Lifelong cognitive reserve, dementia, and mild cognitive impairment among older adults with limited education: a population-based cohort study

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Abstract

Background

Early-life educational attainment represents a major proxy for cognitive reserve (CR) that could benefit late-life cognitive function. We sought to investigate the associations of lifelong CR capacity with dementia and mild cognitive impairment (MCI) among people with limited education, while paying special attention to subtypes of dementia and MCI.

Methods

This population-based cohort study included 2127 participants (age ≥ 60 years; 59.4% women; 81.5% illiteracy or elementary school) who were free of dementia at baseline (August-December 2014) and undertook follow-up examinations in March-September 2018. Lifelong CR at baseline was estimated by integrating early-life education, adulthood occupation and marital status, and late-life physical activity, social activity, and social support using the structural equation models. Dementia, Alzheimer's disease (AD), and vascular dementia (VaD) were diagnosed following the international criteria. MCI and amnestic and non-amnestic MCI were defined following the Petersen's criteria. Data were analyzed using Cox proportional-hazards models.

Results

During the total of 8330.63 person-years of follow-up, 101 were diagnosed with dementia, including 74 with AD and 26 with VaD. Medium and high (vs. low) tertiles of lifelong CR score were associated with multi-adjusted hazards ratio (95% confidence interval, CI) of 0.63 (0.40–1.00) and 0.27 (0.14–0.54) for dementia and 0.60 (0.35–1.02) and 0.18 (0.07–0.49) for AD. The association between higher CR and reduced AD risk was significant in young-old (60–74 years) but not in old-old people (≥ 75 years) ($P_{interaction}$=0.011). Similarly, medium and high (vs. low) CR levels were associated with multi-adjusted hazard ratio (95% CI) of 0.81 (0.62–1.05) and 0.54 (0.40–0.73) for MCI and 0.73 (0.54–0.98) and 0.50 (0.36–0.70) for amnestic MCI. Lifelong CR was not significantly related to VaD or non-amnestic MCI. There was no statistical interaction of lifelong CR with sex and *APOE* genotype on incident dementia or MCI.

Conclusions

High lifelong CR is associated with reduced risks of dementia and MCI, especially AD and amnestic MCI. The association of high CR with reduced AD risk existed only in young-old people. This study highlights the importance of lifelong CR in in maintaining late-life cognitive health even among people with limited education.

Introduction

Cognitive reserve (CR) refers to the individual adaptability of cognitive function in coping with brain aging or pathology.[1] The lifelong CR capacity can be derived from the intellectual factors experienced over the life-course, such as early-life education attainment, adulthood marital status and occupational complexity, and late-life mental activity, physical activity, and social engagement.[2] Population-based studies from high-income countries, where people usually have high educational attainments, have consistently shown that higher CR capacity derived from lifelong cognitive enriching factors is related to lower incidence of dementia[3–5] and mild cognitive impairment (MCI).[6] The associations of CR with dementia and MCI among rural residents or people with limited education have rarely been examined in population-based cohort studies. This is important because early-life high educational attainment is the major contributor to CR capacity,[7] and might affect other CR proxies over the lifespan (e.g., socioeconomic status, work complexity, and social activity).[8] Thus, knowledge regarding the potential role of lifelong CR capacity in late-life cognitive function among illiterate older adults or those with very low education may facilitate preventive interventions to reduce risk of dementia in low- or middle-income countries where people usually have limited education.

In addition, previous studies have suggested that the cognitive benefits of different CR proxies (e.g., education, physical activity, and social activity) might vary depending on types of dementia and MCI.[9–11] Thus, it is worth investigating whether lifelong composite CR capacity is preferably associated with certain subtypes of dementia and MCI. However, this issue has not yet been explored in population-based studies. This knowledge is highly relevant because preferable associations of CR with specific types of dementia or MCI might shed light on the potential neuropathological mechanisms of CR, and thus inform the development of intervention strategies. Furthermore, given that the potential associations of CR proxies with the risk of dementia and MCI might vary by demographic features and genetic susceptibility[12–14], it is relevant to clarify whether lifelong CR capacity could interact with certain demographic factors and *APOE* genotypes to affect the risk of dementia and MCI.

Taken together, although various CR proxies have been linked with the reduced risk of dementia, there is a paucity of literature regarding the relationships of lifelong CR with subtypes of dementia and MCI among rural populations with very limited education. Therefore, in this population-based cohort study, we aimed to investigate the longitudinal associations of lifelong CR capacity with dementia and MCI, especially with regard to main subtypes of dementia and MCI, among rural older adults with no or very limited education, while taking into account *APOE* genotypes and demographics. Our hypothesis was that high lifelong CR capacity could delay the onset of late-life dementia and MCI even among older adults with very limited educational attainments and that the potential cognitive benefits was profound for cognitive phenotypes due primarily to neurodegenerative pathologies.

