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Cognitive and Brain Reserve and the Risk of Postoperative Delirium in Older Patients

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Abstract

Background—Cognitive and brain reserve theories suggest that aspects of neural architecture or cognitive processes modify the impact of neuropathological processes on cognitive outcomes. While frequently studied in the context of dementia, reserve in delirium is relatively understudied.

Methods—We examined the association of three markers of brain reserve (head circumference, MRI-derived brain volume, and leisure time physical activity) and five markers of cognitive reserve (education, vocabulary, cognitive activities, cognitive demand of lifetime occupation, and interpersonal demand of lifetime occupation) and the risk of postoperative delirium in a prospective observational study of 566 older adults free of dementia undergoing scheduled surgery.

Findings—Twenty four percent of patients (135/566) developed delirium during the postoperative hospitalization period. Of the reserve markers examined, only the Wechsler Test of Adult Reading (WTAR) was significantly associated with the risk of delirium. A one-half standard deviation better performance on the WTAR was associated with a 38% reduction in delirium risk ($P = 0.01$); adjusted relative risk of 0.62, 95% confidence interval 0.45–0.85.

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Interpretation—In this relatively large and well-designed study, most markers of reserve fail to predict delirium risk. The exception to this is the WTAR. Our findings suggest that the reserve markers that are important for delirium may be different from those considered to be important for dementia.

BACKGROUND

Delirium, an acute disorder of attention and cognition, is common among hospitalized older patients, occurring in 29–64% of general medicine inpatients and 11–51% of surgical patients.¹ Risk factors such as depression, medical comorbidity, cognitive impairment and older age have been identified in general medical inpatients, surgical populations and the intensive care unit, and serve to stratify patients for delirium risk.¹ An additional factor that has not been well-examined for its role in the development of delirium is reserve capacity.

Reserve capacity, the extent to which an individual can compensate for or withstand changes to the brain, has been examined with respect to cognitive reserve and brain reserve.² Brain reserve refers to the resiliency of the brain and its ability to continue to function despite neuropathologic changes. The premorbid size and architecture of the brain are markers of brain reserve, such as premorbid parenchymal volume and synaptic density. The brain reserve hypothesis suggests that increased premorbid size and complexity of the brain results in a greater capacity to continue to function at a ‘normal’ level despite subsequent neuropathology.²

Cognitive reserve refers to the capacity of the brain to make efficient use of available resources through the recruitment of alternative cognitive strategies.³ Markers of cognitive reserve are typically reflections of lifetime or long-term behaviors and activities, such as educational attainment, complex occupational performance, or participation in cognitively stimulating activities.² Theories of cognitive reserve originated from studies finding discrepancies between expected and observed level of cognitive performance in the presence of dementia neuropathology. For example, a landmark study on cognitive reserve found that among nuns, those with lower brain capacity (operationalized by smaller head circumference) were at higher risk for Alzheimer’s disease, yet higher education mediated this association.⁴ Similar findings have been observed for cognitive, social and physical activity,⁵ occupational attainment,⁶ and IQ.⁷

The cognitive reserve hypothesis posits that higher education or more complex occupations yield a broader range of compensatory cognitive strategies. While markers of cognitive and brain reserve are considered distinct, they may be inter-related. For instance, higher education may be associated with increased brain size and complexity. Cognitive and brain reserve have been extensively examined with respect to dementia onset and progression. Previous studies have generally concluded that higher reserve capacity (e.g., higher education, participation in more cognitively stimulating activities, or larger premorbid brain volume) is associated with better cognitive performance than would be expected given the degree of pathologic changes to the brain (e.g., plaques and tangles).^{8,9} These studies have identified patterns of reserve markers that are associated with increased resilience to developing dementia. We hypothesized that the concept of reserve would also apply to the

development of delirium where some individuals are able to withstand the stressors of a hospitalization without developing delirium while others are not. Indeed, several markers of cognitive and brain reserve have been individually examined for their association with delirium risk. For example, we have shown that both higher educational attainment¹⁰ and more activity participation¹¹ protect against the risk of delirium among hospitalized older adults. However, other markers of reserve have not been examined as risk factors for delirium (e.g., occupational complexity, head circumference) nor have multiple markers of reserve been examined simultaneously, allowing for a comparison of the relative effect of each of the markers.

