Is there a link between cognitive reserve and cognitive function in the oldest-old?

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Abstract

Background The oldest-old (aged ≥ 85 years) are the fastest growing age group, with the highest risk of cognitive impairment and dementia. This study investigated whether cognitive reserve applies to the oldest-old. This has implications for cognitive interventions in this age group.

Methods Baseline and five-year follow-up data from the Newcastle 85+ Study were used (N=845, mean age=85.5, 38% male). A Cognitive Reserve Index (CRI) was created, including: education, social class, marital status, engagement in mental activities, social participation and physical activity. Global (Mini Mental State Examination) and domain specific (Cognitive Drug Research Battery subtests assessing memory, attention and speed) cognitive functions were assessed. Dementia diagnosis was determined by health records. Logistic regression analysis examined the association between CRI scores and incident dementia. Mixed effects models investigated baseline and longitudinal associations between CRI and cognitive function. Analyses controlled for sex, age, depression, and cardiovascular disease history.

Results Higher reserve associated with better cognitive performance on all baseline measures, but not 5-year rate of change. The CRI associated with prevalent, but not incident dementia.

Conclusions In the oldest-old, higher reserve associated with better baseline global and domain-specific cognitive function and reduced risk of prevalent dementia; but not cognitive decline or incident dementia. Increasing reserve could promote cognitive function in the oldest-old. The results suggest there would be little impact on trajectories, but replication is needed. Development of preventative strategies would benefit from identifying the role of each factor in building reserve and why rate of change is not affected.

Key Words cognitive reserve, oldest-old, dementia, cognition, epidemiology

Introduction

Population ageing is a public health priority, with the oldest-old (defined as those aged 85 years and over) being globally the fastest growing age group (1). As the population is ageing there is also an increasing prevalence of cognitive impairment and dementia. However, studies conducted in high income countries have reported decreases in the prevalence and, in some cases, incidence of dementia (2-4). Increased cognitive reserve, primarily linked to educational attainment, is one factor that is thought to contribute to this decrease (5).

Cognitive reserve theory suggests that some individuals experience a delayed onset of cognitive impairment despite increased age- or dementia-related neuropathology (6). Cognitive reserve is accrued across the lifespan via exposure to cognitively stimulating life experiences, and is generally measured by proxy. Factors such as increased education levels, occupational complexity, social participation and engagement in leisure activities, have been shown to be associated with decreased dementia risk and are thought to contribute to cognitive reserve (7-9). As cognitive reserve accumulates throughout life, defining reserve as a combination of proxy measures provides a more accurate indication of an individual's reserve level compared to using a single measure such as educational attainment. It has been shown over the last decade that cognitive reserve components such as education, occupation, and social engagement have independent effects on cognitive change in late-life (e.g. 10). The field of cognitive reserve has moved from single-component assessments, such as years of education, to multi-component assessments (such as the index reported here) to capture reserve more comprehensively.

Meng and D'Arcy (11) reported that high cognitive reserve (indexed by education) was associated with reduced dementia risk in cross-sectional, case-control and cohort studies. However, it is important to note that many studies on cognitive reserve have been undertaken in populations covering the entire older age span (i.e. with a focus on persons aged 65 years or older), rather than focusing on specific age groups. Few studies have focused on a comprehensive cognitive reserve measure exclusively in the oldest-old and, where investigated, findings have been mixed. A nine-year longitudinal study of the oldest-old found that those with higher education had a decreased risk of dementia (12). Furthermore, in oldest-old women, it has been found that more education associates with a lower prevalence of dementia (13), and less cognitive impairment (14). Better cognitive functioning has also been reported in women over 80 years of age with more education (15). However, studies have also failed to find a relationship between education and dementia incidence (16) or rate of terminal decline (17) in the oldest-old. Together, these results suggest that cognitive reserve may be evidenced in the oldest-old, but the exact associations with cognitive function are unclear. The mixed findings may be due to the sole use of education as a proxy measure for cognitive reserve and, to our knowledge, there has been no comprehensive investigation of a complex measure of cognitive reserve in the oldest-old, and its association to cognitive function and dementia risk.

This study aimed to investigate cross-sectional and longitudinal relationships between cognitive reserve, dementia, and cognitive function in an oldest-old cohort, the Newcastle 85+ Study. We sought to comprehensively index cognitive reserve by using a range of proxy measures including education, occupation-based social class, marital status, engagement in mental activities, social participation and physical activity, and, by combining this

information, derive an overall index of cognitive reserve. Understanding the effect of cognitive reserve on cognitive function and dementia status in the oldest-old is critical in the development of interventions and cognitive screening tools for this age group.

