12.8%	9.0%	5.7%	2.3%	8.1%
30 months	4,478	20.2%	24.1%	10.7%	5.1%	13.4%	3,443	12.7%	7.3%	6.2%	2.2%	8.2%

K-MMSE: Korean version of the Mini-Mental State Examination.

Table V. Results of logistic regression analyses predicting cognitive impairment (K-MMSE <16th percentile) after stroke at eight time points, controlling for background variables

Groups	Odds ratio (95% CI)				
	Discharge	6 months	12 months	18 months	24 months
Model 1: Education					
No formal education	1.00 (0.81–1.30)	1.67 (1.19–2.35)**	1.67 (1.17–2.37)**	2.30 (1.62–3.27)***	1.58 (1.10–2.26)*
Primary education	2.81 (2.35–3.35)***	4.83 (3.71–6.30)***	4.28 (3.26–5.63)***	4.23 (3.18–5.63)***	4.34 (3.28–5.74)***
Secondary education	2.04 (1.72–2.33)***	2.84 (2.22–3.63)***	2.47 (1.92–3.19)***	2.56 (1.97–3.35)***	2.36 (1.82–3.07)***
Higher education	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Model 2: Occupation					
No occupation	1.76 (1.36–2.27)***	2.14 (1.47–3.10)***	2.35 (1.53–3.59)***	4.20 (2.50–7.06)***	3.07 (1.90–4.95)***
Non-skilled manual	1.85 (1.29–2.65)***	2.16 (1.32–3.53)**	3.51 (2.09–5.92)***	4.41 (2.36–8.26)***	3.24 (1.77–5.92)***
Skilled manual	1.59 (1.25–2.02)**	1.97 (1.37–2.82)***	2.11 (1.40–3.19)***	3.55 (2.13–5.93)***	2.84 (1.77–4.54)***
Manager/professional	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Model 3: Composite CR score					
Composite CR score	0.73 (0.67–0.80)***	0.59 (0.52–0.68)***	0.56 (0.48–0.65)***	0.52 (0.45–0.61)***	0.56 (0.48–0.65)***

Controls are age, sex, initial National Institute of Health Stroke Scale score, stroke subtype, and the stroke risk factors listed in Supplementary Table I. Education and occupation were coded as dummy variables. Higher education and managerial or professional occupation were the reference groups in each model. CI: confidence interval; K-MMSE: Korean version of the Mini-Mental State Examination. *P<0.05, **P<0.01, ***P<0.001.

Table VI. Results of multi-level model analyses predicting cognitive changes during 30 months after stroke onset (exponential function)

	Unadjusted models			Adjusted models		
Variables	Coefficient	Standard error	t-ratio	Coefficient	Standard error	t-ratio
Model 1 (N=3,109)						
Intercept 1						
Intercept 2	20.11	0.16	128.65***			
Slope						
Intercept 2	-6.18	0.04	−45.12***			
Model 2 (N=3,109)						
Intercept 1						
Intercept 2	10.68	0.50	21.52***	13.46	0.49	27.60***
Primary education	6.68	0.56	11.94 ***	5.35	0.52	10.21***
Secondary education	11.90	0.53	22.30 ***	8.14	0.55	14.89***
Higher education	13.52	0.64	21.15 ***	8.72	0.66	13.16***
Slope						
Intercept 2	−3.80	0.44	−8.73***	−5.33	0.46	−11.62***
Primary education	−0.91	0.49	−1.88	−0.33	0.48	−0.68
Secondary education	−3.26	0.48	−6.79***	−1.14	0.51	−2.24*
Higher education	−4.50	0.60	−7.57***	−1.65	0.64	−2.57**
Model 3 (N=1,699)						
Intercept 1						
Intercept 2	21.62	0.22	97.44***	22.89	0.20	111.76***
Non-skilled manual	3.88	0.48	8.06***	1.77	0.46	3.87***
Skilled manual	3.30	0.28	11.82***	1.12	0.27	4.13***
Manager or professional	5.33	0.38	13.88***	2.37	0.41	5.76***
Slope						
Intercept 2	−6.14	0.24	−25.18***	−6.91	0.25	−27.17***
Non-skilled manual	−0.92	0.79	−1.17	0.42	0.80	0.53
Skilled manual	−2.10	0.37	−5.66***	−0.79	0.38	−2.10*
Manager or professional	−2.97	0.67	−4.45***	−1.10	0.67	−1.64
Model 4 (N=1,699)						
Intercept 1						
Intercept 2	23.66	0.12	189.87***	23.65	0.11	214.38***
Composite CR score	2.37	0.13	18.87***	1.23	0.12	9.92***
Slope						
Intercept 2	−7.32	0.17	−42.52***	−7.32	0.16	−44.96***
Composite CR score	−1.27	0.20	−6.30***	−0.49	0.21	−2.30*

