

# Premature Death Associated With Delirium at 1-Year Follow-up

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**Background:** While previous studies have demonstrated the increased mortality risk associated with delirium, little is known about the mortality time course. The objective of this study is to estimate the fraction of a year of life lost associated with delirium at 1-year follow-up.

**Methods:** Hospitalized patients 70 years and older who participated in a previous controlled clinical trial of a delirium prevention intervention at an academic medical center from March 25, 1995, through March 18, 1998, were followed up for 1 year after discharge, and patients who died were identified, along with the date of death. The adjusted number of days survived were estimated using a 2-step regression model approach and compared across patients who developed delirium during hospitalization and those who did not develop delirium.

**Results:** After adjusting for pertinent covariates (age, sex, functional status, and comorbidity), patients with delirium survived 274 days, compared with 321 days for patients without delirium, representing a difference of 13% of a year (hazard ratio, 1.62;  $P < .001$ ). Results were confirmed with a separate binomial regression analysis.

**Conclusions:** Patients who experienced delirium during hospitalization had a 62% increased risk of mortality and lost an average of 13% of a year of life compared with patients without delirium. Although delirium is an acute condition, it is associated with multiple long-term sequelae that extend beyond the hospital setting, including premature mortality.

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**D**ELIRIUM IS DEFINED AS AN acute decline of cognition and attention, and represents a frequent and morbid problem for hospitalized older patients, with hospital prevalence from 14% to 56% and hospital mortality from 25% to 33%.<sup>1</sup> The consequences of delirium are substantial, and include increased morbidity and mortality, persistent functional decline, increased length of hospital stay and costs per day, higher rates of nursing home placement, increased caregiver burden, and higher health care costs.<sup>2-9</sup>

Although delirium has been considered by many to be a transient syndrome, previous studies<sup>6,10-14</sup> have extensively documented that delirium and its symptoms often persist for at least a year after onset. While populations, definitions, and methods have varied between studies, consistently high rates of persistent delirium have been documented. Rockwood<sup>10</sup> reported persistent delirium at 1 year in 48% of survivors, and McCusker et al<sup>14</sup> reported persistent delirium at 1 year in 49% of survivors with dementia at baseline and 15% of survivors without dementia at baseline. Persistent delirium symptoms (including partial forms of delirium) were present at 3 and 6 months in 79% and 82%

of patients in one study,<sup>6</sup> respectively, and at 12 months in 54% to 62% of patients in another study.<sup>13</sup> Given the long duration of delirium and its symptoms, the exploration of long-term adverse outcomes associated with delirium is important.

While previous studies have documented an increased risk of in-hospital mortality associated with delirium,<sup>15-17</sup> few studies have examined the mortality risk associated with delirium after 1 year or more.<sup>4,18-21</sup> Edelstein et al<sup>19</sup> found that patients developing postoperative delirium following hip fracture were 2.5 times more likely to die within 1 year of discharge than patients without delirium (odds ratio, 2.5; 95% confidence interval [CI], 1.1-4.9). Francis and Kapoor<sup>4</sup> found that patients with delirium had significantly higher mortality risk within 2 years of discharge compared with patients without delirium (relative risk, 1.82; 95% CI, 1.04-3.19). A study by Rockwood et al<sup>21</sup> found that among patients followed up for a median of 32.5 months, those with delirium were 80% more likely to die than those without delirium after adjusting for clinical and demographic covariates (hazard ratio [HR], 1.80; 95% CI, 1.11-2.92). Finally, McCusker and colleagues<sup>20</sup> found an adjusted HR of 2.11 (95% CI, 1.18-3.77) associated with delirium in a sample of 361

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patients followed up for 12 months after discharge. However, none of these studies examined the mortality time course associated with delirium after adjusting for important clinical and demographic covariates.

Evaluating the mortality time course is important in assessing the severity of the mortality risk associated with a disease. If patients with delirium die earlier in the 12-month follow-up than patients without delirium, the mortality risk is worse than if patients died later in the year. Hence, the goal of this study is to estimate the impact of delirium on premature mortality among older hospitalized patients in the 12 months following discharge and to estimate the fraction of a year of life lost associated with delirium.

