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RESEARCH ARTICLE

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The role of cognitive reserve in mediating HIV-associated neurocognitive disorders in older adults living with-treated HIV in Mbeya, Tanzania: A cross-sectional observational study

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Abstract

Introduction: HIV-associated neurocognitive disorders (HAND) are a spectrum of cognitive impairments in chronic HIV infection. HAND is common in sub-Saharan Africa (SSA), despite combination antiretroviral therapy (cART). Older people appear to be at increased risk. It is unknown if cognitive reserve (CR), which is protective in neurodegenerative dementias, protects against HAND.

Objective: To evaluate the association of CR and risk of HAND in an older cART-treated population in SSA.

Methods: Cross-sectional observational study completed in hospital outpatient clinics in Southwest Tanzania. We assessed HIV-positive participants aged ≥50 years established on cART using a neuropsychological test battery, functional assessment, informant history and depression screen. Control participants were HIV-negative individuals attending chronic disease clinics. We used operationalised Frascati criteria for HAND diagnosis. CR was measured using the Cognitive Reserve Index (CRI) and other proxy measures.

Results: The prevalence of HAND was 64.4% (n = 219/343). Lower CRI score [odds ratio (OR) = 0.971, p = 0.009] and less formal education (OR = 4.364, p = 0.026) were independent risk factors for HAND but HIV-severity measures were not. Unemployment and low-skilled manual work were associated with increased risk of HAND in bivariate analysis but not in multivariable analysis.

Conclusions: Higher total CRI score and more formal education appeared to be protective against HAND, in this cohort. Potentially, cognitively and socially stimulating activities and exercise could increase cognitive reserve in later life. Cognitive reserve could possibly be more important than HIV-disease severity in risk of HAND in older people with treated HIV.

Sadler M, Kuhoga E, Paddick S.-M and Mbwele B have both contributed equally to this work as lead and supervising authors respectively.

KEYWORDS
cognitive impairment, epidemiology, HIV, HIV-associated neurocognitive disorders (HAND), neurocognitive disorder, older adults, sub-Saharan Africa

Key points

- Prevalence of HAND is high in older people, but cognitive reserve may be a protective factor.
- There are few epidemiological data on HAND in SSA, particularly for the older population.
- Higher total CR and formal education appeared to be protective for HAND.
- These findings may influence interventions to increase CR and education from a younger age and encourage further research in this area.

1 | INTRODUCTION

An estimated 68% of the 38 million people living with HIV (PLWH) worldwide[1] live in sub-Saharan Africa (SSA).[2] Rollout of combined antiretroviral therapy (cART) has near-normalised life expectancy of HIV-positive individuals globally. Consequently, HIV has evolved into a chronic condition, and the HIV-positive population is ageing. In SSA, the number of PLWH aged 50 and over is expected to triple by 2040.[3]

HIV-associated neurocognitive disorders (HAND) are frequently observed in chronic HIV infection. They are characterised by deterioration in memory, cognition, behaviour and motor function.[4] HAND include three subtypes of increasing severity according to international diagnostic criteria: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD) (Supporting Information S1).[5] HAND increase risk of early mortality[6] and impact quality of life due to increased unemployment, difficulty with activities of daily living,[7] and poor medication adherence.[8]

Although rates of HAD have decreased with cART access, milder forms of HAND persist[9] and overall prevalence remains high[6] even with good long-term virological control.[10–12] In SSA, estimates range from 20% to 80%.[13] Prevalence of HAND is generally higher in older versus younger individuals in high income countries (HICs),[14–17] and increasing age is a consistent risk factor. Despite this, some older PLWH remain free of HAND, irrespective of HIV disease stage or control.[18] Cognitive reserve (CR), an individual's capacity to compensate for brain pathology before clinical manifestations become evident[19] is a possible explanatory factor. Cognitively stimulating life exposures, and early developmental factors like childhood nutrition and disadvantage may influence CR. Proxy measures for CR include education, occupational attainment, and complex leisure activities.[20]

CR may protect from the symptoms of HAND in HIV. HIC data from several studies suggest less education is associated with higher prevalence of cognitive impairment in adults with HIV[21–29] (Supporting Information S2), though data for older adults with HIV are limited.

