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Running title: Delirium and long-term cognitive decline

Delirium Severity Post-Surgery and its Relationship with Long-Term Cognitive Decline in a Cohort of Patients without Dementia

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ABSTRACT

Background: Delirium has been associated with more rapid cognitive decline. However, it is unknown whether increased delirium severity is associated with a higher rate of long-term cognitive decline.

Objective: To evaluate delirium severity and the presence and rate of cognitive decline over 36 months following surgery.

Methods: We examined patients from the Successful Aging after Elective Surgery Study, who were age ≥70 years undergoing major elective surgery (N=560). Delirium severity was determined by the peak Confusion Assessment Method-Severity (CAM-S) score for each patient's hospitalization and grouped based on the sample distribution: scores of 0-2, 3-7, and 8-19. A neuropsychological composite, General Cognitive Performance (GCP), and proxy-reported Informant Questionnaire for Cognitive Decline (IQCODE) were used to examine cognitive outcomes following surgery at 0, 1, 2 months, and every 6 months for up to 3 years.

Results: No significant cognitive decline was observed for patients with peak CAM-S scores 0-2 (-0.17 GCP units/year, 95% confidence interval [CI] -0.35, 0.01). GCP scores decreased significantly in the group with peak CAM-S scores 3-7 (-0.30 GCP units/year, 95% CI -0.51, -0.09), and decreased almost three times faster in the highest delirium severity group (peak CAM-S scores 8-19; -0.82 GCP units/year, 95% CI -1.28, -0.37). A similar association was found for delirium severity and the proportion of patients who developed IQCODE impairment over time.

Conclusion: Patients with the highest delirium severity experienced the greatest rate of cognitive decline, which exceeds the rate previously observed for patients with dementia, on serial

neuropsychological testing administered over 3 years, with a dose-response relationship between delirium severity and long-term cognitive decline.

Key words: delirium, cognition, dementia, aged

INTRODUCTION

Delirium is a common and serious problem for hospitalized older persons, associated with prolonged hospital stays, higher hospital costs, increased functional decline, higher rates of institutionalization, and greater mortality [1, 2]. There is growing evidence that delirium is associated with a subsequent course of more rapid cognitive decline [3]. Among patients undergoing cardiac surgery, delirium is associated with a significant decline in cognitive ability, with a trajectory characterized by an initial decline and prolonged impairment [4]. Moreover, patients with Alzheimer's disease (AD) have a 3-fold increase in the rate of cognitive decline following delirium, compared with those without delirium [5, 6]. In patients without dementia at baseline, those who experienced delirium demonstrated a 4.3-fold greater decline in long-term cognitive performance than the effect of a year of cognitive aging [7]. Although this study [7] and others [8-10] demonstrate that incident delirium is associated with long-term cognitive decline, the critical next step to advance understanding of this relationship is to evaluate whether the severity of delirium is associated with the pace of long-term cognitive decline. This would prove useful for monitoring delirium clinically and for providing a quantifiable dose-response measure for intervention trials seeking to prevent or forestall the long-term cognitive decline associated with delirium.

We have previously shown that delirium severity, as measured by the Confusion Assessment Method-Severity (CAM-S) score [11], demonstrated strong predictive validity for important short-term clinical outcomes associated with delirium, including hospital length of stay, healthcare costs, death, institutionalization, and functional decline [11]. Thus, the Aim of this study was to evaluate whether the severity of delirium was associated with the presence and degree of cognitive decline up to 36 months post-surgery in patients who are free of dementia at

baseline. We hypothesized that there would be a graded relationship, with increasing severity of delirium associated with increasing degrees of long-term cognitive decline.

MATERIALS AND METHODS

Study Population

The Successful Aging after Elective Surgery (SAGES) Study is an ongoing prospective cohort study of older adults undergoing major elective non-cardiac surgery. The study design and methods have been previously described [12]. Briefly, eligible participants were age ≥70 years, English speaking, scheduled for elective surgery at one of two Harvard-affiliated academic medical centers with an anticipated length of stay ≥3 days. 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 colectomy. Exclusion criteria included evidence of dementia, delirium, hospitalization within 3 months, terminal condition, legal blindness, severe deafness, history of schizophrenia or psychosis, and history of alcohol abuse or withdrawal. A total of 566 patients were eligible and enrolled between June 18, 2010 and August 8, 2013. Six patients were subsequently excluded for possible dementia after neuropsychological testing and clinical adjudication (final sample=560; see STROBE diagram and follow-up success rates in the Appendix). This study is in compliance with guidelines on ethical principles for medical research involving human subjects. 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 two study hospitals, and Hebrew SeniorLife, the study coordinating center, all located in Boston, Massachusetts.

Study Procedures

Trained research assistants conducted a 90-minute baseline interview in participants' homes about 2 weeks prior to the index surgery [12, 13]. Following surgery, daily interviews were conducted to assess for delirium. After discharge, home-based interviews were conducted by a separate group of trained research assistants (blinded to delirium status) at 1, 2, 6, and every six months up to 36 months. Interviews included assessments of delirium, cognitive and physical function, described below. Medical records were reviewed for the index hospitalization and readmissions.

Main Study Measures

Delirium. The Confusion Assessment Method (CAM) [14] was used to identify delirium at all time points. The CAM provides a standardized method for identification of delirium, with a sensitivity of 94% (95% confidence interval (CI) 91%-97%), specificity of 89% (95% CI 85%-94%), and inter-rater reliability of 0.70-1.00 [15]. All interviewers underwent training and standardization, and inter-rater reliability was determined in 71-paired observations (weighted kappa=0.92) [14]. Delirium was defined as either a positive rating by CAM or by a validated chart review method [16, 17], used to maximize sensitivity.

Delirium Severity. The 10-item CAM-S long-form was used to measure delirium severity [11]. Each symptom was rated 0 to 2, except acute onset or fluctuation, which is rated 0 or 1 [11], yielding a summary score from 0 to 19 (19=most severe). Because individual patients had multiple CAM ratings during hospitalization, we utilized the highest CAM-S score (peak CAM-S) across all hospital days for each patient to capture the severity of the delirium episode. Peak CAM-S scores (range 0-19) were divided into three groups. Since a minimum of 3 features is required for CAM delirium, the lowest grouping included peak CAM-S scores of 0-2,

representing the group without CAM-defined delirium. While the majority of patients without delirium had a score of 0-2, some patients without delirium received higher scores based on non-specific delirium features (e.g., disorientation, memory impairment, psychomotor agitation), which can be present in conditions unrelated to delirium. Next, the group with delirium (N=134) was divided into two groups based on the median peak CAM-S score. These steps allowed delirium patients to be spread across a range of sub-groups rather than clustering only in the highest group, an approach that is preferred when the sample is imbalanced across the distribution [16]. Thus, a single, median-based cutpoint was applied to our patients with SAGES delirium (N=134) (Table 1), resulting in two delirium groups with CAM-S scores of: 1) 3-7 (N= 67), and 2) 8-19 (N= 66).These cutpoints were then applied across the entire SAGES cohort.

Cognitive Outcome Measures: General Cognitive Performance (GCP) and Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). A neuropsychological test battery, conducted at baseline and each follow-up, included the Visual Search and Attention Test (VSAT) [20], Hopkins Verbal Learning Test-Revised (HVLT-R) [21], Digit Span Forward and Backward [22], Category Fluency (animal naming) [23] Phonemic F-A-S Fluency Tasks [23], Boston Naming Test (BNT) [24], Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Digit Symbol Substitution Test, Trail-Making Tests (Trails) A and B, and intersecting pentagons from the 3MS [25]. We created a weighted composite summary measure, the GCP score following standard procedures (see [26] for a detailed description). We assessed its reliability and validity and calibrated the GCP score to a nationally representative sample of adults age ≥70 years [27] to yield a mean score=50 and standard deviation=10 [25] to improve our ability to make meaningful comparisons to other study populations. The GCP is sensitive to longitudinal change with minimal floor and ceiling effects [26, 28-30].

To account for practice effects, GCP scores were adjusted with a correction factor derived from a control sample of comparable non-surgical patients (N=119) from a primary care clinic, who were administered the identical tests on the same schedule (Appendix). Using an accepted approach [31-33], the mean performance of the control sample at each time point was used to center the observed scores in the surgical sample at matching time points. This control group was used only to correct for retest (learning) effects.

We used IQCODE [34] as a proxy-reported measure of decline in current abilities for daily cognitive tasks (range 1-5). IQCODE ≥3.2 was used to indicate impairment [34].

Death and Nursing Home Placement. We examined death or nursing home placement, obtained from patient/proxy interviews and chart review, as a composite outcome between 6-36 months follow-up. This timeframe was chosen to indicate long-term outcomes, minimizing acute effects of surgery, hospitalization, or rehabilitation.

Other Study Variables. The baseline interview assessed sex, race, ethnicity, education, marital status, living situation, 15-item Geriatric Depression Scale (GDS) [35], Modified Mini-Mental State (3MS) [25], Activities of Daily Living Scale (ADLs) [36], Instrumental Activities of Daily Living Scale (IADLs) [37], and Short Form-12 Health Survey (SF-12) [38]. Age, surgical type, and Charlson comorbidity score [39] were determined from chart review [38].