Methods

Study design and participants

This was a population-based cohort study. Data were derived from the Shandong Yanggu Study of Aging and Dementia (SYS-AD), which targeted people aged 60 years and above in the rural area of Yanlou Town, Yanggu County, western Shandong Province, China.[15] In August 2014–September 2015, a total of 3277 participants took part in the baseline examinations; of these, 278 participants were diagnosed with dementia (n = 206) or had insufficient information for the diagnosis of dementia (n = 72). The follow-up examination was performed in March-September 2018, as a part of the Multimodal Interventions to Delay Dementia and Disability in rural China (MIND-China) project.[16] Out of the 2999 dementia-free participants identified at baseline, 872 were excluded due to missing measures of cognitive reserve at baseline (n = 167), death (n = 229), loss to the follow-up examination (n = 528), or insufficient information for the diagnosis of dementia at follow-up (n = 14). Thus, a total of 2127 participants (70.9% of all eligible participants) who were free of dementia at baseline completed the follow-up examination (analytical sample 1). In addition, a total of 1635 participants were free of MCI at baseline and undertook the follow-up examination (analytical sample 2). Figure 1 shows the flowchart of study participants.

(Insert Fig. 1 *here)*

Data collection and assessments at baseline

At baseline, we collected data through face-to-face interviews, clinical examinations, and laboratory tests. Data included social demographics (e.g., age, sex, education, occupation, and marital status), lifestyles (e.g., smoking, alcohol drinking, physical activity, and social activity), cardiometabolic health conditions (e.g., hypertension, diabetes, hyperlipidemia, coronary artery disease, and stroke), neuropsychological tests, and social support. We categorized early-life educational levels as illiterate (no formal schooling), elementary school (1–5 years), and middle school or above (≥ 6 years). We dichotomized adulthood occupation as farming vs. non-farming, and marital status as married vs. single, divorced, or widowed. Smoking and alcohol consumption were categorized into ever vs. never smoking or drinking alcohol. We defined the frequency of physical activity in late life as at least weekly vs. less than weekly, and frequency of social activity in late life as never or occasional vs. frequent participation according to self-reported information. Social support (e.g., living alone or with family members and support from family members, neighbors, or colleagues) was assessed using the Social Support Rating Scale that was validated among Chinese population, and then dichotomized into low social support (below the mean Social Support Rating Scale score) vs. high social support, as previous reported.[17] We used the structural equation models to generate the lifelong composite CR score by taking into account early-life educational attainment, adulthood occupation and marital status, and late-life physical activity, social activity, and social support, among all participants with all individual CR proxies in the SYS-AD study (n = 3060) (Fig. 2). Accordingly, we categorized lifelong composite CR capacity into low, medium, and high levels according to tertiles of the score.

(Insert Fig. 2 *here)*

Hypertension was defined as self-reported history or systolic pressure ≥ 140 mm Hg or diastolic pressure ≥ 90 mm Hg.[16] Diabetes was defined according to self-reported history of diabetes diagnosed by a physician, fasting serum glucose ≥ 7.0 mmol/L, or current use of hypoglycemic medication.[16] Hyperlipidemia was defined as the total cholesterol level ≥ 6.2 mmol/L, triglyceride ≥ 2.3 mmol/L, low-density lipoprotein cholesterol ≥ 4.1 mmol/L, high-density lipoprotein cholesterol < 1.0 mmol/L, or having a self-reported history of hyperlipidemia.[15] We defined stroke and coronary heart disease according to self-reported history of the disease diagnosed by physicians during the annual health check-ups.[15]

Data collection and APOE genotyping at follow-up

At follow-up, we collected data on neuropsychological status, clinical conditions, and *APOE* genotypes, as previously reported.[16] The trained staff collected venous blood samples, extracted genomic deoxyribonucleic acid from venous blood leukocytes, and then quantified deoxyribonucleic acid using Nanodrop 3300 spectrometry. The sequencing libraries were generated using MultipSeqCustom Panel (iGeneTech, Beijing, China) following standard procedures. Genotyping was conducted by an operator who was blinded to all clinical data. The distribution of *APOE* genotypes conformed to the Hardy-Weinberg equilibrium ($P > 0.05$).

Diagnosis of dementia and mild cognitive impairment

At both baseline and follow-up examinations, dementia was diagnosed following the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,[18] in which a 3-step diagnostic procedure was followed, as previously reported.[15] Briefly, in step 1, the trained medical staff performed the first face-to-face interview, clinical examination, and laboratory tests following a structured questionnaire. In step 2, the neurologists specialized in dementia care (L.C., T.H., S.T., X.H., and Q.Z.) reviewed all the records from step 1 to screen participants who were suspected to have dementia or who had insufficient information for a judgement of dementia for further assessments. Finally, the neurologists conducted the second in-person or telephone interviews with participants who were selected in step 2 or with informants, and the diagnosis was made based on all assessments.