The goal of this paper was to examine the association between established markers of cognitive and brain reserve and the incidence of postoperative delirium. We hypothesized that patients with higher levels of cognitive and brain reserve markers would be less likely to develop delirium when subjected to the stress of major non-cardiac surgery.

METHODS

Setting and Patients

This study is based on an analysis of the data collected for the Successful Aging after Elective Surgery (SAGES) study, an ongoing prospective cohort study of 566 elective surgical patients designed to examine delirium and its outcomes which has been described in detail previously.¹² Briefly, patients were recruited from two large teaching hospitals from June 2010 through August 2013. The eligible elective surgeries were: total hip or knee replacement, cervical or lumbar laminectomy, lower extremity arterial bypass, open abdominal aortic aneurysm repair, and colectomy. Inclusion criteria included: age ≥ 70 years, and ability to communicate in English. Exclusion criteria included diagnosis of dementia as assessed by initial medical record screening, telephone recruitment or enrollment interview; severe cognitive impairment as defined by a score ≤ 69 or its education-adjusted equivalent on the Modified Mini-Mental State (3MS)¹³ examination during baseline interview; delirium at baseline interview; terminal disease; total blindness; and severe deafness. All study procedures were approved by the institutional review boards at the participating sites and written informed consent was obtained from all participating patients.

MRI Subsample

Approximately one-quarter ($n = 146$) of enrolled participants elected to undergo Magnetic Resonance Imaging (MRI) prior to surgery. All subjects received imaging on a 3T HDxt MRI (General Electric Healthcare, Waukesha, WI) scanner using a standard eight-channel head coil. The MRI protocol included: High Resolution three-dimensional (3D) anatomic imaging, High Resolution 3D T2-weighted imaging, and Fluid Attenuated Inversion Recovery (FLAIR).

Assessment of Reserve Factors

We collected multiple measures of cognitive and brain reserve at the baseline (pre-operative) assessment, with the exception of head circumference which was assessed at the one-month follow-up assessment. We chose markers of reserve based on the published

literature, including those identified in two previous meta-analyses of over 29,000 and 47,000 persons as reducing the risk of dementia or cognitive decline by at least 50%.^{8,9} Specific measures are described below.

Measures of Cognitive Reserve—Cognitive reserve markers included years of education, lifetime cognitive activities, occupational complexity and management demand, and the Wechsler Test of Adult Reading (WTAR).¹⁴ Education was self-reported as number of years of formal schooling. The WTAR includes 50 irregularly spelled words of increasing complexity that the participant is asked to read aloud. The total score is the number of words correctly pronounced (range 0–50). The WTAR is similar to other tests such as the Wechsler Adult Intelligence Scale (WAIS) – Vocabulary subtest (respondents produce definitions of presented words) and the National Adult Reading Test (NART)¹⁵ (which like the WTAR presents a list of irregular words for correct pronunciation). The use of vocabulary tests as measures of pre-morbid intelligence was suggested by Yates.¹⁶ The WTAR is considered to be a valid correlate of verbal IQ. For example, Mathias and colleagues¹⁷ found, in a healthy adult sample, that WTAR performance correlated ($r=0.71$) with the verbal intelligence quotient (VIQ) derived from the WAIS. The NART had an effectively equivalent correlation with VIQ ($r=0.72$). More recently, using the Lothian Birth Cohort of 1936, Dykiert and Deary¹⁸ found that the correlation of the NART and the WTAR measured in late life (around age 70) were similarly correlated with IQ measured in late life and at age 11 (correlation coefficients between 0.65 and 0.70).

