Cognitive decline after elective and nonelective hospitalizations in older adults

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Neurology® 2019;92:e690-e699. doi:10.1212/WNL.0000000000006918

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Abstract

Objective

To determine whether emergent and urgent (nonelective) hospitalizations are associated with faster acceleration of cognitive decline compared to elective hospitalizations, accounting for prehospital decline.

Methods

Data came from the Rush Memory and Aging Project, a prospective cohort study of community-dwelling older persons without baseline dementia. Annual measures of cognition via a battery of 19 tests were linked to 1999 to 2010 Medicare claims records.

Results

Of 777 participants, 460 (59.2%) were hospitalized over a mean of 5.0 (SD = 2.6) years; 222 (28.6%) had at least one elective and 418 (53.8%) at least one nonelective hospitalization. Mixed-effects regression models estimated change in global cognition before and after each type of hospitalization compared to no hospitalization, adjusted for age, sex, education, medical conditions, length of stay, surgery, intensive care unit, and comorbidities. Persons who were not hospitalized had a mean loss of 0.051 unit global cognition per year. In comparison, there was no significant difference in rate of decline before (0.044 unit per year) or after (0.048 unit per year) elective hospitalizations. In contrast, decline before nonelective hospitalization was faster (0.076 unit per year; estimate = -0.024 , SE = 0.011, $p = 0.032$), and accelerated by 0.036 unit (SE = 0.005, $p < 0.001$) to mean loss of 0.112 unit per year after nonelective hospitalizations, more than doubling the rate in those not hospitalized.

Conclusions

Nonelective hospitalizations are related to more dramatic acceleration in cognitive decline compared to elective hospitalizations, even after accounting for prehospital decline. These findings may inform which hospital admissions pose the greatest risk to the cognitive health of older adults.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ADL = activities of daily living; **CMS** = Centers for Medicare and Medicaid Services; **ICD-9** = *International Classification of Diseases, Ninth Revision*; **ICU** = intensive care unit; **MAP** = Rush Memory and Aging Project; **MCI** = mild cognitive impairment; **MedPAR** = Medicare provider analysis and review.

Cognitive decline after hospitalization is a common but poorly understood occurrence in older adults.¹ Research over the past decade has shown that hospitalization is not only associated with transient delirium, but also long-term cognitive decline and dementia.^{2–5} The risk of negative cognitive outcomes after hospitalization increases with older age.^{6,7} Given that 35% of all hospitalized patients in the United States are aged 65 years or older, despite comprising only 13% of the population,⁸ hospitalization may constitute a risk factor for cognitive decline and dementia in later life that deserves more attention.

A key unanswered question is whether elective hospitalizations pose the same risk to cognitive health as emergency or urgent (i.e., nonelective) hospitalizations. Such information could have ramifications for older adults, families, and physicians in assessing risks surrounding elective procedures such as hip replacement. A related question is whether older adults who experience worsening cognition after hospitalization were already declining beforehand. Older adults hospitalized for more medical issues may have preceding cognitive impairments that affect posthospital outcomes.⁹ Much of the work in this area comes from hospital cohorts with little to no information on cognitive trajectories before hospitalization, or a comparison group of older persons who were not hospitalized.^{4,6,10–12} Expanding on the limited number of prospective cohort studies^{2,3} that have demonstrated acceleration in cognitive decline years after hospitalization, we propose a modeling scheme that separates change in cognition after hospitalization from change before hospitalization, and from change in those who were not hospitalized. We use data from a prospective cohort study of community-dwelling older adults to test the hypothesis that nonelective hospitalizations are associated with faster acceleration in cognitive decline compared to elective hospitalizations, after accounting for differences in prehospital rate of cognitive decline.

Methods

Participants

Data for this study came from the Rush Memory and Aging Project (MAP), a longitudinal study of aging of older adults without dementia at enrollment from more than 40 senior housing facilities and retirement communities in the Chicago area.¹³ Participants agree to annual evaluation and organ donation at time of death. This study was approved by the institutional review board of the Rush University Medical Center, and informed consent was obtained from all

participants following a review of the risks and benefits of study participation. The request for Medicare records was reviewed and approved by the Centers for Medicare and Medicaid Services (CMS) Privacy Board and research identifiable files were shared through a signed data use agreement with CMS.

MAP began in 1997 and enrollment is ongoing. Participants are asked to provide their Medicare Healthcare Insurance Claim number or social security number at the time of enrollment. In 2012, Medicare records were requested from CMS for 1,593 participants for the years that were available at the time: 1999 to 2010. Medicare records were successfully obtained for 87%, of whom 1,136 had valid MAP and Medicare data with overlapping years. After exclusion criteria were applied as described in figure 1, there were 777 persons available for analyses. Missing annual cognitive assessments and loss to follow-up were minimal and thus ignored in analyses. Compared to the 359 participants with valid MAP and Medicare data who were not included, these 777 participants were younger (80.5 vs 82.2 years, $p < 0.001$), more likely to be female (75.4% vs 66.5%, $p = 0.002$), had slightly higher years of education (14.7 vs 14.3, $p = 0.030$), had higher Mini-Mental State Examination (28.1 vs 25.8, $p < 0.001$) and global cognition scores (0.11 vs -0.33 , $p < 0.001$), lower levels of depression (1.15 vs 1.50, $p = 0.002$), and lower levels of activities of daily living (ADL) disability (0.14 vs 0.39, $p < 0.001$). These differences are as expected, as people with dementia and who were followed only briefly were removed from the analytic sample.

