Is there a combined effect of depression and cognitive reserve on cognitive function? Findings from a population-based study

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ABSTRACT

Objective: To analyse the combined effect of depression and cognitive reserve (CR) on cognition over a three-year follow-up period; and to explore this relationship specifically in individuals aged 65+ years. **Design**: Data from the 'Edad con Salud' project were analysed (*n* =1,144; 50+ years). **Main Outcome Measures**: The Composite International Diagnostic Interview was used to evaluate depression. CR was assessed with the Cognitive Reserve Questionnaire. Episodic memory was assessed with the word list memory and recall. Verbal fluency was measured through the animal naming task. Random coefficient regression analyses were performed. **Results**: Depression was associated with lower scores in episodic memory, whereas increased levels of CR were related with higher scores across all the cognitive tests. Among older-aged individuals, cognition decreased at lower levels of CR regardless of depression, while participants with depression exhibited decreased values in both measures of memory at higher levels of CR. **Conclusion**: Depression and CR were related with cognitive performance. Among older individuals, those with low levels of CR may constitute a vulnerable group with poor cognitive prognosis, whilst a harmful effect of depression on memory performance was observed among individuals with greater CR. Further evidence needs to be gathered to understand these associations.

Keywords: cognitive reserve, depression, cognition, population-based study

INTRODUCTION

Cognitive impairment and dementia constitute a significant global challenge due to its high prevalence, heterogeneous course, and major impact in several domains of functioning.

There are probably diverse synergistic and complex mechanisms that explain the observed variability across individuals in terms of vulnerability to cognitive decline and dementia. Extensive literature has pointed to depression as an important factor linked with a wide range of neurocognitive deficits (Wang & Blazer, 2015). Nevertheless, the nature of this association is not yet clear. The evidence has suggested that cognition may be affected as a result of a depressive disorder. Subjective memory complaints, slower cognitive processing and concentration, and executive difficulties are commonly noted among individuals who suffer from depression (Rock, Roiser, Riedel, & Blackwell, 2014), even after remission from depressive episodes (Semkovska et al., 2019). The impact of depression on cognitive impairment might also depend on the age of onset of the first depressive episode. Longitudinal cohort studies have reported an association between late-life depression and higher incidence of dementia development (Diniz, Butters, Albert, Dew, & Reynolds, 2013; Singh-Manoux et al., 2017), supporting the assertion that late-onset depression might represent a prodromal feature of dementia or that this association may be primarily due to some common underlying neuropathology (Alexopoulos, 2003). In this regard, brain-related abnormalities resulting in cognitive decline, such as hippocampal volume loss and frontostriatal atrophy, have been observed in depressed individuals (Butters et al., 2008; Sawyer, Corsentino, Sachs-Ericsson, & Steffens, 2012). Conversely, recent studies have suggested that having a lifetime history of depression would not be related to increased risk of cognitive deficits (Almeida,

Hankey, Yeap, Golledge, & Flicker, 2016; Olaya, Moneta, Miret, Ayuso-Mateos, & Haro, 2019).

Cognitive reserve (CR) refers to the adaptability of cognitive processes that explain individuals' differences of day-to-day function to brain aging or pathology (Stern et al., 2020). These processes are thought to be influenced by acquired, built, and maintained intellectual and non-intellectual experiences. Earlier studies have generally reported an association between higher levels of CR and better cognitive outcomes in healthy individuals as well as lower risk of developing dementia (Stern, 2012), suggesting a relevant target for prevention and treatment. The effects that depression exert on cognitive functions may be mitigated by CR. On the one hand, the relationship between depression and cognition may depend upon the levels of CR. The presence of varying levels of CR may explain the variation in cognitive function displayed by individuals with depression (Ponsoni, Damiani Branco, Cotrena, Milman Shansis, & Fonseca, 2020). The co-occurrence of depression and lower levels of CR could negatively affect cognitive performance, as these individuals may experience cognitive, social and sensory stimulation to a lesser extent and show reduced resources to face the demands of cognitive tasks, which in turn would lead to greater (risk of) cognitive impairment. By contrast, individuals showing higher levels of CR may buffer the impact of depression on cognition by being more capable of dealing with its detrimental effects. On the other hand, it is possible that depression compromises the protective effect of CR by uncovering cognitive impairment. Opdebeeck and her colleagues (2015) published a narrative systematic review on the role of CR in the association between mood and cognition. The authors concluded that CR moderated the above-mentioned relationship, with a stronger negative association between mood and cognitive performance in individuals with low levels of CR as compared to those with high levels of CR. This review, though valuable, included

studies that mainly used single proxies of CR, measures of depressive symptoms rather than clinically diagnosed depression, and have primarily focused on older-aged individuals. The most recent research has been also equivocal (Cancino, Rehbein Felmer, & Ortiz, 2018; Capogna et al., 2019; Hui et al., 2018; Kim, Kwak, Kim, Youm, & Chey, 2019; Lee et al., 2020; McLaren, Szymkowicz, Kirton, & Dotson, 2015; Opdebeeck et al., 2018; Ponsoni et al., 2020; Sanchez-Carro et al., 2021; Szepietowska, 2019; Venezia et al., 2018). McLaren et al. (2015) suggested that memory deficits related to depressive symptoms may be moderated by levels of education in a community-dwelling sample of 73 adults aged 18-81 years. Likewise, lower years of schooling was significantly associated with worse performance in neuropsychological testing in 74 patients with a diagnosis of major depressive disorder (Sanchez-Carro et al., 2021). On the contrary, data from a large population-based cohort of 6565 English individuals aged 65+ revealed that individual indicators of CR did not influence the negative association between mood and cognition (Opdebeeck et al., 2018). However, CR, when defined by these latter authors as a composite score based on multiple components, did have an effect on this relationship. Finally, no study has explored the combined effect of CR and depression on cognitive function longitudinally to date.