## METHODS

### SAMPLE

The study sample consists of 919 patients who were enrolled in a controlled trial of a delirium prevention intervention at an academic medical center from March 25, 1995, through March 18, 1998. The study sample represents a prospective cohort study with longitudinal follow-up, which has been described previously.<sup>22</sup> Briefly, patients meeting the following criteria were enrolled: consecutive admissions to 3 non-intensive care general medical units, 70 years or older, no evidence of delirium at admission, and at intermediate or high risk for delirium based on a previously developed risk model.<sup>23</sup> Patients who could not participate in interviews (those with profound dementia, a language barrier, profound aphasia, intubation, a coma, or respiratory isolation), had a terminal illness, had a hospital stay of 48 hours or less, or had prior enrollment in the study were excluded. Informed consent for participation and permission to acquire subsequent follow-up data were obtained from the patients or from a proxy for those with substantial cognitive impairment, according to procedures approved by the institutional review board of Yale University School of Medicine.

Delirium was ascertained daily during hospitalization. Patients who developed delirium while hospitalized were identified, and all patients were observed for up to 1 year following discharge to determine mortality rates.

### SOURCES OF DATA

Baseline data on patient demographic characteristics, comorbidities, and functional status were obtained from primary data collected during the controlled trial.<sup>22</sup> Deaths were identified by telephone follow-up at 1, 6, and 12 months following discharge, by daily obituary review, and by the Social Security Death Index. Mortality tracking was complete for all patients. All deaths and dates of death were confirmed by review of medical records, death certificates, or Medicare enrollment and claims files.

### STUDY VARIABLES

Delirium was ascertained using the confusion assessment method,<sup>24,25</sup> with delirium defined by the presence of acute onset and fluctuating course, inattention, and either disorganized thinking or altered level of consciousness. Other study variables included demographic variables (patient age, sex, minority status, years of education, marital status, and whether the patient was admitted from a nursing home), mental status measures (whether the patient had delirium during hospitalization, whether the patient had dementia at admission, and

Mini-Mental State Examination<sup>26</sup> score at admission), functional status measures (impairment in activities of daily living [ADLs]<sup>27</sup> or instrumental ADLs<sup>28</sup> at admission), burden of illness measures (APACHE [Acute Physiology and Chronic Health Evaluation] II score,<sup>29</sup> Charlson Comorbidity Index score,<sup>30</sup> and Burden of Illness Score for Elderly Persons<sup>31</sup>), and characteristics of the index hospitalization (whether the patient received the delirium intervention, length of stay, and total cost). Dementia was assessed using the modified Blessed Dementia Rating Scale<sup>32,33</sup> and the Mini-Mental State Examination, and was defined according to a definition used in previous studies<sup>34,35</sup> as a modified Blessed Dementia Rating Scale score of greater than 4 or a modified Blessed Dementia Rating Scale score of greater than 2 and a Mini-Mental State Examination score of less than 20 and duration of cognitive symptoms of at least 6 months. The APACHE II score, Charlson Comorbidity Index score, and Burden of Illness Score for Elderly Persons were determined by medical record review after patient discharge from the index hospitalization. Study group (intervention status) was used as an initial control variable in all models.

### STATISTICAL ANALYSES

First, proportions or means, where appropriate, were used to describe the demographic and clinical characteristics of the study population at enrollment and the mortality rates during the index hospitalization and 1-year follow-up.

Next, mortality risk and the average fraction of a year of life lost associated with the occurrence of delirium during the index hospitalization were estimated using a 2-step regression model approach. In the first step, a logistic regression model was used to calculate the probability of study participants surviving the index hospitalization according to delirium status. Because only 14 patients died during the index hospitalization, the only independent variable included in the logistic regression model was whether the patient had delirium.

In the second step, mortality among study participants who survived hospitalization was modeled using a Cox proportional hazards regression model in which the outcome was time to death and the censoring event was survival at the end of the 1-year follow-up. Delirium status during hospitalization was the main predictor in the Cox proportional hazards regression model. All other variables previously described were considered as potential covariates, and were entered in a backward elimination selection process if they had an unadjusted association with the time to death outcome with a statistical significance of  $P$  less than .10. If 2 or more variables from the same domain satisfied this criterion (eg, APACHE II score, Charlson Comorbidity Index score, and Burden of Illness Score for Elderly Persons), the measure with the highest unadjusted HR was included in the adjusted model. Intervention status was used as an initial independent variable in all models.

