The interaction of cognitive and brain reserve with frailty in the association with mortality: an observational cohort study

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Summary

Background A higher cognitive reserve and brain reserve could decrease mortality risk, but the interaction of these factors with general age-related loss of physical fitness (eg, frailty) remains unclear with regards to mortality. We investigated the associations of cognitive and brain reserve with mortality and the interaction of cognitive and brain reserve with frailty within these associations.

Methods Within the observational population-based cohort of the Rotterdam Study, we included participants who visited the research centre for a cognitive assessment between March 2, 2009, and March 1, 2012. Participants with an incomplete assessment of cognition, no data on education attainment, no MRI or an MRI of insufficient quality, three or more missing frailty criteria, or a dementia diagnosis were excluded. Participants were followed up until their death or May 1, 2019. Cognitive reserve was defined as a latent variable that captures variance across five cognitive tests. Brain reserve was defined as the proportion of healthy-appearing brain volume relative to total intracranial volume measured with 1·5 Tesla MRI. Frailty was defined according to Fried's frailty phenotype; participants meeting at least one of the five criteria were considered frail. Hazard ratios (HRs) for associations of cognitive reserve, brain reserve, frailty, and reserve–frailty interactions with the risk of mortality were estimated using Cox regression models.

Findings 2878 individuals in the Rotterdam Study who visited the research centre for a cognitive assessment were considered eligible. 1388 individuals were excluded due to incomplete or missing data or a dementia diagnosis. 1490 participants with valid information on cognitive reserve, brain reserve, and frailty were included (mean age 74·3 years [SD 5·5]; 815 [55%] female participants). 810 (54%) participants were classified as frail. A higher cognitive reserve (HR 0·87 per SD, 95% CI 0·76–0·99, p=0·036) and a higher brain reserve (0·85 per SD, 0·72–1·00, p=0·048) were associated with a lower risk of mortality, after adjusting for sex, age, educational level, body-mass index, smoking status, and number of comorbidities. The association between cognitive reserve and mortality was more pronounced (0·77 per SD, 0·66–0·90, p=0·0012) when the cognitive reserve–frailty interaction (p=0·0078) was included, indicating that higher cognitive reserve is related to lower mortality in individuals with frailty. The brain reserve–frailty interaction was non-significant.

Interpretation Higher cognitive reserve and higher brain reserve were associated with a lower mortality risk. Additionally, cognitive reserve and frailty interact in the association with mortality, such that higher cognitive reserve is particularly associated with lower mortality in frail participants.

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Introduction

Age-related neuropathological damage can lead to clinical expression of brain diseases in some individuals and not in others. These differences in susceptibility to exhibiting clinical symptoms of neuropathology might be explained by cognitive reserve and brain reserve, which refer to individual differences in the functionality and structure of the brain.[1] Cognitive reserve and brain reserve can act as moderators between neuropathology (eg, brain atrophy) and clinical symptoms related to that neuropathology (eg, cognitive impairment). Coping mechanisms include greater network efficiency, capacity, or flexibility, or a higher number of neurons and synapses. Greater cognitive and brain reserve have been associated with beneficial health outcomes, in particular a reduced risk of dementia.[2] Additionally, greater cognitive and brain reserve seem to be associated with a lower mortality risk, but it is unclear how physical health affects this association.[3]

Several proxies for cognitive and brain reserve have been investigated. The most commonly used proxy for cognitive reserve is educational attainment.[1] Alternatively, a more detailed method was proposed to estimate cognitive reserve as a function of demographics, brain

Research in context

Evidence before this study

Several proxies of cognitive reserve, brain reserve, and frailty have previously been found to be risk factors for mortality.

