Research Report

Testing the Cognitive Reserve Index Questionnaire in an Alzheimer's Disease Population

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Abstract.
Background: Alzheimer's disease (AD) is the 6th leading cause of death in the United States and has no cure or progression prevention. The Cognitive Reserve (CR) theory poses that constant brain activity earlier in life later helps to deter pathological changes in the brain, delaying the onset of disease symptoms.
Objective: To determine the reliability and validity of the Cognitive Reserve Index questionnaire (CRIq) in AD patients.
Methods: Primary data collection was done using the CRIq to quantify CR in 90 participants. Correlations and multivariable linear regressions were used to assess reliability and validity.
Results: Reliability was tested in 34 participants. A Pearson correlation coefficient of 0.89 ($p < 0.001$) indicated a strong positive correlation. Validity was tested in 33 participants. A Pearson correlation coefficient of 0.30 ($p = 0.10$) indicated an insignificant weak positive correlation.
Conclusion: The CRIq was found reliable. Gaining a better understanding of how CR tools can be used in various cognitive populations will help with the establishment of a research tool that is universally accepted as a true CR measure.

Keywords: Alzheimer's disease, cognitive reserve, reliability and validity, surveys and questionnaires, wechsler scales

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder that results in brain cell death, cognitive decline, and memory loss [1, 2]. There are three general stages that characterize AD progression: mild AD (early stage), moderate AD (middle stage), and severe AD (late stage). The average time frame for mild AD is 2 to 4 years. Moderate AD is typically the longest stage, lasting 2 to 10 years. The severe

AD stage is typically the shortest, lasting 1 to 3 years [3–6]. The progression of AD is often associated with the presence of other preexisting conditions, such as a history of chronic diseases, low educational attainment, and having a low socioeconomic status [7–9]. Likewise, studies show that there are several modifiable lifestyle factors that are protective of AD risk and progressive cognitive decline: constant cognitive activity, social engagement, regular physical activity, a healthy diet, and good heart health [1, 2, 7, 10–13].

The brain changes seen with AD may start 20 or more years before symptoms are detected [7]. It is hypothesized that some individuals are initially able to resist AD pathology accumulation due to cognitive

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reserve (CR). The CR theory is a recent development in AD research. CR is defined as the ability to maintain mental functionality despite accumulating brain pathology. This theory projects that constant brain activity earlier in life later helps deter pathological changes in the brain, delaying disease symptom onset. The CR concept arose from observations that some patients' levels of brain pathology did not match their clinical symptoms. It was hypothesized that individuals with higher levels of CR can cope more efficiently with brain damage therefore delaying the appearance of clinical symptoms [14, 15].

According to Stern, CR represents the brain's ability to cope with damage due to the presence of pre-existing neural networks that use some type of compensatory behavioral mechanism [16–18]. The current gold standard measure for CR is an individual's intelligence quotient (IQ) [14, 15, 17, 19–21]. CR is also commonly measured using three other proxies: education, occupation, and leisurely activity [22–26]. Past studies on CR focus on one proxy as their primary measure of CR, most commonly education or cognitively stimulating activities [20, 27–31]. Only six studies have been identified that used more than one proxy measure to represent CR [30, 31].

Despite having arrived at a consensus on how CR is defined, the debate remains about the true measures of CR [32]. The Cognitive Reserve Index questionnaire (CRIq) is a content validated and reliable tool that quantifies the influence of all three CR proxies over a life span. It accounts for various sources of CR using three subcategories for each CR proxy: education (CRI-Education), working activity (CRI-WorkingActivity), and leisure time activities (CRI-LeisureTime). One study has adapted the CRIq for use in the Greek population. Maiovis and colleagues translated the CRIq into Greek and administered it to healthy Greek participants ranging from ages 18 to 89. They found that it had satisfactory internal consistency and was easy to administer to their population [33]. In their systematic review, Kartschmit et al. compared the characteristics of existing CR measurement questionnaires to determine their accuracy of capturing the CR concept. They found that the CRIq had content validity and concluded that further research needs to be done using it [32].

The concept of CR applies to all individuals whether they are healthy or ill. Despite this established fact, past research on CR has mainly focused on healthy populations. Studies have now started using this construct to explore AD outcomes. The excessive cognitive decline seen with AD is not a normal part of aging and can potentially be delayed via CR because CR is not static. This is important since CR can be increased at any stage of an individual's life and can therefore influence cognitive decline. Increasing CR after an AD diagnosis can potentially slow down symptom progression. Four studies have looked at the relationship between CR and AD progression. They found that an association existed, and CR impacted the clinical progression differently at each stage of AD. It was initially protective of cognitive decline then resulted in a drastic cognitive decline toward the end stage [34–37]. These studies used AD biomarkers and brain imaging to represent CR, choosing methodological approaches that were hard to quantify and make generalizable for future studies to use. In his systematic reviews, Stern examined the clinical implications of CR. He posed the idea that educational, occupational, and leisurely experiences impart some type of reserve that suppresses the appearance of AD pathology [15, 17, 38]. The CRIq was developed to capture all three proxies and has been proven to accurately measure CR in healthy Italian, Greek, and English adults [21, 30, 33]. The CRIq provides a standardized score of CR, which is more generalizable, and needs to be used in cognitively impaired populations to fully explore the impact of CR. Only two studies have been identified that used it in a dementia population [39, 40]. The objective of this study was to determine the reliability and validity of the CRIq in United States (US) AD patients. The use of the CRIq has been proven to be reliable and valid in healthy adults. Therefore, we hypothesized that the CRIq would be found reliable and valid to use for US AD patients as well.

METHODS

Participants

This study was approved by the Saint Louis University Institutional Review Board. Informed consent was obtained from all participants. Participants did not receive incentives.