A broader understanding of the joint association between depression and CR with cognition would provide insight for prevention and the design of specifically tailored interventions that may eventually contribute to delay or reduce cognitive decline. Therefore, the aims of the current study are: i) To analyse the combined effect of depression and CR on diverse measures of cognition over a three-year follow-up period in a sample of middle and older-aged Spanish adults; and ii) To explore the aforementioned relationship in a subsample of individuals aged 65+ years, as the risk of cognitive decline is increasingly apparent at older ages.

MATERIALS AND METHODS

Study design

Data from the Edad con Salud project (www.edadconsalud.com) were analysed. This is a longitudinal, prospective study of a nationally representative sample of the non-institutionalised adult population (aged ≥18 years) conducted in Spain, for which information on a maximum of three waves are available. The baseline survey (wave 1) was collected as part of the Collaborative Research on Ageing in Europe (COURAGE in Europe) study (www.courageineurope.eu) and was conducted between July 2011 and May 2012. The first (wave 2) and second (wave 3) follow-up examinations were carried out between December 2014 and November 2018 at intervals of approximately three years.

Detailed sampling information can be found at Garin et al. (2014). Briefly, a multistage, stratified, clustered area probability design was followed to select potential participants. The Spanish Statistical Office provided data on households. Individuals were administered a computer-assisted personal interviewing programme (CAPI) and a standardized health examination. A shorter version of the questionnaire was administered to a proxy respondent in cases where participants had severe physical or cognitive [MMSE score <16 (Lobo, Ezquerra, Gómez Burgada, Sala, & Seva Diaz, 1979) or family report of dementia diagnosis] limitations that precluded participation in the survey.

A total of 4,753 individuals were initially interviewed at baseline (response rate=69.9%). For the current study, analyses were limited to data collected from waves 2 and 3, as the CR questionnaire was only available in these surveys. The second wave comprised 2,101 individuals aged 50+ years. Of these, 611 (29.1%) were lost to follow-up and 180 (8.6%) were confirmed to have passed away. Moreover, 166 (7.9%)

participants were excluded for insufficient or lacking information on cognitive function, CR or depression. The final analytical sample consisted of 1,144 respondents, of which 571 individuals were 65+ years (**Figure 1**).

[Figure 1 near here]

Ethics statement

The study protocol was reviewed and approved by the Ethics Review Committees of Parc Sanitari Sant Joan de Déu, Barcelona, and Hospital Universitario La Princesa, Madrid. Informed consent was obtained from all respondents in both waves.

Measures

Cognitive function

Three performance tests from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery were used (Morris, Heyman, & Mohs, 1989). These tests consist of a word list memory (immediate recall), a word list recall (delayed recall), and a verbal fluency task. Word list memory and word list recall measured learning ability and episodic memory. Participants were asked to recall 10 unrelated common nouns given in the word lists. Scores were the number of words correctly recalled across three learning trials (range 0-30) and after presentation of a distracting task (range 0-10). Higher values indicate better performance. Verbal fluency tasks involve several cognitive processes, including verbal production, semantic and working memory, and processing speed. Respondents were encouraged to name, within a minute, as many different animals as they could. Proper names (e.g. Flipper) and repetitions were not considered. Scores were the total number of valid responses. Higher values represent greater performance.

Depression

The presence of a major depressive episode was assessed in both waves with an adapted version of the Composite International Diagnostic Interview (CIDI 3.0) (Haro et al., 2006). This structured interview includes a set of questions which allows the establishment of a 12-month major depressive episode diagnosis according to DSM-5 (American Psychiatric Association, 2013). Data on a recent past major depressive episode was also considered from the baseline survey (wave 1).

Cognitive reserve

The Cognitive Reserve Questionnaire (Rami et al., 2011) was used to measure CR at waves 2 and 3. It consists of eight items about the participant's level of education, parents' level of education, training courses, highest level of occupation, musical training, languages, reading activities, and intellectual games. The exact questions and scores for each item are provided elsewhere (Lara et al., 2017). Responses were added up to produce a CR score ranging from 0 to 25, with higher values corresponding to better CR.

Covariates

Covariates were selected on the basis of previous literature (World Health Organization, 2019). Demographic variables included sex and age (in years). The physical activity levels were measured with the Global Physical Activity Questionnaire version 2 (GPAQ v2) (Bull, Maslin, & Armstrong, 2009) and categorized as low, moderate, or high according to the GPAQ guidelines (World Health Organization, 2012). Several chronic conditions were assessed through self-reported physician's diagnosis, symptom-based algorithms, and/or objective measurements to detect undiagnosed cases. Data on diabetes was exclusively based on self-reported diagnosis. Hypertension was endorsed on the basis of self-reported diagnosis and/or blood pressure measurements. Respondents with

systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg were considered to have hypertension (World Health Organization, 2013). A diagnosis of a stroke was established by self-reported diagnosis and/or self-reported symptoms (i.e. affirmative answers to 'Have you ever suffered from sudden onset of paralysis or weakness in your arms or legs on one side of your body for more than 24 hours?' and 'Have you ever had, for more than 24 hours, sudden onset of loss of feeling on one side of your body, without anything having happened to you immediately before?').