Adjusted models were adjusted for background variables: age, sex, initial National Institute of Health Stroke Scale score, stroke subtype, and the stroke risk factors listed in Supplementary Table I. All background variables were centered on the mean. Education and occupation were coded as dummy variables. No education and no occupation were the reference groups in models 2 and 3, respectively. *P<0.05, **P<0.01, ***P<0.001.

Table VII. Results of multi-level model analyses predicting cognitive changes during 30 months after stroke onset (piecewise regression function, unadjusted model)

Variables	Coefficient	Standard error	t-ratio
Model 1 (N=3,109)			
Intercept 1			
Intercept 2	14.53	0.16	92.90***
Slope 1			
Intercept 2	1.93	0.04	44.37***
Slope 2			
Intercept 2	0.02	0.00	3.97***
Model 2 (N=3,109)			
Intercept 1			
Intercept 2	7.18	0.38	19.00***
Primary education	5.84	0.46	12.70***
Secondary education	9.07	0.44	20.66***
Higher education	9.63	0.58	16.71***
Slope 1			
Intercept 2	1.41	0.16	9.02***
Primary education	0.16	0.17	0.96
Secondary education	0.71	0.17	4.21***
Higher education	1.08	0.20	5.46***
Slope 2			
Intercept 2	−0.03	0.02	-1.59
Primary education	0.04	0.02	1.52
Secondary education	0.07	0.02	3.07**
Higher education	0.06	0.02	2.55*
Model 3 (N=1,699)			
Intercept 1			
Intercept 2	17.11	0.18	95.22***
Slope 1			
Intercept 2	2.16	0.05	40.63***
Slope 2			
Intercept 2	0.02	0.00	4.33***
Model 4 (N=1,699)			
Intercept 1			
Intercept 2	16.09	0.27	59.66***
Non-skilled manual	3.18	0.74	4.28***
Skilled manual	1.46	0.39	3.77***
Manager or professional	2.84	0.65	4.35***
Slope 1			
Intercept 2	1.83	0.07	24.48***
Non-skilled manual	0.17	0.25	0.68
Skilled manual	0.61	0.11	5.42***
Manager or professional	0.74	0.20	3.64***
Slope 2			
Intercept 2	0.02	0.01	2.22*
Non-skilled manual	0.01	0.02	0.88
Skilled manual	0.00	0.01	-0.12
Manager or professional	0.02	0.01	1.44
Model 5 (N=1,699)			
Intercept 1			
Intercept 2	17.11	0.18	96.34***
Composite CR score	1.30	0.20	6.58***
Slope 1			
Intercept 2	2.16	0.05	41.02***
Composite CR score	0.33	0.06	5.39***
Slope 2			
Intercept 2	0.02	0.00	4.31***
Composite CR score	0.01	0.00	1.29

Education and occupation were coded as dummy variables. No education and no occupation were the reference groups in each model. *P<0.05, **P<0.01, ***P<0.001.

