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Pathway from Delirium to Death: Potential In-Hospital Mediators of Excess Mortality

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Abstract

OBJECTIVES—(1) To determine the relationship of incident delirium during hospitalization with 90-day mortality; (2) to identify potential in-hospital mediators through which delirium increases 90-day mortality.

DESIGN—Analysis of data from Project Recovery, a controlled clinical trial of a delirium prevention intervention from 1995 to 1998 with follow-up through 2000.

SETTING—Large academic hospital.

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PARTICIPANTS—Patients ≥70 years-old without delirium at hospital admission who were at intermediate-to-high risk of developing delirium and received usual care only.

MEASUREMENTS—(1) Incident delirium; (2) potential mediators of delirium on death including use of restraining devices (physical restraints, urinary catheters), development of hospital acquired conditions (HACs) (falls, pressure ulcers), and exposure to other noxious insults (sleep deprivation, acute malnutrition, dehydration, aspiration pneumonia); (3) death within 90 days of admission.

RESULTS—Among 469 patients, 70 (15%) developed incident delirium. These patients were more likely to experience restraining devices (37% vs. 16%, p<.001), HACs (37% vs. 12%, p<.001), other noxious insults (63% vs. 49%, p=.03), and 90-day mortality (24% vs. 6%, p<.001). The inverse probability weighted hazard of death due to delirium was 4.2 (95% CI=2.8–6.3) in bivariable analyses, increased in a graded manner with additional exposures to restraining devices, HACs, and other noxious insults, and declined by 10.9% after addition of these potential mediator categories, providing evidence of mediation.

CONCLUSION—Restraining devices, HACs, and additional noxious insults were more frequent among patients with delirium, increased mortality in a graded manner, and were responsible for a significant percentage of the association of delirium with death. Additional efforts to prevent potential downstream mediators through which delirium increases mortality may help to improve outcomes among hospitalized older adults.

Keywords

geriatrics; delirium; hospital care; quality of care; hospital-acquired conditions

INTRODUCTION

Delirium is a common, costly, and morbid condition that affects more than one in five hospitalized older adults and costs more than $160 billion per year in the United States alone.[1] Patients who develop delirium while receiving hospital care for medical,[2,3] neurological,[4] and surgical[3,5] conditions have an elevated risk of death during and after hospitalization[6,7] This higher risk of death from delirium has persisted across time in different health care settings and across countries.[1]

While the association of delirium with death is well appreciated, there is lack of agreement as to whether delirium is directly harmful to patients or is instead a marker of their intrinsic vulnerability. Evidence supporting delirium's direct adverse effects include observational data relating delirium to a higher risk of death after controlling for multiple patient factors associated with adverse outcomes including advanced age, cognitive impairment, functional limitations, multimorbidity, and high illness severity.[3,8–10] However, residual confounding may influence these findings, as patients developing delirium generally have greater chronic disease burden and acute illness severity than patients who do not.

It is also not known if mortality from delirium is mediated by its potential downstream consequences including the use of restraining devices, development of hospital-acquired conditions (HACs) such as falls and pressure ulcers, and exposure to other noxious insults

such as sleep deprivation, acute malnutrition, dehydration, and aspiration pneumonia.[11–13] All of these adverse exposures are more common among sicker hospitalized patients,[14–18] many of whom may have delirium.[14,19] These events can result in significant harm [20–22] and have therefore become an increasing focus for quality improvement.[23,24] Yet these adverse exposures still occur at unacceptably high rates to hospitalized patients.[25–30] If commonly associated with the pathway from delirium to death, restraining devices, HACs, and other noxious insults during hospitalization can serve as specific targets for quality improvement in patients with delirium.