Alzheimer's disease (AD) was diagnosed according to the National Institute on Aging-Alzheimer's Association criteria for probable AD.[19] The diagnosis of vascular dementia was made according to the criteria of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences for probable vascular dementia,[20] which was based on the self-reported, clinical, or neuroimaging evidence of stroke, as well as the presence of a clear temporal relation between stroke and the onset of dementia. Dementia cases who could not be classified as either AD or vascular dementia were considered to have other types of dementia.

Among participants who were free of dementia both at baseline and follow-up, MCI was clinically defined by the neurologists via reviewing all records from the interviews, clinical examination, and comprehensive assessments of sub-cognitive domains, following the Petersen's criteria, as previously reported.[21] At

follow-up, participants with MCI were further categorized as having amnestic MCI (aMCI) if the memory domain was impaired or non-amnestic MCI (non-aMCI) if there was no impairment in the memory domain.[22]

Statistical analyses

We compared the baseline characteristics of study participants by age groups (60–74 vs. ≥75 years), using the general linear regression model for continuous variables and the χ^2 test for categorical variables. Next, we used the Cox proportional-hazards models to examine the association of lifelong CR capacity (as both a continuous score and a categorical variable) with incident dementia, AD, and vascular dementia. Likewise, among participants who were free of MCI at baseline, we used the Cox models to examine the association of CR capacity with incident MCI, aMCI, and non-aMCI. Finally, we examined the statistical interaction of CR capacity with sex, age groups, and *APOE* ε4 allele on the risks of dementia, MCI, and their subtypes. If any statistical interaction was detected (P for interaction < 0.05), we further performed the stratified analysis to assess the direction and extent of the interaction. We reported the results from statistical models that were adjusted for age, ever smoking, ever alcohol consumption, hypertension, hyperlipidemia, diabetes, coronary heart disease, and stroke, and if applicable, for sex and *APOE* genotypes. We used Stata Statistical Software: Release16, for Windows (StataCorp LLC, College Station, TX, USA) for all the statistical analyses.

Results

Baseline characteristics of study participants

At baseline, the mean age of the 2127 participants was 70.1 (SD, 4.8) years, 59.4% were women, and 81.5% were illiterate or only attended elementary school. Compared to young-old participants (60–74 years), the old-old participants (≥ 75 years) were more likely to be illiterate, farmers, and single, divorced or widowed, to participate in social activity, to have higher social support, and to have diabetes, and less likely to take part in physical activity, to drink alcohol, to report a history of clinical stroke, or to carry the *APOE* ε4 allele (P< 0.05, Table 1). The old-old participants had a lower CR capacity compared to young-old participants (P< 0.001, Table 1). The two age groups did not differ significantly in the proportion of ever smoking, hypertension, hyperlipidemia, or coronary heart disease (P> 0.05, Table 1).

Table 1
Baseline characteristics of study participants (n = 2127)

Characteristics	Total sample (n = 2127)	Age groups (years)		
		60–74 (n = 1763)	75–91 (n = 364)	*P*-value
Age, years, mean (SD)	70.06 (4.77)	68.33 (2.77)	78.48 (3.20)	< 0.001
Female	1263 (59.38)	1040 (58.99)	223 (61.26)	0.421
Early-life education				< 0.001
Illiterate	818 (38.46)	597 (33.86)	221 (60.71)	
Primary school	983 (46.22)	867 (49.18)	116 (31.87)	
Middle school and above	326 (15.33)	299 (16.96)	27 (7.42)	
Adulthood occupation				0.244
Farmer	1929 (90.69)	1593 (90.36)	336 (92.31)	
Non-farmer	198 (9.31)	170 (9.64)	28 (7.69)	
Adulthood marital status				< 0.001
Married	1606 (75.51)	1412 (80.09)	194 (53.30)	
Single, divorced, or widowed	521 (24.49)	351 (19.91)	170 (46.70)	
Late-life physical activity				0.003
Less than once a week	897 (42.17)	769 (43.62)	128 (35.16)	
At least once a week	1230 (57.83)	994 (56.38)	236 (64.84)	
Late-life social activity				0.015
Never or occasionally	958 (45.04)	773 (43.85)	185 (50.82)	
Frequently	1169 (54.96)	990 (56.15)	179 (49.18)	
Late-life social support				< 0.001
Low	903 (42.45)	701 (39.76)	202 (55.49)	
High	1224 (57.55)	1062 (60.24)	162 (44.51)	
Cognitive reserve				< 0.001

Data were n (%), unless otherwise specified.

*The number of persons with missing values was 6 for ever smoking, 5 for ever alcohol drinking, 10 for hypertension, 1 for hyperlipidemia, 21 for diabetes, 16 for coronary heart disease, 16 for stroke, and 86 for *APOE* genotype.