Statistical Analyses

The overall analytic approaches used general linear mixed effects regression models for the trajectories of GCP score over time. Logistic regression was used for analysis of IQCODE impairment and nursing home placement or death. For GCP, the model included control for delirium severity group, with random effects for baseline GCP level, fixed effects at the 1 and 2 month assessments to capture acute decline and recovery, and random effects for linear change

after the 2-month follow-up. The delirium severity group variable and the acute decline, recovery, and linear change were regressed on baseline GCP to capture differential effects by baseline status. Therefore, delirium severity group was treated as both an intermediate outcome (dependent upon baseline GCP and covariates) and as a predictor of model parameters capturing GCP change following baseline. Change over time was modeled using a three-part piecewise linear model to describe the longitudinal pattern, including an immediate decline following pre-operative baseline to month 1 (acute decline), recovery from month 1 to 2 following the acute decline (recovery) and long-term trajectory from month 2 to 36 months (long-term trajectory) (Appendix). All models adjusted for baseline covariates, including age, gender, non-white race, education, Charlson score, GDS score, IADL impairment, surgery type, and IQCODE. Analyses were conducted with Mplus (Version 7.4, Muthén & Muthén, Los Angeles, CA).

For IQCODE, we used a mixed effects generalized linear model with IQCODE impairment as a repeated outcome at all timepoints. A random effect for the linear slope captured variability in the change over time. For death or nursing home placement, logistic regression was used to model the probability of a participant having the composite of either outcome occurring between months 6–36. Delirium severity was entered as a series of categorical indicators. An interaction between time and delirium severity group captured the differences in linear change over time by severity group. For the death or nursing home analyses with IQCODE, the adjusted models controlled for age, gender, non-white race, education, Charlson score, and surgery type. Baseline IADL and IQCODE were not controlled due to collinearity. Analyses were conducted with Stata software (Version 14.1, Stata Corp, College Station, TX). In analyzing this longitudinal data, our approach to handling data missing at random (MAR) aligns with recommendations by the National Research Council [55].

Sensitivity analyses were completed to: (1) assess the extent to which our findings were robust to extreme assumptions regarding cognitive outcomes of persons who left the cohort early due to drop-out, death, or institutionalization (Appendix), and (2) assess the relationship between long-term cognitive decline and sum of all CAM-S scores (an alternate measure of delirium severity that combines both intensity and duration of the delirium episode) [18] (Appendix).

RESULTS

Table 1 reports baseline characteristics overall and stratified by delirium severity group. The mean age was 76.7 years, and 58% were women. Delirium occurred in 24%. Forty-four percent had a peak CAM-S score of 0-2; 44% with peak scores of 3-7; and 12% with peak scores of 8-19. Patients with the most severe delirium (peak CAM-S 8-19) were older, had greater impairment on the Charlson, and lower GCP, 3MS, and GDS (all $p<0.05$). The Spearman rank correlation coefficients indicating the correlation of each variable with the peak CAM-S score are all trivial to moderate in size.

The median duration of follow-up for this ongoing cohort was 36 months (interquartile range [IQR] 24-37). Deaths occurred in 7% of patients after a median follow-up of 19 months (IQR 12-26). An additional 27 (5%) participants withdrew from follow-up (i.e., drop-outs) after a median of 5 months (IQR 3-12). Rates of death or drop-out differed between the CAM-S groups, and increased with CAM-S severity level (8%, 12%, and 22% respectively, $p=0.01$) A total of 496 (89%) eligible participants completed all planned study visits, with a range of 1-9 visits per participant. Since this is an ongoing study, the number of visits completed per participant varies according to how long they have been enrolled in the study.

We examined cognitive performance by GCP up to 36 months post-surgery (Table 2) by delirium severity. For all groups, GCP scores declined acutely at one month, returned to baseline or above by two months, then remained stable to 3 years, except for the highest severity group

(peak CAM-S =8-19), who experienced progressive decline to 3 years from a mean GCP of 53.8 at baseline to 51.8 at 36 months (2.0 average point decline).

Figure 1 shows the effect of GCP performance over time by delirium severity group. All three groups experienced decline 1 month post-surgery and recovered to baseline or above. The lowest severity group (peak CAM-S=0-2) had no significant decline over months 2-36 (-0.17 GCP units/year, 95% CI -0.35, 0.01). For the group with peak CAM-S=3-7, there was a significant decrease in GCP score (-0.30 GCP units/year, 95% CI -0.51, -0.09). The magnitude of this change was about a third of the change observed in the highest severity grouping, peak CAM-S=8-19 (-0.82 GCP units/year, 95% CI -1.28, -0.37). These results suggest a graded association of delirium severity and the rate of cognitive decline. Compared to patients in the lowest severity group, the most severe delirium group demonstrated a 4.8-fold accelerated decline (-0.82/-0.17). A linear trend test for differences in slope across severity group was significant (p=0.009; Appendix). Moreover, the significant linear relationship between delirium severity and GCP slope remained when peak CAM-S was considered as a continuous measure (see Appendix).

Table 3 shows the prevalence of proxy-rated IQCODE impairment by delirium severity group over time. Sample sizes differ between Table 3 and Table 2 because we could not always locate or interview a suitable proxy informant for every surgical patient. For those in the low severity group (peak CAM-S=0-2), there was no significant change in IQCODE impairment over time. For the other severity groups, the prevalence of IQCODE impairment increased significantly over time, with greater prevalence of IQCODE impairment with increasing delirium severity (odds ratio [OR] 1.2 (95% CI 0.99, 1.5). Similar to the results for GCP, the association with IQCODE impairment suggests a dose response (Figure 2 shows adjusted models), with the

strongest effect in the most severe group; however, the linear trend did not achieve statistical significance (p=0.07).

In total, 103 participants experienced either death or nursing home placement between 6-36 months. At baseline, these participants were older, fewer were married, had higher Charlson comorbidity scores, more depressive symptoms, more ADL and IADL impairment, lower GCP scores (see Appendix for detailed study sample description). They also had higher peak CAM-S scores during hospitalization relative to the 457 participants who did not die and were not placed in a nursing home. We observed increasing incidence across severity groups (15%, 20%, 28% for peak CAM-S 0-2, 3-7, and 8-19, respectively) and a trend which approached but did not achieve statistical significance (p=0.06) (see Appendix for additional details).

DISCUSSION

In this large prospective cohort of older persons without baseline dementia undergoing elective surgery, patients experiencing higher delirium severity had greater rates of long-term cognitive decline by serial neuropsychological testing (GCP). This finding was supported by analyses examining the proxy IQCODE and risk of death or nursing home placement. These findings suggest a dose-response effect where the risk of poor long-term outcomes increases progressively across severity groups. The risk for greater cognitive decline was substantial and statistically significant in the highest delirium severity grouping.

The findings utilizing the composite GCP measure demonstrated a 4.8-fold more rapid decline between the highest and lowest severity groups. The per-year change in GCP in the long-term (months 2-36) is about -0.17 GCP units/year, or -0.02 (-0.17/7.30) standard deviation (SD) units/year in the lowest delirium severity group (peak CAM-S 0-2). Prior studies report declines with cognitive aging in the absence of dementia to range between -0.01 and -0.04 SD units/year [40-42]. Thus, patients with low delirium severity had a rate of cognitive decline (-0.02 SD per

year) comparable to previous studies for cognitively normal persons. By comparison, SAGES patients with moderate severity declined by -0.30 GCP units/year (-0.04 SD units) and those with the most severe delirium declined by -0.82 GCP units/year (-0.11 SD units). Our findings align with prior work in patients undergoing coronary-artery bypass grafting in which the pattern of cognitive decline is predicted by early postoperative cognitive decline (POCD) [42], underscoring similarities in the long-term trajectories of patients with POCD and severe postoperative delirium.

While the substantial short-term adverse outcomes of delirium are well-recognized, our results hold important implications for the longer-term prognosis of delirium. This represents a paradigm shift in the way delirium is currently viewed. Delirium may not be transient and reversible with only acute complications; rather, more severe delirium cases may be associated with long-term and potentially permanent cognitive decline. Furthermore, this work suggests the need to target patients with high delirium severity for strategies to prevent progressive cognitive decline, and potentially increased risk for dementia.

While prior work has established the association of incident delirium with long-term cognitive decline [7-10], these findings are novel in demonstrating that delirium severity is directly associated with long-term cognitive decline in an exposure-response fashion. We acknowledge that causal associations cannot be determined from this observational study. However, the observed exposure-response relationship is a critical first step in demonstrating a direct association between delirium severity and long-term cognitive decline, and is an important criterion used in causal inference for epidemiologic studies [43]. The novelty of our study also includes both the use of a comprehensive measure of delirium severity (peak CAM-S scores, reflecting the height of delirium intensity) and in the serial measurement of cognitive function over a 3-year period following surgery. We chose peak CAM-S as our outcome measure to

reflect maximal intensity of delirium; however, other measures might have been chosen (e.g., sum CAM-S [18], see Appendix). *Future studies should examine other severity measures, including the Memorial Delirium Assessment Scale, Delirium Rating Scale, and Delirium Index have been associated with increased mortality [44, 45], institutionalization [46, 47], and length of stay [48]. Delirium duration has also been associated with increased death rates, increased ventilator-dependent days, and intensive care unit stay [49-52].* The current study is innovative in enabling examination of exposure-response relationships by examining outcomes across multiple levels of severity. Other strengths include the use of a large cohort with thorough data collection, careful characterization of preoperative cognition, repeated neuropsychological testing over time, standardized delirium assessments, and extended post-surgical follow-up. Additionally, exclusion of mild dementia at baseline facilitated examination of the effects of delirium severity free of this potentially confounding influence. This presented a unique opportunity to study cognitive impairment following delirium occurring largely in non-cognitively impaired older patients. Finally, the careful correction for learning effects over time represents another important advance.