We therefore examined the relationship of incident delirium during hospitalization with the risk of short-term mortality using data from Project Recovery,[31] a high quality dataset measuring delirium development, risk factors, and outcomes in older patients hospitalized with a range of medical conditions. We hypothesized that patients developing delirium during hospitalization are at higher risk of 90-day mortality after adjusting for demographic characteristics, lifestyle factors, chronic health history, acute illness severity, and potential downstream mediators linking delirium to death. We also hypothesized that adverse hospital exposures including the use of restraining devices, development of HACs, and occurrence of other noxious insults during hospitalization significantly mediate the association of delirium with death.

METHODS

Study population

We examined 469 older patients who were enrolled in the usual care arm of Project Recovery, a controlled clinical trial of a delirium prevention intervention at Yale-New Haven Hospital from 1995 through 1998, with follow up to 2000.[31] Project Recovery is highly unique in its daily assessments for delirium, intercurrent illnesses, and hospital care practices, as well as its careful mortality tracking after hospital discharge. These daily clinical assessments permitted comprehensive identification of both incident delirium and adverse hospital exposures including restraining devices, HACs, and other noxious insults from hospitalization that are potential mediators of delirium on death. Project Recovery continues to be actively used for ongoing investigations related to delirium.[32]

Patients were included in Project Recovery if they were ≥70 years-old, did not have delirium at hospital admission, and were at intermediate-to-high risk of developing delirium. Patients were excluded if they had terminal illness, were unable to participate in interviews, or had a hospital stay of ≤48 hours.

Data collection

Study researchers performed daily patient assessments and reviewed medical records to collect data. The study team completed 99.8% of all potential daily hospital assessments. Incident delirium during hospitalization, the primary exposure of interest, was identified through daily patient assessment using cognitive screening tests and the Confusion Assessment Method (CAM), a reliable and valid scale for delirium diagnosis.[33,34] The CAM has a sensitivity and specificity of 94 and 89 percent, respectively, against reference standard

ratings by geriatric psychiatrists, as well as high inter-rater reliability.[1] A delirium diagnosis with the CAM required evidence of acute onset and a fluctuating course of symptoms, inattention, and either disorganized thinking or an altered level of consciousness. Interrater reliability of ratings for each of these features was confirmed in 16 paired observations involving all members of the research staff (kappa, 1.0). Delirium was considered as a binary outcome (present or absent) for these analyses.

Adverse hospital exposures that are potential mediators of the relationship of delirium with death were also assessed daily. The use of physical restraints and urinary catheters ("one point restraints"[35]) was identified through daily examination and medical record review. Falls were identified through review of medical records and hospital incident reports. Pressure ulcers were identified by daily bedside observation of 11 pressure points and medical record review. Exposure to other noxious insults was identified through daily patient interviews (sleep deprivation) and medical record review (acute malnutrition, dehydration, aspiration pneumonia). Sleep deprivation was recognized if ≥3 of 6 items indicating sleep deprivation were endorsed during daily patient interviews, which were completed at a high rate (83%) even among patients with delirium. Dehydration was indicated by a blood urea nitrogen/creatinine ratio of ≥18. Acute malnutrition was recognized if dietary supplements were prescribed or if a patient had documented weight loss of ≥5.6 kg during hospitalization. Aspiration pneumonia was identified if respiratory suctioning was performed[36] or if specifically noted in hospital records.

Other variables that were collected and used in our study included: (1) demographic characteristics including age, sex, race, education in years, and marital status; (2) lifestyle factors including current smoking status and alcohol intake; (3) chronic health status including body mass index (BMI), performance in activities of daily living (ADL) and instrumental activities of daily living (IADL) at admission (functional impairment rated as present if patient needed help to perform at least one ADL or IADL), dementia at admission (Mini Mental State Examination [MMSE, purchased from Psychological Assessment Resources, Inc.] score <24 and modified Blessed Dementia Rating Scale score ≥4, and cognitive impairment present for ≥6 months),[37,38] hearing impairment at admission (use of hearing aid or positive whisper test[39]), vision impairment at admission (Jaeger Card Test score ≥10 with corrective lenses), depression at admission (Geriatric Depression Scale score ≥6),[40] Charlson Comorbidity Index score (range 0–15), and living in nursing home; and (4) acute illness severity per the Acute Physiology and Chronic Health Evaluation II (APACHE II) score (range 7–29).