The study sample was recruited from four locations, which included the Geriatric Psychiatry Clinic in an academic institution, in addition to three community-based nursing homes. Individuals were recruited during follow-up visits at the clinic and during family member visits to nursing homes on weekends. Individuals from these locations were also recruited over the phone. To be eligible for the study,

Table 1
ICD-10 Codes for Clinical Diagnoses

Variable Name	ICD-10 Code
Alzheimer's disease	G30
Alzheimer's disease With Early Onset	G30.0
Alzheimer's disease With Late Onset	G30.1
Alzheimer's disease, Unspecified	G30.9
Unspecified Dementia without	F03.90
Behavioral Disturbance	
Depression	F33.2
Major depressive disorder,	F33.9
recurrent, unspecified	
Diabetes	
Type 2 Diabetes mellitus	E11.9
without complications	
Hyperlipidemia, unspecified	E78.5
Essential (primary) hypertension	I10
Obesity	E66.9
Past Head Trauma/Injury	
Unspecified injury of head	S09.90
Traumatic brain injury	Z87.820
Parkinson's disease dementia	G20
Lewy body dementia	G31.83
Vascular dementia	F01.50
Frontotemporal dementia	G31.09
Huntington's disease	G10

participants had to be 45 years or older (the earliest age of AD symptom onset) [1, 2, 12, 41, 42] and have a diagnosis of either AD or Unspecified Dementia without Behavioral Disturbance (UDBD) at the time of data collection. An AD and UDBD diagnosis were defined as having an ICD-10 code clinical diagnosis (Table 1). The creators of the CRIq recommended that if there is any suspicion of cognitive decline a person who knows the patient well should answer the CRIq questions on his/her behalf [21]. Due to the cognitive decline associated with AD and UDBD, participants needed to have a legally authorized representative (LAR) to fill out the CRIq on their behalf. The LAR had to be a family member, spouse, or caregiver. To have been eligible as a LAR, the individual had to have interacted with the patient for at least the last five years on a regular basis (once a month). The LAR answered the CRIq questions based on their knowledge of the patient's life experiences. The question responses were from the LAR alone. Patients did not provide answers to any of the questions due to the cognitive impairment associated with their diagnosis. The primary exclusion criterion was having another neurological diagnosis (Parkinson's disease dementia, Lewy body dementia, vascular dementia, frontotemporal dementia, or Huntington's disease). This was to ensure that any cognitive decline seen was attributable to an AD or UDBD diagnosis alone. After applying exclusion criterion to a total population of

250 people, 193 people were invited to participate. Of these people, 90 agreed to participate. The response rate was therefore 46.6%. The final sample size was influenced by clinic appointment cancellations, non-response, and lack of interest in participating.

Study tools

The study design was primary data collection using a cross-sectional questionnaire, the CRIq. The information collected from the CRIq was used to calculate a CR score. The CRI-Education score was calculated by adding up total years of education that an individual had. Any vocational training courses that occurred for at least six months were also counted. The CRI-WorkingActivity score was based on a five-level scale of the intellectual engagement and the responsibility associated with a job (low skilled manual work, skilled manual work, skilled non-manual, professional occupation, and highly responsible or intellectual occupation). The score was calculated by multiplying the number of years that a person had spent in a profession and the cognitive level of the job. The CRI-LeisureTime score was calculated by summing the total number of years of an activity for which the individual selected often/always for the frequency. The total CRIq score was calculated by averaging the three subscores from each section. The CRIq score fell into 1 of 5 ordered levels: low (less than 70); medium-low (70–84); medium (85–114); medium-high (115–130); and high (more than 130). It is estimated that the CRIq takes 15 minutes to complete [20, 21, 33, 40]. We adapted the CRIq to fit the cultural differences in wording and vocabulary that exist between American and European English. More information about the CRIq and the computation spreadsheet can be found at http://www.cognitivereserveindex.org/.

Since IQ is the gold standard measure for CR, we used the Wechsler Test of Adult Reading (WTAR) to determine validity. WTAR was developed as a neuropsychological assessment tool of intellectual functioning before disease symptom onset. It provides a premorbid estimate of an individual's IQ by looking at verbal and reading skills. WTAR is a word and reading test that involves the pronunciation of 50 words with irregular spellings. It uses demographic data plus word reading ability to derive an estimated intellectual score [43, 44]. The WTAR and CRIq assessments were not done on the same day. The average amount of time that passed between the WTAR and first CRIq scores was 1,302 days. The minimum

amount of time between scores was 66 days, and the maximum amount of time was 3,387 days.

The Clinical Dementia Rating (CDR) scale is a validated and reliable tool that is used by clinicians to determine stage of dementia based on the cognitive and functional capabilities of the patient. It is usually completed during a semi-structured interview that occurs with the patient and a spouse or some type of caregiver. It is composed of 6 domains that evaluate cognitive functioning: memory, orientation, judgment & problem solving, community affairs, home and hobbies, and personal care. A 5-point scale is used to determine the patient's level of cognitive impairment/dementia: 0 (normal), 0.5 (very mild dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia) [45, 46]. Traditionally, the CDR can be scored either using a global score (CDR-GS) or a sum of boxes score (CDR-SB). The CDR-GS looks at each domain separately. The domain that has the highest overall score after summing it up is used to get the CDR-GS (ranges from 0 to 3). The recommended cut-off scores are: 0 (absence of symptoms), 0.5 (questionable), 1 (mild), 2 (moderate), and 3 (severe) [46, 47]. The CDR-SB is calculated by summing up each of the domain scores (range from 0 to 18). The recommended cut-off scores are: 0.5 to 4 (questionable), 4.5 to 9 (mild), 9.5 to 15.5 (moderate), and 16 to 18 (severe) [35, 45–49]. We used the CDR-GS scoring method for the study. More information about the CDR, scoring rules, and a copy of it can be found at https://knightadrc.wustl.edu/CDR/CDR.htm.

Reliability data collection

To test reliability, we performed a Test-Retest procedure. 90 participants were asked to complete the CRIq twice over the course of two weeks [50, 51]. After participating in the study, LARs were given another copy of the CRIq to complete again within two weeks of the first one. A minimum of 30 participants were needed based on the validity power analysis sample size of 65. We obtained a second CRIq from 34 individuals.

Validity data collection

Content validity has been established for the CRIq so concurrent validity was assessed [21]. To do this we compared patients' first CRIq scores to their WTAR scores. The minimum number of participants needed to detect clinically meaningful differences

was 65 based on 80% power, an alpha of 0.05, and a moderate Pearson's correlation of 0.7. We recruited a total of 33 participants for validity.