Despite a growing older population of PLWH, in SSA, there are few epidemiological data on HAND in this group.[30,31] To date, two prevalence studies based on Frascati criteria[5] have been conducted in older SSA populations[32,33] by our team and collaborators. Both suggested high HAND prevalence (47% and 70.3%) despite well-controlled HIV. In these previous studies, HAND were associated with demographic rather than HIV-specific factors. We hypothesised that CR might be a potentially modifiable protective factor in this setting.

Our study is the first in SSA to examine the relationship of CR and HAND in an older cART-treated population. We aimed to measure CR in cART-treated individuals aged ≥50 years in Mbeya, Tanzania using the Cognitive Reserve Index Questionnaire (CRIQ) alongside other CR proxy measures and investigate the association between CR and HAND.

2 | METHODS

2.1 | Study setting and population

We recruited HIV-positive participants aged ≥50 years from government-funded HIV Care and Treatment Centres (CTC) and HIV-negative controls from chronic disease outpatient clinics in Mbeya (Mbeya Zonal Referral Hospital, Mbeya Regional Referral Hospital, Ifsi District Hospital, Igawilo City Hospital, Kiwanampaka Health Centre, Mkoani Hospital).

We collected data over a 6-week period from 25th March 2021. We systematically sampled participants in order of arrival. Age and HIV disease status were determined from patient-held clinic registration cards. Inclusion criteria for participants were age ≥50 years, confirmed HIV-positive and under long-term CTC treatment and follow-up. Controls were aged ≥50 years, without known HIV and attending other chronic disease clinics. In both groups, individuals who lacked capacity to consent, those with acute illness at the time of assessment, or where participation might delay necessary investigations or interventions were excluded from the study.

2.2 | Ethics and consent

Ethical approval was granted by the University of Dar-es-Salaam and by the Tanzanian National Institute of Medical Research (NIMR/

HQR.8a/Vol.IX/3616). Clinicians verbally explained study procedures and gave written information to eligible participants. Participants gave informed consent via a signature, or thumb print if illiterate. We obtained additional informed consent to contact family or other close informant for collateral history of cognitive and functional impairment. Onward referral procedures for those identified with health needs were agreed with hospital management in advance.

2.3 | Data collection

Data were collected by Tanzanian medical students and doctors in training collaborating remotely with UK medical students and Tanzanian and UK senior researchers. We collected sociodemographic information through self-report, which included age, sex, occupation, education, living arrangement, literacy, handedness, and preferred language. The definition of 'literacy' was 'ever being able to read and write a simple note if needed'. In terms of education in Tanzania, complete primary school is 7 years, and secondary a further 4 years. Education category as well as number of years of education were both assessed, since some individuals might start primary/secondary school but not complete it.

2.4 | Medical assessment

Physical measurements included height, weight, temperature, pulse rate, blood pressure (BP) and respiratory rate. The Confusion Assessment Method (CAM) was used to screen for delirium.[34] Patients identified with potential acute physical illness were referred to clinic physicians and excluded from further assessment.

2.5 | Assessment of comorbidities and risk factors

The Mini-International Neuropsychiatric Interview (MINI) depression module was used to screen for current major depressive disorder (MDD). Participants meeting current MDD criteria were subsequently excluded from analysis, due to potential effect of MDD on cognitive performance.[35] Information on comorbidities and cognitive risk factors was collected through self-report questionnaire, including previous stroke, hypertension, visual and hearing impairment, epilepsy, previous head injury, smoking and alcohol use.

2.6 | Measuring cognitive reserve

CR was assessed using the Cognitive Reserve Index Questionnaire (CRIq). The CRIq includes subsections for educational attainment (CRI-Education), occupational attainment (CRI-Work) and participation in leisure activities (CRI-Leisure).[36] The CRIq has been used in previous studies of neurocognitive disorders,[37–39] mostly in HICs, but has also been validated in a Malaysian study analysing CR post-stroke.[40]

CRIq raw scores from each subsection were adjusted for age using a linear regression model, then standardized and transposed to a scale with mean = 100 and SD = 15, as outlined by the original CRIq authors.[36] Sub scores were averaged to produce a total Cognitive Reserve Index score (CRI-Total). Each CRIq section was also analysed independently to assess significance of each category.[36]