Deaths were identified through follow-up interviews with family members, daily review of obituaries, medical record review, and the Social Security Death Index. Dates of death were all confirmed by review of medical records, National Death Index, death certificates, and Medicare enrollment and claims data. Mortality tracking was complete for all patients.

Study Outcome

The primary outcome was death within 90 days of hospital admission. We conducted two major analyses, as follows: (1) the relationship of incident delirium during hospitalization with death within 90 days of the admission date in fully adjusted and propensity-weighted

models; and (2) the extent to which exposure to restraining devices, HACs, and other noxious insults during hospitalization attenuated the relationship of incident delirium with death within 90 days of the admission date in fully adjusted and propensity-weighted models.

Statistical Analyses

We identified demographic, lifestyle, health history, and acute illness severity information for patients who did and did not develop delirium during hospitalization. We compared continuous variables using analysis of variance and categorical variables using chi-square tests. To account for a small amount for missing data in predictor variables (<5%), we performed multiple imputation using multivariate imputation chained equations.[41,42]

We balanced patient characteristics between patients who did and did not develop delirium during hospitalization by constructing regression-based propensity scores with variables for patient demographics, lifestyle factors, health history, and acute illness severity. We calculated inverse probability weights (IPWs) for each patient who developed delirium as the inverse of the predicted probability of developing delirium conditional on observed covariates that were significantly associated ($p<0.05$) with both delirium and death. We calculated weights for patients who did not develop delirium as the inverse of one minus the predicted probability of developing delirium conditional on observed covariates.[43,44]

We calculated unweighted and inverse probability weighted Cox regression models to determine the hazard of death within 90 days of the admission date due to incident delirium and adverse hospital exposures including restraining devices, HACs, and other noxious insults during hospitalization that are potential mediators of delirium on death. We first calculated the hazard of death due to incident delirium and each potential mediator variable using bivariable Cox regression models. We then calculated Cox regression models for death due to incident delirium after adjustment for potential individual mediator variables. We additionally calculated the cumulative incidence of death for persons with and without incident delirium after adjustment for all adverse hospital exposures potentially mediating delirium on death. We also calculated the cumulative incidence of death as a function of the number of adverse hospital exposures (0, 1, 2, 3, ≥4) after adjustment for delirium status.

We defined the presence of mediation as a ≥5 percent change in the parameter estimate of delirium on death with the addition of the potential mediator variable to the model. This definition of mediation is a liberal one relative to the 10% parameter estimate change typically used to define practically important levels of confounding.[45] We used a liberal definition of mediation to be maximally inclusive of potential mediating effects. Our approach to testing mediation based on parameter estimate changes is conceptually equivalent to path analysis approaches that make presumed causal relationships among variables explicit in a visual manner.[46] We tested adverse exposures individually and by group (e.g. any restraining device, any HAC, any hospital stressor). Our final Cox regression analysis adjusted for the presence of delirium and all hospital adverse exposure categories. We did not test for moderation, which would require that we model the statistical interaction of variables, for which we had inadequate statistical power.[46]

Statistical significance was set at an alpha of 0.05. Analyses were performed using STATA 13 (StataCorp LP, College Station, TX).

RESULTS

Of 469 patients, 70 (15%) developed delirium during hospitalization. Thirty-nine patients (8.3%) died within 90 days of admission. The rate of death was greater in patients who developed delirium (n=17, 24%) than in those who did not develop delirium (n=22, 6%) (p<.001). As compared to those who did not develop delirium, patients who developed delirium more often lived in a nursing home (13% vs. 5%, p=.02), more often had impairments in ADLs (56% vs. 32%, p<.001) and IADLs (94% vs. 85%, p=0.04), and had a higher prevalence of dementia (23% vs. 11%, p=0.01) (Table 1).

