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Abstract

Objective: The current study examined the longitudinal relationship between cognitive reserve (CR), depression, and executive function (EF) in a cohort of older adults.

Method: 416 participants were selected from the Wisconsin Registry for Alzheimer's Prevention. They were native English speakers, aged ≥ 50+, and cognitively unimpaired at baseline, with no history of neurological or other psychiatric disorders aside from depression. Depression was assessed with the 20-item Center for Epidemiologic Studies Depression Scale (CES-D). A composite score, based on the premorbid IQ (WRAT-3 Reading subtest) and years of education was used to estimate CR. Another composite score from four cognitive tests was used to estimate EF.

A moderation analysis was performed to evaluate the effects of CR and Depression on EF at follow-up after controlling for age, gender, and APOE risk score. Moreover, a multinomial logistic regression was used to predict conversion to Mild Cognitive Impairment (MCI) from the healthy baseline.

Results: The negative relationship between depression and EF was stronger in individuals with higher CR levels, suggesting a possible floor effect at lower CR levels. In the multinomial regression, the interaction between CR and depression predicted conversion to MCI status, indicating that lower CR paired with more severe depression at baseline was associated with a higher risk of subsequent impairment.

Conclusions: This study sheds light on the intricate relationship between depression and EF over time, suggesting that the association may be influenced by varying levels of CR. Further studies may replicate these findings in clinical populations.

Introduction

Mild Cognitive Impairment (MCI) refers to the intermediate and/or transitional stage from healthy to pathological cognitive ageing in individuals characterized by greater cognitive decline than expected for their age (Petersen et al., 2014). Although some individuals with MCI remain stable, others can revert to normal cognition (Ganguli et al., 2020). Several longitudinal cohort population-based studies (prospective or retrospective) have reported an annual rate of conversion from MCI to dementia of 3%-23% in community samples and 9%-31% in clinical samples (Bruscoli & Lovestone, 2004; Faria et al., 2009; Larrieu et al., 2002; Michaud et al., 2017; Mitchell & Shiri-Feshki, 2009; Thaipisuttikul et al., 2022). Notably, tasks involving executive functions have proven to be crucial in predicting global cognitive decline in the healthy elderly (Clark et al., 2012) or the progression from MCI to dementia (Corbo & Casagrande, 2022; Junquera et al., 2020).

Executive function (EF) encompasses a set of high-level cognitive processes including working memory, inhibition, switching, and cognitive flexibility that are typically affected by cognitive ageing, even in the absence of diseases-related impairment (Fergunson et. al., 2022). Studies revealed that a decline in EF in older adults can lead to difficulties in flexibly and efficiently planning, achieving goals, or adapting to challenges like high-level cognitive tasks (e.g., working memory, switching or reasoning tasks; Cristofori et al., 2019; Doebel, 2020; Ferguson et. al., 2022). This decline is more pronounced among older adults with MCI and can significantly impact everyday functioning (Aretouli & Brandt, 2010; Corbo & Casagrande, 2022). Thus, studying executive deficits and, most importantly, identifying the protective and risk factors associated with EF may play a crucial role in the early detection of cognitive decline or MCI.

Cognitive reserve (CR; Stern, 2002, 2009) has become one of the most studied constructs in understanding the individual variability in ageing-related cognitive decline. According to Stern's hypothesis (2002, 2009), individual differences in cognitive performance can be linked to the efficient and flexible recruitment of brain networks (neural reserve) or alternate (compensation), mostly involving prefrontal cortex processes (Anthony & Lin, 2018; Cabeza et al., 2004; Franzmeier et al., 2017) and associated EF (Tucker & Stern, 2011). A common observation is that adults with high CR can cope better with age-related decline or more tolerate brain pathology before clinical symptoms of cognitive impairment are evident (Barulli & Stern, 2013; Steffener & Stern, 2012; Stern, 2012). This means, for instance, that individuals with a head injury of the same magnitude can experience varying degrees of cognitive impairment and recovery (Stern, 2009), thus further supporting the concept of CR as a potential protective factor for cognitive health. However, because individuals with high CR may be able to tolerate, cope with, and even mask the effects of neuropathology for longer periods, once the neuropathology reaches a critical level, they may experience a faster decline in cognitive functioning (Barulli & Stern, 2013; Stern, 2009).

