



The Cognitive Reserve Model in the Development of Delirium: The Successful Aging After Elective Surgery Study

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Abstract

We evaluated the role of cognitive and brain reserve markers in modifying the risk of postoperative delirium associated with a pathophysiologic marker. The Successful Aging after Elective Surgery study (SAGES) enrolled 556 adults age ≥ 70 years without dementia scheduled for major surgery. Patients were assessed preoperatively and daily during hospitalization for delirium. We used C-reactive protein (CRP) as a pathophysiologic marker of inflammation, previously associated with delirium. Markers of reserve included vocabulary knowledge, education, cognitive activities, occupation type and complexity, head circumference, intracranial volume, and leisure activities. Vocabulary knowledge, cognitive activities, and education significantly modified the association of CRP and postoperative delirium ($P < .01$). However, effect sizes—when statistically significant—were small in magnitude. The strongest effect modification was observed for vocabulary knowledge: high scores were generally protective but not at high levels of CRP. Select reserve markers attenuate the risk of delirium associated with lower grade inflammatory processes, supporting the role of reserve in delirium.

Keywords

delirium, inflammation, reserve

Introduction

Delirium, an acute decline in cognition and attention, is a common disorder affecting 1 in 5 hospitalized adults aged 65 years or older and up to 50% of those undergoing major surgery.¹ Delirium in older persons is associated with poor outcomes including increased morbidity and mortality,²⁻⁴ loss of independence,⁵ and decreased cognitive recovery.^{2,6} Many risk factors for this devastating condition have been identified, including depression, medical comorbidity, cognitive impairment, and older age.¹ The role of neurocognitive reserve in delirium remains to be elucidated.

The concept of reserve is used to explain individual variability of clinical manifestations, given the presence of pathological changes, and can be applied to a number of clinical conditions. In the area of neurocognitive functioning, 2 forms of reserve have been described: brain and cognitive reserve. Brain reserve is conceptualized as a passive process deriving from the brain structure, in particular, brain size or neuronal count or synaptic density.^{7,8} Greater insult can be sustained in larger, denser, or more richly interconnected brains prior to the emergence of clinical deficit, as the remaining neural substrate is sufficient to support normal function.^{9,10} By contrast, cognitive reserve

is conceptualized as an active process that relates to cognitive networks for initiation and coordination of cognitive tasks. Cognitive reserve refers to the brain actively coping with insult through either preexisting cognitive processes in the healthy brain (reserve) or recruiting alternative processes when standard processing networks are disrupted by pathology (compensation) to successfully complete cognitive tasks.

Reserve is challenging to measure directly. Therefore, a variety of markers have been proposed as proxy indicators of

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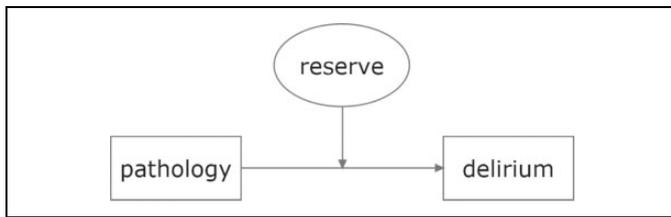


Figure 1. Conceptual framework for reserve hypothesis. This figure represents a conceptual model for the reserve hypothesis in delirium. Reserve acts by modifying the relationship between a brain pathology and risk of postoperative delirium. Merely showing a relationship between a reserve marker and risk of delirium is insufficient to support the reserve hypothesis. In our study, we use C-reactive protein as a measure of systemic inflammatory burden as the marker for brain pathology. We examine multiple markers of brain and cognitive reserve, including educational attainment, vocabulary ability, lifetime cognitive activities, occupational complexity, head circumference, intracranial volume, and physical activity.

brain and cognitive reserve. Effective markers of brain reserve are anatomic measures such as brain volume, head circumference, synaptic count, and dendritic branching.¹¹ In contrast, proxy indicators used for cognitive reserve are long-term/lifetime behavior and activity variables such as educational attainment, occupational achievement, and participation in cognitively stimulating activities.¹¹⁻¹⁴ Despite being considered as distinct entities, markers of cognitive and brain reserve are also associated with one another.