Statistical analyses

Frequencies, proportions, means, and standard deviations (SD) were calculated to describe the sociodemographic and clinical characteristics of the study sample at wave 2 in the overall sample and in individuals aged 65+ years. In order to explore differences grouped by depression, significance tests were carried out using unpaired Student *t*-tests and χ^2 tests for continuous and categorical variables, respectively.

Random coefficient regression analyses were conducted to evaluate the association between depression and CR (exposures) with the repeated measures of immediate and delayed recall, and verbal fluency (outcomes) in the overall sample and in individuals aged 65+ years. This method, based on generalized linear models, assumes that the variation in intercept and slopes are normally distributed with an average of zero and a certain variance (Twisk, 2013). In these models, the regression coefficients are allowed to vary between individuals as data are clustered within the subject. The regression analyses were adjusted for age, sex, physical activity, diabetes, hypertension, and stroke, all measured at wave 2, and recent past depression. These covariates were introduced as categorical variables with the exception of age. Time was also introduced as a categorical variable (0 as wave 2 and 1 as wave 3), without assuming a specific shape with the individual cognitive scores. In addition, we independently explored the

interactions depression*time, CR*time, and depression*CR in these adjusted models. Marginal effects were computed for significant interactions terms ($p<0.05$) to illustrate variations in the predicted estimates for specific cognitive outcomes while keeping all other covariates at their means.

Results from all random coefficient regression models are showed as unstandardized regression coefficients (*B*) with their corresponding 95% confidence intervals (*CIs*). The level of statistical significance was set at $p<0.05$. The statistical analyses were done with Stata 15 (StataCorp, 2017).

RESULTS

A total of 1,144 individuals were included in the current analyses. Ninety-five respondents met criteria for a 12-month episode of depression either at wave 2 or wave 3, of which 19 had depression in both waves. Of these, 45 were individuals aged 65+. **Table 1** shows the sociodemographic and clinical characteristics of the study sample at wave 2. Mean age was 66.1 (*SD*=9.8), and there was a slightly higher proportion of women than men (53.8% vs. 46.2%). Mean score for CR was 8.5 (*SD*=4.9) and almost 40% of the participants engaged in a high level of physical activity. The prevalence of depression, diabetes, and stroke was 4.5%, 18.8%, and 6.1%, respectively, while a considerable proportion of respondents showed hypertension (44.8%). Individuals with depression were more likely to be women, practicing less exercise, and showed recent past depression. Compared to non-depressed respondents, those with depression did not score significantly different in any of the cognitive tests nor showed lower CR values. Older participants with depression were more likely to be women, engaged in a low level of physical activity, had an episode of recent past depression and scored lower on CR and verbal fluency (**Supplementary table 1**).

[Table 1 near here]

Results from the random coefficient regression models exploring the association between depression, CR and cognition over the entire sample are illustrated in **Table 2**. Depression was significantly related to lower performance in the immediate recall test in fully covariate-adjusted models (*B*=-0.78; 95% *CI*=-1.55, -0.01) while recent past depression was significantly related with worse verbal fluency (*B*=-1.18; 95% *CI*=-1.69, -0.54). Higher levels of CR were associated with increased values in all the individual cognitive scores (*B*=0.39; 95% *CI*=0.35, 0.43 for immediate recall; *B*=0.14; 95% *CI*=0.12, 0.16 for delayed recall; *B*=0.55; 95% *CI*=0.49, 0.61 for verbal fluency) after full adjustment for the covariates. Scores from the immediate and delayed recall tests declined by 0.72 and 0.30 points respectively from wave 2 to wave 3, while verbal fluency increased by 0.70 points. Women scored significantly better in memory tests and worse in the verbal fluency task as compared with men. Older age, lower levels of physical activity, diabetes, and stroke were significantly related with lower performance in at least two out of three cognitive tests, while recent past depression was associated with the verbal fluency task. The depression*time and CR*time interactions did not reach statistical significance for any of the cognitive measures, indicating that respondents with depression or lower levels of CR did not present a faster rate of cognitive decline as compared to those non-depressed or with higher CR, respectively. The interaction between depression*CR was not significantly associated with any of these models either. Therefore, fully adjusted regressions for the overall sample were constructed without these interaction terms.

[Table 2 near here]

Table 3 presents the results of the random coefficient regressions assessing the above-mentioned association among individuals aged 65+ years. In this subsample, the depression*CR interaction reached statistical significance for both immediate and

delayed recall (*p*<0.05) and was then included in these models. **Figure 2** depicts the adjusted predictions for these cognitive outcomes in depressed vs. non-depressed respondents at different levels of CR. As compared to non-depressed individuals, participants with depression exhibited significantly decreased values in both measures of memory at higher levels of CR.