Several caveats about this study deserve mention. Although we controlled for learning effects, patients recovered back to or above baseline levels at 2 months, suggesting that: 1) longer-term follow-up is critical to understanding the trajectory of cognitive recovery post-surgery, and 2) this control for learning effects was either incomplete or that patients had depressed cognitive levels at baseline, which may have been due to preadmission pain medications such as narcotics. We encountered missing data due to deaths and drop-outs, and addressed these in sensitivity analyses to assure the robustness of our conclusions (Appendix). Despite using reasonable and established methods, participants who developed delirium may have been on a downward cognitive trajectory prior to surgery, and we could not completely rule

out preclinical (asymptomatic) dementia, or clinically presymptomatic, but AD biomarker positive dementia (as defined by stage 1 of the 2011 NIA criteria for AD), at baseline. Moreover, the observation of a lower GCP in this group was anticipated, given that baseline cognitive impairment has been long recognized as an important risk factor for delirium. Perhaps the more intriguing observation is that participants on average improved back to baseline at 2 months following delirium, and successively declined from 2 to 36 months suggesting a degree of initial resiliency that would not be expected for those with underlying dementia. Similarly, we acknowledge that inclusion of the pending follow-up visits may influence our current findings. In general, we do not anticipate a substantial change in our study conclusions upon incorporating the remaining visits since GCP scores observed for the two lowest delirium severity groups (peak CAM-S 0-2 and 3-7) are relatively stable from around month 24 and onwards, and the GCP scores appear to continue declining in the highest delirium severity group (peak CAM-S 8-19). An additional caveat includes the fact that patients with delirium had lower GCP scores at baseline than those without delirium, although both groups were above the U.S. population mean GCP score=50. It may be that patients who were undergoing cognitive decline prior to surgery may represent individuals at greatest risk for experiencing more severe delirium; however, with only one preoperative cognitive assessment, we were unable to directly test this possibility. We attempted to investigate this possibility by matching patients in the highest severity group (peak CAM-S 8-19) with patients in the other two severity groups on preoperative GCP (see Appendix for Methods and detailed Results), and found the pace of decline was faster in the highest severity group (peak CAM-S 8-19; slope -0.09 SD/year) than in the peak CAM-S 3-7 group (slope -0.04 SD/year), which was in turn faster than the peak CAM-S 0-2 group (slope -0.02 SD/year). We acknowledge that the study population represents a highly educated sample with relatively low racial diversity from a single city; however, the diversity characteristics of our

sample (92% white) are representative of the Boston area (2008-2012 census data) [53]. It is important to note that our choice of a dementia-free, relatively robust elective surgical population may have influenced our findings. Patients with dementia might be more vulnerable to decline after milder cases of delirium [5]. Finally, our use of the peak CAM-S does not discern hypoactive from hyperactive delirium, which may have differing prognoses.

While delirium has previously been considered a transient condition of only short-term significance, our results suggest that for patients with moderate to severe delirium, the declines in cognition may be both substantial and long-term, and most notably exceeds the rate of decline observed for patients with dementia. Although it remains critical to prevent and treat all delirium to minimize well-documented short-term adverse outcomes, our results suggest the need for more targeted strategies (e.g., cognitive rehabilitation, as used for patients with brain injuries [54]) in patients with higher delirium severity to prevent long-term cognitive decline. Our findings underscore the need to heighten efforts to better understand the risk factors and pathophysiology of delirium of moderate to high severity, and to better target prevention and management strategies to mitigate the long-term and potentially permanent adverse sequelae associated with this common, morbid, and costly geriatric syndrome.

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Conflict of Interest Disclosures

The authors state no conflicts of interest to report.

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

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

Table 1. Description of Study Sample

Characteristic	Full Sample (N = 560)	Peak CAM-S score 0 – 2 (N = 244)	3 – 7 (N = 248)	8-19 (N = 68)	Rank Correlation[c]
Age - mean (SD)	76.7 (5.2)	76.0 (4.7)	77.2 (5.7)	77.0 (4.6)	0.09
Female – n (%)	326 (58)	147 (60)	141 (57)	38 (56)	-0.04
Nonwhite – n (%)	42 (8)	12 (5)	25 (10)	5 (7)	0.07
Education – mean years (SD)	15.0 (2.9)	15.6 (2.8)	14.4 (2.9)	14.6 (3.0)	-0.17
Married – n (%)	332 (59)	142 (58)	151 (61)	39 (57)	0.01
Lives Alone – n (%)	167 (30)	79 (32)	66 (27)	22 (32)	-0.03
Charlson score - n (%)					0.12
0	257 (46)	126 (52)	102 (41)	29 (43)	
1	139 (25)	62 (25)	66 (27)	11 (16)	
2+	164 (29)	56 (23)	80 (32)	28 (41)	
GDS15 score - n (%)					0.18
0 - 5	489 (88)	225 (93)	214 (86)	50 (74)	
6 - 15	69 (12)	17 (7)	34 (14)	18 (26)	
GCP score - mean (SD)	57.6 (7.3)	60.5 (6.7)	55.8 (7.3)	53.8 (5.6)	-0.36
3MS score - n (%)					0.13
85-100	523 (93)	237 (97)	225 (91)	61 (90)	
71-84	37 (7)	7 (3)	23 (9)	7 (10)	
Proxy IQCODE (baseline) - n (%)					0.104
Not Impaired	430 (78)	198 (83)	183 (76)	49 (72)	
Impaired	118 (22)	40 (17)	59 (24)	19 (28)	
ADL impairment – n (%)	42 (8)	10 (4)	24 (10)	8 (12)	0.12
IADL impairment – n (%)	152 (27)	51 (21)	77 (31)	24 (35)	0.13
Surgery type - n (%)					-0.03
Orthopedic	454 (81)	196 (80)	201 (81)	57 (84)	
Vascular	35 (6)	11 (5)	18 (7)	6 (9)	
General	71 (13)	37 (15)	29 (12)	5 (7)	
Delirium[b] - n (%)					
None	426 (76)	243 (100)	181 (73)	2 (3)	
Delirium	134 (24)	1[a] (0)	67 (27)	66 (97)	

[a]The patient, with a peak CAM-S score of 2, had chart delirium

[b] Delirium status was determined with daily interviews rating the Confusion Assessment Method, augmented by a validated chart review

[c]Spearman rank correlation coefficient indicates the correlation of each variable with the peak CAM-S score

ADL = Activities of Daily Living, impairment indicated by human assistance to complete any activity

CAM-S = Confusion Assessment Method-Severity

GCP = General Cognitive Performance, composite measure of neuropsychological measures reflecting cognitive domains vulnerable to delirium, see text for details

GDS15= Geriatric Depression Scale 15 point version, range (0-15), higher is worse; a score 6 and above is considered impaired

IADL = Instrumental Activities of Daily Living, impairment indicated by human assistance to complete any activity

IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly, score >3.2 indicates cognitive impairment

3MS = Modified Mini-Mental State Exam, range (0-100), lower score indicates impairment; a score ≤84 is considered impaired

SAGES = Successful Aging after Elective Surgery Study

SD= standard deviation.

The Charlson comorbidity score ranged from 0-35, with higher scores indicating more comorbidity.

Table 2: Corrected GCP Scores over Time

Visit	Full Sample		Peak CAM-S score 0 – 2		3 – 7		8 – 19	
month	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
0	560	57.6 (7.3)	244	60.5 (6.7)	248	55.8 (7.3)	68	53.8 (5.6)
1	548	56.8 (7.9)	243	60.0 (6.9)	242	55.0 (7.9)	63	51.4 (5.8)
2	536	58.0 (7.9)	238	60.9 (7.1)	237	56.2 (8.1)	61	53.8 (5.3)
6	528	58.2 (7.5)	237	61.0 (6.5)	230	56.4 (7.9)	61	54.2 (6.1)
12	511	58.4 (7.6)	227	61.2 (7.0)	224	56.8 (7.6)	60	53.9 (5.4)
18	499	58.3 (8.0)	219	61.5 (6.9)	222	56.5 (7.9)	58	52.7 (7.2)
24	474	58.2 (8.0)	213	61.2 (6.8)	211	56.4 (8.1)	50	52.4 (7.2)
30	325	57.5 (8.2)	132	60.7 (7.5)	152	56.1 (7.9)	41	52.4 (7.3)
36	312	57.1 (8.4)	123	60.6 (7.4)	141	55.8 (8.2)	48	51.8 (7.7)

