

Supplementary material

This supplementary material (including 13 tables and 1 figure) was supporting the results for the manuscript “Influence of cognitive reserve on cognitive trajectories: role of brain pathologies” by Li et al.

Table e-1. Characteristics of the Study Population by Status of Dementia at Baseline (n=1812)

Characteristics	Cognitive reserve ^a		P value
	Dementia-free n=1697	Dementia n=115	
Age, yrs	79.59±7.48	84.91±6.65	0.521
Female	1284 (75.7)	62 (53.9)	<0.001
Life-course cognitive reserve			
Years of education, yrs	14.88±3.26	14.52±3.76	0.316
Early-life cognitive activity	3.04±0.62	2.96±0.67	0.252
Mid-life cognitive activity	3.29±0.64	3.12±0.73	0.020
Late-life cognitive activity	3.19±0.69	2.83±0.89	<0.001
Late-life social activity	2.66±0.57	2.21±0.56	<0.001
Social network	3.00 (6.00-10.00)	3.00 (6.00-9.00)	0.512
BMI, kg/m ²	27.42±5.40	25.10±4.72	<0.001
Alcohol consumption, g/day	0.00 (0.00-5.83)	0.00 (0.00-2.16)	<0.001
Smoking status			
Never	997 (58.8)	67 (62.0)	0.478
Previous smoker	652 (38.5)	40 (37.0)	
Current smoker	46 (2.7)	1 (0.9)	
Physical activity, h/week	2.50 (0.83-4.65)	1.75 (0.00-3.50)	0.001
<i>APOE</i> ε4 carriers	345 (22.8)	36 (36.4)	0.002
Diabetes	235 (13.8)	19 (16.5)	0.424
Hypertension	1249 (73.6)	85 (73.9)	0.941
Heart disease	192 (12.0)	17 (17.0)	0.136
Stroke	142 (9.1)	17 (15.7)	0.024
MMSE	28.07±1.94	18.15±6.73	<0.001
Global cognition	0.10±0.54	-1.55±0.72	<0.001
Episodic memory	0.13±0.65	-1.84±0.79	<0.001
Semantic memory	0.10±0.65	-1.41±1.17	<0.001
Working memory	0.07±0.76	-1.17±0.89	<0.001
Visuospatial ability	0.06±0.80	-1.10±1.09	<0.001
Perceptual speed	0.09±0.77	-1.47±0.80	<0.001

Values are mean ± SD, n (%), or median (interquartile range).

APOE ε4=*apolipoprotein E epsilon 4*; BMI=body mass index; MMSE=Mini-Mental State Examination.

Missing data: BMI=47; Alcohol consumption=12; Smoking status=9; physical activity=4; *APOE* ε4 genotype=197; Heart disease=107; Stroke=147; MMSE=3.

Table e-2. Association of Continuous Cognitive Reserve (CR) at Baseline with Brain Pathologies.

Brain pathologies ^a	Continuous CR
	β (95% CI) ^b
AD pathologies	
Global AD pathology	-0.387 (-0.712 to -0.061)
Diffuse plaque	-0.121 (-0.374 to 0.131)
Neuritic plaque	-0.243 (-0.473 to -0.014)
Neurofibrillary tangles	-0.029 (-0.052 to -0.005)
Chronic infarcts	
Gross infarcts	-0.614 (-1.004 to -0.223)
Microscopic infarcts	-0.204 (-0.608 to 0.200)
Vascular disease pathology	
Cerebral atherosclerosis	-0.275 (-0.739 to 0.189)
Cerebral amyloid angiopathy	-0.298 (-0.747 to 0.151)
Arteriolosclerosis	0.337 (-0.070 to 0.743)
Lewy bodies	0.164 (-0.279 to 0.608)
Hippocampal sclerosis	0.135 (-0.511 to 0.781)

Abbreviations: AD=Alzheimer's disease

^a AD pathologies were continuous measures and the other brain pathologies were dichotomous measures as present/absent.

^b Adjusted for age, sex, body mass index, smoking, alcohol consumption, physical activity, hypertension, stroke, heart disease, diabetes, and *APOE* $\epsilon 4$.

