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Association of Lifespan Cognitive Reserve Indicator With Dementia Risk in the Presence of Brain Pathologies

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Evidence on the association of lifespan cognitive reserve (CR) with dementia is limited, and the strength of this association in the presence of brain pathologies is unknown.

J To examine the association of lifespan CR with dementia risk, taking brain pathologies into account.

, , This study used data from 2022 participants in the Rush Memory and Aging Project, an ongoing community-based cohort study with annual follow-up from 1997 to 2018 (mean follow-up, 6 years; maximum follow-up, 20 years). After excluding 420 individuals who had prevalent dementia, missing data on CR, or dropped out, 1602 dementia-free adults were identified at baseline and evaluated to detect incident dementia. During follow-up, 611 died and underwent autopsies. Data were analyzed from May to September 2018.

Information on CR factors (education; early-life, midlife, and late-life cognitive activities; and social activities in late life) was obtained at baseline. Based on these factors, lifespan CR scores were captured using a latent variable from a structural equation model and was divided into tertiles (lowest, middle, and highest).

Dementia was diagnosed following international criteria. Neuropathologic evaluations for Alzheimer disease and other brain pathologies were performed in autopsied participants. The association of lifespan CR with dementia or brain pathologies was estimated using Cox regression models or logistic regression.

Of the 1602 included participants, 1216 (75.9%) were women, and the mean (SD) age was 79.6 (7.5) years. During follow-up, 386 participants developed dementia (24.1%), including 357 participants with Alzheimer disease–related dementia (22.3%). The multiadjusted hazards ratios (HRs) of dementia were 0.77 (95% CI, 0.59-0.99) for participants in the middle CR score tertile and 0.61 (95% CI, 0.47-0.81) for those in the highest CR score tertile compared with those in the lowest CR score tertile. In autopsied participants, CR was not associated with most brain pathologies, and the association of CR with dementia remained significant after additional adjustment for brain pathologies (HR, 0.60; 95% CI, 0.42-0.86). The highest CR score tertile was associated with a reduction in dementia risk, even among participants with high Alzheimer disease pathology (HR, 0.57; 95% CI, 0.37-0.87) and any gross infarcts (HR, 0.34; 95% CI, 0.18-0.62).

High lifespan CR is associated with a reduction in dementia risk, even in the presence of high brain pathologies. Our findings highlight the importance of lifespan CR accumulation in dementia prevention.

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Supplemental content

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The cognitive reserve (CR) hypothesis has been proposed as a compensatory mechanism to cope with age-related brain damage and to account for interindividual variability in the ability to maintain cognitive function in the presence of brain pathologies.[1] Education, occupation attainment, and social and cognitive activities have been considered as proxy measures of CR.[2-4] However, emerging evidence has suggested that CR is an active construct that develops from continued life experiences.[5] One reserve-enhancing factor during a certain period alone could not fully explain the accumulation of cognitive activities over the life course.[6] So far, evidence on whether and to what extent lifespan CR accumulation may reduce dementia risk is still limited.[6]

According to CR theory, Stern et al[7] have suggested that 3 components are required for CR-related research: a measure of CR, clinical or cognitive performance outcomes, and the status of the brain (reflecting brain pathologies). However, as in vivo measures of neuronal pathology are not widely available, few studies presenting the association of the proxy of CR with dementia have taken brain pathologies into account. Several studies have shown that CR might be directly associated with neuropathology and resist the accumulation of brain pathologies.[8-10] However, other studies have indicated that CR might bypass classic brain pathologies[11] and represent other pathways, such as enhancing brain network efficiency to compensate for dementia pathology.[12,13] Therefore, the role of brain pathologies in the association of CR with cognitive outcomes remains unclear.

We previously reported that more frequent cognitive activities from early to late life and social activities in late life were associated with slower cognitive decline.[14-16] In the present study, we aim to verify the hypothesis that high lifespan CR accumulation is associated with a reduction in clinical dementia risk and to estimate the strength of this association in the presence of brain pathologies using data from a long-term community-based cohort study in which people donated their brains for autopsy.