Lifetime cognitive activity was assessed using a modified version of the Cognitive Activities Scale (CAS).²¹ At baseline, participants were asked about time spent in six activities that involve information processing: visiting the library, reading newspapers, reading magazines, reading books, writing letters, and playing board or card games. Frequency of participation was reported at four time-points over the life-course: 12 years of age, 18 years of age, 40 years of age and present time. Participation was scored for each activity on a six-point scale: five = every day or almost every day, four = several times a week, three = several times a month, two = several times a year, one = once a year or less, and zero = never. Responses to items were combined to yield a composite measure representing total lifetime cognitive activity.

Occupational complexity and management demand were assessed by matching self-reported longest held occupation to entries in the *Dictionary of Occupational Titles (DOT)*, 4th edition.²² The *DOT* contains ratings (e.g. required mathematical aptitude or number of employees who report to you directly) of job characteristics determined by U.S. Department of Labor personnel. Measures of job activity, including the occupational complexity and management demand, were calculated from *DOT* classifications using a factor analysis approach described in detail previously.²³

Measures of Brain Reserve—Measures that we classified as suggesting brain reserve were leisure time physical activity, head circumference, and intracranial cavity volume (ICV). Head circumference and physical activity were assessed in all participants and ICV was measured only in the subset of participants ($n=147$) who underwent MRI. Physical activity was assessed using the Minnesota Leisure Time Activities Questionnaire

(MLTA),²⁴ which asks about time spent in the past two weeks on six activities: walking for exercise, moderately strenuous household chores (such as scrubbing and vacuuming), moderately strenuous outdoor chores (such as mowing and raking), dancing, bowling, and stretching. The scoring algorithm for the MLTA includes established Metabolic Equivalent of Tasks (METs) from which overall (total) METs per week, in minutes, were calculated and used as the main unit of analysis.

Total ICV was obtained by a semi-automated image segmentation method based on three channels: T1-weighted, T2-weighted and FLAIR (FLuid Attenuated Inversion Recovery) images. Intracranial cavity volume (ICV) was calculated by custom Functional Magnetic Resonance Imaging of the Brain Software Library (FSL; Freesurfer, Boston MA) software and reviewed and manually corrected by an investigator who was blind to delirium status (TH).

All SAGES participants underwent standardized head circumference measurements by trained research staff during the one-month follow-up assessment. The circumference was measured from just above the eyebrows to the most posterior occipital protuberance.

Assessment of Delirium

Delirium was assessed using state-of-the-art methods by trained research assessors in a standardized fashion once per day during the day shift. Specifically, the Confusion Assessment Method (CAM)²⁵ was rated based on information from patient interviews including a brief cognitive screen (orientation, short-term recall, sustained attention) described previously,²⁶ the Delirium Symptom Interview (DSI),²⁷ and information related to acute changes in mental status noted by nurses or family members. The CAM is a widely used, standardized method for identification of delirium and has high inter-rater reliability and high sensitivity (94%) and specificity (89%) when compared to clinical expert or consensus-based diagnoses of delirium.²⁸ The SAGES protocol rated the presence or absence of delirium using the CAM diagnostic algorithm, which requires the presence of acute change or fluctuating course, inattention, and either disorganized thinking or an altered level of consciousness.

A standardized chart review method, which has been previously described,²⁹ was also used to identify cases of delirium. Briefly, the chart-based delirium diagnosis abstracted information on acute changes in mental status, time and duration of such episodes, evidence of agitation and reversibility or improvement of the acute confusion from in-patient and pre-operative charts, discharge summaries, and outpatient visit notes. All cases of delirium in the chart were adjudicated by a panel with experience in delirium and discrepancies were resolved during a consensus meeting.

Occurrence of delirium was defined as presence of delirium according to the CAM criteria during one or more days of hospital interviews or by the chart review method at any time during the hospital stay.