Table VIII. Results of multi-level model analyses predicting cognitive changes during 30 months after stroke onset for young and old groups (piecewise regression function, adjusted model)

	Young adults group (age <65years)			Old adults group (age ≥65years)		
Variables	Coefficient	Standard error	t-ratio	Coefficient	Standard error	t-ratio
Model 1 (N=1,287/1,822)						
Intercept 1						
Intercept 2	17.23	0.24	72.38***	12.64	0.20	64.74***
Slope 1						
Intercept 2	2.34	0.07	35.27***	1.62	0.06	28.71***
Slope 2						
Intercept 2	0.05	0.01	9.48***	-0.01	0.01	-1.53
Model 2 (N=1,287/1,822)						
Intercept 1						
Intercept 2	11.82	1.75	6.75***	7.71	0.40	19.17***
Primary education	4.86	1.84	2.65**	4.26	0.47	9.02***
Secondary education	5.45	1.78	3.07**	7.04	0.54	13.11***
Higher education	6.10	1.85	3.29**	7.46	0.84	8.91***
Slope 1†						
Intercept 2	3.79	0.48	7.86***	2.26	0.16	14.17***
Primary education	0.48	0.49	0.98	0.45	0.17	2.67**
Secondary education	1.01	0.48	2.10*	0.70	0.18	3.82***
Higher education	1.14	0.50	2.31*	1.19	0.24	4.85***
Slope 2†						
Intercept 2	1.15	0.05	3.01**	-0.03	0.02	-1.49
Primary education	-0.02	0.05	-0.35	0.04	0.02	1.83
Secondary education	-0.00	0.05	-0.08	0.08	0.03	3.19***
Higher education	0.01	0.05	0.26	0.05	0.03	1.50
Model 3 (N=840/859)						
Intercept 1						
Intercept 2	18.80	0.25	75.35***	15.46	0.25	62.90***
Slope 1						
Intercept 2	2.39	0.08	31.86***	1.92	0.07	25.86***
Slope 2						
Intercept 2	0.04	0.01	7.60***	-0.00	0.07	-0.12
Model 4 (N=840/859)						
Intercept 1						
Intercept 2	18.33	0.49	37.66***	15.22	0.32	46.71***
Non-skilled manual	2.09	0.95	2.20*	1.37	1.26	1.09
Skilled manual	0.21	0.60	0.35	0.45	0.54	0.84
Manager or professional	1.58	0.82	1.93	0.87	1.41	0.62
Slope 1†						
Intercept 2	6.43	0.14	44.60***	4.52	0.15	30.68***
Non-skilled manual	0.23	0.17	1.32	0.15	0.27	0.55
Skilled manual	0.28	0.10	2.75**	0.38	0.12	3.12**
Manager or professional	0.50	0.15	3.47**	0.75	0.27	2.73**
Slope 2†						
Intercept 2	0.11	0.02	6.53***	0.03	0.02	1.63
Non-skilled manual	-0.00	0.02	-0.18	0.03	0.04	0.69
Skilled manual	-0.00	0.01	-0.26	-0.02	0.02	-1.19
Manager or professional	0.01	0.02	0.73	0.01	0.04	0.17
Model 5 (N=840/859)						
Intercept 1						
Intercept 2	18.76	0.24	76.98***	16.13	0.23	55.91***
Composite CR score	0.56	0.27	2.04*	1.54	0.39	3.95***
Slope 1†						
Intercept 2	6.66	0.13	52.18***	5.00	0.15	33.11***
Composite CR score	0.21	0.05	4.52***	0.49	0.08	6.01***
Slope 2†						
Intercept 2	0.11	0.02	7.32***	0.02	0.02	1.20
Composite CR score	0.01	0.01	1.52	-0.00	0.01	-0.32

Sample size is shown as (N=young/old). Models 2, 4, and 5 were adjusted for background variables: age, sex, initial National Institutes of Health Stroke Scale score, stroke subtype,

and the stroke risk factors listed in Supplementary Table I. All background variables were centered on the mean. Education and occupation were coded as dummy variables. No education and no occupation were the reference groups in model 2 and 4. †Slope 1 and slope 2 were adjusted for intercept 1, the initial score on the Korean version of the Mini-Mental State Examination. *P<0.05, **P<0.01, ***P<0.001.