Methods

Study Design, Setting, and Participants

The Rush Memory and Aging Project[17] is an ongoing prospective cohort study that investigates risk factors f
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from 1 (once a year or less) to 5 (every day or about every day). Item scores were summed and averaged to obtain a composite measure of social activity.[20,21]

For social network in late life, participants were asked about the number of children they have and meet monthly. They were also asked about the number of relatives (besides spouse and children) and other close friends to whom they feel close and with whom they felt at ease and could talk to about private matters and could call on for help as well as how many of these people they see monthly. Social network size was the number of these individuals (children, family, and friends) seen at least once per month.[22]

Assessment of Dementia, Alzheimer Disease–Related Dementia, and Mild Cognitive Impairment

Clinical diagnoses of dementia and Alzheimer disease (AD)–related dementia were based on criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association.[23] The diagnosis of mild cognitive impairment (MCI) referred to persons with cognitive impairment diagnosed by the neuropsychologist but without a clinical diagnosis of dementia by the examining clinician.[24,25]

Assessment of Brain Pathologies

Postmortem neuropathologic evaluations were conducted on the 611 autopsied brains (median [interquartile range] postmortem interval, 6.90 [3.53-10.27] hours). Global AD pathology burden, β-amyloid plaques, and tangles were quantified[26] and also categorized as being at low or high levels. Chronic infarcts, including gross infarcts and microinfarcts[14]; cerebral vascular disease pathology, including atherosclerosis, arteriolosclerosis, and cerebral amyloid angiopathy[27]; Lewy bodies[14]; and typical hippocampal sclerosis[28] were assessed as present or absent.

Other Variable Assessments

A broad range of potential confounders and proxies for confounders were considered, including age, sex, smoking, alcohol consumption, physical activity, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), Mini-Mental State Examination (MMSE) score, heart disease, hypertension, diabetes, and apolipoprotein E (*APOE*) ε*4* status. They are described in detail in eMethods 1 in the Supplement.

Statistical Analysis

The characteristics of the study population by dementia or survival status were compared using *t* tests and nonparametric tests (χ^2 and Wilcoxon rank sum tests). To construct the lifespan CR accumulation based on stimulating mental and social activities during life course, structural equation modeling (SEM) was performed to derive a best-fitting measurement modelheusingTJ0/Felh.sease pasmssre 1-81I,1-81I1-81I,437testent

Table 1. Baseline Characteristics of the Study Population by Dementia Status

Characteristic	No. (%)		*P* Value
	Dementia-Free (n = 1216)	Incident Dementia (n = 386)	
Age, mean (SD), y	78.5 (7.6)	83.0 (6.0)	<.001
Female	924 (76.0)	292 (75.7)	.89
Life course cognitive reserve factors			
Education, mean (SD), y	14.8 (3.3)	14.5 (3.1)	.08
Early-life cognitive activity, mean (SD)	3.1 (0.6)	3.0 (0.6)	.11
Midlife cognitive activity, mean (SD)	3.3 (0.6)	3.2 (0.7)	.04
Late-life cognitive activity, mean (SD)	3.2 (0.7)	3.1 (0.8)	.003
Social activity in late life, mean (SD)	2.7 (0.6)	2.5 (0.6)	<.001
Social network, median (IQR)	6.0 (3.0-10.0)	5.0 (3.0-9.0)	.03
Smoking status			
Never	696 (57.2)	245 (63.5)	.08
Ever	483 (39.7)	133 (34.5)	
Current	37 (3.1)	8 (2.0)	
Alcohol consumption[a]			
Never/occasional	731 (60.8)	261 (67.6)	.03

0.99) for those in the middle CR score tertile and 0.61 (95% CI, 0.47-0.81) for those in the highest CR score tertile, and the HRs of AD-related dementia were 0.77 (95% CI, 0.59-1.00) for those in the middle CR score tertile and 0.61 (95% CI, 0.46-0.81) for those in the highest CR score tertile. The association of the CR score with dementia and AD-related dementia risk was dose dependent (**Table 2**).

Kaplan-Meier survival analysis showed that median (interquartile range) dementia onset time was 12.30 (8.78-15.82) years in participants in the lowest CR score tertile, 14.98 (11.14-18.82) years in participants in the middle CR score tertile, and more than 20 years in participants with highest CR. Participants in the highest CR score tertile had later dementia onset by more than 7 years compared with those in the lowest CR score tertile (eFigure 2 in the Supplement).

CR and Dementia Risk in Autopsied Participants

Of the 747 people who died, 611 (81.8%; 440 [72.0%] women; mean [SD] age, 83.0 [5.8] years) underwent autopsy, of whom 241 were diagnosed as having incident dementia. Baseline and neuropathological characteristics of the autopsied participants by dementia status are shown in eTable 2 in the Supplement.

In the post mortem data analysis, multiadjusted multinomial logistic regression analyses showed that compared with the lowest CR score tertile, the middle and highest CR score tertiles at baseline were not associated with the burden of AD pathology and other brain pathologies, except for gross infarcts (OR, 0.49; 95% CI, 0.31-0.78) (eTable 3 in the Supplement). There was no statistically significant association of MCI with global AD pathology (OR, 0.78; 95% CI, 0.37-1.67; $P = .53$) or gross infarcts (OR, 1.04; 95% CI, 0.38-2.82; $P = .94$) among those in the highest CR score tertile.

