Association Between Acute Care and Critical Illness Hospitalization and Cognitive Function in Older Adults

William J. Ehlenbach, MD, MSc
Catherine L. Hough, MD, MSc
Paul K. Crane, MD, MPH
Sebastien J. P. A. Haneuse, PhD
Shannon S. Carson, MD
J. Randall Curtis, MD, MPH
Eric B. Larson, MD, MPH

Context Studies suggest that many survivors of critical illness experience long-term cognitive impairment but have not included premorbid measures of cognitive functioning and have not evaluated risk for dementia associated with critical illness.

Objectives To determine whether decline in cognitive function was greater among older individuals who experienced acute care or critical illness hospitalizations relative to those not hospitalized and to determine whether the risk for incident dementia differed by these exposures.

Design, Setting, and Participants Analysis of data from a prospective cohort study from 1994 through 2007 comprising 2929 individuals 65 years old and older without dementia at baseline residing in the community in the Seattle area and belonging to the Group Health Cooperative. Participants with 2 or more study visits were included, and those who had a hospitalization for a diagnosis of primary brain injury were censored at the time of hospitalization. Individuals were screened with the Cognitive Abilities Screening Instrument (CASI) (score range, 0-100) every 2 years at follow-up visits, and those with a score less than 86 underwent a clinical examination for dementia.

Main Outcome Measures Score on the CASI at follow-up study visits and incident dementia diagnosed in study participants, adjusted for baseline cognitive scores, age, and other risk factors.

Results During a mean (SD) follow-up of 6.1 (3.2) years, 1601 participants had no hospitalization, 1287 had 1 or more noncritical illness hospitalizations, and 41 had 1 or more critical illness hospitalizations. The CASI score was assessed more than 45 days after discharge for 94.3% of participants. Adjusted CASI scores averaged 1.01 points lower for visits following acute care illness hospitalization compared with follow-up visits not following any hospitalization (95% confidence interval [CI], −1.33 to −0.70; $P<.001$) and 2.14 points lower on average for visits following critical illness hospitalization (95% CI, −4.24 to −0.03; $P=.047$). There were 146 cases of dementia among those not hospitalized, 228 cases of dementia among those with 1 or more noncritical illness hospitalizations, and 5 cases of dementia among those with 1 or more critical illness hospitalizations. The adjusted hazard ratio for incident dementia was 1.4 following a noncritical illness hospitalization (95% CI, 1.1 to 1.7; $P=.001$) and 2.3 following a critical illness hospitalization (95% CI, 0.9 to 5.7; $P=.09$).

Conclusions Among a cohort of older adults without dementia at baseline, those who experienced acute care hospitalization and critical illness hospitalization had a greater likelihood of cognitive decline compared with those who had no hospitalization. Noncritical illness hospitalization was significantly associated with the development of dementia.

JAMA. 2010;303(8):763-770 www.jama.com

THE INCIDENCE OF CRITICAL ILLness syndromes such as acute lung injury and severe sepsis and the use of critical care procedures such as mechanical ventilation are increasing in the United States and are higher for older adults.[1-4] These trends, coupled with an aging population and a declining mortality rate among the critically ill, are resulting in a growing number of patients who are survivors of critical illness.

These survivors often have significant long-term morbidity, such as reduced physical function, increased psychological symptoms, and reduced quality of life, that appears to be a direct consequence of critical illness and its treatment.[5-7] Because more than half of intensive care unit (ICU) bed-days in the United States involve patients 65 years old and older, a large proportion of these survivors are in this age group.[8,9] A growing body of literature describes an association between critical illness and long-term cognitive im-

CME available online at www.jamaarchivescme.com and questions on p 795.

Author Affiliations: Department of Medicine, University of Washington, Seattle (Drs Ehlenbach, Hough, Crane, Curtis, and Larson); Health Services Research and Development, Department of Veterans Affairs, Seattle (Dr Ehlenbach); Group Health Research Institute, Seattle (Drs Haneuse and Larson); and Division of Pulmonary and Critical Care Medicine, University of North Carolina, Chapel Hill (Dr Carson).
Corresponding Author: William J. Ehlenbach, MD, MSc, Health Services Research and Development, Department of Veterans Affairs, 1100 Olive Way, Ste 1400, Seattle, WA 98101 (wje1@u.washington.edu).

©2010 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/01/2017

pairment.[6,10-15] Abnormalities in cognitive domains of executive function, attention, and memory appear to be the most common and have been demonstrated as long as 6 years after hospital discharge.[10,11,16] However, to our knowledge, none of the studies thus far has included objective measures of cognitive function before critical illness, and none have evaluated the risk of incident dementia among survivors of critical illness.

Understanding the association between critical illness and neurocognitive impairment has the potential to improve the care of critically ill patients in several ways. First, physicians will be aware of the potential for cognitive decline after hospitalization. Second, establishing that an association exists will help direct research at the contributing factors behind the association or guide the creation of specific rehabilitation programs for these patients. We used an existing cohort study conducting serial cognitive testing on older adults combined with administrative data from hospitalizations to examine associations between hospitalizations for acute illness or critical illness and cognitive decline and dementia in older individuals.