[Table 3 near here]

[Figure 2 near here]

DISCUSSION

To the best of our knowledge, this is the first longitudinal study examining the interactive effect of CR and depression on cognitive performance. Overall, results from the present study suggest that both depression and CR are significant and independently associated with cognitive function. Individuals with depression showed lower scores in tasks of episodic memory, whereas increased levels of CR were associated with higher scores across all the cognitive tests at three-year follow-up. However, none of these variables were related to a faster rate of decline from one wave to the other.

The impact of depression on cognition has been frequently explored, with previous studies reporting poor performance across several measures of cognition among these individuals (Fiske, Wetherell, & Gatz, 2009; Wang & Blazer, 2015). The results of a non-significant association between depression and verbal fluency are somehow surprising given that this task have showed high predictive value to identify individuals at greater risk of developing dementia and detect cognitive impairment in older adults (Henry & Crawford, 2005; Weissberger et al., 2017). Interestingly, a recent past major depressive episode was related with lower performance in the verbal fluency task. The

chronicity of the disorder may have influenced these findings. Future research into this matter is required.

Evidence supports earlier findings that CR has a direct effect on cognition and confirms the benefits this variable has on cognitive performance (Stern, 2012). Individuals with higher levels of CR would perform functionally and clinically better when facing cognitive tasks as compared to those presenting lower levels of CR, which translates into more flexible and effective neural connections, a reduction in the risk of cognitive decline and delays in the symptomatic manifestations of dementia (Cabeza et al., 2018). The fact that neither depression nor CR were associated with a faster rate of cognitive decline would suggest that both depression and CR may aid to describe diversity in test scores at any given time, but do not contribute to individual change over time. It should be noted, however, that longitudinal studies of shorter duration could fail in finding such associations. Indeed, we observed little cognitive change between assessments.

We also found that scores for CR were not significantly lower for individuals with depression as compared to those without depression. However, these scores significantly differed between depressed and non-depressed older adults. According to Barnett et al. (2006) CR would impact on depression by affecting the risk for developing the disorder, in the expression of depressive symptoms, and in patients' functional outcome. Previous research has suggested that individuals with depression appear to show significantly lower CR compared to healthy subjects, yet in other studies there was an opposite relationship or no association (Cancino et al., 2018; Coloma Andrews & Zihl, 2014; Geerlings et al., 2000; Hui et al., 2018; Lee et al., 2020; O'Shea et al., 2015; Opdebeeck, Nelis, Quinn, & Clare, 2015; Szepietowska, 2019; Venezia et al., 2018).

Analyses among individuals aged 65+ years revealed that there was an interactive effect between depression and CR with cognition. More precisely, whilst individuals with low levels of CR would constitute a vulnerable group with poor cognitive prognosis despite the presence of depressive caseness, a harmful effect of depression on memory performance has been observed among individuals with greater CR. Depression may exacerbate pre-existing cognitive decline by reducing the protective effect of CR and further affecting the threshold for manifesting cognitive decline or dementia (Jorm, 2001). Our study findings suggest that this combined effect may be particularly important for older adults, who are often affected by multiple morbidities and are generally at high risk of cognitive and functional decline. Interestingly, a steeper slope of decline was observed among individuals at higher levels of CR and depression in delayed recall. These results are in line with those of O'Shea et al. (2015) who reported, within a community-based sample of 3,484 participants aged 65 years and older, that individuals with higher education and reading abilities showed greater decrements in cognitive performance as depressive symptoms increased in comparison with respondents with low levels of education or reading scores. Similarly, Geerlings and her colleagues (2000) found, using data from two independent older community-based samples from The Netherlands, that depression increased the risk of cognitive decline and dementia only among individuals with higher levels of education. Based on their findings, these authors argued that depression may be indicative of an early manifestation or subclinical expression of the neuropathological process of dementia only in individuals with higher levels of education. In contrast, several studies have suggested that, in individuals with depressive symptoms, lower levels of education or intellectual ability are associated with greater susceptibility to cognitive impairment (Hui et al., 2018; McLaren et al., 2015; Opdebeeck et al., 2018; Venezia et al., 2018). Researchers from these studies claimed that

people with high level of CR may use more effective strategies to deal with task demands than those having lower levels of CR, which in turn may make them more resistant for coping with the negative effect of depression on cognitive decline. Another explanation has been related to the fact that CR is associated with better health outcomes and quality of life (Lara et al., 2017), as individuals with high CR may engage in healthier lifestyle behaviours and would be more conscious about the significance of preventive care. At another level, Jia et al. (2020), using data from 2102 English older adults, explored the effects of CR and a modifiable-risk-factor profile, based on five health and/or lifestyle factors including depression, on the incidence of dementia. The authors showed that among individuals with low CR, a favorable modifiable-risk profile (i.e. ≥ 4 healthy lifestyle factors) was related to a risk of dementia lower than that in individuals with an unfavorable one. However, these protective associations were not found among those with high CR.