To estimate the mean number of days survived during the year of follow-up, we used the fact that the mean is equal to the area under the survival curve.<sup>36</sup> The survival curve was estimated in 2 steps. First, the probability that a patient survived hospitalization was determined using logistic regression. Next, the survival function was estimated conditional on surviving hospitalization using the Cox proportional hazards regression model. To obtain the unconditional survival probability, we used the definition of conditional probability, which implies that the vector of survival curve estimates from the Cox proportional hazards regression model be multiplied by a corresponding vector of probability estimates of surviving hospitalization obtained from the logistic regression model. The mean number of days was then obtained from these adjusted survival curves for the delirium and nondelirium groups by a process of

**Table 1. Characteristics of Patients in the Sample\***

Characteristic	Total Cohort (N = 919)	Died During Study Period (n = 222)	Survived the Study Period (n = 697)
<b>Demographic</b>			
Age, y†	80.0 ± 6.5	80.8 ± 6.8	79.8 ± 6.3
Male sex	365 (39.7)	111 (50.0)	254 (36.4)
Nonwhite race	119 (12.9)	28 (12.6)	91 (13.1)
Married	332 (36.1)	78 (35.1)	254 (36.4)
Education, y‡	11.1 ± 3.5	10.8 ± 3.5	11.2 ± 3.5
Nursing home resident	56 (6.1)	21 (9.5)	35 (5.0)
<b>Mental status</b>			
Delirium	115 (12.5)	48 (21.6)	67 (9.6)
Dementia	121 (13.2)	44 (19.8)	77 (11.0)
MMSE score of <24	406 (44.2)	114 (51.4)	292 (41.9)
<b>Functional status</b>			
ADL score (ordinal scale, 0-7)†	1.0 ± 1.7	1.5 ± 2.2	0.8 ± 1.5
IADL score (ordinal scale, 0-7)†	3.4 ± 2.1	4.0 ± 2.0	3.2 ± 2.1
<b>Burden of illness</b>			
APACHE II score of <16	363 (39.5)	118 (53.2)	245 (35.2)
Charlson Comorbidity Index score of >1	643 (70.0)	189 (85.1)	454 (65.1)
BISEP (ordinal scale, 1-4)†	2.0 ± 1.0	2.5 ± 1.1	1.8 ± 0.9
<b>Hospital indicators</b>			
Received the delirium intervention	450 (49.0)	115 (51.8)	335 (48.1)
Length of stay, d‡	8.1 ± 6.2	9.4 ± 7.0	7.7 ± 5.8
Index hospitalization cost, \$†	6846 ± 7421	7763 ± 7507	6554 ± 7375
<b>Principal diagnosis</b>			
Pneumonia	103 (11.2)	16 (7.2)	87 (12.5)
Chronic lung disease	101 (11.0)	21 (9.5)	80 (11.5)
Congestive heart failure	101 (11.0)	37 (16.7)	64 (9.2)
Ischemic heart disease	79 (8.6)	17 (7.7)	62 (8.9)
Gastrointestinal disease	117 (12.7)	24 (10.8)	93 (13.3)
Diabetes mellitus or metabolic disorder	39 (4.2)	12 (5.4)	27 (3.9)
Cancer	24 (2.6)	18 (8.1)	6 (0.9)
Cerebrovascular disease	21 (2.3)	3 (1.4)	18 (2.6)
Renal failure	18 (2.0)	8 (3.6)	10 (1.4)
Anemia	15 (1.6)	2 (0.9)	13 (1.9)
Other	301 (32.8)	64 (28.8)	237 (34.0)

Abbreviations: ADL, activities of daily living; APACHE, Acute Physiology and Chronic Health Evaluation; BISEP, Burden of Illness Score for Elderly Persons; IADL, instrumental ADL; MMSE, Mini-Mental State Examination.

\*Data are given as number (percentage) of patients in each group unless otherwise indicated.

†Data are given as mean ± SD.

‡There were 7 missing values for this variable: 4 patients died during the study period, and 3 survived.

Riemann integration, which estimated the areas under the curve. Bootstrapping methods<sup>37</sup> were used to provide 95% CIs and standard errors for these estimates. Dividing by 365 days yielded the average fraction of a year survived for each group. Finally, subtracting the average fraction of a year survived by the delirium group from the comparable statistic for the nondelirium group provided an estimate of the average fraction of a year of life lost associated with having delirium during the index hospitalization.