METHODS

Study Sample

This study involves analysis of data from an ongoing prospective cohort study, Adult Changes in Thought (ACT) . The ACT study is a population-based longitudinal study of aging and dementia designed to determine the incidence of cognitive impairment and dementia as well as risk factors for these conditions. The details of this study have been described elsewhere.[17-19] The ACT study population was created from a random sample of individuals without dementia 65 years old and older residing in the Seattle area, not residing in a nursing home at baseline, and belonging to the Group Health Cooperative, a consumer-governed health maintenance organization. Participants were interviewed with structured questionnaires to obtain data including demographic characteristics, medical history, memory and general functioning, and potential epidemiologic risk factors. Participants also received the Cognitive Abilities Screening Instrument (CASI)[20] as initial screening for cognitive function and were retested at each study visit. Those individuals identified as having dementia based on the evaluations performed at the initial study visit were not enrolled in the parent study cohort.

The original cohort was enrolled between 1994 and 1996, with 2581 of 5422 eligible individuals agreeing to participate.[17] Between 2000 and 2002, an expansion cohort was recruited with an additional 811 individuals. In recent years, a continuous enrollment strategy has been used to keep the number of alive and at-risk individuals in the cohort at approximately 2000. Each study participant was evaluated approximately once every 2 years. The ACT study has an excellent completeness of follow-up index of more than 95%.[21] Participants with 2 or more study visits during which a valid cognitive screening score was obtained in the parent study were included in the present study (eFigure, available at http://www.jama.com).

Both the parent study and this specific study were approved by the institutional review board of the Group Health Cooperative. All participants provided written consent to study participation at study enrollment.

Cognitive Performance Test

The CASI provides quantitative assessment of attention, concentration, orientation, short-term memory, long-term memory, language ability, visual construction, list-generating fluency, abstraction, and judgment.[20] The CASI has a potential range of 0 to 100 with higher scores indicating better cognitive performance. A score of 86 corresponds to a Mini-Mental State Examination score of 25 to 26.[22] In prior analyses of data from the ACT study, we found that the CASI had curvilinear scaling properties such that a given number of standard CASI points was associated with a variable amount of cognitive ability at different parts of the ability spectrum. In that same analysis, we performed some simulation studies and demonstrated that use of standard scores with curvilinear tests produced biased estimates of rates of change compared with using item response theory (IRT) scores.[23]

In IRT, tests are conceptualized as collections of items measuring a common underlying ability or trait. Each item has a difficulty level. Cognitive tests such as the CASI have several items with difficulty levels appropriate for individuals with moderate levels of impairment but few very hard questions appropriate for those with excellent cognition. Therefore, for an individual with excellent cognitive ability, a 5-point decline from 100 to 95 represents a relatively large cognitive decline because there are relatively few test items at risk. An individual with moderate impairment whose score declines from 80 to 75 points would have relatively less cognitive decline because there are many more test items at risk. The distribution of item difficulties is not uniform across all ability levels, so standard scores that sum the number of items answered correctly have a curvilinear relationship with the underlying ability measured by the test. IRT scores analyze item-level data, so they have a linear relationship with the underlying ability measured by the test and should be preferred to standard scores for analyses of change over time.[23]

In the current study, we were interested in the effects of hospitalization and critical illness on estimates of cognition over time, so we needed a dependent variable that had linear scaling properties. We therefore performed analyses using IRT scores. We used data about the CASI items (item difficulty and discrimination parameters) from our previously published analyses[23] to generate scores at each study visit. We used the IRT computer program Parscale[24] (Scientific Software International Inc, Chicago, Illinois) and an IRT model called the graded response model,[25,26] which is appropriate for

 ©2010 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/01/2017

items with multiple response categories. The scale for IRT scores was defined such that the mean score was 0 and standard deviation was 1 among individuals without dementia at their most recent study visit.

Exposure Definitions

The present study linked data from this ongoing prospective cohort study with claims data from hospitalizations of study participants that were submitted to the health maintenance organization to which all study participants belonged. We examined diagnosis and procedure codes from all hospitalizations. Hospitalizations were identified as including critical illness by the presence of any 1 of a list of critical illness diagnosis and procedure codes from the *International Classification of Diseases, Ninth Revision* (*ICD-9*) , including shock without mention of trauma (785.5 and all 5-digit breakouts), severe sepsis (995.92), traumatic shock (958.4), postoperative shock (998.0), acute respiratory failure (518.81), other pulmonary insufficiency not elsewhere classified (518.82), acute on chronic respiratory failure (518.84), hypotension (458), respiratory arrest (799.1), cardiac arrest (427.5), cardiopulmonary resuscitation not otherwise specified (99.60), closed chest cardiac massage (99.63), and continuous mechanical ventilation for 96 consecutive hours or more (96.72).

Noncritical illness hospitalization and critical illness hospitalization were each coded with an indicator variable, and this variable changed after the relevant exposure such that visits before such a hospitalization were considered unexposed and visits afterwards were considered exposed. In this way, the exposures to acute care and critical illness hospitalizations were each considered in a time-dependent fashion. We censored individuals who received 1 or more diagnosis codes for primary brain injury during any hospitalization, including ischemic stroke (430, 431, 432.0, 432.1, 432.9, 433.01, 433.11, 433.21, 433.31, 433.91, 434.01, 434.11, 434.9), brain hemorrhage (430, 431, 432.1, 432.0, 432.9), and head trauma (851, 852, 853, 854), at the time such a hospitalization occurred.