These findings might have some implications for social and healthcare providers, decision-makers, and other stakeholders. Following the World Health Organization (2019) statements, the fact that there exist modifiable risk or protective factors amenable to interventions indicates that prevention of cognitive decline and dementia is feasible. On the one hand, some pharmacological interventions among individuals with depression (i.e. vortioxetine) have showed optimal therapeutic efficacy for decreasing the risk of cognitive impairment (Rosenblat, Kakar, & McIntyre, 2015), while evidence on the usefulness of nonpharmacological interventions is yet limited. However, it remains to be determined the path of causality of depression with cognitive function. On the other hand, cumulative evidence has shown that CR might have the potential to prevent or delay cognitive decline and dementia cases by the improvement and maintenance of engagement in cognitive and social activities that can be modified or trained over the life

course, especially among those with lower levels of CR (Soldan, Pettigrew, & Albert, 2020). While the aspects of life experience that supply CR are thought to garner across the lifespan, the promotion of activities occurring at late-life deserve continuing attention. We should pay special attention to people with depression and high CR, as these individuals may present a worse cognitive course than expected.

Strengths and limitations

There are a number of strengths to this study. Data from *Edad con Salud* study derived from a large-scale sample of the Spanish adult population. As opposed to most of the previous work, the present investigation included participants with a broader age range that enable the exploration of the potential prodromal phase of neurocognitive disorders. Furthermore, cognition was based on assessment of diverse aspects, allowing the investigation of different cognitive profiles. In this regard, previous studies have reported the predictive value of verbal recall and verbal fluency tests to detect cognitive impairment in older adults and identify individuals at high risk of developing dementia (Weissberger et al., 2017). In addition, whereas evidence on similar topics has used measures of depressive symptoms, our depression variable was created on the basis of a diagnosis of depression according to DSM-5 criteria (American Psychiatric Association, 2013). Likewise, other studies have assessed CR as a single factor, which might be a less sensitive measure compared to our composite CR questionnaire.

There are still some methodological issues related to our research. First, even if we were able to model the effect of both CR and depression on cognition at different time points, this study is limited by a short follow-up period. Further studies based on longer longitudinal measurements are preferred to better elucidate the pathway among depression and cognition, and the moderating influence of CR on this association. Second, data on CR and depression was retrospectively collected by self-report, which

may result in reporting or recall bias. Moreover, depression was ascertained via a structured interview completed by trained lay interviewers rather than psychiatric evaluations made by clinicians, which would have improved diagnostic validity. However, the CIDI 3.0 has shown generally good diagnostic concordance with clinicians' assessments (Haro et al., 2006). Third, we acknowledge that our assessment of CR comprises a limited number of proxy variables that may not fully capture all of the variance related with CR. This may have ultimately rendered to biased estimates for the association between CR and cognition. Even if the conceptualization of CR is far from a consensus (Kartschmit, Mikolajczyk, Schubert, & Lacruz, 2019), thus limiting comparability between studies, future research should preferably include a broader multidimensional lifespan approach. All in all, lifetime exposures are assumed to represent experiences that uniquely contribute to the development of CR rather than reflect it (Stern et al., 2020). Another issue is related to the relatively low level of CR in our sample, so that our findings may not be generalizable to populations with higher levels of CR. Similarly, because of the relatively small number of people with depression as compared to the large group of those who do not present depression, the power to evaluate the impact of depression on CR and cognition may have been reduced. Fourth, as this survey did not intend to generate clinical diagnoses for dementia, some individuals presenting some forms of cognitive impairment or even mild dementia may have been included in our analytical sample. However, we made use of family-reported dementia diagnosis, and interviewers were trained to identify participants with limited cognitive function. Fifth, we used a set of limited cognitive tests mainly assessing episodic and semantic memory, while other core aspects of cognition (e.g. attention, executive function) were not included in the present study. Fifth, regardless of the evidence that have associated antidepressive treatments with a significant positive effect on cognitive

function (Rosenblat et al., 2015), we were not able to control for the effect of antidepressants due to lack of data. Sixth, given that we used data from waves 2 and 3, our findings have been probably skewed to healthier participants, and this may have led to an underestimation of the true association between depression, CR, and cognition. Finally, this is a longitudinal observational study for which causality cannot be inferred. Reverse causal direction cannot be excluded either. As mentioned earlier, depression may affect cognition either as a result of a depressive disorder or as a prodromal sign of dementia (Rock et al., 2014; Singh-Manoux et al., 2017).

Conclusion

Depression and low CR were related with poor cognitive performance over a three-year follow-up period in middle- and older-aged older adults. Moreover, there seems to be an interactive effect of both variables on cognitive function among those aged 65+ years, so that cognitive performance decreased at lower levels of CR regardless of the presence of depression, whereas depression would mitigate the protective effect of higher CR levels on cognition. Further evidence needs to be gathered to more accurately understand the joint effect of depression and CR on cognitive function.

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Disclosure of interest

JMH is consultant of Elli Lilly and Co, Roche, and Lundbeck. None of these activities are related to the current project. For the remaining authors, none was declared.

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Data Availability Statement

Data not available due to legal restrictions.

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Table 1. Sociodemographic and clinical characteristics of the study sample.