We searched PubMed using the search terms "frailty", "cognitive reserve", "cognitive impairment", "brain reserve", and "mortality" in relevant combinations, with no language restrictions, from database inception up to July 19, 2019. We found no studies that investigated the interaction of these factors with regards to mortality, although an interaction between cognitive or brain reserve and frailty, as an indicator of physical function, has been hypothesised. To the best of our knowledge, interaction of frailty with cognitive factors has been shown only for cognitive impairment and not for cognitive reserve. Additionally, studies over the past decade show that the methods used to estimate cognitive reserve have improved by taking into account current cognitive function, brain pathology, and demographics. However, no studies have assessed the association with mortality using a newly developed proxy of cognitive reserve, which estimates cognitive reserve as a function of demographics, brain pathology, and current level of cognition.

Added value of this study

Our study confirms previously reported associations of cognitive reserve with mortality, with cognitive reserve estimated using a newly developed proxy that incorporates demographics, brain pathology, and current cognitive function. In addition, brain reserve and frailty were also associated with mortality in our population-based sample of older adults. Importantly, we also found an interaction of cognitive reserve and frailty in the association with mortality in older adults but found no interaction between brain reserve and frailty. These results further contribute to our understanding of the concepts of cognitive and brain reserve and their role in mortality.

Implications of all the available evidence

Together with previous literature, our results suggest that cognitive reserve, brain reserve, and frailty should be considered when researching methods to extend the life expectancy and healthy life-years of an individual. Additionally, the concepts of cognitive reserve and frailty interact, suggesting that they should be considered together and not independently. Although causality remains to be determined, we carefully infer that targeting cognitive reserve and frailty together might improve the early prevention of mortality and identification of those at high risk of mortality.

pathology, and current level of cognition.[4,5] Traditionally, proxies for brain reserve include gross whole brain measures, such as total intracranial volume.[1] However, brain reserve has been hypothesised to be better indicated by more fine-grained measures, such as the proportion of healthy-appearing brain volume relative to total intracranial volume. Higher education and a greater proportion of healthy-appearing brain volume, corrected for intracranial volume, have both been associated with a lower risk of mortality,[6,7] but for the more recently developed proxy of cognitive reserve, the association with mortality risk is unknown.

Cognitive and brain reserve might also interact with physical health to affect mortality risk. Physical health can be indicated by frailty, a condition characterised by age-related deterioration in functional reserves across several physiological systems.[3] Frailty is strongly associated with elevated mortality risk[3] and often co-occurs with cognitive impairment or a reduced total brain volume.[8,9] Whether frailty interacts with cognitive and brain reserve with regards to mortality is unknown. Previous literature investigating cognitive impairment, as opposed to cognitive reserve, suggests that cognitive impairment and frailty interact in their association with mortality,[10] although a second study did not show this interaction in the association with mortality.[11] Therefore, frailty might also interact with cognitive reserve in the association with mortality. For brain reserve, the interaction with frailty with regard to the association with mortality remains to be determined. In this population-based study of older adults we aimed to further elucidate the associations of cognitive and brain reserve with mortality risk and investigate the interaction of cognitive and brain reserve with frailty in these associations.

Methods

Study population

This study is part of the Rotterdam Study, a prospective population-based cohort including residents (aged ≥45 years) of Rotterdam, Netherlands.[12] Briefly, the original cohort started in 1990 and was expanded in 2000 and 2006, leading to a total of 14 926 participants. Follow-up visits, consisting of a home interview and multiple visits to the research centre, occurred every 3–6 years. Participants were additionally followed up via linkage with medical and municipality records. For this study, eligible participants were those who visited the research centre for a cognitive assessment between March 2, 2009, and March 1, 2012. Participants were followed up until their death or May 1, 2019. Participants with three or more missing frailty criteria were excluded, and those with one or two missing frailty criteria were not excluded if they had at least three concordant positive or negative criteria. Participants were also excluded if their cognitive assessment was incomplete, no data on educational attainment were available, MRI data were not available or of insufficient quality, or they were diagnosed with prevalent dementia.