There are few studies examining the association between established markers of cognitive and brain reserve and the incidence of delirium. Jones et al reported higher risk of delirium in those with lower educational levels.¹⁵ Saczynski et al did not find a correlation between the risk of delirium and traditional cognitive and brain reserve markers of education, cognitive activities, and head circumference; but the Wechsler Test of Adult Reading (WTAR), a measure of vocabulary knowledge, was associated with delirium risk.¹⁶ It is important to note, however, that these studies do not comprise a formal test of reserve theory in delirium. Such a formal test of reserve theory in delirium would require a demonstration that the reserve marker modifies the relationship between pathology and performance¹⁷ (Figure 1).

Studying reserve in delirium poses a particular challenge since the pathophysiology of delirium remains uncertain. The neuroinflammatory model proposes that infectious, surgical, or traumatic etiologies resulting in acute peripheral inflammation induces a central nervous system inflammatory response and subsequent neuronal and synaptic dysfunction, resulting in the development of delirium. The theory suggests that delirium is a neurological manifestation of systemic disease due to the inflammatory mediators crossing the blood-brain barrier.¹⁸ Supporting this model, acute inflammatory markers, including C-reactive protein (CRP) and selected cytokines, have been demonstrated to be significantly higher in patients with delirium than in those without delirium.¹⁹

To test the reserve theory in delirium, we investigated whether cognitive and brain reserve markers modify the

relationship between pathology, represented by postoperative levels of the inflammatory marker CRP and the occurrence of delirium following elective surgery. Our hypothesis was that higher levels of reserve markers would attenuate the relationship between the inflammatory marker CRP and delirium, thereby lowering the incidence of postoperative delirium.

Methods

The Successful Aging after Elective Surgery (SAGES) study is an ongoing prospective cohort study of older adults undergoing major elective surgery. The study design and methods have been described in detail previously.²⁰ In brief, eligible participants were aged 70 years and older, English-speaking, and able to communicate verbally, scheduled to undergo elective surgery at 2 Harvard-affiliated academic medical centers with an anticipated length of stay of at least 3 days, and available for in-person follow-up interviews. Eligible surgical procedures were total hip or knee replacement, lumbar, cervical, or sacral laminectomy, lower extremity arterial bypass surgery, open abdominal aortic aneurysm repair, and open or laparoscopic colectomy. Exclusion criteria included evidence of dementia, delirium, prior hospitalization within 3 months, legal blindness, severe deafness, terminal condition, history of schizophrenia or psychosis, and history of alcohol abuse or withdrawal. A total of 566 patients were initially eligible. Six patients were excluded for possible dementia after neuropsychological testing and clinical dementia adjudication. In addition, CRP could not be obtained in 4 (1%) persons. Therefore, the sample for this analysis included 556 people. Written informed consent for study participation was obtained from all participants according to procedures approved by the institutional review boards of Beth Israel Deaconess Medical Center and Brigham and Women's Hospital, the 2 study hospitals, and Hebrew Senior-Life, the study coordinating center, all located in Boston, Massachusetts.

Baseline Assessments

Data on health and daily functioning were collected in participants' homes during a 90-minute baseline interview approximately 2 weeks prior to the index surgery. During the hospitalization, patients were assessed daily for the presence of delirium.

Delirium assessment. The Confusion Assessment Method (CAM)²¹ was used to identify delirium. The CAM is a standardized method for identification of delirium, with reported sensitivity of 94% and specificity of 89% for clinician-rated delirium.²² In SAGES, delirium was defined as a positive rating by CAM and was supplemented with a validated chart review method^{23,24} to maximize sensitivity for the detection of delirium. All interviewers underwent training and standardization, and interrater reliability was found to be high ($\kappa = 0.92$)²¹ in 71 paired observations.

Reserve markers. At the baseline interview, approximately 2 weeks prior to surgery, we collected multiple proxy measures of cognitive and brain reserve. An exception was head circumference, which was measured at the 1-month follow-up assessment to minimize patient burden at baseline. Cognitive reserve markers included educational attainment defined as number of years of formal schooling reported by participants, WTAR score, lifetime Cognitive Activities Scale (CAS), and occupational complexity and management demand. Brain reserve markers included head circumference, intracranial volume by magnetic resonance imaging (MRI), and physical energy expenditure.