Characteristic		**Overall** (*n*=1,144)	**Non-depressed** (*n*=1,092)	**Depressed** (*n*=52)	*p-value**
Age in years (mean, *SD*)		66.1 (9.8)	66.2 (9.9)	63.8 (9.1)	0.08
Sex					<0.01
	Male	528 (46.2)	520 (47.6)	8 (15.4)	
	Female	616 (53.8)	572 (52.4)	44 (84.6)	
Cognitive reserve (mean, *SD*)		8.5 (4.9)	8.5 (4.9)	7.2 (5.2)	0.05
Physical activity levels					<0.01
	High	451 (39.4)	431 (39.5)	20 (38.5)	
	Moderate	393 (34.4)	385 (35.2)	8 (15.4)	
	Low	300 (26.2)	276 (25.3)	24 (46.1)	
Comorbidities					
	Diabetes	215 (18.8)	205 (18.8)	10 (19.2)	0.93
	Hypertension	497 (43.4)	475 (43.5)	22 (44.0)	0.91
	Recent past depression[a]	124 (10.9)	100 (9.2)	24 (46.2)	<0.01
	Stroke	70 (6.1)	69 (6.3)	1 (1.9)	0.20
Cognitive scores (mean, *SD*)					
	Immediate recall	15.7 (5.2)	15.7 (5.1)	15.1 (5.1)	0.41
	Delayed recall	4.6 (2.2)	4.6 (2.2)	4.6 (2.5)	0.96
	Verbal fluency	17.6 (6.9)	17.7 (17.3, 18.1)	15.8 (13.9, 17.7)	0.05

Notes. Data are based on the first follow-up examination (wave 2). Values are frequencies and percentages for each category unless otherwise indicated. *SD*=Standard Deviation.

[a] Presence of a 12-month major depressive episode at baseline (wave 1).

*Differences among mean estimates were tested by unpaired Student *t*-tests and χ^2 tests for continuous and categorical variables, respectively.

Table 2. Adjusted random coefficient regression models for verbal memory and verbal fluency tests. Individuals aged 50+ years.

	Immediate recall	**Delayed recall**	**Verbal fluency**
Variables	Coefficient (95% *CI*)	Coefficient (95% *CI*)	Coefficient (95% *CI*)
Depression (ref. no)	**-0.78 (-1.55, -0.01)**	-0.34 (-0.70, 0.02)	-0.57 (-1.69, 0.55)
Cognitive reserve	**0.39 (0.35, 0.43)**	**0.14 (0.12, 0.16)**	**0.55 (0.49, 0.61)**
Time (ref. first follow-up)	**-0.72 (-0.98, -0.46)**	**-0.30 (-0.43, -0.18)**	**0.70 (0.32, 1.09)**
Age (in years)	**-0.18 (-0.21, -0.16)**	**-0.09 (-0.10, -0.08)**	**-0.17 (-0.20, -0.14)**
Women (ref. men)	**1.03 (0.63, 1.43)**	**0.67 (0.48, 0.85)**	**-0.64 (-1.20, -0.07)**
Physical activity (ref. high)			
Moderate	**-0.47 (-0.93, -0.01)**	**-0.23 (-0.45, -0.02)**	-0.45 (-1.10, 0.21)
Low	-0.42 (-0.92, 0.09)	-0.12 (-0.35, 0.11)	**-1.21 (-1.93, -0.49)**
Diabetes (ref. no)	**-0.60 (-1.12, -0.09)**	-0.13 (-0.36, 0.11)	**-1.37 (-2.11, -0.64)**
Hypertension (ref. no)	-0.23 (-0.63, 0.16)	-0.03 (-0.21, 0.15)	-0.07 (-0.64, 0.50)
Recent past depression (ref. no)	-0.33 (-0.98, 0.31)	-0.27 (-0.57, 0.03)	**-1.18 (-1.69, -0.54)**
Stroke (ref. no)	**-0.96 (-1.78, -0.14)**	**-0.47 (-0.85, -0.10)**	-1.15 (-2.31, 0.02)

Notes. Models are mutually adjusted for all variables in the respective columns. Age and cognitive reserve were introduced as continuous variables. In bold, statistically significant values. *CI*=Confidence Interval.

Table 3. Adjusted random coefficient regression models for verbal memory and verbal fluency tests. Individuals aged 65+ years.

	Immediate recall	**Delayed recall**	**Verbal fluency**
Variables	Coefficient (95% *CI*)	Coefficient (95% *CI*)	Coefficient (95% *CI*)
Depression (ref. no)	0.29 (-1.33, 1.92)	0.06 (-0.75, 0.87)	-1.04 (-2.54, 0.46)
Cognitive reserve	**0.39 (0.33, 0.45)**	**0.13 (0.10, 0.16)**	**0.50 (0.42, 0.58)**
Depression*cognitive reserve	**-0.28 (-0.55, -0.01)**	**-0.15 (-0.29, -0.01)**	**-**
Time (ref. first follow-up)	**-1.11 (-1.45, -0.77)**	**-0.47 (-0.65, -0.29)**	0.16 (-0.35, 0.67)
Age (in years)	**-0.20 (-0.24, -0.16)**	**-0.10 (-0.12, -0.08)**	**-0.17 (-0.23, -0.12)**
Women (ref. men)	**0.87 (0.32, 1.41)**	**0.69 (0.44, 0.95)**	**-0.80 (-1.55, -0.05)**
Physical activity (ref. high)			
Moderate	-0.57 (-1.19, 0.06)	**-0.31 (-0.61, -0.02)**	**-1.29 (-2.15, -0.43)**
Low	-0.10 (-0.79, 0.58)	-0.06 (-0.39, 0.26)	**-1.39 (-2.33, -0.45)**
Diabetes (ref. no)	**-0.84 (-1.45, -0.23)**	-0.21 (-0.50, 0.07)	**-1.03 (-1.87, -0.19)**
Recent past depression (ref. no)	-0.46 (-1.36, 0.44)	-0.20 (-0.63, 0.22)	-1.09 (-2.33, 0.15)
Hypertension (ref. no)	-0.08 (-0.60, 0.44)	0.03 (-0.21, 0.28)	0.14 (-0.58, 0.86)
Stroke (ref. no)	**-0.99 (-1.93, -0.05)**	-0.28 (-0.72, 0.16)	**-1.46 (-2.75, -0.17)**