The Rotterdam Study was approved by the Medical Ethics Committee of the Erasmus MC University Medical

Center (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, licence number 1071272–159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register and the WHO International Clinical Trials Registry Platform under the shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Procedures

We estimated cognitive reserve using a structural equation model as described by Petkus and colleagues.[4,13] All participants completed a cognitive test battery at the research centre, including the Rey auditory verbal learning test, the Stroop task, the letter digit substitution task, the word fluency test, and the Purdue pegboard test.[14] Cognitive reserve was defined as a latent variable that captures common variance across these five cognitive tests while adjusting for sociodemographic factors (age, sex, and educational level) and MRI-inferred neuropathological factors (total brain volume and white matter lesion volume). Educational attainment was assessed during the baseline interview and classified into four categories according to the UN Educational, Scientific and Cultural Organization classification: primary education (primary), lower or intermediate general education or lower vocational education (low), intermediate vocational education or higher education (intermediate), and higher vocational education or university (high). A higher cognitive reserve score therefore indicates better cognitive functioning than would be expected based on the individual's age, sex, educational level, and MRI-inferred neuropathological factors.

Brain reserve was defined as the proportion of normal-appearing brain volume (total brain volume minus white matter hyperintensity volume in cm³) relative to the total intracranial volume. To determine brain volumes at baseline, multi-sequence brain MRI was done on a 1·5 Tesla MRI scanner with an eight-channel head coil (GE Signa Excite, GE Healthcare, Milwaukee, WI, USA). The scan and image processing protocol have been described previously.[15] Briefly, images were automatically segmented into brain tissues using a computerised processing algorithm based on a k-nearest-neighbour classifier to classify voxels.[16,17] The fluid-attenuated inversion recovery sequence was used to segment white matter lesions in order to estimate total white matter hyperintensity volume (in cm³). Total brain volume (in cm³) was computed by summing total grey and white matter, which included the white matter hyperintensity volumes. Intracranial volume (in cm³) was computed by summing the total brain and cerebrospinal fluid volume.

Frailty was operationalised using Fried's frailty phenotype,[18,19] which was designed in 2001 and is one of the most commonly used measures of frailty.[20] Further details on the construction of frailty in the Rotterdam Study can be found elsewhere.[19] Five criteria are used to define frailty: weight loss, exhaustion, low physical activity, weakness, and slow walking speed. Weight loss was defined as a decrease of more than 5% in body-mass index (obtained on calibrated scales) compared with the most recent previous examination at the research centre.[19] Exhaustion was defined as answering "occasionally or a moderate amount of the time" or "most or all of the time" to at least one of two items in the Center for Epidemiological Studies Depression scale questionnaire:[21] "I felt that everything I did was an effort" or "I could not get going".[18] Low physical activity was defined for women as expending fewer than 1130 kJ per week (<270 kcal per week) and for men as expending fewer than 1602 kJ per week (<383 kcal per week) on physical activity.[18,22] Weakness was defined as poor grip strength measured on a handgrip dynamometer (kg), using cutoffs stratified by sex and body-mass index.[18] Slow walking speed (m/s) was measured with the GAITRite walkway (CIR Systems, Sparta, NJ, USA), using cutoffs stratified by sex and length.[18] The number of criteria met was summed to indicate frailty. Frailty was defined as meeting three or more frailty criteria or meeting one or two criteria (also defined as pre-frail) because the number of participants meeting three or more criteria in our study was low (n=53). If participants did not meet any criteria, they were considered not frail.

Information on the vital status of participants was obtained on a weekly basis via municipal population registries and through general practitioners and medical records. All-cause mortality was defined as death from any cause during the total follow-up period (to May 1, 2019).

Smoking status was self-reported and categorised as never, former, or current smoker. Previously published guidelines were used to define hypertension, diabetes, osteoporosis, chronic obstructive pulmonary disease, kidney disease, heart failure, stroke, and cancer,[19] based on measurements at our research centre and follow-up of medical records. For participants with complete data on all comorbidities, the total number of comorbidities was calculated.[19] Ancestry was assessed by genotyping based on a blood draw; if these data were missing, self-reported ancestry was used.