Restraining devices, HACs, and other noxious insults were, in most cases, more common among patients developing delirium (Supplementary Table S1). Among patients who did and did not develop delirium, respectively, physical restraints were used in 20% vs. 1% (p<.001), a fall occurred in 9% vs. 2% (p=.003), a pressure ulcer developed in 33% vs. 10% (p<.001), acute malnutrition developed in 39% vs. 13% (p<.001), and aspiration pneumonia occurred in 4% vs. 1% (p=.04). No difference between groups was found in urinary catheter use (23% vs. 15%, p=.10), sleep deprivation (46% vs. 39%, p=.26), or dehydration (3% vs. 4%, p=.71). Patients developing delirium were more likely to receive at least one restraining device (37% vs. 16%, p<.001), develop at least one HAC (37% vs. 12%, p<.001), and experience at least one additional noxious insult (63% vs. 49%, p=.03).

Incident delirium was associated with a greater risk of short-term mortality in both unweighted (Hazard Ratio [HR] 5.0, 95% confidence interval [CI]=2.6–9.4) and inverse probability weighted (HR 4.2, 95% CI=2.8–6.3) analyses. Inverse probability weights were calculated using variables for education level, functional status, dementia, Charlson Comorbidity Index score, and APACHE score, all of which were significantly associated (p's<.05) with both incident delirium and death. In the weighted models, the hazard of death was greater in patients receiving physical restraints (HR 2.0, 95% CI=1.4–2.9) or urinary catheters (HR 1.5, 95% CI=1.1–2.3), patients who fell (HR 3.6, 95% CI=2.4–5.4), developed a pressure ulcer (HR 2.3, 95% CI=1.6–3.2), experienced sleep deprivation (HR 2.5, 95% CI=1.8–3.5), acute malnutrition (HR 3.7, 95% CI=2.7–5.1), or aspiration pneumonia (HR 8.4, 95% CI=5.6–12.6) (Table 2).

The cumulative incidence of death within 90 days of the admission date was higher in persons who developed delirium and in persons experiencing adverse hospital exposures including restraining devices, HACs, and other noxious stimuli. A greater number of adverse hospital exposures (0, 1, 2, 3, ≥4) was associated with a higher risk of death in a graded manner after controlling for the effect of delirium (Figure 1, right panel).

In inverse probability weighted models with delirium and one other adverse hospital exposure, the occurrence of falls, pressure ulcers, acute malnutrition, and aspiration pneumonia changed the parameter estimate of delirium on death by more than 5%, suggesting that these adverse exposures may be mediators on the pathway from delirium to

death within 90 days of hospital admission (Table 3). When risk factor categories were grouped, the use of any restraining device and development of any HAC also changed the parameter estimate of delirium on death by more than 5% (Table 3).

The final inverse probability weighted multivariable model with delirium and all adverse hospital exposure categories (restraining devices, HACs, and other noxious stimuli) resulted in a 10.9% reduction in the parameter estimate of delirium on death compared to the bivariable model with delirium only, suggesting that these adverse hospital exposures are mediators on the pathway between delirium and death (Table 4). In this final model, incident delirium remained independently associated with a greater risk of mortality within 90 days of the admission date (HR 3.6, 95% CI=2.3–5.5).

DISCUSSION

New-onset delirium during hospitalization is strongly predictive of mortality within 90 days of the admission date even after adjusting for baseline characteristics and potential downstream mediators of delirium on death including the use of restraining devices, development of hospital-acquired conditions, and occurrence of additional noxious insults during hospitalization. Almost all of these adverse exposures were more than three-times as likely to occur among patients with delirium, increased mortality in a graded manner, and were responsible for a significant percentage (10.9%) of the association of delirium with death. These findings suggest that additional efforts to prevent use of restraining devices, hospital-acquired conditions, and additional noxious insults that are common during hospitalization may be worthy targets to improve outcomes and reduce mortality for the many million older patients with delirium.