Other locally-appropriate potential CR proxy measures were included following discussion with local clinicians: participation in a formal community leadership role, years of formal education (distinct to CRI-Education score, which does not include adult education) and literacy to account for individuals acquiring literacy outside formal schooling. Measures of childhood disadvantage were included as potential confounders for less education, as well as indicators of lower CR linked with late life cognitive impairment in previous studies including head circumference and femur length.[41]

2.7 | HIV-specific data

Nationally standardised CTC data sheets were used to record HIV-disease outcomes. Information included date of diagnosis, nadir CD4, most recent CD4 count, HIV viral load, WHO HIV stage, current or previous TB, date of starting cART and current cART regimen.

2.8 | Neuropsychological tests

A low-literacy neuropsychological (NP) battery of cortical and subcortical domains previously used by our team in studies of HAND in the Kilimanjaro region of Tanzania was used to measure cognitive impairment.[32,42] Measures included in the battery, corresponding cognitive domains and available validation data are outlined in Supporting Information S3. A team of senior medical students and doctors in training administered the battery following 5 days of face-to-face training and harmonisation delivered by staff from the Kilimanjaro HAND studies, supervised remotely by senior UK investigators.

2.9 | HAND diagnosis

Diagnosis of HAND by Frascati criteria[5] was operationalised by generating local normative scores for NP tests from the NP scores of control participants to determine cognitive impairment 1SD or 2SD below normative means in ≥2 domains. Individuals with an alternative evident cause of cognitive impairment (e.g. positive CAM screening) were excluded following discussion with senior authors.

Identification of functional impairment for symptomatic HAND diagnosis was supported where possible, by collateral history from an informant to corroborate self-reported impairments. This collateral history included a semi-structured interview, and Tanzanian Instrumental Activities of Daily Living (IADL) questionnaire, previously validated for neurodegenerative dementias.[43] Where collateral

history was not available, self-reported impairment and the Karnofsky Performance Status Scale[44] were used to make a judgement on presence or absence of functional impairment.

2.10 | Statistical analysis

Data were uploaded to a secure online database using Kobo Toolbox. All statistical analyses were completed using IBM SPSS Statistics 26. Data were assessed for normality using histograms. Descriptive characteristics were calculated for qualitative and quantitative variables. Parametric and non-parametric statistical tests were selected according to the level and spread of data, including paired *T* test for normally distributed variables and Mann Whitney U and Chi-squared test for non-normally distributed data.

NP test battery cores were demographically corrected by categorising into age and education groups. Age was split into 50–64 and ≥65 years. Education was split into <7 and ≥7 years. Mean and SD were calculated for each NP test, and cognitive impairment in HIV positive participants was identified in comparison to the performance mean and SD of the control participants of the corresponding category to identify those meeting HAND criteria.

For this exploratory analysis, we initially performed bivariate analysis to investigate the association between our cognitive reserve proxy factors and HAND. Significance levels were set at 5%. Any variables that were statistically significant ($p < 0.05$) on bivariate analysis were then included in two separate multivariable logistic regression models to investigate variables independently associated with HAND after adjusting for others. In the first model all significant variables, except CRI-Total, were entered into a stepwise backwards regression model alongside potentially confounding covariates, including HIV disease measures due to well-established associations with HAND(13). A second model was constructed with CRI-Total score and HIV disease measures included. CRI-Total score was modelled separately due to collinearity with the sub-total scores and other CR proxy factors. The HIV disease measures adjusted for were nadir CD4 count, most recent CD4 count, viral load and WHO HIV stage.

3 | RESULTS

The flow of individuals through the study is shown in Figure 1; 340 individuals with HIV and 343 controls participated in the study and had complete data.