Covariates

The covariates that we chose to use in our models were based on the known relationships that they have with AD risk and progression of dementia symptoms [5, 10, 41, 52–58]. The covariates tested in the models included: a depression, diabetes, hyperlipidemia, hypertension, and/or obesity diagnosis; past head trauma/injury; smoking and alcohol history; reported physical activity, stress, and diet; gender; marital status; residence type; living situation; antidepressant drugs taken; and antidementia drugs taken. A diagnosis of a comorbidity (depression, diabetes, hyperlipidemia, hypertension, or obesity) was defined as having an ICD-10 code clinical diagnosis (Table 1) [5, 10, 52–55, 57].

Smoking and alcohol history were coded into 4 categories: never, past, current, or unknown smoker/drinker. Physical activity was coded into 4 categories: the participant reported no physical activity at all (no, no), reported no physical activity at the first visit/assessment then reported physical activity at the last visit/assessment (no, yes); reported physical activity both at the first and last visits/assessments (yes, yes); or reported physical activity at the first visit/assessment but not at the last visit/assessment (yes, no). The diet variable was coded into a 4 categories: the participant did not have a healthy diet at all (no, no); did not have a healthy diet at the first visit/assessment then had a healthy diet at the last visit/assessment (no, yes); had a healthy diet both at the first and last visits/assessments (yes, yes); or had a healthy diet at the first visit/assessment but not at the last visit/assessment (yes, no). The stress variable was coded into 4 categories: the participant reported no stress at all (no, no); reported no stress at the first visit/assessment then reported stress at the last visit/assessment (no, yes); reported having stress both at the first and last visits/assessments (yes, yes); or reported having stress at the first visit/assessment but not at the last visit/assessment (yes, no).

The depression, diabetes, hyperlipidemia, hypertension, and obesity diagnosis as well as past head trauma/injury variables were coded dichotomous, yes or no. Age was treated as a continuous variable, number of years. For race/ethnicity, the original categories were White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian

or Other Pacific Islander, and Other. This variable was collapsed into 3 categories: White, Black, or Other (Asian, American Indian or Alaska Native, or Native Hawaiian or Other Pacific Islander). For gender, the categories were male or female. For marital status, the original categories were single, married, divorced, and widowed. This variable was collapsed into 3 categories: married, widowed, or other (single or divorced). For residence type, the original categories were home, nursing home, independent living, assisted living, memory care, and other. This variable was collapsed into 3 categories: home, nursing home, or other (independent living, assisted living, or memory care). For living situation, the original categories were by myself, with a spouse, with family members, a nursing home, a retirement community, or other. This variable was collapsed into 3 categories: spouse, nursing home, or other (self, family members, or retirement community).

For antidepressant drugs taken, we looked for either the class of Selective Serotonin Reuptake Inhibitor (SSRIs) (Escitalopram, Citalopram, and Sertraline) and/or the following drugs: Trazodone, Mirtazapine, Duloxetine, Venlafaxine, and Bupropion [59]. Participants that were taking more than one of these drugs went into the combination therapy category. The antidepressant drug variable was a 4-category variable (SSRIs, other, combination therapy, and none). For antidementia drugs taken, there were 2 classes of drugs that we looked for: Cholinesterase Inhibitors (Donepezil, Rivastigmine, and Galantamine) and Memantine [60]. Participants that were taking more than one of these drugs went into the combination therapy category. The antidementia drug variable was a 4-category variable (Cholinesterase Inhibitors, Memantine, combination therapy, and none).

Reliability analyses

For the Test-Retest procedure, we ran a Pearson correlation between the two CRIq scores to evaluate the consistency in answers at two different time points. In addition, we used multivariable linear regression to determine the strength of the relationship after adjusting for covariates. The first CRIq score was used to predict the second CRIq score. We expected that the second CRIq score would be similar to the first CRIq score, so we chose to predict the second CRIq score from the first CRIq score for testing reliability. We assumed a Pearson correlation coefficient of 0.7, based on the correlation results found in

Table 2
Pearson's Correlation Coefficient Boundary Interpretations

Value	Interpretation
0.0 to 0.3 (0.0 to – 0.3)	weak to negligible correlation
0.3 to 0.5 (–0.3 to –0.5)	weak positive (negative) correlation
0.5 to 0.7 (–0.5 to –0.7)	moderate positive (negative) correlation
0.7 to 0.9 (–0.7 to –0.9)	strong positive (negative) correlation
0.9 to 1.0 (–0.9 to –1.0)	very strong positive (negative) correlation

the construction of the CRIq [21]. See Table 2 for interpretations of Pearson's correlation coefficient. For this study, a Pearson correlation coefficient of 0.5 and above was considered clinically relevant [61].

Validity analyses

For concurrent validity, we ran a correlation between the CRIq and WTAR scores using Pearson's correlation coefficient and multivariable linear regression to determine the strength of the relationship after adjusting for covariates. The first CRIq score was used to predict the WTAR score. A Pearson correlation coefficient of 0.5 and above was considered acceptable.

Sensitivity analysis

To further examine validity, we tested if time made a difference in the relationship between a participant's first CRIq and WTAR scores. This was done by running a Pearson's correlation of the number of days between the first CRIq and WTAR scores and the absolute difference in value between the scores.

Statistical procedures

Microsoft Excel 2019 for Windows was used for de-identification of participant data. We looked at descriptive statistics for the study population demographics (age, gender, race, marital status, education, residence type, and dementia stage) and CR-related measures by dementia stage. IBM SPSS 26.0 software was used for all analyses (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.). Statistical significance was set at an alpha of less than 0.05 (<0.05).