As a theoretical construct, CR is typically measured through indirect proxies such as education, occupational attainment, and engagement in leisure activities (Boots et al., 2015; Bruno et al., 2014; Lee et al., 2020). Premorbid functioning or premorbid intelligence quotient (IQ) is also assessed as a measure of CR (Ebira et al., 2023; Nogueira et al., 2022) using based-reading tests such as the Wide Range Achievement Test (WRAT; Wilkinson, 1993) or the Test of Premorbid Functioning (ToPF; Joseph et al., 2021) (Arora et al., 2023; Berg et al., 2016; Brickman et al., 2011; Donders & Stout, 2019; Murphy et al., 2022; Tucker & Stern, 2011).

Numerous studies have extensively associated CR proxies with EF (Álvares-Pereira et al., 2022; Oosterman et al., 2021; MacPherson et al., 2017). For instance, in healthy older adults, greater CR (operationalized using premorbid functioning and years of education) has been associated with an increased ability to select the best strategy for performing a task, an effect not observed in a young group (Barulli et al., 2013). Oosterman and colleagues (2021) found that CR (estimated using educational attainment and premorbid functioning proxies) can influence the relationship between age and EF, even in a very old population. Another study examining 160 adults aged 20 to 65 revealed that most tests of EF were positively associated with CR (indexed by premorbid functioning, education, and type of occupation), even after controlling for age, thus suggesting a conceptual overlap between CR and EF (Roldán-Tapia et al., 2012).

Depression, on the other hand, is frequently accompanied by executive deficits such as cognitive control, set-shifting, inhibition, and working memory in older adults without MCI or dementia (Dotson et al., 2020; Dumas & Newhouse, 2015; Lockwood et al., 2002). These cognitive deficits may be caused by reductions in grey matter volume in the frontal-limbic networks (Sexton et al., 2013) or functional alteration between dorsal prefrontal networks and the amygdala (Leaver et al., 2018). Additionally, depression is linked to accelerated cognitive decline in MCI (Gonzales et al., 2017), increased risk of progression to MCI (Steenland et al., 2012) or dementia (Yang et al., 2021). Depression treatment as a modifiable factor may contribute to

preventing or delaying dementia (Dafsari & Jessen, 2020). However, it is a topic of debate whether depression should be considered a risk factor or a prodrome for later-life dementia (Bennett & Thomas, 2014).

A growing body of research suggests that depression and/or mental well-being may be exacerbated by lower levels of CR (Delgado-Gallén et al., 2021; Irigaray et al., 2022; Porricelli et al., 2024). A study involving 4509 participants found that individuals with higher levels of CR and brain reserve were less likely to experience late-life depressive symptoms (Zijlmans et al., 2023). Barnett and colleagues (2006) suggest that a low CR level, as specifically indexed by IQ, combined with depressive symptoms, can increase the risk of developing major depression. Moreover, the presence of different levels of CR across patients with depression can account for the significant heterogeneity in cognitive profiles observed (Ponsoni et al., 2020). While the co-occurrence of depression and lower levels of CR may have a negative impact on cognitive performance (Ponsoni et al., 2020), research suggests that older adults may experience cognitive decline at lower levels of CR, irrespective of depression (Lara et al., 2022). Conversely, individuals with higher CR may still exhibit decreased cognitive performance (Lara et al., 2022). Therefore, it is important to consider these divergent findings to gain a better understanding of how CR may impact the relationship between depression and cognition.

Taken together, previous studies indicate that high CR levels are linked to better EF and reduced risk of depression. However, it remains unclear whether CR moderates the association between depression and EF due to its mixed-moderating effects of CR in the association between cognition and mood (i.e., anxiety and depression; Opdebeeck et al., 2015ab, 2018). Finally, no study has explored the moderating role of CR in the association between depression and EF longitudinally.

To address these research questions, the current study explored the relationship between depression, CR, and EF in older adults at 10-year follow-up. Data were extracted from the

Wisconsin Registry for Alzheimer's Prevention (WRAP; Johnson et al., 2017), a longitudinal cohort of individuals with a parental family history of probable Alzheimer's disease (AD).

At baseline, all the participants received a consensus diagnosis of normal cognitive functioning (i.e., Cognitively Unimpaired Status-CUS; Johnson et al., 2017) and then reviewed cognitive status via consensus conference at follow-up, indicating still CUS, Cognitively Unimpaired-Declining (CUD) status or MCI.

The first aim of the current study was to investigate the role of CR in moderating the longitudinal association between depression and EF. The second aim was to determine whether the interaction between CR and depression would help to identify CUS individuals at the greatest risk of converting to CUD and MCI status about 10 years after the baseline. Specifically, we hypothesized that CR would moderate the association between depression and EF, potentially acting as a modifying factor against the deleterious effects of depression on EF. Moreover, we anticipated that the interaction between CR and depression would predict conversion from CUS to either CUD or MCI.