Other Study Variables

Physical functioning was assessed by the Activities of Daily Living Scale (ADL)³⁰ and Instrumental Activities of Daily Living Scale (IADL),³¹ and general health status by the Short Form Health Survey (SF-12)³² at the baseline interview. Depression was assessed using the short form of the Geriatric Depression Scale (GDS-15).³³ Scores range from 0 to 15, with higher scores reflecting a higher severity of depressive symptoms. Cognitive decline was collected from proxy reports on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).³⁴ The hospital medical record was abstracted for age, surgery type, and the Charlson Comorbidity Index.³⁵

Data Analysis

We used bivariable and multivariable generalized linear models to examine the association between each of the individual markers of reserve and development of postoperative delirium. Our main multivariable models controlled for pre-specified covariables of age, sex, race, and English as a second language (ESL). In a sensitivity analysis, we additionally controlled for variables that differed by delirium status: depression, comorbidity, physical functioning, and proxy report of cognitive decline (IQCODE) (see Table 1). Parameters and relative risk estimates were obtained using a generalized linear regression model with a log link and binomial distribution³⁶ using Stata software (version 13.1, College Station, Texas). Model fit was assessed by the Hosmer and Lemeshow goodness-of-fit test.³⁷ To correct for non-normality in the distribution of reserve markers, we normalized and transformed our reserve markers. There are two aspects of our exposure variable coding: Blom transformation³⁸ and standardizing to two standard deviations.³⁹ We use the Blom transformation in an attempt to protect our inferences from skewed distributions. We standardized to two standard deviations such that the regression coefficients correspond to comparisons at the mean ± 1 standard deviation and are comparable for coefficients obtained for binary predictors.

Statistical Power Considerations

Given our sample size ($N = 566$) and an anticipated cumulative incidence of postoperative delirium of 25%, we had sufficient power to detect small to medium effects in our full sample: standardized mean difference in reserve marker by delirium group of $d = 0.26$, biserial correlation of reserve marker and propensity to develop delirium of $r_{bs} = 0.20$, or a risk ratio for delirium of $RR = 1.72$ or greater (or 0.58 and lower) for every half-standard deviation difference in the continuous reserve marker. In our MRI subsample ($N = 146$), we had power to detect larger effects: $d = 0.52$, $r_{bs} = 0.40$, $RR = 3.2$ (or 0.31).

RESULTS

The average age was 77 years (standard deviation (SD) = five years) at the time of surgery, 58% were female and 92% were white (Table 1). The majority (81%) of participants were undergoing orthopedic surgery; vascular (13%) and gastrointestinal (6%) surgeries were also represented in the study sample. The average score on the Charlson comorbidity index was one (SD=1.3) and approximately one quarter of the cohort had one or more IADL impairments and 7% had one or more ADL impairments. Cognitive performance was

generally high, with an average score in the cohort of 57.5 on the general cognitive performance composite, indicating that our sample was three-quarters of a standard deviation above the population norm for overall cognitive performance. The subset of the sample on which MRI was performed ($n=146$) was significantly younger (76 vs 77 years, $p<0.05$) and had lower comorbidity (Charlson score $\geq 2 = 23\%$ vs. 32% , $p<0.05$) than the cohort that did not undergo MRI. Other baseline and in-hospital characteristics including sex, education, race, Modified Mini-Mental State Examination score, general health status, delirium status, and delirium severity did not differ in those who underwent MRI and those who did not.

Approximately one quarter of participants ($n = 135$; 24%) developed delirium postoperatively. Post-operative lengths of stay had a median of 3 days (interquartile interval, 2–4 days) and ranged up to 24 days. The vast majority (89%) of incident delirium cases occurred within 3 days of surgery. Approximately one half (52%) occurred within a day of surgery. Participants who developed delirium were significantly older, had higher comorbidity, were more likely to have high depressive symptoms, more likely to have self-reported IADL impairment, and had poorer general health related quality of life, as reported on the SF-12. (Table 1) Patients who developed delirium also had experienced greater cognitive decline, as reported by their proxies on the IQCODE.