Table e-3. β -Coefficients and 95% Confidences Intervals (CIs) for the Association of the Cognitive Reserve (CR) with the Changes of Global Cognitive Function and Cognitive Function in Different Domains over Follow-Up Time in Participants with Brain Pathology Data: Results from Linear Mixed-Effects Models

Cognitive reserve (CR)	Global Cognition β (95% CI) ^a	Episodic Memory β (95% CI) ^a	Semantic Memory β (95% CI) ^a	Working Memory β (95% CI) ^a	Visuospatial Ability β (95% CI) ^a	Perceptual Speed β (95% CI) ^a
Baseline						
Continuous CR	0.069 ^b (0.049 to 0.089)	0.075 ^b (0.048 to 0.101)	0.088 ^b (0.066 to 0.111)	0.052 ^b (0.024 to 0.079)	0.069 ^b (0.043 to 0.096)	0.083 ^b (0.055 to 0.110)
Categories CR						
Lowest	Reference	Reference	Reference	Reference	Reference	Reference
Middle	0.136 ^b (0.033 to 0.240)	0.133 (-0.002 to 0.269)	0.231 ^b (0.114 to 0.347)	0.120 (-0.021 to 0.261)	0.120 (-0.017 to 0.256)	0.199 ^b (0.057 to 0.341)
Highest	0.314 ^b (0.206 to 0.422)	0.292 ^b (0.150 to 0.434)	0.408 ^b (0.286 to 0.530)	0.240 ^b (0.092 to 0.387)	0.357 ^b (0.215 to 0.500)	0.441 ^b (0.293 to 0.590)
Longitudinal						
Continuous CR \times time	0.009 ^b (0.004 to 0.015)	0.008 ^b (0.002 to 0.014)	0.007 ^b (0.001 to 0.013)	0.008 ^b (0.003 to 0.013)	0.004 ^b (0.000 to 0.010)	0.005 ^b (0.000 to 0.010)
Categories CR \times time						
Lowest \times time	Reference	Reference	Reference	Reference	Reference	Reference
Middle \times time	0.033 ^b (0.005 to 0.060)	0.031 (-0.002 to 0.063)	0.025 (-0.006 to 0.056)	0.029 ^b (0.003 to 0.055)	0.024 (-0.003 to 0.051)	0.009 (-0.017 to 0.035)
Highest \times time	0.043 ^b (0.016 to 0.071)	0.036 ^b (0.003 to 0.069)	0.030 (-0.001 to 0.062)	0.036 ^b (0.010 to 0.062)	0.030 ^b (0.003 to 0.056)	0.022 (-0.004 to 0.048)

^a Adjusted for age, sex, body mass index, smoking, alcohol consumption, physical activity, hypertension, stroke, heart disease, diabetes, and *APOE* $\epsilon 4$. ^b $P < 0.05$

Table e-4. β -Coefficients and 95% Confidences Intervals (CIs) for the Association of the Cognitive Reserve (CR) with the Changes of Global Cognitive Function and Cognitive Function in Different Domains over Follow-Up Time further Adjusted Brain Pathology: Results from Linear Mixed-Effects Models

Cognitive reserve (CR)	Global Cognition β (95% CI) ^a	Episodic Memory β (95% CI) ^a	Semantic Memory β (95% CI) ^a	Working Memory β (95% CI) ^a	Visuospatial Ability β (95% CI) ^a	Perceptual Speed β (95% CI) ^a
Baseline						
Continuous CR	0.065 ^b (0.045 to 0.086)	0.069 ^b (0.043 to 0.096)	0.087 ^b (0.065 to 0.110)	0.047 ^b (0.020 to 0.075)	0.066 ^b (0.039 to 0.094)	0.079 ^b (0.051 to 0.107)
Categories CR						
Lowest	Reference	Reference	Reference	Reference	Reference	Reference
Middle	0.130 ^b (0.027 to 0.233)	0.122 (-0.012 to 0.257)	0.228 ^b (0.111 to 0.345)	0.111 (-0.030 to 0.252)	0.113 (-0.023 to 0.250)	0.192 ^b (0.050 to 0.334)
Highest	0.298 ^b (0.189 to 0.407)	0.263 ^b (0.121 to 0.406)	0.401 ^b (0.278 to 0.525)	0.217 ^b (0.068 to 0.366)	0.343 ^b (0.199 to 0.487)	0.424 ^b (0.274 to 0.574)
Longitudinal						
Continuous CR \times time	0.010 ^b (0.004 to 0.015)	0.008 ^b (0.002 to 0.014)	0.007 ^b (0.001 to 0.013)	0.008 ^b (0.003 to 0.013)	0.005 ^b (0.000 to 0.010)	0.005 ^b (0.000 to 0.010)
Categories CR \times time						
Lowest \times time	Reference	Reference	Reference	Reference	Reference	Reference
Middle \times time	0.033 ^b (0.005 to 0.060)	0.031 (-0.001 to 0.064)	0.025 (-0.006 to 0.056)	0.029 ^b (0.002 to 0.055)	0.024 (-0.003 to 0.051)	0.009 (-0.017 to 0.035)
Highest \times time	0.044 ^b (0.016 to 0.071)	0.036 ^b (0.004 to 0.069)	0.030 (-0.001 to 0.062)	0.036 ^b (0.010 to 0.062)	0.030 ^b (0.003 to 0.056)	0.022 (-0.004 to 0.048)

