Delirium and Long-term Cognitive Trajectory Among Persons With Dementia

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Background: Delirium is characterized by acute cognitive impairment. We examined the association of delirium with long-term cognitive trajectories in older adults with Alzheimer disease (AD).

Methods: We evaluated prospectively collected data from a nested cohort of hospitalized patients with AD (n=263) in the Massachusetts Alzheimer Disease Research Center patient registry between January 1, 1991, and June 30, 2006 (median follow-up duration, 3.2 years). Cognitive function was measured using the information-memory-concentration (IMC) section of the Blessed Dementia Rating Scale. Delirium was identified using a validated medical record review method. The rate of cognitive deterioration was contrasted using random-effects regression models.

Results: Fifty-six percent of patients with AD developed delirium during hospitalization. The rate of cognitive deterioration before hospitalization did not differ significantly between patients who developed delirium (1.4 [95% CI, 0.7-2.1] IMC points per year) and patients who did not develop delirium (0.8 [95% CI, 0.3-1.3] IMC points per year) (P=.24). After adjusting for dementia severity, comorbidity, and demographic characteristics, patients who had developed delirium experienced greater cognitive deterioration in the year following hospitalization (3.1 [95% CI, 2.1-4.1] IMC points per year) relative to patients who had not developed delirium (1.4 [95% CI, 0.2-2.6] IMC points per year). The ratio of these changes suggests that cognitive deterioration following delirium proceeds at twice the rate in the year after hospitalization compared with patients who did not develop delirium. Patients who had developed delirium maintained a more rapid rate of cognitive deterioration throughout a 5-year period following hospitalization. Sensitivity analyses that excluded rehospitalized patients and included matching on baseline cognitive function and baseline rate of cognitive deterioration produced essentially identical results.

Conclusions: Delirium is highly prevalent among persons with AD who are hospitalized and is associated with an increased rate of cognitive deterioration that is maintained for up to 5 years. Strategies to prevent delirium may represent a promising avenue to explore for ameliorating cognitive deterioration in AD.

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ALZHEIMER DISEASE (AD) IS a progressive and debilitating disorder characterized by impaired memory and loss of independent function.[1] An estimated 4.5 million older adults in the United States have AD.[2] Without advances in prevention or treatment, that number is expected to triple by 2050 to 13.2 million.[3] Identification of modifiable risk factors for cognitive deterioration in AD is a top national priority to develop preventive strategies for slowing the progression of AD severity and reducing morbidity.[4,5]

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Delirium is a common preventable medical syndrome among older hospitalized patients[6-8] and is characterized by acute change in cognitive status, particularly attention and executive function.[9] The results of a recent meta-analysis[10] suggested that delirium is associated with an increased risk for death or requirement of institutional care. The 1-year mortality for hospitalized seniors who develop delirium is 35% to 40%,[11] comparable to the

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mortality associated with sepsis or acute myocardial infarction.[12] Previous research has demonstrated the adverse effect of delirium on cognition and function among older adults without dementia.[12-20]

Delirium complicates care for more than 20% of all hospitalized adults older than 65 years; its prevalence rises to 60% to 89% of patients with AD.[6-8] Moreover, older adults with AD are almost 3 times more likely to experience delirium than older adults without dementia.[12,13,21,22] Despite this, little attention has been paid to the consequences of delirium on cognitive deterioration among patients with AD.[23] The few studies completed have focused on short-term cognitive outcomes. Fong and colleagues[24] reported significant change in cognitive function up to 6 months following delirium among patients with AD; however, that study was unable to address whether this change resulted in an enduring alteration in the trajectory of cognitive function.[25-27]

The objective of the present study was to examine the rate of cognitive deterioration for up to 5 years before and 5 years after the occurrence of delirium among hospitalized older adults with AD. We hypothesized that the development of delirium is associated with cognitive deterioration in patients with AD, defined by long-term change in results on a test of global cognitive function.