Incident Dementia

We screened participants every 2 years using the CASI to identify cases of incident dementia. Scores on the CASI that were less than 86 prompted a full standardized clinical examination.[19] The results of rescreening by the CASI and clinical and neuropsychological examinations were reviewed at a consensus diagnosis conference that included at least the examining physician, a neuropsychologist, another study physician, and the study nurse. Participants who did not meet the criteria for dementia continued to be followed up in the ACT cohort.[17,18] Participants who met the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*)[27] criteria for dementia were considered to have incident dementia. We examined dementia subtype (categorized as vascular dementia using *DSM-IV* criteria,[27] Alzheimer disease using NINCDS-ADRDA criteria,[28] or other) by exposure category using the χ^2 statistic.

Statistical Analysis

For those individuals who were hospitalized, we compared the change in standard total CASI score for the interval that included hospitalization with the change in standard total CASI score for the interval that preceded hospitalization. To further assess the association of critical illness or noncritical illness hospitalizations with cognitive function, we developed multiple linear regression models using population-averaged generalized estimating equations (GEE).[29] An exchangeable correlation matrix was specified, and robust (Huber-White) sandwich-based standard errors[30-33] were used to account for within-subject correlation and ensure valid inference for the GEE estimates.[34]

The outcome variable for these models was CASI score at follow-up study visits. The variables of baseline CASI score, age at study visit, sex, years of education, time since baseline study visit, and presence of self-reported coronary heart disease (CHD) (including a history of congestive heart failure, myocardial infarction, angina, or coronary artery bypass grafting) and cerebrovascular disease (CVD) (including a history of stroke, cerebral hemorrhage, or small stroke/transient ischemic attack) at the baseline visit were added to the model a priori based on known associations between these predictors and the risk of cognitive decline. To evaluate the effect of critical illness and noncritical illness hospitalizations on the slope of CASI decline, we tested interactions between time and the critical illness and noncritical hospitalization indicators. An additional model added race/ethnicity (self-indicated by study participants), baseline presence of self-indicated renal disease, pulmonary disease (including chronic obstructive pulmonary disease and asthma), malignancy (including solid tumors, leukemia, and lymphoma but excluding skin cancer), rheumatologic disease (including rheumatoid arthritis, lupus, or autoimmune disease), and smoking history (with a binary indicator of active cigarette smoking and the total pack-years smoked). Results were compared with our primary model as a sensitivity analysis. These models were repeated using CASI IRT as the outcome variable. The prespecified (primary) analyses for CASI and CASI IRT were performed as complete-case analyses in that observations with missing values for any of the covariates in the models were excluded.

We tested for associations between critical illness and noncritical illness hospitalizations and incident dementia using Cox proportional hazards regression. The time of dementia diagnosis was considered to be the study visit at which the dementia evaluation was initiated (ie, when the individual scored <86 on the CASI) for those individuals subsequently found to meet diagnostic criteria for dementia. This time point was chosen because our hypothesis was that critical illness results in the development of chronic cog-

©2010 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/01/2017

nitive impairment over a relatively short time. This hypothesis was derived from literature demonstrating that a substantial proportion of survivors of critical illness have profound cognitive dysfunction present at hospital discharge.[35] The regression models used age at study visit as the time axis and used age at study entry as the beginning of the time period. Participants who left the study or died before developing dementia were censored at their last examinations, and participants who remained dementia-free at their most recent study visit were censored at the most recent follow-up date. Age at study entry was included in the model. The baseline cognition score, sex, years of education, and self-reported presence of CVD and CHD at study entry were included in the regression model a priori. Sensitivity analysis added race/ethnicity; baseline presence of self-indicated renal disease, pulmonary disease, malignancy, and rheumatologic disease; and smoking history. We included race/ethnicity in sensitivity analyses because scores on cognitive tests have been shown to differ by race for reasons that are not completely understood.[36] The Schoenfeld residual test was used to assess violations of the proportional hazards assumption. The variable indicating the presence of CHD at baseline was found to violate the assumption of proportionality and therefore was included in models as a time-varying covariate. The prespecified (primary) analyses for incident dementia were performed as complete-case analyses in that observations with missing values for any of the covariates in that model were excluded.

Additional sensitivity analyses were as follows: (1) individuals observed for fewer than 4 years were excluded to assess potential bias introduced because those patients who were observed to have experienced hospitalizations during study participation had greater median time under study, to evaluate for potential bias introduced by censoring or death; and (2) for those who died or withdrew from the study, those with a CASI score lower than 86 at his or her final study visit were assumed to have gone on to develop dementia 1 year after their last study visit for the analysis of incident dementia.

We estimate that the study had a power of 0.98 to detect a mean difference in follow-up CASI score of 4.2 points (the difference between mean baseline score and a score of 89, indicating possible mild cognitive impairment) between those with critical illness hospitalization and those without hospitalization. We estimate that this study had power of 0.64 to detect a difference in the survival curves for time to incident dementia between those with critical illness hospitalization and those never hospitalized using the log-rank test.