Table 1 summarises sociodemographic characteristics of the HIV-positive cases and HIV-negative controls. Controls were older than HIV positive participants (median age 62 vs. 57, $p < 0.01$), but similar in sex distribution and educational and occupational background. For HIV-positive participants, most (89.1%) had at least primary level education and most worked in farming (61.8%). Forty-three participants (12.3%) were illiterate. Most (70.3%) had an undetectable HIV viral load according to the most recent CTC

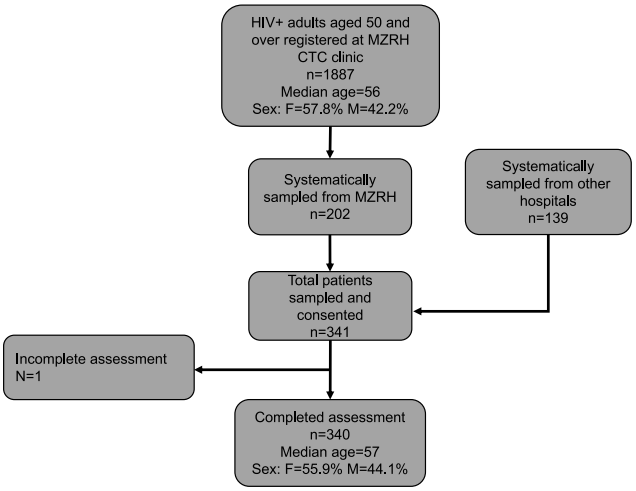

FIGURE 1 Study flowchart.

measurement. Numbers of participants in each age/education category used for normative values are also presented in Table 1. Performance data on individual neuropsychological tests for cases and controls is presented in Supporting Information S4.

The overall prevalence of HAND was 64.4% (n = 219). Prevalence of each subtype is summarised in Figure 2. Six people (1.8%) had other likely causes of impairment including MDD ($n = 3$), delirium ($n = 2$), and stroke ($n = 1$) and were excluded from analysis.

3.1 | Cognitive reserve and HAND

In this cohort, median CRI-Total score was 97.3 (IQR 93.2–103.9). Median scores for CRI-Education, CRI-Working activity and CRI-Leisure time were 98.4 (IQR 96.5–102.6), 96.4 (IQR 91.4–101.5) and 97.4 (IQR 87.9–106) respectively. Median scores for cases and controls are shown in Supporting Information Table S5. In the control group, median CRI-Education (99.8) was higher than in cases, whilst lower CRI-Working activity (96.4) and leisure time (97.4) were lower, though these differences were not significant. Overall cognitive reserve, represented by CRI-Total, was very similar (97.3).

Association of cognitive reserve measures and HAND are shown in Table 2. On bivariate analysis, CRI-Education, CRI-Total, years of formal education, current and previous highest occupation and literacy were associated with HAND.

In multivariable regression analysis, HAND was significantly associated with lower CRI-Total score after adjusting for HIV disease factors (Table 3). In the second model, it was independently associated with lack of formal education, after adjusting for HIV disease factors and other variables.

Another logistic regression model was completed for participants with symptomatic HAND (MND and HAD). Lack of formal education was independently associated with symptomatic HAND compared to ≥7 years of education (Table 4). All other CR measures were not independently associated.

TABLE 1 Sociodemographic data of cases and controls.

Cases ($N = 340$)	Cases ($n = 340$)	Controls ($n = 343$)	Significance
Median age (IQR)	57 (53–63)	62 (57–69)	$t = -8.191$
			$\mathbf{p < 0.01}$
Number of females (n [%])	190 (55.9)	193 (56.2)	$X^2 = 0.053$
			$p = 0.818$
Median education (years)	7	7	
Education by number of years (n [%])			
0 years	34 (10)	51 (14.9)	$U = 54667$
1–4 years	19 (5.6)	28 (8.2)	$Z = -1.115$
5–7 years	239 (70.3)	202 (58.9)	$p = 0.265$
More than 7 years	48 (14.1)	62 (18.1)	
Current occupation (n [%])			
None	31 (9.1)	41 (11.9)	$U = 55562.5$
Low-skilled manual work	232 (68.2)	219 (63.8)	$Z = -0.914$
			$p = 0.361$
Skilled manual work	48 (14.1)	50 (14.6)	
Skilled non-manual work	27 (7.9)	28 (8.2)	
Professional	2 (0.6)	5 (1.5)	
Highly intellectual or responsible occupation	0 (0.0)	0	
Marital status (n [%])			
Married	220 (64.7)	264 (77)	$U = 50677.5$
Widowed	94 (27.6)	64 (18.6)	$Z = -3.255$
			$p = 0.001$
Divorced	22 (6.5)	11 (3.2)	
Single	4 (1.2)	4 (1.2)	
Household status (n [%])			
Living with others	281 (82.6)	295 (86)	$X^2 = 1$
Living alone	50 (17.4)	48 (14)	$p = 0.317$
Literacy (n [%])			
Literate	297 (87.4)	292 (85.1)	$X^2 = 0.751$
Illiterate	43 (12.6)	51 (14.9)	$p = 0.386$

Age and education according to neuropsych test groups	**Age 50–64**	**Age 65+**	**Age 50–64**	**Age 65+**
<7 years education	41	21	24	61
≥7 years education	239	39	177	81

Note: Bold indicates a different section of the table, delineated by age group.