Methods

Participants

The Newcastle 85+ Study is a large population-based longitudinal study of health and ageing in oldest-old adults. Full details of the study have been published elsewhere (18,19). In brief, participants consisted of all surviving adults born in 1921, who turned 85 in 2006 when the study commenced, who were permanently registered with a participating general practice in Newcastle-upon-Tyne and North Tyneside (northeast England). Health status and place of residence did not determine participation. Recruitment and baseline assessment took place over a 17-month period beginning in 2006. Of the 1,042 people recruited, 845 agreed to a health assessment and a review of their general practice (GP) records. These individuals form the analytical sample. Participants were re-assessed at three follow-up points: 18 (Phase 1, n=631), 36 (Phase 2, n=484) and 60 (Phase 3, n=344) months.

Ethics

The Newcastle and North Tyneside 1 Research Ethics Committee approved the study (Reference 06/Q0905/2). Informed written consent was obtained from all participants or their consultee (usually a relative) where capacity to consent was assessed as lacking, for example because of cognitive impairment.

Interviews

At baseline, a detailed multi-dimensional health assessment was completed, including questionnaires about sociodemographic variables, health, and lifestyle; health status measurements (e.g. blood pressure and physical function including grip strength); cognitive tests; and collection of a fasting blood sample. A trained research nurse conducted the health assessment in the participant's usual place of residence. The research nurse team also undertook a review of each participant's GP clinical records to collect information on diseases, current medication, and use of general practice services. All computerized and paper records, including hospital correspondence and the results of any investigations were included in the review. The presence of a predetermined list of diagnoses, including dementia, were recorded along with the date of first diagnosis (18). Data extraction from the GP clinical records has shown agreement between independent research nurses, with moderate intraclass correlations for binary diagnosis variables (18). Participants could decline elements of the protocol, and this did not constitute exclusion. At each of the three follow-ups, repeat measures of core variables including health, cognition and physical function were collected.

Dementia Diagnosis

Dementia status was determined from the GP record reviews at baseline and at 36 and 60 months of follow-up. Those with "dementia or Alzheimer's disease" recorded anywhere in their GP records (irrespective of date) were listed as having dementia in the current study. The diagnosis of dementia was independent to the neuropsychology assessments conducted at each interview wave.

Neuropsychological Assessment

Neuropsychological testing was carried out independent of dementia diagnosis, to assess global and domain specific cognitive function. Global cognitive function was assessed using the Mini Mental State Examination (MMSE) (20), for which scores range from 0 to 30. The MMSE was administered at baseline, 36 and 60 months. As MMSE scores were negatively skewed at each wave they were transformed [MMSE transformed = $\log_{10}(30.5 - X)$] and kept continuous. Lower transformed MMSE scores reflect better cognitive performance.

Domain specific cognitive function was assessed using the Cognitive Drug Research (CDR) computerised assessment system (21). This has been validated in older samples including those with dementia (22), and was found to be both a feasible and useful means of assessing cognitive function in the oldest-old age group in the Newcastle 85+ Pilot Study (23). A trained research nurse conducted the assessment in a one-to-one setting and distraction free environment. If distractions appeared, these were recorded and some parts of the test could be paused (e.g. if the telephone rang) or even restarted (where possible), if it was felt that the instructions had not been clearly understood or the test compromised. Distractions were generally rare; and any problems were usually technical (e.g. due to equipment failure). The battery consisted of the following tasks: Word Presentation, Simple Reaction Time, Digit Vigilance Task, Choice Reaction Time and Word Recognition. These tasks allow assessment of speed, attention and memory. The CDR battery was presented on a high-resolution Windows-based tablet computer (Motion Computing® LE1600 Tablet PC) with a two-button (YES/NO) response box. Administration of the CDR battery was completed in two stages. First, practice training sessions (usually in the interview one week before the CDR assessment interview) were performed to familiarise participants with the computerised testing procedures, using all selected tasks but with fewer stimuli. Second, approximately one week later, the assessment data were collected.

The scores from the CDR tasks were combined to calculate three composite measures: Power of Attention (PoA; a measure of focused attention; measured in milliseconds; *ms*), Continuity of Attention (CoA; a measure of sustained attention or vigilance over time; measured as a trade-off between correct responses and false alarms) and the word recognition accuracy sensitivity index (SI) score (a measure of memory, calculated from the formula presented by Frey and Colliver (24) that combines the ability to recognise target stimuli with the ability to correctly reject distractors; range -1 to 1). Reaction times (RT*; ms)* for each of the three attention tasks (simple, choice and digit vigilance) were also selected for analysis. The CDR battery was administered at baseline, 18 and 36 months.