Our work extends the literature in two ways. Firstly, it strengthens evidence that delirium itself may be directly harmful to patients. We build upon previous studies linking incident delirium with death[3,8–10] by demonstrating a persistent relationship after balancing baseline characteristics of patients who did and did not develop delirium during hospitalization through the use of regression-based propensity scores. In contrast with previous studies, we also adjusted for potential downstream mediators through which delirium may cause harm. Despite these adjustments, the hazard of death for older patients developing delirium during hospitalization is almost four times greater than that for persons who do not develop delirium. Secondly, our work applies research on adverse hospital exposures to the study of delirium and suggests that efforts to minimize use of restraining devices, prevent the occurrence of falls and pressure ulcers, and reduce the likelihood of sleep disturbance, insufficient food intake, and aspiration events may reduce mortality from delirium by a significant extent, as delirium is both common and strongly associated with death. Almost all of these adverse exposures are much more likely to occur among patients with delirium and increase mortality in a graded manner, suggesting that even partially successful preventative efforts can improve outcomes.

This analysis has a number of strengths. We used data from Project Recovery, which included daily ascertainment for delirium and multiple adverse hospital exposures using rigorous, validated approaches. Only 0.2% of daily interviews and assessments were missed.

In addition, detailed data were collected on a wide range of clinically relevant variables that potentially confound the relationship of delirium with death including cognition, functional status, sensory impairments, and acute illness severity. Ascertainment of post-hospital mortality was complete and validated through multiple data sources including the Social Security Death Index, National Death Index, and Medicare databases. Project Recovery therefore continues to be used to examine delirium and its outcomes.[32] We also used regression-based propensity scores to minimize differences in observed characteristics between patients who did and did not develop delirium while hospitalized. This technique is especially useful when examining conditions like delirium that more commonly affect patients with greater vulnerability to adverse outcomes.

Results should also be interpreted in the context of the following potential limitations. Firstly, Project Recovery does not have contemporary data, as data collection occurred between 1995 and 1998, with follow up to 2000. However, our primary relationship of interest between delirium and death would not be expected to be different today, as no interventions have been shown to reduce mortality from delirium.[1] In addition, the CAM remains the tool of choice to identify delirium,[34] and the adverse hospital exposures examined in our study continue to occur at sub-optimally high rates.[25–30] Secondly, we cannot eliminate all sources of bias influencing the relationship of delirium with death. Thirdly, we cannot confirm that restraining devices, HACs, and additional noxious insults during hospitalization were downstream consequences of delirium. However, our finding that these adverse exposures explain a significant proportion of the association of delirium with death and predict mortality in a graded manner suggests that they may be important targets to reduce adverse outcomes among patients with delirium even if not causally related. Fourthly, our use of respiratory suctioning as one way to identify aspiration pneumonia may have suboptimal specificity. However, we used this approach since oropharyngeal and tracheal suction are recommended treatments for witnessed aspiration.[36] Fifthly, the low number of deaths limited our statistical power and precluded our fitting a single model examining the association of all adverse hospital exposures, included individually, with death. However, it is likely that many of these variables are clinically important, as we found that 90-day mortality increases in a graded manner with the number of adverse hospital exposures.

Our findings have implications for clinical practice and research. They underscore the importance of multicomponent interventions designed to prevent delirium, which can reduce rates of incident delirium by 30 to 40 percent.[31] These strategies involve assessment and modification of clinical factors known to precipitate delirium during hospitalization and have lowered delirium incidence in real world practice. Our results also suggest that improved hospital care for older patients with delirium may improve patient outcomes. Targeted strategies shown to reduce urinary catheter use,[47] a broad range of HACs[48,49] and sleep disturbances[50] may be considered once delirium is diagnosed. Future research including intervention trials can prospectively determine the value and effectiveness of proactive strategies to identify delirium and mitigate its downstream consequences within the hospital.