Method

Participants

The WRAP is a longitudinal study involving over 1600 adults aged 36-73 who are followed up with regular assessments. Participants for this study were selected based on having completed at least two visits and having received a consensus diagnosis of normal cognitive functioning (i.e., Cognitively Unimpaired Status-CUS; Johnson et al., 2017) at baseline and reviewed cognitive status via consensus conference at follow-up.

Because of the aims of this study, we excluded participants who were already classified as CUD or MCI status at baseline, or had dementia (220); we also excluded individuals with neurological conditions (e.g., brain injury or tumor, stroke, Parkinson's disease, epilepsy, multiple

sclerosis, etc.), severe psychiatric disorders (e.g., post-traumatic stress disorder, personality disorder, schizophrenia, or other psychosis, etc.) or comorbidities with depression (e.g., mood disorder and alcohol use disorder) (n = 274). Participants who were not native English speakers (n = 24) or aged ≤ 50 at the baseline (n = 438) were also excluded. Finally, we removed individuals who had not completed the cognitive assessment in executive tasks (n = 63). This left us with N = 416 participants (aged 50-68 years) who were CUS at baseline. Of these, 290 were still classified as CUS after 10 years, 97 converted to CUD (Jack et al., 2018), and 29 received a diagnosis of MCI (see "Procedure" for a detailed description of each cognitive status).

All activities for this study were approved by the Health Sciences Institutional Review Board of the Wisconsin School of Medicine and completed in accordance with the Declaration of Helsinki.

Time data analyses

As part of the study, participants were evaluated at two-time points, with the second evaluation taking place approximately ten years after the first one. The follow-up time selected ranged from 9 to 11 years (mean between baseline and follow-up = 9.65 years, SD = 0.27). We selected these two-time points in order to examine the long-term relationship among variables, ensure a sizeable sample alongside a lengthy follow-up, include an adequate number of MCI participants (=~30), and lately gather extensive data on the variables of interest.

Study visit procedure

As described in detail by Johnson and colleagues (2017), each WRAP participant completed an entry assessment (baseline) that included family, personal, and medical history (e.g., self-reported history of cardiovascular status), lifestyle (e.g., stress life events, sleeping, diet, etc.), current medications, neuropsychological testing, assessment of depression (i.e., the Center for

Epidemiologic Studies-Depression Scale [CES-D]; Radloff, 1977), APOE genotyping, laboratory tests (e.g., homocysteine, cholesterol, etc.), vitals measurements (resting heart rate, blood pressure, temperature), and informant questionnaires (e.g., Instrumental Activities of Daily Living Scale; Lawton & Brody, 1970). Each visit required about 5 hours. The first follow-up is approximately 4 years after baseline, then every 2 years.

Classification of cognitive status

The classification of cognitive status in our sample is determined using a two-tiered consensus conference approach (see for details Koscik et al., 2016). Briefly, data collected are first analyzed via an algorithm that selects cases for further review where impairment may exist if they meet one or more of the following criteria: i) performance more than 1.5 standard deviations below internal norms adjusted for age, gender, and literacy level, on: (a) recent assessment for factors scores or individual measures of memory, executive function, language, working memory, or attention (Clark et al., 2016; Koscik et al., 2016), or (b) any two assessments for factors scores in these cognitive domains (Koscik et al., 2014); cognitive performance on one or more tests fell below threshold-specific scores used in other studies as cut-points for clinical MCI diagnoses [(e.g., Wechsler Memory Scale–Revised Logical Memory-II, (Wechsler 1987): a story A score <9: AD Neuroimaging Initiative (Petersen, 2010)]; ii) self-report or informant report of cognitive or functional decline based on questionnaires such as the Informant Questionnaire on Cognitive Decline in the Elderly (Jorm & Jacomb, 1989) or Instrumental Activities of Daily Living Scale (Lawton & Brody, 1970).

Cases that are not flagged by the algorithm for consensus review are automatically categorized as CUS (Koscik et al., 2016). For cases that were flagged, a panel of multidisciplinary dementia experts (clinical neuropsychologists, physicians, and clinical nurse practitioners) (Johnson et al., 2017; Koscik et al., 2016) reviewed the participants' data based on cognitive tests

and additional information related to medical history, lifestyle, subjective cognitive complaints, and informant data collected at prior visits (Johnson et al., 2017; Koscik et al., 2016).