Vocabulary knowledge was measured with the WTAR, which involves the participant reading aloud 50 irregularly spelled words. The number of words pronounced correctly produces the total score ranging from 0 to 50. Performance on the WTAR correlates with verbal intelligence.²⁵⁻²⁷ The WTAR is similar to other vocabulary reading tests such as the National Adult Reading Test,²⁸ a list of irregular words for correct pronunciation, and different from the Wechsler Adult Intelligence Scale Vocabulary subtest, in which respondents are asked to produce definitions of presented words.²⁹

A modified version of the CAS was used to assess lifetime cognitive activities.³⁰ The amount of time participants reported spending in the following 6 activities were noted: visiting the library, reading newspapers, reading magazines, reading books, writing letters, and playing board, or card games. Frequency of participation is asked at 4 ages (12, 18, 40 years of age, and the present time). The composite lifetime measure, representing total lifetime cognitive activity, was created by combining the responses across ages. We used the Dictionary of Occupational Titles (DOT) to make determinations of occupational complexity and management demand. We cross-referenced the patient's self-reported longest held occupation against entries in the DOT. The DOT includes ratings of job characteristics across multiple dimensions. The DOT ratings were combined into aggregate measures of intellectual complexity and management of people using a method described by Cain and Treiman.³¹

The Minnesota Leisure Time Activities Questionnaire was used to assess current physical activity,³² which includes information about time spent by participants on the following 6 activities during the preceding 2 weeks: walking for exercise, moderately strenuous household chores (such as vacuuming), moderately strenuous outdoor chores (such as raking), dancing, bowling, and stretching. Level of activity is captured in terms of estimated energy expenditure.

Intracranial cavity volume was measured in a subset of participants ($n = 146$) who underwent MRI prior to surgery. Magnetic resonance imaging was performed 1 to 4 months prior to head circumference measurement. The MRI protocol for the measurement of intracranial cavity volume included a semiautomated image segmentation method based on 3 channels: T1-weighted, T2-weighted, and T2-weighted-Fluid-Attenuated Inversion Recovery (FLAIR) images. The volume was calculated by custom Functional MRI of the Brain Software Library

(FSL; Freesurfer, Boston, Massachusetts) software. The investigators who performed the processing and analysis of imaging were blinded to clinical data. Head circumference was measured utilizing a tape measure in all participants by trained research staff who were blinded to MRI results.³³

Inflammatory Marker

Blood was collected for study purposes on the morning of the second postoperative day; this was piggybacked onto clinical blood draws when possible. During phlebotomy, mechanical disruption was minimized to prevent platelet activation or hemolysis. Blood was stored on ice in heparinized tubes until processing. During processing, low-speed centrifugation (1500 g for 15 minutes at 4°C) was used to separate plasma from cellular material, and plasma was stored at -80°C until analyzed. C-reactive protein was measured using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) kit from R&D Biosystems, with all standards and samples run in duplicate. The coefficient of variation of duplicate measures were generally $<5\%$. If any CV was $>10\%$, that plasma sample was repeated. An internal calibrator sample was present on every 96-well ELISA plate. The cross-plate variation was consistently below the range of 5% to 10% based on the internal calibrator value. Enzyme-linked immunosorbent assay plates were read using a BioTek MX (Winooski, VT) plate reader at optical density (OD) = 450. A 4-parameter logistic curve was used for final calculations.³⁴

Control and Descriptive Variables

Disability and physical functioning was assessed with scales for the assessment of Activities of Daily Living Scale (ADL), Instrumental Activities of Daily Living Scale (IADL), and the Short Form Health Survey (SF-12 physical functioning composite) at the baseline interview (see Schmitt et al³⁵ for details). Depression was assessed with the short form of the Geriatric Depression Scale (GDS-15).³⁶ Scores ranged from 0 to 15, with higher scores reflecting a greater severity of depressive symptoms. The assessment of cognitive performance included the Modified Mini-Mental State Examination (3MS).³⁷ Trained physician abstractors reviewed detailed medical records to identify age, surgery type, and comorbidities that were scored using the Charlson comorbidity index.³⁸

Statistical Analysis

We used 2 general approaches to examining the reserve hypothesis in the context of delirium. The main difference between the 2 methods was whether the proxies for brain or cognitive reserve were included in the analysis singly (reserve marker at a time) or in combination (formative latent variable model for reserve). We used Stata (version 14.2, College Station, Texas) and Mplus (version 7.2, Muthén & Muthén, Los Angeles, California) software.