METHODS

STUDY SAMPLE

Patients were drawn from a nested longitudinal cohort of participants in the Massachusetts Alzheimer Disease Research Center (MADRC) patient registry. The MADRC was initiated in 1984 at Massachusetts General Hospital in Boston as a specialized research center devoted to the study of memory impairment. The MADRC examining neurologists diagnosed patients as having AD using National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer Disease and Related Disorders Association guidelines.[28]

Eligible participants (n=895) were those diagnosed as having definite, possible, or probable AD who visited the study clinic at least 3 times between January 1, 1991, and June 30, 2006; who were 65 years or older at the first MADRC visit; and who consented to participation in research. We obtained data from Medicare (January 1, 1991, to December 31, 2006) and the National Death Index (because of the 1-year lag in the National Death Index data for the same patients, these data were obtained for a period 1 year later, from January 1, 1992, to December 31, 2007). Medical record reviews were conducted from January 2, 2006, to March 23, 20010. Of the initial 895 patients, 379 (42.3%) were hospitalized, which was a further inclusion criterion. We excluded those enrolled in a Medicare health maintenance organization (n=68) because hospitalizations for this group are not consistently identifiable in Medicare data. The health maintenance organization sample was similar to patients covered by fee-for-service Medicare in terms of sex, race/ethnicity, dementia severity, and baseline cognitive function. In addition, because we needed hospital records to classify delirium, we excluded patients whose hospital record was unavailable (n=48). The resulting sample size was 263 patients with AD.

The MADRC informed consent policy includes joint consent of patients and their next of kin, health care proxy, or legal guardian. Conducted using data from the MADRC, medical record review, Medicare, and the National Death Index, the present study was approved by the institutional review boards of Massachusetts General Hospital, Hebrew Rehabilitation Center–Hebrew SeniorLife, and 46 Massachusetts hospitals where medical records were reviewed.

COGNITIVE FUNCTION

We assessed cognitive function during MADRC clinic visits using the information-memory-concentration (IMC) section of the Blessed Dementia Rating Scale, a brief test of global cognitive function.[29] The IMC section has been validated as a screening tool for dementia using neuropathological features of AD and consensus diagnosis by psychiatrists.[30] The IMC section assesses orientation, memory, concentration, and knowledge of personal information and public events. It is scored from 0 to 37 points based on the number of errors. A score of 0 to 2 is considered typical, and a score above 14 indicates major cognitive impairment.[31] The IMC score is highly correlated with other widely used clinical measures of global cognitive function, including the Mini-Mental State Examination (r range, 0.81-0.85) and the Alzheimer Disease Assessment Scale cognitive subscale (r=0.82).[32]

HOSPITALIZATION

We retrospectively identified hospitalizations using the Medicare Provider Analysis and Review database and confirmed them by review of hospital records. We defined the index hospitalization as the first hospitalization occurring during a patient's follow-up period at the MADRC. Because of the study inclusion criteria, all patients had IMC scores before and after their index hospitalization. We defined the baseline MADRC visit as the most recent MADRC visit preceding the index hospitalization.

DELIRIUM

Delirium was the primary exposure of interest. To classify delirium, we examined hospital records from the index hospitalization using a validated medical record review method.[33] Relative to ratings using direct patient interview with cognitive testing and the Confusion Assessment Method,[34] the medical record review approach has a sensitivity of 74%, specificity of 83%, and chance-corrected agreement (κ value) of 0.41,[33] which is considered moderate agreement.[35] The main reason for missed diagnoses was lack of adequate documentation, which is more likely to occur with mild delirium cases. Sensitivity approached 90% when restricted to more severe cases of delirium.[33] Our medical record review method has been successfully applied in previous studies,[24,36] and retrospective methods like it are increasingly being used.[37]

COVARIATES

Demographic variables included age, sex, marital status, years of education, and race/ethnicity (white vs other). Health-related variables included the number of comorbidities, history of smoking (yes vs no), and informant-reported history of depression (yes vs no). We measured comorbidity burden with the Charlson Comorbidity Index, calculated before or at the time of the index hospitalization based on data from the MADRC, Medicare, and medical record abstractions.[38] Dementia-related variables included informant-reported duration of AD symptoms before diagnosis, speed of initial onset (rapid vs slow), course (fluctuating or stepwise vs stable or improving), family history of AD, and physician-rated dementia severity (range, 0-5, with 5 indicating profound impairment). The severity scale