4 | DISCUSSION

Overall, our reported median scores fell within the 'Medium' CR categorisation from the original CRIq paper.[36] Lower CRI-Total score was associated with HAND, independent of HIV disease severity measures. As CRI-Total is a proxy CR measure, this supports our hypothesis that individuals with higher CR are less likely to meet HAND criteria.

The CRIq has only been used to evaluate CR in one other HAND study.[26] This study also reported that lower CRI-Total was independently associated with HAND, though sample size was smaller (n = 60) and predominantly male (51/60).

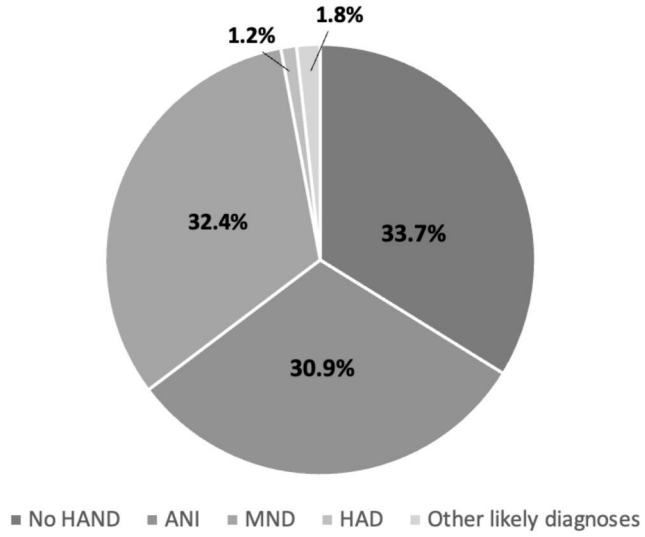

FIGURE 2 Prevalence of HAND subtypes and alternative diagnoses.

Our findings appear similar to other studies from HICs linking higher CR to lower HAND prevalence. In a US study, Foley et al.[25] used a CR composite score consisting of years of education and word-reading ability, and reported that higher CR appeared protective for HAND in older people with HIV.[25]

We used both years of formal education and CRI-Education as proxy CR measures. They differ as CRI-Education includes completed adult education or training. We found that years of formal education was independently associated with HAND after adjustment for other variables, whereas CRI-Education was not. This suggests that childhood education may be more important in this setting although interestingly, measures of childhood disadvantage such as head circumference and femur length were not associated with HAND. Low education may not necessarily be a marker of childhood disadvantage in some LMIC settings and may instead reflect historical lack of access to schooling in rural areas.[45]

We specifically found that 'no education' was independently associated with HAND despite using a low-literacy battery and locally derived norms. This suggests that even elementary education may protect against HAND in this setting. The association between HAND and CR measured through educational level is widely reported, but most HIC studies have identified this relationship in settings with markedly higher education than reported here. The USA MACS(21) is a well-known study reporting that low education (<12 vs. >12 years) increases risk of HAND. Similarly, Milanini et al.[26] reported that CRI-Education was independently associated with HAND(26) in another US cohort with a median 12 years education. A similar relationship has been found in a higher-educated Zambian cohort (mn 10 years education, mn age 41 years),[46] where less education was associated with deficits in executive functioning, learning and processing speed. Whilst education as a predictor of CR has consistently been shown to be a protective factor for HAND in well-educated populations, our findings suggest a similar association in a setting of much lower formal education. It may be that even limited early education can contribute to CR and be protective in later life.[47] Potentially cognitively socially stimulating activities could increase cognitive reserve in mid to later life.[48,49]

Similarly, other HIC studies are difficult to compare as they include younger individuals with advanced HIV. For example, De Ronchi et al. reported that lower educational level was associated with HAND(22) in a cohort where most participants were younger than 28 years and many had symptomatic HIV or a CD4 count below 500.