RESULTS

Study participant demographics

The main descriptive characteristics for the study population were reported. The mean (SD) age of participants was 80 years (10.4). Females made up 66.7% of the study participants. Whites made up most of the sample (88.9%). 42.2% of participants were widowed while 41.1% of participants were married. The

Table 3
Population Demographics

Variable Name	Overall N = 90
Age, mean (SD)	80 (10.4)
Gender, n (%)	
Female	60 (66.7)
Male	30 (33.3)
Race, n (%)	
White	80 (88.9)
Black	9 (10.0)
Other	1 (1.1)
Marital Status, n (%)	
Married	37 (41.1)
Widowed	38 (42.2)
Other	15 (16.7)
Education (y), mean (SD)	14 (3.7)
Residence Type, n (%)	
Home	40 (44.4)
Nursing Home	43 (47.8)
Other	7 (7.8)
Dementia Stage, n (%)	
Mild	31 (34.4)
Moderate	31 (34.4)
Severe	28 (31.2)

SD, standard deviation; WTAR, Wechsler Test of Adult Reading.

mean (SD) years of education was 14 (3.7). A slightly greater portion of participants lived in a nursing home (47.8%) compared to the portion that lived at home (44.4%). Of the 90 participants 31 (34.4%) had mild dementia, 31 (34.4%) had moderate dementia, and 28 (31.2%) had severe dementia at the time of data collection (Table 3).

CR measures

The mean CR score for the first CRIq was 126. Overall, 32.2% of participants had medium CR, and 43.4% of participants had high CR. The first CRIq mean CR score for mild dementia participants was 131. The first CRIq mean CR score for both moderate and severe dementia participants was 123. Over 50% of mild dementia participants had high CR (54.8%). For moderate dementia, most participants had either medium CR (38.7%) or high CR (38.7%). Most severe dementia participants had either medium CR (39.3%) or high CR (35.7%). Over half of the mild dementia participants had a second CRIq score (51.6%), while most moderate (71.0%) and severe (67.9%) participants did not have a second CRIq score. The overall mean CR score for the second CRIq was 125. The second CRIq mean CR score for mild dementia participants was 127. Moderate dementia participants had a mean CR score of 135 for the second CRIq. The second CRIq mean CR score for severe dementia participants was 109. A greater portion of mild participants (67.7%) had a WTAR score. 77.4% of moderate participants and 82.1% of severe participants did not have a WTAR score (Table 4).

Table 4
Cognitive Reserve Measures by Dementia Stage

Dementia Stage at CRIq Administration	Overall N = 90	Mild n = 31	Moderate n = 31	Severe n = 28
1st CRIq score, mean (SD)	126 (19.2)	131 (15.0)	123 (22.8)	123 (18.1)
Had a 2nd CRIq score, n (%)				
No	56 (62.2)	15 (48.4)	22 (71.0)	19 (67.9)
Yes	34 (37.8)	16 (51.6)	9 (29.0)	9 (32.1)
2nd CRIq score, mean (SD)	125 (19.8)	127 (14.3)	135 (25.8)	109 (12.6)
CR Level for 1st CRIq, n (%)				
Medium-low	1 (1.1)	0 (0)	1 (3.2)	0 (0)
Medium	29 (32.2)	6 (19.4)	12 (38.7)	11 (39.3)
Medium-high	21 (23.3)	8 (25.8)	6 (19.4)	7 (25.0)
High	39 (43.4)	17 (54.8)	12 (38.7)	10 (35.7)
Had a WTAR score, n (%)				
No	57 (63.3)	10 (32.3)	24 (77.4)	23 (82.1)
Yes	33 (36.7)	21 (67.7)	7 (22.6)	5 (17.9)
WTAR score, mean (SD)	102 (12.2)	104 (11.1)	104 (16.6)	95 (9.1)
Difference in value of CRIq score and WTAR score, mean (SD)	31 (16.3)	29 (15.2)	31 (20.1)	36 (17.4)
Time between WTAR test and CRIq interview (days), mean (SD)	1,302 (796.8)	1,092 (717.4)	1,397 (668.0)	2,055 (938.1)

SD, standard deviation.

Reliability

For the test-retest analysis, the Pearson Correlation Coefficient was 0.89 ($p < 0.001$). This showed a strong positive correlation between the first and second CRIq scores, indicating the CRIq was reliable. After controlling for each covariate separately, the first CRIq score was found to be a significant predictor of the second CRIq score ($p < 0.001$). After controlling for the first CRIq score, having a diabetes diagnosis was found to be a significant predictor of the second CRIq score. Compared to participants who did not have a diabetes diagnosis, participants with a diabetes diagnosis had a 7-unit increase in the second CRIq score ($\beta = 7.35$, 95% CI: 0.86, 13.84, $p = 0.03$) (Table 5). The variables age, gender, race, marital status, residence type, living situation, depression, hyperlipidemia, hypertension, and obesity diagnosis did not significantly predict the second CRIq score. Similarly, past head trauma/injury, smoking and alcohol history, type of antidepressant drug taken, type

of antidementia drug taken, physical activity, stress, and diet did not significantly predict the second CRIq score.

Validity

The Pearson Correlation Coefficient for validity was 0.30 ($p = 0.10$). This indicated an insignificant weak positive correlation between the first CRIq and WTAR scores. Therefore, the CRIq was found invalid. After controlling for each covariate separately, the first CRIq score was not a significant predictor of the WTAR score. After controlling for the first CRIq score, race was found to be a significant predictor of the WTAR score. Compared to White participants, Black participants had a 27 unit decrease in WTAR score ($\beta = -26.54$, 95% CI: -49.52, -3.55. $p = 0.03$) (Table 6). After controlling for first CRIq score, residence type was found to be a significant predictor of the WTAR score. Compared to participants who lived in a home, participants who lived

Table 5
Diabetes Diagnosis Multivariable Linear Regression Analysis for Predicting 2nd CRIq and WTAR scores

Predictor Variables	β	S.E.	95% CI of β		p
			Lower	Upper	
Reliability					
1st CRIq Score	0.82	0.07	0.68	0.96	**<0.001***
Diabetes					
No	reference	reference	reference	reference	reference
Yes	7.35	3.18	0.86	13.84	**0.03***
Validity					
1st CRIq Score	0.25	0.14	–0.05	0.54	0.10
Diabetes					
No	reference	reference	reference	reference	reference
Yes	2.02	7.32	–12.93	16.97	0.78

*Predictors are statistically significant at $p < 0.05$; S.E., standard error; CI, confidence interval.