Statistical analyses were performed using Stata 10 (StataCorp, College Station, Texas). All reported *P* values were 2-sided, and results were considered statistically significant at the $P < .05$ level.

RESULTS

Analysis of data included 2929 individuals from the study period 1994 through 2007. During a mean (SD) follow-up of 6.1 (3.2) years, 1601 participants had no hospitalizations while enrolled in the study. A total of 1287 study participants who were hospitalized for noncritical illness experienced 2514 hospitalizations. Forty-one patients experienced 43 critical illness hospitalizations, of whom 30 patients also had 95 noncritical hospitalizations. Only 14 of these noncritical hospitalizations in 9 individuals occurred before the first interval during which they experienced a critical illness hospitalization.

There were 2931 follow-up study visits occurring any time after a noncritical illness hospitalization, 76 follow-up study visits occurring after critical illness hospitalization, and 8675 follow-up study visits occurring after no hospitalizations. Participants spent a median of 4.02 years (interquartile range [IQR], 2.01-7.92 years) under study before any hospitalization. Those who experienced acute care hospitalization spent a median of 4.07 years (IQR, 2.02-6.00 years) under study after this hospitalization, and those who experienced a critical care hospitalization spent a median of 3.67 years (IQR, 2.12-7.95 years) under study after critical illness hospitalization. The median time between the most recent noncritical illness hospital discharge and the first study visit following this hospitalization was 307 days (IQR, 150-501 days). The median time between the most recent hospital discharge during an interval that included critical illness and the next study visit following this hospitalization was 365 days (IQR, 196-412 days); 94.3% of the study visits after an interval that included hospitalization took place more than 45 days after the most recent hospital discharge. Individuals experiencing a critical illness hospitalization during study participation were more likely to be men, had slightly lower mean education but slightly higher baseline CASI and CASI IRT scores, and were more likely to indicate a history of CHD at study entry (**Table 1**). There were 28 individuals who had missing values for 1 or more of the covariates included in the primary models (0.95% of the sample) and who were excluded from analyses.

For those individuals with a critical illness hospitalization, the median (IQR) change in CASI score was −1.5 (−3.0 to 1.0) for the interval that included a critical illness hospitalization compared with 0 (−2.1 to 2.0) for the preceding interval. For those individuals with a noncritical hospitalization, the median change in CASI score was −1.0 (−3.6 to 1.0) for the interval that included a noncritical hospitalization compared with −0.2 (−3.0 to 2.0) for the preceding interval. After adjusting for age at study visit, sex, baseline CASI score, years of education, time since baseline visit, and the baseline comorbidities of CHD and CVD, CASI scores were found to be a mean of 1.01 points lower (95% confidence interval [CI], 1.33 to 0.70; $P < .001$) for visits following noncritical illness hospitalization compared with follow-up visits not following any hospitalization and

 ©2010 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/01/2017

2.14 points lower (95% CI, 4.24 to 0.03; $P = .047$) for visits following critical illness hospitalization compared with follow-up visits not following any hospitalization (TABLE 2). We observed similar results when CASI IRT rather than standard CASI scores were used (Table 2). The estimated differences in follow-up CASI and CASI IRT scores for visits following noncritical and critical illness hospitalizations were similar in models adjusting for the more exhaustive list of possible confounders (see eTable 1, available at http://www.jama.com). The rate of decline of CASI scores did not differ significantly before and after critical illness, although the study may have been underpowered to detect a difference (interaction term between time since baseline visit and the indicator variable, $P = .39$ in the model using CASI and $P = .26$ in the model using CASI IRT).

There were 146 cases of dementia among those never hospitalized during study participation, a crude incidence of 14.6 cases per 1000 person-years (95% CI, 12.6 to 17.0). Among those experiencing 1 or more noncritical illness hospitalizations but no critical illness hospitalizations during study participation, there were 228 cases of dementia (33.6 cases per 1000 person-years; 95% CI, 29.2 to 38.5). There were 5 cases of dementia among those experiencing 1 or more critical illness hospitalizations during study participation, with a crude incidence of 31.1 cases per 1000 person-years (95% CI, 12.9 to 74.6). Review of the subtypes of dementia diagnosed shows that among those diagnosed with dementia, a higher proportion of individuals in the never-hospitalized group were diagnosed with Alzheimer disease than in the other 2 groups (76% in the never-hospitalized group vs 60% in the group with 1 or more noncritical illness hospitalizations and 40% in the critical illness hospitalization group; χ^2 test for difference in this proportion across groups, $P = .004$) (TABLE 3). Additionally, 403 individuals referred for dementia evaluation were found to not meet criteria for dementia (157 in the never-hospitalized group, 243 in the noncritical illness hospitalization group, and 4 in the critical illness group). These individuals remained in the study following the assessments for dementia.