Table IX. Results of logistic regression analyses predicting cognitive impairment after stroke at eight time points, controlling for background variables (young adults, < 65 years)

Groups	Odds ratio (95% CI)							
	7 days	Discharge	3 months	6 months	12 months	18 months	24 months	30 months
Model 1: Education								
No formal education	0.67 (0.36–1.24)	0.54 (0.27–1.10)	2.26 (1.11–4.63)*	1.53 (0.63–3.68)	1.37 (0.56–3.34)	1.73 (0.74–4.05)	1.48 (0.54–4.08)	1.66 (0.64–4.31)
Primary education	3.26 (2.47–4.30)***	3.79 (2.87–5.00)***	6.28 (4.37–9.01)***	7.68 (5.07–11.64)***	6.10 (3.99–9.33)***	5.33 (3.41–8.35)***	8.29 (5.19–13.24)***	6.82 (4.34–10.71)***
Secondary education	2.04 (1.70–2.45)***	2.09 (1.72–2.53)***	2.87 (2.16–3.81)***	3.43 (2.43–4.83)***	2.55 (1.79–3.63)***	2.74 (1.89–3.97)***	3.20 (2.14–4.78)***	2.92 (1.99–4.27)***
Higher education	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Model 2: Occupation								
No occupation	1.83 (1.35–2.49)***	2.05 (1.47–2.84)***	2.31 (1.53–3.50)***	2.41 (1.47–3.96)**	2.26 (1.31–3.90)**	4.62 (2.30–9.30)***	3.44 (1.74–6.82)***	4.03 (2.04–7.99)***
Non-skilled manual	1.66 (1.09–2.54)*	1.81 (1.17–2.81)**	1.91 (1.12–3.26)*	2.18 (1.17–4.06)*	3.02 (1.59–5.75)**	4.16 (1.83–9.45)**	3.68 (1.65–8.23)**	3.79 (1.71–8.41)**
Skilled manual	1.29 (0.99–1.67)	1.50 (1.13–2.00)**	1.78 (1.22–2.58)**	2.01 (1.27–3.17)**	1.70 (1.03–2.82)*	3.40 (1.74–6.62)***	2.84 (1.49–5.40)**	2.86 (1.50–5.45)**
Manager/professional	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Model 3: Composite CR score								
Composite CR score	0.74 (0.67–0.81)***	0.69 (0.62–0.77)***	0.57 (0.49–0.67)***	0.53 (0.44–0.64)***	0.55 (0.45–0.68)***	0.50 (0.39–0.63)***	0.42 (0.33–0.55)***	0.44 (0.34–0.57)***

Controls are age, sex, initial National Institute of Health Stroke Scale score, stroke subtype, and the stroke risk factors listed in Supplementary Table I. Education and occupation were coded as dummy variables. Higher education and managerial or professional occupation were the reference groups in each model. CI: confidence interval; K-MMSE: Korean version of the Mini-Mental State Examination. *P<0.05, **P<0.01, ***P<0.001.

Table X. Results of logistic regression analyses predicting cognitive impairment after stroke at eight time points, controlling for background variables (older adults, ≥65 years)

Groups	Odds ratio (95% CI)							
	7 days	Discharge	3 months	6 months	12 months	18 months	24 months	30 months
Model 1: Education								
No formal education	0.82 (0.61–1.10)	0.93 (0.69–1.25)	1.01 (0.69–1.48)	1.25 (0.81–1.91)	1.47 (0.94–2.29)	2.10 (1.34–3.27)**	1.16 (0.78–1.79)	1.84 (1.16–2.93)**
Primary education	2.05 (1.59–2.62)***	2.44 (1.89–3.16)***	2.82 (2.03–3.91)***	3.53 (2.45–5.10)***	3.56 (2.43–5.21)***	3.72 (2.51–5.52)***	2.98 (2.07–4.28)***	3.83 (2.57–5.74)***
Secondary education	1.74 (1.37–2.21)***	1.93 (1.51–2.48)***	2.07 (1.50–2.86)***	2.63 (1.58–3.25)***	2.33 (1.60–3.40)***	2.37 (1.61–3.51)***	1.84 (1.28–2.63)**	2.70 (1.81–4.01)***
Higher education	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Model 2: Occupation								
No occupation	1.78 (1.15–2.75)**	1.76 (1.12–2.75)*	2.34 (1.34–4.11)**	2.04 (1.12–3.72)*	3.22 (1.50–6.88)**	3.95 (1.77–8.81)**	2.84 (1.43–5.64)**	3.53 (1.65–7.57)**
Non-skilled manual	2.87 (1.54–5.36)**	1.83 (0.96–3.51)	1.84 (0.82–4.11)	2.02 (0.88–4.63)	4.04 (1.59–10.27)**	4.11 (1.53–11.07)**	2.43 (0.96–6.22)	3.20 (1.20–8.51)*
Skilled manual	2.01 (1.29–3.12)**	1.76 (1.12–2.78)*	1.98 (1.12–3.50)*	1.90 (1.04–3.48)*	3.12 (1.46–6.67)**	3.52 (1.57–7.89)**	2.76 (1.38–5.52)**	3.73 (1.73–8.00)**
Manager/professional	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Model 3: Composite CR score								
Composite CR score	0.84 (0.74–0.96)***	0.81 (0.71–0.93)**	0.72 (0.61–0.85)***	0.68 (0.56–0.81)***	0.57 (0.46–0.71)***	0.56 (0.45–0.70)***	0.69 (0.57–0.83)***	0.62 (0.50–0.76)***