Table 6
Race Multivariable Linear Regression Analysis for Predicting 2nd CRIq and WTAR scores

Predictor Variables	β	S.E.	95% CI of β		p
			Lower	Upper	
Reliability					
1st CRIq Score	0.82	0.07	0.67	0.97	**<0.001***
Race					
White	reference	reference	reference	reference	reference
Black	4.99	4.83	–4.86	14.83	0.31
Other	–	–	–	–	–
Validity					
1st CRIq Score	0.25	0.13	–0.02	0.52	0.07
Race					
White	reference	reference	reference	reference	reference
Black	–26.54	11.26	–49.52	–3.55	**0.03***
Other	–	–	–	–	–

*Predictors are statistically significant at $p < 0.05$; S.E., standard error; CI, confidence interval.

Table 7
Residence Type Multivariable Linear Regression Analysis for Predicting 2nd CRIq and WTAR scores

Predictor Variables	β	S.E.	95% CI of β		p
			Lower	Upper	
Reliability					
1st CRIq Score	0.90	0.08	0.73	1.06	**<0.001***
Residence Type					
Home	reference	reference	reference	reference	reference
Nursing Home	7.32	3.58	–0.004	14.64	0.05
Other	6.09	4.79	–3.70	15.87	0.21
Validity					
1st CRIq Score	0.23	0.13	–0.04	0.51	0.09
Residence Type					
Home	reference	reference	reference	reference	reference
Nursing Home	–	–	–	–	–
Other	11.94	5.44	0.83	23.06	**0.04***

*Predictors are statistically significant at $p < 0.05$; S.E., standard error; CI, confidence interval.

in other types of residences had a 12-unit increase in WTAR score (β=11.94, 95% CI: 0.83, 23.06, $p = 0.04$) (Table 7). The variables age, gender, marital status, living situation, depression, diabetes, hyperlipidemia, hypertension, and obesity diagnosis did not significantly predict the WTAR score. Similarly, past head trauma/injury, smoking and alcohol history, type of antidepressant drug taken, type of antidementia drug taken, physical activity, stress, and diet did not significantly predict the WTAR score.

Sensitivity analysis

The average amount of time between the WTAR and first CRIq scores was 1,302 days. The mean difference in value between the WTAR and first CRIq scores was 31 units. The Pearson Correlation Coefficient for the number of days between the WTAR and first CRIq scores and the absolute difference in value between the WTAR and first CRIq scores was –0.32 ($p = 0.08$). This showed an insignificant weak negative correlation, indicating time did not make a difference in validity.

DISCUSSION

The CRIq is a validated and reliable CR tool. It accounts for all sources of CR across a lifespan and quantifies them into a score. The study objective was to determine the reliability and validity of the CRIq in AD and dementia patients. We hypothesized that the CRIq would be found reliable and valid. Based on our results, the CRIq was found to be a reliable measure of CR in the AD and dementia population. In addition, having a diabetes diagnosis significantly predicted the second CRIq score. The variables race and resi-

dence were significant predictors of the WTAR score. Despite being found reliable, the study findings did not indicate that the CRIq is a valid measure of CR in the AD and dementia population.

Like previous literature, our results showed that the CRIq is reliable to use in AD patients [31–33, 40]. Such a finding means that this tool is a consistent measure of CR in this population and can therefore be used in other studies assessing CR in a similar population. The CRIq is a faster and cheaper assessment of CR, and it will provide results like that of other CR diagnostic tools such as brain biomarkers and imaging. Furthermore, having a diabetes diagnosis was found to be a significant predictor of the second CRIq score. There have been some inconsistencies found in the literature as to whether or not the rate of AD progression is overall higher in diabetics [58, 62, 63]. A finding like this might indicate that having this AD risk factor makes a difference in how much of an influence CR has on AD progression. It might also show that more focus should be placed on the treatment of this condition in AD patients because of its influence on this relationship. Therefore, more research is needed to further explore the contribution of diabetes to CR and the pathogenesis of AD.

Regarding validity, Blacks had a decrease in WTAR score compared to Whites. This matches the literature that has found older Blacks are more likely to perform worse on cognitive functioning tests than older Whites [64, 65]. Race being a significant predictor of the WTAR score shows that racial disparities exist regarding CR. This might indicate that differences in access to the resources that promote CR buildup exist. Therefore, there is a need for more awareness about the importance of engaging in cognitive activities, especially in minority groups. Further-

more, type of residence was a significant predictor of WTAR score. Participants who lived in other types of residences (independent living, assisted living, or memory care) had an increase in WTAR score compared to participants who lived in a home. This was an unexpected result because previous literature has shown that living at home compared to other types of long-term care has a more beneficial effect on the cognitive and functional status of AD patients due to their comfortability and constant interaction with family [66, 67]. A finding like this may be due to the residential distribution of the study sample. Approximately half of the participants lived at home, and about half of them lived in a nursing home. Only 7.8% of the study sample lived in other types of residences.

The overall finding of invalidity shows that the CRIq might not be fully measuring CR based on the gold standard of IQ. Previous literature has found the CRIq valid to use in the AD and dementia populations [31, 32, 40]. Invalidity of the CRIq might be due to one of several factors. A minimum of 65 participants with a WTAR score were needed to detect significance. It was only clinic AD patients that had an IQ test result, and they made up 52% of the total study sample that was recruited. Another potential explanation for invalidity is that IQ is not the true gold standard measure of CR in this population. IQ is the gold standard measure in healthy individuals, but there is still no gold standard measure specifically for the AD population [14–16, 18, 19, 21, 68]. AD is associated with a decline in functional and intellectual capabilities over time. Therefore, an individual's IQ declines as dementia symptoms progress [19, 43, 69]. Other studies have found that education, one of the CR proxies, and IQ are highly correlated in AD patients [19, 70]. We therefore expected to see a positive correlation for the validity sensitivity analysis [69]. The results showed that time did not make a difference. Time might not have played a role in validity for this population because there was a wide range in the amount of time that passed between WTAR and first CRIq scores. All these observations indicate that using IQ as a gold standard measure for CR might not be appropriate for this population.