Cognitive classification for each recent visit that is determined by the consensus review process may result in CUS, CUD, MCI, or dementia classification for each study visit. For the purpose of the study, only participants categorized as CUS, CUD, or MCI at follow-up were examined as shown in prior WRAP studies (Talamonti et al., 2020; 2021).

The diagnosis of "MCI" (often the precursor to dementia) was based on the following clinical criteria (excluding biomarkers) from Albert and colleagues (2011) and National Institute on Aging–Alzheimer's Association criteria (Albert et al., 2011; McKhann et al., 2011; Jack et al., 2018) and required: (1) patient or informant concern regarding the change in cognition; (2) evidence of impairment in one or more cognitive domains; (3) intact ability to perform the activity of daily living; (4) not meeting criteria for dementia (Johnson et al., 2017; see also McKhann et al., 2011).

The CUD status, previously named "early MCI", represents a transitional cognitive decline that is likely to progress toward MCI (Langhough Koscik et al., 2021). The CUD status corresponds to clinical stage 2 in the 2018 diagnostic framework (Jack et al., 2018). Individuals with CUD show subtle cognitive impairment that does not meet the clinical thresholds of MCI and dementia impairment and may not yet report subjective or informant cognitive complaints or clinical deficits. Cognitive performance in CUD is typically lower-than-expected objective performance (e.g., >1.5 SD below internal robust norms) at most recent visit on cognitive tests based on published/standard normative data (for more details see: "Supplemental Table 2: Diagnostic Criteria for WRAP Consensus" in Langhough Koshik et al., 2021).

Executive function assessment

We calculated an EF composite score using the scores of the following tests: phonemic

(letter) and semantic (category; e.g., “animal”) fluency tasks total word performance for verbal fluency (e.g., words that begin with a given letter such as “C”, “F”, and “L”; Rosen, 1980), Letter-Number Sequencing test for attention and cognitive flexibility (Wechsler Adult Scale of Intelligence-WAIS III, Wechsler, 1997), Digit Span-forward and backward for short-term verbal and working memory (WAIS; Wechsler, 1997), and Trail Making Test for switching ability (TMT A and B; Reitan, 1958) (see Johnson et al., 2017 for the tests included in the WRAP protocol).

The reliability and consistency of cognitive testing are ensured through standardized manual of procedures, regular team meetings to review testing procedures, biannual observations of test administration, and blinded rescoring by a separate rater (20% annually for each psychometrist) (Johnson et al., 2018).

A detailed description of the creation of the composite score can be found in the “Statistical analyses” section. Generally, composite scores using the scores of executive tasks have been found to increase measurement precision and to help identify longitudinal cognitive change or predict conversion to dementia (Gibbons et al., 2012; Jonaitis et al., 2019).

Cognitive Reserve

CR was estimated using years of education and the premorbid functioning assessed through the WRAT (3rd edition; Wilkinson, 1993). In previous research, both measures were adopted as a composite score (Brickman et al., 2011) or individual proxies (O’Shea et al., 2015) to estimate CR in older adults. In this study, we created a composite score for CR (for a more comprehensive explanation of how the composite CR score was computed, please refer to the "Statistical analyses" section).

The WRAT (Wilkinson, 1993) consists of tasks or questions related to reading, spelling, and math skills, and the individual responds orally or in writing. It provides scaled scores, and percentile ranks for each subtest, which indicates an individual’s performance compared to a

normative sample. The WRAT has been shown to estimate abilities, such as reading aloud irregularly spelled words, typically achieved before the onset of brain impairment like brain injury (Johnstone et al., 1996; Joseph et al., 2021; Orme et al., 2004). As a result, the WRAT is often used as an index of premorbid functioning to estimate CR in the old population (Brickman et al., 2011; Murphy et al., 2022; Nogueira et al., 2022; Tucker & Stern, 2011). In a few studies, the WRAT has also been used to estimate the quality of education (Manly et al., 2002; Sayeghet al., 2014).

Depression assessment

Depression was assessed using the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977) scores taken from the baseline visit. The CES-D is a 20-item questionnaire that assesses the frequency of depressive symptoms (e.g., depressed mood, feelings of guilt,loss of interest or pleasure, sleep disturbances, appetite changes, and psychomotor symptoms). Participants are asked torate how often they experienced each symptom over the past week using a 3-point Likert scale, ranging from 0 (rarely or none) to 3 (most or all of the time). Each item can score from 0 to 6, which are summed to calculate a total score ranging from 0 to 60, with the higher scores indicating the presence of more severe symptomatology. A CES-D cut-off of ≤ 16 indicates the presence of not clinically relevant depressive symptoms, while a range of scores 17–23 indicates mild depression and a score of ≥ 24 indicates severe depression.