Characteristics	Total sample (n = 2127)	Age groups (years)		
		60–74 (n = 1763)	75–91 (n = 364)	*P*-value
Low	607 (28.54)	417 (23.65)	190 (52.20)	
Medium	733 (34.46)	623 (35.34)	110 (30.22)	
High	787 (37.00)	723 (41.01)	64 (17.58)	
Ever smoking*	727 (34.18)	612 (34.71)	115 (31.59)	0.312
Ever alcohol consumption*	723 (33.99)	617 (35.00)	106 (29.12)	0.043
Hypertension*	835 (39.26)	700 (39.71)	135 (37.09)	0.525
Hyperlipidemia*	614 (28.87)	501 (28.42)	113 (31.04)	0.547
Diabetes*	190 (8.93)	173 (9.81)	17 (8.95)	0.002
Coronary heart disease*	398 (18.71)	331 (18.77)	67 (18.41)	0.871
Stroke*	173 (8.13)	156 (8.85)	17 (4.67)	0.025
APOE **ε4 allele***				< 0.001
Carrier	317 (14.90)	278 (15.77)	39 (10.71)	
Non-carries	1724 (81.05)	1426 (80.88)	298 (81.87)	
Data were n (%), unless otherwise specified.				
*The number of persons with missing values was 6 for ever smoking, 5 for ever alcohol drinking, 10 for hypertension, 1 for hyperlipidemia, 21 for diabetes, 16 for coronary heart disease, 16 for stroke, and 86 for *APOE* genotype.				

(Insert Table 1 *here)*

Association of cognitive reserve with incident dementia and its subtypes (analytical sample 1)

During the total of 8330.63 person-years of follow-up (mean follow-up time per person, 3.7 years; SD = 0.4), dementia was diagnosed in 101 persons, including 74 with AD, 26 with vascular dementia, and 1 with other type of dementia. Each 1-point increment in the lifelong CR score at baseline was significantly associated with an approximately 20% reduced risk of incident dementia and AD ($P < 0.001$), but not with incident vascular dementia (Table 2). Compared to low CR, both medium and high levels of CR capacity were linearly associated with reduced risk of incident dementia and AD (P for linear trend < 0.001), but not with incident vascular dementia (Table 2).

Table 2
Associations of cognitive reserve with incident dementia, Alzheimer's disease, and vascular dementia (analytical sample 1)

Cognitive reserve score at baseline	No. of subjects	Dementia		Alzheimer's disease		Vascular dementia	
		No.	HR (95% CI)[a]	No.	HR (95% CI)[a]	No.	HR (95% CI)[a]
Continuous (range: -4.2–5.0)	2127	101	0.82 (0.73–0.92)[‡]	74	0.79 (0.69–0.90)[‡]	26	0.91 (0.74–1.12)
Categorical (tertiles)							
Low (-4.2– -1.0)	607	56	1.00 (reference)	47	1.00 (reference)	8	1.00 (reference)
Medium (-1.0–1.2)	733	33	0.63 (0.40–1.00)[*]	22	0.60 (0.35–1.02)	11	0.89 (0.34–2.34)
High (1.2–5.0)	787	12	0.27 (0.14–0.54)[‡]	5	0.18 (0.07–0.49)[†]	7	0.47 (0.15–1.48)
P for trend			< 0.001		< 0.001		0.188

Abbreviations: HR, hazards ratio; CI, confidence interval.

[a]Hazards ratios (95% confidence intervals) were controlled for age, sex, ever smoking, ever alcohol consumption, hypertension, hyperlipidemia, diabetes, coronary heart disease, stroke, and *APOE* genotypes.

[*]P < 0.05, [†]P < 0.01, [‡]P < 0.001.

(Insert Table 2 *here)*

There was a statistical interaction between lifelong CR score and age groups on incident AD (*P* for interaction = 0.011). Stratified analysis by age groups suggested that each 1-point increment in composite CR score was significantly associated with a reduced risk of incident AD in young-old (multi-adjusted hazard ratio [HR] = 0.71; 95% confidence interval [CI]: 0.59–0.86) but not in old-old (0.90; 0.74–1.10) people. Similarly, when categorizing the lifelong CR score into tertiles, compared to low CR tertile, the medium and high tertiles of CR score were related to a lower risk of AD only in young-old but not old-old people (Fig. 3). There was no statistical interaction of composite CR score with sex or *APOE* genotypes on incident dementia, AD, or vascular dementia.