^a Adjusted for age, sex, body mass index, smoking, alcohol consumption, physical activity, hypertension, stroke, heart disease, diabetes, *APOE* ϵ 4, global AD pathology, and gross infarcts. ^b $P < 0.05$

Table e-5. β -Coefficients and 95% Confidences Intervals (CIs) for the Association of the Cognitive Reserve (CR) with the Changes of Global Cognitive Function and Cognitive Function in Different Domains over Follow-Up Time Stratified by Global AD Pathology Burden: Results from Linear Mixed-Effects Models

Cognitive reserve (CR)	Global Cognition β (95% CI) ^a	Episodic Memory β (95% CI) ^a	Semantic Memory β (95% CI) ^a	Working Memory β (95% CI) ^a	Visuospatial Ability β (95% CI) ^a	Perceptual Speed β (95% CI) ^a
Low Global AD Pathology Burden						
Continuous CR \times time	0.004 (-0.003 to 0.010)	0.002 (-0.007 to 0.010)	0.002 (-0.004 to 0.008)	0.003 (-0.003 to 0.010)	0.005 (-0.003 to 0.012)	0.004 (-0.003 to 0.011)
Categories CR \times time						
Lowest \times time	Reference	Reference	Reference	Reference	Reference	Reference
Middle \times time	0.003 (-0.030 to 0.037)	-0.006 (-0.046 to 0.034)	-0.004 (-0.034 to 0.025)	0.004 (-0.027 to 0.035)	0.024 (-0.014 to 0.061)	-0.025 (-0.060 to 0.010)
Highest \times time	0.019 (-0.014 to 0.052)	0.002 (-0.038 to 0.043)	0.001 (-0.028 to 0.030)	0.018 (-0.013 to 0.049)	0.033 (-0.004 to 0.070)	0.010 (-0.025 to 0.044)
High Global AD Pathology Burden						
Continuous CR \times time	0.011 ^b (0.004 to 0.018)	0.009 ^b (0.001 to 0.017)	0.008 (-0.001 to 0.017)	0.010 ^b (0.003 to 0.017)	0.004 (-0.003 to 0.010)	0.005 (-0.002 to 0.011)
Categories CR \times time						
Lowest \times time	Reference	Reference	Reference	Reference	Reference	Reference
Middle \times time	0.048 ^b (0.007 to 0.088)	0.045 (-0.000 to 0.091)	0.037 (-0.015 to 0.089)	0.042 ^b (0.002 to 0.081)	0.020 (-0.018 to 0.057)	0.034 (-0.003 to 0.071)
Highest \times time	0.050 ^b (0.008 to 0.091)	0.045 (-0.002 to 0.091)	0.041 (-0.012 to 0.094)	0.042 ^b (0.003 to 0.082)	0.021 (-0.016 to 0.058)	0.023 (-0.014 to 0.060)

^a Adjusted for age, sex, body mass index, smoking, alcohol consumption, physical activity, hypertension, stroke, heart disease, diabetes, and *APOE* $\epsilon 4$.^b $P < 0.05$

Table e-6. β -Coefficients and 95% Confidences Intervals (CIs) for the Association of the Cognitive Reserve (CR) with the Changes of Global Cognitive Function and Cognitive Function in Different Domains over Follow-Up Time Stratified by Gross Infarcts: Results from Linear Mixed-Effects Models