Cognitive and brain reserve measures, stratified by sex, are presented in Table 2. Participants were highly educated with an average of 15 years of formal education ($SD =$ two) and men had slightly higher education levels than women (15.4 years compared to 14.6 years). Men had slightly lower participation in cognitive activities (demonstrated by the Cognitive Abilities Scale, Table 2) compared to women but higher energy expenditure weekly while engaging in leisure time activities. Men had higher occupational complexity compared to women but slightly lower occupational management demand. Scores on the WTAR were similar in men and women. Men had larger head circumference, and intracranial cavity volume.

Bivariable regression models are presented in Table 3 for each of the reserve markers. Model fit was good for most models. When poor fit was suggested, alternative model specification procedures failed to identify a source of misfit from among the choice of linking function, data transformation, or assumption of linearity. Detailed description of model fit assessment is available upon request. With the exception of the WTAR, none of the reserve markers were significantly associated with the risk of postoperative delirium. In multivariable models adjusting for age, sex, race, and English as a second language; for each half standard deviation increase in performance on the WTAR, the risk for delirium in the overall cohort was nearly 40% lower (relative risk, $RR = 0.62$, $95\% \text{ CI } 0.45, 0.85$, $z = -3.05$) and the association was slightly stronger, and only statistically significant, in women (relative risk, $RR = 0.54$, $95\% \text{ CI } 0.34, 0.83$) than in men (relative risk, $RR = 0.73$, $95\% \text{ CI } 0.46, 1.14$) (Table 4).

Higher education, cognitive activity and management demand in one's occupation, and larger intracranial cavity volume were associated with a reduced risk of delirium in both men and women, but associations were not statistically significant (Tables 3&4). Larger

head circumference was associated with a non-statistically significant reduced risk for delirium in the overall cohort but the direction of the association varied by sex.

Analyses were repeated without the Blom transformation, and demonstrated the same patterns of significance with no impact on the study conclusions. Analyses were repeated using logistic regression rather than log binomial regression, and the same results were obtained. In sensitivity analyses, we repeated our multivariable models including potential confounders identified in Table 1 in addition to our a priori identified confounders: depression, physical functioning, comorbidity, and proxy report of cognitive decline (IQCODE). The results were similar to the findings in the main model: with the exception of the WTAR, reserve markers were not associated with the development of postoperative delirium. We also repeated analyses for the outcome of delirium severity in the group with delirium, and the results were unchanged.

DISCUSSION

We found that in older elective surgery patient's traditional markers of cognitive and brain reserve markers were not associated with the risk for delirium. The exception to this was the WTAR, a measure of vocabulary knowledge, which was associated with a nearly 40% reduced risk of delirium for each half standard deviation increase in performance. The largely negative findings for the association between reserve markers and delirium suggest that the reserve markers that are important for delirium, an acute confusional state, may differ from those that are important for dementia, a chronic, progressive condition.

In our sample of older elective surgery patients, established socioeconomic, anthropometric, and brain volumetric markers of brain and cognitive reserve were not significantly associated with the risk of post-operative delirium. The WTAR was associated with a nearly 40% reduced risk of delirium for each half standard deviation increase in performance. The association between the WTAR and delirium risk were slightly stronger in women compared to men. Our findings suggest that in a relatively healthy, dementia-free population, a measure of vocabulary knowledge is an important predictor of delirium risk among older adults.