In this setting, median CRI-Total was 97.3, compared with 114 in the study by Milanini *et* al. including participants of a similar age.[26] Although we found a consistent association between education and HAND, we did not find the same association for CR subcategories. CRI-Work and CRI-Leisure scores were higher in participants without HAND, but differences were not statistically significant. In contrast, many previous studies include occupational level in CR composite measures and demonstrate less cognitive impairment in those with higher CR(23, 24, 26, 27). It may be that work and leisure are less valid differentiators of CR in this setting. In Tanzania, it is usual to work into old age in farming and traditional occupations. It is unusual to be unemployed. Most of our cohort were occupied in farming or low skilled manual work (61.8% and 68.2% respectively). In this setting where many had similar occupations, effect on CR may be less. The CRIq has not formally been validated in Africa and may therefore have some cultural limitations.

Similarly, in our setting CRI-Leisure was not independently associated with HAND, in contrast to HIC data.[26] Leisure activities are widely used as a proxy for CR in other neurological disorders.[50,51] It seems likely that occupation and leisure activities alone are poor measures of CR in this population, due to sociocultural and economic factors. We also evaluated other potentially more appropriate measures such as formal community roles but found no association. Overall, the effect of education and particularly formal childhood education appears more robust than other proxy CR measures in this setting.

HIV disease factors were not associated with HAND, which is potentially surprising given the association between nadir CD4 count ('legacy effect') and HAND in previous studies.[13] Legacy effect and HIV disease control may be less important in HAND risk in older PLWH with increased comorbidities, and in well-controlled HIV. Similar findings were reported by Patel et al, who found that CR was the most robust predictor for cognitive impairment, above HIV disease severity markers in a study of multiple risk factors.[28]

Previous studies in the Kilimanjaro region of Tanzania, completed by our team and collaborators report similar findings. Although we did not investigate cognitive reserve per se, we found that using a similar methodology, illiteracy and social isolation were independent predictors of symptomatic HAND whereas most HIV-disease factors were not.[52] A major limitation of that study was that HIV viral load measurement was not locally available at the time of data collection (2016). In a subsequent 2019 study, less education was associated with HAND, but HIV disease measures including viral load and nadir CD4 count, were not.[33] These cohorts were

TABLE 2 Bivariate analysis of CR measures for participants with and without HAND.

Variable	HAND ($n = 219$)	No HAND ($n = 115$)	Significance
Median CRI-education (IQR)	98.0 (96.1–102.2)	98.8 (96.9–103.6)	$U = 10363.0$ $Z = 2.66$ **$p = 0.008$**
Median CRI-work (IQR)	96.4 (90.6–100.6)	96.8 (92.2–109.6)	$U = 11045.5$ $Z = 1.845$ $p = 0.065$
Median CRI-leisure (IQR)	97.4 (87.9–104.7)	97.8 (88.2–109.2)	$U = 11906.5$ $Z = 0.818$ $p = 0.413$
Median CRI-total (IQR)	96.8 (92.5–101.9)	97.8 (94.6–107.7)	$U = 9889.5$ $Z = 3.224$ **$p = 0.001$**
Years of formal education [*n* (%)]			$U = 10202.0$ $Z = 3.519$ **$p < 0.001$**
0 years	30 (13.7)	4 (3.5)	
1–4 years	16 (7.3)	3 (2.6)	
5–7 years	147 (67.1)	86 (74.8)	
More than 7 years	26 (11.9)	22 (19.1)	
Current occupation [*n* (%)]			$U = 10671.0$ $Z = 2.817$ **$p = 0.005$**
Not working	23 (10.5)	8 (7)	
Low skilled manual	159 (72.6)	73 (63.5)	
Skilled manual	25 (11.4)	17 (14.8)	
Skilled non-manual	12 (5.5)	15 (13.0)	
Professional	0 (0.0)	2 (1.7)	
Highest previous occupation [*n* (%)]			$U = 10790.5$ $Z = 2.614$ **$p = 0.009$**
Never worked	4 (1.8)	0 (0.0)	
Low skilled manual	158 (72.1)	70 (60.9)	
Skilled manual	33 (15.1)	24 (20.9)	
Skilled non-manual	15 (6.8)	17 (14.8)	
Professional	9 (4.1)	4 (3.5)	
Official community role [*n* (%)]	37 (16.9)	26 (22.6)	$X^2 = 1.608$ $p = 0.205$
Literacy [*n* (%)]			$X^2 = 6.715$ $p =$ **0.01**
Illiterate	35 (16)	7 (6.1)	
Literate	184 (84)	108 (93.9)	
Living situation [*n* (%)]			$X^2 = 0.495$ $p = 0.482$
Lives alone	39 (17.8)	17 (14.8)	
Lives with family	180 (82.2)	180 (85.2)	