Cognitive reserve (CR)	Global Cognition β (95% CI) ^a	Episodic Memory β (95% CI) ^a	Semantic Memory β (95% CI) ^a	Working Memory β (95% CI) ^a	Visuospatial Ability β (95% CI) ^a	Perceptual Speed β (95% CI) ^a
No Gross Infarcts						
Continuous CR \times time	0.009 ^b (0.002 to 0.015)	0.009 ^b (0.001 to 0.017)	0.006 (-0.002 to 0.014)	0.008 ^b (0.002 to 0.013)	0.006 ^b (0.000 to 0.013)	0.008 ^b (0.002 to 0.014)
Categories CR \times time						
Lowest \times time	Reference	Reference	Reference	Reference	Reference	Reference
Middle \times time	0.026 (-0.011 to 0.063)	0.034 (-0.010 to 0.077)	0.017 (-0.026 to 0.061)	0.019 (-0.014 to 0.052)	0.017 (-0.017 to 0.051)	0.010 (-0.024 to 0.044)
Highest \times time	0.038 ^b (0.002 to 0.073)	0.036 (-0.006 to 0.078)	0.021 (-0.021 to 0.063)	0.026 (-0.006 to 0.057)	0.033 ^b (0.000 to 0.066)	0.026 (-0.007 to 0.058)
Any Gross Infarcts						
Continuous CR \times time	0.010 ^b (0.002 to 0.018)	0.006 (-0.003 to 0.016)	0.007 (-0.001 to 0.016)	0.008 (-0.000 to 0.016)	0.003 (-0.005 to 0.011)	0.000 (-0.008 to 0.008)
Categories CR \times time						
Lowest \times time	Reference	Reference	Reference	Reference	Reference	Reference
Middle \times time	0.039 (-0.003 to 0.080)	0.026 (-0.023 to 0.075)	0.025 (-0.018 to 0.068)	0.041 (-0.002 to 0.084)	0.037 (-0.006 to 0.079)	0.009 (-0.031 to 0.049)
Highest \times time	0.050 ^b (0.004 to 0.096)	0.036 (-0.018 to 0.089)	0.035 (-0.012 to 0.082)	0.046 (-0.001 to 0.093)	0.023 (-0.022 to 0.069)	0.017 (-0.026 to 0.060)

^a Adjusted for age, sex, body mass index, smoking, alcohol consumption, physical activity, hypertension, stroke, heart disease, diabetes, and *APOE* $\epsilon 4$. ^b $P < 0.05$

Table e-7. β -Coefficients and 95% Confidences Intervals (CIs) for the Association of the Cognitive Reserve (CR) with the Changes of Global Cognitive Function and Cognitive Function in Different Domains over Follow-Up Time in Baseline MCI-Free Participants: Results from Linear Mixed-Effects Models

Cognitive reserve (CR)	Global Cognition β (95% CI) ^a	Episodic Memory β (95% CI) ^a	Semantic Memory β (95% CI) ^a	Working Memory β (95% CI) ^a	Visuospatial Ability β (95% CI) ^a	Perceptual Speed β (95% CI) ^a
Baseline						
Continuous CR	0.073 ^b (0.062 to 0.085)	0.055 ^b (0.042 to 0.067)	0.098 ^b (0.083 to 0.113)	0.080 ^b (0.061 to 0.099)	0.089 ^b (0.071 to 0.107)	0.098 ^b (0.080 to 0.117)
Categories CR						
Lowest	Reference	Reference	Reference	Reference	Reference	Reference
Middle	0.171 ^b (0.108 to 0.235)	0.108 ^b (0.039 to 0.177)	0.292 ^b (0.209 to 0.374)	0.167 ^b (0.063 to 0.270)	0.225 ^b (0.126 to 0.325)	0.246 ^b (0.144 to 0.348)
Highest	0.344 ^b (0.280 to 0.407)	0.256 ^b (0.186 to 0.326)	0.462 ^b (0.379 to 0.545)	0.378 ^b (0.274 to 0.481)	0.429 ^b (0.329 to 0.529)	0.451 ^b (0.348 to 0.554)
Longitudinal						
Continuous CR \times time	0.004 ^b (0.002 to 0.007)	0.005 ^b (0.001 to 0.009)	0.002 (-0.001 to 0.004)	0.004 ^b (0.001 to 0.006)	0.002 (-0.001 to 0.004)	0.002 (-0.001 to 0.005)
Categories CR \times time						
Lowest \times time	Reference	Reference	Reference	Reference	Reference	Reference
Middle \times time	0.012 (-0.004 to 0.028)	0.019 (-0.002 to 0.039)	0.002 (-0.013 to 0.018)	0.012 (-0.003 to 0.027)	0.003 (-0.011 to 0.017)	-0.008 (-0.024 to 0.008)
Highest \times time	0.022 ^b (0.006 to 0.038)	0.024 ^b (0.005 to 0.044)	0.007 (-0.008 to 0.022)	0.015 ^b (0.001 to 0.030)	0.009 (-0.004 to 0.023)	0.008 (-0.008 to 0.024)

^a Adjusted for age, sex, body mass index, smoking, alcohol consumption, physical activity, hypertension, stroke, heart disease, diabetes, and *APOE* $\epsilon 4$. ^b $P < 0.05$

Table e-8. β -Coefficients and 95% Confidences Intervals (CIs) for the Association of the Cognitive Reserve (CR) with the Changes of Global Cognitive Function and Cognitive Function in Different Domains over Follow-Up Time with Multiple Imputation for Missing Data on Covariates: Results from Linear Mixed-Effects Models