Our *a priori* hypothesis that traditional reserve markers such as education, occupational complexity and brain volume would be associated with risk of delirium was not supported, and with the exception of the WTAR, reserve markers were not significantly associated with post-operative delirium. In previous work we have shown that several markers of cognitive reserve, educational attainment and activity participation, were associated with a reduced risk of delirium^{10,11}. It is possible that the well-established cognitive and brain reserve markers examined in this study are specific to dementia risk, as these studies examined reserve and delirium risk in a cohort with a high proportion of patients with dementia (20% in the study on educational attainment). The SAGES cohort was designed to be free of dementia at enrollment. It is well established that dementia is a risk factor for delirium⁴⁰, and our dementia free cohort uniquely allows us to tease apart risk factors for delirium and dementia.

Our negative findings with respect to traditional cognitive and brain reserve markers and delirium risk suggest that reserve factors which protect against acute insults (e.g., delirium) may be different from those which protect against progressive decline (e.g., dementia). In addition, it is possible that traditional cognitive and brain reserve markers may be associated with long-term outcomes after delirium rather than with the development of delirium per se. For instance, persons who develop delirium and who have high cognitive and brain reserve may have a faster and more complete cognitive recovery compared to those who develop delirium but have lower reserve capacity. These are hypotheses that will need to be examined in future research.

Strengths and Limitations

A major strength of our study is the large, well-characterized cohort with multiple measures of cognitive and brain reserve that include state-of-the-art MRI data collection and processing techniques along with rich clinical and patient-interview data. Another area of strength is the reference standard epidemiologic measures for delirium, including daily bedside delirium assessments combined with a rigorous chart-review method, which included comprehensive review of physician and nursing notes, as well as admission, pre-operative, discharge, and outpatient visit summaries. However, several limitations of this study are important to mention. In addition, our sample was highly educated. Thus, the restricted range may have resulted in attenuated correlations of our reserve markers with delirium. Only a subset of the cohort underwent MRI, thus the sample size was reduced for these analyses. In addition, our study included patients from two hospitals in a single geographical area who were primarily white and who were healthy enough to undergo elective surgery. Thus, the generalizability of our findings will need to be confirmed in future studies.

CONCLUSION

In a well-designed and executed study of cognitive and brain reserve markers and the risk for delirium, most markers of reserve fail to predict delirium risk. The exception to this is the WTAR. The WTAR is a cognitive performance measure that is distinct from other such measures as it is believed to decline less with aging and has been used as a measure of pre-morbid cognitive ability. Put into the context of the cognitive reserve literature, our findings suggest that reserve markers for delirium, an acute confusional state, may be distinct from those for dementia, a chronic, progressive condition.

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Abbreviations

BIDMC	Beth Israel Deaconess Medical Center
BWH	Brigham and Women's Hospital
HMS	Harvard School of Public Health
HSL	Hebrew SeniorLife
MGH	Massachusetts General Hospital
PI	principal investigator
UCONN	University of Connecticut Health Center
UMASS	University of Massachusetts

Panel: Research In Context**Systematic review**

We searched PubMed for reports published in English with no date restriction, combining the search terms “cognitive” “brain” “reserve” and “delirium”. Our review resulted in hundreds of papers, but very few that were focused on delirium as an outcome. Rather, most of the reserve literature is focused on predicting cognitive decline and dementia. Two studies examined cognitive reserve markers and the risk of delirium in the context of reserve. The first focused on educational attainment and showed a decreased risk for delirium with higher education.¹⁰ The second examined regular participation in activity and a reduced risk for delirium.¹¹

Interpretation

Ours is the first study to simultaneously examine multiple markers of cognitive and brain reserve as risk factors for the incidence of postoperative delirium. We have shown that of eight markers of cognitive and brain reserve, only performance on a verbal intelligence test, the Wechsler Test of Adult Reading (WTAR), was associated with the development of delirium. Our results suggest that markers of reserve may have a different association with delirium than with dementia. One important area for future research is to examine whether cognitive and brain reserve markers are associated with functional and cognitive recovery following delirium.