In summary, we found that a significant proportion of the association of delirium with death may be explained by the use restraining devices, development of hospital-acquired conditions, and occurrence of additional noxious insults during hospitalization. We also found that as the number of adverse hospital exposures increase, so does the risk of death following delirium onset. These results suggest that intensified efforts to reduce hospital-acquired insults and complications may improve health outcomes among the more than 2.6 million older Americans that develop delirium while hospitalized each year.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest disclosures (details below):

Elements of Financial/Personal Conflicts	K. Dharmarajan		S. Swami		R. Gou		R. Jones		S. Inouye	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation	X			X		X		X		X
	Centers for Medicare & Medicaid Services									
Grants/Funds		X		X		X		X		X
Honoraria		X		X		X		X		X
Speaker Forum		X		X		X		X		X
Consultant	X			X		X		X		X
	Clover Health									
Stocks		X		X		X		X		X
Royalties		X		X		X		X		X
Expert Testimony		X		X		X		X		X
Board Member	X			X		X		X		X
	Clover Health									
Patents		X		X		X		X		X
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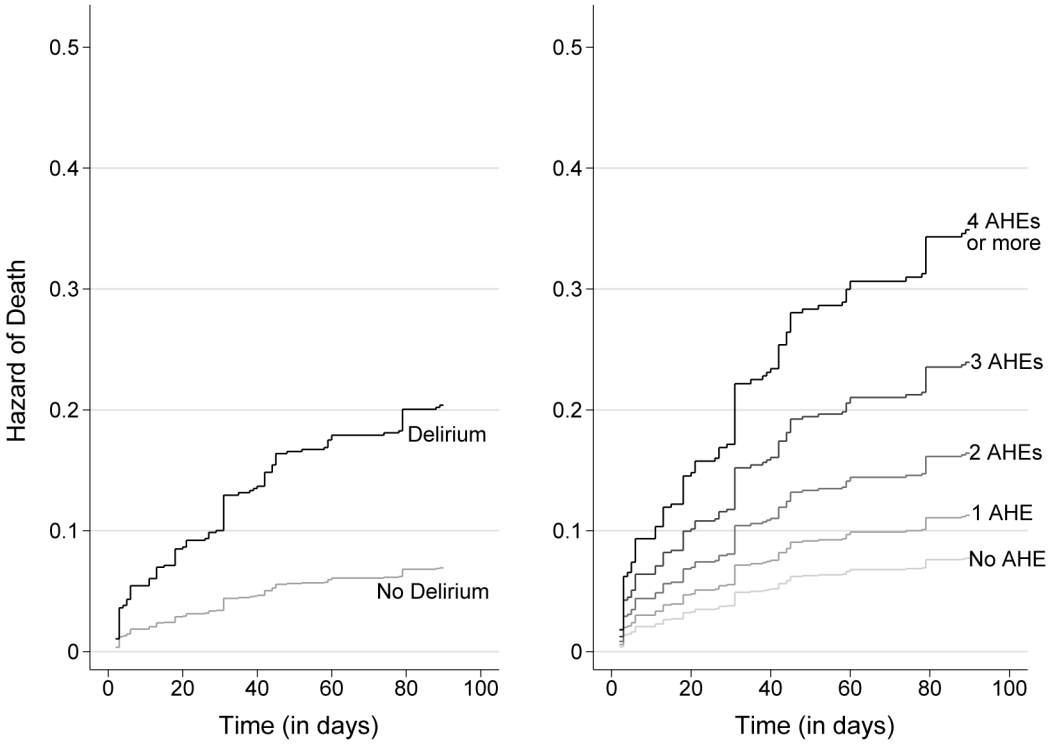

Figure 1. Cumulative Hazard of Death Associated with Delirium and the Number of Adverse Hospital Exposures

The left panel shows data for the cumulative hazard of death associated with incident delirium in the 90 days after hospital admission. Results are adjusted for the presence of adverse hospital exposures, which include the use of physical restraints, use of a urinary catheter, occurrence of a fall, occurrence of a pressure ulcer, occurrence of sleep deprivation, occurrence of acute malnutrition, occurrence of dehydration, and occurrence of aspiration pneumonia. The right panel shows data for the cumulative hazard of death associated with the number of adverse hospital exposures, which include the use of physical restraints, use of a urinary catheter, occurrence of a fall, occurrence of a pressure ulcer, occurrence of sleep deprivation, occurrence of acute malnutrition, occurrence of dehydration, and occurrence of aspiration pneumonia. Results are adjusted for the presence of incident delirium. AHE=Adverse Hospital Exposure.