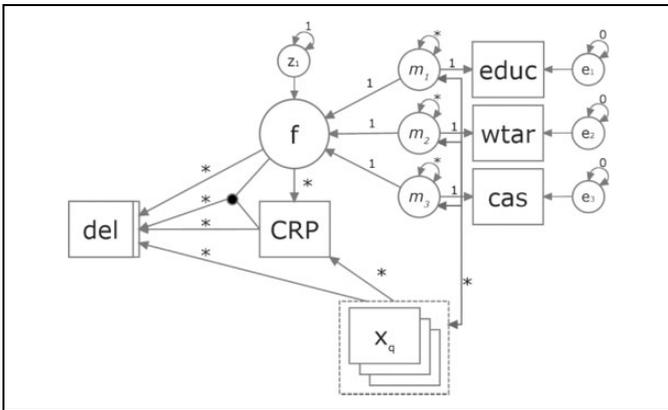


Figure 2. Formative latent variable model of reserve. This figure illustrates the formative latent variable model for reserve and effect modification model tested. The formative latent variable (f) is modeled as caused by 3 reserve markers: education (*educ*), vocabulary knowledge (*WTAR*), and cognitive activities scale (*CAS*). Covariates (x_1 – x_q) are potential causes of delirium and C-reactive protein (*CRP*). f is a potential cause of *CRP* and delirium. The dot-linking delirium, *CRP*, and f is meant to indicate the potential role for effect modification.

Reserve marker at a time. We used logistic regression models to test the significance of effect modification between brain or cognitive reserve markers and a pathology marker (*CRP*) for postoperative delirium. For assessing the presence of effect modification, we examined 5 sets of logistic regression models. In the initial model, we regressed the occurrence of delirium on the reserve marker. In the second, we regressed delirium on *CRP* level. In the third model, we included both *CRP* and the reserve marker as predictors of delirium. In the fourth model, we added the squared effects of the reserve marker and *CRP* to control for possible nonlinear relationships between the reserve marker and *CRP* in delirium risk. Finally, in the fifth model, we added the interaction of the reserve marker raw score and *CRP* level. The inference as to whether effect modification was significant was based on the magnitude of improvement in overall model R^2 comparing models 4 and 5. We also tested the significance of model improvement from model 3 to model 4. The P value was calculated for the null hypothesis that $\Delta R^2 = 0$ tested with an F test following the strategy of Carte and Russell.³⁹ We controlled for the effect of potential confounders using weighting on the basis of inverse probability weights or propensity scores.⁴⁰ Propensity scores given covariates were converted to inverse probability weights. With this procedure, we can describe our models as marginal structural models.⁴¹ Marginal structural models are used to estimate causal effects under strict assumptions.⁴² We also included the covariates as adjustment variables, thereby implementing doubly robust effect estimation.⁴³

Formative latent variable for reserve. We used a formative latent variable model (see Figure 2) to account for the potential role of multiple plausible reserve markers simultaneously. We developed a multivariate model using a formative latent