Notes. Models are mutually adjusted for all variables in the respective columns. Age and cognitive reserve were introduced as continuous variables. The depression*cognitive reserve interaction did not reach statistical significance for verbal fluency and this model was then constructed without this interaction term. In bold, statistically significant values. *CI*=Confidence Interval.

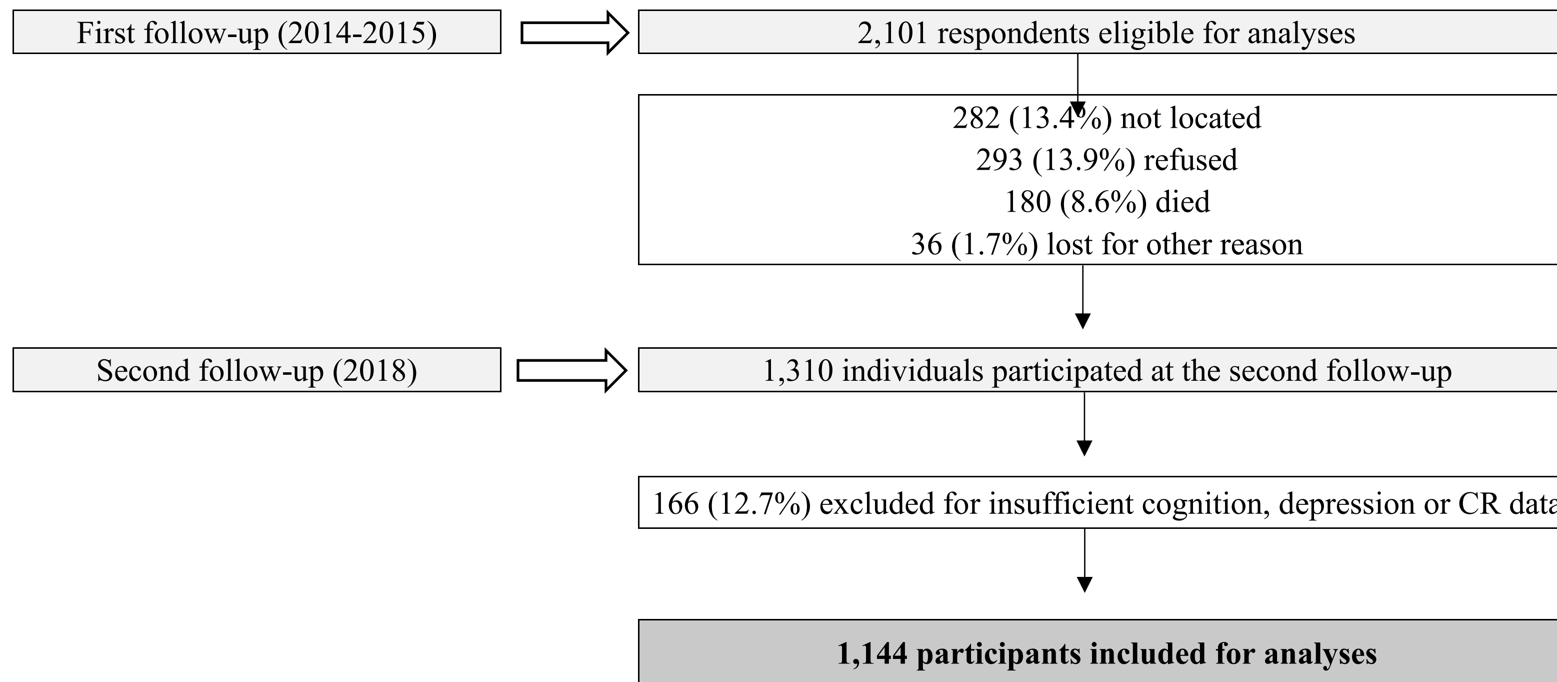

Figure 1. Flowchart of the study sample.
Note. Individuals were eligible for analysis if they were ≥ 50 years old at the first follow-up examination (wave 2).