Table 1. Comparison of Baseline Characteristics in the MADRC Hospitalized Cohort and the NACC Cohort[a]

Characteristic	MADRC Hospitalized Cohort (n = 263)	NACC Cohort (n = 74 169)
Demographic Variables		
Age, mean (SD), y	78.3 (6.0)	77.9 (6.8)
Female sex, No. (%)	150 (57.0)	44 414 (59.9)
White race/ethnicity, No. (%)	14 (5.3)	12 298 (16.6)
Years of education, mean (SD)	13.7 (3.6)	13.2 (4.0)
Married, No. (%)	168 (63.9)	40 070 (56.0)
Dementia-Related Variables		
Blessed IMC score at baseline MADRC visit, mean (SD)[b]	10.7 (6.3)	. . .
Mini-Mental State Examination score at baseline clinic visit, mean (SD)[c]	. . .	21.5 (7.7)
Significant cognitive impairment at baseline, No. (%)[d]	68 (25.9)	18 667 (25.2)

Abbreviations: Blessed IMC, Blessed Dementia Rating Scale information-memory-concentration section (higher Blessed IMC scores indicate poorer cognitive function); MADRC, Massachusetts Alzheimer Disease Research Center; NACC, National Alzheimer Disease Coordinating Center.

[a] Comparisons of demographic characteristics in the MADRC and NACC cohorts revealed trivial to small effect size differences.[44]

[b] Sample statistics were calculated at the baseline MADRC visit, which was the MADRC visit immediately before the index hospitalization.

[c] The baseline NACC visit was the first visit to an Alzheimer disease clinic.

[d] Significant cognitive impairment was considered a score above 14 on the Blessed IMC and below 18 on the Mini-Mental State Examination.

is highly correlated with the Clinical Dementia Rating (Spearman rank correlation $r = 0.87$, $P < .001$).[23,39] To account for the small amount of missing data, which did not exceed 4% for any covariate, we used Bayesian imputation methods with 25 random draws.[40]

HANDLING OF TIME

Patients contributed time between their first and last MADRC visits. We centered time at the index hospitalization. Because of sparse data, we excluded data from MADRC visits beyond 5 years from the index hospitalization.

STATISTICAL ANALYSIS

We characterized patients using descriptive statistics. We compared distributions of age, sex, race/ethnicity, and years of education in the sample with those in the National Alzheimer Disease Coordinating Center to assess the generalizability of the present sample to persons with AD living in the United States.

For the main analysis, we used linear regression models with random effects to characterize changes in IMC scores over time. This approach minimizes bias in parameter estimates and SEs given the longitudinal repeated-measures design. We estimated random effects for intercept and slope parameters to accommodate individually varying IMC scores, individually varying rates of change, and clustering of repeated observations over time within a patient. Models were stratified by delirium status. To address the possibility that the association of delirium with the rate of cognitive deterioration was limited to the follow-up period shortly after the index hospitalization, we included discrete breaks in time at the index hospitalization and at 1 and 2 years after the index hospitalization. To help to interpret the differences in rates of deterioration, we calculated the ratios of rates of cognitive deterioration in the delirium and no delirium groups. This ratio represents the proportionate difference in the rate of cognitive deterioration attributable to delirium.

To control for potential confounding, we adjusted models for age, sex, years of education, dementia severity, family history of AD, number of comorbidities, and duration of AD symptoms before diagnosis. To address differences in preindex trajectory and baseline IMC scores by delirium status, we performed a sensitivity analysis by individually matching (with replacement) patients who developed delirium to patients who did not develop delirium by quintiles of estimated cognitive function at the index hospitalization and rate of cognitive deterioration before hospitalization. In another sensitivity analysis, we excluded rehospitalized patients to assess whether differences in rehospitalization rates by delirium status affected the results.

Analyses were conducted with statistical software (M*plus*, version 6.12; Muthén & Muthén)[41] using robust maximum likelihood estimation, which assumes that observations for the outcome variable are missing at random, conditional on variables in the model.[42] We evaluated model fit by correlating observed and model-implied IMC scores, the square of which is the proportion of variability in observed IMC scores explained by the model (empirical R^2).[43] We checked plots of residuals for normality and random scatter over time. We excluded outlying observations to verify inferences.