Controls are age, sex, initial National Institute of Health Stroke Scale score, stroke subtype, and the stroke risk factors listed in Supplementary Table I. Education and occupation were coded as dummy variables. Higher education and managerial or professional occupation were the reference groups in each model. CI: confidence interval; K-MMSE: Korean version of the Mini-Mental State Examination. *P<0.05, **P<0.01, ***P<0.001.

Table XI. Frequency of cognitive impairment in each educational and occupational group at eight time points (cut-off=23/24)

	Educational groups						Occupational groups					
Time points after onset	N	No formal education	Primary education	Secondary education	Higher education	Total	N	No occupation	Non-skilled manual	Skilled manual	Manager or professional	Total
7 days	7,014	82.3%	62.1%	38.3%	21.6.%	44.8%	4,444	46.2%	33.0%	32.7%	19.8%	36.6%
Discharge	7,120	79.5%	58.2%	32.2%	15.7%	39.6%	4,525	41.2%	26.1%	26.5%	13.5%	30.8%
3 months	5,354	73.1%	50.9%	21.3%	8.9%	30.3%	4,196	36.0%	16.0%	17.5%	7.0%	23.4%
6 months	5,014	66.9%	47.6%	18.3%	7.0%	26.9%	4,042	32.4%	13.7%	14.4%	5.7%	20.4%
12 months	4,778	66.6%	47.2%	16.3%	6.3%	25.5%	3,695	31.3%	17.8%	14.1%	5.0%	19.8%
18 months	4,642	66.5%	44.6%	15.9%	5.9%	24.6%	3,575	30.2%	14.1%	13.5%	3.7%	18.7%
24 months	4,585	65.6%	45.6%	14.9%	6.8%	24.2%	3,539	28.7%	14.0%	14.1%	4.8%	18.5%
30 months	4,478	68.4%	42.5%	16.3%	6.4%	24.3%	3,443	28.8%	12.8%	14.4%	3.1%	18.3%

Table XII. Results of logistic regression analyses predicting cognitive impairment after stroke at eight time points, controlling for background variables (cutoff-23/24)