Assessment of hospitalizations and hospitalization characteristics using Medicare claims records

Data on hospitalizations for MAP participants for the years 1999 to 2010 came from Medicare claims records obtained from CMS through the Research Data Assistance Center research identifiable files request system.¹⁴ Information on years of eligible Medicare Part A coverage came from the master beneficiary summary file. Data on hospitalizations came from the Medicare provider analysis and review (MedPAR) file, which concatenates all claims filed for a hospitalization into a single record. The MedPAR file included an indicator for the type of admission; hospitalizations in this dataset fell into 1 of 3 types: emergency (required immediate medical intervention as a result of severe, life-threatening, or potentially disabling conditions; generally admitted through the emergency room), urgent (required immediate attention for the care and treatment of a physical or mental disorder; generally admitted to the first available and suitable accommodation), and

Figure 1 Sample-size flowchart

Two or more cognitive assessments were required to estimate valid slopes. ESRD = end-stage renal disease; MAP = Rush Memory and Aging Project.

elective (condition permitted adequate time to schedule the availability of suitable accommodations). Emergency and urgent hospitalizations were combined as nonelective hospitalizations for this analysis.

The MedPAR file included an indicator for whether surgery was performed. An indicator for intensive care unit (ICU) stay was created based on days in ICU greater than 0. An indicator for anesthesia use was created based on anesthesia charges more than 0 dollars. Length of hospital stay in days was recorded. The Charlson Comorbidity Index, a measure of severity of illness during hospitalization, was created from ICD-9 codes. ICD-9 codes were also used to create indicator variables for critical illness, as well as primary brain injury including ischemic stroke, brain hemorrhage, and head injury as specified in the Adult Changes in Thought study.⁵

Cognitive evaluation and clinical diagnoses

Cognitive function was assessed annually via a battery of standard tests. Scores for 19 tests were z-transformed and averaged to compute a global cognitive function score, and subsets of tests were used to derive scores for 5 cognitive domains (working memory, episodic memory, semantic

memory, perceptual speed, and visuospatial ability) as previously described.¹⁵ Clinical diagnoses of dementia and probable Alzheimer disease were conducted at each annual evaluation¹⁶ following the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.¹⁷ A diagnosis of mild cognitive impairment (MCI) was made if cognitive impairment was present in the absence of dementia.¹⁸

Other covariates

Covariates were from baseline evaluation. Education was measured in years. Self-reported chronic medical conditions included number present of: diabetes mellitus, hypertension, heart conditions, cancer, thyroid disease, head injury, stroke,¹⁹ congestive heart failure, and claudication. Smoking history was assessed via self-report. ADL disability was assessed via the Katz scale as the number of items on which a participant reported the need for assistance: walking across a small room, bathing, dressing, eating, transferring from a bed to a chair, and toileting. Depressive symptomology was based on the 10-item version of the Center for Epidemiologic Studies–Depression scale. Physical activity was assessed as self-reported time per week engaged in 5 common exercise activities: walking for

exercise, gardening or yardwork, calisthenics or general exercise, bicycle riding, and swimming or water exercise.

Statistical analysis

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).²⁰ We first examined the distributions of characteristics by hospitalization status (hospitalized vs not hospitalized) and tested differences by hospitalization status using *t* tests for continuous variables and χ^2 tests for categorical variables. We then examined differences in hospitalization characteristics for all hospitalizations over follow-up by admission status (elective vs nonelective). We used a series of linear mixed-effects regression models to examine whether hospitalization, and then type of hospital admission, was related to an acceleration in cognitive decline as compared to the rate in those who were not hospitalized, and compared to the rate of change before hospitalization. All models included random-effects terms for intercept and follow-up time, and fixed-effects terms for time, age, sex, race, education, interactions of age with time, chronic medical conditions, vascular disease burden, smoking history, depressive symptoms, ADL disability, and physical activity. The main outcome variable for these analyses was global cognitive function. Models were repeated with the 5 domains of cognitive function as 5 separate outcomes.

First, models were fit with a fixed term for hospitalized (1 = hospitalized at least once over follow-up, 0 = no) and a term for the interaction of hospitalized with time, as well as a time-varying indicator for posthospitalization (1 = all assessments after first hospitalization, 0 = all assessments before hospitalization), and the interaction of this indicator with time. Together, these terms allow the estimation of a difference in the level and rate of change in cognitive function for those who were hospitalized compared to those who were not hospitalized, as well as an additional difference in level and rate of change in cognitive function after hospitalization.