Statistical analysis

All continuous variables in the structural equation model were checked for normality and Z-score standardised. We log-transformed only white matter lesion volume before standardisation due to the skewed distribution. To estimate the cognitive reserve latent variable, the score from each cognitive test was regressed on age, sex, educational status, total brain volume, and log-transformed white matter lesion volume. Total brain volume and log-transformed white matter lesion volume were adjusted for age, sex, and intracranial volume (appendix pp 2–3). Cutoff

See Online for appendix

	Study participants (n=1490)
Age, years	74·3 (5·5)
Sex	
Female	815 (55%)
Male	675 (45%)
Caucasian ancestry*	1428 (96%)
Educational level	
High	280 (19%)
Intermediate	497 (33%)
Low	627 (42%)
Primary	86 (6%)
Body-mass index, kg/m²	27·3 (3·8)
Smoking status	
Never	525 (35%)
Former	850 (57%)
Current	115 (8%)
Comorbidity	
Hypertension	1093 (73%)
Coronary disease	59 (4%)
Diabetes	104 (7%)
Osteoporosis	160 (11%)
Chronic obstructive pulmonary disease	223 (15%)
Anaemia	99 (7%)
Kidney disease	423 (28%)
Heart failure	39 (3%)
Stroke	11 (1%)
Cancer	215 (14%)
Frailty criterion	
Weight loss	277 (19%)
Exhaustion	186 (12%)
Low physical activity	44 (3%)
Weak grip strength	541 (36%)
Slow walking speed	29 (2%)
Frailty	810 (54%)
Reserve measure	
Cognitive reserve†	0 (1)
Brain reserve	0·78 (0·04)

Data are n (%) or mean (SD). Data were missing for some participants for ancestry (n=4), anaemia (n=18), kidney disease (n=7), heart failure (n=6), weight loss (n=90), exhaustion (n=9), low physical activity (n=64), weak grip strength (n=22), and slow walking speed (n=313). *Assessed genetically (n=1293) or self-reported (n=197). †Z-score standardised.

Table 1: **Baseline characteristics of the study population**

values of comparative fit index greater than 0·9, Tucker Lewis index greater than 0·9, root-mean-square error of approximation of less than 0·06, and standardised root mean square residual of less than 0·08 were considered to indicate good model-data fit.[23] The cognitive reserve latent variable was Z-score standardised. The structural equation model was built with the lavaan package in R 3.6.1.

To assess associations of cognitive reserve, brain reserve, and frailty with the risk of mortality we used Cox proportional hazard models. Start of follow-up was defined as the time of the last measurement of participants (ie, the date of MRI scan). The censor date was defined as the date of death, loss to follow-up, or May 1, 2019, whichever came first. Cognitive reserve and brain reserve were Z-standardised in all analyses. Associations of cognitive reserve, brain reserve, and frailty with the risk of mortality were analysed in three separate Cox regression models. In model 1, we adjusted only for age and sex. In model 2, we added additional confounding factors: body-mass index, smoking status, educational level, and the number of comorbidities. Ancestry was not considered as a confounder due to the homogeneity of the study population. In model 3a, we mutually adjusted cognitive reserve or brain reserve and frailty, meaning that cognitive and brain reserve, frailty, and all confounders were added to the model. In model 3b, we added cognitive reserve–frailty and brain reserve–frailty interaction terms to investigate multiplicative interaction. To calculate the interaction terms, we multiplied the variables of cognitive or brain reserve with frailty and included these variables in our model. Analyses comparing participants with no frailty or meeting one to two frailty criteria to those meeting three or more frailty criteria were done to assess whether the association of frailty with mortality was dose-dependent. Significant violation of the proportional hazard assumptions for all analyses was tested with the Schoenfeld residuals test. To visualise interactions, we created survival plots based on four strata using the median dichotomised cognitive and brain reserve and analysed the risk of mortality in each stratum. We additionally repeated analyses using educational attainment as a proxy for cognitive reserve, because this is a commonly used proxy for cognitive reserve and facilitates comparison with previous studies.