There are a few study limitations that must be acknowledged. The main sources of study participants were from one clinic and four nursing homes in the St. Louis, MO area. Limited access to the AD population also resulted in a negligible racial distribution in the study sample. Due to the unanticipated and unprecedented circumstances that arose because of the novel Coronavirus disease (COVID-19) pandemic, patient and resident recruitment was terminated. Nursing homes stopped permitting visitors into their facilities, and the City of St. Louis issued a "Stay at Home" order. This contributed to the final study sample size of 90 participants. Furthermore, potential recall bias might have influenced the results since LARs had to estimate the number of years patients participated in various adulthood activities. However, we are confident that there was little to no recall bias for two main reasons. The construction of the CRIq accounted for this by calculating a CR measure that has been standardized and does not rely on any type of performance or cognitive level [21]. We also applied LAR eligibility criteria for participants. Due to the sample size of 90 participants, we had to individually test the effect of each covariate on CR in separate regression models. This is because the accepted minimum limit of participants per covariate or level of covariate is 10 in order to avoid overfitting the model and decreasing predictive power for future participants [71, 72]. We therefore were not able to control simultaneously for the effect of multiple risk factors. This might have resulted in slight residual confounding. On the other hand, we were still able to account for the main risk factors of AD that are associated with symptom progression, possibly reducing the effect of residual confounding on our results. Since we used WTAR as a retrospective IQ measure in our study, we could not determine the exact stage of dementia that the patient was in when the test was administered. This potentially confounded our results. Unfortunately, we did not have the data and resources available to us to administer both the CRIq and WTAR on the same day. We instead tested for the impact of time on CR in order to control for the potential confounding effect of the time interval differences on the results.

This study has several strengths. Collecting our own data on CR allowed us to quantify a latent construct. We collected CR information directly from the study population ensuring better accuracy and quality of this measure. To our knowledge, we are the first US study to attempt to validate the CRIq [21, 33, 39, 73]. By doing this, we have introduced a new CR tool for future US studies to explore. Past studies focused primarily on one proxy measure to represent CR, which did not account for all the factors that promote CR [20, 28–31]. The CRIq captures all three CR proxies as well as other sources that contribute to lifetime CR development, providing a more accurate and generalizable measure of CR. No study to date

has proven that the CRIq is reliable to use in the US AD population, and our study results showed this.

Interventions that focus on promoting CR buildup from an early age onwards are needed. This is because CR has the potential to delay both AD symptom onset and progression. Implementing activities that promote the increase of CR into daily living can serve as a primary prevention intervention for reducing AD risk later in life. Also, engaging in cognitively stimulating activities after an AD diagnosis can increase CR and positively impact the progression of disease. The CRIq is a less invasive and cheaper alternative method for measuring CR compared to the diagnostic methodologies (brain imaging, biomarkers, and pathology aggregation) that were used in past studies. It provides a standardized measure of CR that accounts for the lifetime cognitive, social, and cultural characteristics of an individual. The CRIq quantifies the three CR proxies, providing a generalizable CR measure that future studies can use to explore the relationship between CR and AD progression. Therefore, more studies are needed to explore the validity of the CRIq. This study attempted to do so but could not due to sample size. Future studies should use a larger sample size and also try using other types of IQ tests for gold standard measures of CR. Gaining a better understanding of how CR tools like the CRIq can be used in different cultural and cognitive populations will help with the establishment of a research tool that is universally accepted as an accurate CR measure.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

REFERENCES

[1] Alzheimer's Association, Alzheimer's and Dementia Facts and Figures, https://www.alz.org/alzheimers-dementia/facts-figures, Accessed March 12, 2020.

[2] Mayo Clinic Staff, Alzheimer's disease, http://www.mayoclinic.org/diseases-conditions/alzheimers-disease/home/ovc-20167098, Accessed March 12, 2020.

[3] Alzheimer's Association, Stages of Alzheimer's https://www.alz.org/alzheimers-dementia/stages, Accessed March 12, 2020.

[4] National Institute on Aging, Alzheimer's Disease Fact Sheet, https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet, Accessed March 12, 2020.

[5] Gaugler J, James B, Johnson T, Marin A, Weuve J (2019) 2019 Alzheimer's disease facts and figures. *Alzheimers Dement* **15**, 321-387.

[6] Heathline, What Are the Stages of Alzheimer's Disease?, https://www.healthline.com/health/stages-progression-alzheimers, Accessed March 12, 2020.

[7] Clare L, Wu YT, Teale JC, MacLeod C, Matthews F, Brayne C, Woods B (2017) Potentially modifiable lifestyle factors, cognitive reserve, and cognitive function in later life: A cross-sectional study. *PLoS Med* **14**, e1002259.

[8] Polidori MC, Nelles G, Pientka L (2010) Prevention of dementia: Focus on lifestyle. *Int J Alzheimers Dis* **2010**, 393579.

[9] Scazufca M, Almeida OP, Menezes PR (2010) The role of literacy, occupation and income in dementia prevention: The Sao Paulo Ageing & Health Study (SPAH). *Int Psychogeriatr* **22**, 1209-1215.

[10] What Causes Alzheimer's Disease?, https://www.nia.nih.gov/health/what-causes-alzheimers-disease, Accessed March 12, 2020.

[11] Hertzog C, Kramer AF, Wilson RS, Lindenberger U (2008) Enrichment effects on adult cognitive development: Can the functional capacity of older adults be preserved and enhanced? *Psychol Sci Public Interest* **9**, 1-65.

[12] Qiu C, Kivipelto M, von Strauss E (2009) Epidemiology of Alzheimer's disease: Occurrence, determinants, and strategies toward intervention. *Dialogues Clin Neurosci* **11**, 111-128.

[13] Rovio S, Kareholt I, Helkala EL, Viitanen M, Winblad B, Tuomilehto J, Soininen H, Nissinen A, Kivipelto M (2005) Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol* **4**, 705-711.

[14] Leon I, Garcia-Garcia J, Roldan-Tapia L (2014) Estimating cognitive reserve in healthy adults using the Cognitive Reserve Scale. *PLoS One* **9**, e102632.

[15] Stern Y (2012) Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol* **11**, 1006-1012.

[16] Stern Y (2002) What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc* **8**, 448-460.

[17] Stern Y (2009) Cognitive reserve. *Neuropsychologia* **47**, 2015-2028.

[18] Stern Y (2003) The concept of cognitive reserve: A catalyst for research. *J Clin Exp Neuropsychol* **25**, 589-593.