RESULTS

Most study patients were female (57.0%) and had at least a high school education (mean years of education, 13.7), and the mean patient age was 78.3 years. Differences in characteristics of our sample compared with the National Alzheimer Disease Coordinating Center sample of 74 169 patients with AD were trivial (**Table 1**).

Patients were evaluated at the MADRC approximately every 6 months during a median follow-up duration of 3.2 years (range, 0.7-14.5 years). On average, patients had 2 MADRC visits before their index hospitalization and 3 visits afterward. The median time between the baseline MADRC visit and the index hospitalization was 10.5 months (range, 0.1-75.2 months). The IMC scores were more likely to be missing for MADRC visits after a patient's index hospitalization ($P < .001$). Whether the IMC scores were missing did not vary by delirium status ($P = .42$).

DELIRIUM INCIDENCE

The overall incidence of delirium in the hospitalized sample was 56.3% (95% CI, 50.2%-62.3%). Compared with patients in the no delirium group, patients in the delirium group were more likely to be male, have fewer

Table 2. Baseline Characteristics of the MADRC Hospitalized Cohort[a]

Characteristic	Delirium Group (n = 148)	No Delirium Group (n = 115)	*P* Value for Group Difference
Demographic Variables			
Age, mean (SD), y	78.3 (6.1)	78.3 (5.8)	.92
Female sex, No. (%)	75 (50.7)	75 (65.2)	.02
White race/ethnicity, No. (%)	139 (93.9)	110 (95.7)	.54
Years of education, mean (SD)	13.2 (3.7)	14.3 (3.5)	.02
Married, No. (%)	102 (68.9)	66 (57.4)	.05
Health-Related Variables, No. (%)			
Charlson Comorbidity Index			
0	64 (43.2)	59 (51.3)	
1	41 (27.7)	36 (31.3)	.09
>2	43 (29.1)	20 (17.4)	
History of smoking	45 (31.5)	20 (17.5)	.01
History of depression	32 (26.2)	25 (28.1)	.77
Rehospitalization	79 (53.4)	44 (38.3)	<.01
Dementia-Related Variables			
Duration of AD symptoms before diagnosis, mean (SD), y	2.8 (1.8)	3.2 (2.6)	.16
Speed of initial onset, No. (%)[b]	11 (7.4)	6 (5.2)	.47
Course, No. (%)[c]	4 (2.7)	2 (1.7)	.60
Family history of AD, No. (%)	12 (8.1)	9 (7.8)	.93
Dementia severity, mean (SD)[d]	2.2 (0.8)	2.0 (0.8)	.06
Follow-up duration, mean (SD), y	3.6 (2.2)	4.1 (2.7)	.06
Admitting diagnosis at index hospitalization, No. of patients[e]			
Syncope, fall, trauma	34	27	
Ischemic heart disease	26	27	
Gastrointestinal disease	16	10	
Pneumonia	7	2	
Musculoskeletal	9	3	
Delirium, mental status change	3	3	.69
Cerebrovascular disease	6	4	
Central nervous system or neurological	5	2	
Urinary tract infection	4	2	
Cancer	2	4	
Other[f]	36	31	

Abbreviations: AD, Alzheimer disease; MADRC, Massachusetts Alzheimer Disease Research Center.

[a] Missing data were as follows: years of education (n = 5), history of smoking (n = 6), history of depression (n = 52), duration of AD symptoms before diagnosis (n = 4), and dementia severity (n = 5).

[b] Informant reported as rapid vs slow.

[c] Informant reported as fluctuating or stepwise vs stable or improving.

[d] Physician rating (range, 0-5 [5 is profound]).

[e] Based on the principal admitting diagnosis at the index hospitalization for the corresponding Medicare claim record.

[f] Other admitting diagnoses include chronic lung disease, congestive heart failure, fever or other infections, dehydration, acute or chronic renal failure, peripheral vascular disease, psychiatric illness, and diabetes mellitus.

years of education, be married, have a history of smoking, and have greater cognitive impairment at the baseline MADRC visit. Reasons for hospitalization did not differ by delirium status (*P* = .69) (**Table 2**).