(Continues)

TABLE 2 (Continued)

Variable	HAND (*n* = 219)	No HAND (*n* = 115)	Significance
Childhood disadvantage measures			$t = 1.316$ $p = 0.189$
Mean head circumference +/− SD	55 +/− 3.6	54.5 +/− 3	
Mean femur length +/− SD	48.3 +/− 5.8	47.3 +/− 5.4	$t = -1.457$ $p = 0.146$
Father's highest occupation [*n* (%)]			$U = 11723.5$ $Z = 1.67$ $p = 0.095$
Never worked	1 (0.5)	1 (0.9)	
Low skilled manual	192 (87.7)	92 (80)	
Skilled manual	16 (7.3)	12 (10.4)	
Skilled non-manual	5 (2.3)	8 (7)	
Professional	5 (2.3)	2 (1.7)	
Mother's highest occupation [*n* (%)]			$U = 12100.5$ $Z = 1.395$ $p = 0.163$
Never worked	3 (1.4)	2 (1.7)	
Low skilled manual	210 (95.9)	103 (89.6)	
Skilled manual	6 (2.7)	5 (4.3)	
Skilled non-manual	0 (0)	3 (2.6)	
Professional	0 (0)	1 (0.9)	

Abbreviation: CRI, Cognitive Reserve Index.

TABLE 3 Multivariable backwards logistic regression analyses of significant variables and HIV measures for HAND.

Variable	HAND (*n* = 219)	No HAND (*n* = 115)	Adjusted odds ratio	95% confidence interval	Significance
Model 1					
CRI-total [median (IQR)]	96.8 (92.5–101.9)	97.8 (94.6–107.7)	0.971	0.949 to 0.993	**$p = 0.009$**
Model 2					
Years of formal education [*n* (%)]					
No education	30 (13.7)	4 (3.5)	4.362	1.198 to 15.883	**$p = 0.026$**
1–4 years	16 (7.3)	3 (2.6)	2.879	0.680 to 12.182	$p = 0.151$
5–7 years	147 (67.1)	86 (74.8)	1.077	0.510 to 2.277	$p = 0.846$
More than 7 years	26 (11.9)	22 (19.1)	1		

Note: Two separate models were constructed for dependent variables. Model 1 included CRI-Total alongside HIV disease measures. Model 2 included the CRI subcategories and the other cognitive reserve variables that were significant on bivariate analysis, including years of formal education, again with HIV disease measures. Only variables that were significant are presented. Bold indicates a different section of the table, delineated by age group.

TABLE 4 Multivariable regression analysis of CR factors significant on univariate analysis for symptomatic HAND.

Variable	Symptomatic HAND (*n* = 114)	No symptomatic HAND (*n* = 220)	Adjusted OR	95% CI	Significance
Years of formal education [*n* (%)]					
No education	19 (16.7)	15 (6.8)	2.834	1.365 to 5.881	**$p = 0.005$**
1–4 years	9 (7.9)	13 (5.9)	1.445	0.589 to 3.543	$p = 0.421$
5–7 years	75 (65.8)	157 (71.4)	1.222	0.435 to 3.122	$p = 0.332$
More than 7 years	11 (9.6)	35 (15.9)	1		

Note: Variables that were significant on bivariate analysis for symptomatic HAND were put into a logistic regression model alongside HIV disease factors. Only years of formal education was significant. Bold indicates a different section of the table, delineated by age group.

educationally similar, with the majority completing primary school but no further/higher education. Taken together, these findings suggest that CR may be a more important predictor of HAND than HIV disease severity in the older SSA population in the post-cART era.