[19] Starr JM, Lonie J (2008) Estimated pre-morbid IQ effects on cognitive and functional outcomes in Alzheimer disease: A longitudinal study in a treated cohort. *BMC Psychiatry* **8**, 27.

[20] Grotz C, Seron X, Van Wissen M, Adam S (2017) How should proxies of cognitive reserve be evaluated in a population of healthy older adults? *Int Psychogeriatr* **29**, 123-136.

[21] Nucci M, Mapelli D, Mondini S (2012) Cognitive Reserve Index questionnaire (CRIq): A new instrument for measuring cognitive reserve. *Aging Clin Exp Res* **24**, 218-226.

[22] Baughman F, Baughman N, Mills S (2012) Cognitive reserve and intelligence: Modulating the effects of damage in ageing dynamical systems. *Proceedings of the Annual Meeting of the Cognitive Science Society*.

[23] Bennett DA, Wilson RS, Schneider JA, Evans DA, Mendes de Leon CF, Arnold SE, Barnes LL, Bienias JL (2003) Edu-

cation modifies the relation of AD pathology to level of cognitive function in older persons. *Neurology* **60**, 1909-1915.

[24] Rentz DM, Locascio JJ, Becker JA, Moran EK, Eng E, Buckner RL, Sperling RA, Johnson KA (2010) Cognition, reserve, and amyloid deposition in normal aging. *Ann Neurol* **67**, 353-364.

[25] Thow ME, Summers MJ, Saunders NL, Summers JJ, Ritchie K, Vickers JC (2018) Further education improves cognitive reserve and triggers improvement in selective cognitive functions in older adults: The Tasmanian Healthy Brain Project. *Alzheimers Dementia (Amst)* **10**, 22-30.

[26] Watson A, Joyce E (2015) Cognitive reserve and neuropsychiatric disorders. *Curr Opin Behav Sci* **4**, 142-146.

[27] Wilson RS, Yu L, Lamar M, Schneider JA, Boyle PA, Bennett DA (2019) Education and cognitive reserve in old age. *Neurology* **92**, e1041-e1050.

[28] Pettigrew C, Soldan A (2019) Defining cognitive reserve and implications for cognitive aging. *Curr Neurol Neurosci Rep* **19**, 1.

[29] Jones RN, Manly J, Glymour MM, Rentz DM, Jefferson AL, Stern Y (2011) Conceptual and measurement challenges in research on cognitive reserve. *J Int Neuropsychol Soc* **17**, 593-601.

[30] Landenberger T, Cardoso NdO, Oliveira CRd, Argimon IIdL (2019) Instruments for measuring cognitive reserve: A systematic review. *Psicologia Teoria Prática* **21**, 58-74.

[31] Opdebeeck C, Martyr A, Clare L (2016) Cognitive reserve and cognitive function in healthy older people: A meta-analysis. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* **23**, 40-60.

[32] Kartschmit N, Mikolajczyk R, Schubert T, Lacruz ME (2019) Measuring Cognitive Reserve (CR) - A systematic review of measurement properties of CR questionnaires for the adult population. *PLoS One* **14**, e0219851.

[33] Maiovis P, Ioannidis P, Nucci M, Gotzamani-Psarrakou A, Karacostas D (2016) Adaptation of the Cognitive Reserve Index Questionnaire (CRIq) for the Greek population. *Neurol Sci* **37**, 633-636.

[34] Lo RY, Jagust WJ (2013) Effect of cognitive reserve markers on Alzheimer pathologic progression. *Alzheimer Dis Assoc Disord* **27**, 343-350.

[35] Sobral M, Pestana MH, Paul C (2015) Cognitive reserve and the severity of Alzheimer's disease. *Arq Neuropsiquiatr* **73**, 480-486.

[36] van Loenhoud AC, van der Flier WM, Wink AM, Dicks E, Groot C, Twisk J, Barkhof F, Scheltens P, Ossenkoppele R (2019) Cognitive reserve and clinical progression in Alzheimer disease: A paradoxical relationship. *Neurology* **93**, e334-e346.

[37] van Loenhoud AC, Van der Flier WM, Wink AM, Dicks E, Groot C, Twisk JW, Barkhof F, Scheltens P, Ossenkoppele R (2018) Disease-stage specific relationship between cognitive reserve and clinical progression in Alzheimer's disease. *Alzheimers Dement* **14**, P158-P160.

[38] Stern Y (2006) Cognitive reserve and Alzheimer disease. *Alzheimer Dis Assoc Disord* **20**, S69-S74.

[39] Arcara G, Mondini S, Bisso A, Palmer K, Meneghello F, Semenza C (2017) The relationship between cognitive reserve and math abilities. *Front Aging Neurosci* **9**, 429.

[40] Almeida-Meza P, Steptoe A, Cadar D (2020) Markers of cognitive reserve and dementia incidence in the English Longitudinal Study of Ageing. *Br J Psychiatry*, doi: 10.1192/bjp.2020.54

[41] Lane CA, Hardy J, Schott JM (2018) Alzheimer's disease. *Eur J Neurol* **25**, 59-70.

[42] Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, Hill GB, McDowell I (2002) Risk factors for Alzheimer's disease: A prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol* **156**, 445-453.

[43] Mathias JL, Bowden SC, Barrett-Woodbridge M (2007) Accuracy of the Wechsler Test of Adult Reading (WTAR) and National Adult Reading Test (NART) when estimating IQ in a healthy Australian sample. *Aust Psychol* **42**, 49-56.

[44] Steward KA, Novack TA, Kennedy R, Crowe M, Marson DC, Triebel KL (2017) The Wechsler Test of Adult Reading as a measure of premorbid intelligence following traumatic brain injury. *Arch Clin Neuropsychol* **32**, 98-103.

[45] Morris JC, Ernesto C, Schafer K, Coats M, Leon S, Sano M, Thal LJ, Woodbury P (1997) Clinical dementia rating training and reliability in multicenter studies: The Alzheimer's Disease Cooperative Study experience. *Neurology* **48**, 1508-1510.

[46] Morris JC (1997) Clinical dementia rating: A reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *Int Psychogeriatr* **9**(Suppl 1), 173-176; discussion 177-178.