We did two sets of sensitivity analyses. First, we did additional analyses in which passive multiple imputation was used to determine frailty status, to account for missing data in frailty criteria. Second, we analysed the association between frailty, cognitive reserve, and brain reserve using frailty as a continuous variable to account for small group sizes.

Missing data on the number of comorbidities (0·02%) were imputed five times using chained equations and the analyses were pooled across imputations. Results were summarised with hazard ratios (HRs) and 95% CIs. A p value of less than 0·05 was considered statistically significant. All analyses were done in R 3.6.1.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 2, 2009, and March 1, 2012, 2878 participants of the Rotterdam Study visited the

	Model 1		Model 2		Model 3a		Model 3b	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Cognitive reserve*	0·86 (0·75–0·98)	0·023	0·86 (0·76–0·99)	0·035	0·87 (0·76–0·99)	0·035	0·77 (0·66–0·90)	0·0012
Frailty status								
Frail	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Not frail	0·60 (0·45–0·80)	0·0006	0·64 (0·48–0·86)	0·0029	0·64 (0·48–0·86)	0·0029	0·65 (0·48–0·87)	0·0053

In model 1, cognitive reserve and frailty were separately adjusted for age and sex. Model 2 had additional adjustment for educational level, body-mass index, smoking status, and number of comorbidities. In model 3a, cognitive reserve and frailty were also mutually adjusted. In model 3b, the cognitive reserve–frailty interaction term was included ($p_{interaction}$=0·0078). HR=hazard ratio. *HRs are per SD increase.

Table 2: **Cox proportional hazard models to estimate associations and interactions of cognitive reserve and frailty with the risk of mortality**

research centre for a cognitive assessment and were potentially eligible for inclusion in this study. 1388 individuals were excluded because of incomplete cognitive assessments, no MRI or MRI of insufficient quality, incomplete frailty assessments, or having a dementia diagnosis. In total, 1490 participants with valid information on cognitive reserve, brain reserve, and frailty were included (appendix p 1).

At baseline, the mean age of participants was 74·3 years (SD 5·5); 815 (55%) of 1490 participants were female. 810 (54%) participants were classified as frail (table 1). Of these participants, 53 met three or more frailty criteria and 757 met one or two criteria (also defined as pre-frail). Of the five frailty criteria, weak grip strength was the most common (541 [37%] of 1467 participants). During the mean follow-up of 5·3 years (SD 1·4), 214 (14%) of 1490 participants died. The mean brain reserve was 0·78 (SD 0·04). The structural equation model for cognitive reserve had a good model fit:[23] comparative fit index 0·99, Tucker Lewis index 0·96, root-mean-squared error of approximation 0·05 (90% CI 0·03–0·07), and standardised root mean square residual 0·01. The cognitive reserve variable was Z-score standardised and therefore has a mean of 0 (SD 1). Participants were slightly younger, less often female, more educated, more often pre-frail, and had a lower brain reserve compared with participants who were excluded from the study (appendix p 4).

A higher cognitive reserve was associated with a lower risk of mortality after adjusting for all covariates and frailty (HR 0·87 per SD, 95% CI 0·76–0·99, p=0·035; table 2, model 3a). No frailty was also associated with a lower risk of mortality compared with frailty (0·64, 0·48–0·86, p=0·0029). This association between frailty and mortality risk was dose-dependent; when compared with participants meeting three or more criteria, those meeting one to two criteria had a lower mortality risk (0·51, 0·32–0·80, p=0·0034) and those meeting no criteria had an even lower risk (0·34, 0·21–0·56, p<0·0001). After including the interaction term of cognitive reserve and frailty in the model (model 3b), a higher cognitive reserve was more strongly associated with a lower mortality risk (0·77 per SD, 0·66–0·90, p=0·0012). The interaction term was also associated with mortality risk (1·48, 1·11–1·98, p=0·0078), indicating that the association of cognitive