Cognitive reserve (CR)	Global Cognition β (95% CI) ^a	Episodic Memory β (95% CI) ^a	Semantic Memory β (95% CI) ^a	Working Memory β (95% CI) ^a	Visuospatial Ability β (95% CI) ^a	Perceptual Speed β (95% CI) ^a
Baseline						
Continuous CR	0.093 ^b (0.082 to 0.104)	0.084 ^b (0.071 to 0.097)	0.113 ^b (0.100 to 0.125)	0.090 ^b (0.076 to 0.105)	0.102 ^b (0.087 to 0.118)	0.106 ^b (0.091 to 0.121)
Categories CR						
Lowest	Reference	Reference	Reference	Reference	Reference	Reference
Middle	0.235 ^b (0.177 to 0.294)	0.192 ^b (0.120 to 0.264)	0.338 ^b (0.269 to 0.408)	0.208 ^b (0.127 to 0.289)	0.237 ^b (0.154 to 0.321)	0.290 ^b (0.206 to 0.375)
Highest	0.435 ^b (0.377 to 0.494)	0.381 ^b (0.309 to 0.452)	0.537 ^b (0.468 to 0.607)	0.422 ^b (0.341 to 0.502)	0.489 ^b (0.406 to 0.572)	0.502 ^b (0.418 to 0.586)
Longitudinal						
Continuous CR \times time	0.004 ^b (0.002 to 0.007)	0.004 ^b (0.001 to 0.007)	0.003 ^b (0.000 to 0.006)	0.003 ^b (0.001 to 0.005)	0.001 (-0.001 to 0.003)	0.002 (-0.001 to 0.004)
Categories CR \times time						
Lowest \times time	Reference	Reference	Reference	Reference	Reference	Reference
Middle \times time	0.005 (-0.009 to 0.019)	0.008 (-0.008 to 0.025)	0.005 (-0.011 to 0.020)	0.006 (-0.007 to 0.019)	0.005 (-0.008 to 0.018)	-0.005 (-0.020 to 0.009)
Highest \times time	0.020 ^b (0.006 to 0.034)	0.021 ^b (0.005 to 0.038)	0.014 (-0.001 to 0.029)	0.015 ^b (0.002 to 0.027)	0.006 (-0.006 to 0.019)	0.005 (-0.008 to 0.019)

^a Adjusted for age, sex, body mass index, smoking, alcohol consumption, physical activity, hypertension, stroke, heart disease, diabetes, and *APOE* $\epsilon 4$. ^b $P < 0.05$

Table e-9. β -Coefficients and 95% Confidences Intervals (CIs) for the Association of the Cognitive Reserve (CR)^a with the Changes of Global Cognitive Function and Cognitive Function in Different Domains over Follow-Up Time: Results from Linear Mixed-Effects Models

Cognitive reserve (CR)	Global Cognition β (95% CI) ^b	Episodic Memory β (95% CI) ^b	Semantic Memory β (95% CI) ^b	Working Memory β (95% CI) ^b	Visuospatial Ability β (95% CI) ^b	Perceptual Speed β (95% CI) ^b
Baseline						
Continuous CR	0.080 ^c (0.068 to 0.093)	0.073 ^c (0.058 to 0.089)	0.101 ^c (0.086 to 0.116)	0.083 ^c (0.066 to 0.100)	0.088 ^c (0.070 to 0.106)	0.085 ^c (0.067 to 0.102)
Categories CR						
Lowest	Reference	Reference	Reference	Reference	Reference	Reference
Middle	0.195 ^c (0.127 to 0.264)	0.179 ^c (0.096 to 0.261)	0.280 ^c (0.197 to 0.363)	0.210 ^c (0.118 to 0.302)	0.210 ^c (0.113 to 0.306)	0.188 ^c (0.091 to 0.284)
Highest	0.366 ^c (0.297 to 0.434)	0.331 ^c (0.247 to 0.414)	0.455 ^c (0.371 to 0.539)	0.374 ^c (0.281 to 0.468)	0.427 ^c (0.330 to 0.525)	0.384 ^c (0.286 to 0.481)
Longitudinal						
Continuous CR \times time	0.004 ^c (0.002 to 0.007)	0.004 ^c (0.001 to 0.008)	0.002 (-0.001 to 0.006)	0.003 ^c (0.000 to 0.006)	0.002 (-0.001 to 0.004)	0.002 (-0.001 to 0.005)
Categories CR \times time						
Lowest \times time	Reference	Reference	Reference	Reference	Reference	Reference
Middle \times time	0.011 (-0.005 to 0.027)	0.011 (-0.008 to 0.029)	0.007 (-0.011 to 0.024)	0.010 (-0.005 to 0.024)	0.009 (-0.005 to 0.022)	-0.003 (-0.019 to 0.012)
Highest \times time	0.023 ^c (0.008 to 0.039)	0.022 ^c (0.004 to 0.041)	0.012 (-0.005 to 0.029)	0.018 ^c (0.004 to 0.032)	0.012 (-0.001 to 0.026)	0.007 (-0.008 to 0.022)