In a second set of models, we split hospitalization by admission type and included fixed terms for elective hospitalization and nonelective hospitalization and the interactions of those terms with time, and time-varying postelective and post-nonelective hospitalization indicators, and corresponding interactions with time. This allowed for estimation of differences in the level and rate of change both before and after each type of hospitalization compared to those who were not hospitalized. Because people who are admitted for nonelective admissions are usually sicker and may undergo more invasive procedures, we adjusted further for a number of hospital characteristics including length of stay, ICU stay, surgery, Charlson Comorbidity Index, the total number of hospitalizations over follow-up, and whether critical illness or primary brain injury were ever experienced over follow-up. All hospital indicators were set to 0 at all assessments prior to first hospitalization, and for all assessments in persons who were not hospitalized.

In secondary analyses, to test whether associations were driven by people who were already cognitively impaired, we

repeated the elective vs nonelective hospitalization analysis after removing those with MCI at baseline and then removing those who developed MCI at any time before hospitalization. To test whether results were influenced by persons hospitalized for primary brain injury (ischemic stroke, brain hemorrhage, or head injury), we repeated analyses after removing persons with these types of hospitalizations. We also repeated analyses after removing persons who had both types of hospitalizations over follow-up. Finally, to assess whether there was a dose-response relationship regarding number of hospitalizations of each type, we ran a separate analysis with time-varying indicators for (1) one hospitalization and (2) 2 or more hospitalizations, for both elective and nonelective admissions.

Data availability policy

In accordance with the Data Use Agreement between Rush University Medical Center and the CMS, only named persons on the Data Use Agreement are granted permission to access Medicare records files. All other data for participants of the MAP is available on request through the Rush Alzheimer's Disease Center Research Resource Sharing Hub: radc.rush.edu.

Results

Of the 777 participants, 460 (59.2%) were hospitalized at least once over an average of 5.0 (SD = 2.6) years of observation. This included 222 (28.6%) with at least one elective and 418 (53.8%) with at least one nonelective admission; 180 (23.2%) had both types of admission. Initial hospitalization occurred a mean of 2 (SD = 1.7) years after study baseline (no significant difference by admission status) and there was a mean of 4.1 (SD = 2.0) years of follow-up after initial hospitalization. Persons who were hospitalized were followed for longer on average (mean 6.1 years vs 3.5 years, $p < 0.001$), and were on average older and had more medical conditions, more depressive symptoms, more ADL disability, and lower levels of physical activity at baseline (table 1). There were no differences by sex, education, baseline Mini-Mental State Examination status, or smoking history.

There were 1,688 hospitalizations over follow-up, including 367 elective and 1,321 nonelective hospitalizations, as described in table 2. About 4 of 5 elective hospitalizations were for surgical procedures and 3 of 5 involved anesthesia, both significantly more than for nonelective procedures. More nonelective hospitalizations involved ICU stays, critical illness, and primary brain injury. Length of stay was slightly shorter and Charlson Comorbidity Index was higher in nonelective hospitalizations.

Hospitalization and cognitive decline

We first tested the association of hospitalization with cognitive decline, regardless of admission type. As shown in table 3, after controlling for age, sex, race, education, interaction of

Table 1 Descriptive characteristics of the entire cohort and by hospitalization status

Characteristic	All (n = 777)	Not hospitalized (n = 317)	Hospitalized (n = 460)	p Value
Age, y, mean (SD)	80.5 (6.6)	79.6 (7.5)	81.2 (5.8)	0.001
Women, %	75.4	74.5	76.1	0.60
Education, y, mean (SD)	14.7 (3.1)	14.9 (3.4)	14.6 (2.8)	0.11
Baseline MMSE score, mean (SD)	28.1 (1.9)	28.1 (2.1)	28.1 (1.8)	0.90
Baseline global cognitive function, mean (SD)	0.11 (0.52)	0.15 (0.58)	0.08 (0.48)	0.066
Chronic medical conditions, n, mean (SD) ^a	1.5 (1.1)	1.3 (1.1)	1.6 (1.1)	0.007
Smoking history, %	38.9	38.6	39.1	0.88
Depressive symptomology, CES-D score, mean (SD)	1.1 (1.7)	1.0 (1.4)	1.3 (1.8)	0.020
Katz ADL disability score, mean (SD) ^b	0.14 (0.51)	0.10 (0.37)	0.17 (0.59)	0.067
Physical activity, h, mean (SD) ^c	3.2 (3.4)	3.6 (3.8)	3.0 (3.1)	0.006

Abbreviations: ADL = activities of daily living; CES-D = Center for Epidemiologic Studies–Depression; MMSE = Mini-Mental State Examination.

^a Self-reported number present of: diabetes mellitus, hypertension, heart disease, cancer, thyroid disease, head injury, stroke, congestive heart failure, and claudication.