CAM-S = Confusion Assessment Method-Severity
GCP = General Cognitive Performance, composite measure of neuropsychological measures reflecting cognitive domains vulnerable to delirium, see text for details
Notes: All postoperative GCP values corrected for practice effects (see text for details). The number of participants completing each the interview/the number of participants eligible for the interview for each time point follows with amount of attrition from the prior time point in brackets. Baseline: 560/560 [0]; Month 1: 548/552 [8]; Month 2: 536/546 [6]; Month 6: 528/539 [7]; Month 12: 511/527 [8]; Month 18: 499/516 [8]; Month 24: 474/489 [13]; Month 30: 325/342 [6]; Month 36: 312/316 [1]

Table 3: Empirically Observed Prevalence of Proxy IQCODE Impairment over Time

			Peak CAM-S score					
Visit	Full Sample		0 – 2		3 – 7		8 – 19	
month	N	n (%)	N	n (%)	N	n (%)	N	n (%)
0	548	118 (22)	238	40 (17)	242	59 (24)	68	19 (28)
6	514	135 (26)	229	46 (20)	226	67 (30)	59	22 (37)
12	487	130 (27)	217	49 (23)	218	60 (28)	52	21 (40)
18	480	142 (30)	208	49 (24)	217	66 (30)	55	27 (49)
24	452	125 (28)	202	46 (23)	205	61 (30)	45	18 (40)
30	314	101 (32)	127	28 (22)	145	54 (37)	42	19 (45)
36	287	94 (33)	118	25 (21)	126	48 (38)	43	21 (49)

CAM-S = Confusion Assessment Method-Severity
IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly
Since the IQCODE is proxy-rated, the sample sizes in this table reflect the availability of proxy-informants over time; 12 patients did not have any proxies available at baseline, yielding a total proxy sample of N=548
N=total possible sample, n=number with proxy IQCODE impairment

Figure 1

Title: Trajectory of General Cognitive Performance by Estimated Peak Confusion Assessment Method-Severity (CAM-S) Score

Legend: Figure 1 demonstrates the relationship between estimated general cognitive performance (GCP) and time following surgery (months) by delirium severity group. The model is adjusted for baseline GCP, age, gender, non-white race, education, Charlson score, Geriatric Depression Scale score, instrumental Activities of Daily Living (IADL) impairment, surgery type, and proxy Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) impairment. For each group, we plot the model-implied trajectory and a solid gray reference line at the baseline value. . The amount of punctuation (acute decline at one month), recovery (up to two months), and long-term decline (two to 36 months) is shown by each CAM-S severity group, 0-2 (dashed black line), 3-7 (dot-dashed black line) and 8-19 (solid gray line). In the acute (punctuation) phase, all groups decline with the most severe group declining the most. This is followed by recovery of cognitive performance, with the less severe groups recovering (at two months) past their baseline (0 months) GCP score, and those in the most severe group showing an incomplete return to baseline. Over long-term follow-up, the less severe groups gradually decline in GCP performance, whereas the most severe group demonstrates a faster pace of decline.
Figure 1

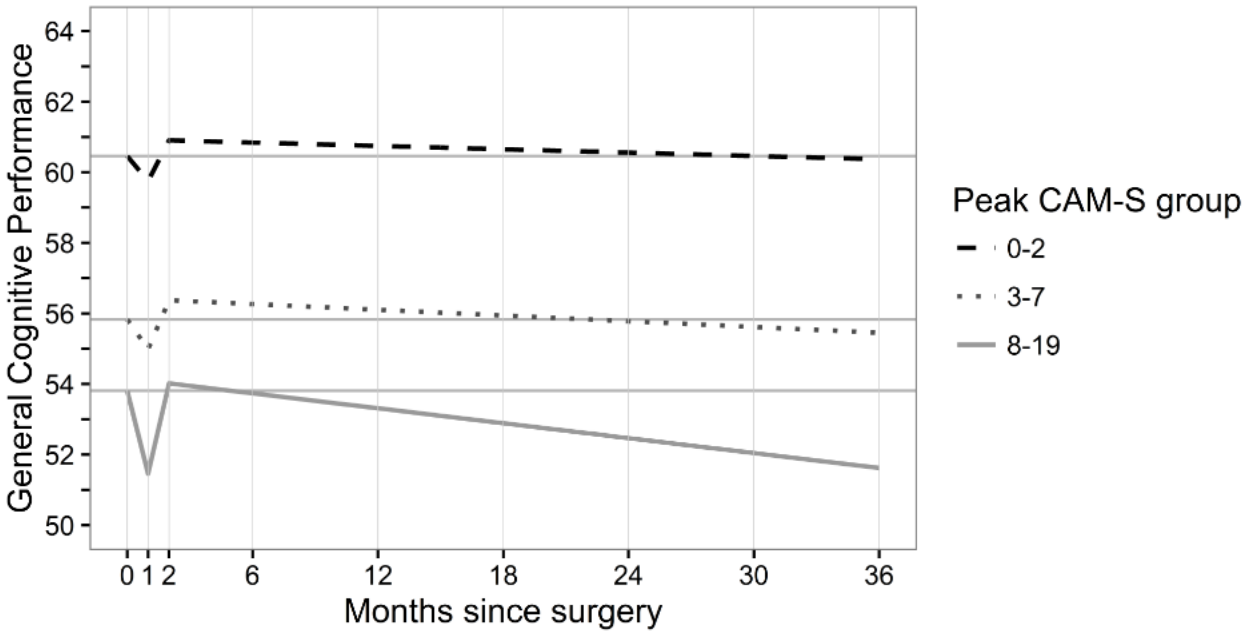
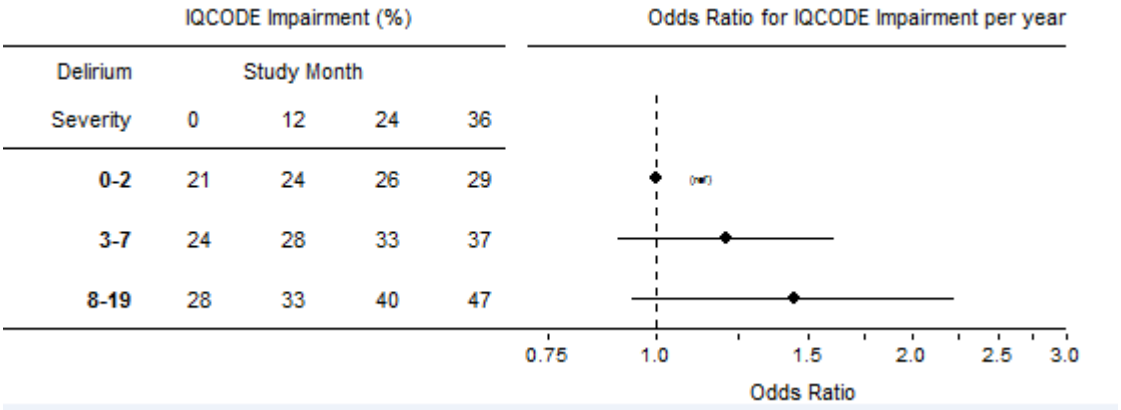


Figure 2

Title: Predicted Prevalence of IQCODE impairment by delirium severity group and study month

Legend: Figure 2 demonstrates the relationship between the prevalence of proxy Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) impairment (score ≥ 3.2) over time (study month) following surgery, calculated using a mixed effects generalized linear model. The odds ratios (OR) are computed from models that controlled for age, gender, non-white race, education, Charlson score, Geriatric Depression Scale score, and surgery type; and thus differ from the ORs derived from the numbers presented in Table 3. Model-implied (or expected) proportions with IQCODE impairment given mean values on covariates are presented in the table. Odds ratios (and 95% confidence bands) illustrate the size and precision of estimates of the delirium severity group by time (in years following surgery) interaction effects. Over time, all groups have increasing probability of being classified as impaired on the IQCODE (p=.05). The per-year odds of IQCODE ≥3.2 for this group is about two times greater than that observed for the lowest delirium severity group.



Vasunilashorn et al., Delirium Severity Post-Surgery and its Relationship with Long-term Cognitive Decline in a Cohort of Patients without Dementia

Appendix

Table of Contents

Overview

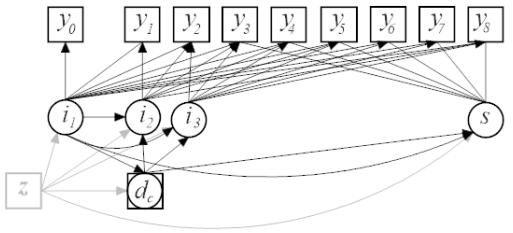
The information in this Supplemental Appendix is provided to: (1) describe our approach for minimizing learning and practice (retest) effects; (2) describe our statistical modeling approach to test our hypotheses regarding the association of delirium and cognitive change following surgery with detailed model results; (3) assess the limits of our inferences in the presence of differing assumptions about missing data [sensitivity analysis 1]; (4) assess the relationship between long-term cognitive decline and an alternate measure of delirium severity, sum of CAM-S scores [sensitivity analysis 2]; (5) describe our analytic sample and follow-up success rates; (6) describe the study sample by death or nursing home placement status; (6) illustrate the association between peak CAM-S as a continuous variable and GCP slope; and (7) consideration of a matched analysis

Consideration of Practice and Retest Effects

Practice and retest effects are pervasive and challenging in studies with repeated measures of cognition over time. No clear consensus exists for the optimal handling of practice (and retest) effects in statistical analyses.[1] The technique we uses was first used in the International Study on Postoperative Cognitive Dysfunction (ISPOCD), and as implemented here is quite similar to the modeling of boost retest effects, described previously,[2] which lends further support for its application here. Our approach involves assessing a comparison sample (n = 119) of otherwise comparable persons (patients in a primary care clinic at one of our study sites) with the same tests and on the same schedule of assessment. The mean performance of this sample at each time point is used to center the observed scores seen in our surgical sample at matching time points. The 6 month assessment in our comparison sample is used as the centering point for all subsequent observations in our surgical sample. The 6 month cutoff was utilized, since most studies consider that practice effects have leveled off by this time. This approach relies upon the assumption that differences in the mean across the repeat performances in the comparison sample represent the mean practice or retest effect free of normative cognitive change. We considered this assumption reasonable given the very short time interval between assessments in a relatively healthy comparison group.