^a Included education, early- and mid-life cognitive activities.^b Adjusted for age, sex, body mass index, smoking, alcohol consumption, physical activity, hypertension, stroke, heart disease, diabetes, and *APOE* $\epsilon 4$. ^c $P < 0.05$

Table e-10. β -Coefficients and 95% Confidences Intervals (CIs) for the Association of the Cognitive Reserve (CR)^a with the Changes of Global Cognitive Function and Cognitive Function in Different Domains over Follow-Up Time: Results from Linear Mixed-Effects Models

Cognitive reserve (CR)	Global Cognition β (95% CI) ^b	Episodic Memory β (95% CI) ^b	Semantic Memory β (95% CI) ^b	Working Memory β (95% CI) ^b	Visuospatial Ability β (95% CI) ^b	Perceptual Speed β (95% CI) ^b
Baseline						
Continuous CR	0.108 ^c (0.094 to 0.122)	0.094 ^c (0.076 to 0.111)	0.131 ^c (0.114 to 0.148)	0.101 ^c (0.081 to 0.120)	0.111 ^c (0.091 to 0.132)	0.141 ^c (0.121 to 0.160)
Categories CR						
Lowest	Reference	Reference	Reference	Reference	Reference	Reference
Middle	0.179 ^c (0.111 to 0.246)	0.123 ^c (0.041 to 0.205)	0.300 ^c (0.217 to 0.383)	0.152 ^c (0.059 to 0.244)	0.226 ^c (0.129 to 0.324)	0.274 ^c (0.180 to 0.369)
Highest	0.421 ^c (0.353 to 0.489)	0.384 ^c (0.301 to 0.467)	0.501 ^c (0.417 to 0.584)	0.367 ^c (0.273 to 0.460)	0.418 ^c (0.320 to 0.516)	0.554 ^c (0.458 to 0.649)
Longitudinal						
Continuous CR \times time	0.006 ^c (0.003 to 0.009)	0.006 ^c (0.002 to 0.010)	0.004 ^c (0.001 to 0.008)	0.004 ^c (0.001 to 0.007)	0.002 (-0.000 to 0.005)	0.003 ^c (0.000 to 0.006)
Categories CR \times time						
Lowest \times time	Reference	Reference	Reference	Reference	Reference	Reference
Middle \times time	0.007 (-0.009 to 0.023)	0.011 (-0.007 to 0.030)	-0.010 (-0.027 to 0.008)	0.006 (-0.009 to 0.020)	0.002 (-0.012 to 0.016)	-0.008 (-0.024 to 0.007)
Highest \times time	0.023 ^c (0.008 to 0.039)	0.023 ^c (0.004 to 0.041)	0.013 (-0.003 to 0.030)	0.017 ^c (0.003 to 0.031)	0.011 (-0.002 to 0.025)	0.007 (-0.008 to 0.022)

^a Included education, early- and late-life cognitive activities, and late-life social activities.^b Adjusted for age, sex, body mass index, smoking, alcohol consumption, physical activity, hypertension, stroke, heart disease, diabetes, and *APOE* $\epsilon 4$. ^c $P < 0.05$

Table e-11. β -Coefficients and 95% Confidences Intervals (CIs) for the Association of the Cognitive Reserve (CR)^a with the Changes of Global Cognitive Function and Cognitive Function in Different Domains over Follow-Up Time: Results from Linear Mixed-Effects Models