^b ADL disability assessed via Katz scale—number of items a participant reported need for assistance: walking across a small room, bathing, dressing, eating, transferring from a bed to a chair, and toileting.

^c Self-reported hours per week engaged in: walking for exercise, gardening or yardwork, calisthenics or general exercise, bicycle riding, and swimming or water exercise.

age with time, chronic medical conditions, smoking history, depressive symptoms, ADL disability, and physical activity, the measure of global cognition declined a mean of 0.052 unit per year in those who were not hospitalized. In those who were hospitalized, the rate of cognitive decline before

hospitalization (0.064 unit per year; estimate = -0.011 , SE = 0.011 , $p = 0.33$) was not significantly different than the rate in those who were not hospitalized. After hospitalization, the rate of cognitive decline accelerated by 0.042 unit per year (SE = 0.005 , $p < 0.001$) to a mean loss of 0.106 unit per year,

Table 2 Hospital characteristics, comparing elective to nonelective hospitalizations over follow-up (among 460 participants with at least one hospitalization)

Characteristic	Elective hospitalizations (n = 367)	Nonelective hospitalizations (n = 1,321)	p Value
Mean no. per person (SD), range			
Among hospitalized	0.8 (1.1), 0–10	2.9 (2.4), 0–13	NA
Among those with at least one of that type	1.7 (1.1), 1–10	3.2 (2.3), 1–13	NA
Surgery, %	81.7	40.0	<0.0001
Anesthesia, %	61.9	16.4	<0.0001
ICU stay, %	16.6	22.5	0.015
Had critical illness, %	1.1	4.7	0.002
Primary brain injury, %	0.3	2.4	0.009
Length of stay, d, mean (SD) ^a			
First hospitalization	3.9 (3.0)	4.0 (3.1)	0.76
All hospitalizations	4.8 (4.7)	4.3 (3.4)	0.012
Charlson Comorbidity Index score, mean (SD)			
First hospitalization	0.72 (0.82)	0.88 (0.95)	0.094
All hospitalizations	0.82 (0.91)	1.07 (1.03)	<0.0001

Abbreviations: ICU = intensive care unit; NA = not applicable.

^a Longer length of stay for elective hospitalizations was attributable to higher proportions of surgery. When examining surgical hospitalizations alone, nonelective hospitalizations (n = 528, mean = 5.6, SD = 4.3) were significantly longer than elective hospitalizations (n = 300, mean = 4.5, SD = 4.6; $p < 0.0001$).

Table 3 Annual rate of change in cognitive function before and after hospitalization, and in those not hospitalized (global and 5 domains)^a

Estimated rate of change (units per y)	Global	Working memory	Episodic memory	Semantic memory	Perceptual speed	Visuospatial
Not hospitalized	-0.053	-0.048	-0.037	-0.055	-0.088	-0.035
Before hospitalization	-0.064	-0.048	-0.054	-0.048	-0.104	-0.038
After hospitalization	-0.106 ^{b,c}	-0.086 ^{b,c}	-0.096 ^{b,c}	-0.083 ^{b,c}	-0.133 ^{b,c}	-0.054

^a From mixed-effects linear regression models with terms for age, sex, race, education, the interaction of age with time, chronic medical conditions, smoking history, depressive symptoms, activities of daily living disability, physical activity, ever hospitalized, the interaction of ever hospitalized with time, time-varying indicator of hospitalization, and the interaction of time-varying indicator of hospitalization with time. The mean rates of cognitive change (i.e., slopes) estimated by the model are presented in this table.

^b Significantly different than rate before hospitalization ($\alpha = 0.05$).

^c Significantly different than rate in those who were not hospitalized ($\alpha = 0.05$).

representing a 65% acceleration in cognitive decline from the prehospital rate, and nearly doubling of the rate in persons who were not hospitalized, as displayed in figure 2. Table 3 also displays the results for separate cognitive domains: all domains showed acceleration in decline in the years after hospitalization, though this did not achieve statistical significance for visuospatial ability.

Elective and nonelective hospitalizations and cognitive decline

We then repeated the modeling scheme above, splitting hospitalizations by admission type. Models were further adjusted for length of hospital stay, ICU stays, operations, Charlson Comorbidity Index, critical illness, primary brain injury, and number of hospitalizations over follow-up. Estimated slopes from this model are presented in table 4 and

displayed in figure 3. Full model outputs including estimates for covariates are available in table 5. Starting level of cognitive function was not significantly different by admission status ($p = 0.32$). Compared to cognitive decline in persons who were not hospitalized (mean loss of 0.051 unit per year), the rate of decline before elective hospitalization was not significantly different (0.044 unit per year; estimate = 0.008, SE = 0.012, $p = 0.49$). After elective hospitalizations, the rate of decline did not significantly deviate from the prehospital rate (0.048 unit per year; estimate = -0.004, SE = 0.008, $p = 0.57$).