(Insert Fig. 3 *here)*

Association of cognitive reserve with incident mild cognitive impairment and its subtypes (analytical sample 2)

Among participants who were free of MCI at baseline (n = 1635), 331 were defined to have MCI at the follow-up, including 270 with aMCI and 61 with non-aMCI. Each 1-point increment in the composite CR score was significantly related to an approximately 15% lower risk of incident MCI and aMCI, but not related to incident non-aMCI (*P* < 0.001, Table 3). When lifelong CR score was treated as a categorial variable, high (vs. low) CR capacity was significantly related to a lower risk of incident MCI (*P* for linear trend < 0.001) (Table 3). In addition, compared to low CR tertile, medium and high tertiles of CR score were related to a lower risk of incident aMCI (*P* for linear trend < 0.05). Neither medium nor high CR capacity was associated with incident non-aMCI (Table 3).

Table 3
Associations of cognitive reserve with incident mild cognitive impairment among participants free of dementia at follow-up (analytical sample 2)

Cognitive reserve score at baseline	**No. of subjects**	**MCI**		**Amnestic MCI**		**Non-amnestic MCI**	
		No.	**HR (95% CI)[a]**	**No.**	**HR (95% CI)[a]**	**No.**	**HR (95% CI)[a]**
Continuous (range: -4.2–5.0)	1635	331	0.85 (0.80–0.91)‡	270	0.84 (0.79–0.90)‡	61	0.92 (0.80–1.06)
Categorical (tertiles)							
Low (-4.2– -1.0)	382	109	1.00 (reference)	95	1.00 (reference)	14	1.00 (reference)
Medium (-1.0–1.2)	540	120	0.81 (0.62–1.05)	93	0.73 (0.54–0.98)*	27	1.33 (0.68–2.57)
High (1.2–5.0)	713	102	0.54 (0.40–0.73)‡	82	0.50 (0.36–0.70)‡	20	0.81 (0.39–1.71)
P for trend			< 0.001		< 0.001		0.478

Abbreviations: MCI, mild cognitive impairment; HR, hazards ratio; CI, confidence interval.

[a]Hazards ratios (95% confidence intervals) were controlled for age, sex, ever smoking, ever alcohol consumption, hypertension, hyperlipidemia, diabetes, coronary heart disease, stroke, and *APOE* genotypes.

*P < 0.05, ‡P < 0.001.

(Insert Table 3 *here)*

Discussion

In this population-based cohort study among Chinese rural-dwelling elderly with very limited education, we found that high lifelong CR capacity was associated with reduced risks of late-life dementia and MCI, especially AD and amnestic MCI, but not with vascular dementia and non-aMCI. In addition, the association between high lifelong CR capacity and reduced risk of AD existed only in young-old but not in old-old people. These results suggested the importance of high lifelong CR capacity in maintaining cognitive health and delaying cognitive aging even among people with no or very limited educational attainment.

The association of high CR capacity with low risk of dementia has been well established mostly among urban or highly educated populations.[3–5] In addition, most of the previous cohort studies have investigated individual CR proxies (e.g., education, mental activity, and social engagement) in association with cognitive outcomes.[23–25] Our study targeted rural-dwelling older adults who had no or very limited schooling education. This is important because very few population-based cohort studies have clarified whether very low education could still benefit late-life cognitive function.[26] Furthermore, our study used the composited CR capacity derived from lifespan cognitively stimulating factors, which could represent the CR capacity cumulated over the life course. Our study confirmed that lifelong composite CR capacity was a relevant determinant of late-life cognitive phenotypes even among rural older adults with no or very limited education. This is in line with the clinicopathological data from the Brazilian Aging Brain Study, which showed that even a few years of formal education could contribute to CR, and thus benefit late-life cognitive function.[27]

Our study further revealed that high lifelong CR capacity was associated with a low risk of Alzheimer type of dementia, but not with vascular dementia. Neuropathological and neuroimaging studies have suggested that high CR capacity could mitigate the detrimental effect of AD-related neurodegenerative pathology on cognitive performance and delay the onset of dementia syndrome,[28–31]. For example, a clinic-based positron emission tomography imaging study found that high CR capacity could maintain cognitive function by tolerating more tau pathology.[31] On the other hand, data from neuroimaging-based studies appeared to show no evidence that higher CR capacity could modify the association of vascular brain injury (e.g., brain infarct and white matter hyperintensities) with poor cognitive function.[32, 33] Similarly, a cross-sectional clinic-based study suggested that high education might compensate for the detrimental effects of cortical thinning, but not cerebrovascular lesions (i.e., white matter hyperintensities and lacune), on cognitive function.[34] Taken together, findings from the literature and our own study support the view that increased CR capacity could compensate mainly for the adverse cognitive consequences owing to neurodegenerative pathologies rather than vascular brain injury.