Statistical Model

Our statistical modeling approach involved the use of generalized linear mixed effects models, or random effects models, that account for: (1) the dependence of pre-operative cognitive performance ($\boldsymbol{y_0}$) on preoperative baseline and background variables ($\boldsymbol{z}$), (2) the dependence of the severity level of delirium ($\boldsymbol{d_c}$) on background variables ($\boldsymbol{z}$) and pre-operative level of cognitive functioning ($\boldsymbol{y_0}$), and (3) the dependence of follow-up cognitive performance ($\boldsymbol{y_t}$) on baseline (preoperative) cognitive performance (y0), delirium (d_c) and background variables (z). A graph summarizing the temporal ordering (left to right) and dependence relationships is shown in Figure S1.



y(0)-y(8) = repeated cognitive performance assessment (0 = baseline, 8 = 36M)
i(1) = pre-operative baseline
i(2) = immediate post-operative decline (punctuation)
i(3) = immediate post-operative recovery
s = long-term slope (months 2-36)
z = background vulnerability factors, confounders
d(c) = delirium severity group (*knownclass mixture*)

Figure S1. A path diagram illustrating the estimated model. Variables include background and pre-operative baseline variables considered as potential confounders ($\boldsymbol{z}$), baseline pre-operative cognitive performance (General Cognitive Performance, GCP; $\boldsymbol{y_0}$), the occurrence and level of delirium severity following surgery ($\boldsymbol{d_c}$), and follow-up cognitive performance (through the scheduled 36 month follow-up; $\boldsymbol{y_1}$- $\boldsymbol{y_9}$). Change in GCP ($\boldsymbol{y}$) is modeled with a piecewise linear latent growth curve model, where the "pieces" refer to "boost" effects at one and two months capturing initial decline and recovery following surgery (which occurs between y_0 and y_1). Latent variables (enclosed in circles) capture baseline (i_1), and initial decline, recovery, and long-term slope (i_2, i_3, s), as well as a categorical known class latent mixture variable ($\boldsymbol{d_c}$) that is identical to observed $\boldsymbol{d_c}$, the post-operative delirium severity group. We regress d_c on i with multinomial logistic regression, which captures the dependency of delirium and its severity on baseline cognitive function. We also regress baseline cognition and delirium severity group, as well as the three slope pieces on background and potentially confounding variables. Finally, we also regress the immediate decline, recovery, and long-term slope effects on baseline.

We are primarily interested in the direct effect of delirium severity group ($\boldsymbol{d_c}$) on follow-up GCP, General Cognitive Performance ($\boldsymbol{y_t}$). The estimated model is one that includes linear regression, multinomial logistic regression, and piecewise linear mixed effect regression models, all estimated simultaneously in a multiple group or known class mixture model. Baseline cognitive performance regressed on background variables are handled with linear regression. The regression of postoperative delirium severity group on preoperative cognition and background variables is handled with logistic regression, as the outcome membership in severity group ($\boldsymbol{d_c}$) is a set of nominal outcomes (0 = in lowest severity class, 1 = in severity class $\boldsymbol{c}$). The piecewise linear mixed effect model for follow-up cognition includes two (fixed) pieces for performance at 1 and 2 months, parameter estimates for which describe the punctuation and recovery effects, respectively, following surgery and/or delirium. Change over time from scheduled study month 2 through 36 was modeled with a mixed effect model, with change over time included as a linear random effect. We considered a quadratic effect to model follow-up time but observed only a small improvement to information criteria (difference in Bayesian information criterion <2, considered an insignificant effect[4]), and the difference in the Akaike information was criteria <1%. Thus, we considered the gain in explanatory power insufficient to justify the added complexity.

Parameter estimates were obtained with Mplus software version 7.4 (Muthén & Muthén, Los Angeles, CA) using robust maximum likelihood (ML) parameter estimation. The mixed effect model included random effects for preoperative baseline and linear slope, meaning that

these parameters were modeled with variances and covariances. Piecewise effects for punctuation and retest were modeled as fixed effects. The modeling approach does not make explicit reference to the covariance structure of the repeatedly observed outcome (cognitive performance, $\boldsymbol{y_0}$, $\boldsymbol{y_t}$) as in other mixed effect modeling approaches, but can be conceptualized as *unstructured* and accounted for by the variances in baseline, linear slope, and also by background variables and delirium severity group ($\boldsymbol{z}$, $\boldsymbol{d_c}$). ML parameter estimation makes use of all available information, and the parameter estimates reflect the most likely parameter estimates for persons with incomplete data over the follow-up period. We had missing data for 2 participants for one background variable (Geriatric Depression Scale, GDS score). The other background variables ($\boldsymbol{z}$, age, gender, non-white race, education, Charlson score, instrumental activities of daily living [IADL], and surgery type) or postoperative delirium ($\boldsymbol{d_c}$) did not have missing data. Bayesian estimation methods were used to impute values for the missing data.

Detailed Model Results

Below, we provide detailed model results, expanded beyond what is displayed in the main manuscript. We omit the effects of covariates here, since all covariates were mean-centered and therefore do not influence the computation of expected values. General cognitive performance (GCP) is centered at the overall sample mean in the model, and estimates in all tables are transformed to reflect the full scale of the GCP.

Table S1. Detailed Model Results Reporting the Association between Delirium Severity (Peak Confusion Assessment Method-Severity score) and General Cognitive Performance (N=560)

Model Parameter	Estimate	95% CI	P-value
Effect of baseline GCP in …			
GCP punctuation	0.53	(0.11, 0.93)	.013
GCP recovery	-0.11	(-0.47, 0.26)	.565
GCP slope, Months 2 – 36 (per year)	0.18	(0.01, 0.37)	.063
Estimated means for latent growth model effects by Delirium (peak CAM-S) severity group			
CAM-S Peak 0-2			
GCP Punctuation	-0.65	(-1.06, -0.23)	.002
GCP Recovery	1.15	(0.79, 1.50)	<.001
GCP Slope, Months 2 - 36 (per year)	-0.17	(-0.35, 0.01)	.073
CAM-S Peak 3-7			
GCP Punctuation	-0.78	(-1.19, -0.28)	<.001
GCP Recovery	1.37	(0.99, 1.76)	<.001
GCP Slope, Months 2 - 36 (per year)	-0.30	(-0.51, -0.09)	.005
CAM-S Peak 8-19			
GCP Punctuation	-2.28	(-3.25, -1.31)	<.001
GCP Recovery	2.55	(1.78, 3.31)	<.001
GCP Slope, Months 2 - 36 (per year)	-0.82	(-1.28, -0.37)	<.001

SAGES = Successful Aging after Elective Surgery, GCP = general cognitive performance, CAM-S = Confusion Assessment Method-Severity score, CI = confidence interval

Sensitivity Analysis 1: **Assessing Robustness of Findings to Extreme Assumptions of Missing Data Due to Drop-Out, Death, or Institutionalization**

There was incomplete follow-up data through the 36 month follow-up visit. Most of this is due to the rolling enrollment of the study design. However, there were some cases of death and dropout.

Table S2. Peak Confusion Assessment Method-Severity scores by study status

	CAM-S Peak Scores							
	Overall		**0-2**		**3-7**		**8-19**	
Study status	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
In study	496	(89)	225	(92)	218	(88)	53	(78)
Death/dropout	64	(11)	19	(8)	30	(12)	15	(22)
Total	560		244		248		68	

CAM-S = Confusion Assessment Method-Severity

The difference in proportion across all delirium severity groups is significant (p = .004). Our main analysis reported in the manuscript summarizes maximum likelihood parameter estimates, which are theoretically unbiased under the assumption that the missing data mechanism is missing at random (MAR). This means that the reason why individuals are missing is not due to the value on the outcome (GCP) that would have been observed, had it been observed (conditional on the effect of observed data). Most of the missing data can be safely assumed to be missing completely at random (MCAR) because it is due to the date of enrollment and no other factor. However, it is possible that for some of the people who dropped out due to death or institutionalization the MAR assumption is overly restrictive. To address this, we performed a set of sensitivity analyses to examine the range of possible effects of a non-ignorable missing data pattern for those participants for whom we are assuming MAR holds. In both sensitivity analyses, we impute values for missing data. We do so under two conditions that represent extreme conditions of possible missing data mechanisms that would be most beneficial and most harmful to our hypothesis that delirium severity influences long-term cognitive decline. Both analyses follow a similar framework. Factor scores for each participant's baseline, decline, recovery, and long-term slope were estimated from the adjusted model shown in the main manuscript. The long-term slope estimates were modified by either adding or subtracting an amount proportional to the standard deviation of the long-term slopes. The original baseline, decline, recovery, and the modified long-term slope factor scores were then used to calculate the missing outcomes for subjects that died or dropped out.