By contrast, in years prior to nonelective hospitalizations, the rate of decline was faster (0.076 unit per year; estimate = -0.024, SE = 0.011, $p = 0.032$) than the rate in those not hospitalized. After nonelective hospitalization, decline accelerated by 0.036 unit (SE = 0.005, $p < 0.001$) to a mean loss of 0.112 unit per year, more than double the rate in those who were not hospitalized. As displayed in figure 3, the rate of cognitive decline after nonelective hospitalization showed the most dramatic deviation from all other slopes.

Figure 2 Rate of decline in global cognition in those who had hospitalization (before and after) or no hospitalization

Blue line indicates mean slope before hospitalization and red line indicates mean slope after hospitalization in a person who was hospitalized, compared to the average slope in a person who was not hospitalized (black line). Dotted line indicates mean time of hospitalization. Break in line after average time of hospitalization indicates lack of observation immediately after hospitalization (mean 213 days between hospitalization and subsequent cognitive assessment).

We also investigated the association of elective and nonelective hospitalization with specific cognitive domains (table 4). All 3 memory domains showed acceleration from pre-hospital rate after nonelective hospitalization only. Rate of decline in all domains except for visuospatial ability was significantly faster after nonelective hospitalization than for persons who were not hospitalized. In secondary analyses, we repeated the model with global cognition as the outcome after removing those with MCI at baseline ($n = 185$) or who developed MCI at any time before hospitalization ($n = 239$), after removing persons with primary brain injury ($n = 8$), and after removing persons who experienced both types of hospitalization over follow-up ($n = 180$). In all cases, the results were similar to the model with the entire cohort and inferences were essentially unchanged. In a model that examined the effect of multiple hospitalizations that included time-varying indicators (1) one hospitalization and (2) 2 or more hospitalizations of each admission type, results indicated a dose-response relationship; there was a trend for faster rate of change after one nonelective hospitalization ($n = 119$;

Table 4 Annual rate of change in cognitive function before and after elective and nonelective hospitalization, and in those not hospitalized (global and 5 domains)^a

Estimated rate of change (units per y)	Global	Working memory	Episodic memory	Semantic memory	Perceptual speed	Visuospatial
Not hospitalized	-0.052	-0.048	-0.038	-0.052	-0.081	-0.033
Before elective hospitalization	-0.044	-0.029	-0.030	-0.042	-0.079	-0.015
After elective hospitalization	-0.048	-0.062	-0.038	-0.063	-0.090	-0.036
Before nonelective hospitalization	-0.076 ^c	-0.050	-0.043	-0.054	-0.109 ^c	-0.041
After nonelective hospitalization	-0.112 ^{b,c}	-0.078 ^{b,c}	-0.097 ^{b,c}	-0.081 ^{b,c}	-0.131 ^c	-0.045

^a From mixed-effects linear regression models with terms for age, sex, race, education, the interaction of age with time, chronic medical conditions, smoking history, depressive symptoms, activities of daily living disability, physical activity, length of hospital stay, intensive care unit stays, operations, Charlson Comorbidity Index, critical illness, primary brain injury, number of total hospitalizations over follow-up, ever hospitalized (elective), the interaction of ever hospitalized (elective) with time, time-varying indicator of hospitalization (elective), the interaction of time-varying indicator of hospitalization (elective) with time, ever hospitalized (nonelective), the interaction of ever hospitalized (nonelective) with time, time-varying indicator of hospitalization (nonelective), the interaction of time-varying indicator of hospitalization (nonelective) with time. The mean rates of cognitive change (i.e., slopes) estimated by the model are presented in this table.

^b Significantly different than rate before hospitalization of that admission status; i.e., acceleration ($\alpha = 0.05$).

^c Significantly different than rate in those who were not hospitalized ($\alpha = 0.05$).

estimate = -0.016 , SE = 0.008 , $p = 0.058$) and a significantly faster rate of change after 2 or more nonelective hospitalizations ($n = 299$; estimate = -0.054 , SE = 0.006 , $p \leq 0.001$). There was no association with faster rate of change for 1, or for 2 or more elective hospitalizations.

Discussion

In this community-dwelling cohort of nearly 800 older adults enrolled without dementia followed for a mean of 5 years, the

rate of cognitive decline accelerated after hospitalization, and showed the most dramatic increases in rate of decline after nonelective emergency and urgent hospitalizations, even after accounting for severity of illness and invasive procedures, as well as prehospital change. Nonelective hospitalization represents a highly prevalent risk factor or marker for cognitive decline in older adults that deserves more attention.