Previously, the Rush Memory and Aging Project has linked higher lifespan CR capacity with a reduced incidence of MCI.[6] Our study extended the previous findings by showing that higher CR capacity was associated with lower risk of aMCI, but not non-aMCI. This has important implications for understanding

the neuropathological mechanisms of CR because the underlying neuropathology, prognosis, and evolution of aMCI and non-aMCI differ. Clinico-neuropathological studies suggested that neurodegenerative lesions are the underlying pathology of aMCI,[35] whereas cerebrovascular lesions play a pivotal role in non-aMCI.[36, 37] Given that higher CR capacity could compensate for the cognitive consequence of neurodegenerative lesions, but not cerebrovascular lesions,[28 32] it was reasonable that higher CR capacity could be preferably related to reduced risk of aMCI rather than non-aMCI.

Notably, we found that the association of high CR capacity with reduced risk of AD was evident mainly in young-old but not old-old people. This could be partly explained by the view that cognitive benefits of high CR capacity might be gradually diminished with the progression and accumulation of brain pathology (e.g., amyloid and tau proteins) as people age; when the load of age-related brain pathology reached the advanced stage or threshold for manifesting symptoms of cognitive impairment, the high CR capacity might no longer be able to tolerate or compensate for the accumulated brain pathology and delay cognitive decline and dementia.[29, 38] This could largely explain our finding that the association of higher CR capacity with lower risk of AD was less pronounced in old-old than in young-old people. These findings may have implications for determining the target population when designing the multimodal interventions that include CR components to delay cognitive decline and dementia.

Our population-based cohort study targeted the rural-dwelling older adults who had no or very limited education, in which the composite CR capacity was quantified from multiple cognitive-enhancing indicators experienced over the lifespan, and MCI was defined by integrating clinical assessments with standard neurocognitive tests. However, our study also had limitations. First, we had no biomarkers of brain pathology (e.g., amyloid-β aggregation, tau-protein, and cerebral microvascular lesions), which limited the potential to investigate the underlying neuropathological mechanisms of CR capacity in maintaining cognitive function. Furthermore, our single-center study targeted the elderly population with very limited education from only one rural area in western Shandong province, which should be kept in mind when generalizing our findings to other populations, even rural populations.

Conclusion

This population-based cohort study indicates that among rural-dwelling elderly with no or limited education, high lifelong CR capacity is associated with low risks of late-life dementia and MCI, especially AD and aMCI, but not vascular dementia and non-aMCI. In addition, the beneficial effects of lifelong CR capacity on reduced AD risk appeared to be evident only in young-old people (e.g., age < 75 years). These findings could inform the development of intervention strategies to maintain late-life cognitive health among rural populations who have very low literacy.

Abbreviations

CR
Cognitive reserve

AD
Alzheimer's disease
MCI
Mild cognitive impairment
aMCI
Amnestic mild cognitive impairment
non-aMCI
Non-amnestic mild cognitive impairment
APOE
Apolipoprotein E gene
SYS-AD
The Shandong Yanggu Study of Aging and Dementia
MIND-China
The Multimodal Interventions to Delay Dementia and Disability in Rural China
HR
Hazards ratio
CI
Confidence interval.

Declarations

Ethics approval and consent to participate

The protocols of both SYS-AD and MIND-China projects were reviewed and approved by the Ethics Committee on Human Experimentation at Shandong Provincial Hospital in Jinan, Shandong. MIND-China study was registered in the Chinese Clinical Trial Registry (Registration No.: ChiCTR1800017758). Written informed consents were obtained from all participants, or if the participants were not able to give the consent, from the informants.

Consent for publication

Not applicable.

Availability of data and materials

Data on which this study is based are derived from the population-based SYS-AD and MIND-China projects (https://www.alz.org/wwfingers/overview.asp). Access to these anonymized data will be available upon reasonable request and approval by the data management committee at Department of Neurology, Shandong Provincial Hospital, Jinan, Shandong, P.R. China.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Y.L., Y.D., and C.Q. conceptualized the study. Y.L., L.S., M.W., X.W., T.H., S.T., and Y.W. obtained data in the SYS-AD and MIND-China projects. Y.L. and Y.R analysed the data. C.Q. and Y.D. supervised the study. All authors interpreted the data, made critical comments on the draft, and approved the formal version of the manuscript.