variable capturing the joint causal effect of reserve markers in the postoperative delirium risk and potentially modifying the relationship between postoperative *CRP* and delirium. The justification for using a formative latent variable model was described in detail in Jones et al.⁸ The formative latent variable allows us to appropriately represent the theoretical causal ordering of observed and latent variables. For example, if educational attainment, vocabulary knowledge, a lifetime of participation in cognitively stimulating activities, and occupational cognitive demand are associated with greater cognitive reserve, it is those experiences and exposures that contribute to or form cognitive reserve in later life, rather than some immeasurable quantity reified as reserve that causes educational attainment, vocabulary knowledge, a lifetime of cognitively demanding activity participation, and occupational cognitive demand. A reflective latent variable, as represented by a typical factor analysis or principal components approach, might misrepresent the theoretical causal ordering of the observed and latent variables (see Jones et al.⁸ for a discussion). Latent variable models were estimated using Mplus software (version 7.3, Muthén & Muthén, Los Angeles, California). It is important to note that the latent variable model does not include inverse probability weighting to adjust for confounding but does include statistical control with structural regressions of the effect of the outcome (delirium) and pathological marker (*CRP*) on potentially confounding variables. Significance of moderation effects was tested in the same nested model fashion as the reserve-indicator-at-a-time models.

Missing Data Handling

Level of educational attainment and performance on the *WTAR* were observed for all participants, as were each of the control variables listed in Table 1. However, some of the reserve markers were incompletely observed and resulted in missing data. We were unable to obtain reports on the *CAS* for 1 participant (<1%). For 42 (8%) participants (24 women and 18 men), we were unable to match a longest held occupation to the DOT and have missing occupational complexity and management data. For 13 (2%) participants, we were unable to obtain a head circumference measure. By design, we only obtained MRI data on a subsample, $n = 143$ included in this analysis. Therefore, 413 (74%) participants did not have data reflecting intracranial volume from MRI. For our reserve-marker-at-a-time models, we used the listwise complete sample in the analysis. In all versions of the formative latent variable models, we used all 556 persons and obtain parameter estimates using a maximum likelihood parameter estimation approach. This approach invokes the assumption that the reason why people were missing data on the reserve markers was not related to the value that would have been observed, had we been able to observe it, conditional on other data in the model.⁴⁴

Results

Table 1 summarizes the baseline sociodemographic and clinical characteristics of the patients by diagnosis of delirium. The

Table 1. Participant Sociodemographic and Clinical Characteristics.

Patient Characteristics, N (%) or as indicated	Delirium ^a (n = 422), N (%)		No delirium, (n = 134), N (%)	
	Age (years), M (SD)	77	(5)	78
Race/ethnicity				
White, not Hispanic	394	(93)	121	(90)
All other race and ethnicity groups	28	(7)	13	(10)
Education level				
Less than high school	17	(4)	7	(5)
High school graduate	99	(24)	38	(28)
Some college	105	(25)	30	(22)
Four years of college	71	(17)	22	(16)
More than 4 years of college	130	(31)	37	(28)
Marital status, N (%)				
Never married	22	(5)	4	(3)
Married or living with partner	250	(59)	79	(59)
Widowed	102	(24)	32	(24)
Divorced or separated	48	(11)	19	(14)
English as a second language	29	(7)	9	(7)
Surgery type				
Orthopedic	345	(82)	105	(78)
Vascular	24	(6)	11	(8)
Gastrointestinal	53	(12)	18	(13)
Charlson comorbidity index, M (SD)	1.0	(1.2)	1.3	(1.3)
Charlson comorbidity index level				
0	201	(48)	54	(40)
1	113	(27)	23	(17)
2 or higher	108	(25)	57	(43)
Geriatric Depression Scale score, M (SD)	2.3	(2.4)	3.0	(2.8)
MOS SF12 physical component summary score, M (SD)	36	(10)	33	(10)
Any IADL impairment	104	(24)	48	(36)
Any ADL impairment	29	(7)	12	(9)
WTAR raw score (0-50), M (SD)	38	(10)	36	(10)
3MS score, M (SD)	94	(5)	92	(6)
CRP, mg/L, Med (IQR)	172	[123-228]	200	[148-243]

Abbreviations: M, mean; SD, standard deviation; MOS SF12, Medical Outcomes Study Short Form 12 Item physical component score; IADL, instrumental activities of daily living; ADL, activities of daily living; WTAR, Wechsler Test of Adult Reading; 3MS, Modified Mini-Mental State Examination; CRP, C-reactive protein assessed on the second postoperative day; Med, median; IQR, interquartile interval.