Table 1

Patient Characteristics.

Characteristic	All Patients (N=469)	Patients With Delirium (N=70)	Patients Without Delirium (N=399)	P Value for Difference Between Patients With and Without Delirium
Demographic characteristics				
Average age in years (SD)	80.1 (6.5)	81.2 (7.2)	79.9 (6.4)	0.100
Male, n (%)	187 (39.9)	29 (41.4)	158 (39.6)	0.773
Non-white race, n (%)	70 (14.9)	15 (21.4)	55 (13.8)	0.098
Average education in years, (SD)	11.0 (3.6)	9.8 (3.5)	11.3 (3.6)	0.002
Married, n (%)	161 (34.3)	19 (27.1)	142 (35.6)	0.170
Lifestyle factors				
Currently smoking, n (%)	43 (9.2)	5 (7.1)	38 (9.5)	0.524
Average alcoholic drinks/week (SD)	2.0 (8.1)	1.9 (10.2)	2.0 (7.7)	0.985
Chronic health status				
Average BMI (kg/m2) (SD)	25.3 (6.3)	25.5 (5.7)	25.3 (6.4)	0.812
Impairment in ADLs,[a] n (%)	165 (35.2)	39 (55.7)	126 (31.6)	<.001
Impairment in IADLs,[b] n (%)	405 (86.4)	66 (94.3)	339 (85.0)	0.036
Dementia,[c] n (%)	60 (12.8)	16 (22.9)	44 (11.0)	0.006
Hearing impairment,[d] n (%)	83 (17.7)	16 (23.1)	67 (16.8)	0.199
Visual impairment,[e] n (%)	131 (27.9)	21 (30.0)	110 (27.6)	0.676
Depression,[f] n (%)	148 (31.6)	26 (37.1)	122 (30.6)	0.276
Average Charlson Comorbidity Index score (SD)	2.7 (2.2)	3.4 (2.5)	2.6 (2.1)	0.003
Living in nursing home, n (%)	30 (6.4)	9 (12.9)	21 (5.3)	0.017
Acute illness severity				
Average Apache II score (SD)	15.6 (4.1)	17.2 (4.6)	15.4 (4.0)	0.001

[a] Impairment in ADLs was defined as needing help to perform at least 1 activity of daily living

[b] Impairment in IADLs was defined as needing help to perform at least 1 instrumental activity of daily living

[c] Dementia was defined as Mini-Mental State Examination Score <24, modified Blessed Dementia Rating Scale score ≥4, and duration of cognitive symptoms for ≥6 months.

[d] Hearing impairment was identified if a patient used a hearing aid or had positive Whisper test.

[e] Visual impairment was identified if a patient scored ≥10 on Jaeger Card Test while wearing corrective lenses.

[f] Depression was identified if Geriatric Depression Scale score ≥6 and ≥8 out of 15 items were answered.

SD=standard deviation; BMI=body mass index; ADL=activity of daily living; IADL=instrumental activity of daily living.

Table 2

Risk of Death Associated with Delirium and Potential Mediators of Delirium on Death in Bivariable Analyses.