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Figures

Figure 1

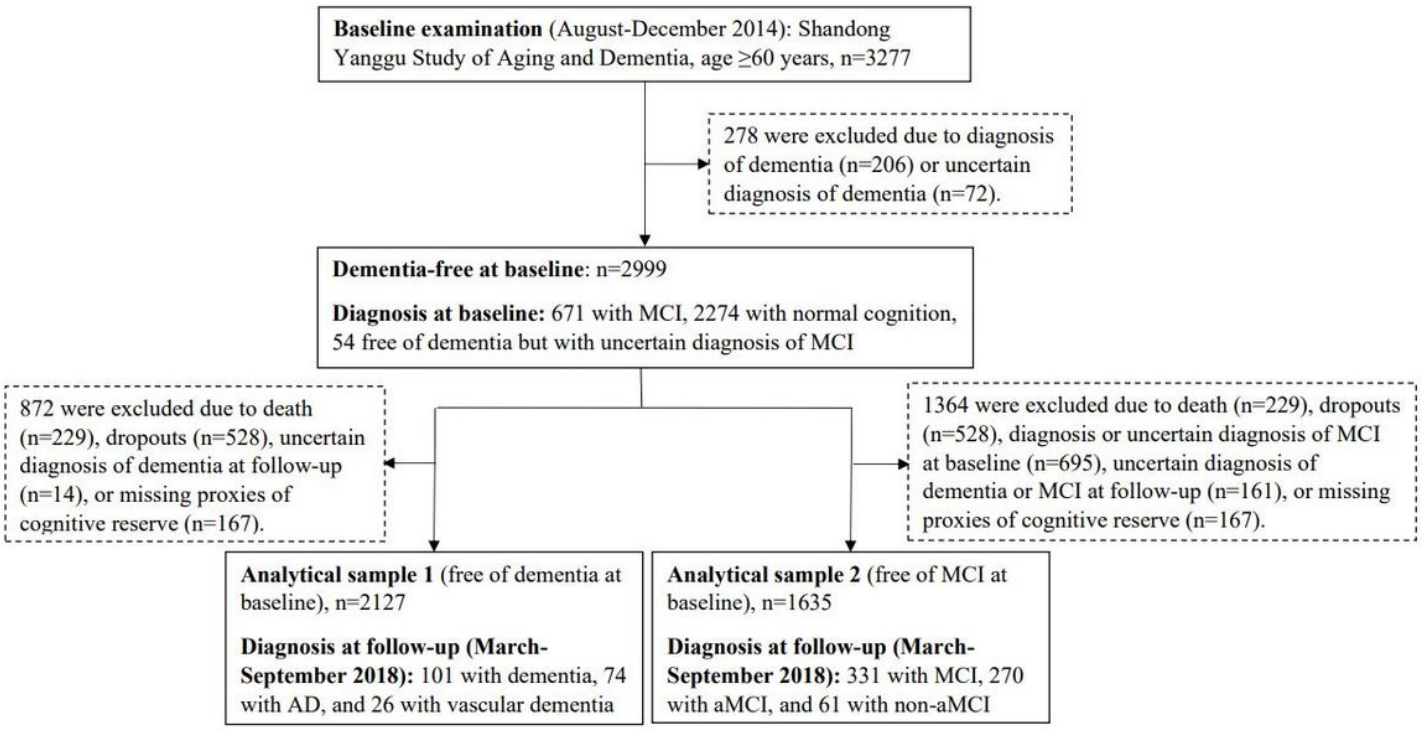

Figure 1

Flowchart of study participants

Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer's disease.