Cognitive reserve (CR)	Global Cognition β (95% CI) ^b	Episodic Memory β (95% CI) ^b	Semantic Memory β (95% CI) ^b	Working Memory β (95% CI) ^b	Visuospatial Ability β (95% CI) ^b	Perceptual Speed β (95% CI) ^b
Baseline						
Continuous CR	0.397 ^c (0.346 to 0.448)	0.328 ^c (0.265 to 0.392)	0.503 ^c (0.441 to 0.566)	0.360 ^c (0.288 to 0.431)	0.408 ^c (0.332 to 0.483)	0.574 ^c (0.503 to 0.646)
Categories CR						
Lowest	Reference	Reference	Reference	Reference	Reference	Reference
Middle	0.257 ^c (0.190 to 0.324)	0.228 ^c (0.146 to 0.310)	0.364 ^c (0.282 to 0.445)	0.161 ^c (0.069 to 0.254)	0.247 ^c (0.150 to 0.344)	0.361 ^c (0.268 to 0.455)
Highest	0.460 ^c (0.393 to 0.528)	0.395 ^c (0.312 to 0.478)	0.550 ^c (0.467 to 0.632)	0.405 ^c (0.312 to 0.498)	0.456 ^c (0.358 to 0.553)	0.638 ^c (0.545 to 0.732)
Longitudinal						
Continuous CR \times time	0.027 ^c (0.015 to 0.039)	0.030 ^c (0.016 to 0.044)	0.020 ^c (0.006 to 0.033)	0.021 ^c (0.010 to 0.032)	0.011 ^c (0.000 to 0.021)	0.017 ^c (0.005 to 0.028)
Categories CR \times time						
Lowest \times time	Reference	Reference	Reference	Reference	Reference	Reference
Middle \times time	0.025 ^c (0.009 to 0.040)	0.034 ^c (0.015 to 0.053)	0.016 (-0.002 to 0.033)	0.030 ^c (0.016 to 0.044)	0.006 (-0.008 to 0.021)	0.015 (-0.001 to 0.030)
Highest \times time	0.031 ^c (0.016 to 0.047)	0.034 ^c (0.015 to 0.052)	0.025 ^c (0.008 to 0.042)	0.024 ^c (0.010 to 0.038)	0.018 ^c (0.004 to 0.031)	0.019 ^c (0.004 to 0.034)

^a Included mid-life and late-life cognitive activities, and late-life social activities^b Adjusted for age, sex, body mass index, smoking, alcohol consumption, physical activity, hypertension, stroke, heart disease, diabetes, and *APOE* $\epsilon 4$. ^c $P < 0.05$

Table e-12. β -Coefficients and 95% Confidences Intervals (CIs) for the Association of the Individual Cognitive Reserve (CR) Factors with the Changes of Global Cognitive Function and Cognitive Function in Different Domains over Follow-Up Time: Results from Linear Mixed-Effects Models

Individual CR	Global Cognition β (95% CI) ^a	Episodic Memory β (95% CI) ^a	Semantic Memory β (95% CI) ^a	Working Memory β (95% CI) ^a	Visuospatial Ability β (95% CI) ^a	Perceptual Speed β (95% CI) ^a
Education \times time	0.001 (-0.001 to 0.003)	0.001 (-0.001 to 0.004)	0.000 (-0.002 to 0.003)	0.001 (-0.001 to 0.003)	-0.000 (-0.002 to 0.001)	0.000 (-0.002 to 0.002)
Early-life cognitive activity \times time	0.010 ^b (0.000 to 0.021)	0.008 (-0.004 to 0.020)	0.006 (-0.006 to 0.017)	0.006 (-0.003 to 0.015)	0.004 (-0.005 to 0.013)	0.003 (-0.007 to 0.013)
Mid-life cognitive activity \times time	0.018 ^b (0.008 to 0.028)	0.018 ^b (0.006 to 0.030)	0.010 (-0.000 to 0.021)	0.013 ^b (0.004 to 0.022)	0.008 (-0.001 to 0.016)	0.009 (-0.000 to 0.019)
Late-life cognitive activity \times time	0.013 ^b (0.004 to 0.023)	0.019 ^b (0.008 to 0.030)	0.011 (-0.000 to 0.021)	0.013 ^b (0.004 to 0.021)	0.003 (-0.005 to 0.012)	0.008 (-0.002 to 0.018)
Late-life social activity \times time	0.031 ^b (0.020 to 0.043)	0.030 ^b (0.016 to 0.044)	0.028 ^b (0.016 to 0.041)	0.022 ^b (0.012 to 0.033)	0.019 ^b (0.008 to 0.029)	0.025 ^b (0.014 to 0.036)

^a Adjusted for age, sex, body mass index, smoking, alcohol consumption, physical activity, hypertension, stroke, heart disease, diabetes, and *APOE* $\epsilon 4$.

^b $P < 0.05$

Table e-13. β -Coefficients and 95% Confidences Intervals (CIs) for the Association of the Cognitive Reserve (CR) with the Changes of Global Cognitive Function and Cognitive Function in Different Domains over Follow-Up Time by Adjusting for Survival Status during the Follow-Up: Results from Linear Mixed-Effects Models