Table 2. Association of Levels of Cognitive Reserve With Dementia and Alzheimer Disease (AD)–Related Dementia Among All Participants

Cognitive Reserve	No. of Participants	Dementia			AD-Related Dementia		
		No.	HR (95% CI)[a]	Multiadjusted HR (95% CI)[b]	No.	HR (95% CI)[a]	Multiadjusted HR (95% CI)[b]
Continuous	1364[c]	349	0.89 (0.85-0.93)	0.93 (0.88-0.97)	320	0.89 (0.85-0.93)	0.92 (0.88-0.97)
Categorical tertile							
Lowest	442	138	1 [Reference]	1 [Reference]	126	1 [Reference]	1 [Reference]
Middle	453	108	0.71 (0.55-0.92)	0.77 (0.59-0.99)	99	0.71 (0.55-0.93)	0.77 (0.59-1.00)
Highest	469	103	0.55 (0.42-0.71)	0.61 (0.47-0.81)	95	0.55 (0.42-0.72)	0.61 (0.46-0.81)
P for trend	NA	NA	<.001	<.001	NA	<.001	<.001

The multiadjusted Cox regression models showed that the highest CR score tertile was significantly associated with a reduction in risk of dementia (HR, 0.60; 95% CI, 0.42-0.86) and AD-related dementia (HR, 0.60; 95% CI, 0.41-0.87) compared with the lowest CR score tertile after additional adjustment for global AD pathology and other brain pathologies. The associations of CR score tertile with risk of dementia and AD-related dementia were dose dependent (eTable 4 in the Supplement).

Compared with those with high brain pathologies but in the lowest CR score tertile, the incident rates of dementia were about 38% to 55% lower in people both in the highest CR score tertile and with high brain pathologies (including global AD pathology, gross infarcts, and microscopic infarcts) (**Figure 2**; eTable 5 in the Supplement). In stratified analysis by level of brain pathology, the association of high CR score tertile with a reduction in dementia risk remained significant in participants with high AD pathology (HR, 0.57; 95% CI, 0.37-0.87) and any gross infarcts (HR, 0.34; 95% CI, 0.18-0.62) (**Table 3**).

Supplementary Analyses

The results were not altered much compared with those from initial analyses when we repeated the following analyses by (1) multiple imputation for missing values (eTable 6 in the Supplement), (2) excluding 420 individuals with MCI at baseline (eTable 7 in the Supplement), (3) using competing risks models in all participants (eTable 8 in the Supplement), (4) removing education from the SEM (eTable 9 in the Supplement), (5) removing late-life cognitive and social activities from the SEM (eTable 10 in the Supplement), and (6) assessing the association of individual factors included in CR with dementia risk (eTable 11 in the Supplement). Finally, we found that sex did not significantly affect the association of CR with dementia risk in all participants (HR, 1.05; 95% CI, 0.78-1.43; $P = .74$) or in autopsied participants (HR, 1.01; 95% CI 0.68-1.49; $P = .97$).

Discussion

In this community-based prospective study of dementia-free older adults, we found that (1) high lifespan CR indicator accumulated through education, early-life cognitive activities, midlife cognitive activities, late-life cognitive activities, and social activities in late life was associated with a reduction in risk of dementia in a dose-dependent manner; (2) CR was not

Table 3. Association of Cognitive Reserve (CR) With Dementia and Alzheimer Disease (AD)–Related Dementia by Presence of Brain Pathology[c]