After adjusting for age at study entry, sex, baseline CASI IRT score, years of education, and the baseline comorbidities of CHD and CVD, the hazard ratio (HR) for incident dementia following a noncritical ill-

Table 1. Characteristics of Study Patients at Baseline Visit Categorized by Subsequent Hospitalization

	No Hospitalizations During Study (n = 1601)	One or More Noncritical Illness Hospitalizations (n = 1287)	One or More Critical Illness Hospitalizations (n = 41)
Women, No. (%)	969 (60.5)	752 (58.4)	18 (44)
Age, mean (SD), y	74.6 (6.0)	75.4 (6.2)	75.4 (6.6)
Race/ethnicity, No. (%)			
White	1415 (88.4)	1191 (92.5)	39 (95)
Black	79 (4.9)	50 (3.9)	1 (2)
Asian	71 (4.4)	32 (2.5)	1 (2)
American Indian/ Alaskan Native	2 (0.1)	3 (0.2)	NA
Other, including multiple	33 (2.1)	11 (0.9)	NA
Missing value	1 (0.1)	NA	NA
Education, mean (SD), y[a]	14.3 (3.1)	13.8 (2.9)	13 (3.1)
Coronary heart disease, No. (%)			
Yes	253 (15.8)	294 (22.8)	15 (37)
No	1344 (84.0)	986 (76.6)	25 (61)
Missing value	4 (0.3)	7 (0.5)	1 (2)
Cerebrovascular disease, No. (%)			
Yes	133 (8.3)	141 (11.0)	4 (10)
No	1459 (91.1)	1142 (88.7)	37 (90)
Missing value	9 (0.6)	4 (0.3)	NA
Pulmonary disease, No. (%)			
Yes	257 (16.1)	228 (17.7)	8 (20)
No	1338 (83.6)	1053 (81.8)	33 (80)
Missing value	6 (0.4)	6 (0.5)	NA
Diabetes, No. (%)			
Yes	125 (7.8)	146 (11.3)	6 (15)
No	1475 (92.1)	1140 (88.6)	35 (85)
Missing value	1 (0.1)	1 (0.1)	NA
Kidney disease, No. (%)			
Yes	85 (5.3)	93 (7.2)	4 (10)
No	1516 (94.7)	1192 (92.6)	37 (90)
Missing value	NA	2 (0.2)	NA
Malignancy, No. (%)			
Yes	267 (16.7)	244 (19.0)	6 (15)
No	1333 (83.3)	1043 (81.0)	35 (85)
Missing value	1 (0.1)	NA	NA
CASI score at baseline, mean (SD)	93.2 (4.7)	92.9 (4.7)	93.9 (4.4)
CASI IRT at baseline, median (IQR)	0.27 (–0.23 to 0.79)	0.23 (–0.25 to 0.72)	0.59 (0.06 to 0.95)
Change in CASI score, mean (SD)[b]	–1.83 (6.48)	–3.81 (8.10)	–5.28 (10.34)
Follow-up time, median (IQR), y	4.1 (2.0 to 9.9)	7.9 (4.1 to 9.9)	8.0 (4.1 to 9.9)
Study visits, mean (IQR), No.	3 (2 to 5)	5 (3 to 6)	4 (3 to 6)

Abbreviations: CASI, Cognitive Abilities Screening Instrument; IQR, interquartile range; IRT, item response theory; NA, not applicable.
[a] Education missing for 1 individual in each category.
[b] Change in CASI score between baseline study visit and last study visit.

©2010 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/01/2017

ness hospitalization was 1.4 (95% CI, 1.1 to 1.7; $P=.001$) and 2.3 following a critical illness hospitalization (95% CI, 0.9 to 5.7; $P=.09$) (TABLE 4). Results of an analysis including the more exhaustive list of comorbidities as possible confounders were not substantially different (eTable 2). When analysis was restricted to those individuals enrolled in the study for at least 4 years, the association between noncritical illness hospitalization and dementia was not substantially different (HR, 1.5; 95% CI, 1.2 to 2.0; $P=.001$), and for critical illness hospitalization, the HR was 2.0 (95% CI, 0.6 to 6.5; $P=.26$). There were 263 cases of dementia in this restricted analysis (99 in those without hospitalization, 161 in those with noncritical hospitalization, and 3 in those with 1 or more critical illness hospitalizations). When those individuals who dropped out or died and whose last observed CASI score was less than 86 were assumed to have developed dementia 1 year after their last study visit, the association between noncritical illness hospitalization and incident dementia remained significant but was attenuated (HR, 1.2; 95% CI, 1.0 to 1.4; $P=.04$) and the nonsignificant association between critical illness hospitalization and incident dementia was also attenuated (HR, 1.7; 95% CI, 0.8 to 3.6; $P=.16$).

Table 2. Difference in Follow-up Cognitive Scores by Hospitalization Status[a]

	Difference in Score (95% CI)[b]			
	Following Noncritical Illness Hospitalization	*P* Value	Following Critical Illness Hospitalization	*P* Value
Follow-up CASI	−2.27 (−2.61 to −1.93)	<.001	−2.92 (−5.00 to −0.86)	.006
Adjusted difference[c]	−1.01 (−1.33 to −0.70)	<.001	−2.14 (−4.24 to −0.03)	.047
Follow-up CASI IRT	−0.28 (−0.32 to −0.24)	<.001	−0.27 (−0.45 to −0.09)	.003
Adjusted difference[c]	−0.12 (−0.16 to −0.08)	<.001	−0.19 (−0.38 to −0.01)	.04

Abbreviations: CASI, Cognitive Abilities Screening Instrument; CI, confidence interval; IRT, item response theory.
[a] Linear regression with generalized estimating equations to account for repeated observations, specifying an exchangeable correlation matrix and robust variance estimates.
[b] The reference category in each comparison was no hospitalization.
[c] Adjusted for age at study visit, sex, baseline cognitive score, years of education, time since baseline visit, and the baseline comorbidities coronary heart disease and cerebrovascular disease.