Table 1

Participant characteristics. N=566

Characteristic	Total N=566	Delirium: No N=431	Delirium: Yes N=135
Women	330 (58.3)	248 (57.5)	82 (60.7)
Age (years) [mean (SD)]	76.7 (5.2)	76.5 (5.3)	77.5 (5.0)
White	523 (92.4)	401 (93.0)	122 (90.4)
Marital status			
Never married	26 (4.6)	22 (5.1)	4 (3.0)
Married or living with partner	335 (59.2)	256 (59.4)	79 (58.5)
Widowed	136 (24.0)	103 (23.9)	33 (24.4)
Divorced/Separated	69 (12.2)	50 (11.6)	19 (14.1)
Education level			
Less than high school	24 (4.2)	17 (3.9)	7 (5.2)
High school graduate	141 (24.9)	102 (23.7)	39 (28.9)
Some college	138 (24.4)	108 (25.1)	30 (22.2)
College graduate	96 (17.0)	74 (17.2)	22 (16.3)
Greater than College	167 (29.5)	130 (30.2)	37 (27.4)
English as a second language	38 (6.7)	29 (6.7)	9 (6.7)
Surgery type			
Orthopedic	460 (81.3)	354 (82.1)	106 (78.5)
Vascular	35 (6.2)	24 (5.6)	11 (8.1)
Gastrointestinal	71 (12.5)	53 (12.3)	18 (13.3)
Charlson Comorbidity, Categorized			
0	260 (45.9)	206 (47.8)	54 (40.0)
1	139 (24.6)	116 (26.9)	23 (17.0)
2 or more	167 (29.5)	109 (25.3)	58 (43.0)
Geriatric Depression Scale [mean (SD)]	2.5 (2.5)	2.3 (2.4)	3.0 (2.8)
SF12 physical composite [mean (SD)]	35.4 (10.0)	36.1 (9.9)	33.0 (9.9)
Any IADL impairment	157 (27.7)	108 (25.1)	49 (36.3)
Any ADL Impairment	42 (7.4)	30 (7.0)	12 (8.9)
IQCODE, Proxy Report [mean (SD)]	3.12 (0.24)	3.10 (0.22)	3.19 (0.29)

Note. All values are n(%) unless otherwise noted. Geriatric Depression Scale range =0–15, higher score reflect more depressive symptoms. SF-12 = Medical Outcomes Study Short Form, range = 0–100.

[†] scaled to a T score with a mean of 50 and standard deviation of 10. IQCODE is the informant questionnaire for cognitive decline in the elderly, with a range of 1–5, and values of less than 3 indicate improvement, between 3 and 3.5 indicate slight decline, between 3.5 and 4.0 indicate moderate decline, and higher scores indicate severe decline.

Table 2

Descriptive statistics for cognitive and brain reserve characteristics. (N=566)

Reserve Markers	Total N=566	Me n=236	Wome n=330
Cognitive Reserve Markers			
Education (years, n = 566)	15.0 (2.9)	15.4 (3.0)	14.6 (2.8)
Vocabulary [†] (z, n = 566)	37.7 (10.0)	37.3 (10.6)	38.0 (9.5)
Cognitive activities score (z, n = 565)	-0.03 (0.94)	-0.14 (1.00)	0.05 (0.88)
Occupational substantive complexity (z, n = 524)	0.87 (0.94)	1.31 (0.93)	0.55 (0.81)
Occupational management demand (z, n = 524)	0.26 (0.75)	0.21 (0.84)	0.29 (0.69)
Brain Reserve Markers			
Head circumference (cm, n = 552)	56.1 (2.4)	57.7 (2.2)	55.0 (1.9)
Intracranial cavity volume* (cc, n = 146)	1417 (158)	1542 (140)	1331 (105)
Activity level [‡] (kcal, n = 566)	814 (1186)	922 (1172)	736 (1192)

Note. All values are mean (SD)

[†] Vocabulary measured by Wechsler Test of Adult Reading (WTAR);