Best case scenario: This scenario provides conditions that are most favorable to our hypotheses. The long-term slope factor scores were modified so that the delirium severity groups would diverge. The participants in the peak Confusion Assessment Method-Severity (CAM-S) 0-2 group had 1 standard deviation (SD) added to their score. The participants in the CAM-S 3-7 group had 0.5 SD added to their score. The participants in the CAM-S 8-19 group had 0.5 SD subtracted from their score.

Worst case scenario: This scenario provides conditions that are least favorable to our hypotheses. The long-term slope factor scores were modified so that the delirium severity

groups would converge. The participants in the CAM-S 0-2 group had 1 SD subtracted from their score. The participants in the CAM-S 3-7 group had 0.5 SD subtracted from their score. The participants in the CAM-S 8-19 group had 0.5 SD added their score.

Table S3. Detailed Model Results Reporting the Association between Delirium Severity (peak Confusion Assessment Method-Severity score) and General Cognitive Performance, Given Extreme Assumptions of Missing Data

	Baseline		Decline		Recovery		Long-term slope	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Original model (for reference)								
Baseline GCP			0.53	(0.11, 0.93)	-0.11	(-0.47, 0.26)	0.18	(-0.01, 0.37)
CAM-S Peak:								
0-2	57.61	(57.12, 58.09)	-0.65	(-1.06, -0.23)	1.15	(0.79, 1.50)	-0.17	(-0.35, 0.01)
3-7	57.61	(57.12, 58.09)	-0.78	(-1.20, -0.35)	1.37	(0.99, 1.76)	-0.30	(-0.51, -0.09)
8-19	57.61	(57.12, 58.09)	-2.28	(-3.25, -1.31)	2.55	(1.78, 3.31)	-0.82	(-1.28, -0.37)
Sensitivity analysis: best case scenario								
Baseline GCP			0.50	(0.10, 0.88)	-0.13	(-0.47, 0.21)	0.20	(0.03, 0.37)
CAM-S Peak:								
0-2	57.61	(57.12, 58.09)	-0.64	(-1.04, -0.24)	1.12	(0.77, 1.47)	-0.09	(-0.26, 0.07)
3-7	57.61	(57.12, 58.09)	-0.80	(-1.22, -0.39)	1.35	(0.98, 1.72)	-0.26	(-0.44, -0.06)
8-19	57.61	(57.12, 58.09)	-2.30	(-3.24, -1.36)	2.57	(1.86, 3.28)	-0.98	(-1.38, -0.57)
Sensitivity analysis: worst case scenario								
Baseline GCP			0.50	(0.10, 0.88)	-0.14	(-0.48, 0.20)	0.26	(0.09, 0.43)
CAM-S Peak:								
0-2	57.61	(57.12, 58.09)	-0.64	(-1.04, -0.24)	1.17	(0.83, 1.52)	-0.28	(-0.45, -0.12)
3-7	57.61	(57.12, 58.09)	-0.80	(-1.22, -0.39)	1.38	(1.01, 1.75)	-0.38	(-0.58, -0.19)
8-19	57.61	(57.12, 58.09)	-2.30	(-3.25, -1.36)	2.49	(1.78, 3.20)	-0.69	(-1.09, -0.28)

GCP = general cognitive performance, CAM-S = Confusion Assessment Method-Severity score, CI = confidence interval

Interpretation of Results for Sensitivity Analysis 1

For the GCP analysis, in both the best and worst case scenario, we arrive at comparable decisions regarding the effect of delirium severity in long term slope (last column in Table S3). In the observed data, best case, and worst case scenario the slope is declining among all severity groups over the 36 month interval. In the best case scenario (i.e., those persons who dropped out were on a steeper cognitive decline trajectory than predicted by their observed data) the dose-response effect is more pronounced than in the observed data. In the worst case scenario (i.e., persons who dropped out were on a much lower decline in cognitive functioning relative to what would be inferred from their observed data), the dose-response effect is more subtle. These differences in the patterns of results set boundaries on the range of plausible effects of delirium in our study. The original maximum likelihood results reported in the top segment, and in the main manuscript, reflect our best estimate of the population parameters, and we believe that if the missing data mechanism is not MAR, the results would be somewhere between the observed results and those of the best case scenario. That is to say, it is more plausible that persons with more severe delirium who went on to die or leave the study due to institutionalization would have steeper cognitive decline slopes than what might be expected given their observed data, rather than shallower cognitive decline slopes. Therefore, we believe that if anything our maximum likelihood results are accurate or perhaps somewhat conservative estimates of the true population parameters.

Sensitivity Analysis 2: **Assessing the Relationship between Sum of CAM-S Scores and Long-Term Cognitive Decline**

Table S4. Relationship of Peak Confusion Assessment Method-Severity (CAM-S) to Sum of all CAM-S Scores

	Peak CAM-S score			
Sum CAM-S score	0-2	3-7	8-19	Total
0-2	112	0	0	112
3-16	131	222	14	367
17-max	1	26	54	81
Total	244	248	68	560

Table S5. Sum of CAM-S Scores by Corrected GCP Scores over Time

Visit	Full Sample		Sum CAM-S score					
			0 – 2		3 – 16		17 – max	
Month	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
0	560	57.6 (7.3)	112	60.9 (6.2)	367	57.6 (7.3)	81	53.3 (6.1)
1	548	56.8 (7.9)	112	60.3 (6.2)	359	57.1 (7.8)	77	50.6 (6.5)
2	536	58.0 (7.9)	109	61.4 (6.3)	352	58.1 (8.0)	75	52.6 (6.2)
6	528	58.2 (7.5)	109	61.4 (6.1)	347	58.2 (7.6)	72	53.4 (6.9)
12	511	58.4 (7.6)	105	61.7 (6.6)	334	58.5 (7.6)	72	53.3 (6.3)
18	499	58.3 (8.0)	104	61.5 (6.7)	323	58.6 (7.7)	72	52.2 (7.7)
24	474	58.2 (8.0)	101	61.3 (6.2)	311	58.4 (7.9)	62	51.9 (7.9)
30	325	57.5 (8.2)	67	61.1 (7.2)	213	57.3 (8.2)	45	52.8 (7.4)
36	312	57.1 (8.4)	62	61.4 (7.3)	201	57.1 (8.2)	49	52.0 (7.8)

CAM-S = Confusion Assessment Method-Severity
GCP = General Cognitive Performance

Table S6. Empirically Observed Prevalence of Proxy IQCODE Impairment over Time

			Sum CAM-S score					
Visit	Full Sample		0 – 2		3 – 16		17 – max	
month	N	*n* (%)	N	*n* (%)	N	*n* (%)	N	*n* (%)
0	548	118 (22)	111	20 (18)	356	71 (20)	81	27 (33)
6	514	135 (26)	107	17 (16)	336	91 (27)	71	27 (38)
12	487	130 (27)	102	15 (15)	320	89 (28)	65	26 (40)
18	480	142 (30)	99	12 (12)	311	96 (31)	70	34 (49)
24	452	125 (28)	97	20 (21)	296	82 (28)	59	23 (39)
30	314	101 (32)	65	10 (15)	203	67 (33)	46	24 (52)
36	287	94 (33)	59	10 (17)	184	61 (33)	44	23 (52)

CAM-S = Confusion Assessment Method-Severity
IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly
N=total possible sample, n=number with proxy IQCODE impairment

Figure S2. Trajectory of Estimated General Cognitive Performance by Sum of Confusion Assessment Method-Severity (CAM-S) Groups

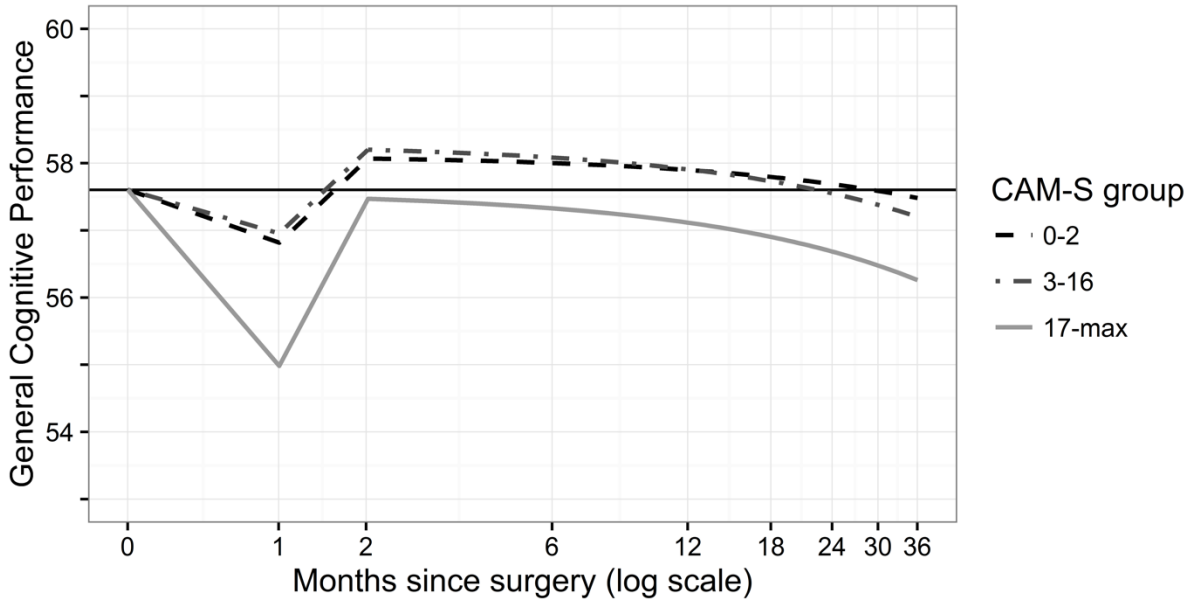


Figure S2 Legend:

Figure S2 demonstrates the relationship between estimated general cognitive performance (GCP) and time following surgery (months, natural log scale) by delirium severity groups. The model is adjusted for baseline GCP, age, gender, non-white race, education, Charlson score, Geriatric Depression score, instrumental activities of daily living (IADL) impairment, surgery type, and proxy Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) impairment. The solid horizontal line indicates the average GCP score prior to surgery. Delirium severity group is observed after baseline, and is dependent on baseline, and therefore the figure is plotted showing no mean difference in GCP at baseline by delirium severity group. The amount of punctuation (acute decline at one month), recovery (up to two months), and long-term decline (two to 36 months) is shown by each CAM-S severity group, 0-2 (dashed black line), 3-16 (dot-dashed black line) and 17-max (solid grey line). In the acute (punctuation) phase, all groups decline with the most severe group declining the most. This is followed by recovery of cognitive performance, with the less severe groups recovering (at two months) past their baseline (0 months) GCP score, and those in the most severe group showing an incomplete return to baseline. Over long-term follow-up, the less severe groups gradually decline in GCP performance, whereas the most severe group demonstrates a more accelerated rate of decline.

Figure S3. Predicted Prevalence of Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) Impairment by delirium severity group (sum CAM-S) and study month

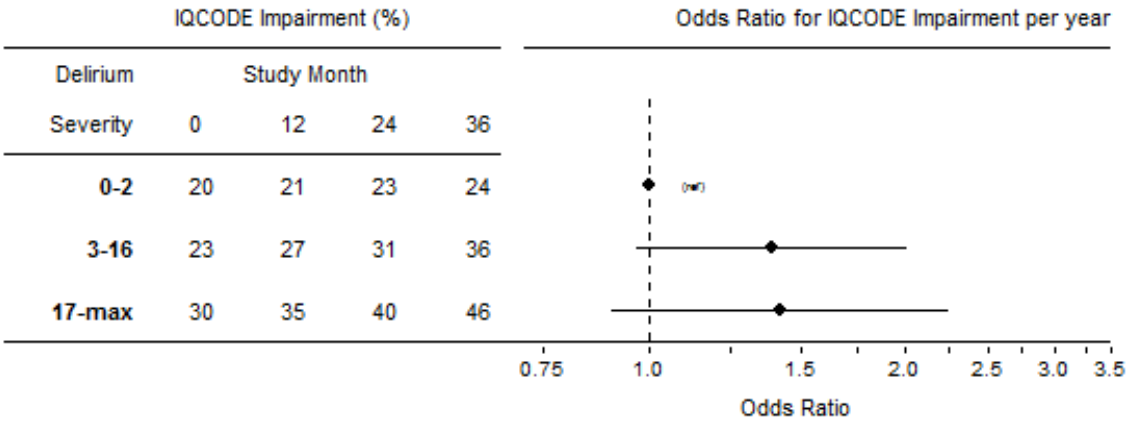


Figure S3 legend:

Figure S3 demonstrates the relationship between the prevalence of proxy IQCODE impairment (score ≥ 3.2) over time (study month) following surgery, calculated using a mixed effects generalized linear model. The model controlled for: age, gender, non-white race, education, Charlson score, Geriatric Depression Scale score, and surgery type. Model-implied (or expected) proportions with IQCODE impairment given mean values on covariates are presented in the table. Odds ratios (and 95% confidence bands) illustrate the size and precision of estimates of the delirium severity group by time (in years following surgery) interaction effects. Over time, all groups have increasing probability of being classified as impaired on the IQCODE, but the slope over time is significantly (p=.02) faster only for patients with the most severe delirium (sum of CAM-S scores 17-max). The per-year odds of IQCODE ≥3.2 for this group is about 2.0 times greater than that observed for the lowest delirium severity group.

Table S7. Detailed Model Results Reporting the Association between Delirium Severity (Sum Confusion Assessment Method-Severity) and General Cognitive Performance (N=560)

Model Parameter	Estimate	95% CI	P-value
Effect of baseline GCP in …			
GCP punctuation	0.44	(0.01, 0.85)	.043
GCP recovery	-0.12	(-0.48, 0.23)	.497
GCP slope, Months 2 - 36	0.27	(0.08, 0.46)	.006
Estimated means for latent growth model effects by Delirium (sum CAM-S) severity group			
CAM-S Sum 0-2			
GCP Punctuation	-0.74	(-1.33, -0.13)	.017
GCP Recovery	1.24	(0.70, 1.78)	<.001
GCP Slope, Months 2 - 36	-0.18	(-0.42, 0.07)	.167
CAM-S Sum 3-16			
GCP Punctuation	-0.60	(-0.94, -0.25)	.001
GCP Recovery	1.23	(0.93, 1.53)	<.001
GCP Slope, Months 2 - 36	-0.32	(-0.49, -0.15)	<.001
CAM-S Sum 17-max			
GCP Punctuation	-2.57	(-3.38, -1.75)	<.001
GCP Recovery	2.47	(1.77, 3.17)	<.001
GCP Slope, Months 2 - 36	-0.39	(-0.81, 0.02)	.065

CAM-S = Confusion Assessment Method-Severity score, GCP = general cognitive performance

Figure S4. STROBE Diagram of the Analytic Sample

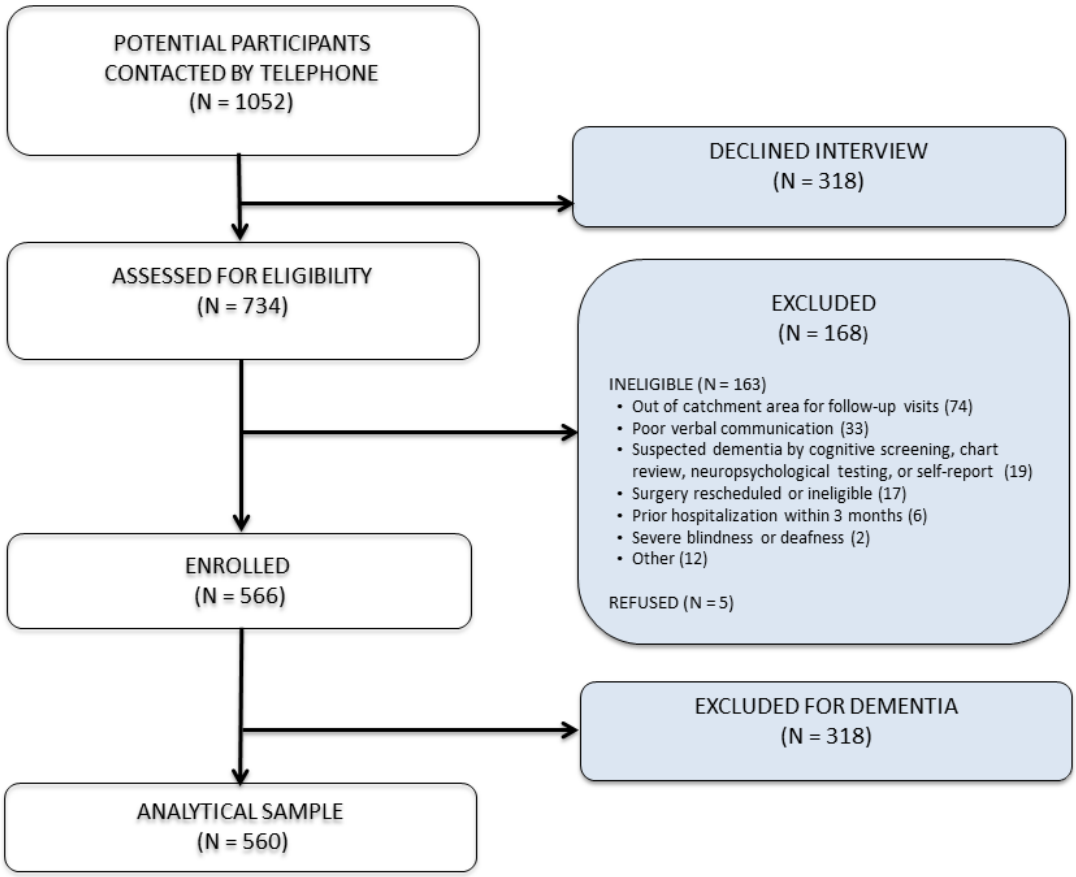


Table S8. SAGES Follow-up Success Rate

	Potential Interviews	Pending Interviews	Completed Interview N (%)	Refused or Unobtainable	Deaths	Drop-Outs
1 Month	560	0	550 (98)	2	1	7
2 Month	552	0	537 (97)	10	1	4
6 Month	547	0	531 (97)	10	3	3
12 Month	541	0	513 (95)	23	3	4
18 Month	534	0	504 (94)	26	3	3
24 Month	520	8*	478 (92)	19	10	13
30 Month	360	145*	326 (91)	25	7	2
36 Month	321	175*	316 (98)	2	3	0

*Pending interviews indicates that the subjects have not yet reached the time for their scheduled follow-up interviews.