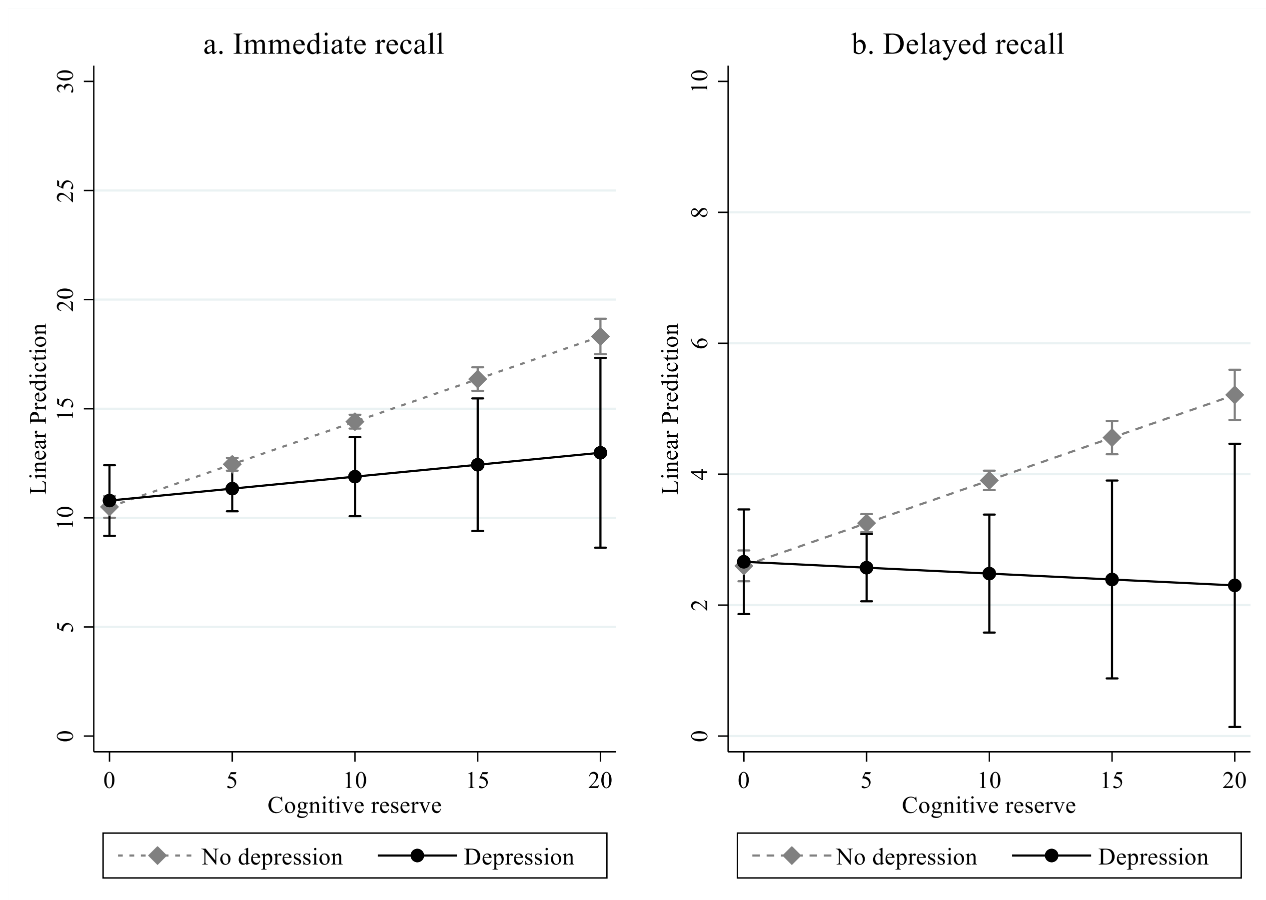

Figure 2. Predictive estimates and 95% *CI* for verbal memory tests by the presence of depression and different levels of cognitive reserve. *Notes*. Individuals aged 65+ years. Margins were computed from the fully-adjusted random coefficient regression models when fixing covariates at their means. *CI*= Confidence Interval.

SUPPLEMENTARY MATERIAL

Supplementary table 1. Sociodemographic and clinical characteristics of individuals aged 65+ years.

Characteristic		**Non-depressed** (*n*=546)	**Depressed** (*n*=25)	*p- value**
Age in years (mean, *SD*)		74.5 (6.7)	72.0 (5.4)	0.07
Sex				<0.01
	Male	260 (47.6)	0 (0)	
	Female	286 (52.4)	25 (0)	
Cognitive reserve (mean, *SD*)		7.2 (4.6)	4.5 (4.0)	<0.01
Physical activity levels				<0.01
	High	187 (34.3)	10 (40.0)	
	Moderate	202 (37.0)	2 (8.0)	
	Low	157 (28.7)	13 (52.0)	
Comorbidities				
	Diabetes	138 (25.3)	8 (32.0)	0.45
	Hypertension	275 (52.1)	14 (58.3)	0.55
	Recent past depression [a]	46 (8.4)	12 (48.0)	<0.01
	Stroke	46 (8.4)	1 (4.0)	0.41
Cognitive scores (mean, SD)				
	Immediate recall	13.4 (4.6)	13.2 (3.3)	0.49
	Delayed recall	3.7 (2.1)	3.5 (1.6)	0.58
	Verbal fluency	15.7 (6.2)	13.1 (5.8)	0.04

Notes. Data are based on the first follow-up examination (wave 2). Values are frequencies and percentages for each category unless otherwise indicated. *SD*=Standard Deviation.

[a] Presence of a 12-month major depressive episode at baseline (wave 1).

*Differences among mean estimates were tested by unpaired Student *t*-tests and χ^2 tests for continuous and categorical variables, respectively.