COGNITIVE DETERIORATION

Comparisons of observed and model-implied changes in cognitive trajectories over time by the delirium and no delirium groups are summarized in the **Figure**. The covariate-adjusted model fit the data well (empirical R^2 = 0.89). During the study period, 119 patients (45.2%) died, and 62 patients (23.6%) were lost to follow-up because of other reasons. Our modeling accounted for these losses using robust estimation methods. At baseline, the observed mean IMC score was higher in the delirium group (difference, 1.5 [95% CI, 0.2-2.9] IMC points), but this difference was not significant after adjustment for potential confounders (**Table 3**). In addition, observed and model-implied rates of cognitive deterioration were similar in the 2 groups preceding the index hospitalization (observed difference, 0.8 [95% CI, –0.1 to 1.7] IMC points per year; model-implied difference, 0.6 [95% CI, –0.1 to 1.3] IMC points per year) (**Table 4**). The clinical significance of an additional 0.6 points can be summarized using the expected time to detect a 0.5-SD decline in IMC score, which would be about 3.9 years in the no delirium group and 2.3 years in the delirium group.

Observed and model-implied cognitive deterioration worsened during the year following the index hospitalization in both groups (Table 4). This deterioration was significantly greater in the delirium group (difference, 1.7 [95% CI, 0.3-3.1] IMC points per year) and remained so through the end of the study period (*P* = .003). The ratio of these group differences suggests that delirium is associated with a 2.2-fold increased rate of cognitive deterioration in the

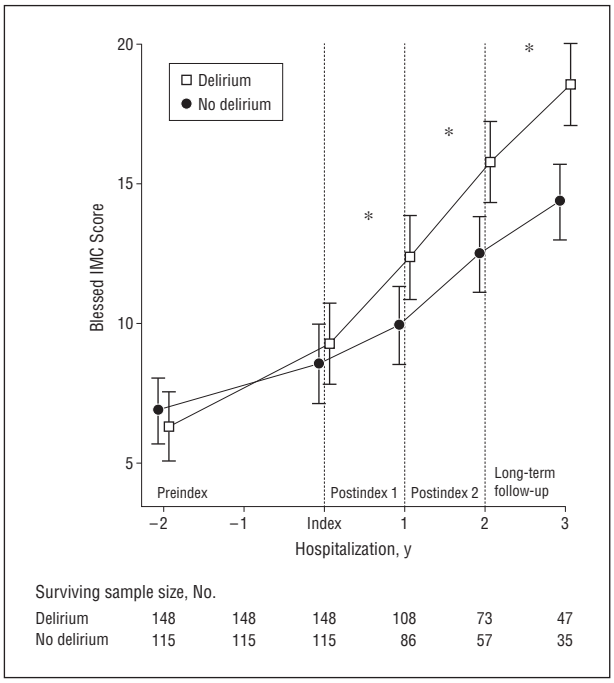

Figure. Estimated cognitive function among 263 hospitalized patients who developed delirium or did not develop delirium, showing model-implied trajectories with 95% CIs of cognitive performance at discrete time points from a random-effects regression model of the Blessed Dementia Rating Scale information-memory-concentration section (Blessed IMC) score during Massachusetts Alzheimer Disease Research Center follow-up periods. The model is adjusted for age, sex, years of education, family history of Alzheimer disease, dementia severity, number of comorbidities, and duration of Alzheimer disease symptoms before diagnosis. Missing covariate data were multiply imputed using Bayesian imputation methods with 25 data sets. The timescale depicted includes the middle 80% of study visits nearest in time to the index hospitalization (although statistical models used data up to 5 years before and 5 years after the index hospitalization). The surviving sample size is the number of patients who survived up to each year. Asterisks indicate $P < .05$ on test of group differences in observed annualized change in Blessed IMC score between delirium and no delirium groups.

year following the index hospitalization and with a 1.7-fold increased rate of cognitive deterioration during the 5-year period following the index hospitalization.