The CES-D is considered an adequate screening instrument to assess degrees of depressive symptoms and detect at-risk individuals in the old population, demonstrating good reliability and validity in assessing older adults from various ethnic backgrounds (Dozeman et al., 2011; Chen & Mui, 2013; O'Halloran et al., 2014; Irwin et al., 1999). In this particular sample, the CES-D showed a reliable internal consistency with Cronbach's alpha .89.

APOE status

Apolipoprotein E (APOE) is a protein that supports lipid transport injury repair in the brain (Yang et al., 2023; Liu et al., 2013). This gene may have three types of alleles: ε2, ε3, and ε4. It is well-established that the ε4 allelerepresents a genetic risk factor for AD (Yang et al., 2023).

The present study collected APOE genotype information through blood tests from the baseline visit. A risk score based on the APOE gene status was calculated, with a higher risk score indicating a higher genetic risk for AD. The e2/e3/e4 genotype odds ratio (OR) was utilised to calculate risk as a functionof APOE status. The determination of the APOE genotype has been described in detail by Darst and colleagues (2017).

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 26. A p-value threshold of 0.05 was set throughout all the analyses (Andrade, 2019). The Kolmogorov–Smirnov test was used to test the normality of the main variables. As depression, CR, and EF (composite scores) were not normally distributed, we ran a Spearman correlation to observe statistical relationships between these variables at baseline. However, QQ plots showed that the residuals were normally distributed, thus meeting the main requirement for linear regression. Furthermore, all predictors had a Variance Inflation Factor (VIF) score below 5 (Menard, 2001). Mahalanobis distance, residual statistics, and Cook's distance were used to identify outliers (Bobbitt, 2020; Cook, 1977). Cook's distance values exceeding 1 were excluded (Field, 2013; Pallant, 2016). Notably, 13 outliers (N=10 at baseline and N=3 at follow-up) were excluded based on analyses of Mahalanobis distance, residuals, and Cook’s distance measure. Baseline characteristics of the total sample were summarized as percentages for categorical variables (e.g., ethnicity, gender) and mean and standard deviations for continuous variables (i.e., age, CR, CES-D, EF). Moderation analyses were

run using the PROCESS Macro Version 3.4.1 (bootstrap samples=5000; Hayes, 2018) to probe whether CR moderated the relationship between Depression and EF. In this analysis, baseline demographic variables such as age and gender, as well as the APOE risk factor, were included as covariates. In addition, the predictors of CR, depression, and the interaction between CR and depression (CR*Depression) were also considered. The Johnson-Neyman technique (Johnson & Fay, 1950; Preacher et al., 2007) was used to identify "regions of significance," that is, points at which there were significant moderated relationships between depression and EF. Significant interactions between depression and CR were graphed with high, moderate, and low CR corresponding to ±1 SD from the mean, respectively. This technique offers a more complete picture than the simple-slopes analysis especially when the moderator is a continuous variable (Preacher et al., 2007). Before performing these analyses, two composite scores were created to assess CR and EF. For CR, an index score was computed by summing the baseline z-scores of the years of education and premorbid IQ using the WRAT test. For the outcome EF, follow-up raw scores of four executive tests [i.e., Digit span (forward and backward), Verbal Fluency (total letter/animal), Letter-Numbers sequencing, and TMT (A and B)] were initially standardized. Then, an index score of EF was computed by summing the z-scores of the executive tasks, allowing each cognitive task to receive equal weightage as indicated by Andrade (2021) and supported by previous research related to CR (Narbutas et al., 2021). For clarity, we ran the analyses with both averaged and added z-score data and obtained similar results. For tests where lower scores indicate better performance, test scores were multiplied by − 1 so that when the scores are added to other tests, the composite score could correctly indicate the direction of change (Andrade, 2021; Oosterman et al., 2021). To note, we used the baseline scores of EF to conduct correlation analyses, whereas we incorporated EF follow-up scores in the regression analyses. Finally, a multinomial regression analysis was run to explore which variables among CR proxies, depression, interaction CR*Depression, and APOE risk factor predicted the progression of CUS individuals towards CUD

and MCI status.

Results

Results report baseline statistics, assumptions check, longitudinal linear regression, and multinomial regression analysis.

Baseline analyses are reported in Table 1.