Table S9. Description of Study Sample by Death or Nursing Home Placement Status

Characteristic	Full Sample (N = 560)	Death or Nursing Home Placement (N = 103)	No Death or Nursing Home Placement (N = 457)
Age - mean (SD)	76.7 (5.2)	78.9 (5.6)	76.2 (4.9)
Female – n (%)	326 (58)	62 (60)	264 (58)
Nonwhite – n (%)	42 (8)	6 (6)	36 (8)
Education – mean years (SD)	15.0 (2.9)	15.1 (3.0)	14.9 (2.9)
Married – n (%)	332 (59)	52 (50)	280 (61)
Lives Alone – n (%)	167 (30)	36 (35)	131 (29)
Charlson score - n (%)			
0	257 (46)	36 (25)	221 (48)
1	139 (25)	23 (22)	116 (25)
2+	164 (29)	44 (43)	120 (26)
GDS15 score - n (%)			
0 - 5	489 (88)	84 (82)	405 (89)
6 - 15	69 (12)	19 (18)	50 (11)
GCP score - mean (SD)	57.6 (7.3)	55.5 (7.6)	58.1 (7.1)
3MS score - n (%)			
85-100	523 (93)	96 (93)	427 (93)
71-84	37 (7)	7 (7)	30 (7)
Proxy IQCODE (baseline) - n (%)			
Not Impaired	430 (78)	74 (72)	356 (78)
Impaired	118 (22)	26 (26)	92 (21)
ADL impairment – n (%)	42 (8)	14 (14)	28 (6)
IADL impairment – n (%)	152 (27)	40 (39)	112 (25)
Surgery type - n (%)			
Orthopedic	454 (81)	81 (79)	373 (82)
Vascular	35 (6)	8 (8)	27 (6)
General	71 (13)	14 (14)	57 (12)
Delirium[a] - n (%)			
None	426 (76)	74 (72)	352 (77)
Delirium	134 (24)	29 (28)	105 (23)
Peak CAM-S Score	1.7 (0.7)	1.8 (0.7)	1.7 (0.7)
Peak CAM-S Score – n (%)			
0 – 2	244 (44)	37 (36)	207 (45)
3 – 7	248 (44)	48 (47)	200 (44)
8 – 19	68 (12)	18 (17)	50 (11)

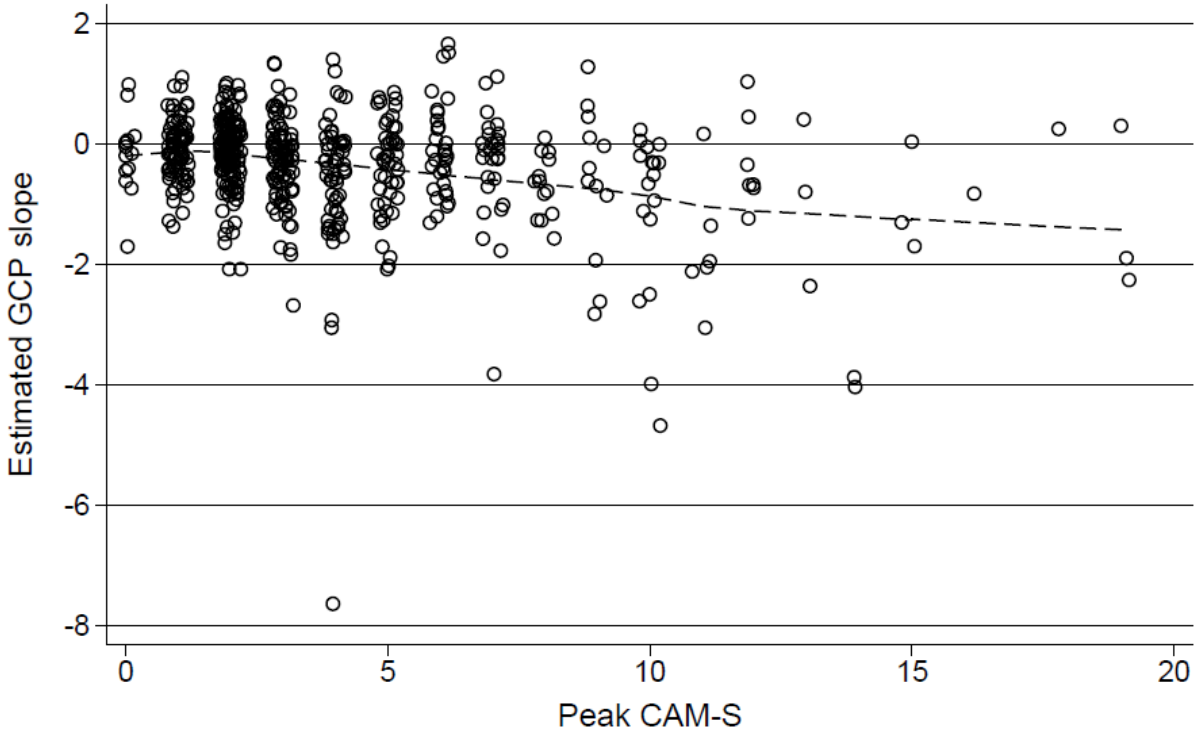
[a]Delirium status was determined with daily interviews rating the Confusion Assessment Method, augmented by a validated chart review

ADL = Activities of Daily Living, impairment indicated by human assistance to complete any activity

CAM-S = Confusion Assessment Method-Severity

GCP = General Cognitive Performance, composite measure of neuropsychological measures reflecting cognitive domains vulnerable to delirium, see text for details
GDS15= Geriatric Depression Scale 15 point version, range (0-15), higher is worse; a score 6 and above is considered impaired
IADL = Instrumental Activities of Daily Living, impairment indicated by human assistance to complete any activity
IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly, score >3.2 indicates cognitive impairment
3MS = Modified Mini-Mental State Exam, range (0-100), lower score indicates impairment; a score ≤84 is considered impaired
SAGES = Successful Aging after Elective Surgery Study
SD= standard deviation.
The Charlson comorbidity score ranged from 0-35, with higher scores indicating more comorbidity.

Figure S5. Continuous Peak CAM-S Measure by GCP slope



* Estimated GCP slope is the estimated linear annual change in GCP from month 2 to 36.

Matched Analysis

Upon the excellent suggestion of an anonymous reviewer, we tested our hypothesis that delirium was related to cognitive decline using a matched design. Surgical patients in the most severe post-operative delirium category (peak CAM-S 8-19, N=68) were matched on the basis of pre-operative GCP score coarsened within 0.4 population SD units to patients in the peak CAM-S 3-7 group and patients in the peak CAM-S 0-2 group (mildest group). We used coarsened exact matching[4] to match patients in the most severe group (peak CAM-S 8-19) with at least two observations in the 2-36 month follow-up window to one patient from the peak CAM-S 3-7 score group and another patient from the peak CAM-S 0-2 group. Matching was performed on the basis of pre-operative GCP score binned in units of 4 (0.4 population SD units). We were able to match 62 of 68 patients. The mean (SD) GCP score at baseline had a mean of 54 and the standard deviation was 5 in each of the three groups. The pace of decline was faster in the peak CAM-S 8-19 group (slope -0.090 population SD units per year) than in the peak CAM-S 3-7 group (slope -0.035 SD/year) which was faster than the peak CAM-S 0-2 group (slope -.017 SD/year). The difference between the 0-2 group and 8-19 group was statistically significant (difference of .073 SD/year, P = .01) but was not different between the 0-2 group and the 3-7 group (difference of .018 SD/year, P = .55). These findings are consistent with the findings we report in the manuscript using the covariate adjusted but not matched patients.

Table S10. Results of Matched Analysis (N=186, n=62 in each delirium subgroup)

	Peak CAM-S Group		
	0-2 (n=62)	3-7 (n = 62)	8-19 (n = 62)
Baseline GCP, mean (SD)	54.2 (5.0)	54.2 (5.2)	54.2 (5.0)
Mixed model results			
Difference at baseline (GCP, est, P)	--	-1.1 (.31)	-1.3 (.22)
Slope from M2-M36 (GCP/y; est, P)	-0.17 (.44)	--	--
Difference in slope (GCP/y; est P)	--	-0.18 (.55)	-.73 (.01)

CAM-S=Confusion Assessment Method-Severity; GCP=general cognitive performance; M=month; SD=standard deviation

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