As a confirmatory analysis, we also used a binomial regression model to calculate mortality risk ratios associated with delirium. The same independent variables that remained in the model previously described were included in the model, namely, delirium status, whether the patient had any impairment in ADLs, age, sex, Charlson Comorbidity Index score, and intervention status. All analyses were performed using SAS statistical software, version 8.2.<sup>38</sup>

## RESULTS

The characteristics of patients in the study sample are reported in **Table 1**. Of the 919 patients in the study co-

hort, 222 (24.2%) died during the study period. More patients who died had delirium compared with patients who survived the study period. Patients who died during the study period were also disproportionately men and nursing home residents. In addition, patients who died generally had a higher burden of illness as indicated by higher rates of dementia, greater impairment in ADLs and instrumental ADLs, worse scores on the severity of illness and comorbidity measures, longer lengths of stay during the index hospitalization, and higher costs associated with the index hospitalization.

**Table 2** reports results from the unadjusted and adjusted Cox proportional hazards regression models predicting mortality among those patients who survived the index hospitalization. Because 14 patients died during the index hospitalization, 905 individuals were available for the Cox proportional hazards regression models. In the unadjusted analyses, patients with delirium were significantly more likely to die during the year after discharge. In addition, male patients and nursing home

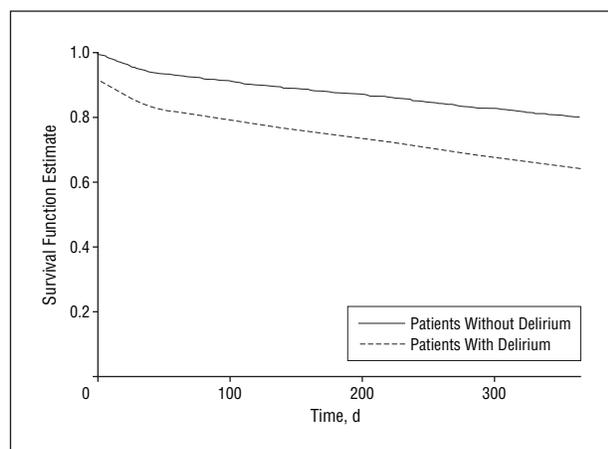
**Table 2. Bivariate and Multivariate Survival Analysis for 905 Patients During 1-Year Follow-up Using Cox Proportional Hazards Regression Models\***

Predictor Variables	Unadjusted Data		Adjusted Data	
	HR (95% CI)	P Value	HR (95% CI)	P Value
<b>Demographic</b>				
Age (range, 70-99 y)	1.02 (0.99-1.04)	.07	1.02 (1.00-1.04)	.11
Male sex (yes vs no)	1.63 (1.25-2.14)	<.001	1.74 (1.32-2.30)	<.001
Nonwhite race (yes vs no)	0.96 (0.64-1.44)	.86	NA	NA
Married (yes vs no)	0.96 (0.72-1.27)	.76	NA	NA
Education (range, 0-20 y)†	0.97 (0.94-1.01)	.17	NA	NA
Nursing home resident (yes vs no)	1.72 (1.07-2.76)	.02	NA	NA
<b>Mental status</b>				
Delirium (yes vs no)	1.95 (1.37-2.77)	<.001	1.62 (1.13-2.33)	.009
Dementia (yes vs no)	1.84 (1.31-2.58)	<.001	NA	NA
MMSE score ( $\leq 23$ vs $\geq 24$ )	1.35 (1.03-1.78)	.03	NA	NA
<b>Functional status</b>				
ADL score (range, 0-7)	1.22 (1.14-1.30)	<.001	1.18 (1.10-1.26)	<.001
IADL score (range, 0-7)	1.20 (1.12-1.28)	<.001	NA	NA
<b>Burden of illness</b>				
APACHE II score ( $\geq 17$ vs $\leq 16$ )	1.89 (1.44-2.48)	<.001	NA	NA
Charlson Comorbidity Index score ( $\geq 2$ vs 0 or 1)	2.74 (1.87-4.02)	<.001	2.32 (1.57-3.41)	<.001
BISEP (range, 1-4)	1.76 (1.55-2.00)	<.001	NA	NA
<b>Hospital indicators</b>				
Received the delirium intervention	1.19 (0.90-1.56)	.22	NA	NA
Length of stay (range, 2-60 d)	1.03 (1.01-1.04)	.002	NA	NA
Index hospitalization cost (range, \$907-\$10 532)	1.01 (0.99-1.03)	.22	NA	NA

Abbreviations: ADL, activities of daily living; APACHE, Acute Physiology and Chronic Health Evaluation; BISEP, Burden of Illness Score for Elderly Persons; CI, confidence interval; HR, hazard ratio; IADL, instrumental ADL; MMSE, Mini-Mental State Examination; NA, data not applicable.