These results build on a growing body of research demonstrating worsening cognitive decline after hospitalization in older adults.^{1–7} Much of this work utilizes data from hospital cohorts or other designs that have no comparison group of nonhospitalized older adults, no information on change in the time before hospitalization, and typically short follow-up (1 year or less).^{4,6,10–12,21} Recently, a small number of prospective cohort studies have been published with both hospitalized and nonhospitalized older persons and lengthy follow-up time (between 6 and 14 years) both before and after hospitalization.^{2,3,5} All 3 studies reported greater cognitive decline in persons in the years after hospitalization compared to those who were not hospitalized and compared to before hospitalization. Our work further extends on these studies by allowing the rate of change before hospitalization to be separated from the rate of change in those who were not hospitalized, and by separating elective and nonelective hospitalizations, thus helping to clarify the relationship.

The reasons for acceleration of cognitive decline after nonelective hospitalization are not clear. Specific hospital procedures that have received attention as potential threats to cognition including critical/intensive care,^{4,5,21} as well as surgery and use of general anesthesia,^{22–24} did not account for our findings.¹² This echoes previous findings that surgery with anesthesia is not a risk factor for long-term cognitive impairment after critical illness.²⁵ Another potential reason is that persons presenting for emergency or urgent hospitalizations are

Figure 3 Rate of decline in global cognition in those who had elective hospitalization, nonelective hospitalizations, or no hospitalization

Green lines indicate mean slopes before (dashed) and after (solid) the mean time of hospitalization in a person experiencing an elective hospitalization, and red lines indicate mean slopes before and after hospitalization for a person experiencing a nonelective hospitalization, compared to average slope in a person who was not hospitalized (black). Break in the after average time of hospitalization indicates lack of observation immediately after hospitalization (mean 213 days between hospitalization and subsequent cognitive assessment).

Table 5 Full results of mixed-effects regression models, adjusted for demographics, and fully adjusted

Term	Estimate (SE, <i>p</i> value)	Estimate (SE, <i>p</i> value)
Outcome	Global cognition	Global cognition
Intercept	0.1836 (0.0267, <0.0001)	0.2175 (0.0408, <0.0001)
Age (centered at 81 y)	−0.0239 (0.0025, <0.0001)	−0.0229 (0.0025, <0.0001)
Male sex	−0.1470 (0.0381, 0.0001)	−0.1573 (0.0388, 0.0001)
Education (centered at 15 y)	0.0579 (0.0054, <0.0001)	0.0566 (0.0055, <0.0001)
Time × age	−0.0048 (0.0007, <0.0001)	−0.0048 (0.0007, <0.0001)
Time	−0.0524 (0.0078, <0.0001)	−0.0521 (0.0078, <0.0001)
Had elective hospitalization	0.0407 (0.0393, 0.30)	0.0325 (0.0514, 0.53)
Time × had elective	0.0083 (0.0117, 0.48)	0.0081 (0.0117, 0.49)
Postelective hospitalization	0.0095 (0.0272, 0.73)	0.0102 (0.0273, 0.71)
Time × postelective	−0.0043 (0.0075, 0.57)	−0.0043 (0.0075, 0.57)
Had nonelective hospitalization	−0.0380 (0.0358, 0.29)	−0.0340 (0.0530, 0.52)
Time × had nonelective	−0.0235 (0.0110, 0.032)	−0.0237 (0.0110, 0.03)
Post-nonelective hospitalization	0.0874 (0.0193, <0.0001)	0.0873 (0.0194, <0.0001)
Time × post-nonelective	−0.0367 (0.0054, <0.0001)	−0.0364 (0.0054, <0.0001)
Chronic conditions		0.0047 (0.0153, 0.76)
Depressive symptoms (CESD-10)		−0.0187 (0.0102, 0.067)
ADL disabilities		−0.0539 (0.0323, 0.096)
Physical activities		−0.0008 (0.0048, 0.87)
Smoking history		−0.0178 (0.0337, 0.60)
Length of stay (first hospitalization)		−0.0010 (0.0071, 0.89)
ICU stay		0.0430 (0.0451, 0.34)
Surgery		0.0680 (0.0629, 0.28)
Anesthesia		−0.0049 (0.0559, 0.93)
Charlson Comorbidity Index (first hospitalization)		−0.0378 (0.0238, 0.11)
Total no. of hospitalizations		−0.0095 (0.0092, 0.31)
Critical illness		0.0812 (0.0682, 0.23)
Primary brain injury		−0.1016 (0.0868, 0.24)

Abbreviations: ADL = activities of daily living; CESD-10 = 10-item version of the Center for Epidemiologic Studies–Depression scale; ICU = intensive care unit.

very sick. We controlled for severity of illness in a number of ways, but we cannot exclude confounding by unmeasured aspects of health or underlying illnesses that contribute to cognitive deterioration. Investigators have also focused on the threat to cognition posed by hospital events such as delirium^{26–29} and sepsis.³⁰ While these events may have an important role, they were reported in very limited number in these claims and thus we were unable to investigate their influence. For example, only 16 participants had delirium as indicated by ICD-9 codes,³¹ which likely underestimates the actual prevalence of hospital-related delirium in this cohort.

Underreporting of delirium³² and sepsis³³ in claims data is widely recognized. Other less explored explanations are stress level, use of sedatives, mechanical ventilation, multiple medications, nosocomial infections, and interruption of sleep.