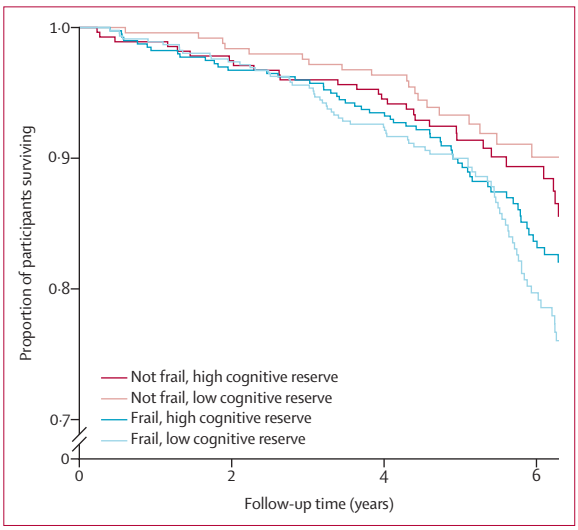

Figure 1: **Adjusted survival curves in groups stratified by frailty status and median cognitive reserve**

Patients were classified as not frail, high cognitive reserve (n=352, 40 events); not frail, low cognitive reserve (n=328, 31 events); frail, high cognitive reserve (n=393, 79 events); or frail, low cognitive reserve (n=417, 91 events).

reserve with mortality differs between those who are frail and those who are not frail. Stratified survival curves for the four groups split by the median cognitive reserve and frailty are shown in figure 1. Compared with frail participants with a low cognitive reserve, non-frail participants with either a low cognitive reserve (0·54, 0·36–0·82, p=0·0042) or a high cognitive reserve (0·58, 0·40–0·86, p=0·0066) had a lower risk of mortality. We found no significant differences between non-frail participants with a high or low cognitive reserve. Analyses using educational attainment as a proxy for cognitive reserve showed no significant associations with mortality, nor a significant interaction with frailty with regards to mortality risk (appendix p 5).

Higher brain reserve was associated with a lower risk of mortality, even after adjusting for all covariates (HR 0·83 per SD, 95% CI 0·70–0·97, p=0·024; table 3, model 2). However, when frailty was included (model 3a), the association between higher brain reserve and a lower risk of mortality was attenuated (0·85 per SD, 0·72–1·00, p=0·048). No frailty was associated with a lower risk of

	Model 1		Model 2		Model 3a		Model 3b	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Brain reserve*	0·80 (0·68–0·93)	0·0051	0·83 (0·70–0·97)	0·024	0·85 (0·72–1·00)	0·048	0·87 (0·72–1·04)	0·12
Frailty status								
Frail	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Not frail	0·60 (0·45–0·80)	0·0006	0·64 (0·48–0·86)	0·0029	0·66 (0·49–0·88)	0·0056	0·63 (0·46–0·87)	0·0053

In model 1, brain reserve and frailty were separately adjusted for age and sex. Model 2 had additional adjustment for educational level, body-mass index, smoking status, and number of comorbidities. In model 3a, brain reserve and frailty were also mutually adjusted. In model 3b, the brain reserve–frailty interaction term was included ($p_{interaction}$=0·55). HR=hazard ratio. *HRs are per SD increase.

Table 3: **Cox proportional hazard models to estimate associations and interactions of brain reserve and frailty with the risk of mortality**

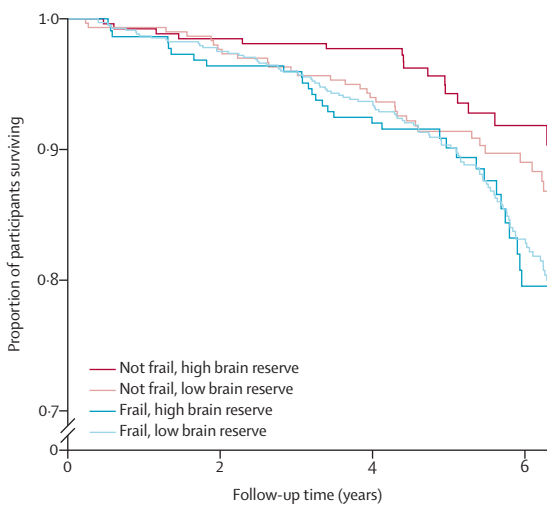

Figure 2: **Adjusted survival curves in groups stratified by frailty and median brain reserve**