As reaction times scores were positively skewed they were converted into seconds (s) and logarithmically ($\log_{10}$) transformed. PoA scores were also $\log_{10}$ transformed, whereas CoA scores were negatively skewed and transformed using the following equation: CoA transformed = $\sqrt{K - x}$ (where K = maximum score + 1). Lower transformed scores for the reaction times (simple RT, choice RT, and digit vigilance RT), PoA and CoA variables indicate better performance.

Cognitive Reserve Measures and the Cognitive Reserve Index (CRI)

To generate the CRI, six proxy measures for reserve were identified from a recent systematic review (7), and extracted from the baseline data including education, occupation-based social class, marital status, engagement in mental activities, social participation and physical activity level. A description of each variable and its categorisation is shown in Table 1. To create the CRI, each proxy variable was coded between 0 (low reserve) and 1 (high reserve) using the same methodology that has been used to calculate the frailty index components

(25). This ensured that each variable was equally weighted. The six variables were then summed and the score divided by six to create a CRI ranging from 0 to 1. Higher scores indicate greater reserve.

Potential Confounding factors

Potential confounders considered in the analysis include: sex (0=male, 1=female), depression and a history of cardiovascular disease (CVD). Depression was assessed using the 15-item Geriatric Depression Scale and scores were coded into three groups: none, mild or severe (26). CVD was defined as the presence of a history of stroke, ischemic heart disease or heart failure from the GP record review (0=no condition present, 1=one or more of the conditions present).

Statistical Analysis

All analyses were completed using STATA Version 14. Summary statistics including means (and standard deviations: SD) for continuous variables and counts (and percentages) for categorical variables were used to determine the baseline sample characteristics. Demographic differences in people with and without CRI scores at baseline were tested using the t-test (for continuous variables) or the Chi-squared test (for categorical variables).

The association between the CRI scores and prevalent dementia was assessed using an independent sample t-test. A Boxplot was drawn to show the distribution of CRI scores in persons with and without dementia at baseline. After excluding people with prevalent dementia at baseline, logistic regression analysis, controlling for sex, age at study entry, depression and history of CVD was used to assess the association between the CRI scores

(grouped into tertiles with the highest reserve group used as the referent category) and five-year risk of incident dementia.

The association between the CRI and cognitive test scores (MMSE and CDR), in persons without dementia at baseline, over the five-years follow-up were modelled using repeated-measures mixed-effects models. As there were only up to three measures per person for each cognitive test, a model describing change as occurring at a constant rate over the entire follow-up time was fitted. Mixed models were estimated using maximum likelihood estimation and estimates were robust under a missing at random assumption. All models were adjusted for sex, age at study entry (centred at age 85; this was done due to small age differences at baseline with age ranging from 84.5 to 86.6 years, as recruitment took place over a 17-month period), depression and history of CVD. Inclusion of an interaction term between time and CRI allowed for the estimation of the effect of CRI on rate of change in cognition. There was no interaction between time and sex or time and baseline age and therefore these interaction terms were not included in the final models.

Results

Of the 845 individuals seen at baseline, the CRI could be mapped in 753 participants (89%) with a mean baseline age of 85.5 years (SD=0.4), including 457 (60.7%) women and 50 (6.6%) with prevalent dementia. Of these 753 participants, 588, 455, and 322 were re-seen at 18, 36, and 60-month follow-up interviews, respectively. Loss to follow-up was mainly due to death as shown in Table 2. CRI scores ranged from 0.04 (low reserve) to 0.88 (high reserve) and their distribution is shown in Figure 1. Missing data on the CRI occurred mostly due to missing on the social class (n=47) and physical activity (n=33) variables. Individuals with missing values in the CRI score components (and therefore, whose CRI scores were not

calculated) did not differ from individuals with complete data in terms of baseline age or years of education, but were more likely to be female (p=0.008).

Dementia Results

CRI scores were found to be significantly higher (t-test, p=0.002) at baseline in persons without dementia (mean=0.46, standard deviation SD=0.15) compared to persons with dementia (mean=0.39, SD=0.14). Figure 2 shows the distribution of CRI scores by dementia status at baseline. Of the 703 people without dementia at baseline, there were n=41 incident cases over the five years follow-up. There was no association between CRI scores and reduced risk of five-year incident dementia when controlling for baseline age, sex, depression and CVD (OR=0.98; 95%CI: 0.72 to 1.33, p=0.901).