___Please insert Table 1 about here___

Prior to hypothesis testing, Spearman's correlation was used to examine the relationship between the main variables (i.e., depression, CR, and EF) at baseline. Overall, correlation analyses showed that CR (composite score) was significantly and negatively related to Depression (CES-D), $r_s(416) = -.10$, $p = .03$, and positively associated with EF, $r_s(416) = .33$, $p <. 001$. In contrast, Depression was found to be significantly and negatively related to EF, $r_s(416) = -.13$, $p = .008$.

A *Moderation analysis* was performed to investigate whether the relationship between Depression and EF depends on the CR levels. For this analysis, we employed the baseline scores of demographics (age and gender) and APOE risk factor as covariates. The other predictors were CR, depression, and the CR*Depression interaction. The follow-up scores of EF were used as the dependent variable.

The moderation regression results are shown in Table 2. Moderation model was found significant, $R^2 = .124$, $F(1,409) = 9.68$, $p <. 001$, resulting in an overall explanation of variance of 12.4%. Results showed that age ($B = -.10$, $p = .40$) and gender ($B = .03$, $p = .40$) and APOE risk factor ($B = -.10$, $p = .52$) were non-significant predictors of EF. After controlling for these

variables, both Depression (CES-D; B = -.44; p < .001) and CR (B = .45; p = < .001) were found to be significant predictors of EF. Additionally, results showed that the interaction was found to be significant, B = -.16, 95% CI [-.27, -.04], t = -2.57, p = .01, indicating that the relationship between Depression and EF was moderated by CR. In particular, at low levels of CR, the association between Depression and EF was negative but not significant, B = -.19, 95% CI [-.45, .08], t = -1.38, p = .17 (see also Fig. 1 and 2). At moderate CR levels, the relationship between Depression and EF was still negative and became significant, B = -.44, 95% CI [-.68, -.19], t = -3.54, p <. 001. When levels of CR were high, there was a significant and stronger negative relationship between Depression and EF, B = -.69, 95% CI [-.1.03, -.34], t = -3.88, p <. 001.

___Please insert Table 2 about here___

Inspection of Figure 1 revealed that the association between Depression and EF was stronger at higher levels of CR.

__Please insert Figure 1 about here__

Figure 2 presents the conditional effect of the focal predictor (depression) at three values of the moderator (CR). Results showed a significant negative relationship between Depression and EF, B = -0.25, 95% CI [-.49, .00], t = -1.97, p = 0.05 with a threshold for significance starting at -1.22 and ending at 5.24. As values of CR increase, the strength of the relationship goes from a small negative effect (B = -0.25) to a fairly strong negative one (B = -1.25). These results are not consistent with our research hypothesis.

___Please insert Figure 2 about here__

Multinomial logistic regression was performed to investigate the association of the baseline predictors (e.g., CR, depression, APOE risk factor) with each of the two different groups (versus the reference CUS group). Specifically, this analysis aimed to determine which predictor variables contributed to the conversion from CUS to CUD and MCI status.

The final model was statistically significant, $X^2(8, N = 416) = 81.84$, Nagelkerke $R^2 = .23$, $p < .001$. The analysis revealed that depression ($\beta = .75$, $p < .001$) and the interaction CR*Depression ($\beta = .16$, $p = .03$) were significant predictors of conversion from CUS to CUD (see Table 3). Overall, the odd ratio values indicated that for every unit increase in depression and the interaction CR*depression, the odds of a person classifying as CUD status changed by a factor of 2.12 and 1.18, respectively, confirming that higher depression (and lower CR) was associated with greater risk of conversion to CUD status. Moreover, the analysis revealed that, when converting from CUS to MCI, significant predictors were APOE risk score ($\beta = 1.02$, $p <. 001$), depression ($\beta = .82$, $p < .001$), CR ($\beta = -.64$, $p < .001$), and the interaction CR*Depression ($\beta = .17$, $p = .04$). The results indicated that the probability of developing MCI significantly increased with high APOE risk factor [odds ratio (OR) = 2.79, 95% confidence interval (CI) = 1.66, 4.64], low CR (OR = .53, 95% CI = .40, .69), and depression (OR = 2.27, 95% CI = 1.47, 3.49). Moreover, the odd ratio values for interaction CR*Depression were 1.19, 95% CI [1.03, 1.40], suggesting that CR and depression pull in opposite directions: the former is a protective factor against cognitive decline, while the latter mitigates its beneficial effects. A clear example of this lies in the CUS to MCI analysis: while an extra unit of the CR composite nearly halved the risk of MCI, and an extra unit of the depression composite more than doubled the risk by combining CR and depression, the risk was reduced to ORs of 1.19.