Patients were classified as not frail, high brain reserve (n=412, 25 events); not frail, low brain reserve (n=268, 46 events); frail, high brain reserve (n=333, 35 events); or frail, low brain reserve (n=477, 135 events).

mortality compared with frailty (0·66, 0·49–0·88, p=0·0056; table 3, model 3a). This association between frailty and mortality risk was dose-dependent; when compared with participants meeting three or more frailty criteria, those meeting one to two criteria had a lower mortality risk (0·49, 0·31–0·77, p=0·0022), and those meeting no criteria had an even lower risk (0·34, 0·21–0·57, p<0·0001). The interaction between brain reserve and frailty was not associated with mortality (0·90, 0·66–1·23, p=0·55). Survival curves for the four groups split by the median brain reserve and frailty are shown in figure 2. Compared with frail participants with a low brain reserve, non-frail participants with either a low brain reserve (0·70, 0·49–0·99, p=0·048) or a high brain reserve (0·51, 0·32–0·83, p=0·0063) had a lower risk of mortality. We found no significant differences between participants without frailty with a high or low brain reserve.

Sensitivity analyses using passive multiple imputation to define the frailty status for those with one or two missing frailty criteria showed similar results for both cognitive and brain reserve (appendix p 6). Additionally, analyses using frailty as a continuous variable showed associations in a similar direction for both cognitive and brain reserve. These analyses should be interpreted with caution because residuals suggested a non-linear association that could not be improved by transformation of the continuous frailty score (appendix p 7).

Discussion

In a population-based sample of older adults, we showed that higher cognitive and brain reserves were associated with a lower risk of mortality. We found that cognitive reserve and frailty interact in the association with mortality, such that cognitive reserve lowers the risk of mortality in individuals with frailty. We found no interaction between brain reserve and frailty in the association with mortality.

To date, the association between cognitive reserve and mortality has been investigated only by using educational level as a proxy for cognitive reserve. However, this proxy has several limitations because it might be influenced by sociodemographic and cultural factors.[24,25] The static concept of highest attained educational level might not capture the dynamic nature of cognitive reserve well enough. Indeed, our analyses did not show an association between educational attainment and mortality. Using a more advanced method of estimating cognitive reserve,[4,5] we show in this study that lower cognitive reserve increases mortality risk in community-dwelling older men and women. To date, the mechanisms underlying cognitive reserve and its association with mortality remain unknown. One hypothesis is that the brain uses pre-existing cognitive processing approaches or recruits compensatory approaches to cope with brain pathology.[2] The association of cognitive reserve with lower mortality risk could be due to coping with cognitive decline,[26] which is associated with an increased mortality risk.[27] However, cognitive decline could also be symptomatic of dementia, non-dementia brain pathology, or systemic pathologies, such as metabolic imbalances, that can increase mortality risk.[27]

Additionally, our work suggests that cognitive reserve and frailty interact in the association with mortality.

Two previous studies have investigated the interaction between cognitive impairment and frailty in the association with mortality.[10,11] Cognitive impairment is suggested to be inversely related to the concept of cognitive reserve and underlying mechanisms might differ. Although our measure is designed to capture cognitive reserve, it is possible that a low cognitive reserve at least partly captures cognitive impairment. Interaction of cognitive impairment and frailty was observed in a study of 11 266 individuals, which found that cognitive impairment at baseline moderated the effect of frailty on mortality over 3 years of follow-up.[10] However, a second study (n=1751) with 5 years of follow-up found no interaction between frailty and cognitive impairment in predicting mortality.[11] Studies investigating frailty and cognitive impairment suggest that hormonal dysregulation, insulin resistance, sarcopenia, nutritional deficiency, chronic inflammation, cardiovascular risks, and depression are underlying factors in the interaction between cognitive impairment and frailty.[28] Whether similar mechanisms are involved in the interaction between cognitive reserve and frailty remains to be determined.