\*The 14 persons who died during the index hospitalization were not included in these models.

†Because of missing data, the model with the education predictor has a sample size of 898.



**Figure.** Fitted survival curves for patients with and without delirium.

residents were also at greater risk of death. Patients scoring lower on any of the mental or functional status measures, or with worse scores on the burden of illness variables, were at increased risk of death as well. Patients with a longer length of stay during the index hospitalization had a slightly higher mortality risk, but the effect of index hospitalization cost was not statistically significant.

Results from the adjusted Cox proportional hazards regression model are presented in Table 2. Five variables were included in the final model: age, male sex, delirium, ADL impairment, and Charlson Comorbidity Index score. Even after controlling for these other covariates, patients with

delirium had significantly higher mortality risk than patients without delirium. Notably, intervention status was not a significant predictor of mortality and did not influence the overall results ( $P=.22$ ).

The fitted survival curves from the 2-part model for patients with and without delirium are plotted in the **Figure**. The curve for patients with delirium has a larger decrease at time=0 than the curve for patients without delirium because most patients who died during the index hospitalization had delirium (10 of the 14 deaths). The survival curve for patients with delirium also decreases faster during the follow-up than the curve for patients without delirium.

Adjusted and unadjusted fractions of a year of life survived for patients with and without delirium are presented in **Table 3**. These estimates were calculated by computing the areas under the adjusted curve in the Figure. After adjusting for other covariates in the model, patients with delirium survived an average of 273.75 days during the year (0.75 of a year), compared with 321.20 days (0.88 of a year) among patients without delirium. This corresponds to a difference of 47.5 days (0.13 of a year) of life lost associated with delirium ( $P<.001$ ).

The results of the binomial regression model were similar to those of the 2-part model. The unadjusted predicted probability of survival for the group without delirium was 0.78, compared with 0.58 for the group with delirium, a difference of 0.20. These results confirmed those of our earlier analyses, and indicated that these results were conservative estimates of the effect of delirium on mortality.

Finally, we conducted bivariate and multivariate analyses of 1-year mortality and delirium severity during hospitalization, using a severity scoring system that was developed in a previous study.<sup>22</sup> We found a significant dose-response relationship for delirium severity and mortality in the bivariate analysis, with mortality increasing from 18.5% in the group without delirium (n=596) to 30.3% in the group with mild delirium (n=264) and to 40.0% in the group with severe delirium (n=40) (Mantel-Haenszel  $\chi^2=22.2$ ,  $P<.001$  for trend). We also repeated the Cox proportional hazards regression models using the delirium severity measure and found that patients with more severe delirium had a larger HR (HR, 1.89; 95% CI, 1.13-3.14;  $P=.02$ ) than patients with less severe delirium (HR, 1.62; 95% CI, 1.21-2.17;  $P=.001$ ), using patients without delirium as the referent group.

## COMMENT

This study examined premature mortality associated with delirium in hospitalized older patients. The results indicate that patients who experienced delirium during hospitalization had a 62% increased risk of mortality in the 12 months following discharge and survived an average of 47.5 fewer days (13% of a year) than patients without delirium. Hence, although delirium is an acute condition, these results demonstrate that premature mortality is one of several long-term sequelae that extend beyond the hospital setting.<sup>2-9</sup> The strengths of this study include the detailed follow-up of patients, with complete tracking of vital status for all patients at 1 year; the state-of-the-art methods for determination of delirium diagnoses, the key predictor variable; and the clinically rich baseline data collection that allowed adjustment for key covariates in this analysis.

The mortality risk associated with delirium is substantial. In our sample of 919 hospitalized patients aged 70 to 99 years, 48 individuals with delirium died during the follow-up, which corresponds to a mortality of 5.2%, or 5223 deaths per 100 000. This rate is higher than the rate corresponding to any of the 15 leading causes of death among individuals aged 75 to 84 years during 1998, the last year of the study.<sup>39</sup> Only the national mortality rate for heart disease among individuals 85 years and older was higher (6010 per 100 000) than the rate corresponding to delirium in our sample. While extrapolations from our single-site sample are necessarily limited, when one considers that up to half of delirium cases are preventable,<sup>22,40</sup> such a high mortality rate is clearly cause for concern. In addition, the contribution of delirium to earlier (more accelerated) mortality raises even greater cause for concern.