* N=146

[‡] physical activity measured by the Minnesota Leisure Time Activities Questionnaire (MLTA); kcal = kilo calories; z = z-score which is standardized to mean of 1, standard deviation of 0. cc = cubic centimeters

Table 3

Risk of post-operative delirium as a function of brain and cognitive reserve markers: bivariable association.
(N=566)

Reserve marker	Men and Women RR (95% CI)	Men RR (95% CI)	Women RR (95% CI)
Cognitive Reserve Markers			
Education (years)	0.82 (0.61, 1.10)	0.78 (0.50, 1.21)	0.87 (0.59, 1.29)
Vocabulary [†] (z)	0.64 (0.48, 0.85)	0.74 (0.48, 1.14)	0.56 (0.38, 0.81)
Cognitive activities score (z)	0.92 (0.68, 1.23)	0.95 (0.61, 1.48)	0.87 (0.59, 1.30)
Occupational substantive complexity (z)	0.94 (0.69, 1.28)	0.95 (0.57, 1.58)	1.03 (0.67, 1.59)
Occupational management demand (z)	0.88 (0.65, 1.19)	0.93 (0.59, 1.46)	0.82 (0.53, 1.24)
Brain Reserve Markers			
Head circumference (cm)	0.94 (0.70, 1.26)	0.72 (0.41, 1.26)	1.25 (0.79, 1.98)
Intracranial cavity volume* (cc)	0.93 (0.51, 1.73)	1.10 (0.26, 4.64)	1.46 (0.55, 3.93)
Activity level [‡] (kcal)	0.91 (0.67, 1.22)	0.79 (0.49, 1.28)	1.01 (0.69, 1.47)

Note: RR denotes risk ratios, and expresses the relative risk per half standard deviation difference in the predictor. CI = confidence interval;

[†] Vocabulary measured by Wechsler Test of Adult Reading (WTAR);

* N=146;

[‡] physical activity measured by the Minnesota Leisure Time Activities Questionnaire (MLTA); kcal = kilo calories; z = z-score which is standardized to mean of 1, standard deviation of 0. cc = cubic centimeters

Table 4

Multivariable adjusted risk of post-operative delirium as a function of brain and cognitive reserve markers.
(n=566)

Reserve marker	Men and Women RR (95% CI)	Men RR (95% CI)	Women RR (95% CI)
Cognitive Reserve Markers			
Education (years)	0.84 (0.63, 1.13)	0.77 (0.49, 1.22)	0.88 (0.60, 1.29)
Vocabulary [†] (z)	0.62 (0.45, 0.85)	0.73 (0.46, 1.14)	0.54 (0.34, 0.83)
Cognitive activities score (CAS, z)	0.92 (0.68, 1.23)	0.96 (0.61, 1.51)	0.89 (0.60, 1.31)
Occupational substantive complexity (z)	1.02 (0.74, 1.42)	0.92 (0.55, 1.53)	1.07 (0.70, 1.64)
Occupational management demand (z)	0.86 (0.63, 1.16)	0.96 (0.62, 1.48)	0.81 (0.54, 1.23)
Brain Reserve Markers			
Head circumference (cm)	1.02 (0.71, 1.47)	0.80 (0.44, 1.44)	1.18 (0.74, 1.88)
Intracranial cavity volume* (cc)	1.41 (0.60, 3.32)	1.20 (0.26, 5.50)	1.61 (0.56, 4.68)
Activity level [‡] (kcal)	0.97 (0.72, 1.31)	0.82 (0.50, 1.32)	1.05 (0.72, 1.54)

Note: RR denotes risk ratios, and expresses the relative risk per half standard deviation difference in the predictor. cc = cubic centimeters

[†] Vocabulary measured by Wechsler Test of Adult Reading (WTAR);

* N=146;

[‡] physical activity measured by the Minnesota Leisure Time Activities Questionnaire (MLTA); Estimates are adjusted for the effect of sex (in men and women combined), age, non-white race/ethnicity, and English as a second language.