Groups	Odds ratio (95% CI)							
	7 days	Discharge	3 months	6 months	12 months	18 months	24 months	30 months
Model 1: Education								
No formal education	7.54 (5.78–9.82)***	8.45 (6.51–10.98)***	9.79 (7.10–13.48)***	8.70 (6.16–12.30)***	9.75(6.79–13.99)***	10.85 (7.50–15.68)***	9.07 (6.34–12.98)***	11.17 (7.69–16.21)***
Primary education	3.16 (2.63–3.80)***	3.66 (3.02–4.43)***	4.59 (3.55–5.92)***	4.96 (3.74–6.60)***	5.52 (4.09–7.45)***	5.25 (3.85–7.17)***	4.89 (3.63–6.58)***	4.53 (3.33–6.16)***
Secondary education	1.85 (1.58–2.16)***	2.05 (1.73–2.43)***	2.14 (1.69–2.73)***	2.24 (1.71–2.94)***	2.23 (1.67–2.99)***	2.32 (1.71–3.13)***	1.85 (1.38–2.46)***	2.18 (1.62–2.93)***
Higher education	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Model 2: Occupation								
No occupation	1.69 (1.30–2.20)***	2.92 (1.43–2.57)***	2.45 (1.66–3.59)***	2.28 (1.48–3.51)***	2.17 (1.35–3.50)**	3.52 (2.05–6.04)*	2.27 (1.40–3.69)***	3.61 (1.99–6.53)***
Non-skilled manual	1.67 (1.14–2.43)**	1.84 (1.23–2.75)**	2.00 (1.18–3.37)**	1.97 (1.01–3.52)*	3.08 (1.70–5.60)***	3.41 (1.74–6.70)***	2.50 (1.32–4.73)**	3.49 (1.68–7.25)***
Skilled manual	1.80 (1.40–2.32)***	2.03 (1.54–2.69)***	2.26 (1.55–3.31)***	2.09 (1.36–3.21)***	2.23 (1.39–3.57)***	3.28 (1.91–5.62)***	2.63 (1.62–4.26)***	4.16 (2.31–7.50)***
Manager/professional	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Model 3: Composite CR score								
Composite CR score	0.65 (0.59–0.71)***	0.59 (0.53–0.66)***	0.49 (0.43–0.57)***	0.45 (0.38–0.54)***	0.41 (0.34–0.50)***	0.39 (0.32–0.47)***	0.45 (0.37–0.54)***	0.43 (0.35–0.52)***

Controls are age, sex, initial National Institute of Health Stroke Scale score, stroke subtype, and the stroke risk factors listed in Supplementary Table I. Education and occupation were coded as dummy variables. Higher education and managerial or professional occupation were the reference groups in each model. CI: confidence interval; K-MMSE: Korean version of the Mini-Mental State Examination. *P<0.05, **P<0.01, ***P<0.001.

Table XIII. Results of logistic regression analyses predicting cognitive impairment (K-MMSE <16th percentile) after stroke at eight time points, controlling for background variables and recurrence

Groups	Odds ratio (95% CI)					
	3 months	6 months	12 months	18 months	24 months	30 months
Model 1: Education						
N†	3,674	2.970	2,442	2,131	1,876	1,660
No formal education	0.96 (0.60–1.54)	0.91 (0.45–1.85)	0.84 (0.33–2.10)	0.91 (0.35–2.35)	0.51 (0.14–1.88)	0.74 (0.19–2.96)
Primary education	4.28 (3.15–5.81)***	6.61 (4.30–10.15)***	7.18 (4.28–12.07)***	6.05 (3.42–10.67)***	7.04 (3.77–13.15)***	9.30 (4.47–19.37)***
Secondary education	2.43 (1.84–3.21)***	3.42 (2.29–5.13)***	3.76 (2.30–6.15)***	3.65 (2.14–6.24)***	4.06 (2.24–7.35)***	5.71 (2.84–11.48)***
Higher education	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Model 2: Occupation						
N†	3,461	2,832	2,315	2,021	1,781	1,582
No occupation	2.66 (1.80–3.92)***	2.02 (1.25–3.28)**	2.68 (1.42–5.03)**	2.55 (1.27–5.09)**	4.72 (1.85–12.08)**	2.54 (1.11–5.81)*
Non-skilled manual	2.44 (1.47–4.07)***	3.00 (1.64–5.48)***	3.97 (1.89–8.33)***	3.30 (1.44–7.58)**	5.57 (1.87–16.57)**	4.03 (1.53–10.61)**
Skilled manual	2.21 (1.52–3.22)***	2.09 (1.31–3.34)**	2.70 (1.46–5.00)**	2.74 (1.40–5.38)**	5.38 (2.14–13.55)***	3.34 (1.49–7.45)**
Manager/professional	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Model 3: Composite CR score						
N†	3,461					
Composite CR score	0.64 (0537–0.69)***	0.58 (0.49–0.69)***	0.53 (0.43–0.65)***	0.58 (0.47–0.73)***	0.49 (0.37–0.63)***	0.51 (0.39–0.66)***

Controls are age, sex, initial National Institute of Health Stroke Scale score, stroke subtype, recurrence, and the stroke risk factors listed in Supplementary Table I. Education and occupation were coded as dummy variables. Higher education and managerial or professional occupation were the reference groups in each model. CI: confidence interval; K-MMSE: Korean version of the Mini-Mental State Examination. †Number of cases was smaller than original analysis because of missing data in recurrence. *P<0.05, **P<0.01, ***P<0.001.