A series of dose-response analyses demonstrated a strong relationship between delirium severity during hospitalization and 1-year mortality. While we demonstrated a higher HR for severe delirium (HR, 1.89) than for less severe delirium (HR, 1.62), we were unable to document a significant difference between these 2 HRs given the relatively small sample sizes in these 2 groups. However, the direct relationship of delirium severity to mortality in these analyses lends strong support for our hypothesis that delirium is the underlying cause of the premature mortality.

**Table 3. Average Fractions of a Year of Life Lost Among Patients With and Without Delirium**

Result	Fraction of Year Survived (95% Confidence Interval)		Difference*
	Patients Without Delirium	Patients With Delirium	
Unadjusted	0.87 (0.85-0.89)	0.67 (0.60-0.75)	0.20
Adjusted†	0.88 (0.86-0.90)	0.75 (0.68-0.81)	0.13

\* $P<.001$  for the difference between patients with and patients without delirium. The standard errors used in the  $t$  tests for comparing 2 large sample means were obtained by bootstrapping methods.

†Adjusted for activities of daily living disability status, age, male sex, and the Charlson Comorbidity Index score. The logistic regression model providing step 1 of the 2-step model only included the delirium predictor because of the few deaths during the index hospitalization.

In 2 previous studies of the long-term mortality risk associated with delirium among patients 65 years and older who were admitted to an acute care hospital, Rockwood et al<sup>21</sup> found an adjusted HR of 1.71 (95% CI, 1.02-2.87) and McCusker and colleagues<sup>20</sup> found an adjusted HR of 2.11 (95% CI, 1.18-3.77). The HR associated with delirium in our sample (HR, 1.62; 95% CI, 1.13-2.33;  $P=.009$ ) was slightly smaller than those found in these earlier studies, but comparable. However, our study included considerably more patients (919 vs 203 and 361 in the Rockwood et al and McCusker et al studies, respectively) and investigated the difference in the adjusted number of days of life lost during the follow-up.

How do we interpret the average of 0.13 of a year of life lost in patients with delirium compared with patients without delirium? We were unable to find comparable statistics for other disorders. Several studies calculate 1-year mortality rates associated with other diseases, and identify factors affecting those rates. However, we are not aware of any other studies that have directly examined the timing of mortality during the follow-up and, hence, we were unable to compare our finding of the number of days of life lost associated with delirium with that of other diseases. Thus, our method also represents an innovative approach to addressing this important issue that holds substantial implications for various other medical conditions. The timing of mortality is important, because the mortality risk is more severe when patients die earlier in the follow-up.

Some limitations of the analysis deserve comment. Our estimate of the average fraction of a year of life lost associated with delirium is potentially biased because follow-up was truncated after 1 year. If delirium is associated with further shortening of life after 1 year, then the average estimated during just the first year would be an underestimate. However, we believe that the bias for our estimate of the fraction of a year of life lost is small because the effect of delirium is likely to diminish over time so that deaths after 1 year are less likely to be attributable to the delirium episode. Nevertheless, if patients were followed up over a longer period, the number of days lost would likely be greater.

A second limitation relates to the generalizability of the study. The study involved a single-site controlled trial. Nev-

ertheless, patients enrolled in the study were drawn from a large sample representative of older patients admitted to an acute care hospital. Our analyses controlled for whether patients received the delirium prevention intervention, and documented no effect of the intervention on 1-year mortality. Thus, the interventional nature of the original controlled trial does not invalidate our approach.

This study shows that delirium among hospitalized older patients is associated with premature mortality after discharge and a significantly smaller fraction of a year survived compared with patients who do not develop delirium in the hospital. The finding of premature mortality is consistent with the notion that delirium is a morbid condition with prolonged adverse effects. Moreover, the existence of premature mortality suggests that limiting clinical efforts that target delirium to the period of hospitalization alone may be insufficient to prevent adverse events, including premature mortality, that occur after hospitalization. Just as previous efforts to identify risk factors for the development of delirium have led to successful hospital-based interventions designed to prevent delirium, so the finding of premature mortality should spur efforts to identify the underlying mechanisms and to design longer-lasting interventions that may reduce premature mortality. Such interventions will likely need to incorporate components extending to the vulnerable period after hospitalization, and, to our knowledge, have not yet been developed or tested. The substantial long-term mortality risk associated with delirium should spur efforts to mitigate this clinically significant and costly problem.

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