Cognitive Test Results

For the cognitive test score analyses, all individuals with a diagnosis of dementia at baseline (n=50) were first excluded. The results of the repeated measures mixed effect model are shown in Table 3. As shown, higher CRI scores were associated with better baseline performance in persons without dementia on all cognitive measures including attention, speed, memory and global cognitive function. However, higher CRI scores were associated with small, non-significant rates of change on all measures, except CoA, where CRI scores increase as CoA performance gets worse (B=0.24, SE=0.11, p=0.03). This result is in the opposite direction to that expected.

Discussion

This study aimed to examine cross-sectional and longitudinal associations between cognitive reserve, dementia and domain-specific and global cognitive function in the oldest-old. Using

a comprehensive composite index of cognitive reserve, results showed that higher reserve was associated with a reduced prevalence, but not incidence, of dementia. In addition, those with high cognitive reserve demonstrated better global and domain specific cognitive performance, including attention, memory, and speed at baseline; however, cognitive reserve did not appear to affect the rate of cognitive change over five years.

Cognitive Reserve and Dementia

Higher cognitive reserve was associated with reduced dementia prevalence at baseline but not with risk of five-year incident dementia. These findings are generally in accordance with previous literature in the oldest-old where it has been reported that higher cognitive reserve is associated with reduced dementia prevalence (women only) (13), but not dementia incidence (16) or rate of terminal decline (17), with one exception (12). However, the cohort assessed by Rastas et al. (12) is different to ours in that educational attainment (their cognitive reserve proxy) was much lower across the cohort (<5 years on average) with greater variance, and the follow-up was nine years.

It should be noted that these previous studies in the oldest-old examined education, whereas the current study measured cognitive reserve with a comprehensive index. This is a strength of the study, given the known independent effects of a range of cognitive reserve proxy measures and the importance of accounting for cumulative experience. We did not consider the CRI components separately as each measure in the index is likely to be highly correlated (e.g. people with better education also tend to have higher social class, etc.) and therefore our method accounts for this correlation in a much better way than investigating each variable alone.

In older cohorts not restricted to the oldest-old, cognitive reserve measures such as education, occupational attainment, premorbid IQ, and mental activity have been associated with reduced risk of incident dementia (see Valenzuela and Sachdev (27) for a systematic review). It may be that cognitive reserve is protective of incident dementia in the young-old, but that the trajectory of decline is less malleable to cognitive lifestyle in the oldest-old. This echoes findings from vascular risk factor and dementia studies, whereby these risk factors confer strong risks in the young-old but not in the oldest-old (28). Vascular risk factors and cognitive reserve are the primary modifiable risk factors for late-life dementia (29), but it may well be that they have less of an effect on cognitive function as we enter very late-life, pointing to the need for early intervention.

Cognitive Reserve and Cognitive Function

The findings from the current study broadly support previous research, and suggest that increasing cognitive reserve via modifiable factors promotes general and domain-specific cognitive function in the oldest-old; however, there is little impact on the trajectory of cognitive decline. There have been limited studies assessing these associations in the oldest-old specifically: reserve proxies (higher education and intellectual activities before age 80) have been reported to associate with better general cognitive performance (i.e. MMSE) in centenarians (30), and higher education with better attention and processing speed performance (but not verbal memory) in the oldest-old (31). In the broader literature, research has shown that cognitive reserve is associated with cognitive functioning, but may be unrelated to cognitive decline (32-35). This study is the first to report this pattern of effects in the oldest-old, suggesting that high cognitive reserve affords initial cognitive benefits that are relied upon through to early and mid-adulthood, but does not modify rates of change in very late-adulthood (35).

Future Considerations and Implications

In this study, cognitive reserve was indexed via a combined proxy measure, consisting of education, occupation-based social class, marital status, engagement in mental activities, social participation and current physical activity level. This index is much broader than previously used measures that typically assess reserve using a single proxy such as educational attainment. Whilst results may have differed had only years of education been used, taking multiple proxies into account is a strength of this research, as there are likely several indicators that supply cognitive reserve (7). It is possible that combining these variables may render the importance of individual variables less obvious (see Cosentino and Stern (36) for a discussion), and this should be considered when interpreting the effects of the CRI and proxies in isolation. However, combining several proxies of cognitive reserve renders a more precise measure that is less biased by factors unrelated to cognitive reserve (37).