^aDelirium or no delirium in hospital by interview or chart review.

mean age was 77 (standard deviation = 5) years. Most patients, 404 of 556 (81%), underwent orthopedic surgery. The sample was highly educated with 70% having more than high school education. Postoperative delirium occurred in 134 of 556 (24%) patients. The group with delirium had higher levels of comorbidity with 43% (57 of 134) having a Charlson index score of ≥ 2 and lower 3MS (both $P < .05$). Patients who developed delirium had higher scores on the GDS, higher frequency of IADL impairment, and lower level of physical functioning as captured by the SF-12 physical functioning composite (all with $P < .05$).

Table 2. Summary of Single Indicator Effect Modification Models.^a

Reserve Marker	Modification Effect Size (f^2)	Modification P Value
Single indicators		
Vocabulary ability (WTAR score)	0.030	<.001
Lifetime cognitive activities (CAS) score	0.015	.005
Educational attainment	0.014	.007
Head circumference	0.006	.07
Physical activity energy expenditure	0.006	.07
Occupational complexity	0.002	.27
Occupation management role	0.002	.28
Intracranial volume (MRI) ^b	0.003	.52

Abbreviations: CRP, C-reactive protein; CCI, Charlson comorbidity index; GDS, Geriatric Depression Scale score; MOS SF-12, Medical Outcomes Study Short Form 12; MRI, magnetic resonance imaging.

^aModification effect sizes (f^2) can be interpreted as the fraction of unexplained variance accounted for by the interaction of the reserve marker and CRP. Cohen (1988) defined the values of 0.02 as small, 0.15 as medium, and 0.35 as large. The effects in the table, therefore, suggest, trivial to small effect sizes. Models are double robust and use inverse probability weights and regression adjustment for the effects of sex, age, age², minority race or ethnicity, English as a second language, marital status, surgery type (vascular), Medical Outcomes Study Short Form 12 (MOS SF-12) Physical Component Score, IADL and ADL impairment, GDS, GDS², CCI, and CCI².

^bN = 143, all other models N = 556.

Reserve Markers in a Single Indicator Model (Reserve Marker at a Time)

The effect modification between brain and cognitive reserve markers and a pathology marker, CRP, for postoperative delirium is shown as a single indicator model in Table 2 and as a formative latent variable model in Table 3. In Table 2, modification effect size (f^2) and significance (P value) of the effect modification are shown for each single reserve marker. Modification effect sizes (f^2) can be interpreted as the percentage of unexplained variance in the development of delirium that is attributable to the effect modification of the reserve marker and CRP. Cohen⁴⁵ defined values of .02 as small, .15 as medium, and .35 as large for effect sizes. In our analysis, the effect sizes were small in magnitude for the reserve markers. The strongest effect was observed for WTAR score ($f^2 = .03$, small to medium effect). This result suggests about 3% of the unexplained variance for the development of postoperative delirium could be attributed to the interaction between the reserve marker of vocabulary ability measured by WTAR score and CRP. P values for the modification effect suggest that vocabulary ability measured by WTAR score, lifetime cognitive activities (CAS score), and educational activity are each significant effect modifiers of CRP and postoperative delirium risk (all P values $< .01$). Other reserve markers, including head circumference, physical activity expenditure, occupational complexity, occupational management demand, and intracranial volume (MRI), were not significant effect

Table 3. Summary of Formative Latent Variable Composite Effect Modification Models.^a

Reserve Marker	Modification effect size (f^2)	Modification, P Value
Latent variable composites		
WTAR score + CAS score + education	0.024	.08
WTAR score + CAS score + education + head circumference + occupational complexity + occupational management role + intracranial volume	0.023	.06
Head circumference + intracranial volume	0.002	.61

Abbreviations: ADL, Activities of Daily Living Scale; CCI, Charlson comorbidity index; GDS, Geriatric Depression Scale score; IADL, Instrumental Activities of Daily Living Scale.