There are limitations to this study. Using administrative records, we could only observe what is billed for, limiting resolution to examine hospital characteristics, procedures, and diagnoses that could further explain these findings. The study design did not allow for a thorough exploration of whether underlying illness caused both cognitive decline and

nonelective hospitalization (i.e., confounding) or whether rapid cognitive decline directly led to nonelective hospitalization (i.e., reverse causality). The study design also did not allow assessment of acute onset of cognitive impairment in the weeks immediately after hospitalization. Participants come from a selected, predominantly white and higher socioeconomic status volunteer sample, which limits generalization to more diverse populations and may underestimate the effects in the general population. Medicare claims records are known to underreport certain conditions such as delirium and sepsis that may have influenced findings. Strengths include assessment of hospitalization from Medicare claims records rather than participant report, and annual cognitive assessment of all participants with a robust battery. Cognitive assessment was independent of hospitalization status and cognitive change before and after hospitalization could be modeled. The modeling scheme allowed for the estimation of acceleration in rate of cognitive change above and beyond prehospital change and accounting for inherent baseline differences in health and cognitive function between persons who experience elective vs nonelective hospitalizations vs no hospitalization.

Although rarely perceived as a common risk factor for cognitive decline in old age, hospitalization may have a significant role in the public health burden of cognitive impairment and dementia in an aging society. Studies showing that nonelective hospitalizations, specifically, appear to be associated with deterioration in cognitive health of older adults are rare. This may ease some concerns regarding the scheduling of elective procedures; however, one should be cautious in overinterpretation or making recommendations based on these data. It is likely that healthier older individuals self-select for elective hospitalizations, and physicians will recommend or clear procedures in individuals deemed healthy enough to tolerate the risks. Nonetheless, these data suggest the selection process is providing some measure of cognitive safety for older adults. However, it is imperative in our aging society that there is more research on factors associated with emergency and urgent care that accelerate cognitive decline. This includes answering remaining questions regarding whether it is the underlying critical illness, hospital procedures or environment, or some combination of these factors that places certain older patients at risk. Future research will explore the influence of specific illnesses, medications, and procedures on subsequent cognitive decline after nonelective hospital stays.

Acknowledgment

The authors thank the participants of the Memory and Aging Project, and the staff of the Rush Alzheimer's Disease Center. The authors are indebted to the statisticians at the Rush Alzheimer's Disease Center, especially Woojeong Bang and Wenqing Fan, for help with statistical programming.

Study funding

This work was funded by the National Institute on Aging grants K01AG050823 (James), R01AG17917 (Bennett,

James), R01AG033678 (Boyle, James), R01AG035117 (Ely), R01AG027472 (Ely), and P30AG010161 (Schneider), and the Illinois Department of Public Health.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* May 31, 2018. Accepted in final form December 14, 2018.

Appendix Authors

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Bryan D. James, PhD	Rush Alzheimer's Disease Center	First author	Conceived of and designed the study, conducted the analysis, and drafted the manuscript for intellectual content
Robert S. Wilson, PhD	Rush Alzheimer's Disease Center	Author	Conceived of the study and contributed to study design and interpretation; critically revised the manuscript
Ana W. Capuano, PhD	Rush Alzheimer's Disease Center	Author	Contributed to statistical analysis as well as study design and interpretation; critically revised the manuscript
Patricia A. Boyle, PhD	Rush Alzheimer's Disease Center	Author	Contributed to interpretation of the work; critically revised the manuscript
Raj C. Shah, MD	Rush Alzheimer's Disease Center	Author	Contributed to data acquisition, conception, and interpretation; critically revised the manuscript
Melissa Lamar, PhD	Rush Alzheimer's Disease Center	Author	Contributed to study design and interpretation; critically revised the manuscript
E. Wesley Ely, MD	Vanderbilt Medical School, Vanderbilt University, VA GRECC	Author	Contributed to interpretation of the work; critically revised the manuscript
David A. Bennett, MD	Rush Alzheimer's Disease Center	Author	Principal investigator of MAP study, contributed to data acquisition, conception, study design, and interpretation; critically revised the manuscript
Julie A. Schneider, MD	Rush Alzheimer's Disease Center	Senior author	Contributed to data acquisition, conception, study design, and interpretation; critically revised the manuscript

References

- Mathews SB, Arnold SE, Epperson CN. Hospitalization and cognitive decline: can the nature of the relationship be deciphered? *Am J Geriatr Psychiatry* 2014;22:465–480.
- Brown CH, Sharrett AR, Coresh J, et al. Association of hospitalization with long-term cognitive and brain MRI changes in the ARIC cohort. *Neurology* 2015;84:1443–1453.
- Wilson RS, Hebert LE, Scherr PA, Dong X, Leurgans SE, Evans DA. Cognitive decline after hospitalization in a community population of older persons. *Neurology* 2012;78:950–956.

4. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–1316.
5. Ehlenbach WJ, Hough CL, Crane PK, et al. Association between acute care and critical illness hospitalization and cognitive function in older adults. *JAMA* 2010;303:763–770.
6. Chen CC, Chiu MJ, Chen SP, Cheng CM, Huang GH. Patterns of cognitive change in elderly patients during and 6 months after hospitalisation: a prospective cohort study. *Int J Nurs Stud* 2011;48:338–346.
7. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet* 1998;351:857–861.
8. Wier L, Levit K, Stranges E, et al. HCUP Facts and Figures: Statistics on Hospital-Based Care in the United States, 2008. Rockville, MD: Agency for Healthcare Research and Quality; 2010.
9. Ferrante LE, Murphy TE, Gahbauer EA, Leo-Summers LS, Pisani MA, Gill TM. Pre-intensive care unit cognitive status, subsequent disability, and new nursing home admission among critically ill older adults. *Ann Am Thorac Soc* 2018;15:622–629.
10. Helvik AS, Selbaek G, Engedal K. Cognitive decline one year after hospitalization in older adults without dementia. *Dement Geriatr Cogn Disord* 2012;34:198–205.
11. Canet J, Raeder J, Rasmussen LS, et al. Cognitive dysfunction after minor surgery in the elderly. *Acta Anaesthesiol Scand* 2003;47:1204–1210.
12. Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med* 2001;344:395–402.
13. Bennett DA, Schneider JA, Buchman AS, Barnes LL, Boyle PA, Wilson RS. Overview and findings from the Rush Memory and Aging Project. *Curr Alzheimer Res* 2012;9:646–663.
14. Research Data Assistance Center (ResDAC). Research Identifiable File (RIF) Requests [online]. Available at: resdac.org/cms-data/request/research-identifiable-files. Accessed Feb 3, 2018.
15. Wilson RS, Barnes LL, Krueger KR, Hoganson G, Bienias JL, Bennett DA. Early and late life cognitive activity and cognitive systems in old age. *J Int Neuropsychol Soc* 2005;11:400–407.
16. Bennett DA, Schneider JA, Buchman AS, Mendes de Leon C, Bienias JL, Wilson RS. The Rush Memory and Aging Project: study design and baseline characteristics of the study cohort. *Neuroepidemiology* 2005;25:163–175.
17. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–944.
18. Wilson RS, Schneider JA, Arnold SE, Tang Y, Boyle PA, Bennett DA. Olfactory identification and incidence of mild cognitive impairment in older age. *Arch Gen Psychiatry* 2007;64:802–808.
19. Wilson RS, Mendes De Leon CF, Barnes LL, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA* 2002;287:742–748.
20. SAS Institute Inc. SAS/STAT 9.4 User's Guide. Cary: SAS Institute Inc.; 2015.
21. Guerra C, Linde-Zwirble WT, Wunsch H. Risk factors for dementia after critical illness in elderly medicare beneficiaries. *Crit Care* 2012;16:R233.
22. Avidan MS, Evers AS. Review of clinical evidence for persistent cognitive decline or incident dementia attributable to surgery or general anesthesia. *J Alzheimers Dis* 2011;24:201–216.
23. Chen PL, Yang CW, Tseng YK, et al. Risk of dementia after anaesthesia and surgery. *Br J Psychiatry* 2014;204:188–193.
24. Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology* 2008;108:18–30.
25. Hughes CG, Patel MB, Jackson JC, et al. Surgery and anesthesia exposure is not a risk factor for cognitive impairment after major noncardiac surgery and critical illness. *Ann Surg* 2017;265:1126–1133.
26. Devore EE, Fong TG, Marcantonio ER, et al. Prediction of long-term cognitive decline following postoperative delirium in older adults. *J Gerontol A Biol Sci Med Sci* 2017;72:1697–1702.
27. Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK. The interface between delirium and dementia in elderly adults. *Lancet Neurol* 2015;14:823–832.
28. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after post-operative delirium. *N Engl J Med* 2012;367:30–39.
29. Davis DH, Muniz-Terrera G, Keage HA, et al. Association of delirium with cognitive decline in late life: a neuropathologic study of 3 population-based cohort studies. *JAMA Psychiatry* 2017;74:244–251.
30. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010;304:1787–1794.
31. Israni J, Lesser A, Kent T, Ko K. Delirium as a predictor of mortality in US Medicare beneficiaries discharged from the emergency department: a national claims-level analysis up to 12 months. *BMJ Open* 2018;8:e021258.
32. McCoy TH, Snapper L, Stern TA, Perlis RH. Underreporting of delirium in statewide claims data: implications for clinical care and predictive modeling. *Psychosomatics* 2016;57:480–488.
33. Jolley RJ, Sawka KJ, Yergens DW, Quan H, Jetté N, Doig CJ. Validity of administrative data in recording sepsis: a systematic review. *Crit Care* 2015;19:139.