In our study, a higher brain reserve was associated with a lower risk of mortality. Previous research found similar associations between brain volume corrected for intracranial volume and mortality.[7,29] The association in our study was attenuated when adjusted for frailty status. Because frailty is a measure of loss of functional reserve across multiple physiological systems, it could possibly also affect brain reserve. We defined brain reserve as the proportion of healthy-appearing brain volume relative to total intracranial volume, as opposed to intracranial volume itself, to take into account dynamic changes of brain reserve. We excluded participants with dementia so that our approach was likely to distinguish the structural characteristics of brain reserve from the neuropathological volume loss secondary to dementia.[1] Mechanisms underlying brain reserve are largely unclear. Initially, brain reserve was only hypothesised to be quantitative, such that a brain with more neurons or synapses has more to lose. However, it might be more nuanced; for example, stimulating environments promote neurogenesis and upregulate brain-derived neurotrophic factor, which promotes neuroplasticity.[2] Brain reserve is possibly associated with mortality by limiting global atrophy, which has been associated with mortality.[29] A higher brain reserve could also lower mortality risk by lowering the risk of Alzheimer's disease,[13] other dementias, and non-dementia brain pathology that can increase the risk of mortality.

Causality remains to be determined, but we carefully infer that targeting cognitive reserve and frailty might help in the early prevention of mortality and identification of those at high risk of mortality. Our study also shows that these concepts should be considered together, instead of as independent issues. Further research is needed to determine whether novel strategies or therapies could improve cognitive reserve and physical functioning in individuals with frailty, and whether these therapies could extend healthy life-years. However, we do not yet know whether frailty affects the association of cognitive reserve with mortality or, vice versa, whether cognitive reserve affects the association of frailty with mortality.

A limitation of our measure of cognitive reserve is that the associations in the structural equation model might lack unknown brain variables and non-linear associations or interactions that have a role in cognitive reserve, possibly biasing our estimate.[4] Additionally, weight loss was based on examinations during centre visits and did not take into account whether it was unintentional or not,[18] which could have led to a dilution of the association. Certain criteria could be more significant than others when defining frailty, which needs to be studied further. For all self-reported variables (eg, smoking), self-reporting bias is possible. Further bias might have been introduced by excluding persons who did not have complete data, with missing data probably not missing completely at random. Because all variables were collected at baseline, a change of comorbidities during the follow-up of this study could bias the associations. Our study was done in a Dutch, largely Caucasian, population-based sample of older people, and generalising these results to other groups should be done with caution. Although our results were in line with a larger study investigating the interaction between frailty and cognitive impairment in a sample of 11 266 community-dwelling Koreans aged 65 years and older,[10] further research investigating cognitive reserve in other groups is required to ensure the current findings are generalisable. The strengths of our study are the prospective cohort design, making it less prone to information and selection bias, and the large sample size of the population.

In conclusion, a higher cognitive reserve seems to particularly protect against mortality in individuals with physical frailty. A higher brain reserve is associated with a lower risk of mortality in both frail and not frail individuals. Considering cognitive reserve as well as frailty might help in the early prevention of mortality and identification of those at high risk of mortality. Strategies or novel therapies that support cognitive and physical functioning might help to extend healthy life-years.

Contributors

JLZ, MAI, and AIL contributed to study design. JLZ and SL did the data verification and analyses. JLZ and AIL drafted the manuscript. SL, LL, MWV, MKI, and MAI critically reviewed the manuscript. All authors had access to all the data reported in the study. AIL had full access to all of the data and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data can be obtained upon request. All requests should be directed towards the management team of the Rotterdam Study

(secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

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