Table 3. Dementia Subtype (Categorized According to *DSM-IV*) by Hospitalization Status

	No. (%)		
	No Hospitalizations During Study (n = 146)	One or More Noncritical Illness Hospitalizations (n = 228)	One or More Critical Illness Hospitalizations (n = 5)
Alzheimer type	111 (76)	138 (60)	2 (40)
Vascular	10 (7)	26 (11)	1 (20)
Other[a]	25 (17)	64 (28)	2 (40)

Abbreviation: *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).
[a] Includes dementias due to general medical conditions, substance-induced persisting dementia, dementia due to multiple etiologies, and other or unknown cause.

Table 4. Risk of Incident Dementia by Hospitalization Status[a]

	No Hospitalizations During Study (n = 1601)	One or More Noncritical Illness Hospitalizations (n = 1287)	*P* Value	One or More Critical Illness Hospitalizations (n = 41)	*P* Value
Cases of incident dementia, No.	146	228		5	
Risk of incident dementia, HR (95% CI)	1 [Reference]	1.5 (1.3 to 1.9)	<.001	1.7 (0.7 to 4.0)	.27
Adjusted risk of incident dementia, HR (95% CI)[b]	1 [Reference]	1.4 (1.1 to 1.7)	.001	2.3 (0.9 to 5.7)	.09

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Cox proportional hazards regression with age at study visit as the time axis and age at study entry as the beginning of the time period.
[b] Adjusted for age at study entry, sex, baseline Cognitive Abilities Screening Instrument item response theory score, years of education, and baseline comorbidities of coronary heart disease and cerebrovascular disease, with presence of coronary heart disease at baseline included as a time-varying covariate.

COMMENT

Our study showed that noncritical and critical illness hospitalizations were each associated with greater decline in cognitive functioning scores in a cohort of older adults. The mechanism of this association is uncertain. Hospitalization may be a marker for cognitive decline or dementia that has not been diagnosed. This is the first study to our knowledge to find an association between critical illness and cognitive decline after adjusting for premorbid cognitive screening scores as well as comorbid illness. These results also could suggest that factors associated with acute illness, and to a greater degree with critical illness, may be causally related to cognitive decline.

Noncritical illness hospitalizations were significantly associated with incident dementia, while critical illness hospitalization and incident dementia were not statistically significantly associated, although this comparison had low power to detect a difference. This significant association further strengthens the existing evidence regarding an association between hospitalization and cognitive impairment and underscores its clinical relevance. Given the absence of a significant interaction between time and our exposure indicators, we did not find evidence that the rate of cognitive decline changed after either noncritical or critical illness hospitalization. This suggests that an acute or critical illness may cause an abrupt loss of cognitive function rather than steepening the slope of decline or simply being a marker of cognitive decline.

 ©2010 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/01/2017

The mechanisms through which critical illness may contribute to neurocognitive impairment are multiple, with evidence suggesting that hypoxemia,[35,37,38] delirium,[39-41] hypotension,[42] glucose dysregulation,[43] systemic inflammation,[44] and sedative and analgesic medications[45,46] all may potentially play a role. Older adults are at greatly increased risk of dementia, and preexisting risk factors for cognitive decline likely put patients in this age group at elevated risk of brain injury from the mechanisms listed herein. Patients cared for in an ICU are more likely to experience these exposures, but the exposures are likely present to a lesser degree in many acutely ill patients hospitalized outside of an ICU and not meeting our criteria for critical illness. While previous studies of long-term cognitive function in survivors of acute lung injury have failed to show an association between severity of illness and cognitive impairment,[6,30] those studies have only examined small groups of patients with uniformly high severity of illness. In clinical practice, severity of acute illness exists on a continuum. Our study suggested a dose-effect based on point estimates of decline in cognitive function among survivors of critical illness compared with noncritically ill hospitalized patients, but the CIs overlapped.

Future research should clarify the role that specific aspects of critical illness or its treatment play in the development of cognitive impairment. Such information will be important in the search for factors that are modifiable, with the hope of reducing the prevalence of cognitive impairment among survivors of critical illness. Such information will also assist clinicians in providing patients and their loved ones with better information about long-term outcomes as they make the difficult decisions that often surround critical illness. The ability to predict who has greatest risk of cognitive impairment might also bolster the feasibility of early cognitive rehabilitation programs for survivors of critical illness. Finally, a better understanding of the mechanisms linking critical illness and cognitive impairment may advance our understanding of the pathophysiology of dementia more generally.

There are several important limitations of this study. First, since our definition of critical illness is derived only from administrative data, it relies on *ICD-9* diagnosis and procedure codes. This definition has not been validated, and there is a risk of misclassification of exposure. However, a gold-standard definition of what constitutes critical illness does not exist and misclassification seems likely to bias the results toward the null hypothesis, which would make our estimates of cognitive decline due to critical illness conservative. Second, the time interval between study visits was substantial. While the longitudinal nature of this study is a strength, the fact that study visits occurred every 2 years means that a hospitalization is only 1 of a number of possible significant events that could result in cognitive decline.