These findings also have implications for the development of preventative/treatment strategies and models for predicting risk of cognitive impairment and dementia in the oldest-old. As the effects of cognitive reserve are evident even in the oldest-old, targeting modifiable factors (such as physical, social, and mental activities) could benefit cognitive function in this age group. However, engaging in activities to promote cognitive reserve may be less beneficial once cognitive decline becomes evident. Future research in this area should consider the independent contribution of proxies in the oldest-old, and whether this differs from young-old cohorts.

Strengths and Limitations

There are several strengths to this study. The Newcastle 85+ Study is a large population-based cohort of the oldest-old, socio-demographically representative of this age group in the UK, including individuals in institutions (18). Home-based assessments were undertaken that helped to avoid selection bias inherent in clinic based assessment of this age group. In addition, relatively long follow-up has been undertaken (five-years) with little loss to follow-up apart from death (19). The cognitive battery incorporated a wide variety of tests including measures of global and domain specific cognitive function: memory, attention and speed. There are some limitations. First, as with any study of ageing, follow-up is associated with loss, mainly due to death. Second, not all cognitive measures were administered at every follow-up wave due to time restrictions. However, mixed effects models are flexible enough to account for unequally spread observations and produce results robust to random missing observations. Given that each cognitive measure (MMSE and CDR) was administered at three time points only linear change could be modelled. Third, dementia was extracted from GP record review and therefore there is a chance that it is under-diagnosed, possibly affecting the power of the dementia analysis (18). Further studies in other oldest-old populations with more in-depth dementia assessment are therefore needed to replicate the results. Fourth, while we had access to historical as well as current mental activity we were only able to assess current physical activity levels (which may be restricted due to physical limitations). Assessing physical activity earlier in life would have been informative, particularly as midlife physical activity has been shown to affect late-life cognitive function and dementia risk (38,39). Fifth, although the CDR battery assesses a range of cognitive domains, there is no test of episodic memory. As episodic memory is sensitive to the effects of cognitive ageing (40), it is possible that we underestimated associations between the CRI and cognitive trajectories. Last, the CRI was kept constant at the baseline level however it is possible that over time marital status, physical activity levels and enagment in mental activities may well

have changed. Therefore, futher work is needed to assess the impact of changes in level of reserve on cognitive function over time in very old age.

Conclusion

In this study, we have demonstrated that cognitive reserve is related to dementia prevalence and baseline general and domain-specific cognitive performance in a large cohort of oldest-old participants. However, across a five-year period, cognitive reserve was not significantly related to incident dementia or trajectories of cognitive performance. This study provides, to our knowledge, the first investigation of these associations in an oldest-old cohort using a comprehensive measure of cognitive reserve, with a combination of six proxies. This study not only adds to reserve theory, by detailing specific effects within an oldest-old cohort, but has implications for preventative and treatment strategies. By targeting modifiable lifestyle and environmental factors conducive to cognitive reserve, in all stages of the lifespan, cognitive function and the prevalence of dementia could be beneficially affected even in the oldest-old. More work is needed, however, to identify intervention strategies that specifically target the trajectory and rate of cognitive decline.

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Table 1 Variables used to create the brain reserve index (BRI) in the Newcastle 85+ Study

Components	Description and categories
Education	< 9 years = 0 , 10/11 years = 0.5 and ≥12 years = 1.
Socio-economic Status	Routine and Manual=0, Intermediate=0.5 and Higher Administration/Managerial=1.
Current Physical Activity	Scores were taken from a self-reported questionairre regarding sporting activities, gardening, housework, DIY work, and walking. Physical activity was categorized as low = 0, moderate = 0.5 and high (≥3 activity sessions per week) = 1.
Marital Status	Single=0, widowed/separated/divorced=0.5 and partnered (married/re-married)=1.
Social Participation	Combined social index score incorporating eight items: *During the last 4 weeks how often have you:* 1. *Done any volunteer work?* 2. *Helped other people (with anything other than volunteer work)?* 3. *Played bingo?* 4. *Been on the phone to any of your friends or relatives?* 5. *Visited, or been visited by, any of your relatives or friends?* 6. *Been in e-mail contact with any of your friends or relatives?* 7. *Taken part in any church activities?* 8. *Taken part in any club activities?* There were 4 response categories including: every day (score=1), every week (score=0.66), once (score=0.33) or not at all (score=0). Scores across the eight items were summed. Quintiles were used to create five groups from the summed score: none=0, very low=0.25, low=0.5, moderate=0.75 and high=1.
Mental Activities	Combined mental activities score incorporating seven items: *During the last four weeks how often have you:* 1. *Listened to the radio?* 2. *Watched television?* 3. *Read newspapers, magazines or books?* 4. *Spent time on a hobby?* 5. *Done any DIY around the house or garden?* 6. *Played card or board games?* 7. *Visited a restaurant, theatre, cinema, art gallery or museum?* There were 4 response categories including: every day (score=1), every week (score=0.66), once (score=0.33) or not at all (score=0). Scores across the seven items were summed. Quintiles were used to create five groups from the summed score: none=0, very low=0.25, low=0.5, moderate=0.75 and high=1.