Variable	N (%)	Unweighted Model HR (95% CI)	Inverse Probability Weighted Model HR (95% CI)
Incident delirium	70 (14.9)	5.0 (2.6–9.4)	4.2 (2.8–6.3)
Restraining devices			
Physical restraints	17 (3.6)	3.5 (1.2–9.8)	2.0 (1.4–2.9)
Urinary catheter use	76 (16.2)	2.4 (1.2–4.7)	1.5 (1.1–2.3)
Hospital-acquired conditions (HACs)			
Fall	14 (3.0)	2.8 (0.9–9.0)	3.6 (2.4–5.4)
Pressure ulcer	63 (13.4)	2.6 (1.3–5.3)	2.3 (1.6–3.2)
Other noxious insults			
Sleep deprivation	186 (39.7)	1.2 (0.7–2.4)	2.5 (1.8–3.5)
Acute malnutrition	77 (16.4)	4.9 (2.6–9.3)	3.7 (2.7–5.1)
Dehydration	17 (3.6)	1.4 (0.3–5.9)	0.3 (0.1–1.2)
Aspiration pneumonia	7 (1.5)	4.2 (1.0–17.4)	8.4 (5.6–12.6)

Data are based on unweighted and inverse probability weighted Cox regression models.

HR= Hazard ratio; CI= Confidence interval.

Table 3

Potential Mediation Effects of Delirium on Death After Adjustment for Individual Adverse Hospital Exposures.

Risk Factor	HR for Delirium (95% CI)	HR for Adverse Hospital Exposure (95% CI)	Percent Change in Parameter Estimate of Delirium
Delirium only	4.2 (2.8–6.3)		
Restraining devices			
Physical restraints	4.0 (2.6–6.1)	1.2 (0.8–1.8)	3.6%
Urinary catheter use	4.2 (2.8–6.3)	1.5 (1.0–2.2)	0.3%
Any restraining device	3.9 (2.5–5.9)	1.4 (1.0–2.0)	5.6%
Hospital-acquired conditions (HACs)			
Fall	3.7 (2.5–5.7)	2.6 (1.7–3.9)	8.0%
Pressure ulcer	3.7 (2.4–5.7)	1.6 (1.1–2.3)	8.9%
Any HAC	3.9 (2.5–5.9)	1.3 (0.9–1.9)	5.6%
Other noxious insults			
Sleep deprivation	4.2 (2.8–6.3)	2.5 (1.8–3.5)	0.3%
Acute malnutrition	3.3 (2.1–5.0)	2.8 (2.0–3.9)	17.5%
Dehydration	4.2 (2.8–6.4)	0.3 (0.1–1.1)	−0.7%
Aspiration pneumonia	3.6 (2.4–5.5)	6.4 (4.2–9.7)	9.9%
Any noxious insult	3.9 (2.6–5.9)	2.3 (1.6–3.3)	4.9%

Data are based on results of inverse-probability weighted Cox regression models. Hazard ratios for death within 90 days of admission are shown for delirium only and for delirium plus one additional adverse hospital exposure. The final column shows the percentage change in parameter estimate of delirium on death with the addition of individual adverse hospital exposure variables. A change in the parameter estimate of delirium of more than 5% provides evidence for mediation.

HR=hazard ratio; CI=confidence interval.

Table 4

Potential Mediation Effects of Delirium on Death After Adjustment for All Adverse Hospital Exposure Categories.

Risk Factor	HR (95% CI)	Percent Change in Parameter Estimate of Delirium
Bivariable model		
Delirium	4.2 (2.8–6.3)	--
Multivariable model		
Delirium	3.6 (2.3–5.5)	10.9%
Restraining devices	1.1 (0.8–1.6)	
Hospital-acquired conditions	1.2 (0.8–1.9)	
Other noxious insults	2.2 (1.5–3.2)	

Data are based on results of inverse-probability weighted Cox regression models. Hazard ratios for death within 90 days of admission are shown for delirium only and for delirium plus all adverse hospital exposure categories. The final column shows the percentage change in parameter estimate of delirium on death with the addition all adverse hospital exposure categories to the Cox regression model. A change in the parameter estimate of delirium of more than 5% provides evidence for mediation. HR=hazard ratio; CI=confidence interval.