Brain Pathology	CR Tertile	No. of Participants	Dementia			AD-Related Dementia		
			No.	HR (95% CI)[a]	Multiadjusted HR (95% CI)[b]	No.	HR (95% CI)[a]	Multiadjusted HR (95% CI)[b]
Global AD pathology burden								
Low	Lowest	94	32	1 [Reference]	1 [Reference]	30	1 [Reference]	1 [Reference]
	Middle	91	21	0.58 (0.33-1.02)	0.66 (0.36-1.23)	17	0.53 (0.30-0.92)	0.58 (0.30-1.12)
	Highest	102	29	0.55 (0.32-0.94)	0.63 (0.35-1.13)	26	0.51 (0.28-0.93)	0.60 (0.33-1.11)
High	Lowest	104	63	1 [Reference]	1 [Reference]	58	1 [Reference]	1 [Reference]
	Middle	95	45	0.87 (0.59-1.27)	0.94 (0.63-1.39)	43	0.88 (0.59-1.30)	0.97 (0.64-1.47)
	Highest	83	38	0.63 (0.42-0.95)	0.57 (0.37-0.87)	37	0.64 (0.43-0.98)	0.58 (0.37-0.90)
Gross infarcts								
No	Lowest	113	47	1 [Reference]	1 [Reference]	44	1 [Reference]	1 [Reference]
	Middle	112	33	0.63 (0.39-0.96)	0.64 (0.40-1.03)	32	0.63 (0.42-0.97)	0.65 (0.40-1.05)
	Highest	138	48	0.61 (0.42-0.95)	0.61 (0.40-0.93)	46	0.62 (0.39-0.98)	0.60 (0.39-0.93)
Any	Lowest	85	48	1 [Reference]	1 [Reference]	44	1 [Reference]	1 [Reference]
	Middle	74	33	0.83 (0.53-1.31)	0.78 (0.49-1.23)	28	0.80 (0.49-1.29)	0.74 (0.46-1.22)
	Highest	47	19	0.41 (0.23-1.31)	0.34 (0.18-0.62)	17	0.39 (0.22-0.72)	0.32 (0.17-0.61)

Abbreviation: HR, hazard ratio.

[a] Adjusted for age and sex.

[b] Adjusted for age, sex, smoking, alcohol consumption, physical activity, body mass index, heart disease, hypertension, cerebrovascular disease, diabetes, and apolipoprotein E ε4.

[c] A total of 43 participants had missing data (body mass index, 11; cerebrovascular disease, 26; and apolipoprotein E ε4, 6).

associated with most brain pathologies, and the association of CR with dementia remained significant after additional adjustment for brain pathologies; and (3) high CR could be associated with a reduction in dementia risk even in the presence of high AD burden and vascular pathologies. Neuropathological and neuroimaging studies have suggested that many people may tolerate considerable AD-related neuropathology without expressing the clinical syndrome.[1] Indeed, about 25% of cognitively healthy older adults have increased levels of β-amyloid plaques in the brain.[4] The concept of CR refers to the capacity to be resilient to age-related brain changes and the disease-related pathology in the brain without developing clinical dementia[29] through enhanced brain network efficiency, capacity, or flexibility.[13] Although a number of CR-related factors, including higher education attainment,[2,30] complex occupation status,[29] and rich cognitive and social activities,[3,31,32] have been individually associated with a reduction in dementia risk, the association of each individual component with dementia could also be because of many alternative paths instead of a direct relation to the hypothesized CR. For example, lower education that is associated with dementia risk may also contribute to the deleterious effects of low socioeconomic status or cardiovascular disorders.[33]

In recent years, the use of CR indices has been suggested to evaluate the CR based on cumulative reserve factors,[34,35] and the specific weight of each proxy indicator has been controversial. In the present study, to extract the CR score, we used SEM based on lifespan (ie, through early life, midlife, and late life) cognitive-enhancing activities and social activities in late life, and the weight of each CR factor was generated from SEM according to its contribution to the score, which was not equally weighted. We found that lifespan CR indicators in the middle and highest tertiles were associated with an approximately 23% to 39% reduction in risk of dementia. Furthermore, the association of CR with dementia was dose dependent, suggesting that accumulative educational and mentally stimulating activities throughout life are of great significance, given that there is currently no effective treatment for dementia.

So far, few studies presenting the association of the proxy of CR with dementia have taken brain pathologies into account. A 1999 study[8] found that lower education was associated with the occurrence of cerebral infarcts. However, many other studies have failed to find a direct association of CR factors (such as education,[11] cognitive activity,[16] or cognitive lifestyle score[36]) with common dementia neuropathology. In the present study, we found that high lifespan CR indicator was not associated with most brain pathologies, except for gross infarcts, and baseline MCI status did not modify the association of brain pathology with CR. Further, high CR indicator was associated with a reduction in the risk of dementia independently of AD, vascular, and other brain pathologies. In addition, high lifespan CR indicator may be associated with a reduction in the risk of dementia even in the presence of high AD and vascular pathologies. These results were consistent with other studies[11] and the CR theory[7] that CR could reduce dementia risk and compensate for or cope with dementia pathology through other pathways rather than avoiding pathology directly.

Strengths and Limitations

This study has high rates of clinical evaluation and autopsy, which might minimize selective bias. Furthermore, the use of latent factors could capture the comprehensive effect of multiple CR factors across the lifespan. Nonetheless, some

limitations need to be pointed out. First, the generalizability of the findings is limited because the study participants were volunteers. Second, as the brains were obtained at the

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