Table 2 Number of participants in the study and loss to follow-up at each interview wave

	Interviewed	Missing	
		Died	Lost to Follow-up
Baseline*	753		
18 months	588	114	51
36 months	455	86	47
60 months	322	106	27

*Total number of participants with CRI scores from the total sample (N=845)

Table 3 Results of repeated measures mixed-effects linear regression models analysing the association between CRI scores and cognitive function in persons without dementia at baseline

	Intercept			Slope		
	B Coef.*	**SE**	**p-value**	**B Coef.***	**SE**	**p-value**
MMSE	-0.49	(0.10)	<0.001	0.03	(0.03)	0.36
Memory (SI)	0.22	(0.06)	<0.001	-0.03	(0.03)	0.20
Attention (PoA)	-0.09	(0.02)	<0.001	0.00	(0.01)	0.82
Attention (CoA)	-1.42	(0.27)	<0.001	0.24	(0.11)	0.03
Simple RT	-0.17	(0.05)	<0.005	0.00	(0.02)	0.87
Choice RT	-0.16	(0.05)	<0.005	0.03	(0.03)	0.30
DVRT	-0.06	(0.02)	<0.001	0.00	(0.01)	0.88

*All models controlled for age at baseline, sex, depression and a history of CVD

Key
SI Sensitivity Index; **CoA** Continuity of attention; **DVRT** Digit vigilance reaction time; **MMSE** Mini Mental State Examination; **PoA** Power of attention

Figure 1 Distribution (Kernel Density estimator) of the CRI scores at baseline (whole population including people with and without prevalent dementia)

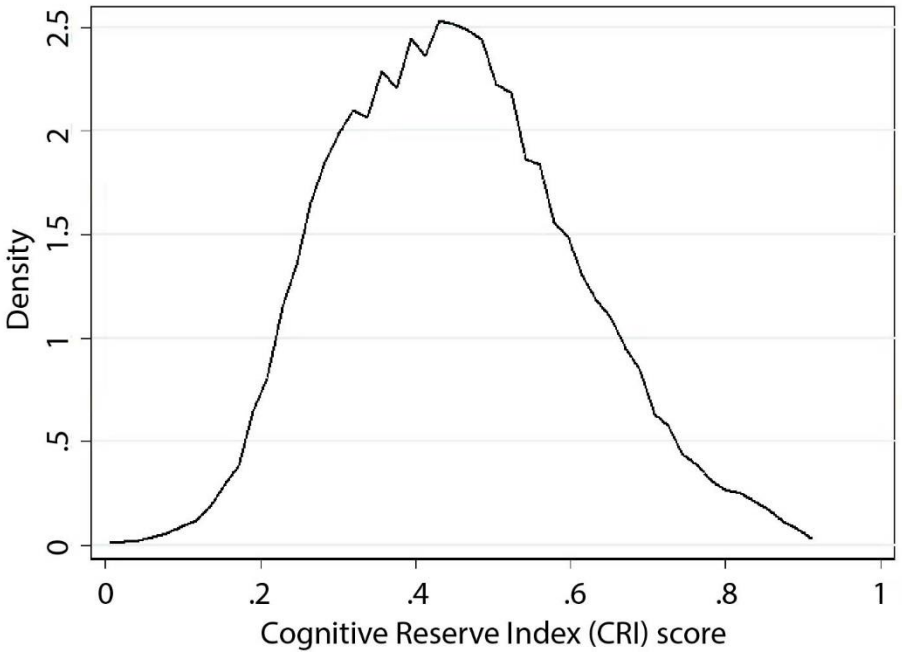

Figure 2 Difference in the distribution of Cognitive Reserve Index (CRI) scores in persons with (n=50) and without (n=703) dementia at baseline