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Discussion

The first aim of the present study was to examine whether CR moderated the association between depression and EF in a longitudinal cohort study of older adults. The second aim was to explore whether the interaction between CR and Depression was a significant predictor of the conversion from CUS to CUD and MCI status, respectively at a 10-year follow-up. Results showed a stronger and negative relationship between depression and EF for high levels of CR. Moreover, we found that the interaction between CR and Depression predicted the conversion from CUS to MCI, with low CR paired with high levels of depression predicting a higher risk of MCI.

Analysis of the correlation coefficient values revealed that high levels of CR were linked to better EF performance (regardless of depression). This in part supports the Cognitive Reserve hypothesis (Stern, 2002, 2009), which outlines the crucial role of CR in brain efficiency and flexibility against age-related changes or pathology over time, thus potentially acting as a protective factor. In our study, such benefits can be reflected in the optimal performance in executive tasks (Bruno et al., 2014; Roldán-Tapia et al., 2012), particularly among older adults classified still as CUS who are linked to greater EF compared to CUD and MCI at follow-up. However, we cannot exclude that lower EF levels in individuals with low CR may reflect lower lifelong intellectual functioning, as opposed to CR providing a protective effect against declining EF.

Contrary to our expectation, we found that the negative association between Depression and EF was stronger for those with higher levels of CR. These results in part align with the O'Shea and colleagues' study (2015) that used the same depression questionnaire (CES-D) and CR proxies (education and/or WRAT scores). In this study involving a sample of 6565 healthy older participants, the authors reported a greater cognitive decline in those with higher CR but not in

those with lower CR. However, contrary to our results, their study showed that depression was associated with poorer cognitive performance. Findings closely and similarly related to our results came also from another longitudinal study (Geerlingset al., 2000) demonstrating that depressive symptoms were associated with an increased risk of cognitive decline but only in those who were highly educated. Taken together, we interpret these findings to suggest that individuals with lower CR levels, whose EF are also generally lower, may be encountering a floor effect whereby the detrimental effects of depression on EF are limited by the already lower EF score. However, because individuals with high levels of CR are thought to be able to compensate for and, therefore, sustain greater amounts of neuropathology, higher levels of CR are also hypothesized to be associated with a faster rate of cognitive decline once neuropathology reaches a level severe, enough to impact cognitive functioning (Barulli & Stern, 2013; Stern, 2009).

It is worth noting that a systematic review (Opdebeeck et al., 2015b) reported mixed moderating effects (e.g., studies with moderating effect or not moderating effect) suggesting that the association between mood and cognition may depend on the CR levels. However, in this systematic review, several factors may account for the discrepant findings. Most studies considered the differences between those with clinically diagnosed major depression and those with no depression. Other factors may involve differences in the operationalization of CR, outcome measures, or geographical differences in the study cohorts. For instance, four studies that reported a moderating effect of CR on the association between mood and cognition were conducted in Europe, while two studies in which there was no moderation effect were conducted in the USA.

Furthermore, the present study showed that the interaction between CR and depression significantly predicted the conversion from normal cognition to MCI, indicating that low CR paired with high depression was significantly associated with an increased risk of MCI. These results may indicate a strong association between CR and depression for those who may represent a vulnerable group with poor cognitive prognosis (Barnett et al., 2006). It is plausible to suppose

that a combined effect of more severe depression and poorer CR levels may have potentially led to greater EF deficits in individuals with MCI (Lara et al., 2022; Zijlmans et al., 2023). However, it is worth noting that the conversion from CUS to MCI accounted for multiple factors (e.g., APOE risk factor, high depression, low CR, etc.), indicating the complexity and multifactorial aetiopathogenic mechanisms underlying MCI. Consistent with previous research showing the association of APOE genotype with cognitive decline and MCI (Liu et al., 2013; Oveisgharan et al., 2018), this genetic risk factor was the most significant predictor of the conversion to MCI.

Some limitations in the present study should be considered. A potential limitation may arise from the conceptualization and measure of CR. Although the current study adopted the most common proxies used for measuring CR in older adults (O'Shea et al., 2015; Nogueira et al., 2022), it is possible that static CR proxies (education, IQ) compared to dynamic proxies (e.g., leisure activities, social support) may reflect a specific timeframe and thus not represent completely the multi-dimensional and dynamic construct of CR that changes over time (Malek-Ahmadi et al., 2017). Therefore, a more comprehensive analysis of CR which includes dynamic vs. static proxies is needed to fully understand the multidimensional construct of CR and its impact, as well as the variability in cognitive outcomes over time.