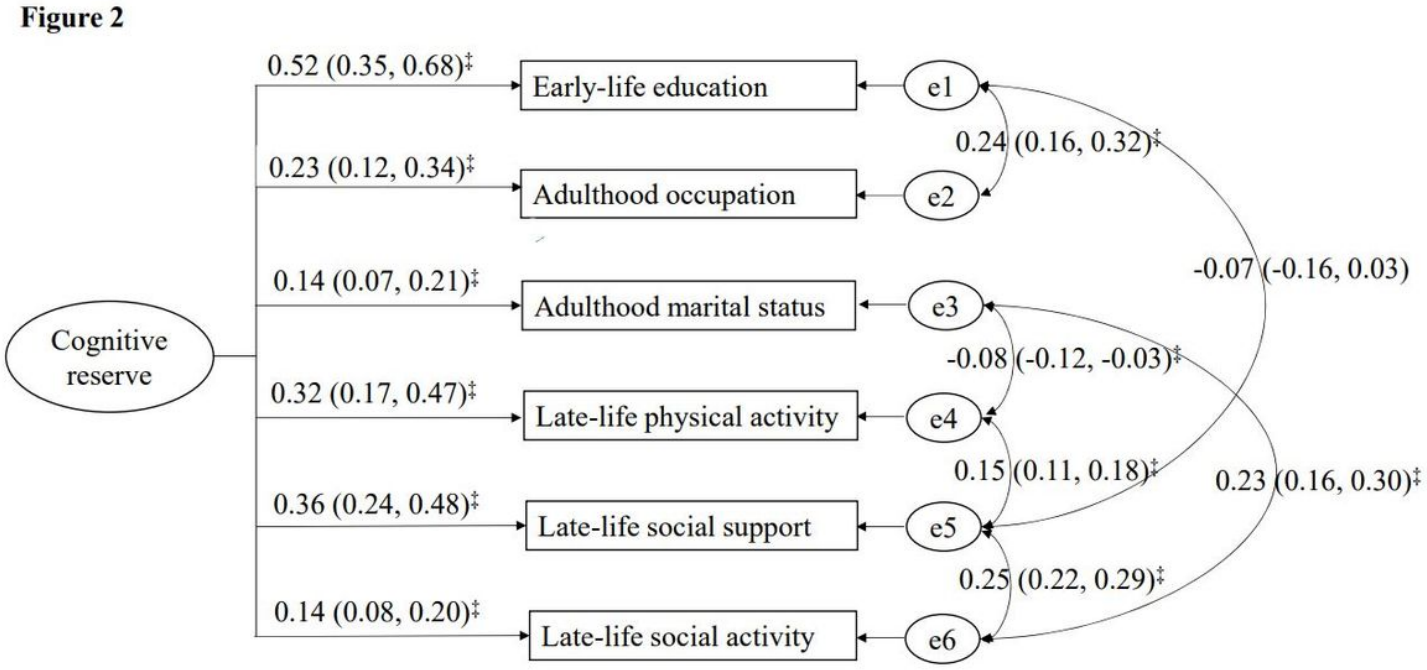

Figure 2

Standardized estimates for the composite cognitive reserve score (n=3060)

The values indicate the β-coefficients (95% confidence intervals) of the six observable factors to the composite cognitive reserve score from the structural equation models. e1, e2, e3, e4, e5, and e6 represent the measurement error for each of the six observable factors in estimating the composite cognitive reserve score.

Fit statistics of the structural equation model: chi-square = 7.37, *P* = 0.061; Comparative fit index = 0.996; Standardized root mean squared residual = 0.010; Root mean squared error of approximation = 0.022; Modification index: 6.57.

‡P<0.001.

Figure 3

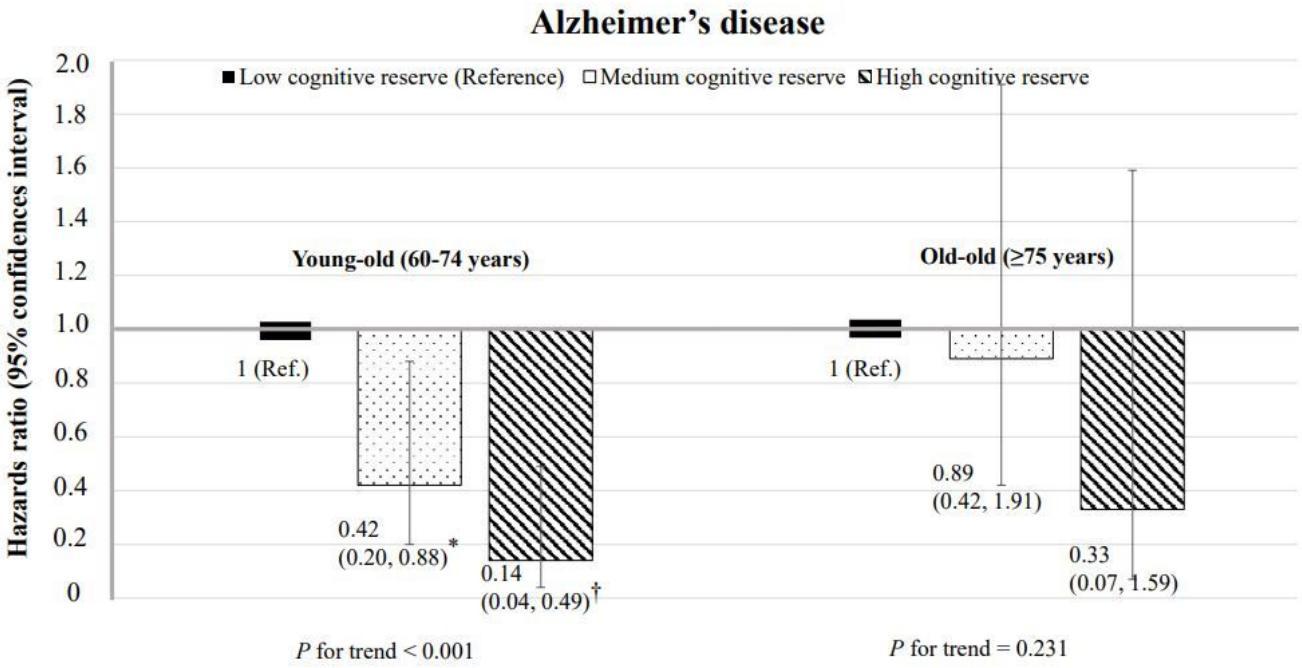

Figure 3

Associations of lifelong cognitive reserve with incident Alzheimer's disease by age groups (analytical sample 1)

Hazards ratios (95% confidence intervals) were controlled for age, sex, ever smoking, ever alcohol consumption, hypertension, hyperlipidemia, diabetes, coronary heart disease, stroke, and *APOE* genotypes.

*P<0.05, †P<0.01.