[47] Wyman-Chick KA, Scott BJ (2015) Development of clinical dementia rating scale cutoff scores for patients with parkinson's disease. *Mov Disord Clin Pract* **2**, 243-248.

[48] O'Bryant SE, Lacritz LH, Hall J, Waring SC, Chan W, Khodr ZG, Massman PJ, Hobson V, Cullum CM (2010) Validation of the new interpretive guidelines for the clinical dementia rating scale sum of boxes score in the national Alzheimer's coordinating center database. *Arch Neurol* **67**, 746-749.

[49] O'Bryant SE, Waring SC, Cullum CM, Hall J, Lacritz L, Massman PJ, Lupo PJ, Reisch JS, Doody R (2008) Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: A Texas Alzheimer's research consortium study. *Arch Neurol* **65**, 1091-1095.

[50] Boult L, Boult C, Pirie P, Pacala JT (1994) Test-retest reliability of a questionnaire that identifies elders at risk for hospital admission. *J Am Geriatr Soc* **42**, 707-711.

[51] Gennuso KP, Matthews CE, Colbert LH (2015) Reliability and validity of 2 self-report measures to assess sedentary behavior in older adults. *J Phys Act Health* **12**, 727-732.

[52] Alzheimer's Disease & Dementia, http://www.alz.org/ alzheimers_disease_what_is_alzheimers.asp, Accessed March 12, 2020.

[53] Alzheimer's Association, Causes and Risk Factors, https://www.alz.org/alzheimers-dementia/what-is-alzheimers/causes-and-risk-factors, Accessed March 12, 2020.

[54] Alzheimer's Association, Women and Alzheimer's, https://alz.org/alzheimers-dementia/what-is-alzheimers/women-and-alzheimer-s, Accessed March 12, 2020.

[55] National Institute on Aging, Depression and Older Adults, https://www.nia.nih.gov/health/depression-and-older-adults, Accessed March 12, 2020.

[56] Hebert LE, Scherr PA, McCann JJ, Beckett LA, Evans DA (2001) Is the risk of developing Alzheimer's disease greater for women than for men? *Am J Epidemiol* **153**, 132-136.

[57] Hebert LE, Weuve J, Scherr PA, Evans DA (2013) Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology* **80**, 1778-1783.

[58] Hersi M, Irvine B, Gupta P, Gomes J, Birkett N, Krewski D (2017) Risk factors associated with the onset and pro-

gression of Alzheimer's disease: A systematic review of the evidence. *Neurotoxicology* **61**, 143-187.

[59]	Han L, McCusker J, Cole M, Capek R, Abrahamowicz M (2011) Antidepressant use and cognitive functioning in older medical patients with major or minor depression: A prospective cohort study with database linkage. *J Clin Psychopharmacol* **31**, 429-435.

[60]	Doody RS, Dunn JK, Clark CM, Farlow M, Foster NL, Liao T, Gonzales N, Lai E, Massman P (2001) Chronic donepezil treatment is associated with slowed cognitive decline in Alzheimer's disease. *Dement Geriatr Cogn Disord* **12**, 295-300.

[61]	Casson RJ, Farmer LD (2014) Understanding and checking the assumptions of linear regression: A primer for medical researchers. *Clin Exp Ophthalmol* **42**, 590-596.

[62]	Curb JD, Rodriguez BL, Abbott RD, Petrovitch H, Ross GW, Masaki KH, Foley D, Blanchette PL, Harris T, Chen R, White LR (1999) Longitudinal association of vascular and Alzheimer's dementias, diabetes, and glucose tolerance. *Neurology* **52**, 971-975.

[63]	Luchsinger JA, Tang MX, Stern Y, Shea S, Mayeux R (2001) Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *Am J Epidemiol* **154**, 635-641.

[64]	Weuve J, Barnes LL, Mendes de Leon CF, Rajan KB, Beck T, Aggarwal NT, Hebert LE, Bennett DA, Wilson RS, Evans DA (2018) Cognitive aging in Black and White Americans: Cognition, cognitive decline, and incidence of Alzheimer disease dementia. *Epidemiology* **29**, 151-159.

[65]	Early DR, Widaman KF, Harvey D, Beckett L, Park LQ, Farias ST, Reed BR, Decarli C, Mungas D (2013) Demographic predictors of cognitive change in ethnically diverse older persons. *Psychol Aging* **28**, 633-645.

[66]	Boland L, Légaré F, Perez MMB, Menear M, Garvelink MM, McIsaac DI, Painchaud Guérard G, Emond J, Brière N, Stacey D (2017) Impact of home care versus alternative locations of care on elder health outcomes: An overview of systematic reviews. *BMC Geriatr* **17**, 20.

[67]	Olsen C, Pedersen I, Bergland A, Enders-Slegers M-J, Jøranson N, Calogiuri G, Ihlebæk C (2016) Differences in quality of life in home-dwelling persons and nursing home residents with dementia – a cross-sectional study. *BMC Geriatr* **16**, 137.

[68]	Scarmeas N, Stern Y (2004) Cognitive reserve: Implications for diagnosis and prevention of Alzheimer's disease. *Curr Neurol Neurosci Rep* **4**, 374-380.

[69]	Harrington KD, Dang C, Lim YY, Ames D, Laws SM, Pietrzak RH, Rainey-Smith S, Robertson J, Rowe CC, Salvado O (2018) The effect of preclinical Alzheimer's disease on age-related changes in intelligence in cognitively normal older adults. *Intelligence* **70**, 22-29.

[70]	Pavlik VN, Doody RS, Massman PJ, Chan W (2006) Influence of premorbid IQ and education on progression of Alzheimer's disease. *Dement Geriatr Cogn Disord* **22**, 367-377.

[71]	Austin PC, Steyerberg EW (2015) The number of subjects per variable required in linear regression analyses. *J Clin Epidemiol* **68**, 627-636.

[72]	Hanley JA (2016) Simple and multiple linear regression: Sample size considerations. *J Clin Epidemiol* **79**, 112-119.

[73]	Mondini S, Madella I, Zangrossi A, Bigolin A, Tomasi C, Michieletto M, Villani D, Di Giovanni G, Mapelli D (2016) Cognitive reserve in dementia: Implications for cognitive training. *Front Aging Neurosci* **8**, 84.