^aN = 556. Modification effect sizes (f^2) can be interpreted as the fraction of unexplained variance accounted for by the interaction of the reserve marker and CRP. Cohen (1988) defined the values of 0.02 as small, 0.15 as medium, and 0.35 as large. The effects in the table, therefore, suggest small to trivial effect sizes. P values are based on the difference in model log likelihood. Models include covariate adjusted for the effects of sex, age, age², minority race, or ethnicity, English as a second language, marital status, surgery type (vascular), MOS SF-12 Physical Component Score, IADL and ADL impairment, GDS, GDS², CCI, and CCI².

modifiers of the relationship between CRP and postoperative delirium.

Figure 3 illustrates the results of the model testing for effect modification of CRP and preoperative vocabulary ability (WTAR score) in the risk of developing postoperative delirium. We show observed and model-implied curves representing the change in prevalence of delirium, given CRP for persons scoring in the low, mid, and high tertile on the WTAR. In general, risk of delirium is higher with higher CRP. This effect is stronger (the slope of the line is steeper) when the baseline (preoperative) performance on the WTAR falls in the highest or best-performing tertile, and shallowest (flatter) when preoperative WTAR performance is in the lowest (worst-performing) tertile. In the best performing WTAR tertile when the CRP level is high, little protection from delirium was demonstrated with a high baseline WTAR score.

Reserve Markers in a Formative Latent Variable Model

In Table 3, the effect sizes (f^2) and significance (P value) of effect modification are shown for summarizing the effect of multiple reserve markers in a latent variable composites model. In Table 3, we show 3 different composites, each summarizing effect of (1) selected cognitive reserve markers that were found a significant effect modifier as a single indicator (education, WTAR score, cognitive activities CAS), (2) all brain and cognitive reserve markers, and (3) selected brain reserve markers (head circumference and intracranial volume). The cognitive reserve composite effect size ($f^2 = .024$, $P = .08$) is slightly greater than the average of the 3 individual components in the

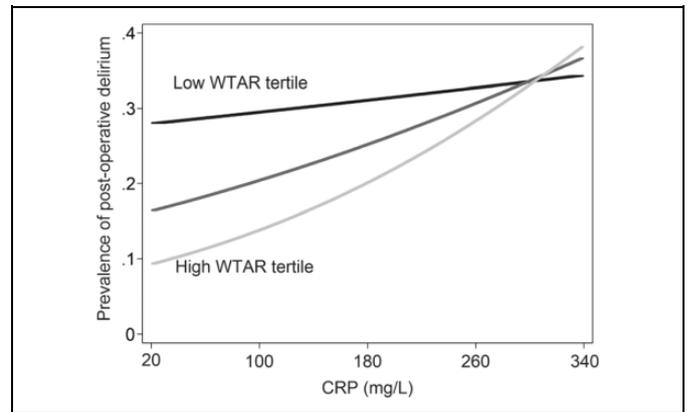


Figure 3. Effect modification of C-reactive protein (CRP) by preoperative vocabulary ability. This figure summarizes fitted estimates from a logistic regression model characterizing the risk of postoperative delirium as a linear function of CRP in 3 tertiles of performance on the Wechsler Test of Adult Reading (WTAR). Higher scores on the WTAR are better. Models are double robust and use inverse probability weights and regression adjustment for the effects of sex, age, age², minority race, or ethnicity, English as a second language, marital status, surgery type (vascular), Medical Outcomes Study (MOS) twelve item short form (SF-12) Physical Component Score, Instrumental Activities of Daily Living Scale (IADL) and Activities of Daily Living Scale (ADL) impairment, Geriatric Depression Scale score (GDS), GDS², Charlson comorbidity index (CCI), CCI².

reserve-marker-at-a-time models reported previously, making these results consistent. A composite based on all reserve indicators ($f^2 = .023$, $P = .06$) was similar, and the composite based on brain volume measures seems to be very clearly not a modifier of the effect of CRP in delirium risk ($f^2 = .002$, $P = .61$).