Table XIV. Results of logistic regression analyses predicting cognitive impairment after stroke at eight time points, controlling for background variables and recurrence (cutoff-23/24)

Groups	Odds ratio (95% CI)					
	3 months	6 months	12 months	18 months	24 months	30 months
Model 1: Education						
N†	3,674	2.970	2,442	2,131	1,876	1,660
No formal education	9.06 (5.91–13.90)***	17.27 (9.53–31.30)***	14.74 (7.47–29.08)***	20.04 (8.71–46.11)***	15.42 (6.75–35.24)***	18.47 (7.42–45.95)***
Primary education	4.76 (3.37–6.73)***	8.42 (5.02–14.13)***	8.03 (4.47–14.44)***	11.05 (5.22–23.42)***	10.90 (5.28–22.51)***	9.82 (4.33–22.23)***
Secondary education	1.97 (1.41–2.75)***	3.27 (1.96–5.44)***	2.84 (1.59–5.10)***	4.84 (2.31–10.15)***	3.31 (1.61–6.81)***	4.04 (1.81–9.02)***
Higher education	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Model 2: Occupation						
N†	3,531	2,892	2,362	2.063	1,819	1,618
No occupation	3.01 (1.86–4.87)***	2.75 (1.50–5.04)**	2.09 (1.04–4.18)*	2.50 (1.16–5.39)*	2.47 (1.02–5.99)*	2.30 (0.88–6.03)
Non-skilled manual	3.00 (1.62–5.56)***	3.54 (1.66–7.54)**	3.33 (1.43–7.75)**	3.69 (1.46–9.29)**	4.47 (1.57–12.73)**	3.92 (1.27–12.16)*
Skilled manual	2.89 (1.79–4.67)**	2.86 (1.57–5.23)***	2.52 (1.26–5.02)**	2.75 (1.28–5.89)**	3.85 (1.60–9.22)**	3.19 (1.23–8.28)*
Manager/professional	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Model 3: Composite CR score						
N†	3,461	2,832	2,315	2,021	1,781	1,582
Composite CR score	0.47 (0.39–0.56)***	0.39 (0.30–0.49)***	0.42 (0.32–0.55)***	0.40 (0.29–0.54)***	0.38 (0.27–0.53)***	0.38 (0.27–0.55)***

Controls are age, sex, initial National Institute of Health Stroke Scale score, stroke subtype, recurrence, and the stroke risk factors listed in Supplementary Table I. Education and occupation were coded as dummy variables. Higher education and managerial or professional occupation were the reference groups in each model. CI: confidence interval; K-MMSE: Korean version of the Mini-Mental State Examination. †Number of cases was smaller than the original analysis because of missing data in recurrence. *P<0.05, **P<0.01, ***P<0.001.

Table XV. Results of multi-level model analyses predicting cognitive changes during 30 months after stroke onset, controlling for background variables and the initial score on the Korean version of the Mini-Mental State Examination (for the subjects without history of recurrence)