SENSITIVITY ANALYSES

To control for baseline cognitive status, we performed a sensitivity analysis by individually matching patients on baseline IMC score and on preindex trajectory. Findings were consistent with those of the main analysis. The results are likely conservative because the observed matched mean IMC score in the delirium group was almost 1 point lower (less impaired) at baseline than that in the no delirium group (9.5 vs 10.4 IMC points). However, observed and model-implied mean IMC scores were higher (more impaired) in the delirium group by the end of the follow-up period.

Rehospitalization occurred more often among patients in the delirium group (79 [53.4%]) than among patients in the no delirium group (44 [38.3%]) ($P < .01$) (Table 2). Most patients were rehospitalized within 2 years of their index hospitalization, during which time the proportions differed between the delirium group (70 [47.3%]) and the no delirium group (37 [32.2%]) ($P = .01$). After 2 years, the proportions of patients who were rehospitalized did not differ by delirium status ($P = .60$). When we excluded rehospitalized patients, the model-implied rate of cognitive deterioration during the year following the index hospitalization remained worse in the delirium group (3.5 IMC points per year) than that in the no delirium group (1.5 IMC points per year) ($P = .07$); these estimates are slightly larger than those that include rehospitalized patients ($P = .24$) (Table 4). This trend continued 1 to 2 years after the index hospitalization ($P = .04$) and after 2 years ($P = .02$). Therefore, overall findings were similar when we excluded rehospitalized patients.

Table 3. Baseline Cognitive Scores by Delirium Group Among 263 Patients in the MADRC Hospitalized Cohort

Variable[a]	Blessed IMC Score at Baseline MADRC Visit, Mean (95% CI)[b]
Delirium group (n = 148)	
Observed	9.8 (8.9 to 10.7)
Adjusted model	9.3 (7.9 to 10.7)
No delirium group (n = 115)	
Observed	8.3 (7.3 to 9.3)
Adjusted model	8.5 (7.4 to 9.6)
Group difference (N = 263)[c]	
Observed	1.5 (0.2 to 2.9)
Adjusted model	0.8 (–0.8 to 2.2)

Abbreviations: Blessed IMC, Blessed Dementia Rating Scale information-memory-concentration section (higher Blessed IMC scores indicate poorer cognitive function); MADRC, Massachusetts Alzheimer Disease Research Center.

[a] Adjusted models are adjusted for age, sex, years of education, family history of Alzheimer disease, dementia severity, number of comorbidities, and duration of Alzheimer disease symptoms before diagnosis.

[b] Baseline observed Blessed IMC scores taken from the MADRC visit before the index hospitalization. Adjusted values are predicted (model implied) values at the index hospitalization.

[c] Group differences in Blessed IMC score between delirium and no delirium groups.

COMMENT

In this prospective study of hospitalized older adults with AD, we investigated the association of delirium with the long-term rate of cognitive deterioration. Delirium developed in 56.3% of patients and was associated with significantly greater long-term cognitive deterioration. This finding was independent of dementia severity, demographic characteristics, and level and rate of cognitive deterioration before the index hospitalization and persisted throughout the 5-year follow-up duration. Therefore, delirium among patients with AD is associated with a significantly elevated rate of cognitive deterioration from baseline levels.

Rehospitalization after the index hospitalization was common during the MADRC follow-up evaluation.[36] However, rehospitalization is a highly prevalent consequence of delirium and may serve as a marker or mediator through which delirium influences cognitive trajectories: patients with delirium tend to be discharged sicker, have worse prognosis for rehabilitation, and have elevated risk for rehospitalization.[11,45] To adjust for rehospitalizations may potentially remove part of the total observed association between delirium and cognitive decline.[46] Despite this conjecture, our sensitivity analysis that excluded rehospitalizations found little evidence to suggest that rehospitalizations account for the findings in this study.