Third, a minimal clinically relevant decline in CASI score has not been established, which creates challenges in interpreting the clinical relevance of follow-up CASI scores that were 2.14 points lower, on average, following critical illness. However, patients experiencing a noncritical illness hospitalization were found to have a significantly higher risk of incident dementia than those not hospitalized, an outcome with clear clinical significance. Fourth, survivors of critical illness who continued to participate in the ACT study may not be representative of all older survivors of critical illness, and this may limit the generalizability of the study findings. However, since such patients continuing in the study may be healthier and likely have better cognitive and physical functioning than survivors as a whole, our findings may underestimate the association.

Finally, the fact that there were only 41 individuals identified who experienced critical illness and were observed for 1 or more study visits after such a hospitalization limited the power of this study to detect a statistically significant association between critical illness and incident dementia. This lack of power also prevented exploration of specific critical illness syndromes and cognitive decline. Despite these limitations, this is the first study to our knowledge to include a control group and adjust for baseline cognitive function, thereby providing stronger support for the hypothesis that critical illness leads to significant decline in cognitive function in some patients.

CONCLUSION

We found associations between acute care and critical illness hospitalizations and greater cognitive decline in analyses that adjusted for baseline (premorbid) cognitive function. We also found an association between acute care hospitalization and the subsequent risk for incident dementia. The point estimate for the association between critical illness and the subsequent risk for incident dementia was of greater magnitude but not statistically significant. Further studies are needed to better understand the factors associated with acute and critical illness that may contribute to cognitive impairment.

Author Contributions: Dr Ehlenbach had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Ehlenbach, Hough, Carson, Curtis, Larson.
Acquisition of data: Larson.
Analysis and interpretation of data: Ehlenbach, Hough, Crane, Haneuse, Curtis, Larson.
Drafting of the manuscript: Ehlenbach, Larson.
Critical revision of the manuscript for important intellectual content: Ehlenbach, Hough, Crane, Haneuse, Carson, Curtis, Larson.
Statistical analysis: Ehlenbach, Hough, Haneuse, Curtis.
Obtained funding: Hough, Crane, Larson.
Administrative, technical, or material support: Crane, Larson.
Study supervision: Curtis, Larson.
Financial Disclosures: None reported.
Funding/Support: The Adult Changes in Thought study is funded by a National Institutes of Health (NIH) National Institute on Aging Cooperative Grant (UO1 AG06781; principal investigator [PI]: Dr Larson). Additional funding for this study was provided by the John A. Hartford Foundation (PI: Dr Hough), a K24 Award from the National Heart, Lung, and Blood Institute (1 K24 HL068593; PI: Dr Curtis), and an R01 from the National Institute on Aging (R01 AG029672; PI: Dr Crane). Dr Ehlenbach was supported by an NIH Respiratory Research Training Grant (5T32HL007287-30; PI: Leonard Hudson, MD, University of Washington) and a Department of Veterans Affairs Health Services Research and Development Postdoctoral Fellowship.

©2010 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/01/2017

Role of the Sponsor: The funding agencies had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Online-Only Material: The eFigure and eTables 1 and 2 are available at http://www.jama.com.
Additional Contributions: Our colleague Steven L. Balch, MA, MBA, of the Group Health Research Institute, assisted with data cleaning, management, and analysis data set creation. He did not receive compensation for these contributions.