Cognitive reserve (CR)	Global Cognition β (95% CI) ^a	Episodic Memory β (95% CI) ^a	Semantic Memory β (95% CI) ^a	Working Memory β (95% CI) ^a	Visuospatial Ability β (95% CI) ^a	Perceptual Speed β (95% CI) ^a
Baseline						
Continuous CR	0.088 ^b (0.075 to 0.100)	0.077 ^b (0.062 to 0.093)	0.110 ^b (0.095 to 0.125)	0.087 ^b (0.070 to 0.104)	0.093 ^b (0.075 to 0.111)	0.101 ^b (0.084 to 0.118)
Categories CR						
Lowest	Reference	Reference	Reference	Reference	Reference	Reference
Middle	0.221 ^b (0.154 to 0.288)	0.178 ^b (0.096 to 0.259)	0.336 ^b (0.255 to 0.418)	0.205 (0.112 to 0.297)	0.236 (0.139 to 0.332)	0.264 ^b (0.170 to 0.358)
Highest	0.409 ^b (0.341 to 0.477)	0.346 ^b (0.263 to 0.428)	0.520 ^b (0.438 to 0.603)	0.395 ^b (0.302 to 0.489)	0.455 ^b (0.357 to 0.552)	0.481 ^b (0.386 to 0.576)
Longitudinal						
Continuous CR \times time	0.005 ^b (0.003 to 0.008)	0.005 ^b (0.002 to 0.009)	0.003 ^b (0.000 to 0.006)	0.004 ^b (0.001 to 0.006)	0.002 (-0.000 to 0.005)	0.003 (-0.000 to 0.005)
Categories CR \times time						
Lowest \times time	Reference	Reference	Reference	Reference	Reference	Reference
Middle \times time	0.015 (-0.001 to 0.031)	0.016 (-0.002 to 0.035)	0.009 (-0.008 to 0.026)	0.014 (-0.000 to 0.028)	0.007 (-0.007 to 0.021)	-0.004 (-0.019 to 0.012)
Highest \times time	0.028 ^b (0.012 to 0.043)	0.028 ^b (0.010 to 0.046)	0.017 (-0.000 to 0.034)	0.019 ^b (0.005 to 0.033)	0.013 (-0.000 to 0.026)	0.010 (-0.005 to 0.025)

^a Adjusted for age, sex, body mass index, smoking, alcohol consumption, physical activity, hypertension, stroke, heart disease, diabetes, *APOE* ϵ 4, and death status; ^b $P < 0.05$

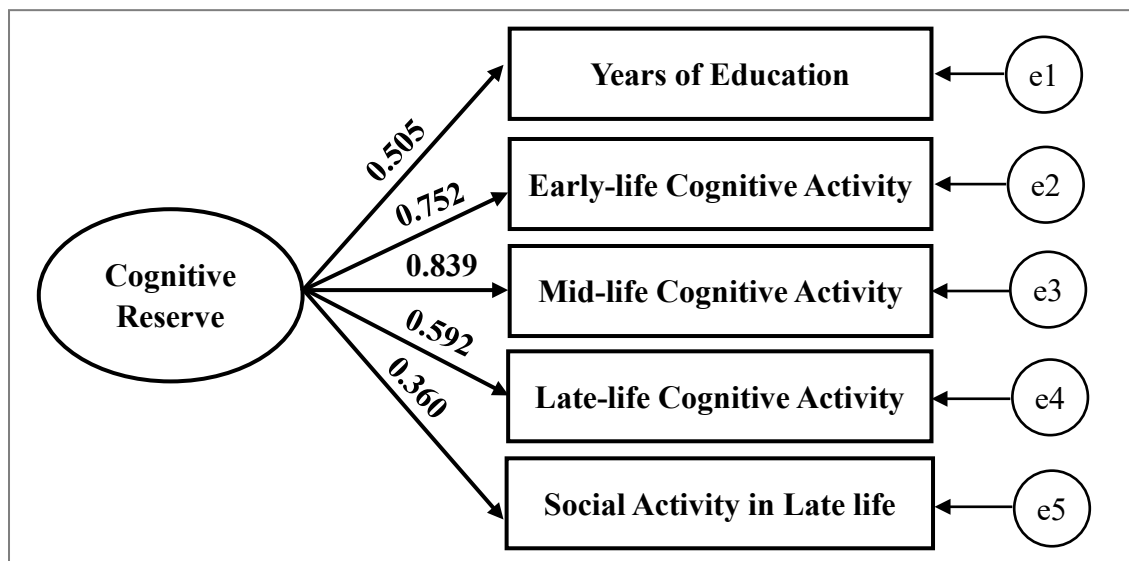


Figure e-1. Standardized Estimates from the Structural Equation Model with Five Observable Indicators of a Latent Reserve Construct

The values indicate the loadings of the 5 factors to cognitive reserve. e1, e2, e3, e4, and e5 indicate the measurement error for each cognitive reserve factor.

SEM fit statistics:

$\chi^2 = 42.396$, $df = 5$, $P < 0.001$

Comparative fit index = 0.981

Standardized root mean squared residual (SRMR) = 0.025

Root mean squared error of approximation (RMSEA) = 0.066