Variables	Coefficient	Standard error	t-ratio
Model 1 (N=525)			
Intercept 1			
Intercept 2	12.18	2.43	5.02***
Primary education	5.78	2.47	2.35*
Secondary education	7.10	2.46	2.89**
Higher education	7.40	2.53	2.93**
Slope 1†			
Intercept 2	6.19	0.44	13.97***
Primary education	0.64	0.44	1.46
Secondary education	1.21	0.44	2.76**
Higher education	1.57	0.45	3.47**
Slope 2†			
Intercept 2	0.10	0.05	1.77
Primary education	-0.02	0.05	-0.35
Secondary education	-0.01	0.05	-0.09
Higher education	0.00	0.05	0.02
Model 2 (N=505)			
Intercept 1			
Intercept 2	19.11	0.43	43.98***
Non-skilled manual	0.37	1.06	0.35
Skilled manual	-0.23	0.62	-0.37
Manager or professional	-0.27	0.99	-0.28
Slope 1†			
Intercept 2	7.07	0.20	35.91***
Non-skilled manual	-0.06	0.11	-0.32
Skilled manual	0.06	0.18	0.56
Manager or professional	0.42	0.01	2.30*
Slope 2†			
Intercept 2	0.09	0.02	3.90***
Non-skilled manual	0.00	0.02	0.01
Skilled manual	-0.01	0.01	-0.94
Manager or professional	0.01	0.02	0.28
Model 3 (N=505)			
Intercept 1			
Intercept 2	19.02	0.25	74.87***
Composite CR score	0.25	0.31	0.81
Slope 1†			
Intercept 2	7.17	0.18	39.42***
Composite CR score	0.27	0.06	4.72 ***
Slope 2†			
Intercept 2	0.08	0.02	3.92***
Composite CR score	0.00	0.01	0.60

Models were adjusted for background variables: age, sex, initial National Institute of Health Stroke Scale score, stroke subtype, and the stroke risk factors listed in Supplementary Table I. All background variables were centered on the mean. Education and occupation were coded as dummy variables. No education and no occupation were the reference groups in each model. CR: Cognitive reserve. †Slope 1 and slope 2 were adjusted for intercept 1, the initial score on the Korean version of the Mini-Mental State Examination. *P<0.05, **P<0.01, ***P<0.001.

Table XVI. Results of multi-level model analyses predicting cognitive changes during 30 months after stroke onset, controlling for background variables and the initial score on the Korean version of the Mini-Mental State Examination (cutoff-23/24)

Variables	Coefficient	Standard error	t-ratio
Model 1 (N=3,107)			
Intercept 1			
Intercept 2	13.45	0.35	38.71***
Primary education	0.11	0.41	0.28
Secondary education	0.93	0.45	2.08*
Higher education	0.62	0.64	0.96
Slope 1†			
Intercept 2	2.68	0.12	22.16***
Primary education	0.44	0.11	3.80***
Secondary education	0.81	0.12	6.64***
Higher education	1.05	0.16	2.73***
Slope 2†			
Intercept 2	0.01	0.02	0.61
Primary education	0.05	0.01	3.17**
Secondary education	0.07	0.02	4.30**
Higher education	0.05	0.02	2.50*
Model 2 (N=1,660)			
Intercept 1			
Intercept 2	15.96	0.26	61.41***
Non-skilled manual	1.28	1.48	1.48
Skilled manual	0.47	1.21	1.21
Manager or professional	0.93	1.19	1.19
Slope 1†			
Intercept 2	5.17	0.11	47.50***
Non-skilled manual	0.38	0.18	2.11*
Skilled manual	0.36	0.08	4.41***
Manager or professional	0.61	0.16	3.79***
Slope 2†			
Intercept 2	0.06	0.01	4.11***
Non-skilled manual	0.01	0.02	0.47
Skilled manual	-0.01	0.01	-0.84
Manager or professional	0.01	0.02	0.56
Model 3 (N=1,630)			
Intercept 1			
Intercept 2	16.25	0.17	95.49***
Composite CR score	0.29	0.25	1.14
Slope 1†			
Intercept 2	5.39	0.10	52.45***
Composite CR score	0.36	0.05	7.00 ***
Slope 2†			
Intercept 2	0.06	0.01	4.31***
Composite CR score	0.00	0.01	0.49

Models were adjusted for background variables: age, sex, initial National Institute of Health Stroke Scale score, stroke subtype, and the stroke risk factors listed in Supplementary Table I. All background variables were centered on the mean. Education and occupation were coded as dummy variables. No education and no occupation were the reference groups in each model. CR: Cognitive reserve. †Slope 1 and slope 2 were adjusted for intercept 1, the initial score on the Korean version of the Mini-Mental State Examination. *P<0.05, **P<0.01, ***P<0.001.

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