REFERENCES

1. Rubenfeld GD, Herridge MS. Epidemiology and outcomes of acute lung injury. *Chest*. 2007;131(2):554-562.
2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310.
3. Carson SS, Cox CE, Holmes GM, Howard A, Carey TS. The changing epidemiology of mechanical ventilation: a population-based study. *J Intensive Care Med*. 2006;21(3):173-182.
4. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med*. 2005;353(16):1685-1693.
5. Herridge MS, Cheung AM, Tansey CM, et al; Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348(8):683-693.
6. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF Jr. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2005;171(4):340-347.
7. Jackson JC, Hart RP, Gordon SM, et al. Six-month neuropsychological outcome of medical intensive care unit patients. *Crit Care Med*. 2003;31(4):1226-1234.
8. Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J Jr; Committee on Manpower for Pulmonary and Critical Care Societies (COMPACCS). Caring for the critically ill patient: current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? *JAMA*. 2000;284(21):2762-2770.
9. Carson SS. The epidemiology of critical illness in the elderly. *Crit Care Clin*. 2003;19(4):605-617.
10. Suchyta MR, Hopkins RO, White J, Jephson A, Morris AH. The incidence of cognitive dysfunction after ARDS [abstract]. *Am J Respir Crit Care Med*. 2004;169:A18.
11. Rothenhausler HB, Ehrentraut S, Stoll C, Schelling G, Kapfhammer HP. The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: results of an exploratory study. *Gen Hosp Psychiatry*. 2001;23(2):90-96.
12. Al-Saidi F, McAndrews MP, Cheung AM, et al. Neuropsychological sequelae in ARDS survivors [abstract]. *Am J Respir Crit Care Med*. 2003;167:A737.
13. Hopkins RO, Herridge MS. Quality of life, emotional abnormalities, and cognitive dysfunction in survivors of acute lung injury/acute respiratory distress syndrome. *Clin Chest Med*. 2006;27(4):679-689.
14. Sukantarat KT, Burgess PW, Williamson RC, Brett SJ. Prolonged cognitive dysfunction in survivors of critical illness. *Anaesthesia*. 2005;60(9):847-853.
15. Marquis K, Curtis J, Caldwell E, et al. Neuropsychological sequelae in survivors of ARDS compared with critically ill control patients [abstract]. *Am J Respir Crit Care Med*. 2000;161:A383.
16. Hopkins RO, Jackson JC. Long-term neurocognitive function after critical illness. *Chest*. 2006;130(3):869-878.
17. Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. *Arch Neurol*. 2002;59(11):1737-1746.
18. Wang L, van Belle G, Kukull WB, Larson EB. Predictors of functional change: a longitudinal study of nondemented people aged 65 and older. *J Am Geriatr Soc*. 2002;50(9):1525-1534.
19. Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann Intern Med*. 2006;144(2):73-81.
20. Teng EL, Hasegawa K, Homma A, et al. The Cognitive Abilities Screening Instrument (CASI): a practical test for cross-cultural epidemiological studies of dementia. *Int Psychogeriatr*. 1994;6(1):45-58.
21. Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. *Lancet*. 2002;359(9314):1309-1310.
22. Wang L, van Belle G, Crane PK, et al. Subjective memory deterioration and future dementia in people aged 65 and older. *J Am Geriatr Soc*. 2004;52(12):2045-2051.
23. Crane PK, Narasimhalu K, Gibbons LE, et al. Item response theory facilitated cocalibrating cognitive tests and reduced bias in estimated rates of decline. *J Clin Epidemiol*. 2008;61(10):1018-1027.
24. Parscale for Windows [computer program] version 4.1. Chicago, IL: Scientific Software International; 2003.
25. Samejima F. Estimation of latent ability using a response pattern of graded scores. *Psychometrika*. 1969;34(4):129-301.
26. Samejima F. *Graded Response Model*. New York, NY: Springer; 1997.
27. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
28. 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(7):939-944.
29. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42(1):121-130.
30. Jackson JC, Gordon SM, Burger C, Ely EW, Thomason JW, Hopkins RO. Acute respiratory distress disorder and long-term cognitive impairment: a case study [abstract]. *Arch Clin Neuropsychol*. 2003;18:687-807.
31. Huber PJ. The behavior of maximum likelihood estimates under nonstandard conditions. In: *Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability*. Berkeley: University of California Press; 1967:221-233.
32. White H. A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. *Econometrica*. 1980;48:817-830.
33. Diggle PJ, Liang KY, Zeger SL. *Analysis of Longitudinal Data*. Oxford, England: Clarendon Press; 1994.
34. Diggle PJ, Heagerty P, Liang K, Zeger SL. *Analysis of Longitudinal Data*. New York, NY: Oxford University Press; 2002.
35. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson LV. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1999;160(1):50-56.
36. Zsembik BA, Peek MK. Race differences in cognitive functioning among older adults. *J Gerontol B Psychol Sci Soc Sci*. 2001;56(5):S266-S274.
37. Hopkins RO, Gale SD, Johnson SC, et al. Severe anoxia with and without concomitant brain atrophy and neuropsychological impairments. *J Int Neuropsychol Soc*. 1995;1(5):501-509.
38. Hopkins RO, Kesner RP, Goldstein M. Item and order recognition memory in subjects with hypoxic brain injury. *Brain Cogn*. 1995;27(2):180-201.
39. Jackson JC, Gordon SM, Hart RP, Hopkins RO, Ely EW. The association between delirium and cognitive decline: a review of the empirical literature. *Neuropsychol Rev*. 2004;14(2):87-98.
40. Girard TD, Jackson JC, Pandharipande PP, Thompson JL, Shintani AK, Ely EW. Duration of delirium as a predictor of long-term cognitive impairment in survivors of critical illness [meeting abstract]. *Am J Respir Crit Care Med*. 2009;179(1):A5477.
41. Rudolph JL, Marcantonio ER, Culley DJ, et al. Delirium is associated with early postoperative cognitive dysfunction. *Anaesthesia*. 2008;63(9):941-947.
42. Hopkins RO, Weaver LK, Chan KJ, Orme JF Jr. Quality of life, emotional, and cognitive function following acute respiratory distress syndrome. *J Int Neuropsychol Soc*. 2004;10(7):1005-1017.
43. Hopkins RO, Jackson JC, Wallace C. Neurocognitive impairments in ICU patients with prolonged mechanical ventilation [abstract 60]. International Neuropsychological Society 33rd Annual Meeting; St Louis, MO; February 2005.
44. Elenkov IJ, Iezzoni DG, Daly A, Harris AG, Chrousos GP. Cytokine dysregulation, inflammation and well-being. *Neuroimmunomodulation*. 2005;12(5):255-269.
45. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA*. 2007;298(22):2644-2653.
46. Starr JM, Whalley LJ. Drug-induced dementia: incidence, management and prevention. *Drug Saf*. 1994;11(5):310-317.

 ©2010 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/01/2017