Table 4. Comparison of Changes in Cognitive Scores During Follow-up Periods Among 263 Patients in the MADRC Hospitalized Cohort

Variable[a]	Blessed IMC Points (95% CI) per Year[b]			
	Preindex	Postindex 1	Postindex 2	Long-term Follow-up
Delirium group (n = 148)				
Observed	1.7 (1.2 to 2.2)	2.1 (1.6 to 2.6)	1.7 (1.3 to 2.1)	2.2 (1.7 to 2.7)
Adjusted model	1.4 (0.7 to 2.1)	3.1 (2.1 to 4.1)	3.2 (2.6 to 3.8)	3.1 (2.5 to 3.7)
No delirium group (n = 115)				
Observed	0.9 (0.5 to 1.3)	1.3 (0.8 to 1.8)	0.9 (0.4 to 1.4)	1.7 (1.2 to 2.2)
Adjusted model	0.8 (0.3 to 1.3)	1.4 (0.2 to 2.6)	2.0 (1.3 to 2.7)	1.9 (1.4 to 2.4)
Group difference (N = 263)[c]				
Observed	0.8 (-0.1 to 1.7)	0.8 (0.1 to 1.6)	0.8 (0.0 to 1.7)	0.5 (-0.7 to 1.7)
Adjusted model	0.6 (-0.1 to 1.3)	1.7 (0.3 to 3.1)	1.2 (0.5 to 2.1)	1.2 (0.5 to 1.8)

Abbreviations: Blessed IMC, Blessed Dementia Rating Scale information-memory-concentration section (higher Blessed IMC scores indicate poorer cognitive function); MADRC, Massachusetts Alzheimer Disease Research Center.

[a] Adjusted models are adjusted for age, sex, years of education, family history of Alzheimer disease, dementia severity, number of comorbidities, and duration of Alzheimer disease symptoms before diagnosis.

[b] Preindex is years before index hospitalization, Postindex 1 is years 0 to 1, Postindex 2 is years 1 to 2, and Long-term Follow-up is years 2 to 5.

[c] Group differences in Blessed IMC score between delirium and no delirium groups.

Patients who develop delirium may differ in baseline characteristics from patients who do not develop delirium. However, our cohort is uniquely able to provide information about cognitive performance long before and after delirium. We conducted a sensitivity analysis by matching patients on preindex trajectory of IMC scores and on baseline IMC scores. Our inferences were unchanged, suggesting that the differences in baseline trajectory were not contributing substantially to the findings.

Several caveats deserve comment. First, the semiannual intervals between MADRC visits did not allow us to capture the maximal acute effect of delirium on the rate of cognitive deterioration, which would be most pronounced shortly after delirium onset. However, this limitation likely introduces a conservative bias. We included breaks in the cognitive trajectory at 1 and 2 years after the index hospitalization to accommodate the potential for only short-term deterioration, but we observed deterioration during 5 years. This finding suggests that delirium may fundamentally alter the cognitive trajectory in a sustained fashion. Second, we had no way to detect the occurrence of delirium in home settings. However, episodes that did not result in hospitalization were likely milder, and we accounted for rehospitalizations in sensitivity analyses. Third, the medical record review method is an imperfect strategy for classifying delirium and likely leads to an underestimate of the true delirium prevalence because features of delirium may be more difficult to document from a medical record review in patients with dementia.[35,47] However, based on published sensitivity and specificity for medication review among patients with delirium,[33] we would expect 41% of the no delirium group to include false-negative cases but only 9% of the delirium group to include false-positive cases.[33] Therefore, although we cannot determine with certainty, group differences in the rate of cognitive deterioration are likely conservative estimates. Fourth, self-report measures of depression symptoms were unavailable. Fifth, we had no information about new diagnoses (such as stroke) during the follow-up period. However, we controlled for many important potential confounders, and our sensitivity analyses that excluded rehospitalized patients help to strengthen our inferences.

We used a well-characterized clinical sample of community-dwelling patients with AD and included rich, rigorously collected longitudinal data on cognitive function, dementia staging, and control variables. Our results challenge the notion that delirium is transient and reversible in AD. Delirium is recognized by physicians and nurses in less than 30% of hospitalized patients.[48-50] Lack of recognition may be attributed in part to the widely held notion that the impact of delirium is unimportant and inevitable during hospitalization and has no long-term significance in patients with AD.[9] If delirium worsens the long-term course of cognitive function among persons with AD, it should be handled as a genuine medical emergency, meriting changes to incorporate routine delirium prevention in the standard practice for patients with dementia to ensure timely intervention to prevent long-term cognitive deterioration. Ongoing education of physicians, nurses, and other health care providers and widespread availability of brief cognitive screening tests and the use of the Confusion Assessment Method would help to improve delirium screening at the bedside.[11] In high-risk patients, application of tested protocols (such as reorientation, mobility, hydration, and therapeutic activities) from the Hospital Elder Life Program may help to prevent delirium in this population.[9] Delirium prevention is an important area for future investigation.