Discussion

In this prospective cohort study of patients who are 70 years and older without dementia undergoing major noncardiac surgery, we tested the reserve model of delirium, which hypothesizes that reserve manifests by modifying the relationship between a marker of pathology and clinical signs and symptoms (postoperative delirium). We found evidence that 3 of the 7 reserve markers—vocabulary knowledge measured by WTAR performance, lifetime cognitive activities, and educational attainment—significantly modified the relationship between a pathology marker (CRP) and postoperative delirium ($P < .01$). These findings support the reserve model in the development of postoperative delirium. We had hypothesized that greater level of cognitive reserve would attenuate the association of a neuropathological marker and postoperative delirium and confirmed this hypothesis for some markers of cognitive reserve. When CRP is high, the inflammatory insult may be too massive for WTAR to provide a benefit. At lower levels of CRP, there is a clearer gradient in delirium risk given WTAR tertile. Thus, strong (highest tertile) vocabulary ability seems to protect against the deliriogenic effects of inflammation as long as the inflammatory burden is not too high. The

protective effect of high vocabulary ability for postoperative delirium diminishes significantly at the highest levels of CRP.

Strengths of our study include a relatively large sample size, high-quality data collection, well-validated delirium assessments, a longitudinal study design with very little loss of follow-up, nearly complete capture of multiple cognitive and brain markers, and state-of-art MRI techniques and serum biomarker assays. The limitations of this study are that our cohort—the SAGES study—includes patients from a circumscribed geographic region and as a group tended to have high education. This may place some limits on the generalizability of our findings. Moreover, some reserve markers (such as MRI measures) were not collected on the entire cohort, so well-accepted approaches were utilized to handle missing data.

A further limitation is we have no information about pre-existing neuropathologic burden. It may be that markers of cognitive or brain reserve do not modify the impact of inflammation directly. It may be that other confounders or mechanisms, such as persons with lower WTAR scores or education being less likely to receive anti-inflammatory treatments, are responsible for explaining the observed effects. Such questions can be addressed in future research.

An additional limitation of our research is the use of CRP as a marker of neuropathology. Insofar as the pathophysiology of delirium is unknown, the validity of our test of reserve theory in delirium is contingent upon the validity of our use of systemic inflammation as a marker for neuroinflammation. Barnett et al⁴⁶ have pointed out that investigations of cognitive reserve in the context of neuropsychiatric disease without validated pathology marker is a limited approach. Because the neuropathological basis of delirium is poorly understood, definitive measures of pathology in delirium remain uncertain. It is possible that other or different patterns of results would have been observed if we had access to more definitive indicators of the brain pathology(-ies) that underlie postoperative delirium.

Despite the extensive investigation of the role of reserve in dementia, few studies have examined the role of reserve in delirium. Our dementia-free cohort allowed us to test the reserve hypothesis for delirium while minimizing the potential for confounding by preexisting dementia. Although the relationship between reserve and postoperative delirium has been reported previously,^{15,16,47,48} the formal test of the reserve hypothesis demonstrating effect modification between pathology and postoperative delirium has not been tested previously. The evidence for the existence of effect modification in our study may form the basis of future studies elucidating the role of reserve in delirium. Since delirium is an acute condition without a long prodromal phase, studying reserve in delirium may provide important insights into the role of reserve in late life cognitive decline.⁴⁹

Reserve theory⁷ is consistent with the theory of cognitive plasticity in cognitive aging⁵⁰ that describes plasticity as active adaptation to the environment at the neuronal level (eg, neurogenesis and neuron remodulation) and cognitive level (acquisition of new skills).⁵¹⁻⁵³ Individual differences in plasticity can manifest as cognitive or brain reserve.⁸ Neurofunctional

imaging (eg, MRI-guided neuronavigated transcranial magnetic stimulation, electroencephalography, and electromyography) for the assessment of brain dynamics and the mechanisms of cortical plasticity would provide an opportunity to test reserve hypothesis and quantify neurocognitive reserve in delirium. Future studies using plasticity as a proxy indicator of reserve are warranted. In addition, if cognitive reserve is modifiable,⁵⁴ our findings suggest a potential target for developing interventions (eg, mental training^{55,56}) to boost cognitive reserve and decrease the risk of postoperative delirium.

Appendix

Sages Study Group

(Presented in alphabetical order within activity; individuals listed may be part of multiple groups, but are listed only once under major activity, listed in parentheses).

Overall principal investigator: Sharon K. Inouye, MD, MPH (Overall PI, Administrative Core, Project 1; HSL, BIDMC, HMS).

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