Although associated with overall HAND, CRI-Total was not associated with symptomatic HAND (MND/HAD). Comparison with existing data is challenging. Most previous studies of CR and HAND have not assessed functional impairment.[21–25,28,29] Only one HIC study to date has looked at CR in relation to symptomatic HAND(27) reporting that CR scores were lower in individuals with symptomatic HAND relative to those with asymptomatic HAND. This is a HIC study with a predominantly male sample and therefore difficult to compare directly to our cohort.[53]

Functional impairment is challenging to measure and heavily reliant on subjective measures such as self and informant-report. Consequently, symptomatic HAND may be under or over-estimated. It is possible that high CR does not prevent manifestation of functional deficits, but may delay or prevent cognitive impairment. Lack of formal education was significantly associated with symptomatic HAND. This finding supports evidence from Morgan et al. showing CR to be protective for syndromic HAND(27). As CRI-Total showed no association with symptomatic HAND, this might suggest that education is a more powerful predictor of CR in this setting than the CRIq. Further studies are required as the relationship between CR and functional impairment is unclear.

4.1 | Limitations

Our sample included only people actively attending clinic follow-up leading to potential bias towards individuals motivated to attend healthcare appointments.

There were limitations in our operationalised HAND diagnosis. Participants were not evaluated for cognitive and neurological impairment by a specialist. Although we excluded a small number of individuals where there was a clear alternative diagnosis such as severe depression, delirium, or stroke, it is possible that other individuals met HAND operationalised criteria where another diagnosis may have been made following specialist evaluation. This could not be avoided due to resource limitations and the restrictions of the COVID-19 pandemic. Similarly, determination of functional impairment as in other studies relied heavily on self and informant report and might therefore be susceptible to bias. We elected not to exclude individuals unable to provide an informant, to increase generalisability, but in those cases identification of functional impairment relied on self-report and clinician assessment.

We selected the CRIq because it was being utilised by collaborators in Malaysia and we were not able to identify a validated measure for Africa. Although we discussed and minimally adapted the measure with local clinicians prior to the study, the CRIq questions may not be optimal CR measures in an African setting.

Background demographic and clinical data to compare to our systematically selected sample were only available from the lead MZRH site, and we were not able to obtain equivalent data from the other satellite hospitals to determine whether our recruited samples were representative of the background hospital populations. Nevertheless, the fact that our controls were significantly older than HIV positive cases, but similar in educational and occupational background and CRIQ score suggests less possibility of bias.

5 | CONCLUSIONS

To our knowledge, this is the first study to date to investigate CR and HAND in an older population in SSA. This study supports previous findings from other settings that low CR is associated with HAND.

Low education appears to be strongly associated with HAND even in this low-literacy setting, but there is a potential broader additional effect of CR. If this association with education were to be a consistent finding, this might influence public health policy with regard to school leaving age for example, Interventions to increase CR in individuals without formal education or low CR might also be considered.

The role of CR in mediating functional impairment in HAND was unclear as was the role of occupational attainment and leisure activities. It is also difficult to draw firm conclusions due to the cross-sectional nature of the study. Further research is required to investigate the role of occupation and leisure in LMIC setting, and to obtain longitudinal data.

AUTHOR CONTRIBUTIONS

This work is done in the context of a research collaboration agreement between the University of Dar es Salaam and Newcastle University and in conjunction with the Mbeya Zonal Referral Hospital (MZRH) Staff. The contents of this publication are the sole responsibility of the authors and do not necessarily reflect the views of any agency. Contributors BM, SMP, GL and RW conceptualised this study and designed the protocol. MS performed the analysis and drafted the manuscript supervised by BM WKG and SMP. EK led on the clinical protocol and training implementation and contributed to interpretation of study results and manuscript. MS, NTR, and EK led on data collection and supported the interpretation of the results assisted by KS, EC, MK, BM. All authors reviewed the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Deidentified data from this study are available on reasonable application to the lead authors subject to Tanzania National Institute for Medical Research (NIMR) approvals as appropriate.

ETHICS STATEMENT

This study was approved by the Mbeya College of health Sciences UDS-MCHAS research ethics committee and the Tanzanian Institute for Medical Research (NIMR).

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