Another potential limitation may be related to the number of participants, which may have added noise within the multinomial conversion analysis from the healthy baseline to the various groups. Regarding CUD, the modest number of CUD participants (n=97) may have affected the generalization and applicability of our findings. Notably, this cognitive status, referred to as "transitional cognitive decline" (Jack et al., 2018) could have significant implications in discriminating between temporary cognitive impairments and major neurocognitive disorders. Therefore, future studies would need to investigate the role of CR and depression in a larger cohort of older individuals with CUD status. Furthermore, we did not classify MCI into different subtypes (e.g., amnestic MCI vs. non-amnestic MCI; Petersen et al., 2014), as shown previously in several

longitudinal studies (Michaud et al., 2017; Poulose et al., 2023). Consequently, MCI was treated as a single entity despite its well-documented heterogeneity. This omission raises the possibility that the impact of risk and protective factors could vary among different MCI subtypes.

The limited range of depressive symptoms in our study sample may represent a limitation. Based on the CES-20 cut-off score (≤ 16), the sample was largely not clinically depressed (the baseline mean for CES-D for the total sample is 7.43). However, 11% of individuals exhibited moderate depression (score range 17-27), and 6% of these exhibited severe depression (score range > 24). In the future, it would be beneficial to either include a larger sample size or target a specific population with higher rates of depression in order to capture a wider range of depressive symptoms. Moreover, Vilagut and colleagues (2016) suggest that a cut-off of 20 may be more appropriate than 16 for identifying people with depression in the normal population. As a result, CES-D may need adaptation for use with people with cognitive impairment.

Besides, research has revealed that depression is more prevalent in women than men (Albert, 2015). and the symptoms of depression may relatively vary among genders (Martin et al., 2013). For instance, in the CED-20, item 17 ("I had crying spells") has been found biased by gender (Cole et al., 2000). As our sample included 71% female participants, the generalizability of our findings could be in part limited. To overcome this potential limitation, however, gender was added as a covariate in the moderation analyses. Results showed that gender was not found to be a significant predictor of EF or the relationship between CR and depression, suggesting that there was no evidence of gender bias.

Another limitation stems from the WRAP cohort's characteristics. The WRAP sample is upper-middle-class and highly educated, thus further limiting the generalizability to the general population. It is important to note that the average level of education (Mean = 16.22; SD = 2.69) may suggest a sample that overrepresents individuals with higher CR and cognitive abilities.

Individuals with high education may benefit from experiences and possibilities (e.g., increased access to resources, health, and social status; Mirowsky & Ross, 2003) that can contribute to maintaining cognitive abilities (Lövdén et al., 2020). However, recent studies have found that individuals with higher levels of education may also experience increased levels of stress, particularly related to work and financial issues, and may not necessarily be immune from developing depression (Liu et al., 2024; Lunau et al., 2015; McCloud & Bann, 2019). Future research should consider various factors such as psychosocial factors, stressors, environmental influences, and comorbidities to better understand the relationship between CR using education as a proxy and cognitive abilities. Additionally, it should be noted that our sample is predominantly racially/ethnically homogeneous (90% white/Caucasian). The poor participation of different minority groups in the WRAP study can be attributed to several factors, including linguistic barriers, the need for a parental autopsy, or access to medical records to establish AD diagnosis limits. Therefore, further efforts will be necessary to increase the ethnic diversity of the WRAP sample for a deep understanding of the protective and risk factors in ageing and MCI/dementia.

Lastly, a further consideration is that we opted not to include EF at the baseline in our analyses to avoid overfitting the model, following the approach adopted by previous research investigating the relationship between CR, mood, and cognitive function (Opdebeeck et al., 2015ab, 2018). However, for comparison, we also ran post-hoc analyses controlling for baseline EF. The results continue to show that CR is still a significant predictor of follow-up EF (β = .21, p < .001), while Depression (β = -.20, p = .06), and the interaction are not significant (β = -.06, p = .20). These additional results suggest, as per our initial considerations, that CR is associated with future EF performance.

Conclusion

This study found that the association between depression and EF becomes stronger as CR

levels increase, suggesting that participants with higher CR appear to be more susceptible to depression. It can be argued that the association between late-life depression and core aspects of EF varies depending on one's level of CR. Additionally, this study contributes to providing evidence that the CR-Depression interaction can be involved in the early detection of MCI, highlighting the importance of tackling CR and depression to assess cognitive decline. Thus, this study may have relevant implications for the development of appropriate prevention and intervention strategies for the elderly.

Future longitudinal research would be fundamental to fully provide a more comprehensive understanding of the complex and multifaceted relationship between CR, depression, and EF in preserving normal cognition or detecting early cognitive decline.

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