Previous research suggests that targeted delirium prevention programs might help to reduce delirium for at least 27% of patients with AD, which represents 1.2 million persons in the United States and 4 million people worldwide.[3,6-8] Given that the national costs of delirium are estimated to be $40 to $150 billion annually,[51] strategies that affect even a fraction of these costs have the potential for far-reaching cost savings for our health care system,[52,53] greatly exceeding the costs of current pharmacological treatments for AD. Future work is urgently needed to determine whether prevention of delirium in the population with AD will improve the trajectory of cognitive decline demonstrated in this study, with resultant improvements in quality of life for patients and their families.

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INVITED COMMENTARY

The Danger of Delirium

We in medicine have long wondered if a period spent in delirium during a hospitalization leads to a change in the trajectory of cognitive decline (a phenomenon any busy clinician would vouch he or she has seen many times) or if that accelerated decline is due to other comorbidities. Whereas many hospital-acquired conditions are considered short-term complications (eg, hospital-acquired pneumonia), we increasingly recognize that the effect of hospitalization on patients' functional and cognitive health may be prolonged or permanent.

The long-term effects of hospitalization on cognition are highlighted by a pair of recent studies. In a large prospective community cohort, Ehlenbach et al[1] demonstrated a 40% increased risk of incident dementia up to 6 years following hospitalization for a noncritical illness (hazard ratio, 1.4; 95% CI, 1.1-1.7) and an even greater risk among the critically ill (hazard ratio, 2.3; 95% CI, 0.9-5.7). In another cohort of community-dwelling older patients, Wilson et al[2] showed that hospitalization was independently associated with a 2.4-fold increase in the rate of global cognitive function decline.

Each study raised important questions about the mechanism by which hospitalizations lead to incident and accelerated cognitive decline. Sepsis, critical illness, and surgical procedures seem to have a role, but they do not tell the whole story.[3,4] In each case, the development of delirium has been hypothesized to be an important hospital-acquired condition that may be a critical mediator of the subsequent acquisition of a long-term dementia-like disability. This has been recently supported by important studies[5,6] that demonstrated independent relationships between hospital-acquired delirium and short-term and long-term cognitive impairments.

The study by Gross et al[7] in this issue of the *Archives of Internal Medicine* seeks to highlight further the role of hospital-acquired delirium in the progression of cognitive decline. This study examines a unique cohort of 263 hospitalized patients with preexisting Alzheimer dementia. This cohort was followed up for a median of 3.2 years, during which 56.3% developed delirium during their index hospitalization. The authors subsequently found that the development of hospital-acquired delirium was independently associated with cognitive deterioration up to 5 years after hospitalization at a rate 2.2 times greater than that among patients without delirium.

A methodological challenge of studying the long-term effects of hospitalization is appropriately considering the cognitive status before hospitalization. Without prehospitalization information, one is at risk of erroneously concluding that hospitalization, or a hospital-acquired condition such as delirium, independently affects posthospitalization outcomes, when in fact the relationship may be alternatively explained by patients' prehospitalization cognitive function or trajectory. This study has gone to great lengths to overcome this bias by examining a cohort with frequent and robust measures of cognitive function before hospitalization. By limiting the population to those followed up for at least 3 clinic visits, the authors were able to adjust for baseline and trajectory of cognitive decline. As a result, significantly greater certainty exists that the hospitalization event was a major factor in the subsequent cognitive decline.

The authors' primary question was whether delirium was the hospital-acquired event that accounted for rapid progression of cognitive decline. This question is a more challenging one given the complex nature of hospitalization and the limitations of medical record–based di-